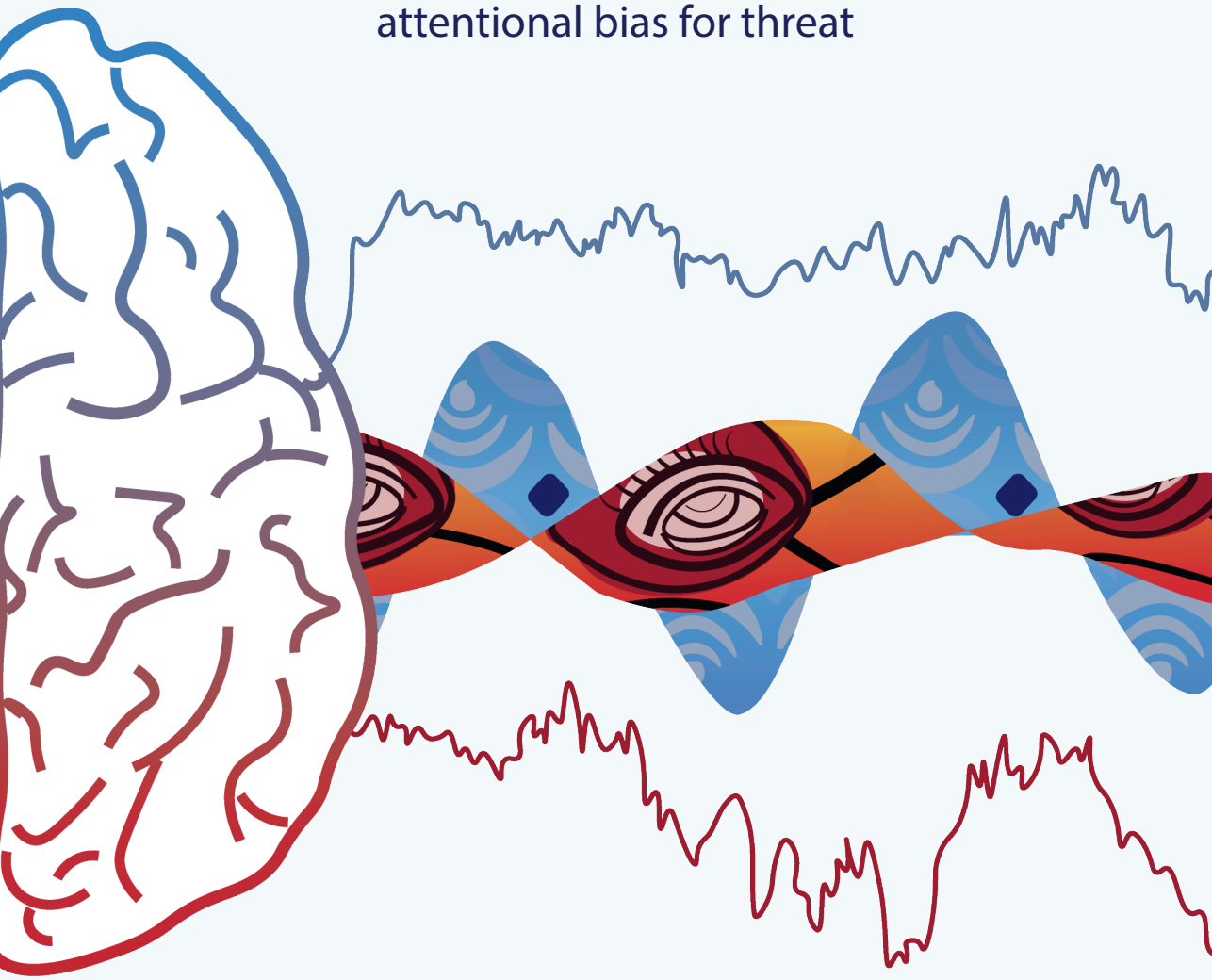
EEG theta/beta ratio: a marker of executive control and its relation with anxiety-linked attentional bias for threat

Son, D. van

EEG theta/beta ratio

A marker of executive control and its relation with anxiety-linked attentional bias for threat



Dana van Son

EEG Theta/Beta Ratio

A Marker of Executive Control and its Relation with Anxiety-Linked Attentional Bias for Threat

Dana van Son

Cover by Lieke van Son
Printing by GVO drukkers & vormgevers B.V.

ISBN: 978-94-6332-477-9

This research was supported by a grant from the Netherlands Organization for Scientific Research (NWO; #452-12-003) to Dr. P. Putman. Collaboration between Leiden University and the University of Wollongong was supported by the Leiden University Fund (LUF; CWB # 7518 SV) granted to D. van Son. NWO or LUF were not involved in any part of this thesis.

EEG Theta/Beta Ratio

A Marker of Executive Control and its Relation with Anxiety-Linked Attentional Bias for Threat

Proefschrift

Ter verkrijging van de graad van Doctor aan de Universiteit Leiden op gezag van Rector Magnificus Prof. Mr. C.J.J.M. Stolker volgens het besluit van College voor Promoties te verdedigen op woensdag 24 april 2019, klokke 16:15 uur.

door

Danielle Maria Elisa van Son

geboren te Naarden

in 1990

Promotoren

Prof. dr. A. J. W. van der Does

Dr. P. L. J. Putman

Promotiecommissie

Prof. dr. E. R. A. de Bruijn

Prof. dr. R. J. Barry

Dr. D. J. L. G. Schutter

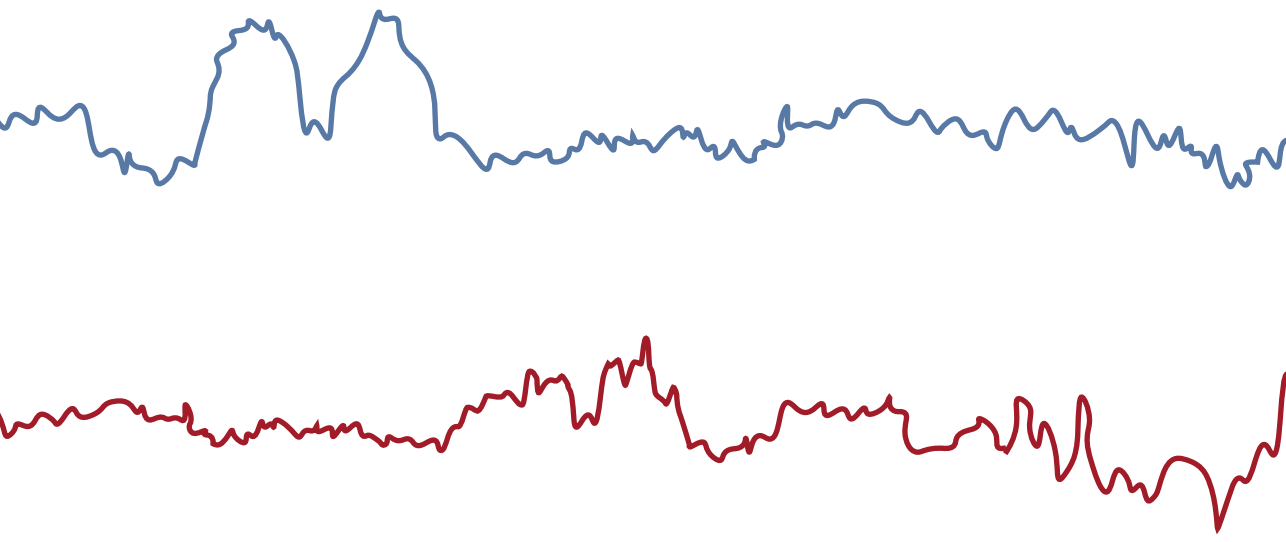
Dr. M. J. W. van der Molen

CONTENT

Tien jaar geleden kon nog gesproken worden van ‘natuurbehoud’,
nu moet men spreken van ‘milieu restauratie’.

- uit het Proefschrift van Sylvia Bruisten, 1989

Introduction



Anxiety disorders are among the most prevalent forms of psychopathology (Kessler, Berglund, Demler, Jin, Merikangas, & Walters, 2005; Kessler, Chiu, Demler, & Walters, 2005) and are associated with a significant impairment in overall functioning and reduction in quality of life (American Psychiatric Association, 2013). Research into the mechanisms that underlie anxiety disorders and/or maladaptive anxiety states is critical to help in treatment consideration.

Anxiety has often been related to certain attentional deficits (e.g. Mogg & Bradley, 1998; 2016; Derryberry & Reed, 2002; Eysenck, Derakshan, Santos and Calvo, 2007), more specifically, anxious individuals were found to often have an enduring automatic tendency to attend preferentially to threat related information (e.g. see Derryberry & Reed, 2002; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg & van IJzendoorn, 2007). These tendencies are also called '*attentional biases'* favoring threatening information. Attentional biases to threat were for example suggested to maintain anxiety complaints, as anxious (distracting) information is not well regulated in, for example anxiety disorders (Mogg & Bradley, 1998; 2016). Moreover, attentional biases to threat are considered to causally relate to heightened trait anxiety (Bar-Haim et al., 2007; Mathews & MacLeod, 2002; van Bockstaele, Verschuere, Tibboel, De Houwer, Crombez, & Koster, 2014).

Critically however, several lines of evidence argued that the attentional processes that underlie attentional biases to threat fluctuate across time and context and depend on individual trait-differences (e.g. Mogg & Bradley et al., 1998; 2016; Iacoviello, Wu, Abend, Murrough, Feder, Fruchter et al., 2014; Kruijt, Field & Fox, 2016; Notebaert, Clarke & MacLeod, 2016). One example is individuals' capacity to control their attention, in other words, *attentional control.* Attentional control can be defined as the ability to control attention in relation to thought and reaction patterns (Derryberry & Reed, 2002). Impaired attentional control was found to be a predictor for certain anxiety disorders, which will be further outlined in subsequent sections of this introduction. Several studies furthermore found low attentional control to directly relate to stronger attentional biases/ disturbed threat processing (e.g. Derryberry & Reed, 2002; Eysenck et al., 2007; Koster, Crombez, Verschuere, & De Houwer, 2004) making attentional control an important concept to further investigate. In the current doctoral thesis, the specific role of attentional control in processing threatening information will be reviewed, along with the use of a related physiological marker; *EEG theta/beta ratio*.

Attentional control

Attention is the means by which the 'limited-capacity brain' allocates processing resources (Posner & Petersen, 1990). Giving attention to some features of our environment may cause partial or full exclusion of attention to other features (Driver, 2001). In other words, attention denotes concentration or distractibility (Lawrence, Ross, Hoffmann, Garavan, & Stein, 2003). *Attentional control,* as a key concept in this thesis*,* is the ability to effortfully control attention to support tasks and goals.

Attentional control has been described by different theoretical models in psychological research, including different component processes, contributing to the broader construct of 'cognitive control'. Miyake, Friedman, Emerson, Witzki, Howerter and Wager (2000) described several processes involved in cognitive 'executive' control functions. They used a latent variable analysis to identify the basic control functions for

attention by selecting cognitive tasks on lower level functions. Three major functions were identified: 1) Inhibition: one's ability to deliberately inhibit dominant, automatic responses when necessary; this involves using attentional control to resist disruption or interference from task-irrelevant stimuli or responses, e.g., assessed by anti-saccade and Stroop tasks. 2) Shifting: shifting back and forth between multiple tasks, operations, or mental sets; this function involves adaptive changes in attentional control based on task demands. 3) Updating: updating and monitoring of working memory representations e.g. assessed by working memory tasks. Miyake et al. (2000) noted that correlations between shifting, updating and inhibition measures have an underlying commonality. This definition of executive functions underlying attentional control may reflect a shared requirement to maintain goals in working memory and/ or a common inhibitory process. In an update of their model, Miyake and Friedman (2012) propose that 'inhibition' can be seen as a common factor that is fundamental for all aspects of executive control. In this revised model, two factors are proposed to be subordinate of the common 'inhibition' factor; a separate shifting-specific and updating-specific factor.

In line with Miyake and Friedman (2012), Derryberry and Reed, (2002) describe attentional control as the top-down command over different components of attention. They point out that attentional control consists of two dimensions. *Attentional Focus* is the ability to maintain attentional engagement in the face of distraction, while *Attentional Shifting* is the ability to execute attentional disengagement, in other words to shift attention away from a distraction or toward a new task. Individual differences in attentional control can be measured reliably, both by self-report and performance measures (Derryberry & Reed, 2002). Attentional control may be conceptualized as a trait capturing the control of information processing (Derryberry & Reed, 2002).

Eysenck et al. (2007) proposed an attentional control theory, in which working memory and attention are controlled by two attentional systems: a bottom-up, stimulus-driven system, and a goal-directed top-down system. During anxious states for example, the bottom-up processing of threatening stimuli is automatically increased. This causes misbalance between both systems and bottom-up processes become favoured. The goal-directed top-down system on the other hand, supports two key functions as part of attentional control: inhibition of task-irrelevant information and responses, and switching between tasks (Berggren & Derakshan, 2013; Snyder, Miyake & Hankin, 2015).

Attentional control and anxiety disorders

As briefly mentioned before, low capacity of attentional control has repeatedly been associated with a broad spectrum of anxiety disorders (for a review see Cisler & Koster, 2010). Post-Traumatic Stress Disorder (PTSD) for example, may be characterized by trauma related impaired attentional control, that was most apparent when the threat cue was in the patient's domain of concern (PTSD relevant threat; see Bomyea, Risbrough, & Lang, 2012). PTSD patients' persistence of distressing intrusive thoughts may also stem from ineffective utilization of cognitive systems – specifically aspects of attentional functioning – to inhibit or down-regulate all information (e.g., Anderson & Levy, 2009; Joormann, Yoon, & Siemer, 2010; Verwoerd, de Jong, & Wessel, 2008). Hagenaars and Putman (2011) provided further evidence for the relationship between intrusive memories and attentional control. Healthy participants who were low in attentional control showed a self-perceived tonic immobility when

viewing an aversive film, which in turn predicted intrusion frequency during the subsequent week. People with better attentional control were more resilient to this relationship.

General Anxiety Disorder (GAD) has also been associated with impaired attentional control (Amir, Beard, Burns, & Bomyea., 2009). In GAD, anxiogenic cognitions take the form of perseverative worry, which consists of repeated thoughts about everyday concerns (Armstrong, Zald, & Olatunji, 2011; Burns, Keortge, Formea, & Sternberger, 1996) and are thought to start as uninhibited selective thought-processing, akin to automatic attentional processing of threat-information (Hirsch & Mathews, 2012). Individuals suffering from GAD moreover experience related impairments, such that one's ability to manage attentional resources toward the prevention of 'unwanted negative thoughts' is undermined.

Similarly, social anxiety disorder (SAD) is characterized by a biased internal activation system of threatening thoughts such as fears of evaluation by others (Schmidt, Richey, Buckner, & Timpano, 2009). These threatening thoughts impact working memory and other attentional mechanisms (Hirsch & Mathews, 2012). Adapting and performing well in one's environment depends on capacity-limited attention and on executive functions like working memory. Individuals suffering from cognitive performance anxiety (also a sub-classification of SAD; American Psychiatric Association, 2013) often encounter comparable intrinsic thoughts that disturb cognitive functions and thus performance (Osborne & Franklin, 2002). Cognitive performance anxiety is generally defined as experienced fears about some domain of one's cognitive performance and about others' evaluations thereof. Test anxiety is a clear example of cognitive performance anxiety. Although moderate levels of stress may increase performance, severe cognitive performance anxiety will have a detrimental effect on actual cognitive performance (Cassady & Johnson, 2002; Eum & Rice, 2011).

These described lines of research lead to the hypothesis that enhancing attentional control may be helpful for persons who suffer from anxiety disorders and who are characterised by disrupted attentional processing. Enabling patients to exert more cognitive control over their attentional resources may help them direct attention to cognitive tasks instead of to distracting intrusions. Therefore, it is important to understand the underlying mechanisms of attentional processing, in particular threat selective attention.

Threat selective attention and threat avoidance

Selective attention is the means by which certain features in the environment are selected by individuals for attentional focus (e.g. Driver, 2001; Derryberry & Reed, 2002; Koster et al., 2004). As already mentioned, anxious individuals (scoring high on *trait-anxiety*) selectively and automatically attend to emotional, mainly threat-related, stimuli, compared to neutral stimuli (for reviews see Bar-Haim et al., 2007; Cisler, Bacon & Williams, 2009; Cisler & Koster, 2010; Koster et al., 2004; Mogg & Bradley, 1998; 2016). In other words, anxious individuals have '*attentional biases*' favoring threatening information. These biases are important in that the attention selectively facilitates early threat processing, thereby influencing the cognitive and emotional processes related to anxiety (further referred to as '*threat selective attention*'; Mathews, May, Mogg & Eysenck, 1990; Williams, Mathews, & MacLeod, 1996).

Mogg and Bradley (1998; 2016) described threat selective attention as that being vulnerable to anxiety

disorders stems mainly from a bias caused by automatic threat evaluation. This idea includes that an intrinsic stimulus threat value might be automatically assessed by a *valence evaluation system*, influenced by several variables (e.g. stimulus features, context, prior learning, state- and trait-anxiety). This intrinsic system is more reactive to threat cues in individuals prone to anxiety disorders. In the absence of threat, the system processes goal-relevant stimuli, but inhibits processing of minor task-irrelevant negative cues. However, if the *valence evaluation system* judges a stimulus to have a high threat value, this triggers automatic attention to the threat and interrupts all goal-related activity. Because anxiety prone individuals tend to evaluate mildly threatening stimuli as having a high motivational salience, they are more likely to direct attention to those stimuli. Hence, threat selective attention, specifically to mildly threatening stimuli may be an index of anxiety-proneness. In this way, threat selective attention actually maintains anxiety, as anxiety-prone individuals are more likely to notice minor threat cues in the environment, which enhances their perception of the world as aversive and unsafe, and increases their state anxiety (Bardeen & Orcutt, 2011; Derryberry & Reed, 2002; Putman, Arias-Garcia, Pantazi, & van Schie, 2012; Schoorl, Putman, van der Werff & van der Does, 2014; Taylor, Cross, and Amir., 2016; Peers & Lawrence, 2009).

Among others, Mogg et al., (1987) reported that initial threat selective attention may be opposed by *threat avoidance* in controlled attention-related strategies. Avoidance was proposed to reflect an attempt to reduce subjective discomfort or perceived danger, making avoidance possibly more apparent at higher levels of threat or anxiety (Mogg, Weinman, & Mathews, 1987). Whereas avoidant attention-related strategies may reduce immediate distress, they may not be useful on the long-term by causing habituation and thus persistence of anxiety (Mogg & Bradley, 2016). These considerations carry possible implications for the currently popular attentional bias modification (ABM) paradigm and its attempts to train attentional bias away from threat with the objective of effecting more adaptive, healthy attentional processing styles. The ABM-threat-avoidance training may cause strategic avoidance of threat, making it unhelpful for anxious individuals.

Neural mechanisms of attentional control and threat selective attention

Understanding the neural underpinnings of attentional control and threat selective attention may be fundamental for improvement of maladaptive anxiety states. Scientific research on these mechanisms points out that the bottom-up sensory and top-down control processes interact to determine how much 'attention' threat-related stimuli receive (e.g. Bishop, 2008; Hermans, Henckens, Joels & Fernandez, 2014). Top-down attentional control and inhibition of such stimulus-driven attention seems to be carried out by e.g. the dorsal anterior cingulate cortex and the dorso-lateral prefrontal cortex (DL-PFC; Fani, Jovanovic, Ely, Bradley, Gutman, et al., 2012). Bottom up processes of salient and threat-related distracters (which have also been classified as the 'salience network') seem to be mediated by sub-cortical brain areas like the ventral anterior cingulate cortex, the medial prefrontal cortex (mPFC), parahippocampal gyrus and the angular gyrus (e.g. Bishop, 2008).

Neural resources that are allocated towards this salience network seem to be highly influenced by catecholamines (e.g., norepinephrine and dopamine) in terms of mediating earliest responses to acute threat (Hermans et al., 2014). The goal oriented, top-down attentional control mediated by prefrontal cortex (PFC) networks is also dependent on adequate catecholamine action (Hermans et al., 2014; Arnsten, 2009a). Stress and

anxiety trigger a variety of neurochemical changes, including increased influx of dopamine and nor-adrenaline into the PFC (Joëls & Baram, 2009). Both dopamine and nor-adrenaline influence PFC in a dose-dependent, inverted U-shaped manner (Arnsten, 2009a). While moderate levels are needed for good prefrontal executive control, dopaminergic and noradrenergic over-stimulation leads to decreased PFC function. In other words, increasing levels of catecholamines are associated with increasing performance until a tipping point is reached, after which further catecholamine stimulation will harm executive performance, including top-down attentional control (Arnsten, 2009a; Arnsten & Rubia, 2012; Hermans et al., 2014). This tipping point for the effects of stress-induced catecholamines (the apex of the inverted U-shape relation between catecholamines and cognitive performance) was found to be dependent on catecholamine-driven basal prefrontal function, and is therefore different for every individual (Arnsten, 2009a; Arnsten 2009b; Cools & D'Esposito, 2011). This implies that a well-dosed manipulation of catecholamine systems could increase attentional control over threat-bias, depending on individual differences in anxiety and baseline PFC function or catecholamine levels (Arnsten, 2006; Arnsten, 2011b).

In addition, it was found that the manipulation of attentional focus, threat-value, and stimulus presentation parameters (e.g. stimulus delay) have different influences upon subcortical areas and prefrontal activation to threatening stimuli (Bishop, 2008). For example, high perceptual load causes competition for perceptual resources and appears to inhibit the processing of threat distractors at an early stage, eliminating the amygdala response to these distractors. On the other hand, for low perceptual load the automatic bottom-up activity can be sufficient for such threat distractors to cause amygdala activity (Bishop, Jenkins & Lawrence, 2006; Pessoa, Padmala, & Morland, 2005). It can be argued that salient distractors compete for processing resources, such as entry to working memory and guidance of response selection. This is in line with the previously described attentional control theory (Eysenck et al., 2007); in low perceptual load, prefrontal cortical regions cause top-down attentional control to be electively activated in response to the occurrence of threat-related distractors (Bishop et al., 2006).

Moreover, individual differences in anxiety seem to modulate the strength of the amygdala signal to threat stimuli, even when participants are not attending to or consciously aware of these stimuli (Bishop, Duncan & Lawrence, 2004; Etkin, Klemenhagen, Dudman, Rogan, Hen, et al., 2004). Elevated anxiety is also associated with disrupted recruitment of prefrontal control mechanisms and thus executive control, in response to processing competition from threat-related distractors (Bishop et al., 2006; Bishop et al., 2004).

Taken together; (neural) individual differences of e.g. attentional control, catecholamine functioning and anxiety are important aspects when investigating threat selective attention and their contribution to threat processing should be further investigated. The concept of attentional control in particular seems to play a key role in a neural model of threat selective attention. Attentional control has mainly been measured by self-report, but research may benefit from using objective markers of attentional control (see also Bardeen & Daniel, 2018). An objective measure for attentional control, such as a psychophysiological marker, could prevent possible response biases of self-reports and provide a more accurate representation of attentional control (Kihlstrom, Eich, Sandbrand, & Tobias, 2000).

EEG theta/beta ratio as a marker of executive control

Electroencephalogram (EEG) measures represent the combined electrical fluctuations in membrane potentials generated from the interactions of the primary inhibitory and excitatory neurons (Gordon, 2000; Nunez, 1995) which reflects the number of neurons that discharge synchronously (Klimesch, 1999). Spectral analysis of a resting state EEG signal produces measures for power in different frequency bands, for example, the theta band, a low frequency band with signals oscillating between 4 and 7 Hz, or a high frequency band such as the beta band (13-30 Hz). Typically measured under resting conditions, the ratio between the theta and beta band (*theta/beta ratio; TBR*) has been utilized as a source of information about the baseline state of the brain (in terms of maturation and/or arousal) as well as a predictor for any subsequent brain activity that may be associated with increased cognitive demand (Barry, Clarke, & Johnstone, 2003).

Several lines of evidence further point out that the TBR is possibly of interest when investigating attentional control. A robust finding for example is that TBR scores are higher in patients diagnosed with attention-deficit/ hyperactivity disorder (ADHD; Barry et al., 2003). Also, administration of methylphenidate (a stimulant that is beneficial for ADHD) is effective through restoration of sub-optimal prefrontal cortical executive function via upregulation of post-synaptic PFC catecholamine function and normalizes the TBR (Clarke, Barry, McCarthy, Selikowitz & Johnstone, 2007). This fits the previously described inverted U-shape relation between catecholamines and cognitive performance. Furthermore, high TBR scores were related to poor prefrontal cortical mediated attentional and inhibitory functions, (i.e. Arns, Conners, & Kraemer, 2013; Barry et al., 2003) and likely reflects functional reciprocal cortical-subcortical interactions in both healthy and clinical populations (Knyazev, 2007; Schutter & Knyazev, 2012).

TBR has been used as an electrophysiological marker of (top-down, PFC-regulated) attentional control to investigate its effect on attentional bias and trait anxiety in healthy adults (Angelidis, Hagenaars, van Son, van der Does, & Putman, 2018). TBR was also found to negatively correlate with motivational decision making and the learning processes involved therein (Schutter & van Honk, 2005; Massar, Rossi, Schutter, & Kenemans, 2012; Massar, Kenemans, & Schutter, 2014; Schutte, Kenemans, & Schutter, 2017). Putman et al. (2010) found that TBR correlated negatively with the ability to modulate response inhibition in an emotional go/no-go task (Putman, van Peer, Maimari, & van der Werff, 2010). A similar correlation between TBR and self-reported attentional control was observed. The emotional go/no-go task utilizes emotional stimuli to induce a response bias in terms of longer response latencies and more errors. This response is in turn modulated by activity in the amygdala, as well as in the lateral orbitofrontal cortex (Schulz, Fan, Magidina, Marks, Hahn & Halperin, 2007). In other words, TBR may reflect voluntary top-down processes of executive control (including attentional control), mediated by (dorso-lateral) PFC, over bottom-up processes from limbic areas, such as the anterior cingulate cortex, hippocampus and amygdala; (Bishop, 2008; Gregoriou, Rossi, Ungerleider, Desimone, 2014; Knyazev, 2007; Schutter & Knyazev, 2012).

In sum, frontal TBR is considered to reflect PFC regulated executive control; it might therefore as well be related to individual differences of the catecholamine tipping point, as described before. The established model of inverted U-shape relations between prefrontal catecholamine activity and cognitive attentional control (Arnsten, 2006; Arnsten, 2009a; Cools and D'Esposito, 2011) would predict that if TBR indeed represents executive

control, it is also regulated by prefrontal catecholamine levels (Arnsten, 2006; Hermans et al., 2014). Frontal TBR as an electrophysiological marker for executive control thus might be a useful approximation of individual differences in baseline prefrontal catecholamine function that could be used when investigating catecholamine manipulation, for example. Including other measures that reflect basal PFC regulated executive control can also improve outcomes of studies of effects of pharmaca on prefrontal cognitive processing. Likely, EEG TBR measurement is a useful tool in psychopharmacological studies.

Multiple studies to date found that TBR is (directly) negatively correlated with ACS scores (Angelidis, van der Does, Schakel, & Putman, 2016; Putman et al., 2010; Putman, Verkuil, Arias-Garcia, Pantazi, & van Schie, 2014; but see Morillas-Romero, Tortella-Feliu, Bornas & Putman, 2015; Angelidis et al., 2018). Also, TBR was found to correlate to task-based measures of attentional control in patients suffering from multiple sclerosis, having clinically impaired attention (Keune, Hansen, Weber, Zapf, Habich, Muenssinger et al., 2017). TBR was reported to have a very high one-week and two-week re-test reliability (Angelidis et al., 2016; Keune et al., 2017), supporting the validity of TBR as a reflection of trait attentional control. TBR thus seems to be a marker of executive control and attentional control and requires further investigation to explore its specific functions/applications. As attentional control plays an important role in threat processing, further research was needed to investigate TBR's relation to threat related and emotional processes, which will be further discussed in the next section.

EEG theta/beta ratio, stress, threat and emotional processes

The prefrontal cortex (PFC) is often viewed as the control center, exerting executive control over various bottom-up processes, e.g. regulating fearful responses driven by the amygdala (Bishop et al., 2004). The finding of TBR being negatively related to attentional control indicates that the relationship between PFC regulated executive control and theta/beta ratio might reflect a continuum of brain-behaviour correlation of which, for example, attentional deficits represent a far end of the spectrum. Baseline resting state TBR has been similarly related to stimulus evoked behaviour (e.g., Massar et al., 2012; Putman et al., 2010; Schutter & van Honk, 2005), self-reported emotional and motivational traits (Putman et al., 2010) and psychiatric diagnosis reflecting dynamic behaviour over extended periods (Clarke, Barry, McCarthy & Selikowitz, 2002). The inter-individual variance of TBR thus seems to reflect the inter-individual variance of a certain brain state that specifically determines one's response to environmental challenges. These are indications that TBR may be useful in the study of, for example, performance in the presence of environmental stressors. Putman et al., (2014) actually tested the prediction that TBR moderates the deleterious effects of anxious stress on state attentional control. As expected, resting state TBR did moderate the effects of stress on change in state attentional control, which favours the idea that TBR predicts resilience/vulnerability to the effects of performance anxiety-like stress on self-reported state attentional control.

Furthermore, a number of associations have been found between attentional control and emotion regulation capability, suggesting that the two functional mechanisms are related (e.g. Rothbart & Rueda, 2005). Cognitive reappraisal, which is an emotion regulation strategy premised on reinterpretation of the meaning of a stimulus in order to regulate the emotional response to it, has been a particularly successful strategy in terms of regulating subjective and physiological responses (Gross, 1998). Ochsner and Gross (2005) reported that 'cold'

forms of emotional control are strikingly similar to the consistently found activations observed in cognitive reappraisal. If cognitive reappraisal relies on the same functional mechanism as 'cold' forms of cognitive control, it is reasonable to expect that individuals with biased cognitive control, accompanied by an elevated TBR will be similarly poorer in their capability to apply cognitive reappraisal. TBR can therefore be indirectly related to emotion regulation which is also supported by more recent studies (Morillas-Romero et al., 2015; Tortella-Feliu, Morillas-Romero, Balle, Llabrés, Bornas, & Putman, 2014). Spontaneous emotion down regulation has for example previously been found to be predicted by attentional control and a slowing down of heart rate (Morillas-Romero et al., 2015). Also, TBR as a measure of attentional control was suggested to be associated with discomfort ratings and time needed to downregulate negative emotion after subjects were exposed to negative pictures (Tortella-Feliu et al., 2014). These results contribute to a better understanding of the involvement of TBR in emotion regulation processes, however more studies are needed to further extend and elaborate these findings.

TBR might therefore be a useful electrophysiological marker of emotion-attentional control interactions for research on anxiety and should be studied further.

The role of mind wandering as involuntary, distracting thought patterns

Lower TBR has consistently been linked to 'on task' processes and the processes that accompany performance on a task. Importantly, Braboszcz & Delorme (2011) found that increased theta and decreased beta (in other words, increased TBR) was specifically present during mind wandering episodes (uncontrolled thought), and the opposite (decreased TBR) during controlled thought periods. We therefore assumed that TBR might be a marker for these uncontrolled thought/ controlled thought processes. Since mind wandering is described as a deficit in working memory and attention (McVay & Kane, 2009) and a predictor for performance errors (Smallwood & Schooler, 2006), poor attentional control might cause a higher tendency to mind wander. In other words, more frequent and lengthy occurrences of mind wandering episodes during the standardized ~8 minutes "resting state" assessment of spontaneous TBR might be responsible for the negative correlation between the average TBR during such measurements and attentional control.

Along these lines, it will be interesting to investigate whether mind wandering is the underlying responsible mechanism of the TBR – attentional control relationship as previously described, and will possibly provide better understanding of the functional and neural mechanisms that are responsible for the relationship between TBR and executive control. An effective way of measuring mind wandering episodes is to include the underlying neural mechanisms such as functional connectivity of mind wandering related brain regions. Mind wandering was mainly found to activate the Default Mode Network (Karapanagiotidis, Bernhardt, Jefferies & Smallwood, 2017; Smallwood, Beach, Schooler & Handy, 2008); a network of interacting neural regions, known to have activity that is highly correlated within this network during task unrelated thoughts (Stawarczyk, Majerus, Maquet, & D'Argembeau, 2011). Also, it was found that regions within the 'Executive Control Network', which consists of the DL-PFC, dorsal anterior cingular cortex (dACC) and posterior parietal regions (Seeley, Menon, Schatzberg, Keller, Glover, Kenna et al., 2007), became active during awareness of mind wandering, attentional shifting and sustained attention (Hasenkamp, Wilson-Mendenhall, Duncan, & Barsalou, 2012; Christoff, Ream,

Geddes, & Gabrieli 2003). Additional insights can thus be obtained when looking at functional connectivity within the Default Mode Network and the Executive Control Network during mind wandering episodes, and what role it plays in the hypothesized underlying responsible mechanism of mind wandering on the TBR and attentional control relation.

Manipulating EEG theta/beta ratio

Increased slow-wave activity coupled with decreased fast wave activity was first observed in ADHD in the early 1970s (Loo & Makeig, 2012; Satterfield, Cantwell & Satterfield, 1974). This work primed the interest in determining EEG abnormalities in ADHD children, and more research has been carried out since, to replicate the findings (e.g. Barry et al., 2003; Hermens, Kohn, Clarke, Gordon, & Williams, 2005; Lazzaro, Gordon, Whitmont, Meares, & Clarke, 2001; Monastra, Lubar, & Linden, 2001; Ogrim, Kropotov, & Hestad, 2012). Main findings were that ADHD was associated with increased EEG theta and decreased beta bands; in other words; increased theta/beta ratio (for review and meta-analysis, see Arns et al., 2013; Barry et al., 2003). Several studies reported that manipulating TBR using Neurofeedback training (NFT) could successfully reduce the TBR and ADHD-related symptoms in individuals diagnosed with ADHD (e.g. hyperactivity, impaired attention; e.g. Kouijzer, de Moor, Gerrits, Congedo and van Schie, 2009, for a review see Vernon, 2005).

The study of the potential beneficial effects of reducing TBR with NFT in healthy adults seems warranted, given the abovementioned relations between TBR and various psychological regulatory constructs. However, some studies reported that no changes in EEG were actually observed when applying a commonly used NFT method (Janssen, Bink, Weeda, Geladé, van Mourik, Maras, & Oosterlaan, 2017; Shönenberg, Wiedemann, Schneidt, Scheeff, Logemann, Keune et al., 2017; Doppelmayr & Weber, 2011). Further replications and extensions of studies on exact changes therefore seem imperative to ascertain the effects of TBR NFT in healthy adults, and whether it can provide a tool to study causality in this relation and possibly even enhance human performance.

Integration and scientific relevance

The above-mentioned relationships between TBR, attentional control and emotional processes further reinforce the notion that frontal TBR has a unique and independent predictive value in the study of executive control and threat selective attention, specifically, control over information in an emotional context. These relationships may provide valuable information for investigating emotion-regulation related disorders, as these disorders have previously been linked to executive or attentional problems in anxiety. The role of attentional control and its relation with aberrant attentional threat-processing in the diagnosis, maintenance and treatment of anxiety disorders should not be underestimated (Mogg & Bradley, 2016). TBR seems to provide a promising variable of interest for such research.

Aim of this thesis

Considering that TBR is a potentially useful marker of executive/attentional control, both in healthy and clinical samples, we designed studies in healthy adults to further investigate the relation of TBR with threat selective attention. We manipulated threat value and attentional stages; catecholamine functioning; uncontrolled thought (mind wandering) and the executive control brain network. We also explored if TBR in a healthy adult sample is affected by NFT. In summary, we aimed to answer the following research questions.

General research questions

1) What is the role of TBR in attentional processing? (Chapters 1 and 2)

2) What is the role of TBR and attentional control in effects of catecholamine-related pharmacological manipulations, such as caffeine administration? (Chapter 2).

3) Is the TBR - attentional control relationship as observed possibly driven by mind wandering episodes? (Chapters 3 and 4).

4) Is the TBR – mind wandering relationship related to functional connectivity in the default mode network and the executive control neural network? (Chapter 4).

5) Can TBR be manipulated by means of neurofeedback training to possibly further enable future clinical interventions and to enable studies assessing causal effects of TBR? (Chapter 5).

References

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (DSM-5). *American Psychiatric Pub.*

Amir, N., Beard, C., Burns, M., & Bomyea, J. (2009). Attention modification program in individuals with generalized anxiety disorder. *Journal of abnormal psychology, 118*(1), 28.

Anderson, M. C., & Levy, B. J. (2009). Suppressing unwanted memories. *Current Directions in Psychological Science, 18*(4), 189-194.

Angelidis, A., van der Does, W., Schakel, L., and Putman, P. (2016). Frontal EEG theta/beta ratio as an electrophysiological marker for attentional control and its test-retest reliability. *Biological Psychology, 121(Pt A),* 49-52.

Angelidis, A., Hagenaars, M., van Son, D., van der Does, W., & Putman, P. (2018). Do not look away! Spontaneous frontal EEG theta/beta ratio as a marker for cognitive control over attention to mild and high threat. *Biological psychology, 135,* 8-17.

Armstrong, T., Zald, D. H., & Olatunji, B. O. (2011). Attentional control in OCD and GAD: Specificity and associations with core cognitive symptoms. *Behaviour research and therapy, 49*(11), 756-762.

Arnsten, A. F. (2009a). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature reviews. Neuroscience, 10*(6), 410.

Arnsten, A. F. (2009b). Toward a new understanding of attention-deficit hyperactivity disorder pathophysiology. *CNS drugs, 23* (1), 33-41.

Arnsten, A.F.T (2011b). Catecholamine influences on dorsolateral prefrontal cortical networks. *Biological Psychiatry, 69*, 89-99.

Arnsten, A. F. T. (2006). Stimulants: Therapeutic actions in ADHD *Neuropsychopharmacology*, *31*, 2376-2383.

Arnsten, A. F., and Rubia, K. (2012). Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(4), 356-367.

Arns, M., Conners, C. K., and Kraemer, H. C. (2013). A decade of EEG Theta/Beta Ratio Research in ADHD: a meta-analysis. *J Atten Disord, 17*(5), 374-383.

Bardeen, J. R., & Orcutt, H. K. (2011). Attentional control as a moderator of the relationship between posttraumatic stress symptoms and attentional threat bias. *Journal of Anxiety Disorders, 25*(8), 1008-1018.

Bardeen, J. R., & Daniel, T. A. (2018). Anxiety sensitivity and attentional bias to threat interact to prospectively predict anxiety. *Cognitive Behaviour Therapy,* 1-13.

Barry, R. J., Clarke, A. R., & Johnstone, S. J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clinical neurophysiology, 114*(2), 171-183.

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & Van Ijzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychological bulletin, 133*(1), 1.

Berggren, N., & Derakshan, N. (2013). Attentional control deficits in trait anxiety: why you see them and why you don't. *Biological Psychology, 92*(3), 440-446.

Bishop, S. J. (2008). Neural mechanisms underlying selective attention to threat. *Ann N Y Acad Sci, 1129*, 141-152.

Bishop, S. J., Duncan, J., & Lawrence, A. D. (2004). State anxiety modulation of the amygdala response to unattended threat-related stimuli. *Journal of Neuroscience, 24*(46), 10364-10368.

Bishop, S. J., Jenkins, R., & Lawrence, A. D. (2006). Neural processing of fearful faces: effects of anxiety are gated by perceptual capacity limitations. *Cerebral cortex, 17*(7), 1595-1603.

Bomyea, J., Risbrough, V., & Lang, A. J. (2012). A consideration of select pre-trauma factors as key vulnerabilities in PTSD. *Clinical psychology review, 32*(7), 630-641.

Braboszcz, C., & Delorme, A. (2011). Lost in thoughts: neural markers of low alertness during mind wandering. *Neuroimage, 54*(4), 3040-3047.

Burns, G. L., Keortge, S. G., Formea, G. M., & Sternberger, L. G. (1996). Revision of the Padua Inventory of obsessive compulsive disorder symptoms: distinctions between worry, obsessions, and compulsions. *Behaviour research and therapy, 34*(2), 163-173.

Cassady, J. C., & Johnson, R. E. (2002). Cognitive test anxiety and academic performance. *Contemporary educational psychology, 27*(2), 270-295.

Cisler, J. M., & Koster, E. H. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clin Psychol Rev, 30*(2), 203-216. doi:10.1016/j.cpr.2009.11.003

Cisler, J. M., Bacon, A. K., & Williams, N. L. (2009). Phenomenological characteristics of attentional biases towards threat: A critical review. *Cognitive therapy and research, 33*(2), 221-234.

Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., & Johnstone, S.J. (2007). Effects of stimulant medications on the EEG of girls with attention-deficit/hyperactivity disorder. Clinical Neurophysiology, 118, 2700-2708.

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2002). EEG analysis of children with attention-deficit/hyperactivity disorder and comorbid reading disabilities. *Journal of Learning Disabilities, 35*(3), 276-285.

Cools, R., & D'Esposito, M. (2011). Inverted-U–shaped dopamine actions on human working memory and cognitive control. *Biological psychiatry, 69*(12), e113-e125.

Christoff, K., Ream, J. M., Geddes, L., & Gabrieli, J. D. (2003). Evaluating self-generated information: anterior prefrontal contributions to human cognition. *Behavioral neuroscience, 117*(6), 1161.

Derryberry, D., & Reed, M. A. (2002). Anxiety-related attentional biases and their regulation by attentional control. *Journal of Abnormal Psychology, 111*(2), 225-236.

Doppelmayr, M., & Weber, E. (2011). Effects of SMR and theta/beta neurofeedback on reaction times, spatial abilities, and creativity. *Journal of Neurotherapy, 15*(2), 115-129.

Driver, J. (2001). A selective review of selective attention research from the past century. *British Journal of Psychology, 92*(1), 53-78.

Etkin, A., Klemenhagen, K. C., Dudman, J. T., Rogan, M. T., Hen, R., Kandel, E. R., & Hirsch, J. (2004). Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. *Neuron, 44*(6), 1043-1055.

Eum, K., & Rice, K. G. (2011). Test anxiety, perfectionism, goal orientation, and academic performance. *Anxiety, Stress, & Coping, 24*(2), 167-178.

Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: attentional control theory. *Emotion, 7*(2), 336.

Fani, N., Jovanovic, T., Ely, T.D., Bradley, B., Gutman, D., et al. (2012). Neural correlates of attention in bias to threat in post-t raumatic stress disorder. *Biological Psychology, 90,* 134-142.

Gordon, E. (2000). Integrative neuroscience: Bringing together biological, psychological and clinical models of the human brain. London, UK: Harwood Academic.

Gregoriou, G. G., Rossi, A. F., Ungerleider, L. G., & Desimone, R. (2014). Lesions of prefrontal cortex reduce attentional modulation of neuronal responses and synchrony in V4. *Nature Neuroscience, 17*(7), 1003-1011. doi:10.1038/nn.3742

Gross, J. J. (1998). The emerging field of emotion regulation: an integrative review. *Review of general psychology, 2*(3), 271.

Hagenaars, M. A., & Putman, P. (2011). Attentional control affects the relationship between tonic immobility and intrusive memories. *Journal of Behavior Therapy and Experimental Psychiatry, 42*(3), 379-383.

Hasenkamp, W., Wilson-Mendenhall, C. D., Duncan, E., & Barsalou, L. W. (2012). Mind wandering and attention during focused meditation: a fine-grained temporal analysis of fluctuating cognitive states. *Neuroimage, 59*(1), 750-760.

Hermans, E. J., Henckens, M. J., Joels, M., & Fernandez, G. (2014). Dynamic adaptation of large-scale brain networks in response to acute stressors. *Trends Neurosci, 37*(6), 304-314. doi:10.1016/j.tins.2014.03.006

Hermens, D. F., Kohn, M. R., Clarke, S. D., Gordon, E., & Williams, L. M. (2005). Sex differences in adolescent ADHD: Findings from concurrent EEG and EDA. *Clinical Neurophysiology, 116*, 1455-1463.

Hirsch, C. R., & Mathews, A. (2012). A cognitive model of pathological worry. *Behaviour Research and Therapy, 50*(10), 636-646.

Iacoviello, B. M., Wu, G., Abend, R., Murrough, J. W., Feder, A., Fruchter, E., ... & Neumeister, A. (2014). Attention bias variability and symptoms of posttraumatic stress disorder. *Journal of Traumatic Stress, 27*(2), 232-239.

Janssen, T. W., Bink, M., Weeda, W. D., Geladé, K., van Mourik, R., Maras, A., & Oosterlaan, J. (2017). Learning curves of theta/beta neurofeedback in children with ADHD. *European child & adolescent psychiatry, 26*(5), 573-582.

Joëls, M., & Baram, T. Z. (2009). The neuro-symphony of stress. *Nature reviews neuroscience, 10*(6), 459.

Joormann, J., Yoon, K. L., & Siemer, M. (2010). Cognition and emotion regulation. *Emotion regulation and psychopathology: A transdiagnostic approach to etiology and treatment*, 174-203.

Karapanagiotidis, T., Bernhardt, B. C., Jefferies, E., & Smallwood, J. (2017). Tracking thoughts: Exploring the neural architecture of mental time travel during mind-wandering. *Neuroimage, 147*, 272-281.

Keune, P. M. , Hansen, A., Weber, E., Zapf, F., Habich, J., Muenssinger, J., Wolf, S., Schonenberg, M., Oschmann, P. (2017). Exploring neurophysiologic monitoring parameters and cognitive functioning in multiple sclerosis (MS): resting-state brain oscillatory activity and attention performance. *Clinical neurophysiology, 128*(9), 1746-1754.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry, 62*(6), 593-602.

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry, 62*(6), 617-627.

Kihlstrom, J. F., Eich, E., Sandbrand, D., & Tobias, B. A. (2000). Emotion and memory: Implications for self-report. The science of self-report: Implications for research and practice, 81-99.

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain research reviews, 29*(2-3), 169-195.

Knyazev, G. G. (2007). Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neuroscience and Biobehavioral Reviews, 31*(3), 377-395.

Kouijzer, M. E., de Moor, J. M., Gerrits, B. J., Congedo, M., & van Schie, H. T. (2009). Neurofeedback improves executive functioning in children with autism spectrum disorders. *Research in Autism Spectrum Disorders, 3*(1), 145-162.

Koster, E. H., Crombez, G., Verschuere, B., & De Houwer, J. (2004). Selective attention to threat in the dot probe paradigm: Differentiating vigilance and difficulty to disengage. *Behaviour research and therapy, 42*(10), 1183-1192.

Kruijt, A. W., Field, A. P., & Fox, E. (2016). Capturing dynamics of biased attention: are new attention variability measures the way forward?. *PloS one, 11*(11), e0166600.

Lawrence, N. S., Ross, T. J., Hoffmann, R., Garavan, H., & Stein, E. A. (2003). Multiple neuronal networks mediate sustained attention. *Journal of cognitive neuroscience, 15*(7), 1028-1038.

Lazzaro, I., Gordon, E., Whitmont, S., Meares, R., & Clarke, S. (2001). The modulation of late component event related potentials by pre-stimulus EEG theta activity in ADHD. *International Journal of Neuroscience, 107,* 247-264.

Loo, S. K., & Makeig, S. (2012). Clinical utility of EEG in attention-deficit/hyperactivity disorder: A research update. *Neurotherapeutics, 9*, 569-587.

McVay, J. C., & Kane, M. J. (2009). Conducting the train of thought: working memory capacity, goal neglect, and mind wandering in an executive-control task. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 35*(1), 196.

Massar, S. A., Kenemans, J. L., & Schutter, D. J. (2014). Resting-state EEG theta activity and risk learning: sensitivity to reward or punishment? *Int J Psychophysiol, 91*(3), 172-177. doi:10.1016/j.ijpsycho.2013.10.013

Massar, S. A., Rossi, V., Schutter, D. J., & Kenemans, J. L. (2012). Baseline EEG theta/beta ratio and punishment sensitivity as biomarkers for feedback-related negativity (FRN) and risk-taking. *Clin Neurophysiol, 123*(10), 1958-1965.

Mathews, A., & MacLeod, C. (2002). Induced processing biases have causal effects on anxiety. *Cognition & Emotion, 16*(3), 331-354.

Mathews, A., May, J., Mogg, K., & Eysenck, M. (1990). Attentional bias in anxiety: selective search or defective filtering? *Journal of Abnormal Psychology, 99*(2), 166-173.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive psychology, 41*(1), 49-100.

Miyake, A., & Friedman, N. P. (2012). The nature and organization of individual differences in executive functions: Four general conclusions. *Current directions in psychological science, 21*(1), 8-14.

Mogg, K., & Bradley, B. P. (1998). A cognitive-motivational analysis of anxiety. *Behaviour Research and Therapy, 36*(9), 809-848.

Mogg, K., & Bradley, B. P. (2016). Anxiety and attention to threat: Cognitive mechanisms and treatment with attention bias modification. *Behav Res Ther, 87*, 76-108.

Mogg, K., Weinman, J., & Mathews, A. (1987). Memory Bias in Clinical Anxiety. *Journal of Abnormal Psychology, 96*(2), 94-98.

Monastra, V. J., Lubar, J. F., & Linden, M. (2001). The develop- ment of a quantitative electroencephalographic scanning process for attention deficit-hyperactivity disorder: Reliability and validity studies. *Neuropsychology, 15,* 136-144.

Morillas-Romero, A., Tortella-Feliu, M., Bornas, X., & Putman, P. (2015). Spontaneous EEG theta/beta ratio and delta-beta coupling in relation to attentional network functioning and self-reported attentional control. *Cogn Affect Behav Neurosci, 15*(3), 598-606.

Notebaert, L., Clarke, P. J., & MacLeod, C. (2016). Does attentional bias to threat ameliorate or exacerbate the detrimental effect of trait anxiety on behavioural preparedness for real-world danger?. *Australian Journal of Psychology, 68*(3), 166-177.

Nunez, P. L. (1995). Neocortical dynamics and human EEG rhythms. New York: Oxford University Press.

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends in cognitive sciences, 9*(5), 242-249.

Ogrim, G., Kropotov, J., & Hestad, K. (2012). The quantitative EEG theta/beta ratio in attention deficit/hyperactivity disorder and normal controls: Sensitivity, specificity, and behavioral correlates. *Psychiatry Research, 198,* 482-488.

Osborne, M. S., & Franklin, J. (2002). Cognitive processes in music performance anxiety. *Australian Journal of Psychology, 54*(2), 86-93.

Peers, P. V., & Lawrence, A. D. (2009). Attentional control of emotional distraction in rapid serial visual presentation. *Emotion, 9*(1), 140-145. doi:10.1037/a0014507

Pessoa, L., Padmala, S., & Morland, T. (2005). Fate of unattended fearful faces in the amygdala is determined by both attentional resources and cognitive modulation. *Neuroimage, 28*(1), 249-255.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual review of neuroscience, 13*(1), 25-42.

Putman, P., Arias-Garcia, E., Pantazi, I., & van Schie, C. (2012). Emotional Stroop interference for threatening words is related to reduced EEG delta-beta coupling and low attentional control. *International Journal of Psychophysiology, 84*(2), 194-200.

Putman, P., van Peer, J., Maimari, I., & van der Werff, S. (2010). EEG theta/beta ratio in relation to fear-modulated response-inhibition, attentional control, and affective traits. *Biol Psychol, 83*(2), 73-78.

Putman, P., Verkuil, B., Arias-Garcia, E., Pantazi, I., & van Schie, C. (2014). EEG theta/beta ratio as a potential biomarker for attentional control and resilience against deleterious effects of stress on attention. *Cognitive Affective & Behavioral Neuroscience, 14*(2), 782-791.

Rothbart, M. K., & Rueda, M. R. (2005). The development of effortful control. *Developing individuality in the human brain: A tribute to Michael I. Posner*, 167-188.

Satterfield, J. H., Cantwell, D. P., & Satterfield, B. T. (1974). Pathophysiology of the hyperactive child syndrome. *Archives of General Psychiatry, 31*, 839-844.

Schönenberg, M., Wiedemann, E., Schneidt, A., Scheeff, J., Logemann, A., Keune, P. M., & Hautzinger, M. (2017). Neurofeedback, sham neurofeedback, and cognitive-behavioural group therapy in adults with attention-deficit hyperactivity disorder: a triple-blind, randomised, controlled trial. *The Lancet Psychiatry, 4*(9), 673-684.

Schoorl, M., Putman, P., Van Der Werff, S., & Van Der Does, A. J. (2014). Attentional bias and attentional control in Posttraumatic Stress Disorder. *J Anxiety Disord, 28*(2), 203-210. doi:10.1016/j.janxdis.2013.10.001

Schulz, K. P., Fan, J., Magidina, O., Marks, D. J., Hahn, B., & Halperin, J. M. (2007). Does the emotional go/no-go task really measure behavioral inhibition?. Convergence with measures on a non-emotional analog. *Archives of Clinical Neuropsychology, 22*(2), 151–160.

Schutte, I., Kenemans, J. L., & Schutter, D. (2017). Resting-state theta/beta EEG ratio is associated with reward- and punishment-related reversal learning. *Cogn Affect Behav Neurosci*. doi:10.3758/s13415-017-0510-3

Schutter, D. J., & Knyazev, G. G. (2012). Cross-frequency coupling of brain oscillations in studying motivation and emotion. *Motiv Emot, 36*(1), 46-54. doi:10.1007/s11031-011-9237-6

Schutter, D. J. L. G., & Van Honk, J. (2005). Electrophysiological ratio markers for the balance between reward and punishment. *Cognitive Brain Research, 24*(3), 685-690. doi:10.1016/j.cogbrainres.2005.04.002

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., ... & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience, 27*(9), 2349-2356.

Smallwood, J., & Schooler, J. W. (2006). The restless mind. *Psychological bulletin, 132*(6), 946.

Smallwood, J., Beach, E., Schooler, J. W., & Handy, T. C. (2008). Going AWOL in the brain: Mind wandering reduces cortical analysis of external events. *Journal of cognitive neuroscience, 20*(3), 458-469.

Schmidt, N. B., Richey, J. A., Buckner, J. D., & Timpano, K. R. (2009). Attention training for generalized social anxiety disorder. *Journal of abnormal psychology, 118*(1), 5.

Snyder, H. R., Miyake, A., & Hankin, B. L. (2015). Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. *Frontiers in psychology, 6*, 328.

Stawarczyk, D., Majerus, S., Maquet, P., & D'Argembeau, A. (2011). Neural correlates of ongoing conscious experience: both task-unrelatedness and stimulus-independence are related to default network activity. *PloS one, 6*(2), e16997.

Taylor, C. T., Cross, K., & Amir, N. (2016). Attentional control moderates the relationship between social anxiety symptoms and attentional disengagement from threatening information. *J Behav Ther Exp Psychiatry, 50*, 68-76.

Tortella-Feliu, M., Morillas-Romero, A., Balle, M., Llabrés, J., Bornas, X., & Putman, P. (2014). Spontaneous EEG activity and spontaneous emotion regulation. International Journal of *Psychophysiology, 94*(3), 365-372.

van Bockstaele, B., Verschuere, B., Tibboel, H., De Houwer, J., Crombez, G., & Koster, E. H. (2014). A review of current evidence for the causal impact of attentional bias on fear and anxiety. *Psychological bulletin, 140*(3), 682.

Vernon, D. J. (2005). Can neurofeedback training enhance performance? An evaluation of the evidence with implications for future research. *Applied psychophysiology and biofeedback, 30*(4), 347.

Verwoerd, J., de Jong, P. J., & Wessel, I. (2008). Low attentional control and the development of intrusive memories following a laboratory stressor. *Journal of Psychopathology and Behavioral Assessment, 30*(4), 291-297.

Williams, J. M. G., Mathews, A., & MacLeod, C. (1996). The emotional Stroop task and psychopathology. *Psychological bulletin, 120*(1), 3.

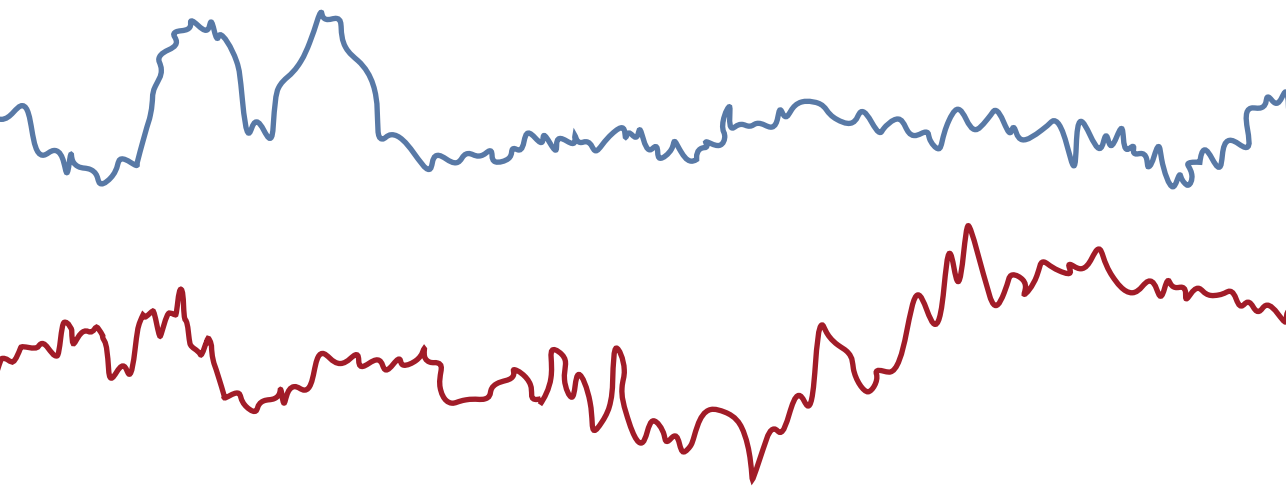
CHAPTER 1.

Early and late dot probe attentional bias to mild and high threat pictures: relations with EEG theta/beta ratio, self-reported trait attentional control and trait anxiety

Dana van Son, Angelos Angelidis, Muriel A. Hagenaars, Willem van der Does, Peter Putman

Published as

van Son, D., Angelidis, A., Hagenaars, M. A., van der Does, W., & Putman, P. (2018). Early and late dot-probe attentional bias to mild and high threat pictures: Relations with EEG theta/beta ratio, self-reported trait attentional control, and trait anxiety. *Psychophysiology*, e13274.



ABSTRACT

Frontal EEG theta/beta ratio (TBR; negatively associated with attentional control, or AC) was previously reported to moderate threat-level dependent attentional bias in a pictorial dot-probe task (DPT), interacting with trait anxiety. Unexpectedly, this was independent from processing stage (using cue-target delays of 200 and 500 ms) and also not observed for self-reported trait AC. We therefore aimed to replicate these effects of TBR and trait anxiety and to test if effects of early versus late processing stages are evident for shorter cue-target delays. This study also revisited the hypothesis that TBR and self-reported trait AC show similar effects. Fifty-three participants provided measurements of frontal TBR, self-reported trait AC, trait anxiety and DPT-bias for mild and high threat pictures using the same DPT, but this time with 80 and 200 ms cue-target delays. Results indicated that higher TBR predicted more attention to mild than high threat, but this was independent from trait anxiety or delay. Lower self-reported trait AC predicted more attention to mild than high threat, only after 200 ms (also independent of trait anxiety). We conclude that the moderating effect of TBR on threat-level dependent DPT-bias was replicated, but not the role of trait anxiety, and this study partially confirms that effects of trait AC are more dominant in later processing.

Vigilance to highly threatening stimuli is a natural and adaptive response (Ohman, 1993, 1994; Whalen, 1998). An efficient response when task-irrelevant stimuli are subjectively evaluated as being only mildly aversive, would be to direct attention away from them (e.g. Bradley, Mogg, Falla, & Hamilton, 1998; Koster, Verschuere, Crombez, & Van Damme, 2005; MacLeod, Mathews, & Tata, 1986). Highly anxious individuals have a tendency to appraise mildly threatening stimuli and situations as highly threatening (see Mogg & Bradley,1998; 2016; Cisler & Koster, 2010). Many studies have indeed demonstrated a vigilant bias to high threat in most people, which extends toward mild threat when people are more anxious (for reviews and meta-analysis, see Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, van IJzendoorn, 2007; Cisler & Koster, 2010; van Bockstaele, Verschuere, Tibboel, De Houwer, Crombez, & Koster, 2014). This attentional over-processing of mild threat, or 'attentional bias to threat', may occur automatically and is probably a maintenance factor of anxiety disorders (van Bockstaele et al.). In highly anxious individuals, however, attentional avoidance might also occur (e.g. Koster et al., 2005; Mogg, Bradley, Miles, & Dixon, 2004; Schoorl, Putman, van der Werff, & van der Does, 2014; Wald, Shechner, Bitton, Holoshitz, Charney, Muller, et al., 2011). This attentional avoidance may occur especially for highly threatening stimuli (Mogg & Bradley, 2016), e.g., phobia- or trauma-related stimuli or scenes cueing immediate threats to physical integrity (e.g., Koster et al., 2007; Schoorl et al., 2014; Mogg, Philippot & Bradley, 2004; Pine et al., 2005). Trait attentional control may have a crucial influence in this (Mogg & Bradley, 1998; 2016). Attentional avoidance may result from a secondary process, mediated by strategic, top-down attentional control (Mogg & Bradley, 2016). The question of whether such avoidance is indeed controlled or if it also occurs automatically is still open to empirical study. For instance, more avoidance of trauma-related pictures was observed in patients with post-traumatic stress disorder (PTSD) who also reported low attentional control, suggesting that avoidance was the more automatic response (Schoorl et al., 2014). Also, the time course of such a supposedly secondary avoidant response is far from clear and it may occur even earlier than 200 ms after cue presentation (Koster, Crombez, Verschuere, Vanvolsem & De Houwer, 2007; Mackintosh & Mathews, 2003).

Consequently, individual differences in trait attentional control (AC) may be of crucial importance in the manifestation of attentional bias to threat. Trait AC may be measured by self-report (attentional control scale, ACS; Derryberry & Reed, 2002). Most studies on trait AC and attentional bias used the ACS (e.g., Bardeen & Orcutt, 2011; Derryberry & Reed, 2002; Putman, Arias-Garcia, Pantazi, & van Schie, 2012; Schoorl et al., 2014; Taylor, Cross, and Amir., 2016; Peers & Lawrence, 2009) and three studies used an objective (performance-based) measure of AC (Hou, Moss-Morris, Risdale, Lynch, Jeevaratnam, Bradley & Mogg, 2014; Reinholdt-Dunne, Mogg, & Bradley, 2009; Bardeen & Daniel, 2017). Research into the role of trait AC in attentional threat bias may benefit from using self-report as well as objective markers of trait AC to obtain converging evidence for different methods (see also Bardeen & Daniel, 2017).

A potential objective electrophysiological measure for trait AC can be derived from spontaneous (also known as "resting-state") activity in electroencephalography (EEG). Frontal theta/beta ratio (TBR) reflects the ratio between power in the slow (theta) frequency band and the fast (beta) frequency band. High TBR is related to poor prefrontal cortex (PFC) mediated attentional and inhibitory functions, as seen in attention deficit/hyperactivity disorder (ADHD; for reviews and meta-analyses see Arns, Conners, & Kraemer, 2013; Barry,

Clarke, & Johnstone, 2003). TBR has been suggested to reflect functional reciprocal cortical-subcortical interactions in healthy as well as clinical populations (Knyazev, 2007; Schutter & Knyazev, 2012) and it might reflect voluntary top-down processes of executive control (including AC), mediated by (dorso-lateral) PFC, over bottom-up processes from limbic areas (such as the anterior cingulate cortex, hippocampus and amygdala; Bishop, 2008; Gregoriou, Rossi, Ungerleider, Desimone, 2014; Knyazev, 2007; Schutter & Knyazev, 2012; Hermans, Henckens, Joels, & Fernandez, 2014). Besides TBR's association with ADHD, its status as an index of AC is based on repeated observations that frontal TBR is associated with PFC-mediated cognitive and cognitive-emotional processes (Angelidis, van der Does, Schakel, & Putman, 2016; Putman, van Peer, Maimari, & van der Werff, 2010; Putman, Verkuil, Arias-Garcia, Pantazi, & van Schie, 2014; Angelidis, Hagenaars, van Son, van der Does, & Putman, 2018; Keune, Hansen, Weber, Zapf, Habich, Muenssinger & Wolf et al., 2017; Schutter & van Honk, 2005a; Massar, Kenemans, & Schutter, 2014; Schutte, Kenemans, & Schutter, 2017; Sari, Koster, Pourtois, & Derakshan, 2015). PFC-mediated cognitive control seems to play an important role in the attentional processing of threatening information (see also Mogg & Bradley, 2016; Shechner & Bar-Haim, 2016).

Accordingly, TBR was positively correlated with attention toward mild threat and negatively correlated with attention toward high threat, as measured with a dot-probe task (Angelidis et al., 2018). The latter correlation was mostly evident for low anxious people. Those data confirmed that adaptive attentional responding to varying threat levels depends on cognitive control and that TBR can be used to study these processes. The *first aim* of the present study was to replicate these novel findings for TBR and trait anxiety in relation to threat-level dependent attentional bias, using the same dot probe task as Angelidis et al. Because of the theoretical assumption that processes of trait AC in attentional threat-bias need some time to develop as they might rely on secondary PFC-mediated control over fast and automatic initial bottom-up processes (Ohman, 1993, 1994; Whalen, 1998; Derryberry & Reed, 2002; Mogg & Bradley, 1998; 2016; Bardeen & Orcutt, 2011; Koster et al., 2007), Angelidis et al. (2018) tested if effects of TBR would be different in early and late processing stages. However, contrary to expectations, the results of Angelidis et al. were independent of processing stage: a 200 ms cue-target delay (intended to capture the early attentional processes) showed no different results than a 500 ms cue-target delay (late attentional processes). We concluded that 200 ms delay may have been too long to capture early attentional processes and that the delay-hypothesis should be revisited. The *second aim* of the present study was therefore to revisit the hypothesis that AC should influence attentional bias more in later and controlled than in earlier and automatic processing stages, using shorter cue-target delays than in Angelidis et al.: a short delay of 80 ms and a long delay of 200 ms.

Another unexpected finding in Angelidis et al. (2018) was that self-reported trait AC was not related to threat-bias or to TBR. To show the role of trait AC in attentional processing of threat using converging methods (EEG and self-report) would strengthen the interpretation of these findings. Therefore, the *third aim* of the current study was to re-examine the relationship between attentional bias and trait AC, using ACS scores as well as TBR as indices of trait AC. We hypothesized that TBR and ACS would be negatively correlated – when controlling for trait anxiety (c.f., Putman et al., 2010; 2014; Angelidis et al., 2016) and that both indices would show similar relations with anxious attentional bias to threat.

In summary, building on the findings of Angelidis et al. (2018) and theoretical frameworks on the effects of threat-level and processing stages in relation to anxiety as outlined above (e.g. Mogg & Bradley, 1998; 2016), we aimed to investigate whether frontal EEG TBR is related to attentional bias in response to mild and high threatening stimuli (also in interaction with trait anxiety), if these effects are more pronounced in later (controlled) than earlier (automatic) processing stages and if self-reported trait AC and TBR (which are expected to correlate negatively) show converging effects. We used the same design as in Angelidis et al., (2018), but the dot-probe task contained a similar but new set of stimuli and shorter cue-target delays (80 and 200 ms). We tested the following hypotheses:

Hypothesis 1a: Frontal TBR moderates attentional responding to threat-level dependent bias in a dot-probe task, and high frontal TBR will be related to relatively more attention toward mild threatening pictures and relatively more attention away from high threatening pictures.

Hypothesis 1b: Self-reported trait anxiety moderates the relationship of hypothesis 1a between frontal TBR and effect of threat-level.

Hypothesis 2: These effects of hypothesis 1a and 1b should be more pronounced after a long cue-target delay (200 ms) than after a short cue-target delay (80 ms).

Hypothesis 3: Self-reported trait AC correlates negatively to TBR when controlling for trait anxiety.

Hypothesis 4a: Self-reported trait AC moderates attentional responding to threat-level dependent bias in a dot-probe task, and low trait AC will be related to relatively more attention toward mild threatening pictures and relatively more attention away from high threatening pictures.

Hypothesis 4b: Self-reported trait anxiety moderates the relationship of hypothesis 4a between self-reported trait AC and effect of threat-level.

Hypothesis 5: These effects of hypothesis 4a and 4b should be more pronounced after a long cue-target delay (200 ms) than after a short cue-target delay (80 ms).

These hypotheses were tested in a sample of healthy students, unselected for anxiety levels, looking at the average TBR of the frontal electrodes F3, Fz and F4 as in almost all relevant previous studies in heathy participants.

Methods

Participants

Fifty-three students (47 women) took part in this study. All participants signed informed consent. Participants had to be between 18 and 30 years old. Exclusion criteria were: presence of a mood, anxiety, or attention disorder; frequent use of psychoactive substances; and (history of) a neurological disorder. The study was approved by the local ethics review board (CEP#5927902162).

Materials

Questionnaires. Participants completed the trait version of the State-Trait Anxiety Inventory (STAI-t; Spielberger, 1983; Van der Ploeg, Defares & Spielberger, 1980) and the Attentional Control Scale (ACS; Derryberry & Reed, 2002; Verwoerd, de Jong, &Wessel, 2006). The STAI-t assesses trait anxiety (20 items, range 20-80;

Cronbach's alpha in the current study = 0.89) and the ACS assesses self-reported attentional control in terms of attentional focus, attentional switching and the capacity to quickly generate new thoughts (20 items, range 20-80; Cronbach's alpha in the current study = 0.85).

Dot-Probe task pictures and IAPS ratings. For the dot-probe task, 60 pictures were used from the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 1999), a standardized set of emotion eliciting color pictures with normative ratings on valence and arousal. The pictures (stimuli) were selected according to the ratings for valence and arousal (scale 1-9; valence 1: very unpleasant to 9: very pleasant and arousal scales; 1: not arousing at all to 9: very arousing) provided by Lang et al (2005)[1]. The mean valence score for mild threatening (MT) stimuli was $M = 2.52$ ($SD = 0.66$) and for high threatening (HT) stimuli $M = 1.63$ ($SD = 0.33$); the mean arousal scores were $M = 5.98$ ($SD = 0.91$) and $M = 6.79$ ($SD = 0.55$), respectively.

Of the 48 stimuli that were used in the main task, 32 were neutral (N; e.g. shoes), eight were high threatening (e.g. mutilated body), and eight were mild threatening (e.g. angry dog) in content. Three types of stimulus pairs were created: N-N, MT-N and HT-N. N-N trials were included to avoid habituation to threatening stimuli; the results on these trials are not reported here. A total of 8 N-N, 8 HT-N and 8 MT-N stimulus pairs were created. The remaining 12 neutral stimuli were selected for twelve N-N practice trials. Each pair of stimuli was subjectively matched on color and composition. We tested whether the average valence and arousal ratings reported by Center for the Study of Emotion and Attention (1999) differed between the categories. HT stimuli had lower valence ratings than MT ($t(31) = 3.42$, $p = 0.004$), and neutral stimuli ($t(31) = 13.20$, $p < 0.001$). MT stimuli also had more unpleasant ratings than neutral stimuli ($t(31) = 10.40$, $p < 0.001$). No difference was found between arousal ratings of HT stimuli and MT stimuli ($t(31) = -2.16$, $p = 0.53$), HT and MT pictures were both more arousing than neutral pictures (HT-N: $t(31) = -7.15$, $p < 0.001$; MT-N: $t(31) = -4.68$, $p < 0.001$).

EEG recording and software. EEG recording was done using 32 Ag/AgCl electrodes placed in an extended 10-20 montage using the ActiveTwo BioSemi system (BioSemi, The Netherlands). Electrodes placed on the left and right mastoids were used for offline re-referencing of the scalp signals to the mastoid signals. The dot-probe task and questionnaires were programmed and presented using E-Prime V2.0 (Psychology Software Tools, Pittsburgh, PA).

Procedure

General Procedure. After informed consent had been obtained, participants completed the STAI-t and the ACS. This was followed by the measurement of resting state EEG in eight alternating one-minute blocks of eyes open/closed recording. The dot-probe task was performed afterwards. The study took approximately 1 hour to complete.

Attentional bias. The dot-probe task was as in Angelidis et al. (2018), however we used a largely different stimulus set and different intervals for short and long probe-delays. During the task, participants sat at a distance of 80 cm away from the screen. The task consisted of 12 practice and 192 test trials, consisting of 64 HT-N, 64 MT-N and 64 N-N trials. In test trials, all stimulus pairs were presented eight times in random order, fully

counterbalanced for cue-target delay (80 or 200 ms), probe position (left/right), and congruency. Each trial started with a random inter-trial interval (ITI) between 500 and 1500 ms. The ITI was followed by a black fixation cross that was presented for 1000 ms in the center of a grey screen, and participants were instructed to look at this cross. The fixation cross was followed by two pictures that appeared vertically centered, 2.2 cm left and right from the screen. Pictures were presented with a height of 7.6 cm and width of 10.7 cm. Immediately after offset of the pictures, a probe (black dot; 5 mm diameter) appeared below the left or right picture location. The participants were asked to indicate the probe location as fast and accurately as possible by pressing response boxes attached to the left and right arm of their chair with their index fingers.

Data Processing

Dot-Probe data. Incorrect responses were excluded from analyses. One participant made 27 errors (more than five standard deviations above mean) and was excluded from further dot-probe task analyses. The average number of errors of the remaining participants was 3.57 (*SD* = 2.5) with a range from 0 to 11. Probe detection was measured in milliseconds and reaction times (RTs) that were shorter than 300 ms or longer than 1000 ms were defined as outliers and removed from the data. After applying this first filter, RTs that deviated more than three standard deviations from the individual mean RT were also removed as outliers (mean total number of removed outliers per participant was 4.27 (*SD* = 2.61)). The number of outliers per participant ranged from 0 to 14. An average of 2.1% of the data were removed in total; mean RT of remaining data was 335 ms (*SD* = 36). Bias scores were calculated for HT-N and MT-N trials separately in short cue-target delay trials (80 ms) and long cue-target delay trials (200 ms) by subtracting the average response time on congruent trials from incongruent trials. Positive bias scores indicate selective attention towards threat whereas negative scores indicate attentional avoidance. Mean RTs and SDs per stimulus-pair per condition and bias scores are presented in **Table 1**. Finally, Δthreat-level contrast scores were calculated separately for short and long delay conditions by subtracting average bias scores of HT-N trials from average bias scores of MT-N trials (a higher score reflecting a relatively stronger attentional bias toward mild compared to high threatening stimuli).

EEG processing. Offline data processing was done using Brain Vision Analyzer V2.0.4 (Brain Products GmbH, Germany). Data was high-pass filtered at 0.1 Hz, low-pass filtered at 100-Hz and a 50-Hz notch filter was applied. The data were automatically corrected for ocular artifacts (Gratton, Coles & Donchin, 1983) in segments of 4 seconds. Remaining segments containing muscle movements, amplitudes above 200 μV or other artifacts were removed. Fast Fourier transformation (Hamming window length 10%) was applied to calculate power density for the beta (13-30 Hz) and theta (4-7 Hz) band. The present research questions concerned the average of the frontal electrodes (F3, Fz and F4, as in Angelidis et al., 2018; see also Angelidis et al., 2016; Putman et al., 2010; Putman et al., 2014; Schutter & Van Honk, 2005). These frontal averages were therefore calculated for both the beta and theta band, other electrodes were used for exploratory purposes that were not meant to be reported. One participant had extremely high theta activity (more than four standard deviations above the mean) and was excluded from further EEG analyses. Frontal theta/beta ratio was calculated by dividing the frontal theta by frontal

beta power density. Frontal theta/beta ratio was non-normally distributed and therefore log10-normalized.

Statistical analyses. The mean bias scores were analyzed using a cue-target delay x threat-level (2 x 2) repeated measures analysis of variance (rm ANOVA). To test if TBR moderated the effect of threat-level on bias score (hypothesis 1a), a 2 level (threat-level) repeated measures ANOVA was performed, this time with frontal TBR added as a covariate to the model. This concerns a directional planned replication hypothesis, so a one-sided test was performed. Mahalonobis distance tests were used to check for bivariate outliers. To test hypothesis 1b and 2, the 2 level (threat-level) rm ANOVA was repeated, followed by a cue-target delay (2) x threat-level (2) rm ANOVA with centered frontal TBR, centered STAI-t, and their interaction term added as covariates to both models. Centered variables were used as predictor variables in the model to control for multicollinearity. Partial correlation testing was done to test hypothesis 3 for the association between TBR and ACS, and to control for confounding by STAI-t (see Putman et al., 2010; 2014; Angelidis et al., 2016). The same analyses that were done for hypotheses 1a, 1b and 2 were repeated for hypotheses 4a, 4b, and 5 but centered frontal TBR was replaced by centered ACS.

Results

Participants

Participants (N = 53) had a mean age of 21.7 years; (SD = 2.6), mean STAI-t score of 37.7 (SD = 9.9) and mean ACS score of 51 (SD = 8.4). The mean frontal TBR that was measured during resting state was 1.26 (SD = 0.54).

Dot-Probe

Mean RTs and bias scores are presented in Table 1 (see **Table 1)**. No significant main effect or interaction effects were observed: cue-target delay (F(1,51) = 0.067, p = 0.798, η_p^2 = 0.001); threat-level (F(1,51) = 0.504, p = 0.481, η_p^2 = 0.01) cue-target delay x threat-level (F(1,51) = 3.283, p = 0.076, η_p^2 = 0.06). Overall bias score compared to zero was also not significant, t(51) = - 0.169, p = 0.866. In sum, without taking into account variables of individual differences, no clear pattern of biases occurred for the dot-probe task; see **Table 1**.

Footnotes:

[1]The following pairs of pictures numbers were used: **HT-N**: 3010-1616, 5661-3130, 3000-7195, 3053-7200, 7496-3064, 7291-3080, 3051-7482, 7110-3068; **MT-N**: 7330-1300, 6570-5890, 3350-5532, 5480-8485, 9265-1590, 5622-9584, 5470-3530, 5830-9921; **N-N**: 2514-1540, 5471-5593, 1731-7490, 2388-2594, 5833-2398, 5010-5201, 5731-2515, 5250-7031.

Table 1. *Mean RTs and bias scores (and standard deviations) in ms for the two probe-delays and threat-levels in the dot-probe task (n = 53).*

Probe-target delay	Threat-level	Congruent	Incongruent	Bias score
80 ms	MT-N	339 (36)	341 (41)	2 (20)
	HT-N	340 (35)	337 (38)	-3 (16)
200 ms	MT-N	330 (39)	326 (39)	-4 (16)
	HT-N	330 (38)	333 (38)	3 (21)
Total	MT-N	334 (41)	333 (39)	-1 (10)
	HT-N	335 (35)	335 (37)	-0.4 (14)

Hypothesis 1a; Frontal TBR moderates attentional responding to threat-level dependent bias in a dot-probe task

Mahalonobis distance tests revealed a significant bivariate outlier case for the relationship between frontal TBR and threat-bias ($D^2 = 7.46$; $p < 0.05$ for MT bias and $D^2 = 14.06$; $p < 0.001$ for HT bias). This case was removed for analyses on TBR and dot-probe task data. The main effect of threat-level was non-significant ($F(1,48) = 0.142$, $p = 0.708$, $\eta_p^2 = 0.003$), but interaction effect of frontal TBR x threat-level was significant (one-tailed) ($F(1,48) = 3.038$, $p = 0.044$, $\eta_p^2 = 0.06$). The effect remained significant (one-tailed) when controlling for STAI-t ($F(1,47) = 3.831$, $p = 0.028$, $\eta_p^2 = 0.075$). **Figure 1.1** depicts this interaction as the relation between TBR and Δthreat-level. It can be seen that high frontal TBR is associated with relatively more attention toward mild threat than toward high threat. Follow-up tests showed no significant correlation between frontal TBR and bias for MT ($r = -0.19$, $p = 0.19$) but a significant negative correlation between frontal TBR and bias for HT ($r = -0.41$, $p = 0.003$). Hypothesis 1a was therefore confirmed.

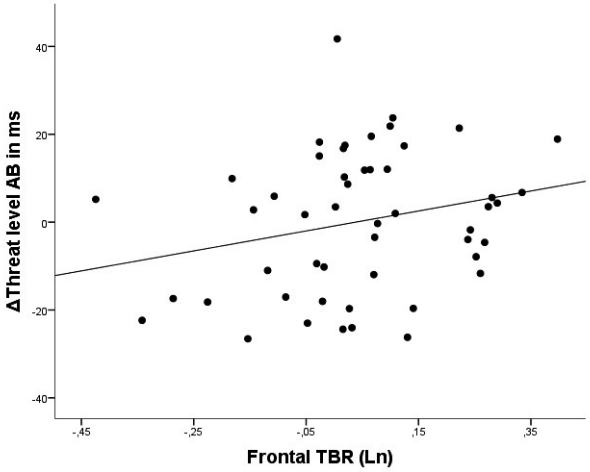


Figure 1.1 The relation between Ln-normalized frontal EEG TBR and ΔThreat level (Bias for MT stimuli – Bias for HT stimuli).

Hypothesis 1b; Self-reported trait anxiety moderates the relationship between frontal TBR and effect of threat-level

The crucial interaction effect between frontal TBR, STAI-t and threat-level was not significant, $F(1,46) = 0.046$, $p = 0.831$, $\eta_p^2 = 0.001$. Hypothesis 1b was therefore rejected.

Hypothesis 2; Cue-target delay related to TBR and TBR x trait anxiety in threat-level dependent dot-probe performance

The crucial interaction effect between frontal TBR x cue-target delay x threat-level was not significant, $F(1,48) = 0.016$, $p = 0.898$, $\eta_p^2 < 0.001$. When we added STAI-t and the frontal TBR x STAI-t interaction term, there was no significant crucial STAI-t x TBR x cue-target delay x threat-level interaction, $F(1,46) = 1.005$, $p = 0.321$, $\eta_p^2 = 0.021$. Thus, hypothesis 2 was rejected.

Hypothesis 3: The relation between TBR and trait-AC

TBR was significantly negatively correlated to trait AC (as measured by the ACS; when controlling for STAI-t, the partial correlation was $r = -0.32$; $p = 0.024$). Frontal TBR also correlated significantly negatively to STAI-t when controlling for ACS (partial $r = -0.336$; $p = 0.016$). Hypothesis 3 was thus confirmed.

Hypothesis 4a and 4b; The effect of trait AC and trait AC x trait anxiety in threat-level dependent dot-probe performance

We performed the same moderation analyses for trait AC (as measured by the ACS), as we did for TBR using the 2 level (threat-level) repeated measures ANOVA with ACS as covariate. This showed no significant ACS x

threat-level interaction, $F(1,50) = 0.149$, $p = 0.701$, $\eta_p^2 = 0.003$. To test if the interaction of ACS x STAI-t moderated effect of threat-level, the model was repeated using ACS, STAI-t and their interaction in the model. This revealed no significant ACS x STAI-t x threat-level interaction, $F(1,48) = 0.167$, $p = 0.685$, $\eta_p^2 = 0.003$. Hypotheses 4a and 4b are therefore rejected.

Hypothesis 5; Cue-target delay related to trait AC x trait anxiety in threat-level dependent dot-probe performance

A significant ACS x cue-target delay x threat-level interaction was found, $F(1,50) = 7.339$, $p = 0.009$, $\eta_p^2 = 0.128$. This interaction remained significant when we controlled for STAI-t, $F(1,49) = 7.863$, $p = 0.007$, $\eta_p^2 = 0.138$. This confirms hypothesis 5. Follow-up analyses showed a trend-level ACS x threat-level interaction in the short delay condition, $F(1,50) = 3.174$, $p = 0.08$, $\eta_p^2 = 0.06$. **Figure 1.2, left panel**, depicting this interaction as the correlation between ACS and Δthreat-level, clarifies the nature of this interaction; higher ACS scores were associated with a tendency toward higher difference scores for bias for mild minus high threat. ACS was negatively associated with bias toward HT ($r = -0.29$, $p = 0.04$) and not with bias for MT ($r = 0.09$, $p = 0.53$) in the short delay condition.

In the long delay condition, there was a significant ACS x threat-level interaction, $F(1,50) = 5.046$, $p = 0.03$, $\eta_p^2 = 0.092$, which remained significant when controlling for STAI-t , $F(1,50) = 5.696$, $p = 0.02$, $\eta_p^2 = 0.104$. **Figure 1.2** clarifies the nature of this interaction; lower ACS scores were associated with a tendency toward higher difference scores for bias for mild minus high threat. ACS was significantly negatively correlated to bias to MT ($r = -0.28$, $p = 0.04$) and non-significantly positively correlated with bias to HT ($r = 0.20$, $p = 0.15$).

To test if ACS and STAI-t interactively moderated a cue-target delay x threat-level effect on bias scores, the cue-target delay (2) x threat-level (2) ANOVA was run with ACS, STAI-t and their interaction term in the model. This showed no significant STAI-t x ACS x cue-target delay x threat-level interaction, $F(1,48) = 0.001$, $p = 0.973$, $\eta_p^2 < 0.001$. Hypotheses 5 is thus partially confirmed.

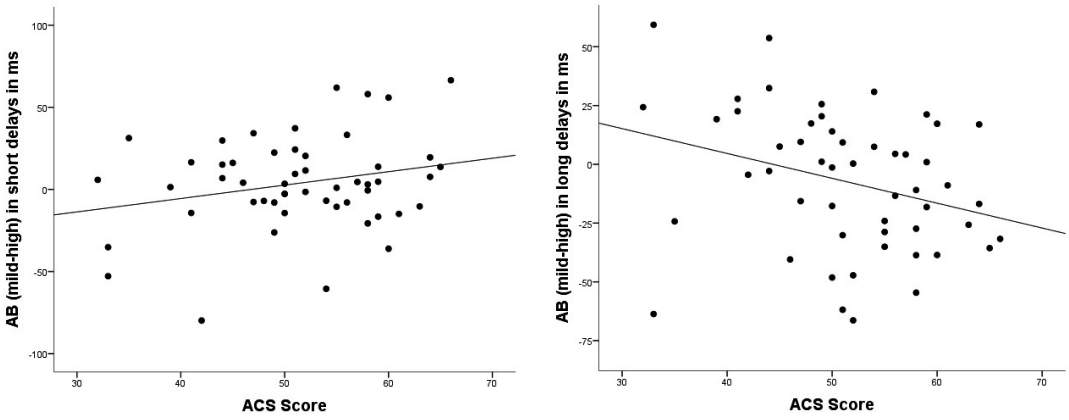


Figure 1.2. The relationship between Δthreat-level (bias score MT – bias score HT) in ms and attentional control in short (80 ms, left) and long (200 ms, right) cue-target delays.

Discussion

This study investigated whether frontal EEG TBR is related to threat-level dependent attentional bias, alone and in interaction with trait anxiety, if results were more pronounced after a longer cue-target delay than after a shorter delay and if findings for self-reported trait AC and for TBR converged, to further test the construct validity of TBR as a marker of trait AC and its role in attentional bias. Results showed that lower TBR was associated with more attention toward high than toward mild threat. Trait anxiety did not interact with TBR's relation to threat-level dependent bias, contrary to expectation. The TBR threat-level interaction was not affected by cue-target delay. As expected, TBR and ACS were negatively correlated, and ACS moderated attentional bias to different threat-levels in a similar manner as TBR did. ACS did not interact with trait anxiety either, but the association between ACS and threat-level was dependent on cue-target delay, as predicted: the ACS x threat-level interaction was specific to the longer cue-target delay. These results are further discussed below.

The finding that TBR moderates attentional bias to different threat-levels replicates our previous study (Angelidis et al., 2018). We tested this hypothesis one-sided since it concerns a planned replication hypothesis, but it should be noted that this was a statistical trend ($p = 0.056$) when tested two-sided, likely due to our somewhat smaller sample size. Angelidis et al. (2018) reported that higher TBR (low cognitive control) was associated with relative avoidance of high threatening stimuli compared to mild threatening stimuli and the current data show the same interaction for TBR and threat-level. This is in line with the cognitive motivational model of attentional bias (Mogg & Bradley, 1998; 2016), indicating that attentional bias towards threat may be opposed by mechanisms of avoidance and that individual differences in cognitive control are crucial in the actual manifestation of threat-bias toward or away from threat (Mogg, Weinman & Mathews, 1987; Mogg & Bradley, 2016).

Our next hypothesis was that the moderation of TBR on threat-level would be different in early (80 ms cue-target delays) compared to later (200 ms cue-target delays) stages of attention. However, our data did not show this, similar as in Angelidis et al. (2018) where cue-target delays of 200 and 500 ms were used. The expectation that cue-target delay would affect the results originates from the assumption that the cognitive control mechanisms that regulate automatic attention away from threat (attentional avoidance) occur at later stages of attentional processing (Derryberry & Reed, 2002; Cisler & Koster, 2010; Mogg & Bradley, 1998; 2016). The current results for TBR and the results of Angelidis et al., (2018) do not support this notion. One methodological explanation of the current findings might be that the short cue target delay was too short for sufficient emotional-attentional processing so no bias might be measured at all. However, ACS scores were significantly associated with bias (toward high threat) in the short delay condition. This suggests that the short cue target delay condition was sufficient to allow measurement of attentional bias. An 80 ms delay is known to allow orienting of visuospatial attention (Posner & Cohen, 1984) and in dot-probe tasks, anxious selective attention toward threat has been observed already after 50 ms (Armony & Dolan, 2002) and even after 34 ms, using subliminal presentation (Fox, 2002). All in all, we do not think that the cue-target delay of 80 ms was too short. Another possible methodological explanation for the current data might be that the difference between 80 ms and 200 ms is not large enough to distinguish between early and late attentional processes. Importantly though, we did find a significant delay-dependent ACS moderation of threat-level, where the association was stronger in the longer cue-target condition, as expected. In conclusion, we do not have a ready explanation for the absence of a delay effect for TBR, especially considering the current positive finding for ACS. The latter finding is in line with two previous studies (Derryberry & Reed, 2002, Bardeen & Orcutt, 2011) that also measured visuospatial threat-biased attention, albeit with different cue-target delays. Considering a delay effect for one measure of trait AC (ACS) but no such effect for the other index of trait AC (TBR), we conclude that our results on this issue are inconclusive. Measuring the time-course of attention remains notoriously difficult (see also Mogg & Bradley, 2016). Different methods such as emotional cueing tasks (Koster et al., 2007), event-related potential tasks (Harrewijn, Schmidt, Westenberg, Tang, & van der Molen, 2017) or even non-spatial emotional-attention tasks such as interference tasks (Clarke et al., 2013) or serial presentation tasks (Peers & Lawrence, 2009) might be used in future studies to assess the time-course of selective attention, attentional avoidance and attentional control.

We hypothesized that the moderation of TBR on threat-level would interact with trait anxiety, but this was not observed. A possible explanation might be that we used different stimuli than in Angelidis et al. (2018). We cannot compare the sets because the ratings of the stimuli in Angelidis et al. (2018) were collected in a different sample and in a different experimental setting than the IAPS ratings. Perhaps pre-selecting participants on high trait anxiety and/or manipulation of state anxiety could be helpful in resolving this issue, as attentional threat bias might depend on interaction between trait and state anxiety (Egloff & Hock, 2001).

Contrary to Angelidis et al. (2018), a significant correlation between TBR and ACS scores (independent of trait anxiety) was found in the current sample, which is in line with previous studies from our lab (Putman et al., 2010; 2014; Angelidis et al., 2016) and with reported negative correlations between TBR and task-based objective measures of attention (Keune et al., 2017). Conceptualizing TBR as a marker of attentional control, we also

predicted that ACS scores (which indicate trait AC) would show a similar relation with dot-probe task performance as TBR. This was partially confirmed: lower ACS was related to relative avoidance of high threatening stimuli and also to attentional bias toward mild threatening stimuli. This conceptually replicates the TBR effect, but only when taking cue-target delay into consideration, which is largely consistent with our predictions. Although TBR was reported to have a very high one and two-week re-test reliability (Angelidis et al., 2016; Keune et al., 2017), little is known about transient state-fluctuations of TBR and operationally our TBR measure was done at a single point in time. Since acute fluctuations in trait AC may occur as a function of factors as diverse as fatigue (van der Linden, Frese & Meijman, 2003) or circadian rhythm (van Dongen & Dinges, 2000), results for trait and state measures of trait AC should not be expected to correlate perfectly. As such it is encouraging that results of the current study for trait ACS and TBR converged. This solidifies the interpretation of the current TBR results as well as the similar results of Angelidis et al., (2018), supporting the construct validity of TBR as a reflection of neural processes underlying trait AC.

Altogether, our findings that both TBR and ACS are related to attentional processing of cues with different threat-levels, indicate that executive control plays a critical role in threat processing. The current study emphasizes the importance of threat-level; different attentional responses were found for high versus mild threatening stimuli, moderated by frontal TBR and ACS. Schechner & Bar-Haim (2016) recently also emphasized the importance of subjective threat evaluation (influences of state anxiety) in the manifestation of threat-avoidant attentional bias. Their findings and ours carry possible implications for the currently popular attentional bias modification paradigm and its attempts to train attentional bias away from threat with the objective of effecting more adaptive and healthy attentional processing styles (Cristea, Kok & Cuijpers, 2015).

Potential limitations of this study include that we used a smaller sample and a lower number of males than the previous study (Angelidis et al., 2018). The stimulus set included eight high and eight mild threatening stimuli, which may be considered a fairly small set. The fact that our results for TBR and threat-level dependent attention partially replicate Angelidis et al. (2018) who used a largely different stimulus-set, is reassuring. Still, future research could consider using larger sets of stimuli to avoid possible artefacts resulting from narrow stimulus sampling.

To conclude, this study partially replicated previously reported relations between TBR and threat-level dependent dot probe bias and as such supports the notion of frontal TBR as an electrophysiological marker for executive control, i.e. regulation of attentional processing of threatening stimuli. The direction of attentional bias depends on individual differences in attentional control and threat level of the stimuli. The issue of early and automatic versus late and controlled attentional processing remains unresolved as only effects of self-reported trait AC, but not of TBR, were confined to a later stage of processing and requires further investigation. Finally, converging results were found for TBR and an often used and validated (Judah, Grant, Mills, & Lechner, 2014) self-report measure of trait AC, supporting construct validity.

References

Amir, N., Foa, E. B., & Coles, M. E. (1998). Automatic activation and strategic avoidance of threat-relevant information in social phobia. *Journal of Abnormal Psychology, 107*(2), 285-290.

Angelidis, A., Hagenaars, M., van Son, D., van der Does, W., & Putman, P. (2018). Do not look away! Spontaneous frontal EEG theta/beta ratio as a marker for cognitive control over attention to mild and high threat. *Biological psychology, 135*, 8-17.

Angelidis, A., van der Does, W., Schakel, L., & Putman, P. (2016). Frontal EEG theta/beta ratio as an electrophysiological marker for attentional control and its test-retest reliability. *Biological psychology, 121*, 49-52.

Armony, J. L., & Dolan, R. J. (2002). Modulation of spatial attention by fear-conditioned stimuli: an event-related fMRI study. Neuropsychologia, 40(7), 817-826.

Arns, M., Conners, C. K., & Kraemer, H. C. (2013). A decade of EEG Theta/Beta Ratio Research in ADHD: a meta-analysis. *J Atten Disord, 17*(5), 374-383.

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & van, I. M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychol Bull, 133*(1), 1-24.

Bardeen, J. R., & Orcutt, H. K. (2011). Attentional control as a moderator of the relationship between posttraumatic stress symptoms and attentional threat bias. *J Anxiety Disord, 25*(8), 1008-1018.

Bardeen, J. R., & Daniel, T. A. (2017). A longitudinal examination of the role of attentional control in the relationship between posttraumatic stress and threat-related attentional bias: An eye-tracking study. *Behaviour research and therapy, 99*, 67-77.

Barry, R. J., Clarke, A. R., & Johnstone, S. J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clin Neurophysiol, 114*(2), 171-183.

Beck, A. T. (1976). *Depression: Clinical, experimental, and theoretical aspects.* New York: Hoeber.

Bishop, S. J. (2008). Neural mechanisms underlying selective attention to threat. *Ann N Y Acad Sci, 1129*, 141-152.

Bradley, B. P., Mogg, K., Falla, S. J., & Hamilton, L. R. (1998). Attentional Bias for Threatening Facial Expressions in Anxiety: Manipulation of Stimulus Duration. *Cognition and Emotion, 12*(6), 737-753.

Center for the study of Emotion and Attention, National Institute of Mental Health. (1999). *The International Affective Picture System.* Gainesville, FL: University of Florida

Cisler, J. M., & Koster, E. H. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clin Psychol Rev, 30*(2), 203-216.

Clarke, P. J., MacLeod, C., & Guastella, A. J. (2013). Assessing the role of spatial engagement and disengagement of attention in anxiety-linked attentional bias: a critique of current paradigms and suggestions for future research directions. *Anxiety, Stress & Coping, 26*(1), 1-19.

Cristea, I. A., Kok, R. N., & Cuijpers, P. (2015). Efficacy of cognitive bias modification interventions in anxiety and depression: meta-analysis. *The British Journal of Psychiatry, 206*(1), 7-16.

Derryberry, D., & Reed, M. A. (2002). Anxiety-related attentional biases and their regulation by attentional control. *Journal of Abnormal Psychology, 111*(2), 225-236.

Egloff, B., & Hock. M. (2001). Interactive effects of state anxiety and trait anxiety on emotional Stroop interference. *Personality and Individual Differences, 31,* 875-882.

Eysenck, M. W., & Calvo, M. G. (1992). Anxiety and performance: The processing efficiency theory. *Cognition & Emotion, 6*(6), 409-434.

Fox, E. (2002). Processing emotional facial expressions: The role of anxiety and awareness. *Cognitive, Affective, & Behavioral Neuroscience, 2*(1), 52-63.

Gratton, G., Coles, M. G., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. Electroencephalography and clinical neurophysiology, 55(4), 468-484.

Gregoriou, G. G., Rossi, A. F., Ungerleider, L. G., & Desimone, R. (2014). Lesions of prefrontal cortex reduce attentional modulation of neuronal responses and synchrony in V4. *Nat Neurosci, 17*(7), 1003-1011.

Harrewijn, A., Schmidt, L. A., Westenberg, P. M., Tang, A., & van der Molen, M. J. (2017). Electrocortical measures of information processing biases in social anxiety disorder: A review. *Biological Psychology.*

Hermans, E. J., Henckens, M. J., Joels, M., & Fernandez, G. (2014). Dynamic adaptation of large-scale brain networks in response to acute stressors. *Trends Neurosci, 37*(6), 304-314.

Hou, R., Moss-Morris, R., Risdale, A., Lynch, J., Jeevaratnam, P., Bradley, B. P., & Mogg, K. (2014). Attention processes in chronic fatigue syndrome: attentional bias for health-related threat and the role of attentional control. *Behav Res Ther, 52*, 9-16.

Judah, M. R., Grant, D. M., Mills, A. C., & Lechner, W. V. (2014). Factor structure and validation of the attentional control scale. *Cognition & emotion, 28*(3), 433-451.

Keune, P. M., Hansen, S., Weber, E., Zapf, F., Habich, J., Muenssinger, J., ... & Oschmann, P. (2017). Exploring resting-state EEG brain oscillatory activity in relation to cognitive functioning in multiple sclerosis. *Clinical Neurophysiology, 128*(9), 1746-1754.

Knyazev, G. G. (2007). Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neuroscience and Biobehavioral Reviews, 31*(3), 377-395.

Koster, E. H., Crombez, G., Verschuere, B., Vanvolsem, P., & De Houwer, J. (2007). A time-course analysis of attentional cueing by threatening scenes. *Exp Psychol, 54*(2), 161-171.

Koster, E. H., Verschuere, B., Crombez, G., & Van Damme, S. (2005). Time-course of attention for threatening pictures in high and low trait anxiety. *Behav Res Ther, 43*(8), 1087-1098.

Lang, P. J. (2005). International affective picture system (IAPS): Affective ratings of pictures and instruction manual. *Technical report*.

LeDoux, J. E. (1995). EMOTION - CLUES FROM THE BRAIN. *Annual Review of Psychology, 46*, 209-235.

Mackintosh, B., & Mathews, A. (2003). Don't look now: Attentional avoidance of emotionally valenced cues. *Cognition & Emotion, 17*(4), 623-646.

MacLeod, C., Mathews, A., & Tata, P. (1986). Attentional bias in emotional disorders. *Journal of Abnormal Psychology, 95*(1), 15-20.

Massar, S. A., Kenemans, J. L., & Schutter, D. J. (2014). Resting-state EEG theta activity and risk learning: sensitivity to reward or punishment? *Int J Psychophysiol, 91*(3), 172-177.

Mogg, K., Bradley, B., Miles, F., & Dixon, R. (2004). BRIEF REPORT Time course of attentional bias for threat scenes: Testing the vigilance-avoidance hypothesis. *Cognition and Emotion, 18*(5), 689-700.

Mogg, K., & Bradley, B. P. (1998). A cognitive-motivational analysis of anxiety. *Behaviour Research and Therapy, 36*(9), 809-848.

Mogg, K., & Bradley, B. P. (2002). Selective orienting of attention to masked threat faces in social anxiety. *Behav Res Ther, 40*(12), 1403-1414.

Mogg, K., & Bradley, B. P. (2016). Anxiety and attention to threat: Cognitive mechanisms and treatment with attention bias modification. *Behav Res Ther, 87*, 76-108.

Mogg, K., Philippot, P., & Bradley, B. P. (2004). Selective attention to angry faces in clinical social phobia. *Journal of abnormal psychology, 113*(1), 160.

Mogg, K., Weinman, J., & Mathews, A. (1987). Memory Bias in Clinical Anxiety. *Journal of Abnormal Psychology, 96*(2), 94-98.

Morillas-Romero, A., Tortella-Feliu, M., Bornas, X., & Putman, P. (2015). Spontaneous EEG theta/beta ratio and delta-beta coupling in relation to attentional network functioning and self-reported attentional control. *Cogn Affect Behav Neurosci, 15*(3), 598-606.

Ohman, A. (1993). Fear and anxiety as emotional phenomena: Clinical phenomenology, evolutionary perspectives, and information-processing mechanisms. In M. Lewis, & J. M. Haviland (Eds.), Handbook of emotions (pp. 511e536). New York: Guilford Press.

Ohman, A. (1994). The psychophysiology of emotion: Evolutionary and nonconscious origins. In G. d'Ydewalle, P. Eelen, & P. Bertelsen (Eds.), International perspectives on psychological science (Vol. 1, pp. 197e226). Hillsdale, NJ: Erlbaum. The state of the art.

Peers, P. V., & Lawrence, A. D. (2009). Attentional control of emotional distraction in rapid serial visual presentation. *Emotion, 9*(1), 140-145.

Pine, D. S., Mogg, K., Bradley, B. P., Montgomery, L., Monk, C. S., McClure, E., . . . Kaufman, J. (2005). Attention bias to threat in maltreated children: implications for vulnerability to stress-related psychopathology. *Am J Psychiatry, 162*(2), 291-296.

Posner, M. I., & Cohen, Y. (1984). Components of visual orienting. Attention and performance X: *Control of language processes, (32)*, 531-556.

Putman, P., Arias-Garcia, E., Pantazi, I., & van Schie, C. (2012). Emotional Stroop interference for threatening words is related to reduced EEG delta-beta coupling and low attentional control. *International Journal of Psychophysiology, 84*(2), 194-200.

Putman, P., van Peer, J., Maimari, I., & van der Werff, S. (2010). EEG theta/beta ratio in relation to fear-modulated response-inhibition, attentional control, and affective traits. *Biol Psychol, 83*(2), 73-78.

Putman, P., Verkuil, B., Arias-Garcia, E., Pantazi, I., & van Schie, C. (2014). EEG theta/beta ratio as a potential biomarker for attentional control and resilience against deleterious effects of stress on attention. *Cognitive Affective & Behavioral Neuroscience, 14*(2), 782-791.

Reinholdt-Dunne, M. L., Mogg, K., & Bradley, B. P. (2009). Effects of anxiety and attention control on processing pictorial and linguistic emotional information. *Behaviour Research and Therapy, 47*(5), 410-417.

Sari, B. A., Koster, E. H., Pourtois, G., & Derakshan, N. (2016). Training working memory to improve attentional control in anxiety: A proof-of-principle study using behavioral and electrophysiological measures. *Biological Psychology, 121*, 203-212.

Schoorl, M., Putman, P., Van Der Werff, S., & Van Der Does, A. J. (2014). Attentional bias and attentional control in Posttraumatic Stress Disorder. *Journal of Anxiety Disorders, 28*(2), 203-210.

Schutte, I., Kenemans, J. L., & Schutter, D. (2017). Resting-state theta/beta EEG ratio is associated with reward- and punishment-related reversal learning. *Cogn Affect Behav Neurosci.*

Schutter, D. J., & Knyazev, G. G. (2012). Cross-frequency coupling of brain oscillations in studying motivation and emotion. *Motiv Emot, 36*(1), 46-54.

Schutter, D. J. L. G., & Van Honk, J. (2005). Electrophysiological ratio markers for the balance between reward and punishment. *Cognitive Brain Research, 24*(3), 685-690.

Shechner, T., & Bar-Haim, Y. (2016). Threat Monitoring and Attention-Bias Modification in Anxiety and Stress-Related Disorders. *Current Directions in Psychological Science, 25*(6), 431-437.

Spielberger, C. D. (1983). *Manual for the State–Trait Anxiety Inventory (STAI form Y)*. Palo Alto: Consulting Psychologists Press.

Taylor, C. T., Cross, K., & Amir, N. (2016). Attentional control moderates the relationship between social anxiety symptoms and attentional disengagement from threatening information. *J Behav Ther Exp Psychiatry, 50*, 68-76.

Van Bockstaele, B., Verschuere, B., Tibboel, H., De Houwer, J., Crombez, G., & Koster, E. H. (2014). A review of current evidence for the causal impact of attentional bias on fear and anxiety. *Psychol Bull, 140*(3), 682-721.

Van der Linden, D., Frese, M., & Meijman, T. F. (2003). Mental fatigue and the control of cognitive processes: effects on perseveration and planning. *Acta Psychologica, 113*(1), 45-65.

Van der Ploeg, H. M., Defares, P. B., & Spielberger, C. D. (1980). *ZBV: Handleiding bij de zelf-beoordelings vragenlijst: Een Nederlandstalige bewerking van Spielberger State–Trait Anxiety Inventory STAI-Y*. Amsterdam: Harcourt.

Van Dongen, H. P., & Dinges, D. F. (2000). Circadian rhythms in fatigue, alertness, and performance. *Principles and practice of sleep medicine, 20,* 391-9.

Verwoerd, J., de Jong, P. J., & Wessel, I. (2006). *ACS: Dutch translation of the Attentional Control Scale, originally developed by Derryberry and Reed (2002)*.

Wald, I., Shechner, T., Bitton, S., Holoshitz, Y., Charney, D. S., Muller, D., & Bar-Haim, Y. (2011). Attention bias away from threat during life threatening danger predicts PTSD symptoms at one-year follow-up. *Depress Anxiety, 28*(5), 406-411.

Whalen, P. J. (1998). Fear, vigilance, and ambiguity: Initial neuroimaging studies of the human amygdala. *Current directions in psychological science, 7*(6), 177-188.

Williams, J. M. G., Watts, F. N., MacLeod, C., & Mathews, A. (1988). Cognitive psychology and emotional disorders. *John Wiley & Sons*.

Wischnewski, M., Zerr, P., & Schutter, D. J. (2016). Effects of Theta Transcranial Alternating Current Stimulation Over the Frontal Cortex on Reversal Learning. *Brain Stimul, 9*(5), 705-711.

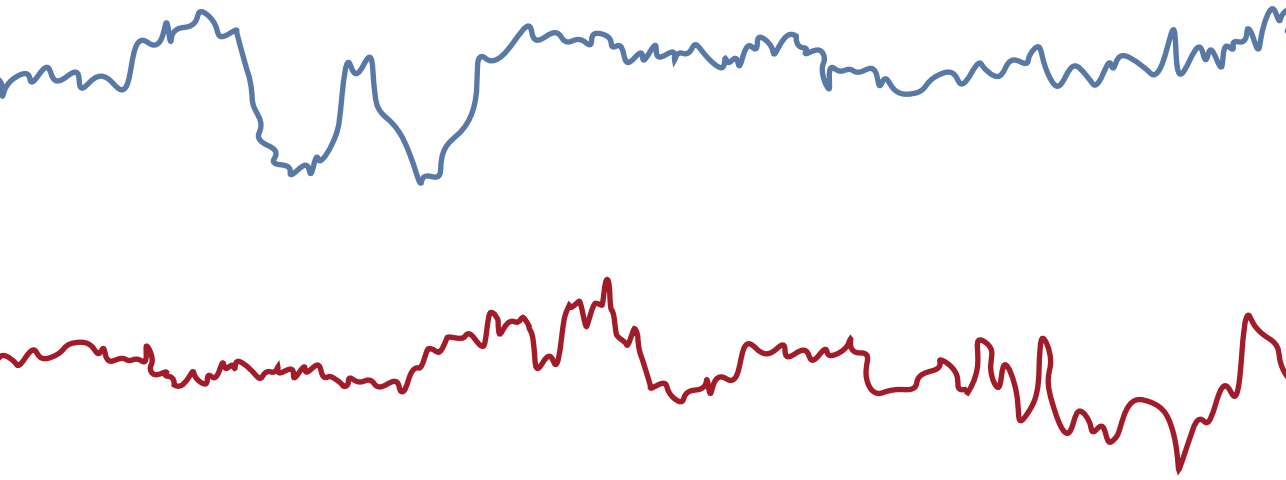
CHAPTER 2.

Acute effects of caffeine on threat selective attention: moderation by anxiety and EEG theta/beta ratio

Dana van Son, Rik Schalbroeck, Angelos Angelidis, Nic van der Wee, Willem van der Does, Peter Putman.

Published as

van Son, D., Schalbroeck, R., Angelidis, A., van der Wee, N. J., van der Does, W., & Putman, P. (2018b). Acute effects of caffeine on threat-selective attention: moderation by anxiety and EEG theta/beta ratio. *Biological psychology, 136,* 100-110.



ABSTRACT

Background: Spontaneous EEG theta/beta ratio (TBR) probably marks prefrontal cortical (PFC) executive control, and its regulation of attentional threat-bias. Caffeine at moderate doses may strengthen executive control through increased PFC catecholamine action, dependent on basal PFC function.

Goal: To test if caffeine affects threat-bias, moderated by baseline frontal TBR and trait-anxiety.

Methods: A pictorial emotional Stroop task was used to assess threat-bias in forty female participants in a cross-over, double-blind study after placebo and 200 mg caffeine.

Results: At baseline and after placebo, comparable relations were observed for negative pictures: high TBR was related to low threat-bias in low trait-anxious people. Caffeine had opposite effects on threat-bias in low trait-anxious people with low and high TBR.

Conclusions: This further supports TBR as a marker of executive control and highlights the importance of taking baseline executive function into consideration when studying effects of caffeine on executive functions.

Anxiety disorders are one of the most common mental health problems with point prevalence rates estimated around 7.3% worldwide (Baxter, Scott, & Whiteford, 2013). Individuals with an anxiety disorder excessively attend to threatening information and this may also be observed in individuals at risk (Mogg and & Bradley, 2016; Ledoux; 1995). This tendency is usually referred to as an *attentional bias* (AB) towards threat.

A large number of studies have confirmed a positive relation between anxiety levels and AB toward (mild) threat and it is thought that threat AB might maintain anxiety disorders (Mogg & Bradley, 1998; 2016; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg & van IJzendoorn, 2007; Cisler & Koster, 2010; van Bockstaele, Verschuere, Tibboel, De Houwer, Crombez & Koster, 2014). AB is also thought to partially explain the well-documented association between anxiety and reduced cognitive performance through facilitating the processing of task-unrelated threatening information at the cost of task-directed attentional control and working memory capacity (Hembree, 1988; Putwain, 2009; Owens, Stevenson, Hadwin & Norgate, 2012; Eysenck, Derakshan, Santos & Calvo, 2007; Derakshan & Eysenck, 2009; Cassady & Johnson, 2002; Bishop, 2008). Bottom-up processing of salient information might cause selective and automatic attention to threat, while top-down cognitive control facilitates more goal-directed cognition and behavior (e.g., Eysenck et al., 2007; Hermans, Henckens, Joels & Fernandez, 2014; Mogg & Bradley, 2016). This is in line with findings of Derryberry and Reed (2002) who found that trait attentional control, as assessed with the attentional control scale (ACS; Derryberry & Reed 2002) regulates automatic attention to threatening stimuli. Since their original study, several studies have reported that individual differences in attentional control (AC) are associated with the occurrence of threat-bias (often depending on levels of trait anxiety). In these studies, AC was measured either by self-report (e.g., Bishop, Jenkins & Lawrence, 2007; Derryberry & Reed, 2002; Putman, Arias-Garcia, Pantazi & van Schie, 2012; Schoorl, Putman, van der Werff, & van der Does, 2014; Taylor, Cross & Amir, 2016) or with objectively assessed measures (Hou, Moss-Morris, Risdale, Lynch, Jeevaratnam, Bradley & Mogg, 2014; Reinholdt-Dunne, Mogg & Bradley, 2009; Angelidis, Hagenaars, van Son, van der Does & Putman, 2018; van Son, Angelidis, Hagenaars, van der Does & Putman, 2018).

Goal oriented, top-down attentional control is mediated by prefrontal-cortical networks (Derakshan & Eysenck, 2009; Bishop, 2008; Gregoriou, Rossi, Ungerleider & Desimone, 2014), whose function is dependent on adequate catecholamine action (Hermans et al., 2014; Arnsten, 2009a). Stress and anxiety trigger a variety of neurochemical changes (Joëls &Baram, 2009), including increased influx of the catecholamines dopamine and nor-adrenaline into the prefrontal cortex (PFC). These processes are partly genetically determined and individually different (Kvetnansky, Sabban & Palkovits, 2009). Both types of catecholamines influence PFC in a dose-dependent, inverted U-shaped manner (Arnsten, 2009). While moderate levels are needed for good prefrontal executive control, dopaminergic and noradrenergic over-stimulation leads to decreased PFC function. In other words, increasing levels of catecholamines are associated with increasing performance until a tipping point is reached, after which further catecholamine stimulation will harm executive performance, including top-down attentional control (Arnsten, 2009a; Arnsten, 2011b; Arnsten & Rubia, 2012; Hermans et al., 2014). This tipping point for the effects of stress-induced catecholamines (the apex of the inverted U-shape relation between catecholamines and cognitive performance) has been found to be dependent on catecholamine-driven basal

prefrontal function, and is therefore different for every individual (Arnsten, 2009a; Arnsten 2009b; Cools & D'Esposito, 2011). This implies that a well-dosed manipulation of catecholamine systems could increase attentional control over threat-bias, depending on individual differences in anxiety and baseline PFC function or catecholamine levels (Arnsten, 2006; Arnsten, 2011b).

A pharmacon that has repeatedly been linked to facilitated attentional and working memory functioning is caffeine (Lorist & Tops, 2003). Caffeine works as an antagonist of adenosine receptors. Because adenosine inhibits release of nor-adrenaline and dopamine, caffeine indirectly stimulates dopamine and nor-adrenaline release in subcortical and cortical areas of the brain (Nehlig, Daval, & Debry, 1992). Our interest is in caffeine's agonistic effects on PFC noradrenergic and dopaminergic post-synaptic activation (Sebastião & Ribeiro, 2009) which is thought to mediate how caffeine affects PFC processes such as executive control and working memory, which is in line with the existing literature on caffeine and cognitive performance (Klaassen, de Groot, Evers, Snel, Veerman, Ligtenberg & Veltman, 2013; Haller, Rodriguez, Moser, Toma, Hofmeister, Sinanaj & Lovblad, 2013; Greer, McLean & Graham, 1998). The effects of caffeine consumption on such PFC-regulated cognitive performance are dose-dependent and thereby seem to follow a similar inverted U-shape curve as described for the effects of stress and catecholamines on PFC-regulated performance (Arnsten, 2009a). In particular, in healthy humans, smaller doses (i.e., up to 200 mg) have positive effects on performance, while higher doses (e.g. above 400 mg) have no further benefit for cognitive functioning or even impair performance (Einöther & Giesbrecht, 2013; Pasman, van Baak, Jeukendrup & de Haan, 1995; Smillie & Gökçen, 2010; Wood, Sage, Shuman & Anagnostaras, 2014). The first aim of the present study was therefore to investigate whether caffeine administration affects control over attentional threat bias depending on anxiety levels and basal PFC executive control.

A potential objective electrophysiological measure for PFC regulated attentional control can be derived from spontaneous (also known as "resting-state") activity in electroencephalography (EEG). Previous studies reported that the ratio between power in the theta (4-7 Hz) and the beta (13-30 Hz) frequency bands (theta/beta ratio; TBR) was negatively correlated to self-reported trait attentional control in healthy participants (ACS; Putman, van Peer, Maimari & van der Werff, 2010; Putman, Verkuil, Arias-Garcia, Pantazi & van Schie, 2014; Angelidis, van der Does, Schakel & Putman, 2016) and to objectively assessed attentional control in multiple sclerosis patients with mild cognitive impairment (Keune, Hansen, Weber, Zapf, Habich, Muenssinger, Wolf & Oschmann, 2017) and is positively correlated to stress-induced decline of state attentional control (Putman et al., 2014). Recent studies from our own lab showed that TBR moderated AB to stimuli of different threat-levels (Angelidis et al., 2018; van Son et al., 2018). Also, increased frontal TBR has been related to PFC-mediated attentional and inhibitory functions as seen in attention deficit/hyperactivity disorder (ADHD; for reviews and meta-analyses see Arns, Conners, & Kraemer, 2013; Barry, Clarke, & Johnstone, 2003). Frontal TBR is suggested to reflect inhibitory functional cortical-subcortical interactions (Knyazev, 2007; Schutter & Knyazev, 2012) and to reflect voluntary top-down processes like attentional control carried out by the dorso-lateral PFC (Bishop, 2008; Gregoriou et al., 2014) over automatic bottom-up processes mediated by limbic areas such as the anterior cingulate cortex and the amygdala which facilitate attention to salient information (Hermans et al., 2014).

Interestingly, the administration of methylphenidate as treatment for ADHD improves cognitive

functioning by enhancing dopamine and nor-adrenaline transmission in the PFC (Arnsten, 2006), and was also found to reduce theta and increase beta waves (thus normalized TBR; Clarke et al., 2007; Moreno-García, Delgado-Pardo & Roldán-Blasco, 2015). Additionally, a positive relation was found between TBR reduction caused by methylphenidate administration and ADHD symptom reduction (Loo, Cho, Hale, McGough, McCracken & Smalley, 2013). Again, when referring to the 'inverted U-shape' relation of cognitive performance and catecholaminergic activity, it is expected that effects of methylphenidate are most favourable in individuals with low PFC activity (thus lower attentional control; Devilbiss & Berridge, 2008). The findings that methylphenidate reduces frontal TBR, while ameliorating PFC-mediated cognitive difficulties in ADHD (Arns et al., 2013; Barry et al., 2003; Loo et al., 2013) again support the relation between frontal TBR and executive (attentional) control.

Altogether, frontal TBR is suggested to be a reliable electrophysiological marker of executive and attentional control. This may in particular be the case during the processing of emotional information (Morillas-Romero, Tortella-Feliu, Bornas, & Putman, 2015), making frontal TBR a promising tool to investigate cognitive-affect regulation. This includes the study of the effects of psychopharmacological manipulations on attentional control over salient emotional distracters, which likely depend on baseline PFC functioning. This was the second topic that we aimed to address in the present study.

To assess distraction by negative (threatening) task-irrelevant information on cognitive performance, we chose to use the *Pictorial Emotional Stroop Task (PEST).* The emotional Stroop task in its common form presents neutral and emotionally relevant stimuli in different colors. Participants have to indicate the color as fast as possible while ignoring the irrelevant (emotional) content of the stimuli. When the color-naming of emotional stimuli is slower relative to the color-naming of neutral stimuli, emotional interference is said to have occurred, either as a result of inability to inhibit the automatic attentional processing of the stimuli or because a bottom-up threat detection triggers the automatic inhibition of ongoing cognitive and behavioral activity, causing reduced task performance (Algom, Chajut & Lev, 2004; Williams, Mathews & McLeod, 1996; Mogg & Bradley, 2016). Emotional interference by threatening stimuli is most easily demonstrated in people with elevated anxiety and for stimuli of great personal or acute relevance (Williams et al., 1996). In order to sensitively measure interference in a healthy sample, we opted to use a variant of the emotional Stroop task using highly arousing photographical stimuli of threatening and positive scenes. Although attentional avoidance of highly arousing threatening stimuli is also reported, mostly for tasks that measure visual-spatial attention (e.g., Cisler & Koster, 2010; Eysenck et al., 2007) and as a function of trait anxiety and cognitive control levels (Mogg & Bradley, 2016; Angelidis et al., 2018; van Son et al., 2018), we expected to find strong interference in baseline and placebo conditions which should enable to clearly test effects of our psychopharmacological manipulation on attentional control over threat-bias. Also, fear and anxiety modulate the influence of limbic structures such as the amygdala within the salience network. PFC –mediated executive control modulates the manifestation of such emotional and motivational bottom-up processes (Hermans et al., 2014). We therefore also expect interference for threat to be dependent on individual differences in trait anxiety (as also predicted by influential theoretical models and abundantly supported by empirical findings; Mogg & Bradley, 1998, 2016; Bar-Haim et al., 2007; Cisler & Koster, 2010; van Bockstaele et al., 2014), via modulation of bottom-up processes, which will then also likely interact with any

relations with TBR (c.f. Angelidis et al., 2018) or effects of caffeine.

In summary, the goal of the present study was to investigate the effects of a single caffeine administration on threat-bias, taking into account possible moderating effects of frontal TBR and trait anxiety. Since frontal TBR is considered to reflect basal functioning of PFC executive control (and hence possibly catecholamine function) and should therefore be related to individual differences of the catecholamine tipping point, we expected frontal TBR to moderate the effect of caffeine on threat-bias. Furthermore, trait anxiety was expected to further moderate these effects. We used a moderate dose of caffeine in a relatively caffeine-naïve sample (max daily consumption of 100 mg), to prevent influence of caffeine withdrawal effects (Juliano & Griffiths, 2004). We hypothesized that:

I) Increased frontal TBR is related to interference in the *PEST* as measured on baseline or after placebo.

II) A moderate dose of caffeine, moderated by individual differences in frontal TBR should reduce interference as measured with the *PEST*.

III) Trait anxiety interacts with these relations between frontal TBR and interference and the effects of caffeine thereon.

IV) A caffeine-induced reduction of TBR will mediate effects of caffeine on interference in the *PEST*.

These hypotheses were primarily aimed at the threatening stimuli, especially hypothesis III. However, for relations with frontal TBR and caffeine (hypotheses I and II), it is possible that also distraction by positive stimuli and effects of caffeine thereon are moderated by frontal TBR, especially since TBR has been related to reward-motivated biases in cognition (Schutter & van Honk, 2005; Massar et al., 2012; Massar et al., 2014). Therefore, also a condition with positive stimuli was added to the *PEST* in order to assess valence-specificity. These hypotheses were tested as part of a larger study wherein also effects of caffeine on measures of non-emotional working memory were tested (reported elsewhere).

Methods

Participants

Forty female participants (between 18 and 25 years old) recruited at Leiden University took part in this study. The participants were preselected for consuming a maximum of 100 mg caffeine per day (equivalent of about one cup of coffee). Caffeine consumption was assessed via self-report. Exclusion criteria were factors which could likely adversely affect participation or alter effects of caffeine on EEG or attention, including daily smoking, severe physical or psychological dysfunction, and/or the use of psychotropic medication. Participants were asked to abstain from caffeine and alcohol consumption for 12 hours before the start of lab sessions. Informed consent was obtained prior to testing, and participants received a monetary reimbursement for their participation. The study protocol was pre-registered (Clinicaltrials.gov: NCT02940808) and approved by the local medical-ethical review board.

Materials

Questionnaires. Participants completed the trait version of the State-Trait Anxiety Inventory (STAI-t; Spielberger, 1983; Van der Ploeg, Defares & Spielberger, 1980) and the Attentional Control Scale (ACS; Derryberry & Reed, 2002; Verwoerd, de Jong, &Wessel, 2006). The STAI-t assesses trait anxiety (20 items, range 20-80; Cronbach's alpha in the current study = 0.85), by indicating their agreement with items like 'I feel nervous and restless' and 'I have disturbing thoughts' on a four-point Likert scale. The ACS assesses self-reported attentional control in terms of attentional focus, attentional switching and the capacity to quickly generate new thoughts (20 items, range 20-80; Cronbach's alpha in present study = 0.86), by indicating agreement with items like 'I can quickly switch from one task to another' and 'I have a hard time concentrating when I'm excited about something'.

Caffeine. Participants orally consumed either one capsule containing 200 mg of caffeine or an undistinguishable placebo capsule containing a filler only. A capsule was administered during a second and third test session, while no capsule was administered during the first test session which served as a baseline condition (see below). Thus, there were three test sessions in total, all separated by approximately one week. The order of administration of the capsules during the second and third session was counterbalanced and randomized, and researchers and participants were blind to the contents of the capsules. Caffeine and placebo capsule preparation, labelling and blinding was done by the pharmacy of the Leiden University Medical Center (LUMC).

Pictorial Emotional Stroop Task (PEST) stimuli. For the Pictorial Emotional Stroop task (*PEST*), 72 pictures[1] (24 per test-day) were used from the International Affective Picture System (IAPS, Center for the Study of Emotion and Attention, 1999), a standardized set of emotion eliciting, colour pictures with normative ratings for valence and arousal. Of these pictures, per test-day, eight were categorized as positive (e.g. people enjoying sports), eight as negative (almost all depicting cues to immediate threat to bodily integrity, e.g. mutilated bodies, interpersonal attack and dangerous animals) and eight as neutral pictures (e.g., a towel). The pictures were subjectively matched on colour and composition. The pictures were selected according to the ratings for valence and arousal (scale 1-9; valence 1: very unpleasant to 9: very pleasant and arousal scales; 1: not arousing at all to 9: very arousing) provided by Lang et al (2005). The mean valence score over all test moments for positive stimuli was $M = 7.22$ ($SD = 1.54$), neutral $M = 5.00$ ($SD = 1.16$) and for negative stimuli $M = 2.42$ ($SD = 1.54$); the mean arousal scores were $M = 5.33$ ($SD = 2.21$), $M = 2.70$ ($SD = 1.91$) and $M = 6.33$ ($SD = 2.21$), respectively.

EEG recording and software. Recordings for frontal theta and beta activity were obtained from the Fz, F3, and F4 10/20 positions using Ag/AgCl electrodes of the ActiveTwo BioSemi system (BioSemi, The Netherlands). Electrodes placed on the left and right mastoids were used for offline re-referencing of the scalp signals to the mastoid signals. The *PEST* and questionnaires were programmed and presented using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA).

Procedure

General Procedure. Participants were tested on three separate days. Each of the three lab sessions was separated by approximately one week ($M = 7.7$ days, $SD = 2.5$). On the first testing day (will be referred to as 'baseline results') participants completed questionnaires including demographics, ACS and STAI-t. In addition, baseline EEG was measured to provide a trait-like measure for TBR (see Angelidis et al., 2016 and Keune et al., 2017 for re-test reliability of TBR which ranged between $r = 0.86$ and $r = 0.93$). Baseline TBR as measured during this first session will be used for all analyses of baseline TBR in this paper. Participants were then familiarized and practiced with tasks measuring different aspects of cognition (besides the *PEST*, these were a measure of attentional control for non-emotional processing and a working memory task for non-emotional processing; these outcome measures are used for different research questions that are reported elsewhere). Participants completed these tasks on the first day to reduce the occurrence of learning effects between drug-testing sessions and to provide an indication for baseline performance. Hypotheses for caffeine administration were tested by comparing the results for the cross-over drug-testing days 2 and 3.

During the second testing day, participants had to complete short questionnaires assessing their current alertness, fatigue, arousal and attentional control, Participants then received an eight-minute recording of spontaneous (resting-state) EEG and eye blink rate (EBR; reported elsewhere) in alternating one-minute blocks of eyes open/closed (reported elsewhere). Subsequently, participants ingested a capsule containing either caffeine (200 mg) or placebo (double-blind, randomized administration). As it takes some time for caffeine to affect CNS activity after oral administration (Nehlig, Daval, & Debry, 1992), the participants did some passive recreation (e.g., read magazines) for 30 minutes. This was again followed by the same eight-minute recording of spontaneous (resting-state) EEG and EBR. Finally, participants completed the same cognitive tasks as they completed on the first day. On the third testing day, the testing protocol of the second day was repeated, except that the other, remaining caffeine (200 mg) or placebo capsule was administered.

To examine whether blinding was successful, debriefing interviews were held at the end of the final lab session in which participants were asked to guess which capsule they had consumed in which session. Additionally, participants were asked to rate how certain they were that their guess was correct, on a scale of 1 ("Not certain at all") to 10 ("Very certain").

PEST. During the *PEST*, participants sat at a distance of 70 cm from the screen on which the stimuli were presented. The task consisted of 24 practice and 96 test trials. Every picture was presented in a random order with 32 positive, 32 negative and 32 neutral trials. Each trial started with an inter-trial interval (ITI) of 2000 ms. The ITI was followed by a picture with a height of 10.2 cm and width of 13.6 cm that was presented in the center of a 30 cm x 50 cm grey screen. After 200 ms, a coloured square of 1.3 cm by 1.3 cm was superimposed on the picture. The coloured squares were presented for 1800 ms (irrespective of response time) and were randomly chosen from three possible options (red, yellow, or blue) on each trial. For each picture, a coloured square appeared once in each of four possible locations: either 1.5 cm from the two edges of the left upper corner, right upper corner, left bottom corner, or right bottom corner of the picture. The participants were asked to indicate as fast as

possible without making too many mistakes the colour of the square with same coloured buttons using the index, middle or ring finger of their dominant hand using buttons of a response box (Psychology Software Tools, Pittsburgh, PA).

Data Processing

PEST data pre-processing. Incorrect responses were excluded from analyses. Color discrimination was measured in milliseconds and individual reaction times (RTs) that were shorter than 300 ms or longer than 1200 ms were defined as outliers and removed from the data. Secondly, individual RTs that deviated more than 2.5 standard deviations from the individual RT mean after this first filtering were also defined as outliers and were removed. This resulted in a total average percentage of 7.76% trials removed. Interference scores were calculated per condition separately for positive and negative trials. Interference scores were calculated for positive trials by distracting mean RTs of the neutral condition from mean RTs of the positive condition, and negative interference scores were calculated by distracting mean RTs of the neutral condition from mean RTs of the negative condition. Positive interference scores reflect longer RTs for trials with emotional pictures (or increased cognitive responding to emotional pictures) and negative scores reflect shorter RTs for trials with emotional pictures (or decreased processing of emotional pictures).

EEG pre-processing. Data processing was done using Brain Vision Analyzer V2.0.4 (Brain Products GmbH, Germany). Data was high-pass filtered at 0.1 Hz, low-pass filtered at 100-Hz and a 50-Hz notch filter was applied. The data was automatically corrected for ocular artifacts (Gratton, Coles & Donchin, 1983) in segments of 4 seconds. Fast Fourier transformation (Hamming window length 10%) was applied to calculate power density for the beta (13-30 Hz) and theta (4-7 Hz) band. Our interest was the power density average of the frontal electrodes and power density average of the F3, Fz and F4 positions as in Putman et al. (2010; 2014) and Angelidis et al. (2016; 2018), therefore these frontal averages were calculated for both the beta and theta band. Frontal TBR was calculated by dividing the frontal theta by frontal beta power density. A high frontal TBR reflects relatively more theta than beta power. Frontal TBR values were non-normally distributed and therefore log-normalized with a log10 transformation.

Analyses

The main outcome variables of interest for the *PEST* are the interference scores. All hypotheses and follow-up tests were tested using repeated measures ANOVAs, univariate ANOVAs, paired sample t-tests, Pearson's correlations and simple slope analyses. Analyses for the influence of TBR were done using baseline TBR. For effects of Drug on TBR, we used the pre- and post-administration TBRs for placebo and caffeine conditions. All analyses reported were repeated controlling for contraceptive use and all statistical tests that were significant in the primary analyses remained significant when controlling for this factor. These secondary analyses with this factor are therefore not reported. Because the design of our study already controls for the order of Drug condition (counterbalancing of order and the inclusion of a baseline day), our primary analyses are done without also

adding statistical control for this design-controlled factor; this results in the statistically most powerful and straightforward analysis for this design. We post-hoc also re-ran the crucial analyses controlling for the factor Order. Because including this factor never influenced the significance of the relevant tests, we do not report those secondary analyses. Furthermore, we measured state anxiety using the STAI-state questionnaire (Spielberger, 1983; Van der Ploeg, Defares & Spielberger, 1980) on every testing day before capsule administration and before cognitive testing. State anxiety did not change as a function of Drug condition and time of measurement and results remained the same when including it as a covariate, therefore state anxiety will not be further reported. Finally, as secondary analyses, relations between STAI-t, ACS and TBR were assessed. Because it has been previously found that all three variables correlated significantly with each other, we report partial correlations between TBR and STAI-t or ACS, controlling for each other to control confounding (c.f. Putman et al., 2010, Putman et al., 2014; Angelidis et al., 2016). A two-sided statistical alpha of 0.05 was used throughout.

Results

Participants

Visual inspection before data analysis showed that EEG data of two participants were of bad quality and these participants were removed from all analyses. Remaining participants (N = 38) had a mean age of 21.90 years (SD = 2.05, range: 18-25) mean STAI-t score was 34.6 (SD = 6.7, range 23-53). The mean frontal TBR of the remaining participants that was measured during resting state on the first testing day (baseline results) was 1.25 (SD = 0.63, range 0.49-2.60 [non log-normalized]). Participants had an average caffeine consumption of approximately 53 milligram per day. Twenty-nine of the 38 participants (76%) indicated to use either oral contraceptives or a hormonal intra-uterine device.

PEST results

The average number of errors out of 96 trials was 3.97 (SD = 5.25) in the baseline condition, 3.34 (SD = 2.39) in the caffeine condition and 3.71 (SD = 2.18) in the placebo condition. Mean RTs and SDs per trial-type per condition and interference scores of the *PEST* are presented in **Table 2**.

Table 2. *Mean RTs and interference scores (standard deviations between parentheses) in milliseconds for the Pictorial Emotional Stroop task in the conditions 'baseline results', 'placebo' and 'caffeine' (N = 38).*

	Condition	*Neutral*	*Positive*	*Negative*
RT	Baseline	586 (82)	609 (89)	636 (97)
	Placebo	557 (78)	564 (81)	591 (93)
	Caffeine	544 (61)	559 (67)	582 (72)
Interference	Baseline		22 (32)	50 (38)
	Placebo		7 (27)	34 (31)
	Caffeine		14 (20)	37 (28)

Note: RT= reaction time. All interference scores, for baseline, placebo and caffeine conditions, were different from 0 with $p < 0.001$. All interference scores for negative pictures were significantly larger than for positive pictures with $p < 0.001$. Test-retest correlations of positive interference scores in the placebo condition with those in the caffeine condition were $r = 0.318$, $p = 0.058$ and correlations of negative interference scores in placebo condition with those in the caffeine condition were $r = 0.353$, $p = 0.035$. The interference scores in caffeine or placebo condition did not correlate significantly with those in baseline condition.

Baseline PEST interference scores

We first analyzed the baseline interference scores using a repeated measures analysis of variance (RM ANOVA) with Valence (interference scores for positive and negative stimuli) as the within-subjects factor. A main effect of Valence was found, $F(1,37) = 16.49$, $p < 0.001$, $\eta p^2 = 0.31$, indicating larger interference for negative compared to positive stimuli. Follow-up *t*-tests showed that for this baseline data, both the interference score for positive stimuli ($t(1,37) = 4.97$, $p < 0.001$) as well as negative stimuli ($t(1,37) = 8.09$, $p < 0.001$) were significantly different from 0.

Moderation analyses for the role of frontal TBR and trait anxiety at baseline

Next, we investigated whether baseline frontal TBR moderated interference for positive versus negative stimuli, by adding TBR as covariate to the RM ANOVA. No significant main effect was found for frontal TBR, $F(1,36) = 0.46$, $p = 0.502$, $\eta p^2 = 0.013$, and there was no moderation effect for frontal TBR on Valence (interference for positive stimuli vs negative stimuli), $F(1,36) = 0.55$, $p = 0.465$, $\eta p^2 = 0.015$. This rejects hypothesis I for the baseline condition: TBR, without STAI-t, does not moderate *PEST* performance.

Furthermore, we investigated the role of trait anxiety on the TBR × Valence interaction, by adding STAI-t as a covariate to the model. No significant main effect of TBR, $F(1,34) = 0.88$, $p = 0.356$, $\eta p^2 = 0.025$, or TBR × STAI-t interaction, $F(1,34) = 1.25$, $p = 0.271$, $\eta p^2 = 0.036$ was found. However, a significant frontal TBR × STAI-t × Valence interaction was found, $F(1,34) = 4.95$, $p = 0.033$, $\eta p^2 = 0.127$.

To further test this three-way interaction; interference scores for negative and positive stimuli were tested separately in univariate ANOVAs, again adding frontal TBR and STAI-t as covariates to the model. No main effect of TBR was present for interference for positive stimuli, $F(1,34) = 0.32$, $p = 0.574$, $\eta p^2 = 0.009$, or interference for negative stimuli, $F(1,34) = 0.98$, $p = 0.328$, $\eta p^2 = 0.028$. Also, no three-way interaction of TBR × STAI-t for interference for positive stimuli was found, $F(1,34) = 0.08$, $p = 0.778$, $\eta p^2 = 0.002$, but a trend level three-way interaction effect was present for interference for negative stimuli, $F(1,34) = 3.98$, $p = 0.054$, $\eta p^2 = 0.105$. Because the results indicated a near-significant moderation of interference for negative stimuli by the frontal TBR × STAI-t interaction, we conducted a simple slopes analysis for the dependent variable of interference for negative stimuli (Aiken, West & Reno, 1991) to illustrate this interaction, see **Figure. 2.1**. We performed these follow-up analyses even though the interaction just failed to reach significance, in order to provide the necessary information for later comparison between baseline *PEST* performance and placebo *PEST* performance. These analyses revealed that the frontal TBR × STAI-t interaction was different for individuals with low STAI-t (1 SD below the mean; $\beta = -19.22$, $t(1,34) = -1.18$, $p = 0.24$) mean STAI-t ($\beta = 2.99$, $t(1,34) = 0.25$, $p = 0.80$) and high STAI-t (1 SD above the mean; $\beta = 25.19$, $t(1,34) = -1.55$, $p = 0.13$). As can be seen, the trend-level effect of TBR × STAI-t is such that for low STAI-t people, low TBR (1 SD below the mean) is associated with high interference for negative stimuli, but interference is lower for high TBR (1 SD above the mean). For people with high STAI-t, the influence of TBR is reversed with less interference for low compared to high TBR. Thus, although the crucial interaction is only just above the statistical alpha of .05, this rejects hypothesis III for the baseline condition.

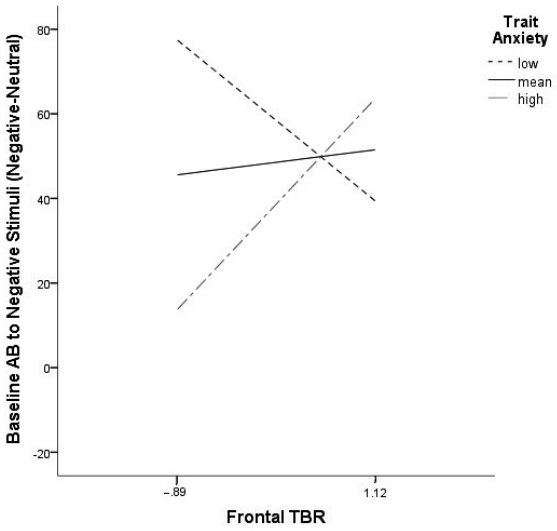


Figure 2.1. Simple slopes for the moderation of trait anxiety on the effect of Ln-normalized frontal EEG on negative interference (AB = attentional bias) in the PEST baseline results frontal TBR = Log-normalized theta/beta ratio.

Placebo versus Caffeine

PEST: Placebo versus Caffeine. To investigate the effects of caffeine on *PEST* responding, interference scores were analyzed using a Drug-type (2; placebo vs caffeine) × Valence (2; positive vs negative interference scores) repeated measures ANOVA. No main effect was found for Drug-type, $F(1,37) = 0.20$, $p = 0.65$, $\eta p^2 = 0.005$. We again found a main effect of Valence, $F(1,37) = 34.49$, $p < 0.001$, $\eta p^2 = 0.48$, but no interaction effect was found between Drug-type and Valence, $F(1,37) = 0.03$, $p = 0.87$, $\eta p^2 = 0.001$.

Moderation analyses for the role of frontal TBR and trait anxiety, Placebo versus Caffeine. A Mahalonobis distance test revealed two significant bivariate outliers for the relationship between frontal TBR and *PEST* interference in the placebo and caffeine conditions (D^2 (2,36) = 10.01; $p = 0.007$; D^2 (2,36) = 10.87; $p = 0.004$). These cases were removed for all further analyses on *PEST* data.

To test the role of frontal TBR in this model, again a Drug-type × Valence (2 × 2) repeated measures ANOVA was performed with frontal TBR (baseline) as a covariate to the model. No main effect of TBR, $F(1,34) = 0.88$, $p = 0.354$, $\eta p^2 = 0.025$), or interaction effect was found for Drug-type × TBR, $F(1,34) = 0.80$, $p = 0.376$, $\eta p^2 = 0.023$). There was a significant Drug-type × TBR × Valence interaction, $F(1,34) = 7.95$, $p = 0.008$, $\eta p^2 = 0.19$. To

follow up on this interaction, separate Valence x TBR ANOVAs were performed for placebo and caffeine conditions. Both showed no significant main effects for TBR or significant TBR x Valence interactions. This rejects hypothesis I for both placebo and caffeine conditions separately: TBR, without STAI-t, does not moderate *PEST* performance.

Also, post-hoc correlations were performed between TBR and contrast scores of interference between Drug-type condition (interference in placebo condition minus interference in caffeine condition) separately for interference for negative and positive stimuli to directly assess effects of Drug on relations between TBR and *PEST* performance; higher TBR was significantly related to lower interference scores for negative stimuli in the placebo compared to the caffeine condition (r = -0.37, p = 0.029), but there was no significant correlation for this contrast for interference scores for positive stimuli (r = 0.17, p = 0.313). This confirms hypothesis II for threatening stimuli only: caffeine reduces *PEST* interference for negative stimuli in low TBR. In high TBR, caffeine increases interference for negative stimuli.

To see whether trait anxiety has an effect on this Drug-type × Valence × frontal TBR interaction, the Drug-type × Valence repeated measures ANOVA was performed with frontal TBR and STAI-t as covariates in the model. No main effect of TBR regardless of valence $F(1,32) = 1.67$, $p = 0.206$, $\eta p^2 = 0.049$, or interaction effect regardless of valence was found for TBR × STAI, $F(1,32) = 1.26$, $p = 0.270$, $\eta p^2 = 0.038$). However, a significant interaction was present for frontal TBR × Drug-type × STAI-t × Valence $F(1,32) = 9.49$, $p = 0.004$, $\eta p^2 = 0.23$.

To investigate separate effects of positive and negative stimuli, two rm ANOVAs were conducted with positive or negative interference scores as dependent variables, using Drug (2) as the within-subject factor and TBR and STAI-t as covariates. The interaction of frontal TBR × STAI-t × Drug-type was not found for the positive interference score, $F(1,32) = 0.94$, $p = 0.340$, $\eta p^2 = 0.03$, but was present for the negative interference score, $F(1,32) = 5.77$, $p = 0.022$, $\eta p^2 = 0.15$ Thus, hypothesis III concerning effects of caffeine is confirmed for negative interference only.

To clarify this complex four-way interaction and its constituent three-way interactions, additional simple slope analyses with interference for negative stimuli as a dependent variable were conducted separately for the caffeine and the placebo condition. It was found that TBR was negatively related to interference for negative stimuli for low STAI-t (1 SD below the mean; β = -47.19, $t(1,32) = -3.77$, $p = 0.001$) and mean STAI-t (β = -20.40, $t(1,32) = -2.23$, $p = 0.033$), whereas it was positive and not significant for high STAI-t (1 SD above the mean; β = 6.40, $t(1,32) = 0.50$, $p = 0.619$) see **Figure 2.2a**. As can be seen, the results for placebo are comparable to the baseline results (interference scores are overall lower for high TBR now): for low STAI-t participants, low TBR is associated with high interference for negative stimuli, but interference is lower for high TBR. For people with high STAI-t there seems little effect of TBR.

For the Caffeine condition, univariate ANOVA did not show a main effect of TBR, $F(1,34) = 0.18$, $p = 0.670$, $\eta p^2 = 0.005$. Also, the TBR × STAI-t ×Valence interaction was not significant, $F(1,34) = 0.19$, $p = 0.665$, $\eta p^2 = 0.006$. Simple slope analyses showed no effects of TBR for low STAI-t (β = 0.43, $t(1,32) = 0.03$, $p = 0.97$) mean STAI-t (β = 4.51, $t(1,32) = 0.46$, $p = 0.65$) or high STAI-t (β = 8.59, $t(1,32) = 0.63$, $p = 0.53$) see **Figure 2.2b**. The influences of

individual difference variables that were observed in the placebo condition are absent with all participants showing moderate interference scores for negative stimuli.

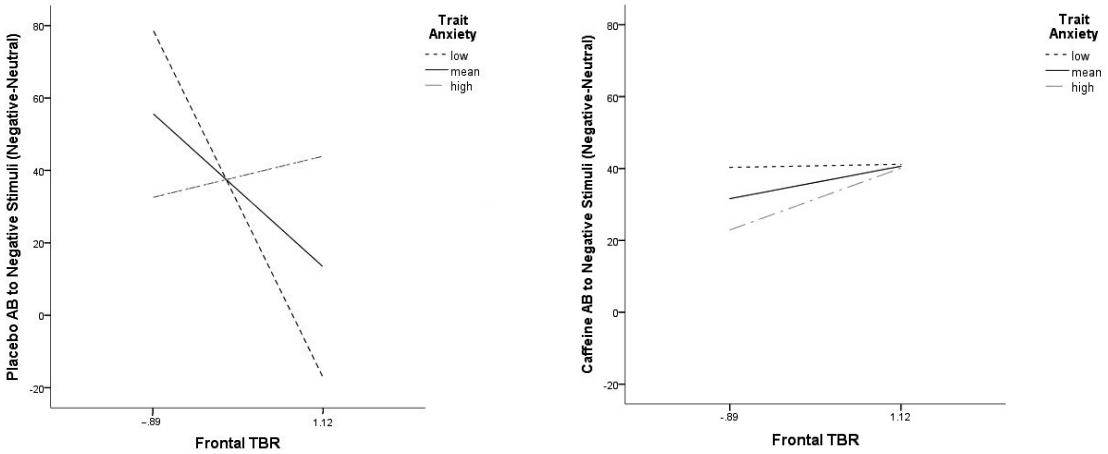


Figure 2.2ab. Simple slopes for the moderation of STAI-t on the effect of Ln-normalized frontal EEG on negative interference in the EST after consumption of placebo (a:left) or caffeine (b:right). Frontal TBR = Ln-normalized frontal theta/beta ratio. In the placebo condition, increased frontal TBR was associated with stronger negative interference; an effect which was only significant for individuals with lower trait anxiety. No effects were found however in the caffeine condition.

Drug effects on EEG

To examine the effects of caffeine consumption on EEG, we conducted a 2 (Drug) x 2 (Time) rm ANOVA for the pre- and post-administration EEG recording of the second and third session. No effect was found for TBR x Time, $F(1, 37) = 0.130$, $p = 0.721$, $\eta p^2 = 0.003$. Looking at the theta and beta bands separately in further rm ANOVAs for caffeine and placebo separately, caffeine consumption significantly decreased power compared to the placebo condition in the theta band, $F(1, 37) = 20.526$, $p < 0.001$, $\eta p^2 = 0.357$, and in the beta band, $F(1, 37) = 48.297$, $p < 0.001$, $\eta p^2 = 0.566$. To compare theta and beta only at 'post drug administration' between the placebo and caffeine condition, post-hoc paired samples *t*-tests were conducted. Theta was significantly lower after caffeine ($M = 14.76$, $SD = 6.02$), compared to the placebo administration, ($M = 17.86$, $SD = 8.46$; $t(37) = 4.354$, $p <$ 0.001; the descriptives are for the data before log-normalization for a more intuitive appreciation but the statistical

tests were performed on log-nomalized data. Beta was significantly lower as well after caffeine (M = 11.86, SD = 5.29), compared to placebo administration, (M = 15.18, SD = 8.19; $t(37) = 5.328$, $p < 0.001$). As no effects of caffeine were found on TBR, the hypothesized mediation of caffeine's effect on TBR- *PEST* interference cannot be tested and hypothesis IV is rejected.

Secondary analyses

TBR did not correlate significantly with ACS score (partial r = 0.277, p = 0.107) or STAI-t score (partial r = 0.119, p = 0.495) when controlling for one another. There was a trend level bivariate ACS and STAI-t correlation (r = -0.301, p = 0.074).

Drug condition awareness

Of the 38 participants included in the analyses, 33 (86.8%) correctly guessed on which day they consumed caffeine. A binomial test showed that this percentage was significantly above 50% chance level, $p <$ 0.001. Participants reported a mean certainty of making a correct guess of 7.27 on a 1-10 scale (SD = 1.57). Often reported reasons for guessing which capsule was consumed included feeling more awake or alert and noticing physiological changes (e.g., feeling more tense or dizzy) on days on which caffeine was thought to be consumed, in contrast to feeling sleepier or noticing no difference in functioning on days on which placebo was thought to be consumed.

Discussion

This study investigated whether frontal EEG TBR moderates the effect of caffeine on threat-bias. We found a significant interaction effect of TBR with trait-anxiety on interference from negative stimuli in the placebo condition and a near-significant similar effect at baseline. Specifically, higher TBR related to lower interfering effect of negative (threatening) stimuli in the Pictorial Emotional Stroop Task (*PEST*) in low anxious participants. TBR on its own did moderate the effect of caffeine on threat interference, although this effect might have been driven by low anxious participants as TBR and trait anxiety interactively influenced caffeine effects on *PEST* performance: caffeine administration had opposite effects on threat-interference for people with low and high TBR (high and low PFC functioning) and low or high trait anxiety, effectively cancelling out individual differences and a main effect for caffeine.

Our first hypothesis that TBR would be related to interference in the *PEST* was not confirmed as results were only present for low anxious individuals. This interaction is however in line with many studies of the past decades: several studies have reported that attentional control (as measured with self-report) and trait anxiety predicted attentional processing of threat (e.g. Bardeen & Orcutt, 2011; Derryberry & Reed, 2002; Reinholdt-Dunne et al., 2009; Schoorl et al., 2014; Taylor et al., 2016) and recently we reported the same for TBR as measure of attentional control (Angelidis et al., 2018). In low anxious individuals, our data indicate that the relation of TBR with interference was valence-specific; the effect was only present in arousing-threatening images, but not in arousing positive images. Note that this is to be expected given the interaction with trait anxiety: much research has established relations between anxiety and threat bias, hardly ever with bias toward positive stimuli (Mogg &

Bradley, 1998, 2016; Bar-Haim et al., 2007; Cisler & Koster, 2010; van Bockstaele et al., 2014, Angelidis et al., 2018). The role of TBR (as basal PFC functioning) had not previously been investigated using both threatening and positive images. Some studies looked only at negative arousal. It was for instance reported that TBR predicted reductions in self-reported attentional control after a socially threatening stress-manipulation (Putman et al., 2014). Also, higher TBR was related to less effective spontaneous down-regulation of the negative affect evoked by arousing negative stimuli (Tortella-Feliu, Morillas-Romero, Balle, Llabres, Bornas & Putman, 2014). Another study (Putman et al., 2010) did include positive and negative stimuli and reported that TBR was related to a contrasting effect on RTs from fearful and happy faces in an emotional go-no go task, but contrary to the current study, this study did not compare these arousing conditions with a condition with neutral stimuli and therefore does not allow any firm conclusions for the specific processing of negative and positive stimuli. The current study directly tested and showed that the relation is specific for negative information, in interaction with trait anxiety. This finding implies that TBR possibly reflects the interplay between an executive attention-network and a salience network that is more active in states of negative arousal (Hermans et al., 2014; Kohn, Hermans & Fernández, 2017). The current study showed that TBR was not related (alone or in interaction with trait anxiety) to a bias for our positive stimuli, but perhaps future studies could further test the valence-specificity of TBR's relation to attentional bias using different and maybe more arousing positive stimuli (e.g. erotic stimuli as in Putman & Berling, 2010).

Data for the baseline and placebo conditions showed that TBR was negatively related to interference from threatening pictures, again only in low anxious participants. When comparing our baseline and placebo results, the relation between TBR and interference effects might seem to deviate looking at the direction of the mean slopes for interference for negative stimuli. However, there were no significant main effects of TBR and when comparing these results one should only consider the pattern of interaction between TBR and STAI-t (which was highly significant in the placebo condition and only just missed significance in the baseline condition).This comparison shows that in baseline and placebo conditions alike the pattern is such that for low TBR, low anxious people show higher interference for threat than high anxious participants and this pattern is the reverse in people with high TBR. We therefore conclude that our study shows a quite stable pattern of TBR-anxiety interactions in our sample when not influenced by caffeine.

It has previously been reported for other variants of the Emotional Stroop Task (EST), that lower cognitive control over automatic processing of threat information resulted in higher interference for threatening words (Jha, Krompinger & Baine, 2007; Putman et al., 2012, for a review see Bar-Haim et al., 2007). TBR (negatively related to attentional control; see Lansbergen, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse. 2011; Zhang, Roodenrys, Li, Barry, Clarke, Wu, et al., 2017; Keune et al., 2017; Putman et al., 2010, Putman et al., 2014; Angelidis et al., 2016) was therefore expected to correlate positively with interference in the *PEST*. Our results demonstrated a negative relation between TBR and interference for threat (in low anxious individuals) with individuals with higher TBR showing less interference or even negative interference scores on the *PEST*. Although studies using an EST have often found an interference effect of threatening words (e.g. Amir, Elias, Klumpp & Przeworski, 2003; Putman et al., 2012; Gorlin & Teachman, 2015) other EST studies have reported response facilitation (faster color naming responses to threatening than neutral stimuli) which is usually interpreted as reflecting attentional avoidance of

the threatening content of the stimuli (e.g. Dandenau & Baldwin, 2004; Egloff & Hock, 2001; Edelstein & Gillath, 2008; Putman, Hermans & van Honk, 2004). Similar attentional avoidance has often been reported for spatial attention tasks for emotional information (for overviews see Cisler & Koster, 2010; Mogg & Bradley, 2016), where the avoidant response is evident from slower responses to trials where threatening stimuli cue the location of a subsequent target location (e.g. Amir, Foa, & Coles, 1998; Koster, De Raedt, Goeleven, Franck & Crombez, 2005; Mogg, Bradley, Miles, & Dixon, 2004; Schoorl et al., 2014; Wald et al., 2011).

Such attentional avoidance in spatial tasks seems to occur mostly for very highly threatening (pictorial) stimuli and/or stimuli that are of a phobic nature to anxious participants (see Mogg & Bradley, 2016). Many of the stimuli that we used were also highly threatening pictures cueing direct and acute threat to well-being (e.g. mutilated bodies and attacking animals) which seem more likely to evoke attentional avoidance in anxious people (anxiety is negatively related to attentional control). The model by Mogg and Bradley (1998; 2016) predicts that anxious hypervigilance is more likely to be evoked by mild threatening pictures whereas low levels of anxiety and high levels of cognitive control should be related to adaptive vigilance toward survival-relevant highly threatening pictures. Indeed, our healthy sample as a whole demonstrated strong average interference score of 50 and 34 ms for baseline and placebo conditions to our threat pictures. The finding that for low anxious individuals, higher TBR was associated with reduced interference is as predicted from this theoretical framework and is in line with recent findings from two studies in our lab, similarly reporting more vigilance/less avoidance for such highly threatening pictures in people with low TBR (Angelidis et al., 2018; van Son et al., 2018). The spatial dot-probe task and emotional cueing task that previously demonstrated anxious attentional avoidance of graphic threat seem greatly influenced by response facilitation or a slow-down in responding when attention needs to be disengaged from a threatening cueing stimulus preceding the target response (Koster, et al., 2005; Koster, Crombez, Verschuere & De Houwer, 2006; Mogg et al., 2004) and also overall response slowing has been observed for trials with threatening cues (Koster et al., 2005). This response-slowing in disengagement processes might not be fundamentally different from slowed response in our *PEST*. Especially because influences on disengagement of spatial attention from salient visual information cannot be excluded for the *PEST* since it is not unlikely that the colour targets often appear in another location of the background pictures than the parts that especially draw or hold attention.

One of the purposes of this study was to see whether trait anxiety would moderate the effect of frontal TBR on threat interference. Relations between trait anxiety and automatic influences on attention to threat (as often reported; Mogg & Bradley, 1998, 2016; Bar-Haim et al., 2007; Cisler & Koster, 2010; van Bockstaele et al., 2014) likely result from anxiety's facilitation of bottom-up attentional processing, which is further controlled by prefrontal executive control. The data confirmed such an interaction with trait anxiety; the effect of TBR seemed only to be present in individuals with lower trait anxiety. Studies investigating the specific relation between trait anxiety and executive control have had rather inconsistent results. Derryberry & Reed (2002) reported that attentional control is essentially effective for threat selective attention in highly anxious individuals, and Schoorl et al., (2014) also reported a stronger effect of AC on mildly threatening stimuli in higher anxious individuals suffering from post-traumatic stress disorder (PTSD). More recent data (Angelidis et al., 2018) however, suggest

that the effect of TBR as PFC-regulated executive control was mainly present in low trait anxious individuals (for highly threatening stimuli). These results are in line with the current study. However, the Dot Probe task that was used in Angelidis et al. (2018) had separate categories of mild and high threatening stimuli, which was not the case in the *PEST* as presently used, making our results difficult to compare. We therefore refrain from drawing any strong conclusion about the exact role of trait anxiety. For now, we speculate that threat-related stimuli usually involve automated uncontrolled responses (e.g. Ledoux, 1995), likely especially in high anxious individuals (Bar-Haim et al., 2007; Cisler & Koster, 2010) and therefore individual differences in attentional control might have only limited influence in high anxious people. Nevertheless, we conclude that it remains unclear what the role of trait anxiety is in the effects of caffeine administration on control over threat selective attention. Future studies should revisit this issue in designs allowing better control over the influence of anxiety, for instance by preselecting participants on levels of trait anxiety or manipulating state anxiety, as well as target the effect of stimuli of different threat-levels.

No correlation was found between TBR, self-reported attentional control and trait anxiety ACS score or ACS and STAI-t, although a commonly observed negative relation between self-reported attentional control and trait anxiety (e.g., Derryberry & Reed, 2002) was observed as a statistical trend. Previous studies did report relations of TBR with ACS and STAI-t (e.g. Putman et al., 2010; Putman et al., 2014; Angelidis et al., 2016). Two other studies however did not replicate the TBR - ACS relation (Tortella-Feliu et al., 2014; Angelidis et al., 2018). Absence of a TBR-ACS relation in the current study is possibly explained by the fact that the current participant sample was pre-selected on having a very low caffeine usage, possibly making it difficult to compare this sample to previously used groups of healthy subjects, since caffeine is thought to affect executive cognitive function (Klaassen et al., 2013; Haller et al., 2013; Greer et al., 1998) and we ourselves suggested that it might affect TBR. The occasional absence of the TBR – ACS relation and various findings of relations between TBR and executive processing of typically emotional information (e.g., Tortella-Feliu et al., 2014; Putman et al., 2010; Putman et al., 2014; Angelidis et al., 2018; Schutte, Kenemans & Schutter, 2017) might indicate that TBR mainly represents executive control in emotional contexts such as during threat processing or threat interference (see also Morillas-Romero et al., 2015). Importantly, the current results for TBR's relation with anxious threat-processing and effects of caffeine thereon, support this notion.

Caffeine did not affect TBR, but unexpectedly reduced both theta and beta. Previous literature reported effects of caffeine on separate EEG theta and beta activity (e.g., Kaplan et al., 1997; Landolt et al., 2004; Keane & James, 2008), but mixed results have been found depending on the sample studied (e.g., caffeine non-consumers versus regular consumers), design employed (e.g., acute effects versus long-term consumption), and dose of caffeine administered, making it quite difficult to compare our results to these previous studies. As beta has commonly been found to be related to motor inhibition (e.g. Engel & Fries, 2010), one possible explanation is then that our caffeine manipulation, due to caffeine's generally arousing and motor-behavior increasing effects (Fisone, Borgkvist & Usiello, 2004; for a review see Rivera-Oliver & Díaz-Ríos, 2014) decreased motoric inhibition. Furthermore, having a strong test-retest correlation (Angelidis et al., 2016; Keune et al., 2017), when being measured during resting state, TBR might possibly reflect more structural or tonal aspects of brain organization

compared to the phasic processes that one would expect after such transient and relatively mild psychopharmacological effects as our moderate caffeine administration. Though studies investigating the effects on TBR after ADHD medication suggest otherwise (e.g. see Clarke et al., 2007) and found TBR to change, therefore this issue remains unclear and needs further investigation. More research, possibly controlling for motoric inhibitions, is required for resolving the exact effects of caffeine on the theta and beta bands.

Importantly though, despite the absence of an effect of caffeine on state TBR, baseline TBR of low anxious individuals showed a significant direct relation with responding in the *PEST* and this was clearly influenced by caffeine administration. Participants with low trait anxiety and higher TBR who showed less interference/more facilitation in baseline and placebo conditions showed more interference/less facilitation in the caffeine condition. Contrariwise, participants with lower TBR who showed more threat interference/less facilitation in baseline and placebo conditions showed less interference after caffeine administration. This pattern of responding is in line with the predicted moderation of caffeine's effects by baseline TBR. Given the evidence that lower TBR is related to better prefrontal cortical control (Angelidis et al., 2016; Barry et al., 2003; Keune et al., 2017), and better prefrontal cortical control over the automatic attentional processing of salient threatening stimuli (Putman et al., 2010; Angelidis et al., 2018; van Son et al., 2018) and assuming that such basal prefrontal attentional control is regulated by prefrontal catecholamine levels (Arnsten, 2006; Hermans et al., 2014), the established model of inverted U-shape relations between prefrontal catecholamine activity and cognitive attentional control (Arnsten, 2006; Arnsten, 2009a; Cools and D'Esposito, 2011) would predict just that.

Several studies have already provided evidence for the inverted U-shape effect of caffeine and its relation to PFC moderation of catecholamines (for a review see Dobson and Hunt, 2013). Larger doses of caffeine resulted in poor PFC mediated cognitive functioning (Wood et al., 2014; Kaplan, Greenblatt, Ehrenberg, Goddard, Cotreau & Shader et al., 1997). It was also reported that performance of individuals on short-term memory and attentional tasks depended on caffeine-dose in an inverted U-shape function (Anderson, 1990; Anderson & Revelle, 1983; Gilliland, 1980, Revelle, Humphreys, Simon & Gilliland, 1980). Studies in rats support this notion; rats with lower baseline working memory performance showed a stronger increase in performance when measured PFC dopamine efflux was higher compared to rats with higher initial baseline working memory performance (Phillips, Ahn & Floresco, 2004; Murphy, Arnsten, Goldman-Rakic & Roth, 1996; for a review see Cools & D'Esposito, 2011). Similarly, Aston-Jones & Cohen (2005) found nor-adrenaline levels in the locus coeruleus of monkeys to modulate performance on attentional tasks in the same inverted-U-shaped relation. In the current study, caffeine affected participants with better baseline attentional control (as evident from baseline TBR and baseline/placebo *PEST* performance) in such a way that their performance after caffeine resembled more the baseline/placebo performance of participants with less attentional control. Performance of people with less attentional control resembled more the baseline/placebo performance of people with better attentional control after caffeine administration. Therefore, the results of our study support the notion that effects of caffeine on executive cognitive performance, like catecholamine manipulations, depend on (likely catecholamine-mediated) baseline prefrontal executive performance and indirectly support the notion that effects of caffeine on executive function likely follow an inverted U-shape dose-response relation (Arnsten, 2009a; Einöther & Giesbrecht, 2013; Pasman et

al., 1995; Wood et al., 2014; see Figure 2.3. for an illustration of the hypothesized relation between basal PFC (catecholamine) function, executive performance and our moderate caffeine administration). As stated before, caffeine affects neural processing in several different brain areas (Nehlig et al., 1992; Sebastião & Ribeiro, 2009, van Dort, Baghdoyan, Lydic, 2009). Our study and interpretation of the results is based on caffeine's established effects on prefrontal cortical function. Though it cannot be excluded that caffeine's effects in other brain areas contributed to the results in our study, we believe our results are most compatible with the prefrontally mediated effects that we explain above.

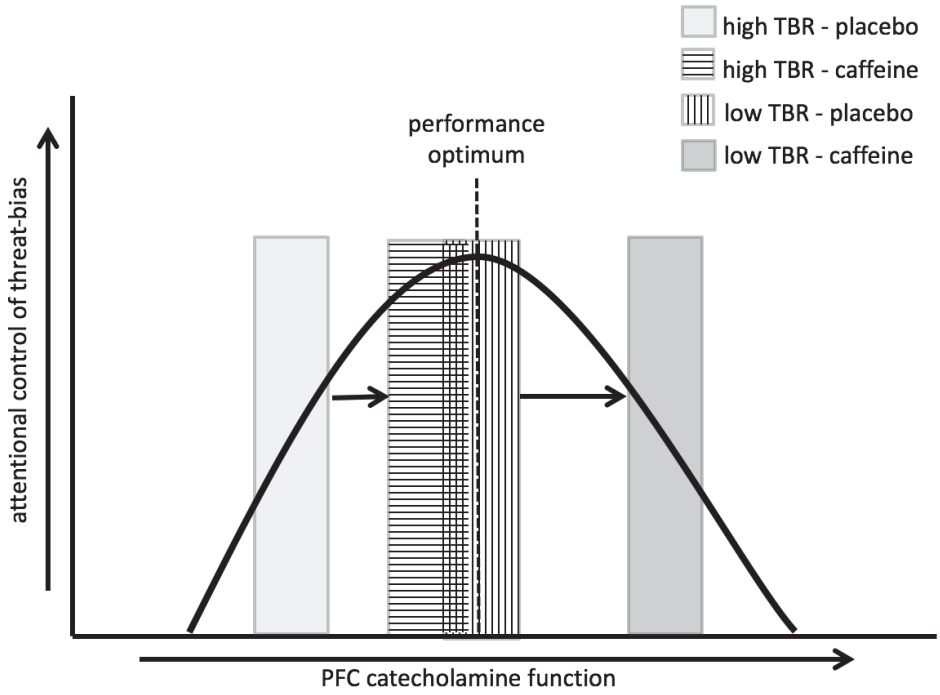


Figure 2.3. The hypothesized inverted U-shape relation between TBR as an indicator of (catecholamine) PFC function and PFC-mediated attentional control (AC) of threat bias and effects of caffeine thereon, as based on the theoretical model of Arnsten (2006; 2009a). Gray-patterned planes represent TBR – drug condition combinations. Trait anxiety influences limbic regulation of bottom-up response tendencies to threat. PFC-mediated executive control further determines the manifestation of selective attention. After placebo, participants with high TBR perform sub-optimally and participants with low TBR perform optimally. After caffeine administration and resulting upregulation of PFC catecholamine function, the high TBR participants move toward the optimal performance that low TBR participants displayed after placebo. The latter participants however, overshoot their optimal performance zone after caffeine's further increase of prefrontal catecholamine function.

To sum up, we aimed to study effects of caffeine on attentional control over threat-bias and how baseline frontal TBR interacts with these effects. Results were as expected; caffeine administration influenced interference in the *PEST*, moderated by baseline TBR, used as a marker of basal PFC executive control, and trait anxiety. Our findings likely confirm previous suggestions that TBR reflects executive control in healthy individuals (Angelidis et al., 2016; Putman et al., 2010, 2014; Angelidis et al., 2018; van Son et al., 2018). Previous reports describe that caffeine up-regulates PFC activity, but has different effects on attentional performance depending on baseline catecholamine activity in the PFC (Arnsten, 2009a; Arnsten 2009b; Cools & D'Esposito, 2011). Including measures that reflect basal PFC regulated executive control might thus improve studies of effects of caffeine on prefrontal cognitive processing, making TBR a possibly useful tool in psychopharmacological studies, e.g. when investigating the role of catecholamines in attentional performance. Moreover PFC-mediated attentional control was found to have a key function in the processing of emotional information such as selective attention to threat or cognitive appraisal (Ochsner, Silvers, & Buhle, 2012), which is usually impaired in different types of psychopathology (Etkin & Wager, 2007; Joormann & Gotlib, 2010), therewith using TBR can be beneficial when studying for example threat selective attention and emotion regulation.

Potential limitations of this study include that the threat-level of the pictures used in the *PEST* was not manipulated. As discussed above, whether participants direct attention toward or away from a stimulus, depends on whether stimuli are highly or mildly threatening (Angelidis et al., 2018; van Son et al., 2018; Mogg & Bradley, 2016; Bar-Haim et al., 2007). Follow-up studies should therefore explicitly target the effect of stimuli of different threat-levels. Also, although this study did control for contraceptive use, in a design like ours with three lab visits in two weeks, it is fairly difficult to control for participant's menstrual cycle phase, which was therefore not controlled. Furthermore, participants guessed accurately whether caffeine or placebo was administered and were therefore not blind to the manipulation – at least at the end of the second drug/placebo testing session though not necessarily during *PEST* performance. Theoretically, results might thus have been affected by an expectancy bias due to the participant's knowledge of whether caffeine was given or not. Given that interference as measured by the *PEST* is relatively implicit, and the finding that the effect of caffeine was solely present when including a physiological measure, we assume it to be unlikely that the non-blindness of our study has influenced the final results. However, this finding demonstrates a larger issue in studies of caffeine administration and many other psychopharmacological experiments in human subjects. Such studies rarely measured or reported whether participants were aware of the drug they had received in a manner similar to ours (see Ahluwalia & Herrick, 2015). Our inclusion of debriefing the participants about condition awareness should thus foremost be seen as a methodological strength and future studies should surely implement this methodological control.

In conclusion, this study supports the notion of frontal TBR as an electrophysiological marker for executive control and is possibly a useful approximation of individual differences in baseline prefrontal catecholamine function that could be used when, for example, investigating catecholamine manipulation. It also confirms that caffeine can affect attentional control over automatic threat-attention depending on baseline individual differences.

References

Ahluwalia, N., and Herrick, K. (2015). Caffeine intake from food and beverage sources and trends among children and adolescents in the United States: review of national quantitative studies from 1999 to 2011. *Advances in Nutrition: An International Review Journal*, *6*(1), 102-111.

Aiken, L. S., West, S. G., & Reno, R. R. (1991). Multiple regression: Testing and interpreting interactions. Sage.

Algom, D., Chajut, E., and Lev, S. (2004). A rational look at the emotional stroop phenomenon: a generic slowdown, not a stroop effect. *Journal of experimental psychology: General, 133*(3), 323.

Amir, N., Foa, E. B., and Coles, M. E. (1998). Automatic activation and strategic avoidance of threat-relevant information in social phobia. *Journal of Abnormal Psychology, 107*(2), 285-290.

Amir, N., Elias, J., Klumpp, H., and Przeworski, A. (2003). Attentional bias to threat in social phobia: facilitated processing of threat or difficulty disengaging attention from threat? *Behaviour research and therapy*, *41*(11), 1325-1335.

Anderson, K. J. (1990). Arousal and the inverted-u hypothesis: A critique of Neiss's" Reconceptualizing arousal.".

Anderson, K. J., and Revelle, W. (1983). The interactive effects of caffeine, impulsivity and task demands on a visual search task. *Personality and Individual Differences*, *4*(2), 127-134.

Angelidis, A., Hagenaars, M., van Son, D., van der Does, W., Putman, P., Do not look away! Association of frontal EEG theta/beta ratio as a marker for cognitive control with (mal)adaptive attention to stimuli of different threat intensity. *Biological Psychology, 135,* 8-17.

Angelidis, A., van der Does, W., Schakel, L., and Putman, P. (2016). Frontal EEG theta/beta ratio as an electrophysiological marker for attentional control and its test-retest reliability. *Biological Psychology, 121*(Pt A), 49-52.

Arnsten, A. F. (2009a). Stress signalling pathways that impair prefrontal cortex structure and function. Nature reviews. *Neuroscience, 10*(6), 410.

Arnsten, A. F. (2009b). Toward a new understanding of attention-deficit hyperactivity disorder pathophysiology. *CNS drugs*, *23*(1), 33-41.

Arnsten, A.F.T (2011b). Catecholamine influences on dorsolateral prefrontal cortical networks. *Biological Psychiatry, 69*, 89-99.

Arnsten, A. F. T. (2006). Stimulants: Therapeutic actions in ADHD, *Neuropsychopharmacology (Vol. 31,* pp. 2376-2383).

Arnsten, A. F., and Rubia, K. (2012). Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*(4), 356-367.

Arns, M., Conners, C. K., and Kraemer, H. C. (2013). A decade of EEG Theta/Beta Ratio Research in ADHD: a meta-analysis. *J Atten Disord, 17*(5), 374-383.

Aston-Jones, G., and Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu. Rev. Neurosci.*, *28*, 403-450.

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., and van IJzendoorn, I. M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychol Bull, 133*(1), 1-24.

Barry, R. J., Clarke, A. R., and Johnstone, S. J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clin Neurophysiol, 114*(2), 171-183.

Baxter, A. J., Scott, K. M., Vos, T., and Whiteford, H. A. (2013). Global prevalence of anxiety disorders: a systematic review and meta-regression. *Psychological medicine*, *43*(5), 897-910.

Bishop, S. J. (2008). Neural mechanisms underlying selective attention to threat. *Ann N Y Acad Sci, 1129*, 141-152.

Bishop, S. J., Jenkins, R., and Lawrence, A. D. (2007). Neural processing of fearful faces: effects of anxiety are gated by perceptual capacity limitations. *Cereb Cortex, 17*(7), 1595-1603.

Cassady, J. C., and Johnson, R. E. (2002). Cognitive test anxiety and academic performance. *Contemporary educational psychology*, *27*(2), 270-295.

Center for the study of Emotion and Attention, National Institute of Mental Health. (1999). The International Affective Picture System. Gainesville, FL: University of Florida.

Cisler, J. M., and Koster, E. H. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clin Psychol Rev, 30*(2), 203-216.

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., and Johnstone, S. J. (2007). Effects of stimulant medications on the EEG of girls with Attention-Deficit/Hyperactivity Disorder. *Clin Neurophysiol, 118*(12), 2700-2708.

Cools, R., and D'Esposito, M. (2011). Inverted-U–shaped dopamine actions on human working memory and cognitive control. *Biological psychiatry*, *69*(12), e113-e125.

Dandeneau, S. D., and Baldwin, M. W. (2004). The inhibition of socially rejecting information among people with high versus low self-esteem: The role of attentional bias and the effects of bias reduction training. *Journal of Social and Clinical Psychology*, *23*(4), 584-603.

Derakshan, N., and Eysenck, M. W. (2009). Anxiety, Processing Efficiency, and Cognitive Performance New Developments from Attentional Control Theory. *European Psychologist, 14*(2), 168-176.

Derryberry, D., and Reed, M. A. (2002). Anxiety-related attentional biases and their regulation by attentional control. *Journal of Abnormal Psychology, 111*(2), 225-236.

Devilbiss, D. M., and Berridge, C. W. (2008). Cognition-enhancing doses of methylphenidate preferentially increase prefrontal cortex neuronal responsiveness. *Biological psychiatry, 64*(7), 626-635.

Dobson, N. R., and Hunt, C. E. (2013). Pharmacology review: caffeine use in neonates: indications, pharmacokinetics, clinical effects, outcomes. *NeoReviews*, *14*(11), e540-e550.

Edelstein, R. S., and Gillath, O. (2008). Avoiding interference: Adult attachment and emotional processing biases. *Personality and Social Psychology Bulletin*, *34*(2), 171-181.

Egloff, B., and Hock. M. (2001). Interactive effects of state anxiety and trait anxiety on emotional Stroop interference. *Personality and Individual Differences, 31*, 875-882.

Einöther, S. J., and Giesbrecht, T. (2013). Caffeine as an attention enhancer: reviewing existing assumptions. *Psychopharmacology, 225*(2), 251-274.

Etkin, A., and Wager, T. D. (2007). Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry*, *164*(10), 1476-1488.

Engel, A. K., & Fries, P. (2010). Beta-band oscillations—signalling the status quo? *Current opinion in neurobiology, 20*(2), 156-165.

Eysenck, M. W., Derakshan, N., Santos, R., and Calvo, M. G. (2007). Anxiety and cognitive performance: attentional control theory. *Emotion, 7*(2), 336-353.

Gilliland, K. (1980). The interactive effect of introversion-extraversion with caffeine induced arousal on verbal performance. *Journal of Research in Personality*, *14*(4), 482-492.

Fisone, G., Borgkvist, A., & Usiello, A. (2004). Caffeine as a psychomotor stimulant: mechanism of action. *Cellular and Molecular Life Sciences CMLS, 61*(7-8), 857-872.

Gorlin, E. I., and Teachman, B. A. (2015). Inhibitory control as a moderator of threat-related interference biases in social anxiety. *Cognition and Emotion*, *29*(4), 723-735.

Gratton, G., Coles, M. G., and Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and clinical neurophysiology, 55*(4), 468-484.

Gregoriou, G. G., Rossi, A. F., Ungerleider, L. G., and Desimone, R. (2014). Lesions of prefrontal cortex reduce attentional modulation of neuronal responses and synchrony in V4. *Nat Neurosci, 17*(7), 1003-1011.

Greer, F., McLean, C., and Graham, T. E. (1998). Caffeine, performance, and metabolism during repeated Wingate exercise tests. *Journal of applied physiology, 85*(4), 1502-1508.

Haller, S., Rodriguez, C., Moser, D., Toma, S., Hofmeister, J., Sinanaj, I., ... and Lovblad, K. O. (2013). Acute caffeine administration impact on working memory-related brain activation and functional connectivity in the elderly: a BOLD and perfusion MRI study. *Neuroscience, 250*, 364-371.

Hembree, R. (1988). Correlates, causes, effects, and treatment of test anxiety. *Review of educational research*, *58*(1), 47-77.

Hermans, E. J., Henckens, M. J., Joels, M., and Fernandez, G. (2014). Dynamic adaptation of large-scale brain networks in response to acute stressors. *Trends Neurosci, 37*(6), 304-314.

Hou, R., Moss-Morris, R., Risdale, A., Lynch, J., Jeevaratnam, P., Bradley, B. P., and Mogg, K. (2014). Attention processes in chronic fatigue syndrome: attentional bias for health-related threat and the role of attentional control. *Behav Res Ther, 52*, 9-16.

Joëls, M., and Baram, T. Z. (2009). The neuro-symphony of stress. *Nature reviews. Neuroscience*, *10*(6), 459.

Jha, A. P., Krompinger, J., and Baime, M. J. (2007). Mindfulness training modifies subsystems of attention. *Cognitive, Affective, and Behavioral Neuroscience*, *7*(2), 109-119.

Joormann, J., and Gotlib, I. H. (2010). Emotion regulation in depression: relation to cognitive inhibition. *Cognition and Emotion*, *24*(2), 281-298.

Juliano, L. M., and Griffiths, R. R. (2004). A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features. *Psychopharmacology, 176*(1), 1-29.

Kaplan, G. B., Greenblatt, D. J., Ehrenberg, B. L., Goddard, J. E., Cotreau, M. M., Harmatz, J. S., and Shader, R. I. (1997). Dose-dependent pharmacokinetics and psychomotor effects of caffeine in humans. *The Journal of Clinical Pharmacology, 37*(8), 693-703.

Keane, M. A., & James, J. E. (2008). Effects of dietary caffeine on EEG, performance and mood when rested and sleep restricted. Human Psychopharmacology*: Clinical and Experimental, 23*(8), 669-680.

Keune, P. M., Hansen, S., Weber, E., Zapf, F., Habich, J., Muenssinger, J., ... & Oschmann, P. (2017). Exploring resting-state EEG brain oscillatory activity in relation to cognitive functioning in multiple sclerosis. *Clinical Neurophysiology, 128*(9), 1746-1754.

Klaassen, E. B., de Groot, R. H., Evers, E. A., Snel, J., Veerman, E. C., Ligtenberg, A. J., ... and Veltman, D. J. (2013). The effect of caffeine on working memory load-related brain activation in middle-aged males. *Neuropharmacology, 64*, 160-167.

Koster, E. H., Verschuere, B., Crombez, G., and Van Damme, S. (2005). Time-course of attention for threatening pictures in high and low trait anxiety. *Behav Res Ther, 43*(8), 1087-1098.

Kohn, N., Hermans, E. J., and Fernández, G. (2017). Cognitive benefit and cost of acute stress is differentially modulated by individual brain state. *Social cognitive and affective neuroscience*, nsx043.

Koster, E. H., De Raedt, R., Goeleven, E., Franck, E., and Crombez, G. (2005). Mood-congruent attentional bias in dysphoria: maintained attention to and impaired disengagement from negative information. *Emotion*, *5*(4), 446.

Koster, E. H. W., Crombez, G., Verschuere, B., and De Houwer, J. (2006). Attention to threat in anxiety-prone individuals: Mechanisms underlying attentional bias. *Cognitive Therapy and Research, 30*(5), 635-643.

Knyazev, G. G. (2007). Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neuroscience and Biobehavioral Reviews, 31*(3), 377-395.

Kvetnansky, R., Sabban, E. L., and Palkovits, M. (2009). Catecholaminergic systems in stress: structural and molecular genetic approaches. *Physiological reviews, 89*(2), 535-606.

Landolt, H. P., Rétey, J. V., Tönz, K., Gottselig, J. M., Khatami, R., Buckelmüller, I., & Achermann, P. (2004). Caffeine attenuates waking and sleep electroencephalographic markers of sleep homeostasis in humans. *Neuropsychopharmacology, 29*(10), 1933.

Lang, P. J. (2005). International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical report.

Lansbergen, M. M., van Dongen-Boomsma, M., Buitelaar, J. K., and Slaats-Willemse, D. (2011). ADHD and EEG-neurofeedback: a double-blind randomized placebo-controlled feasibility study. *Journal of neural transmission, 118*(2), 275-284.

Ledoux, J. E. (1995). EMOTION - CLUES FROM THE BRAIN. *Annual Review of Psychology, 46*, 209-235.

Loo, S. K., Cho, A., Hale, T. S., McGough, J., McCracken, J., and Smalley, S. L. (2013). Characterization of the theta to beta ratio in ADHD: identifying potential sources of heterogeneity. *Journal of attention disorders, 17*(5), 384-392.

Lorist, M. M., and Tops, M. (2003). Caffeine, fatigue, and cognition. *Brain and cognition, 53*(1), 82-94.

Massar, S. A. A., Rossi, V., Schutter, D. J. L. G., & Kenemans, J. L. (2012). Baseline EEG theta/beta ratio and punishment sensitivity as biomarkers for feedback-related negativity (FRN) and risk-taking. *Clinical Neurophysiology, 123*(10), 1958-1965.

Massar, S. A., Kenemans, J. L., & Schutter, D. J. (2014). Resting-state EEG theta activity and risk learning: sensitivity to reward or punishment? *International Journal of Psychophysiology, 91*(3), 172-177.

Mogg, K., Bradley, B., Miles, F., and Dixon, R. (2004). BRIEF REPORT Time course of attentional bias for threat scenes: Testing the vigilance-avoidance hypothesis. *Cognition and Emotion, 18*(5), 689-700.

Mogg, K., and Bradley, B. P. (1998). A cognitive-motivational analysis of anxiety. *Behaviour Research and Therapy, 36*(9), 809-848.

Mogg, K., and Bradley, B. P. (2016). Anxiety and attention to threat: Cognitive mechanisms and treatment with attention bias modification. *Behaviour Research and Therapy, 87*, 76-108.

Moreno-García, I., Delgado-Pardo, G., and Roldán-Blasco, C. (2015). Attention and response control in ADHD. Evaluation through integrated visual and auditory continuous performance test. *The Spanish journal of psychology, 18*.

Morillas-Romero, A., Tortella-Feliu, M., Bornas, X., and Putman, P. (2015). Spontaneous EEG theta/beta ratio and delta-beta coupling in relation to attentional network functioning and self-reported attentional control. *Cogn Affect Behav Neurosci, 15*(3), 598-606.

Murphy, B. L., Arnsten, A. F., Goldman-Rakic, P. S., and Roth, R. H. (1996). Increased dopamine turnover in the prefrontal cortex impairs spatial working memory performance in rats and monkeys. *Proceedings of the National Academy of Sciences, 93*(3), 1325-1329.

Nehlig, A., Daval, J. L., and Debry, G. (1992). Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. *Brain Research Reviews, 17*(2), 139-170.

Ochsner, K. N., Silvers, J. A., and Buhle, J. T. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences, 1251*(1).

Owens, M., Stevenson, J., Hadwin, J. A., and Norgate, R. (2012). Anxiety and depression in academic performance: An exploration of the mediating factors of worry and working memory. *School Psychology International, 33*(4), 433-449.

Pasman, W. J., van Baak, M. A., Jeukendrup, A. E., and de Haan, A. (1995). The effect of different dosages of caffeine on endurance performance time. *International journal of sports medicine, 16*(04), 225-230.

Phillips, A. G., Ahn, S., and Floresco, S. B. (2004). Magnitude of dopamine release in medial prefrontal cortex predicts accuracy of memory on a delayed response task. *Journal of Neuroscience, 24*(2), 547-553.

Putman, P., & Berling, S. (2011). Cortisol acutely reduces selective attention for erotic words in healthy young men. *Psychoneuroendocrinology, 36*(9), 1407-1417.

Putman, P., Hermans, E., and van Honk, J. (2004). Emotional stroop performance for masked angry faces: it's BAS, not BIS. *Emotion*, *4*(3), 305.

Putman, P., Arias-Garcia, E., Pantazi, I., and van Schie, C. (2012). Emotional Stroop interference for threatening words is related to reduced EEG delta-beta coupling and low attentional control. *International Journal of Psychophysiology, 84*(2), 194-200.

Putman, P., Verkuil, B., Arias-Garcia, E., Pantazi, I., and van Schie, C. (2014). EEG theta/beta ratio as a potential biomarker for attentional control and resilience against deleterious effects of stress on attention. *Cognitive Affective and Behavioral Neuroscience, 14*(2), 782-791.

Putwain, D. W. (2009). Assessment and examination stress in Key Stage 4. *British Educational Research Journal*, *35*(3), 391-411.

Reinholdt-Dunne, M. L., Mogg, K., and Bradley, B. P. (2009). Effects of anxiety and attention control on processing pictorial and linguistic emotional information. *Behaviour Research and Therapy, 47*(5), 410-417.

Revelle, W., Humphreys, M. S., Simon, L., and Gilliland, K. (1980). The interactive effect of personality, time of day, and caffeine: A test of the arousal model. *Journal of Experimental Psychology: General*, *109*(1), 1.

Ribeiro, J. A., and Sebastião, A. M. (2010). Caffeine and adenosine. *Journal of Alzheimer's Disease*, *20*(S1), 3-15.

Rivera-Oliver, M., & Díaz-Ríos, M. (2014). Using caffeine and other adenosine receptor antagonists and agonists as therapeutic tools against neurodegenerative diseases: a review. *Life sciences*, *101*(1-2), 1-9.

Schoorl, M., Putman, P., van der Werff, S., and van der Does, A. J. (2014). Attentional bias and attentional control in Posttraumatic Stress Disorder. *J Anxiety Disord, 28*(2), 203-210.

Schutter, D. J. L. G., and Van Honk, J. (2005). Electrophysiological ratio markers for the balance between reward and punishment. *Cognitive Brain Research, 24*(3), 685-690.

Schutter, D. J., and Knyazev, G. G. (2012). Cross-frequency coupling of brain oscillations in studying motivation and emotion. *Motiv Emot, 36*(1), 46-54.

Schutte, I., Kenemans, J. L., & Schutter, D. J. (2017). Resting-state theta/beta EEG ratio is associated with reward-and punishment-related reversal learning. *Cognitive, Affective, & Behavioral Neuroscience, 17*(4), 754-763.

Sebastião, A. M., & Ribeiro, J. A. (2009). Adenosine Receptors and the Central Nervous System. *Adenosine Receptors in Health and Disease, 193*, 471–534.

Smillie, L. D., and Gökçen, E. (2010). Caffeine enhances working memory for extraverts. *Biological psychology, 85*(3), 496-498.

Spielberger, C. D. (1983). Manual for the State–Trait Anxiety Inventory (STAI form Y). *Palo Alto: Consulting Psychologists Press.*

Taylor, C. T., Cross, K., and Amir, N. (2016). Attentional control moderates the relationship between social anxiety symptoms and attentional disengagement from threatening information. *J Behav Ther Exp Psychiatry, 50*, 68-76.

Tortella-Feliu, M., Morillas-Romero, A., Balle, M., Llabres, J., Bornas, X., and Putman, P. (2014). Spontaneous EEG activity and spontaneous emotion regulation. *Int J Psychophysiol, 94*(3), 365-372.

van Bockstaele, B., Verschuere, B., Tibboel, H., De Houwer, J., Crombez, G., and Koster, E. H. (2014). A review of current evidence for the causal impact of attentional bias on fear and anxiety. *Psychol Bull, 140*(3), 682-721.

van der Ploeg, H. M., Defares, P. B., and Spielberger, C. D. (1980). ZBV: Handleiding bij de zelf-beoordelings vragenlijst: Een Nederlandstalige bewerking van Spielberger State–Trait Anxiety Inventory STAI-Y. Amsterdam: Harcourt.

van Son, D., Angelidis, A., Hagenaars, M. A., van der Does, W., & Putman, P. (2018). Early and late dot-probe attentional bias to mild and high threat pictures: Relations with EEG theta/beta ratio, self-reported trait attentional control, and trait anxiety. *Psychophysiology*, e13274.

Van Dort, C. J., Baghdoyan, H. A., & Lydic, R. (2009). Adenosine A1 and A2A receptors in mouse prefrontal cortex modulate acetylcholine release and behavioral arousal. *Journal of Neuroscience, 29*(3), 871-881.

Wald, I., Shechner, T., Bitton, S., Holoshitz, Y., Charney, D. S., Muller, D., . . . Bar-Haim, Y. (2011). Attention bias away from threat during life threatening danger predicts PTSD symptoms at one-year follow-up. *Depress Anxiety, 28*(5), 406-411.

Williams, J. M. G., Mathews, A., and MacLeod, C. (1996). The emotional Stroop task and psychopathology. *Psychological bulletin*, *120*(1), 3.

Wood, S., Sage, J. R., Shuman, T., and Anagnostaras, S. G. (2014). Psychostimulants and cognition: a continuum of behavioral and cognitive activation. *Pharmacological reviews, 66*(1), 193-221.

Zhang, D. W., Roodenrys, S., Li, H., Barry, R. J., Clarke, A. R., Wu, Z., ... and Wang, Y. (2017). Atypical interference control in children with AD/HD with elevated theta/beta ratio. *Biological Psychology, 128*, 82-88.

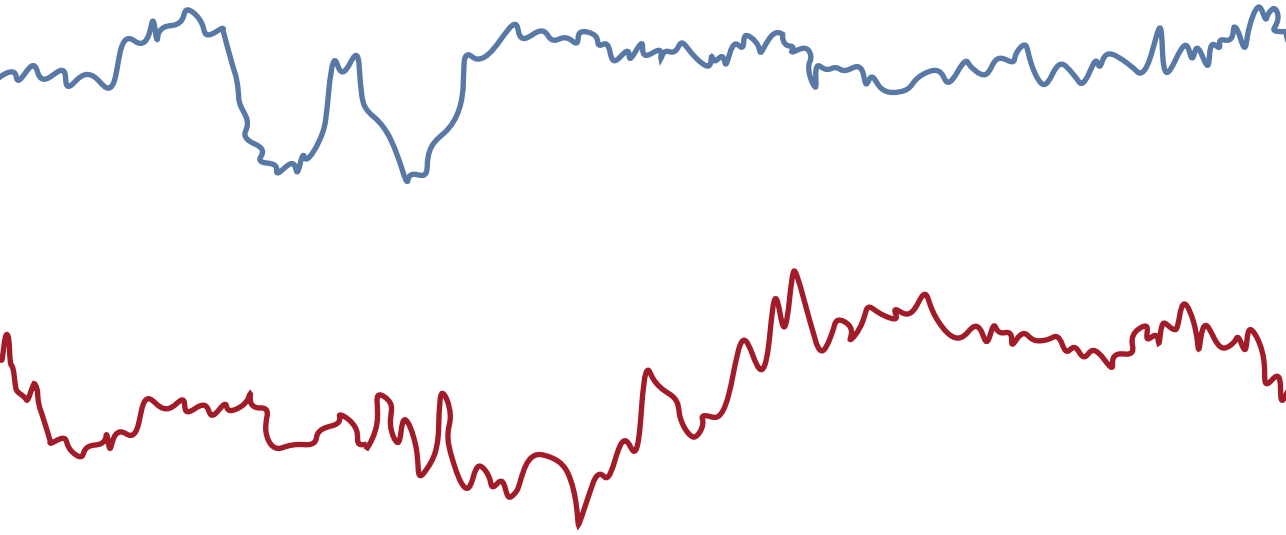
CHAPTER 3.

Frontal EEG theta/beta ratio during mind wandering episodes

Dana van Son, Frances M. De Blasio, Jack S. Fogarty, Angelos Angelidis, Robert J. Barry, Peter Putman

Published as

van Son, D., De Blasio, F. M., Fogarty, J. S., Angelidis, A., Barry, R. J., & Putman, P. (2019). Frontal EEG theta/beta ratio during mind wandering episodes. *Biological psychology*, 140, 19-27.



ABSTRACT

Background: In resting-state EEG, the ratio between frontal power in the slow theta frequency band and the fast beta frequency band (the theta/beta ratio, TBR) has previously been negatively related to attentional control. Also, increased theta and reduced beta power were observed during mind wandering (MW) compared to episodes of focused attention. Thus, increased resting-state frontal TBR could be related to MW, suggesting that previously observed relationships between TBR and attentional control could reflect MW episodes increasing the average resting state TBR in people with low attentional control.

Goals: To replicate and extend the previous theta and beta MW effects for frontal TBR recordings and test if MW related changes in frontal TBR are related to attentional control.

Methods: Twenty-six healthy participants performed a 40-minute breath-counting task, after a baseline EEG recording, while EEG was measured and participants indicated MW episodes with button presses.

Results: Frontal TBR was significantly higher during MW episodes than during on-task periods. However, no relation between frontal TBR and attentional control was found.

Conclusions: This confirms that frontal TBR varies with MW, which is thought to reflect, among other things, a state of reduced top-down attentional control over thoughts.

The electroencephalographic (EEG) signal represents the combined electrical fluctuations in membrane potentials generated from the interactions of the primary inhibitory and excitatory neurons (Gordon, 2000; Nunez, 1995) and can be decomposed into power estimates of different frequency bands. Typically measured under resting conditions, the ratio between the slow wave theta (4-7 Hz) and fast wave beta (13-30 Hz) band power, in other words the theta/beta ratio (TBR), has been utilized as a source of critical information about brain activity that may be associated with increased cognitive demand (Barry, Clarke, & Johnstone, 2003). TBR has also been found to have a very high test-retest reliability (Angelidis, van der Does, Schakel, & Putman, 2016; Keune, Hansen, Weber, Zapf, Habich, Muenssinger, Wolf, et al., 2017).

Several lines of evidence suggest that TBR is of interest when investigating attentional control. A frequently replicated finding, for example, is that TBR is increased in patients diagnosed with attention-deficit/hyperactivity disorder (ADHD; Barry et al., 2003), though also non-findings have been reported (Arns, Vollebregt, Palmer, Spooner, Gordon & Kohn et al., 2018; Loo, Cho, Hale, McGough, McCracken, & Smalley, 2013; Kitsune, Cheung, Brandeis, Banaschewski, Asherson, McLoughlin, & Kuntsi, 2015). Additionally, TBR was negatively correlated with self-reported trait attentional control (using the Attentional Control Scale, or ACS; Derryberry & Reed, 2002) in healthy participants (especially when controlling for an often-correlated measure of trait anxiety; Putman, van Peer, Maimari & van der Werff, 2010, replicated by Putman, Verkuil, Arias-Garcia, Pantazi & van Schie, 2014, Angelidis et al., 2016; van Son, Angelidis, Hagenaars, van der Does & Putman, 2018a). Also, TBR was negatively related to objectively measured attentional control in multiple sclerosis patients with mild cognitive impairment (Keune et al., 2017). Furthermore, TBR was found to be positively correlated with a stress-induced decline in state attentional control (Putman et al., 2014). All in all, the relation between TBR and attentional control seems to span the spectrum from healthy student samples to clinically impaired groups (Keune et al., Barry et al., 2003; Arns, Conners & Kraemer, 2013). Frontal TBR has been suggested to reflect cortical-subcortical interactions associated with inhibitory functioning and cortical inhibition of subcortical processes (Knyazev, 2007; Schutter & Knyazev, 2012; Putman et al., 2014). This could reflect voluntary top-down processes like attentional control carried out by the dorsolateral prefrontal cortex (Bishop, 2008; Gregoriou, Rossi, Ungerleider, & Desimone, 2014) over automatic bottom-up processes mediated by limbic areas such as the anterior cingulate cortex and the amygdala, facilitating attention to salient information (Hermans, Henckens, Joëls & Fernández, 2014).

Recent studies from our lab showed that TBR moderated attentional bias to stimuli of different threat levels (Angelidis, Hagenaars, van Son, van der Does & Putman, 2018; van Son et al., 2018a) as predicted for attentional control in influential models of attentional bias (Mogg & Bradley, 1998, 2016). However, attentional bias does not solely include attentional processing of external stimuli. Anxious people, for example, also worry a lot, which represents biased internal activation of threatening cognitions in working memory, and shares mechanisms with biased attention (Hirsch & Mathews, 2012). Worry can be seen as self-generated off-task thought, and is sometimes referred to as a negative form of the umbrella term 'mind wandering' (Ottaviani, Shahabi, Tarvainen, Cook, Abrams & Shapiro, 2015).

Like worry, mind wandering (MW) episodes correspond to the emergence of task-unrelated affects and thoughts that draw attention away from the task at hand (Smallwood & Schooler, 2006). MW can occur while

performing a task, and is manifested as thinking of something else while executing a task (Mason, Norton, Van Horn, Wegner, Grafton, & Macrae, 2007). MW has been shown to play a role in processes like prospection and future planning (Baumeister & Masicampo, 2010; Baumeister, Masicampo & Vohs, 2011), creativity (Baird, Smallwood, Mrazek, Kam, Franklin & Schooler, 2012) and mental breaks, remediating an unpleasant mood (Ruby, Smallwood, Engen, & Singer, 2013). Besides its relation with these more beneficial processes, others have repeatedly conceptualized MW as a state of reduced working memory and attentional control (McVay & Kane, 2009; Unsworth & McMillan, 2014), and as a predictor of performance errors (Smallwood & Schooler, 2006). MW has furthermore directly been related to reduced attention and focus (Smallwood, Nind, & O'Connor, 2009; Stawarczyk, Majerus, Catale, & D'Argembeau, 2014; Unsworth & McMillan, 2014). Also, ADHD was found to relate to increased MW (Bozhilova, Michelini, Kuntsi, & Asherson, 2018). It is this latter aspect of MW that is addressed in our paper: MW as a state of reduced cognitive control and vigilance, as related to working memory performance and cognitive failure.

In a proof of principle study, Braboszcz and Delorme (2011) reported that higher EEG theta band power and lower EEG beta band power were related to a state of MW. Participants were asked to focus on counting their breaths and to press a button as soon as they became aware that their mind had wandered off task. EEG spectral analysis showed higher theta and lower beta (likely higher TBR) before the button press, but lower theta and higher beta (likely lower TBR) after the button press, when they again focused on breath counting. These results were observed for windows of a -8 to -2 second period before the button press and a 2 to 8 second period after the button press, omitting the four seconds surrounding the button press. These time-windows correspond with theoretical and empirical observations concerning short periods of low, but growing awareness and a shift in attentional orientation just before and after the button press respectively (Hasenkamp, Wilson-Mendenhall, Duncan & Barsalou, 2012). The two seconds immediately before the button press were considered as 'participants becoming aware that their mind wandered off', and the two seconds immediately after the button press as 'getting back into breath-counting'.

As outlined above, MW itself is described as a deficit in working memory and attentional control (McVay & Kane, 2009; Unsworth & McMillan, 2014) and is a predictor for performance errors (Smallwood & Schooler, 2006); TBR's relation to attentional control might therefore be associated with a higher tendency to mind wander during resting state, increasing the average TBR in people with low attentional control. Studying this hypothesis would greatly benefit our understanding of TBR's relation to attentional control in healthy people (Putman et al., 2010; 2014; Angelidis et al., 2016; van Son et al., 2018a) and clinical samples (Keune et al., 2017; Arns et al., 2013; Barry et al., 2003). If the TBR–attentional control relationship reflects mainly changes in TBR when people engage in mind wandering episodes, it might also be interesting to consider possible interactions between the number of mind wandering episodes and the assumed TBR–attentional control correlation. Therefore, if the TBR-ACS relation is observed in our present sample (despite null-findings reported in Morillas-Romero, Tortella-Feliu, Bornas, & Putman, 2015; Angelidis et al., 2018), this hypothesis regarding the mediating underlying processes causing the relation between TBR and attentional control can be tested.

The aim of the current study was to replicate and extend the design and results of Braboszcz and

Delorme (2011) as pertaining to the MW related changes in EEG, in order to gain further insight into the role of TBR during MW episodes. Our primary hypotheses will be tested using frontal TBR, since previous studies examining TBR in relation to executive processes using healthy participants focused almost exclusively on frontal TBR (Putman et al., 2010, 2014; Angelidis et al., 2016, 2018; van Son et al., 2018a; Schutter & van Honk, 2004; Schutter & van Honk, 2005; Sari, Koster, Pourtois, & Derakshan, 2016; Tortella-Feliu, Morillas-Romero, Balle, Llabrés, Bornas, & Putman, 2014; Morillas-Romero et al., 2015). We hypothesized that:

I) Frontal TBR is higher during MW episodes than during on-task periods.

II) Baseline spontaneous frontal TBR is expected to negatively correlate with attentional control as measured by the ACS when controlling for trait anxiety.

III) The MW related changes in frontal TBR (assessed in hypothesis I) are related to baseline TBR during resting state and ACS.

IV) The MW related changes in frontal TBR (assessed in hypothesis I) mediate the correlation between baseline spontaneous TBR and ACS (hypothesis II).

These hypotheses were tested in a female sample (unlike Braboszcz and Delorme [2011] who included both males and females) since the majority of previous studies on TBR in healthy samples were (mostly) female and because of the gender imbalance in our available participants. Also, it is yet to be verified if TBR at frontal regions is the optimal predictor of attentional control and MW, thus the present study additionally explores the topographical occurrence of MW-related TBR. Furthermore, after testing the hypotheses for the MW versus focused attention epochs corresponding to Braboszcz and Delorme's (2011) analysis, we further explore effects of time within these 6 second epochs (pre- and post-button press) as visual inspection of their data suggests that TBR increased following the button press. Finally, we correlated EEG data with the number of button presses that the participants made, as the occurrence of MW awareness might be related to the qualitative nature of mind wandering episodes; that is, less profound mind wandering might occur in participants who often become aware of their mind wandering.

Methods

Participants

Fifty-three female participants (between 18 and 30 years old) recruited at Leiden University took part in this study. Only females were included because of the low prevalence of men signing up to participate in the study and for better comparison with previous studies of relations between TBR and attentional control functions in healthy participants. Exclusion criteria were factors which would likely adversely affect participation, EEG, or attention; these included severe physical or psychological dysfunction, and/or the use of psychotropic medication. As described in detail below, 27 participants were excluded because they retained too few (<11) acceptable mind wandering epochs of acceptable EEG data quality. Informed consent was obtained prior to testing, and participants received a monetary reimbursement for their participation. The study was approved by the Leiden University local ethics review board.

Materials

Questionnaires. Participants completed the trait version of the State-Trait Anxiety Inventory (STAI-t; Spielberger, 1983) and the Attentional Control Scale (ACS; Derryberry & Reed, 2002). The STAI-t assesses trait anxiety (20 items, range 20-80; Cronbach's alpha in the current study = 0.88), by indicating agreement with items like 'I feel nervous and restless' and 'I have disturbing thoughts' on a four-point Likert scale. The ACS assesses self-reported attentional control in terms of attentional focus, attentional switching and the capacity to quickly generate new thoughts (20 items, range 20-80; Cronbach's alpha in present study = 0.80), by indicating agreement with items like 'I can quickly switch from one task to another' and 'I have a hard time concentrating when I'm excited about something'.

Breath counting task. The breath counting task was reproduced from Braboszcz and Delorme (2011). Participants were asked to keep their eyes closed and count their breath cycles (one inhalation and one exhalation) from 1 to 10 and then start from 1 again during two blocks of 20 minutes. They were instructed to press a button when they realized they had stopped counting, continued counting further than 10, or when they had to reflect intensively on what the next count would be. Participants were instructed to refocus on breath-counting again after any button presses. In order to maintain procedural consistency with Braboszcz and Delorme (2011), a passive auditory oddball task was presented concurrently with the breath counting task and participants were instructed to ignore the auditory stimuli. We were not interested in studying oddball-related EEG, but since it is possible that this particular detail of the procedure could influence mind wandering, we included it for the sake of close methodological replication. For the same reason, we also presented some debriefing questions at the end of each block (as done by Braboszcz and Delorme, 2011) that were not analyzed here.

EEG recording and software. EEG recordings were obtained continuously from 31 electrodes at 10/20 positions using Ag/AgCl electrodes of the ActiveTwo BioSemi system (BioSemi, The Netherlands). Electrodes placed on the left and right mastoids were used for offline re-referencing. Data were collected with a sampling rate of 1024 Hz with a gain of 16x at a bandwidth between DC-400 Hz. For processing purposes, data were down-sampled to 256 Hz.

Procedure

General Procedure. After informed consent had been obtained, participants completed the ACS and the STAI-t. This was followed by the measurement of resting-state EEG for ten minutes with eyes closed, and then the breath counting task was conducted while recording EEG.

Data Reduction

Button presses. For each subject, the EEG data were segmented into 16 second data epochs around their button presses. We considered that participants were mind wandering during the -8 to -2 second period preceding the button press, and that participants were concentrating on their breath during the 2 to 8 second

period that followed the button press (as in Braboszcz & Delorme, 2011). One participant pressed the button 111 times (more than 3 standard deviations above the mean number of button presses) and was therefore removed from further analysis. Twenty-seven subjects did not have enough clean (i.e., artefact free) data epochs to be considered for further analysis; specifically, these participants had below 11 button presses with EEG data of sufficient quality and were excluded.

EEG pre-processing and FFT during resting-state. EEG baseline data were re-referenced offline to the linked mastoids and automatically corrected for ocular artifacts (Gratton, Coles, & Donchin, 1983) in segments of 4 seconds using Brain Vision Analyzer V2.04 (Brain Products GmbH, Germany). Baseline resting state EEG was then subjected to a Fast Fourier transformation (Hanning window length 10%) to calculate power for the beta (13-30 Hz) and theta (4-7 Hz) band. Theta/beta ratio was calculated by dividing the theta by the beta power. All EEG baseline variables were non-normally distributed and therefore log-normalized with a log10 transformation.

EEG pre-processing and Fourier analysis during the breath-counting task. For the EEG data during the breath counting task, offline re-referencing and ocular correction procedures were done as for the resting-state EEG. Neuroscan 4.5 Edit software was then used to interpolate bad channels and extract single trial epochs for 8.25 second pre- to 8.25 second post-button press. The remaining data quantification was completed within MATLAB (The Mathworks, Version 8.0.0.783, R2012b) using EEGLAB (Version 13.4; Delorme and Makeig, 2004) and custom scripts. For each electrode and for each participant, 1 second intervals of sequential and non-overlapping data from 8 to 2 second before, and 2 to 8 second after each button press were individually selected, DC corrected, and then a 10% Hanning window was applied. Discrete Fourier Transformation (DFT) was used to derive the frequency spectra at 1 Hz resolution, and a correction was applied for the use of the Hanning window. Wide band power data were then computed for the delta (1-3 Hz), theta (4-7 Hz), alpha (8-12 Hz) and beta (13-30 Hz) bands. Theta/beta ratio was calculated by dividing the theta power by the beta power.

Event-related spectral perturbations (ERSP) for EEG during the breath-counting task. To inspect differences in EEG pre-versus post-button press in more detail within the time-frequency domain, we computed Event Related Spectral Perturbations (ERSPs). For these analyses, we decomposed the EEG signal in brief overlapping segments using DFT. DFT separates oscillations in short epochs thus we considered this method to be better suited for studying effects over time within the 6s window after the button press, as opposed to wavelet decomposition as was utilized by Braboszcz and Delorme (2011); e.g., see Figure 2, Barry, Fogarty, De Blasio, and Karamacoska (2018). Following Braboszcz and Delorme (2011), baseline corrections were not applied to either the full-length epochs or their ERSP data. Each ERSP used 257 sliding DFT windows with a size of 128 data points (500 ms). Data in each window were DC corrected, and a 10% Hanning window was applied. Data were zero padded to 256 data points (1 second duration) and subjected to DFT. This gave us EEG power data at 1 Hz frequency resolution, with a 62.5 ms time resolution. We assessed DC to 30 Hz.

Each ERSP resulted in a three-dimensional matrix of EEG power at each frequency step and at each time

point, containing all the information in the EEG throughout the trial. These ERSPs were obtained from 8 seconds before to 8 seconds after the button press for each trial and then averaged to obtain a mean ERSP for each subject. Contrary to Braboszcz and Delorme (2011), we did not assess the auditory oddball task as we were mainly interested in the spectral composition during mind wandering and breath focus.

For the explorative topographical analyses, the following division in electrodes per region were made: Frontal; Fp1, Fp2, F3, Fz, F4, F7, F8, AFz, FCz, FC3, FC4, FT7, FT8; Central; C3, Cz, C4, CP3, CPz, CP4, T7, T8, TP7, TP8; Posterior; P3, Pz, P4, P7, P8, O1, Oz, O2; Left; Fp1, F7, F3, FT7, FC3, T7, C3, TP7, CP3, P7, P3, O1; Midline; AFz, Fz, FCz, Cz, CPz, Pz, Oz; Right; Fp2, F4, F8 FC4, FT8, C4, T8, CP4, TP8, P4, P8, O2.

Statistical analyses

All four formal hypotheses are tested using Fourier transformations for extraction of power estimates in baseline TBR and the pre- and post-button press windows for close comparison with previous studies. Results from ERSP analyses are also provided for a more comprehensive and in-depth approach to the additional explorative questions, as mentioned in the Introduction (e.g., visual inspection of other frequency bands and the time-course of TBR during the post-button-press-window). To test whether TBR was different pre- versus post-button press (hypothesis I), a 2-level (time) repeated measures analysis of variance (rm-ANOVA) was carried out. Next, four 2-level (time) rm-ANOVA's were conducted to exploratively test pre- versus post-button press differences in theta, beta, delta and alpha. We used Pearson's correlations to check whether there was a correlation between TBR change (pre- versus post-) and baseline TBR; baseline TBR and ACS; TBR pre-button press and ACS; TBR post-button press and ACS, and TBR change pre- vs post- and ACS (hypotheses II and III). These correlations were repeated by using partial correlations controlling for STAI-t score. To inspect the changes in the frequency bands of interest (theta, beta and TBR) pre-versus post-button press in more detail within the time-frequency domains, ERSP outcomes were examined. To test time differences using the ERSP data, mean narrow-band frontal ERSP data (across F3, Fz and F4) were summed to form the theta (4-7 Hz) and beta (13-30 Hz) frequency bands. These data were then averaged in 1 second non-overlapping sections to provide 6 averages from -8 to -2 seconds pre-button press, and 6 averages from 2 to 8 seconds post-button press. The same averages were calculated for theta/beta ratio by dividing the theta data by the corresponding data in beta. Then, a 6 level (time-points) multivariate analysis of variance [MANOVA] for time-points pre-button press and a 6 level (time-points) MANOVA for time-points post-button press, were conducted for Frontal TBR to explore the linear trend over the time points. Furthermore, we exploratively evaluated topographical differences by conducting a 2 (pre-post) x 3 (sagittal; frontal [F], central [C], posterior [P]) x 3 (lateral; left [L], midline [M], right [R]) MANOVA for TBR. Finally, we exploratively checked whether differences pre- versus post- button press for theta, beta and TBR were correlated to the number of button presses by using Pearson's correlations. All baseline EEG variables and ERSP-derived EEG power values were non-normally distributed and therefore normalized with a log10 transformation. Bonferroni corrections for multiple testing were applied and reported where appropriate.

Results

Participants

The 26 remaining participants had a mean age of 22.8 years (*SD* = 2.6, range: 19-28). Mean ACS score was 53.88 (*SD* = 5.44, range 41-63), mean STAI-t score was 38.54 (*SD* = 6.32, range 29-50). The mean frontal TBR of the participants measured during the resting state (baseline) was 1.22 (*SD* = 0.49, range 0.52-2.47 [non log-normalized]). All subjects had between 11 and 60 button presses (*M* = 23.76, *SD* = 12.54).

EEG activity pre- and post-button press average differences

TBR was found to be significantly higher pre- compared to post-button press; $F(1,25) = 28.05$, $p < 0.001$, $\eta_p^2 = 0.53$. This confirms hypothesis I.

We exploratively tested pre- and post-differences for theta, beta, delta and alpha. Theta was significantly higher pre- versus post-button press; $F(1,25) = 13.60$, $p = 0.004$, $\eta_p^2 = 0.35$ (p-value is Bonferroni corrected by factor 4 as 4 bands were tested). Beta, on the other hand, was lower pre- compared to post-button press; $F(1,25) = 18.58$, $p = 0.001$, $\eta_p^2 = 0.43$ (Bonferroni corrected). Delta was significantly higher pre- versus post-button press; $F(1,25) = 9.07$, $p = 0.024$, $\eta_p^2 = 0.27$ (Bonferroni corrected). Alpha was significantly lower pre- versus post-button press; $F(1,25) = 17.64$, $p = 0.001$, $\eta_p^2 = 0.41$ (Bonferroni corrected).

EEG baseline TBR related to ACS and TBR change pre- versus post- and ACS.

When controlling for STAI-t, no significant correlation was found between ACS and baseline frontal TBR (partial $r = 0.14$, $p = 0.518$). This correlation was also absent without controlling for STAI-t; $r = 0.16$, $p = 0.423$, this rejects hypothesis II. Also, no significant correlation was found between TBR change pre- versus post- and baseline TBR, $r = 0.06$; $p = 0.758$. Also, ACS did not correlate significantly with the difference score of frontal pre-minus-post TBR; $r = 0.17$, $p = 0.540$. This was also the case when controlling for STAI-t; ACS did not correlate with frontal TBR pre-button press (partial $r = 0.25$, $p = 0.220$), post-button press (partial $r = 0.16$, $p = 0.435$), or difference score of frontal pre-minus-post TBR; partial $r = 0.15$, $p = 0.483$. Thus, hypothesis III was rejected. Because of these non-significant results for relations between baseline TBR, TBR change and ACS, hypothesis IV (mediation) was not tested.

Event Related Spectral Perturbations (ERSPs).

First, we visually inspected the output of the ERSP analyses (**Figure 3.1**). The ERSP included averages for all epochs of -8 to 8 seconds around the button press for all participants and all electrodes. As our hypotheses were based on previous findings with frontal TBR, we visualized ERSP data of frontal electrode positions (average of F3, Fz and F4) averaged over all participants. This figure suggests that the power decreases post compared to pre-button press occurred not only in theta, but also in delta, while power increases were apparent not only in beta, but also alpha post-button press. **Figure 3.1** also suggests that prior to the end of the post-button press epoch, theta power starts to increase again, and beta power starts to decrease.

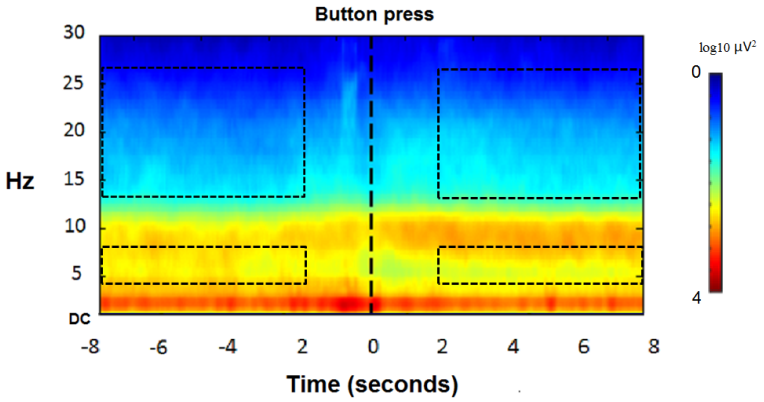


Figure 3.1, ERSP plot of the frontal average (across F3 Fz F4 sites) at 1 Hz frequency resolution, and 62.5 ms time resolution. Mind wandering was considered to have occurred in the -8 to -2 second period preceding the button press, and breath focus was considered to have occurred in the+2 to +8 second period following the button press. Rectangular frames highlight these data of interest.

ERSP pre- and post-button press slopes and topography

The values of the 6 pre- and 6 post-button press averages for frontal TBR are visualized in **Figure 3.2.** Testing ERSP time effects, a significant difference was found for TBR from pre- to post-, $F(1,25) = 26.69$, $p < 0.001$, $\eta_p^2 = 0.52$. Frontal TBR did not have a significant linear slope trend over time pre-button press, $F(1,25) = 0.44$, $p = 0.516$, $\eta_p^2 = 0.02$), but (as can be seen in **Figure 3.2**) there was a significant linear slope trend over time post-button press, $F(1,25) = 34.84$, $p < 0.001$, $\eta_p^2 = 0.58$ (Bonferroni corrected by a factor of 2), showing that TBR increased over time 2 to 8 seconds after the button press.

As for topographical differences, TBR was dominant in the midline compared to the lateral regions (M > L/R: $F = 66.96$, $p < 0.001$, $\eta_p^2 = 0.73$), and in the frontal compared to the posterior regions (F > P: $F = 36.53$, $p < 0.001$, $\eta_p^2 = 0.59$). TBR also showed two-way interactions, with the midline dominance significantly larger in the frontal than posterior regions (M > L/R x F > P: $F = 7.65$, $p = 0.011$, $\eta_p^2 = 0.23$). The midline TBR dominance was also significantly larger in central compared to frontal/posterior regional mean (M > L/R x C > F/P: $F = 15.61$, $p = 0.001$, $\eta_p^2 = 0.38$). Pre- vs post-button press interactions showed greater midline than lateral reductions (M > L/R x pre > post: $F = 4.50$, $p = 0.044$, $\eta_p^2 = 0.15$), particularly in posterior compared to frontal regions (M > L/R x P > F x pre > post: $F = 6.04$, $p = 0.021$, $\eta_p^2 = 0.19$). Thus, the effect of MW on TBR was maximal in the posterior midline region. The two-way interaction with TBR on midline over frontal and posterior regions and the pre- vs post-button press midline and posterior dominance effect would however become non-significant after Bonferroni correction.

ERSP data pre- and post-differences related to number of button presses.

As differences were found pre-versus post-button press, we explored whether these differences were related to the number of button presses that participants made. To analyse this, we first computed the average of the ERSP pre- (-8 to -2 seconds) and post-button press (2 to 8 seconds) and calculated the difference scores between these for frontal (average F3, Fz and F4) theta and beta band and the TBR. Correlational analysis showed no significant correlation between the number of button presses and the difference scores in theta ($r = 0.07$, $p = 0.741$), beta ($r = -0.24$, $p = 0.234$), or TBR ($r = 0.10$, $p = 0.618$). Thus, MW-related TBR change was independent of the number of button presses.

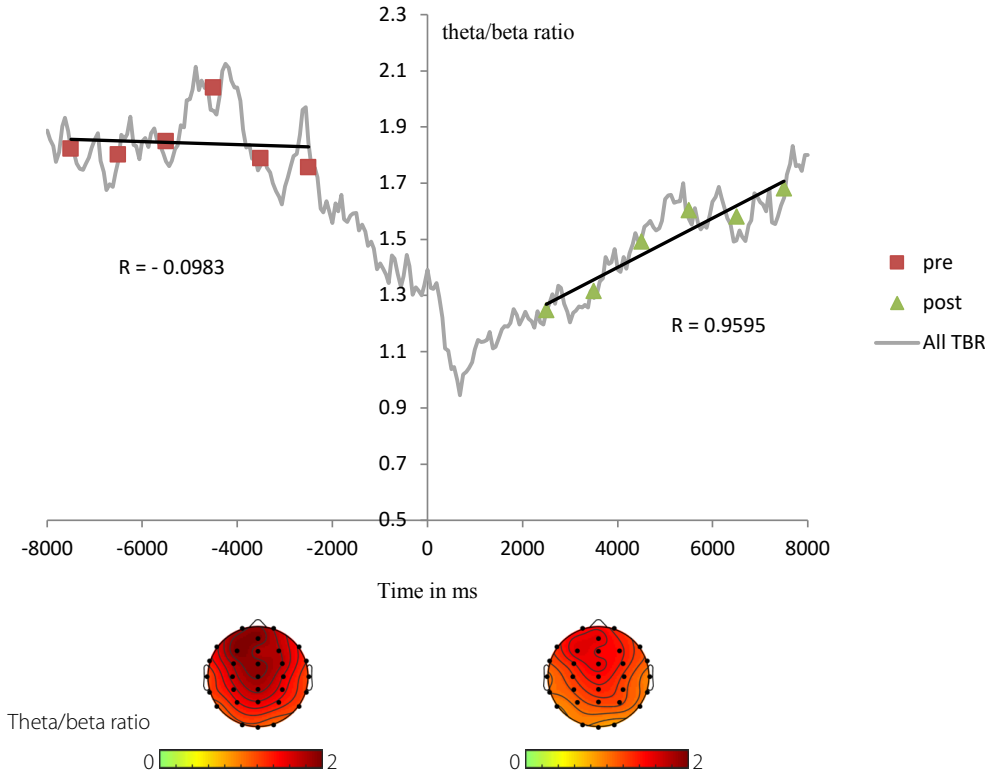


Figure 3.2. Plot of the ERSP-derived theta/beta ratio (TBR; non-logtransformed) data for Frontal electrode mean (F3, Fz and F4) showing slope trends plotted over six- 1 second averages pre- and post-button press. Topographic map of power pre (left) and post (right) button press is shown for TBR averaged from –8 to –2 second before and 2 to 8 second after the button press.

Discussion

This study aimed to replicate and extend the design and results of Braboszcz and Delorme (2011) as pertaining to the MW related changes in EEG, to gain further insight into the role of frontal TBR during MW episodes. In our all-female sample, we found that frontal TBR was significantly higher during MW episodes compared to on-task time periods; this TBR – MW effect was strongest in the midline, particularly in posterior regions. When considering the EEG bands separately, theta power was higher and beta power was lower during MW episodes as opposed to on-task periods. Frontal baseline TBR did not correlate with ACS or the TBR-MW effect, resulting in an inability to test our hypothesis that previously observed relations between ACS and TBR might be mediated by EEG changes during MW.

Our first hypothesis that frontal TBR would be higher during MW episodes was confirmed. TBR's change between MW and focused episodes was stronger along the midline regions compared to the lateral regions and this effect was stronger in posterior compared to central and frontal regions, although these effects were relatively small and did not remain significant after correction for multiple testing. This finding seems comparable to the results of Braboszcz & Delorme, (2011) who found the MW effect on separate theta and beta bands to be strongest in parieto-occipital regions. Previous crucial findings for TBR however, repeatedly assessed TBR as measured frontally which was associated with prefrontally-mediated cognitive and emotional processes (Putman et al., 2010, 2014; Angelidis et al., 2016; 2018; van Son et al., 2018a; Tortella-Feliu et al., 2014). For example, it predicted acute stress-induced changes in self-reported state attentional control in addition to its reported correlation with self-reported trait and state attentional control (Putman et al, 2014; Angelidis et al., 2016). Moreover, working memory training was found to decrease frontal TBR (Sari et al., 2015). Also, a theta-based brain stimulation procedure that has been shown to enhance working memory, decreased frontal and central TBR and increased flexible implicit rule learning in motivated decision making (Wischnewski, Zerr & Schutter, 2016). Additionally, Schutter and van Honk (2005), used a reward-punishment reversal learning task to measure higher order cognitive integration of emotional information, and good performance on this same task correlated negatively with baseline frontal TBR; a similar result was also found in another more recent study (Schutte, Kenemans, Schutter, 2017). Additionally, several studies from our lab have provided evidence that resting-state frontal TBR predicted spatial attentional bias for threatening pictures, also interacting with individual differences in trait anxiety (Angelidis et al., 2018; van Son et al., 2018a). Relations between frontal TBR and attentional interference from high threat pictures were also altered by administration of caffeine, a catecholamine agonist that affects executive functioning in the PFC (van Son, Schalbroeck, Angelidis, van der Wee, van der Does & Putman, 2018b). Currently, as in Braboszcz and Delorme (2011), MW-related changes in TBR were not stronger over other than frontal areas. Therefore, if future studies would verify our hypothesis concerning relations between baseline TBR, executive functions like attentional control and MW, this would imply that research into relations between baseline TBR and executive function should also consider non-frontal areas more extensively (see also Putman et al., 2014a; Putman, Verkuil, Arias-Garcia, Pantazi, & Van Schie, 2014b). Combination of EEG and other neuro-imaging techniques, like functional magnetic resonance imaging (fMRI), can possibly further investigate more precise localization of TBR and MW-correlates in the brain. For instance, since MW has been

associated with connectivity of the default mode network (DMN; Karapanagiotidis, Bernhardt, Jefferies, & Smallwood, 2017; Smallwood, Beach, Schooler & Handy, 2008; Christoff, Ream, Geddes, & Gabrieli, 2003), MW-related EEG changes might be related to increased activation of this network and reduced activation of an executive control network. Although (dorsolateral) prefrontal cortical areas are importantly involved in the latter (Seeley, Menon, Schatzberg, Keller, Glover, Kenna et al., 2007), the DMN consists of other cortical and subcortical areas and EEG activity related to activation of this network need not be restricted to frontal areas.

Our data confirm and extend the findings by Braboszcz and Delorme (2011), and show that phasic changes in TBR are related to variation of mental state between uncontrolled MW and focused attention, or perhaps meta-cognitive vigilance. One view of MW is that it represents a state of reduced cognitive control (McVay & Kane, 2009; Unsworth & McMillan, 2014), reduced vigilant processing of external stimuli, and increased bottom-up, memory-driven self-referential thought (Mason et al., 2007). Changes in brain function that are associated with MW and these underlying cognitive processes include increased activation of the posterior cingulate cortex, medial PFC and para-hippocampal regions – and decreased activation in (pre-frontal) cortical areas such as the dorso-lateral PFC and lateral inferior parietal regions (Hasenkamp et al., 2012; Karapanagiotidis et al., 2017; Hopfinger, Buonocore, & Mangun, 2000; Corbetta & Schulman, 2002; Delaveaux, Arruda Sanchez, Steffen, Deschet, Jabourian, Perlbarg, & Fossati, 2017). Also, it has been found that ADHD was related to altered deactivation of the DMN (Uddin, Kelly, Biswal, Margulies, Shehzad, Shaw, & Milham, 2008), which again strengthens the assumption of MW to represent a state of reduced cognitive control. The current data then likely again support the conjecture that baseline TBR represents relative activation of top-down (prefrontal) cortical versus more bottom-up and subcortical processes, as first suggested by Schutter and van Honk (2005) and Knyazev (2007), and supported by our own work (Putman et al., 2010; 2014a; Angelidis et al., 2018; van Son et al., 2018a), and that from several other labs (Schutter & van Honk, 2004; Schutter & van Honk, 2005; Sari et al., 2016; Tortella-Feliu et al., 2014; Morillas-Romero et al., 2015; Keune et al., 2017; Clarke, Barry, McCarthy, & Selikowitz, 2001). Additionally, the current confirmation that TBR may be used as a marker of MW-related changes in brain activity can likely be very useful for the study of MW (Smallwood & Schooler, 2006) and inattention (Jap, Lal, Fischer, & Bekiaris, 2009; Lorist, Bezdan, ten Caat, Span, Roerdink, & Maurits, 2009).

The breath-counting MW method as used in this study and in Braboszcz and Delorme's (2011) research (see also Hasenkamp et al., 2012, for a closely related method), has the potential limitation that it relies on introspection. Since the MW episodes that are examined are self-reported, their underlying brain activity might be different from other MW episodes that might have remained undetected, or from earlier phases of the reported MW episodes. Also, it is reasonable to assume that participants who were better able to realize that their mind wandered off the breath-counting, pressed the button more often, resulting in the results being driven by these participants. In other words, one could speculate that using the time periods before a button press might not capture episodes representative of all MW, but possibly predominantly MW episodes that are associated with more meta-attentional control or awareness. If this were so, one would expect that participants who are more aware of their MW episodes (and press the button more often than participants who are less aware of this) would show different EEG results. We tested if there was a correlation between the number of button presses and the

TBR change, and this was not the case. The absence of this correlation is reassuring and likely indicates that the results are not confounded by meta-attentional introspective awareness. Also, if our results and the results from Braboszcz and Delorme (2011) partially reflect biased influence of MW episodes that are subsequently introspectively detected, one would expect that this should lead to a smaller pre- to post- button press effect. One could thus speculate that the results found using this method might, if anything, underestimate the effect of spontaneous, inattention related, mind wandering on TBR. Moreover, given that the currently-used method specifically instructed the participants to focus (on counting breaths), the most straight-forward assumption is that the periods before and after the button press represent unfocussed and focussed periods, rather than, for example, task related interference or deliberate mind wandering (e.g. Ruby et al., 2013), although these options cannot be fully excluded. However, future studies might opt to include MW measurements that are not self-generated, but instead rely on more qualitative experimenter-controlled thought-probing.

We used ERSP-derived one-second averages to further investigate slope changes over time in frontal TBR. The plotted slopes revealed that frontal TBR after a drop that started just before the button press, increased again quite rapidly post-button press. This pattern of pre- versus post-button press raises an interesting speculation: is it really *high* TBR that we see during MW episodes, or perhaps rather *low* TBR shortly and briefly after the button press? Looking at the relatively fast rebound of frontal TBR, one explanation might be that individuals start to lapse back into a new MW episode again relatively quickly after the button press. We are however unsure how likely it is that they would often start to mind wander again within eight seconds of becoming aware of their mind wandering. Another potentially interesting speculation concerning this seemingly quick rebound of frontal TBR is that the on-task focused periods might represent a short hypervigilant meta-awareness or meta-attentional control (realising that one lost count and was mind wandering, and subsequently increasing the use of executive resources for goal-directed monitoring of breath counting), which possibly contributed to the frontal TBR change post- versus pre-button press. This would be in line with literature on increased hypervigilance after error realization (e.g. Hollins, Harper, Gallagher, Owings, Lim, Miller et al., 2009; Weymar, Keil & Hamm, 2013). This hypervigilance can be described as meta-cognition of one's attentional control and could possibly disappear relatively quickly without having to engage back into a MW episode per se. It should be noted however, that such error realization is associated with short-lived *increased* theta activity (Hollins et al., 2009; Weymar et al., 2013), which seems at odds with our finding of *decreased* TBR (and theta) around the time of mind wandering realization. As mentioned before, future studies could take this speculation into account and compare MW periods with non-MW periods by using a design that does not rely on error related realizations.

All in all, the current results suggest frontal TBR to be related to changes in focused attention and possibly meta-attentional control or awareness. Beta is found to be involved in top- down executive functions like behavioural inhibition, inhibitory motoric processes, sequential encoding of processed items in working memory, retrieval from long-term memory and visual attention (Brown, 2007; Baker, 2007; Jenkinson & Brown, 2011; Engel & Fries, 2010; Marrufo, Vaquero, Cardoso, & Gomez, 2001; Wróbel, 2000). Considering that beta activity has a strong coherence between frontal and parietal regions during top-down compared to bottom-up visual attention (Buschman & Miller, 2007; 2009; Engel & Fries, 2010) it was speculated that beta activity is to some extent related

to the establishment of reciprocal control of bottom-up and top-down processes (Engel & Fries, 2010). Theta activity on the other hand has been associated with subjective sleepiness (Strijkstra, Beersma, Drayer, Halbesma, & Daan, 2003), decreased vigilance (e.g. Daniel, 1967; Belyavin, & Wright, 1987), and was suggested to be generated in limbic structures involved in a brain network subserving more bottom-up automatic attention as opposed to more cortically mediated executive control (Hermans et al., 2014; Seidenbecher, Laxmi, Stork, & Pape, 2003). These lines of research fit with functional correlates of TBR and its role in mind wandering conceived as a state of reduced executive attentional control and automatic self-generated thought (Mason et al., 2007; McVay & Kane, 2009; Unsworth & McMillan, 2014; Smallwood, 2013; Christoff et al., 2003).

Exploratively, we additionally tested differences in the delta and alpha bands, and found that delta was significantly higher during MW episodes compared to on-task focus periods, while alpha was significantly higher during on-task focus periods compared to MW episodes. Changes in delta were similar to changes in theta, possibly because these bandwidths are adjacent and their functions possibly have some overlap. Some studies have indeed described overlays in functionality for delta and theta in for example hippocampal – prefrontal coherent activity (Aleksanov, Vainstein & Preobrashenskaya, 1986) and homeostatic and motivational processes (Knyazev, 2012). Putman et al. (2010) found similar correlations for theta/beta ratio and delta/beta ratio with fearful modulation of response inhibition in an emotional go/no-go task. As for alpha, a post-button press increase in power similar to beta was found. Alpha activity has been positively related to inhibitory processes (Uusberg, Uibo, Kreegipuu, & Allik, 2013; Haegens, Luther, & Jensen, 2012; see also Pfurtscheller, Stancak, & Neuper, 1996; Klimesch, Sauseng, & Hanslmayr, 2007, for reviews). Like beta, alpha is found to be involved in top-down processes, and more specifically, control over stored motoric information via inhibition of the retrieval of interfering information (e.g. Hummel, Andres, Altenmüller, Dichgans, & Gerloff, 2002; Klimesch, 2012), and attentional control over sensory information (Wolfe & Bell, 2004). Moreover, alpha activity was related to timing of neural activity to facilitate different behavioural states (Nicolelis & Fanselow, 2002; Klimesch et al., 2007). As described above, beta is also related to top-down executive processes, which might explain why also alpha similarly varied as a function of mind wandering. The functions in which these bands are involved might have some overlap, explaining their similar increase during focused attention periods in the current results. The expected correlations between baseline TBR, changes in TBR pre- versus post-button press and ACS were not found in the current study. A relation between baseline TBR and this difference in TBR during MW episodes and on-task periods would possibly affirm that higher TBR over the longer period of spontaneous TBR as measured during a typical resting state measurement is influenced by episodes of mind wandering, which could theoretically explain previously observed relations between such spontaneous TBR and attentional control and other cognitive executive processes (e.g. Putman et al., 2010; 2014a; Angelidis et al., 2016). As the current sample showed no correlation between spontaneous TBR and ACS, our study confirms that MW is related to changes in frontal TBR but did not confirm the larger hypothesis that relations between executive control and baseline TBR are related to MW-related changes in brain activity. The absence of a significant correlation between baseline frontal TBR and attentional control is unexpected and contrary to several reports of this relation (Putman et al., 2010; 2014a; Angelidis et al., 2016; van Son et al., 2018a; Keune et al., 2017; but see Morillas-Romero et al., 2015;

Angelidis et al., 2018), which include negative correlations between TBR and subjectively as well as objectively measured attentional control. It is also unexpected in light of many observations of high TBR in AD(H)D (Barry et al., 2003; Arns et al., 2013). The current EEG measurements, both during baseline and the breath counting task, were recorded with only eyes closed to keep the procedure methodologically consistent with Braboszcz and Delorme (2011); this diverged from the alternating eyes-open-closed method that is typically used in previous studies of spontaneous TBR. Unpublished data from our lab, however, suggested no systematic differences between eyes-open or eyes-closed measurements in terms of frontal TBR in relation to other variables. It is therefore not clear if this difference in resting-state method contributed to the absence of a frontal TBR-ACS relation in the current data. Note also that previous reports of TBR-ACS relations were based on larger samples than the current one. Future studies might seek to investigate the relation between TBR and attentional control using both task-based and self-report measures of attentional control (see Angelidis et al., 2018, van Son et al., 2018a, Morillas-Romero et al., 2015; van Son et al., 2018b). All in all, it is not clear why the current data show no relation between baseline TBR, attentional control and MW-related TBR changes. This study confirms that MW, here conceived as a state of reduced attentional control, is related to higher TBR, but the larger hypothesis related to trait attentional control should be revisited in future studies.

Potential limitations of this study include that the implemented method causes a high between-subjects variance in the number of button presses. A substantial number of participants had to be excluded from analyses as they had too few analysable button presses or clean data epochs around the button press to reliably conduct analysis on (as in Braboszcz & Delorme, 2011). However, we retained 26 participants, which is more than twice the number of participants ($N = 12$) as assessed in Braboszcz and Delorme's (2011) study, providing a robust replication of their proof of principle study. Also, the present study assessed only female participants which should be taken into account for the generalizability of our findings. No clear gender differences in TBR have been found to our knowledge, however, some studies suggest resting-state beta activity to be higher in females compared to males (Putman, Arias-Garcia, Pantazi, & van Schie, 2012; Jaušovec, & Jaušovec, 2010; Wada, Takizawa, Zheng-Yan, & Yamaguchi, 1994). Such gender differences have not yet been investigated in MW-effects on EEG however, and future studies should therefore aim to include male subjects as well. Finally, although the results show a strong relation between scalp based EEG and mind wandering, and there is much evidence suggesting that TBR might reflect interactions between cortical and subcortical brain processes which could account for this finding, this interpretation remains based in indirect evidence. Future studies might attempt to revisit relations between TBR and mind wandering using for instance fMRI imaging to directly bridge this empirical gap.

In conclusion, this study confirms that increased frontal TBR is related to mind wandering, which is thought to reflect, among other things, a state of reduced top-down attentional control over thoughts, but unexpectedly found no relations between EEG and self-reported attentional control. This should be revisited in future studies, possibly combining EEG and fMRI.

[1]Used picture numbers in the *PEST*: **Negative**: 1120, 1220, 2981, 3053, 3120, 3230, 6315, 6560, 1070, 1205, 2900, 3110, 3261, 6260, 6540, 3000, 3064, 1114, 1300, 2800, 3051, 3060, 6313, 6570; **Positive**: 1340, 2058, 8120, 8186, 8200, 8205, 8540, 8350, 1710, 2070, 7325, 8040, 8192, 8370, 8460, 8490, 8470, 1750, 2040, 8161, 8300, 8400, 8497, 8620; **Neutral**: 5731, 7000, 7002, 7035, 7041, 7056, 7060, 7491, 5130, 7006, 7040, 7050, 7052, 7059, 7170, 7490, 5740, 7009, 7025, 7090, 7175, 7500, 7710, 7950.

References

Aleksanov, S. N., Vainstein, I. I., & Preobrashenskaya, L. A. (1986). Relationship between electrical potentials of the hippocampus, amygdala, and neocortex during instrumental conditioned reflexes. *Neuroscience and behavioral physiology, 16*(3), 199-207.

Angelidis, A., van der Does, W., Schakel, L., & Putman, P. (2016). Frontal EEG theta/beta ratio as an electrophysiological marker for attentional control and its test-retest reliability. *Biological psychology, 121*, 49-52.

Angelidis, A., Hagenaars, M., van Son, D., van der Does, W., & Putman, P. (2018). Do not look away! Spontaneous frontal EEG theta/beta ratio as a marker for cognitive control over attention to mild and high threat. *Biological psychology, 135*, 8-17.

Arns, M., Conners, C. K., & Kraemer, H. C. (2013). A decade of EEG theta/beta ratio research in ADHD: a meta-analysis. *Journal of attention disorders, 17*(5), 374-383.

Baird, B., Smallwood, J., Mrazek, M. D., Kam, J. W., Franklin, M. S., & Schooler, J. W. (2012). Inspired by distraction: mind wandering facilitates creative incubation. *Psychological science, 23*(10), 1117-1122.

Baker, S. N. (2007). Oscillatory interactions between sensorimotor cortex and the periphery. *Current opinion in neurobiology, 17*(6), 649-655.

Barry, R. J., Clarke, A. R., & Johnstone, S. J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. C*lin Neurophysiol, 114*(2), 171-183.

Barry, R. J., Fogarty, J. S., De Blasio, F. M., & Karamacoska, D. (2018). EEG phase states at stimulus onset in a variable-ISI Go/NoGo task: Effects on ERP components. *Biological psychology, 134*, 89-102.

Baumeister, R. F., & Masicampo, E. J. (2010). Conscious thought is for facilitating social and cultural interactions: How mental simulations serve the animal–culture interface. *Psychological review, 117*(3), 945.

Baumeister, R. F., Masicampo, E. J., & Vohs, K. D. (2011). Do conscious thoughts cause behavior? *Annual review of psychology, 62*, 331-361.

Belyavin, A., & Wright, N. A. (1987). Changes in electrical activity of the brain with vigilance. *Electroencephalography and clinical Neurophysiology, 66*(2), 137-144.

Bishop, S. J. (2008). Neural mechanisms underlying selective attention to threat. *Annals of the New York Academy of Sciences, 1129*(1), 141-152.

Bozhilova, N. S., Michelini, G., Kuntsi, J., & Asherson, P. (2018). Mind wandering perspective on attention-deficit/hyperactivity disorder. *Neuroscience and Biobehavioral Reviews, 92*, 464-476.

Braboszcz, C., & Delorme, A. (2011). Lost in thoughts: neural markers of low alertness during mind wandering. *Neuroimage, 54*(4), 3040-3047.

Brown, P. (2007). Abnormal oscillatory synchronisation in the motor system leads to impaired movement. *Current opinion in neurobiology, 17*(6), 656-664.

Buschman, T. J., & Miller, E. K. (2007). Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science, 315*(5820), 1860-1862.

Buschman, T. J., & Miller, E. K. (2009). Serial, covert shifts of attention during visual search are reflected by the frontal eye fields and correlated with population oscillations. *Neuron, 63*(3), 386-396.

Christoff, K., Ream, J. M., Geddes, L., & Gabrieli, J. D. (2003). Evaluating self-generated information: anterior prefrontal contributions to human cognition. *Behavioral neuroscience, 117*(6), 1161.

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2001). EEG-defined subtypes of children with attention-deficit/hyperactivity disorder. *Clinical Neurophysiology, 112*(11), 2098-2105.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews neuroscience, 3*(3), 201.

Daniel, R. S. (1967). Alpha and theta EEG in vigilance. *Perceptual and Motor Skills, 25*(3), 697-703.

Delaveau, P., Arruda Sanchez, T., Steffen, R., Deschet, K., Jabourian, M., Perlbarg, V., ... & Fossati, P. (2017). Default mode and task-positive networks connectivity during the N-Back task in remitted depressed patients with or without emotional residual symptoms. *Human brain mapping, 38*(7), 3491-3501.

Derryberry, D., & Reed, M. A. (2002). Anxiety-related attentional biases and their regulation by attentional control. *Journal of Abnormal Psychology, 111(2)*, 225-236.

Engel, A. K., & Fries, P. (2010). Beta-band oscillations—signalling the status quo? Current opinion in neurobiology, 20(2), 156-165.

Gordon, N. (2000). REVIEW Cognitive functions and epileptic activity. *Seizure-European Journal of Epilepsy, 9*(3), 184-188.

Gregoriou, G. G., Rossi, A. F., Ungerleider, L. G., & Desimone, R. (2014). Lesions of prefrontal cortex reduce attentional modulation of neuronal responses and synchrony in V4. *Nature neuroscience*, *17*(7), 1003.

Gratton, G., Coles, M. G., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Neurophysiology, 55*, 468-484.

Haegens, S., Luther, L., & Jensen, O. (2012). Somatosensory anticipatory alpha activity increases to suppress distracting input. *Journal of cognitive neuroscience, 24*(3), 677-685.

Hasenkamp, W., Wilson-Mendenhall, C. D., Duncan, E., & Barsalou, L. W. (2012). Mind wandering and attention during focused meditation: a fine-grained temporal analysis of fluctuating cognitive states. *Neuroimage, 59*(1), 750-760.

Hermans, E. J., Henckens, M. J., Joëls, M., & Fernández, G. (2014). Dynamic adaptation of large-scale brain networks in response to acute stressors. *Trends in neurosciences*, *37*(6), 304-314.

Hirsch, C. R., & Mathews, A. (2012). A cognitive model of pathological worry. *Behaviour Research and Therapy, 50*(10), 636-646.

Hollins, M., Harper, D., Gallagher, S., Owings, E. W., Lim, P. F., Miller, V., ... & Maixner, W. (2009). Perceived intensity and unpleasantness of cutaneous and auditory stimuli: an evaluation of the generalized hypervigilance hypothesis. *Pain, 141*(3), 215-221.

Hopfinger, J. B., Buonocore, M. H., & Mangun, G. R. (2000). The neural mechanisms of top-down attentional control. *Nature neuroscience, 3*(3), 284.

Hummel, F., Andres, F., Altenmüller, E., Dichgans, J., & Gerloff, C. (2002). Inhibitory control of acquired motor programmes in the human brain. *Brain, 125*(2), 404-420.

Jap, B. T., Lal, S., Fischer, P., & Bekiaris, E. (2009). Using EEG spectral components to assess algorithms for detecting fatigue. *Expert Systems with Applications, 36*(2), 2352-2359.

Jaušovec, N., & Jaušovec, K. (2010). Resting brain activity: differences between genders. *Neuropsychologia, 48*(13), 3918-3925.

Jenkinson, N., & Brown, P. (2011). New insights into the relationship between dopamine, beta oscillations and motor function. *Trends in neurosciences, 34*(12), 611-618.

Karapanagiotidis, T., Bernhardt, B. C., Jefferies, E., & Smallwood, J. (2017). Tracking thoughts: Exploring the neural architecture of mental time travel during mind-wandering. *Neuroimage, 147,* 272-281.

Keune, P. M., Hansen, S., Weber, E., Zapf, F., Habich, J., Muenssinger, J., ... & Oschmann, P. (2017). Exploring resting-state EEG brain oscillatory activity in relation to cognitive functioning in multiple sclerosis. *Clinical Neurophysiology, 128*(9), 1746-1754.

Kitsune, G. L., Cheung, C. H., Brandeis, D., Banaschewski, T., Asherson, P., McLoughlin, G., & Kuntsi, J. (2015). A matter of time: the influence of recording context on EEG spectral power in adolescents and young adults with ADHD. *Brain topography, 28*(4), 580-590.

Klimesch, W. (2012). Alpha-band oscillations, attention, and controlled access to stored information. *Trends in cognitive sciences, 16*(12), 606-617.

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition–timing hypothesis. *Brain research reviews, 53*(1), 63-88.

Knyazev, G. G. (2007). Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neuroscience and Biobehavioral Reviews, 31*, 377-395.

Knyazev, G. G. (2012). EEG delta oscillations as a correlate of basic homeostatic and motivational processes. *Neuroscience & Biobehavioral Reviews, 36*(1), 677-695.

Loo, S. K., Cho, A., Hale, T. S., McGough, J., McCracken, J., & Smalley, S. L. (2013). Characterization of the theta to beta ratio in ADHD: identifying potential sources of heterogeneity. *Journal of attention disorders, 17*(5), 384-392.

Lorist, M. M., Bezdan, E., ten Caat, M., Span, M. M., Roerdink, J. B., & Maurits, N. M. (2009). The influence of mental fatigue and motivation on neural network dynamics; an EEG coherence study. *Brain Research, 1270*, 95-106.

Marrufo, M. V., Vaquero, E., Cardoso, M. J., & Gomez, C. M. (2001). Temporal evolution of α and β bands during visual spatial attention. *Cognitive Brain Research, 12*(2), 315-320.

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: the default network and stimulus-independent thought. *Science*, *315*(5810), 393-395.

McVay, J. C., & Kane, M. J. (2009). Conducting the train of thought: working memory capacity, goal neglect, and mind wandering in an executive-control task. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *35*(1), 196.

Mogg, K., & Bradley, B. P. (1998). A cognitive-motivational analysis of anxiety. *Behaviour research and therapy*, *36*(9), 809-848.

Mogg, K., & Bradley, B. P. (2016). Anxiety and attention to threat: cognitive mechanisms and treatment with attention bias modification. *Behaviour Research and Therapy*, *87*, 76-108.

Morillas-Romero, A., Tortella-Feliu, M., Bornas, X., & Putman, P. (2015). Spontaneous EEG theta/beta ratio and delta–beta coupling in relation to attentional network functioning and self-reported attentional control. *Cognitive, Affective, & Behavioral Neuroscience, 15*(3), 598-606.

Nicolelis, M. A., & Fanselow, E. E. (2002). Thalamocortical optimization of tactile processing according to behavioral state. *Nature neuroscience, 5*(6), 517.

Nunez, P. L., & Cutillo, B. A. (Eds.). (1995). *Neocortical dynamics and human EEG rhythms*. Oxford University Press, USA.

Ottaviani, C., Shahabi, L., Tarvainen, M., Cook, I., Abrams, M., & Shapiro, D. (2015). Cognitive, behavioral, and autonomic correlates of mind wandering and perseverative cognition in major depression. *Frontiers in neuroscience, 8,* 433.

Pfurtscheller, G., Stancak Jr, A., & Neuper, C. (1996). Event-related synchronization (ERS) in the alpha band—an electrophysiological correlate of cortical idling: a review. *International journal of psychophysiology, 24*(1-2), 39-46.

Putman, P., Van Peer, J., Maimari, I., & Van der Werff (2010). EEG theta/beta ratio in relation to fear-modulated response-inhibition, attentional control, and affective traits. *Biological Psychology, 83*, 73-78.

Putman, P., Arias-Garcia, E., Pantazi, I., & van Schie, C. (2012). Emotional Stroop interference for threatening words is related to reduced EEG delta–beta coupling and low attentional control. *International Journal of Psychophysiology, 84*(2), 194-200.

Putman, P., Verkuil, B., Arias-Garcia, E., Pantazi, I., & Van Schie, C. (2014a). EEG theta/beta ratio as a potential biomarker for attentional control and resilience against deleterious effects of stress on attention. *Cognitive, Affective, & Behavioral Neuroscience, 14*, 782-791.

Putman, P., Verkuil, B., Arias-Garcia, E., Pantazi, I., & Van Schie, C. (2014b). Erratum to: EEG theta/beta ratio as a potential biomarker for attentional control and resilience against deleterious effects of stress on attention. *Cognitive, Affective, & Behavioral Neuroscience*, 14, 1165.

Ruby, F. J., Smallwood, J., Engen, H., & Singer, T. (2013). How self-generated thought shapes mood—the relation between mind-wandering and mood depends on the socio-temporal content of thoughts. *PloS one, 8*(10), e77554.

Sari, B. A., Koster, E. H., Pourtois, G., & Derakshan, N. (2016). Training working memory to improve attentional control in anxiety: A proof-of-principle study using behavioral and electrophysiological measures. *Biological Psychology, 121*, 203-212.

Schooler, J. W. (2002). Re-representing consciousness: Dissociations between experience and meta-consciousness. *Trends in cognitive sciences, 6*(8), 339-344.

Schutte, I., Kenemans, J. L., & Schutter, D. J. (2017). Resting-state theta/beta EEG ratio is associated with reward-and punishment-related reversal learning. *Cognitive, Affective, & Behavioral Neuroscience, 17*(4), 754-763.

Schutter, D. J., & Knyazev, G. G. (2012). Cross-frequency coupling of brain oscillations in studying motivation and emotion. *Motivation and emotion, 36*(1), 46-54.

Schutter, D. J. L. G., & Van Honk, J. (2005). Electrophysiological ratio markers for the balance between reward and punishment. *Cognitive Brain Research, 24*(3), 685–690.

Schutter, D. J., & Van Honk, J. (2004). Decoupling of midfrontal delta-beta oscillations after testosterone administration. *International Journal of Psychophysiology, 53*(1), 71–73.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., ... & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience, 27*(9), 2349-2356.

Seidenbecher, T., Laxmi, T. R., Stork, O., & Pape, H. C. (2003). Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. *Science, 301*(5634), 846-850.

Smallwood, J., Beach, E., Schooler, J. W., & Handy, T. C. (2008). Going AWOL in the brain: Mind wandering reduces cortical analysis of external events. *Journal of cognitive neuroscience, 20*(3), 458-469.

Smallwood, J. (2013). Distinguishing how from why the mind wanders: a process–occurrence framework for self-generated mental activity. *Psychological bulletin, 139*(3), 519.

Smallwood, J., Brown, K., Baird, B., & Schooler, J. W. (2012). Cooperation between the default mode network and the frontal–parietal network in the production of an internal train of thought. *Brain research, 1428*, 60-70.

Smallwood, J., Nind, L., & O'Connor, R. C. (2009). When is your head at? An exploration of the factors associated with the temporal focus of the wandering mind. *Consciousness and cognition, 18*(1), 118-125.

Smallwood, J., & Schooler, J. W. (2006). The restless mind. *Psychological bulletin, 132*(6), 946.

Stawarczyk, D., Majerus, S., Catale, C., & D'Argembeau, A. (2014). Relationships between mind-wandering and attentional control abilities in young adults and adolescents. *Acta psychologica, 148*, 25-36.

Strijkstra, A. M., Beersma, D. G., Drayer, B., Halbesma, N., & Daan, S. (2003). Subjective sleepiness correlates negatively with global alpha (8–12 Hz) and positively with central frontal theta (4–8 Hz) frequencies in the human resting awake electroencephalogram. *Neuroscience letters, 340*(1), 17-20.

Tortella-Feliu, M., Morillas-Romero, A., Balle, M., Llabrés, J., Bornas, X., & Putman, P. (2014). Spontaneous EEG activity and spontaneous emotion regulation. *International Journal of Psychophysiology, 94*(3), 365-372.

Uddin, L. Q., Kelly, A. C., Biswal, B. B., Margulies, D. S., Shehzad, Z., Shaw, D., ... & Milham, M. P. (2008). Network homogeneity reveals decreased integrity of default-mode network in ADHD. *Journal of neuroscience methods, 169*(1), 249-254.

Unsworth, N., & McMillan, B. D. (2014). Similarities and differences between mind-wandering and external distraction: A latent variable analysis of lapses of attention and their relation to cognitive abilities. *Acta Psychologica, 150*, 14-25.

Uusberg, A., Uibo, H., Kreegipuu, K., & Allik, J. (2013). EEG alpha and cortical inhibition in affective attention. *International Journal of Psychophysiology, 89*(1), 26-36.

van Son, D., Angelidis, A., Hagenaars, M. A., van der Does, W., & Putman, P. (2018a). Early and late dot-probe attentional bias to mild and high threat pictures: Relations with EEG theta/beta ratio, self-reported trait attentional control, and trait anxiety. *Psychophysiology*, e13274.

van Son, D., Schalbroeck, R., Angelidis, A., van der Wee, N. J., van der Does, W., & Putman, P. (2018b). Acute effects of caffeine on threat-selective attention: moderation by anxiety and EEG theta/beta ratio. *Biological psychology, 136,* 100-110.

Wada, Y., Takizawa, Y., Zheng-Yan, J., & Yamaguchi, N. (1994). Gender differences in quantitative EEG at rest and during photic stimulation in normal young adults. *Clinical Electroencephalography, 25*(2), 81-85.

Weymar, M., Keil, A., & Hamm, A. O. (2013). Timing the fearful brain: unspecific hypervigilance and spatial attention in early visual perception. *Social cognitive and affective neuroscience, 9*(5), 723-729.

Wischnewski, M., Zerr, P., & Schutter, D. J. (2016). Effects of Theta Transcranial Alternating Current Stimulation Over the Frontal Cortex on Reversal Learning. *Brain stimulation, 9*(5), 705-711.

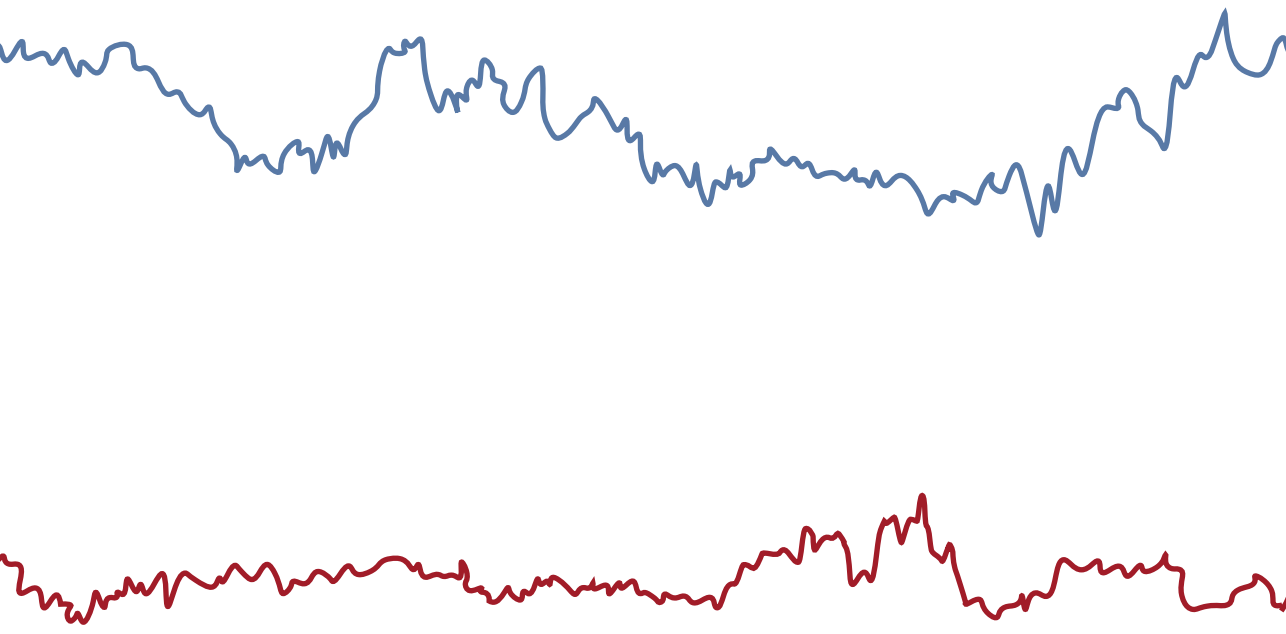
Wolfe, C. D., & Bell, M. A. (2004). Working memory and inhibitory control in early childhood: Contributions from physiology, temperament, and language. *Developmental psychobiology, 44*(1), 68-83.

Wróbel, A. (2000). Beta activity: a carrier for visual attention. *Acta neurobiologiae experimentalis, 60*(2), 247-260.

CHAPTER 4.

EEG theta/beta ratio co-varies with mind wandering versus controlled thought and functional connectivity in the executive control network

Dana van Son, Mischa de Rover, Frances M. De Blasio, Willem van der Does, Robert J. Barry, Peter Putman



ABSTRACT

Background: The ratio between frontal resting state EEG power in the theta and beta frequency bands (theta/beta ratio, TBR) has been negatively related to cognitive control, but it is unknown which psychological processes during resting state account for this relation. Increased theta and reduced beta power have been observed during mind wandering (MW). MW has been related to decreased connectivity in the executive control network (ECN) of the human brain and increased connectivity in the default mode network (DMN). Possibly then, high resting state TBR might reflect MW-related fluctuations in TBR, associated with variation in ECN and DMN connectivity. Direct evidence for these relationships is still lacking.

Goal: To clarify the relations between TBR during resting state and during MW versus controlled thought, and its neural correlates reflected in ECN and DMN connectivity.

Methods: Thirty-eight healthy participants performed a 40-minute breath-counting task once while EEG was measured and again during MRI scanning. Participants indicated awareness of MW-episodes with button presses.

Results: Frontal TBR was higher during MW-episodes than during controlled thought and this was marginally related to resting state TBR. DMN connectivity was higher and ECN connectivity was lower during MW episodes. Greater ECN connectivity during focus than MW was correlated to lower TBR during focus than MW.

Conclusions: These results provide the first evidence of the neural correlates of TBR and its functional dynamics and further establish frontal TBR to be a useful tool in the study of executive control, in normal and potentially abnormal psychology.

Resting state EEG provides measures of neural oscillatory activity in different frequency bands, such as the slow theta (4-7 Hz) and faster beta (13-30 Hz). Lubar (1991) reported higher theta-beta ratio (TBR) in attention deficit-hyperactivity disorder (ADHD) and attention deficit disorder (ADD), which has been frequently replicated since (e.g. see Arns, Conners, & Kraemer, 2013; Barry, Clarke, & Johnstone, 2003; Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009). Research into the relation between TBR and AD(H)D has remained largely descriptive, however – with the exception of studies that demonstrated that the administration of catecholamine agonists is therapeutic in AD(H)D through restoration of sub-optimal prefrontal cortical control (i.e., normalizing TBR; (Arns et al., 2009; Arnsten, 2006; Clarke et al., 2007; Loo, Lenartowicz, & Makeig, 2016; Loo, Teale, & Reite, 1999). This further suggests that high TBR scores may reflect the (frontal) cortical hypoactivity which characterizes these disorders (e.g. Bush, 2011).

The functional cognitive significance of TBR has been further investigated in non-AD(H)D samples. High TBR in a healthy sample correlated with sub-optimal performance on motivated decision-making tasks which require executive reversal learning and inhibition of dominant approach-motivated behavior (Massar, Rossi, Schutter, & Kenemans, 2012; Massar, Kenemans, & Schutter, 2014; Schutter & Van Honk, 2005a). TBR is also negatively related to other functions requiring prefrontal executive control: modulation of response inhibition in an emotional go/no-go task (Putman, van Peer, Maimari, & van der Werff, 2010) and down-regulation of negative affect (Tortella-Feliu, Morillas-Romero, Balle, Llabrés, Bornas, & Putman, 2014). In healthy samples, TBR correlated negatively with self-reported trait (Angelidis, van der Does, Schakel, & Putman, 2016; Putman et al., 2010; Putman, Verkuil, Arias-Garcia, Pantazi, & van Schie, 2014; van Son, Angelidis, Hagenaars, van der Does & Putman, 2018a) and state attentional control (Putman et al., 2014) and with the controlled modulation of threat selective attention (Angelidis, Hagenaars, van Son, van der Does, & Putman, 2018; van Son et al., 2018a; van Son, Schalbroeck, Angelidis, van der Wee, van der Does, & Putman, 2018b). TBR also correlated inversely with objectively-measured attentional control in a sample of multiple sclerosis patients with clinically-impaired attention (Keune et al., 2017). Taken together, these studies in non-AD(H)D samples demonstrate that TBR is negatively related to a variety of psychological functions that require prefrontal executive regulation of emotional and motivational processes which are likely subcortically mediated. It also indicates that TBR reflects a continuum of executive cognitive processing efficiency, rather than being a marker of a particular disorder. Almost all previous studies examining TBR in relation to executive processes assessing healthy participants focused on frontal TBR, which is also the focus of the current study (Angelidis et al., 2018; Angelidis et al., 2016; Putman et al., 2010, 2014; Sari, Koster, Pourtois, & Derakshan, 2016; Schutter & Van Honk, 2004, 2005a; van Son et al., 2018a; Tortella-Feliu et al., 2014; van Son et al., 2018b).

It should be noted, that TBR is typically measured during several minutes of resting state, without manipulation of executive processes. Consequently, the evidence that TBR reflects executive control functions remains indirect. It is unclear exactly which processes these relations reflect or what are TBR's neurological underpinnings. A more thorough understanding would require continuous measurement of TBR during the execution of experimentally identified psychological functions.

The processes related to TBR, including threat selective attention, are not restricted to attentional

processing of external stimuli. 'Mind wandering' (MW; Ottaviani et al., 2015) occurs when thoughts are not controlled by top-down processes such as attentional control (McVay & Kane, 2009; Unsworth & McMillan, 2014). MW is a predictor of performance errors (Smallwood & Schooler, 2006) and poor executive cognitive control (Smallwood, Nind, & O'Connor, 2009; Stawarczyk, Majerus, Maquet, & D'Argembeau, 2011; Unsworth & McMillan, 2014). Consequently, the frequently observed relation between resting-state TBR and indices of executive cognitive control might reflect more frequent or prolonged episodes of MW occurring during the resting state measurement in people with low attentional control.

Higher EEG theta band power and lower EEG beta band power have been observed during states of MW compared to focussed attention (Braboszcz & Delorme, 2011). Participants in that study were asked to press a button as soon as they realized that their mind had wandered off a breath-counting task. Higher TBR occurred during a 6 s window just before a button press and lower TBR during a 6 s window just after the button press, when participants refocused on their breath counting. We recently replicated this study and similarly found higher frontal TBR during the MW episodes compared to the task focused periods (van Son, De Blasio, Fogarty, Angelidis, Barry & Putman, 2018c). These results support a hypothesis that relations between resting state TBR and executive control might reflect the brain dynamics which occur when participants engage in MW, or related states of reduced cognitive control during the resting state measurement. This warrants a comparison between EEG-based TBR and functional-Magnetic Resonance Imaging (fMRI)-based localization of the corresponding cortical and subcortical activity.

fMRI studies have revealed that areas including the posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), parahippocampal gyrus and the angular gyrus are active during MW (Hasenkamp, Wilson-Mendenhall, Duncan, & Barsalou, 2012; Ward, Schultz, Huijbers, Van Dijk, Hedden, & Sperling, 2014). These areas are jointly referred to as the default mode network (DMN; Greicius, Krasnow, Reiss, & Menon, 2003). Functional connectivity within this network is high during task-irrelevant thoughts (Stawarczyk et al., 2011) and is related to MW (Christoff, Ream, Geddes, & Gabrieli, 2003; Karapanagiotidis, Bernhardt, Jefferies, & Smallwood, 2017; Smallwood, Beach, Schooler, & Handy, 2008) and also to ruminative thoughts (Delaveau et al., 2017). Moreover, it has been reported that the dorso-lateral prefrontal cortex (DLPFC), dorsal anterior cingular cortex (dACC) and posterior parietal regions became active during awareness of MW, during subsequent attentional shifting back to task performance and during subsequent sustained attention in a breath-counting task (Christoff et al., 2003; Hasenkamp et al., 2012). These brain regions are elements of the so-called executive control network (ECN, Seeley et al., 2007). The ECN is active during cognitive tasks involving demanding top-down processes including working memory, mental calculation and spatial working memory (Mazoyer et al., 2001), and this network is associated with goal-directed attentional control (Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002; Seeley et al., 2007).

In summary, states of MW versus controlled attention have been associated with increased TBR (Braboszcz & Delorme, 2011; van Son et al., 2018c) and with decreased activity in brain areas that are involved in executive control (Hasenkamp et al., 2012), but in separate studies. Together, these findings support the hypothesis that low TBR reflects a state of increased top-down cognitive control, involving functional connectivity

in the ECN, whereas high TBR reflects uncontrolled thought and functional connectivity in the DMN. The aim of the current study was to further clarify the relations between resting state TBR and TBR's dynamic relation with states of increased/decreased cognitive control and their neurobiological underpinning in terms of ECN/DMN connectivity. We assessed MW and focused attention during EEG and fMRI measurements in the same participants on two separate days, exploiting TBR's excellent retest reliability (Angelidis et al., 2016; Keune et al., 2017).

We tested the following hypotheses:
I) Frontal TBR is higher during MW episodes than during focused episodes, and this MW-related change in frontal TBR is related to resting-state (i.e., baseline) frontal TBR. We also conducted an exploratory assessment of changes in the EEG delta and alpha bands in the present investigation, as MW-related changes in these bands were observed in van Son et al., (2018c) and Braboszcz and Delorme (2011).
II) MW-related changes in frontal TBR mediate a e relationship between resting-state frontal TBR and attentional control.
III) Functional connectivity within the ECN is stronger during focused episodes than during MW episodes, with the opposite pattern of functional connectivity within the DMN.
IV) MW-related EEG changes are positively correlated with MW-related changes of the functional connectivity within the DMN and negatively with changes of connectivity in the ECN.

Methods

Participants

Eighty-four right-handed participants between 18 and 32 years (35 men) were recruited from Leiden University. Exclusion criteria were factors which would likely adversely affect participation, EEG, MRI or attention, including severe physical or psychological dysfunction, and/or the use of psychotropic medication, and having typical contraindications for MRI scanning. Baseline resting-state TBR and MW-related EEG were assessed during the first session, and only those participants who reported sufficient MW episodes for analysis (defined here as >24 reported episodes) were invited to return for a second session on a separate day to perform the same task in the MRI scanner; this was done in order to increase the chance of obtaining enough button presses during MRI for reliable analysis. Informed consent was obtained prior to testing, and participants received a monetary reimbursement of €15 at the end of each session to compensate them for their participation. The study was approved by the Medical Ethics Committee of Leiden University Medical Center (LUMC).

Materials

Questionnaires. Participants completed the trait version of the State-Trait Anxiety Inventory (STAI-t; Spielberger, Gorsuch, & Lushene, 1970) and the Attentional Control Scale (ACS; Derryberry & Reed, 2002). The STAI-t assesses trait anxiety (20 items, range 20-80; Cronbach's alpha in the current study = 0.89) with items like 'I feel nervous and restless' and 'I have disturbing thoughts' on a four-point Likert scale. The ACS assesses self-

reported attentional control in terms of attentional focus, attentional switching and the capacity to quickly generate new thoughts (20 items, range 20-80; Cronbach's alpha in the present study = 0.86), with items like 'I can quickly switch from one task to another' and 'I have a hard time concentrating when I'm excited about something'.

Breath counting task. The breath counting task was as in van Son et al. (2018c), based on Braboszcz and Delorme (2011). Participants were asked to count their breath cycles (one inhalation and one exhalation) from 1 to 10 and then start from 1 again (with eyes closed). They were instructed to press a button whenever they realized they had stopped counting, continued counting further than 10, or had to reflect intensively on what the next count was. Prior to performance of the task, participants were instructed to bring their focus back to breath-counting after pressing the button. To retain consistency with the procedure of Braboszcz and Delorme (2011), and subsequently van Son et al. (2018c), a passive auditory oddball was presented during the task and debriefing questions were presented at the end of each block as it is possible that this might influence the occurrence of MW episodes. The oddball related EEG and fMRI data were not of interest here and so participants were instructed to ignore the tones, and the responses to the debriefing questions were not analyzed.

EEG recording. Continuous EEG was measured from 31 Ag/AgCl electrodes electrodes located according to the 10-20 system, using an ActiveTwo BioSemi system (BioSemi, The Netherlands). Electrodes were also placed on the left and right mastoids for offline re-referencing. EEG data were collected at a sampling rate of 1024 Hz and amplified with a gain of 16x at a bandwidth between DC-400 Hz, and were down-sampled to 256 Hz for offline processing.

MRI recording parameters. A whole-brain 3D T1-weighted structural scan and two task scans (T2*-weighted echo-planar images; EPIs) were acquired using a 3-T Philips Achieva scanner equipped with a 32-channel head coil. The T1-weighted scan (field of view (FOV): 224 x 177.33 x 168 mm; 140 slices; in-plane voxel resolution = 0.88 × 0.88 mm; slice thickness = 1.2 mm; TR: 9.8 ms; TE: 4.59 ms; flip angle 8°; acquisition matrix: 192 x 192; scan duration: 5 min.) was used for registration to the standard 2-mm MNI152 template image. The task scans consisted of 542 whole brain T2*-weighted EPIs (FOV: 220 x 114.7 x 220 mm; 38 slices; in-plane voxel resolution = 2.75 x 2.75 mm; slice thickness = 2.75 mm + 0.275 mm slice gap; TR: 2200 ms; TE: 30 ms; flip angle 80°; acquisition matrix: 80 x 80; scan duration: 20 min. each).

Procedure

General Procedure. During the first session, informed consent was obtained and participants completed the ACS and the STAI-t. EEG equipment was then fitted and used to measure activity during a ten minute resting-state with eyes closed, and then during the breath counting task which comprised two 20 minute blocks (40 minutes in total) with a ~2-minute break between. Participants who reported sufficient instances of MW episodes (>24) at this session were invited to participate in a second session within seven days. During this second session,

participants repeated the breath counting task during MRI acquisition.

Data Reduction

Defining epochs for MW and focussed attention. Previous studies (Braboszcz & Delorme, 2011; van Son et al., 2018c) analysed the -8 s to -2 s window prior to the button press as MW episodes, and the 2 s to 8 s window following the button press as focussed attention. However, due to the reduced temporal precision of MRI data acquisition (a repetition time [TR] of 2.2 s), we selected only those TRs that fitted fully within those windows for fMRI hypothesis-testing. This resulted in the selection of a pre-button press MW window of -7.1 s to -2.7 s and a post-button press focused attention window of 1.7 s to 6.1 s (thus 2 TRs each; corresponding to the TR windows of fMRI data of -1.1 s to 3.3 s and 7.7 to 12.1 s when taking into account the standard 6 s for the heamodynamic response function [HRF]). These narrower epochs were therefore used to quantify the MW (i.e., -7.1 to -2.7 s) and focussed attention (i.e., 1.7 to 6.1 s) windows for both the EEG and fMRI data, facilitating their joint analysis.

EEG spectral composition: Resting-state. For all EEG analyses, frontal EEG measures were calculated by averaging the data from F3, Fz and F4 positions. Resting-state EEG data were re-referenced offline to the linked mastoids and automatically corrected for ocular artifacts (Gratton, Coles, & Donchin, 1983) in segments of 4 seconds using Brain Vision Analyzer V2.04 (Brain Products GmbH, Germany). Baseline resting state EEG was then subjected to a Fast Fourier Transformation (Hamming window length 10%) to calculate power density in the theta (4-7 Hz) and beta (13-30 Hz) bands. TBR was calculated by dividing the power density in theta by that in beta. Baseline EEG values were non-normally distributed and were therefore log-normalized with a log10 transformation.

EEG spectral composition: Breath-counting task. The EEG data recorded during the breath counting task was similarly pre-processed in Brain Vision Analyzer V2.0.4 (Brain Products GmbH, Germany). This was used to re-reference the data offline, apply an ocular correction, interpolate bad channels, and extract single trial epochs for 8.25 s pre- to 8.25 s post- each button-press. The remaining data quantification was completed within MATLAB (The Mathworks, Version 8.0.0.783, R2012b) using EEGLAB (Version 13.4; Delorme & Makeig, 2004) and custom scripts.

Event Related Spectral Perturbation (ERSP) data were derived at each site for each participant using 257 applications of a 500 ms (128 point) sliding Discrete Fourier Transform (DFT) window. The data in each window were DC corrected, multiplied by a 10% Hanning window, and zero padded to 1 s (256 points) prior to the application of the DFT, and a subsequent correction was applied for the use of the Hanning window. This yielded absolute power ERSP data from -8 to +8 s relative to the button-press at 1 Hz spectral resolution, and 62.5 ms temporal resolution. Mean (across button-press) ERSP data were computed within-subjects, and the associated mean ERSP band powers were derived at each site for delta (1-3 Hz), theta (4-7 Hz), alpha (8-12 Hz), and beta (13-30 Hz) during the 4.4 s MW (-7.1 to -2.7 s) and focused attention (1.7 to 6.1 s) windows of interest. These data were

not normally distributed and were therefore normalized with a log10 transformation prior to analysis.

Functional MRI analysis. Data were pre-processed using FSL version 5.0.7 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). First, brain extraction tool (BET as implemented in FSL) was used to subtract non-brain tissue from the structural images. Next, all task data (the EPIs) were motion corrected, high-pass filtered (100 s), registered to the structural images (12 dof), and spatially smoothed using a 5mm full width half maximum (FWHM) Gaussian kernel. Probabilistic Independent Component Analysis (Beckmann, Mackay, Filippini, & Smith, 2009) was carried out using MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) Version 3.05 as implemented in FSL. The pre-processed task data of all participants were decomposed into 15 components. The components representing DMN and ECN networks were selected based on Smith et al., (2009). The set of spatial maps from the DMN component and ECN component were used to generate subject-specific versions of the spatial maps, and associated timeseries, using dual regression (Beckmann et al., 2009). For each subject, the set of spatial maps was regressed per component (as spatial regressors in a multiple regression) into the subject's 4D space-time dataset, resulting in a set of subject-specific time-points, one set of beta values for each component. The beta values for the DMN and ECN components were selected for further analysis. All beta values were normalized by subtracting the average of each value per brain network and then log10 transformed to correct for skewness.

Results

Participants

Of the 84 participants that completed the first session, 56 participants reported sufficient instances of MW episodes (>24) and were invited to participate in the second session within seven days (mean number of days between sessions = 2.8, $SD = 1.9$; range 1-7 days). Only those participants with enough clean EEG data epochs (>10), and sufficient instances of MW episodes in the MRI scanner (>14), were considered for inclusion in this study, resulting in complete data for 27 participants (16 males). These participants had a mean age of 24.7 (SD = 2.7 range: 18-30) years. Their mean ACS score was 51.70 ($SD = 7.83$, range 39-69), and their STAI-t score was 39.15 ($SD = 8.95$, range 26-60). One participant had raw EEG theta and beta values more than three SDs above the mean in the breath counting task; the participant's data were therefore omitted from this study.

Hypothesis I: MW related changes in frontal TBR related to baseline TBR.

In the breath-counting task, participants had between 21 and 92 button presses during the EEG session ($M = 47.96$, $SD = 20.54$), and between 15 and 115 button presses during the MRI session ($M = 49.41$, $SD = 21.55$). Number of button presses did not differ significantly between these sessions, $t(26) = 0.36$, $p = 0.723$, but were significantly correlated ($r = 0.51$; $p = 0.007$). The grand mean frontal ERSP data (across F3, Fz, F4) are visualized in **Figure 4.1** for this task. Mean frontal ERSP data (across F3, Fz, F4) in the pre- and post-button press windows of interest, representing MW and focused episodes, respectively, were assessed using paired samples t-tests; these analyses were conducted independently for the theta and beta bands, and for the TBR. As seen in **Figure 4.1**,

theta power was significantly higher during the MW (pre) then focused (post) episodes (t[25] = 2.38, p = 0.025, d = 0.47), and beta was significantly lower during the MW (pre) compared to focused (post) episodes (t[25] = -3.79, p = 0.001, d = 0.74). TBR was confirmed to be significantly higher during MW (pre) compared to focused (post) episodes (t[25] = 5.72, p < 0.001, d = 1.13), and these values (TBR in MW and focused attention) were highly correlated, (r[24] = 0.93, p < 0.001).

TBR of the mean frontal resting-state power-densities (across F3, Fz, F4) in these same participants was 1.09 (SD = 0.60, range 0.35-3.06 [raw, un-normalized values]). Frontal resting-state TBR was correlated marginally with the MW-related change in frontal TBR (i.e., MW minus focused frontal TBR, or pre- minus post-button press); r(24) = 0.35, p = 0.078. That is, higher resting or baseline TBR predicted a greater difference in TBR between MW relative to focus periods. Together these findings confirm Hypothesis I.

Additional post-hoc paired-samples t-tests were conducted to test changes in frontal alpha and frontal delta band power for the same MW (pre) versus focused (post) episodes. Frontal alpha power was significantly reduced during the MW compared to focused episodes (t[25] = -3.19, p = 0.004, d = 0.63), although delta showed no significant change between the MW and focused attention episodes (t[25] = 1.62, p = 0.117, d = 0.32).

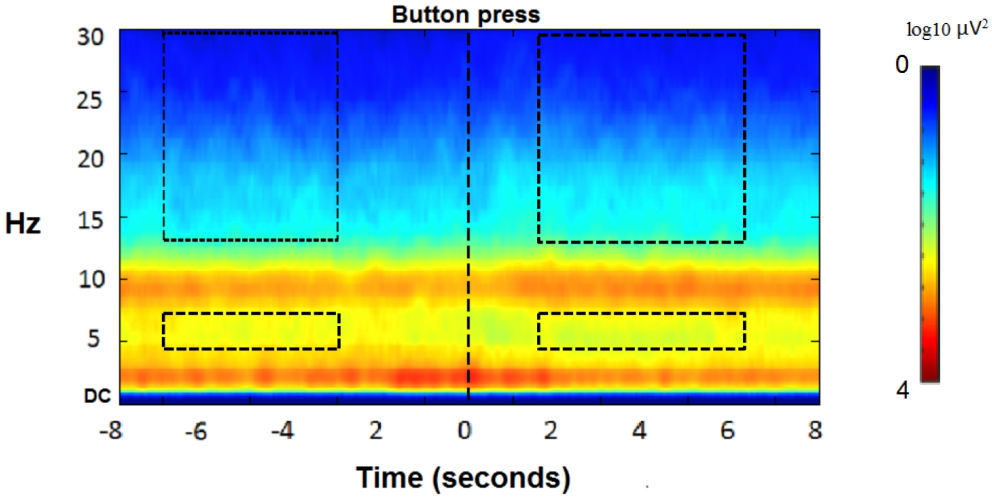


Figure 4.1. ERSP spectral plot of the frontal average (across F3 Fz F4 sites) at 1 Hz frequency resolution, and 62.5 ms time resolution. Rectangular frames highlight the epochs of primary interest corresponding to the two 'real time' 2-TR epochs that fall within the pre-defined periods for MW and focussed attention (the upper, high frequency frames are for beta, the lower for theta).

Hypothesis II: baseline frontal TBR and attentional control, mediated by changes in TBR

Pearson correlation was used to test for a relationship between frontal resting-state TBR and ACS. This correlation was not significant (r[24] =-0.14, p = 0.51), and remained non-significant when controlling for STAI-t (c.f. Angelidis et al., 2016; Putman et al., 2010, 2014; van Son et al., 2018a); r(23) =-0.03, p = 0.90. Consequently, hypothesis II was not supported. Additional analyses revealed that resting-state frontal TBR was correlated positively with STAI-t score (r[24] =0.43, p = 0.029), and this relationship remained significant when controlling for ACS (r[24] =0.41, p = 0.041).

Hypothesis III: Changes in DMN and ECN functional connectivity.

One participant had DMN normalized functional connectivity values over all time points of more than three standard deviations above the mean, and was therefore removed from all further analyses involving fMRI data. Averages for the DMN and ECN were calculated for the MW (pre) and focused (post) periods, and subjected to a 2 (time) x 2 (networks) repeated measures (RM) ANOVA on DMN and ECN functional connectivity during MW (pre) and focused (post) periods. No main effect was found for time F(1,25) = 0.89, p = 0.354, η_p^2 = 0.04, however, there was a main effect for networks, F(1,25) = 5.78, p = 0.024, η_p^2 = 0.19, with activity greater in ECN than DMN (see **Figure 4.2**.). A significant interaction effect was found between time and networks; F(1,25) = 31.04, p < 0.001, η_p^2 = 0.55. As seen in **Figure 4.2** and confirmed by post-hoc t-tests, DMN functional connectivity was significantly higher during MW (pre) than focused (post) episodes; t(26) = 5.59, p < 0.001, d = 1.10, whereas ECN functional connectivity was significantly lower during MW (pre) compared to focused (post) episodes; t(25) = -4.66, p < 0.001, d = 0.92. This supports hypothesis III.

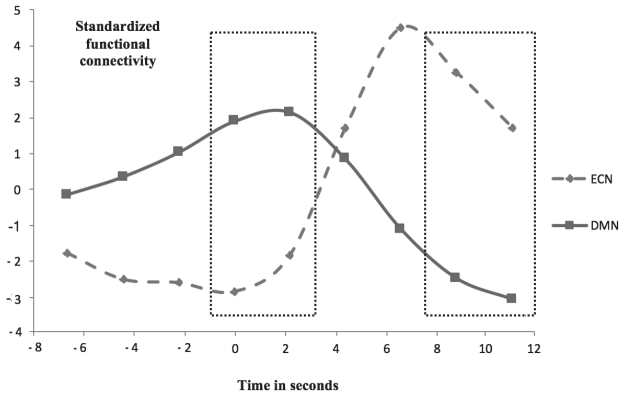


Figure 4.2. Slopes of normalized functional connectivity over time for the executive control network (ECN) and the default mode network (DMN). Rectangular frames highlight the epochs of interest. After correction for the HRF delay, the button press occurs at 6s. The y-axis shows the demeaned beta values resulting from the first stage of the dual regression, representing functional connectivity.

Hypothesis IV: Relation between MW-related EEG and fMRI changes.

The 2 (time) x 2 (networks) RM ANOVA from hypothesis III was repeated, with the MW-related frontal TBR change (computed as MW minus focused attention frontal TBR) added as a covariate into the model to assess if MW-related TBR is related to MW-related connectivity. A significant interaction effect was found for time x networks x MW-related frontal TBR changes; $F(1,23) = 7.01$, $p = 0.014$, $\eta_p^2 = 0.23$.

To further investigate this relation, post-hoc Pearson correlations were calculated between the frontal MW-related TBR change scores and the corresponding difference scores (MW minus focused attention) for the functional connectivity in DMN and ECN. No association was found between the MW-related changes in both frontal TBR and DMN functional connectivity; $r(23) = 0.30$, $p = 0.15$. However, a significant correlation was found between the MW-related changes in both frontal TBR and ECN functional connectivity; $r(23) = -0.58$, $p = 0.002$. **Figure 4.3** displays the scatterplot of the latter correlation, and visual inspection suggested that this relationship may have been driven by one or two influential data points. We therefore repeated each analysis using Spearman's rank order correlation which although less powerful is more robust against such influences (Nešlehová, 2007). The outcomes supported the results from the Pearson correlations; the MW-related changes in both frontal TBR and DMN functional connectivity were again non-significant ($r[23] = 0.19$, $p = 0.36$), while a significant correlation was found for the MW-related changes in both frontal TBR and ECN functional connectivity; $r(23) = -0.54$, $p = 0.006$. These outcomes support hypothesis IV in relation to the ECN, but not for the DMN.

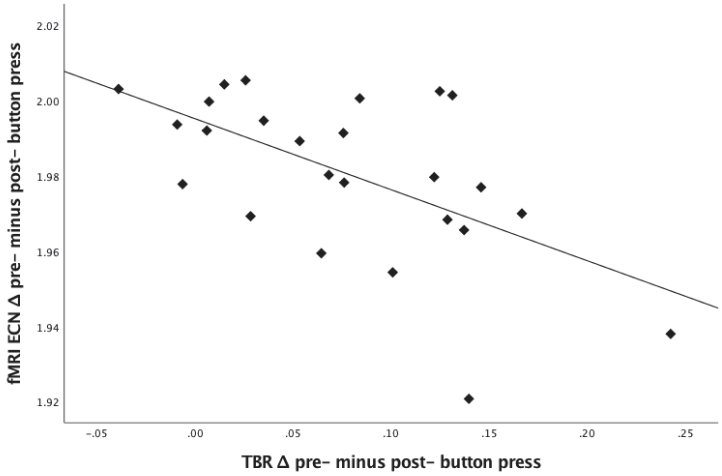


Figure 4.3. Scatterplot of the significant relation between the MW-related changes in frontal EEG theta beta ratio (TBR; x-axis) and the corresponding changes in ECN functional connectivity (y-axis); r(23) = -0.58, p = 0.002. Spearman's ranked order correlation (insensitive to outliers) was also significant; Spearman's r(23) = -0.54, p = 0.006). The plot shows log-transformed data.

EEG and fMRI pre- and post-differences related to number of button presses.

As differences were found pre-versus post-button press, we explored whether these differences were related to the number of button presses. Correlational analysis showed a significant correlation between the number of button presses during EEG and during fMRI; $r(23) = 0.49$, $p = 0.01$. No significant correlations were found between the number of button presses during EEG measurement and frontal TBR difference score; $r(24) = 0.12$, $p = 0.55$ or between the number of button presses during fMRI measurement and the difference scores in DMN functional connectivity; $r(24) = -0.24$, $p = 0.24$, or ECN functional connectivity; $r(24) = 0.24$, $p = 0.23$. Thus, MW-related EEG and fMRI change were independent of the number of button presses.

Discussion

The aim of this study was to investigate the relations between resting state and MW-related TBR, self-reported attentional control, and their neurobiological underpinning in terms of ECN and DMN connectivity. We found that resting state TBR was related to increased TBR during MW. Furthermore, DMN connectivity was higher and ECN connectivity was lower during MW. For ECN this process-related difference was related to the process-related difference in TBR.

TBR during rest was first associated with ADHD (Barry et al., 2003; Lubar, 1991), and later linked to various psychological functions and cognitive/emotional processes that rely on executive cognitive control, including trait and state attentional control, reversal learning, working memory training and control over automatic attentional threat-biases (Angelidis et al., 2018; Angelidis et al., 2016; Keune et al., 2017; Putman et al., 2010, 2014; Schutter & Van Honk, 2005b; van Son et al., 2018a; Tortella-Feliu et al., 2014; van Son et al., 2018b). The current

results support the hypothesis that the association between TBR and executive control functions reflect TBR dynamics occurring during the resting state measurement which are caused by fluctuations in the balance between cognitive control and associative thoughts.

TBR is driven by both the theta and beta power bands. The known functions of these two bands are in line with the current findings. Theta power has for example been related to decreased vigilance (e.g. Belyavin & Wright, 1987; Daniel, 1967). Beta is involved in behavioural inhibition (Brown, 2007; Engel & Fries, 2010), inhibitory motoric processes (Baker, 2007; Jenkinson & Brown, 2011), and other controlled cognitive processes such as working memory, visual attention (Jensen & Lisman, 2005; Rosanova et al., 2009; Vázquez Marrufo, Vaquero, Cardoso, & Gómez, 2001; Wróbel, 2000) and attentional vigilance (Valentino, Arruda, & Gold, 1993). These lines of evidence on beta and theta activity separately support the conjecture that TBR reflects an interplay between top-down executive control (beta) and activity in limbic, partially subcortical areas (theta: Klimesch, Sauseng, & Hanslmayr, 2007; Knyazev, 2007; Schutter & Van Honk, 2005b). This fits with functional correlates of TBR and its role in mind wandering, conceived as a state of reduced executive cognitive control and uncontrolled self-generated thought (Christoff et al., 2003; Mason et al., 2007; McVay & Kane, 2009; Smallwood, 2013; Unsworth & McMillan, 2014; van Son et al., 2018c). Our additional finding of increased alpha during 'controlled thoughts' periods also indicates increased involvement of top-down processes during these periods, as alpha activity has been involved in inhibitory processes and attentional control over sensory information (Klimesch et al., 2007; Wolfe & Bell, 2004). As beta activity is similarly involved in top-down executive processes, both bands might have some overlap in functionality, explaining their similar increase during controlled thought periods in the current study.

The current data additionally show that the difference score of TBR during controlled versus uncontrolled thought was positively correlated to a baseline measure of resting state TBR (as a statistical trend, but note that one-sided testing of this directional hypothesis would seem appropriate and would confirm the hypothesis). Whereas resting state TBR previously remained a 'black box', we suggest that people with less cognitive control experience more frequent and/or more profound states of uncontrolled thought during the typical EEG measurements of several minutes at rest, as individual differences between mind wandering and cognitive control are correlated (Christoff et al., 2003; Mason et al., 2007; McVay & Kane, 2009; Smallwood, 2013; Unsworth & McMillan, 2014). Because the relation between resting state TBR and the MW-related TBR increase was only marginally significant, this hypothesis needs to be revisited in a more powerful study with a larger sample. Unexpectedly, the often-observed negative correlation between TBR and self-reported (trait) attentional control was not observed in the present sample and our mediation hypothesis could not be tested. The observed positive correlation between MW-related TBR and resting state TBR does however support the likelihood of this hypothesis, and future studies should revisit this particular test of our hypothesis. Several factors might explain the current null-finding for the relation between TBR and attentional control. Participants in this study were preselected on fMRI inclusion criteria, and more than half of the sample was male, whereas previous participant samples were predominantly female. Furthermore, a positive relation between trait anxiety and baseline TBR was found, which contradicts the occasionally-found negative relation between these two variables (see Angelidis et

al., 2018; Putman et al., 2010) and suggests that the current sample differed in some relevant aspect from previous samples. Alternatively, the eyes-closed only TBR assessment in this study (resting state TBR is typically based on eyes-open and –closed measurement) might explain this null-finding for the TBR-attentional control relation.

Our fMRI data during the same task, collected on another day, showed that functional connectivity in the ECN was lower during MW compared to controlled thought periods, and that connectivity in the DMN was higher during MW compared to controlled thought periods. The DMN includes the posterior cingulate, medial PFC, parahippocampal gyrus and the angular gyrus. Functional activity and connectivity within this network was found to be high during task unrelated thoughts (Stawarczyk et al., 2011), and also to directly relate to MW (Karapanagiotidis et al., 2017; Smallwood et al., 2008). Also, a recent study of Delaveau et al. (2017) found that depressed out-patients had a decreased negative functional connectivity (anticorrelation) between the DMN and the salience-network when ruminating, as compared to focused-control. They also found an increased anticorrelation between the DMN and the so called task-positive network during focused-control. The latter network is functionally related to the ECN and involves working memory processes and attention directed to the external world. The ECN that was observed in the current study showed stronger functional connectivity after than before the button-press. The ECN that was selected for this study was as defined by Smith et al., (2009), and covers several frontal areas including the dorsolateral PFC (dl-PFC), anterior cingulate and the para-cingulate. This ECN is based on a broad scope of prior (fMRI) research defining executive control. Functional MRI studies showed that areas like the lateral prefrontal cortex, dl-PFC, ACC, inferior frontal junction, as well as parietal regions are all involved in executive control functions as described by Miyake et al., (2000): attentional inhibition and shifting and the updating of working memory representations.

Crucially, changes in EEG dynamics in this study were related to fluctuations in the ECN, which, for the first time, directly supports the notion that TBR dynamics are related to functional connectivity in brain networks involved in executive cognitive control (the relation between TBR change and DMN change of a near medium effect size was in the predicted direction, but non-significant). The fMRI results from our study thus demonstrate that the transition between MW episodes and episodes of controlled thoughts (and meta-cognitive awareness) as measured with the breath-counting task, is associated with increased connectivity between brain areas that have been convincingly shown to be crucial for attentional control and executive cognitive processing. The observed relation between MW- related changes in TBR and ECN functional connectivity strengthens previous conceptualizations of TBR as reflecting voluntary top-down processes of executive control (including attentional control), mediated by (dorso-lateral) PFC, over bottom-up processes from limbic areas (Angelidis et al., 2018; Angelidis et al., 2016; Bishop, 2008; Knyazev, 2007; Schutter & Knyazev, 2012). For instance, recent studies from our lab reported that TBR moderated automatic attentional threat-biases as measured by a dot probe task (Angelidis et al., 2018; van Son et al., 2018a), and by an emotional threat interference task (van Son et al., 2018b) in the manner predicted by theories explaining the role of catecholamines in PFC mediated executive functioning (Arnsten, 2009; Cools & D'Esposito, 2011) and theoretical models describing the role of cognitive control over such automatic attentional biases to threat (see Mogg & Bradley, 1998, 2016). It has been suggested that exposure to such acute threat prompts a reallocation of resources to the salience network at the cost of the executive

control network (Hermans, Henckens, Joëls, & Fernández, 2014). Also, worry (noticeably increased in affective disorders of anxiety and depression; see Brosschot, Gerin, & Thayer, 2006; Rood, Roelofs, Bögels, Nolen-Hoeksema, & Schouten, 2009, for reviews) represents biased internal activation of threatening cognitions in working memory, and shares mechanisms with biased attention (Hirsch & Mathews, 2012). Worry can be seen as self-generated off-task thought, and is sometimes referred to as a 'negative form' of MW (Ottaviani et al., 2015). Our current findings support the suggestion that TBR's role in regulation of automatic attentional threat bias reflects such interplay between bottom-up, mainly sub-cortical, and top-down prefrontal cortical networks (Hermans et al., 2014) as first suggested by Schutter and van Honk (Schutter & Van Honk, 2005b) and Knyazev (2007), and supported by various studies of our own and other labs (Angelidis et al., 2018; Angelidis et al., 2016; Belyavin & Wright, 1987; Clarke, Barry, McCarthy, & Selikowitz, 2001; Keune et al., 2017; Massar et al., 2012; Massar et al., 2014; Morillas-Romero, Tortella-Feliu, Bornas, & Putman, 2015; Putman et al., 2010, 2014; Sari et al., 2016; Schutter & Van Honk, 2005b; van Son et al., 2018a; Tortella-Feliu et al., 2014; van Son et al., 2018b; Wischnewski, Zerr, & Schutter, 2016). Our current findings further underline the importance of TBR in executive functions and its possible applicability when investigating these. TBR may be used as a marker of MW-related changes in brain activity and can likely be very useful for the study of MW (Smallwood & Schooler, 2006) and inattention (Jap, Lal, Fischer, & Bekiaris, 2009; Lorist et al., 2009).

Interestingly, the ERSP derived spectral plot and the functional connectivity plot (see **Figures 4.1** and **4.2**) revealed that after a 'drop' that started just before the button press, already within the post-button press window of ~6 s, TBR seems to be going up again, and also connectivity of ECN seems to quickly return towards pre- button press values. For EEG, this was previously observed (van Son et al., 2018c), and explorative post-hoc tests (not reported) confirmed this temporal pattern for TBR/ECN connectivity. This could possibly indicate that individuals start to lapse back into a new MW episode again within our defined window of 1.7 to 6.1 s seconds after the button press, but that seems unlikely, so shortly after their becoming aware of mind wandering. A potentially more interesting speculation is that the focused periods (controlled thought) might represent a short hypervigilant meta-awareness (realising that one lost count and was mind wandering, and subsequently increasing the use of executive resources for goal-directed monitoring of breath counting), contributing to the frontal TBR change pre- versus post-button press (see also van Son et al., 2018c). This would be in line with literature on EEG changes in theta and increased hypervigilance after error realization (Hollins et al., 2009; Weymar, Keil, & Hamm, 2014). Future studies could take this speculation into account by examining a shorter post-button press period.

A potential limitation of this study is that the EEG and fMRI measurement took place several days apart (M = 2.8 days). Simultaneous testing of EEG and fMRI would be even more powerful. However, the fact that we did find the predicted correlation between changes in TBR and fMRI measures validates the robustness of our method, and of TBR and its functional neural correlates. Another noteworthy issue is that the breath-counting MW method as used in this study and in van Son et al. (2018c), (see also Braboszcz & Delorme, 2011) has the potential limitation of relying on introspection. Since the MW episodes that are examined are self-reported and in close temporal proximity of this self-reported awareness, their underlying brain activity might not represent all

MW-related brain activity. Future studies might correlate EEG and/or connectivity dynamics of this method with methods of probing MW that do not solely rely on self-report. On a related note, it might be argued that participants who were better capable of detecting their own MW episodes pressed the button more often, resulting in data being driven by these participants. This could then potentially imply that our findings are not similarly representative for people with good versus poor meta-attentional introspective awareness. However, this alternative explanation seems ruled out by the absence of significant correlations between the numbers of button presses and the observed effects of MW on EEG and fMRI measures.

In sum, the present study importantly contributes to research into TBR as an electrophysiological marker of executive control. Our findings provide clear indications of the neuropsychological functional nature of TBR as well as its neural underpinnings, something that was much needed after several decades of TBR research. This increases our understanding of TBR's relation to psychiatric symptomatology and more firmly establishes frontal TBR as a useful and easy, low-cost tool in the study of executive control in normal as well as abnormal psychology.

References

Angelidis, A., Hagenaars, M., van Son, D., van der Does, W., & Putman, P. (2018). Do not look away! Spontaneous frontal EEG theta/beta ratio as a marker for cognitive control over attention to mild and high threat. *Biological psychology, 135*, 8-17.

Angelidis, A., van der Does, W., Schakel, L., & Putman, P. (2016). Frontal EEG theta/beta ratio as an electrophysiological marker for attentional control and its test-retest reliability. *Biological psychology*, *121*, 49-52.

Arns, M., Conners, C. K., & Kraemer, H. C. (2013). A decade of EEG theta/beta ratio research in ADHD: a meta-analysis. *Journal of attention disorders, 17*(5), 374-383.

Arns, M., de Ridder, S. Strehl, U., Breteler, M., & Coenen, A. (2009). Efficacy of neurofeedback treatment in ADHD: the effects on inattention, impulsivity and hyperactivity: a meta-analysis. *Clinical EEG and neuroscience, 40*(3), 180-189.

Arnsten, A. F. T. (2006). Stimulants: Therapeutic actions in ADHD. *Neuropsychopharmacology. 31*(11), 2376.

Arnsten, A. F. T. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*, *10*(6), 410.

Baker, S. N. (2007). Oscillatory interactions between sensorimotor cortex and the periphery. *Current Opinion in Neurobiology*, *17*(6), 649-655.

Barry, R. J., Clarke, A. R., & Johnstone, S. J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clinical Neurophysiology*, *114*(2), 171-183.

Barry, R. J., Clarke, A. R., Johnstone, S. J., McCarthy, R., & Selikowitz, M. (2009). Electroencephalogram θ/β Ratio and Arousal in Attention-Deficit/Hyperactivity Disorder: Evidence of Independent Processes. *Biological Psychiatry, 66*(4), 398-401.

Beckmann, C., Mackay, C., Filippini, N., & Smith, S. (2009). Group comparison of resting-state FMRI data using multi-subject ICA and dual regression. *NeuroImage*, *47*(Suppl 1), S148.

Belyavin, A., & Wright, N. A. (1987). Changes in electrical activity of the brain with vigilance. *Electroencephalography and Clinical Neurophysiology*, *66*(2), 137-144.

Bishop, S. J. (2008). Neural mechanisms underlying selective attention to threat. In *Annals of the New York Academy of Sciences*, *1129*(1), 141-152.

Braboszcz, C., & Delorme, A. (2011). Lost in thoughts: Neural markers of low alertness during mind wandering. *NeuroImage*, *54*(4), 3040-3047.

Brosschot, J. F., Gerin, W., & Thayer, J. F. (2006). The perseverative cognition hypothesis: A review of worry, prolonged stress-related physiological activation, and health. *Journal of Psychosomatic Research*, *60*(2), 113-124.

Brown, P. (2007). Abnormal oscillatory synchronisation in the motor system leads to impaired movement. *Current Opinion in Neurobiology*, *17*(6), 656-664.

Bush, G. (2011). Cingulate, frontal, and parietal cortical dysfunction in attention-deficit/hyperactivity disorder. *Biological Psychiatry, 69*(12), 1160-1167.

Christoff, K., Ream, J. M., Geddes, L. P. T., & Gabrieli, J. D. E. (2003). Evaluating Self-Generated Information: Anterior Prefrontal Contributions to Human Cognition. *Behavioral Neuroscience*, *117*(6), 1161.

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2001). EEG-defined subtypes of children with attention-deficit/hyperactivity disorder. *Clinical Neurophysiology, 112*(11), 2098-2105.

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., Johnstone, S. J., Hsu, C. I., … Croft, R. J. (2007). Coherence in children with Attention-Deficit/Hyperactivity Disorder and excess beta activity in their EEG. *Clinical Neurophysiology, 118*(7), 1472-1479.

Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry*, 69(12), 113-125.

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The Reorienting System of the Human Brain: From Environment to Theory of Mind. *Neuron*, 58(3), 306-324.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience, 3*(3) 201.

Daniel, R. S. (1967). Alpha and Theta EEG in Vigilance. *Perceptual and Motor Skills*, *25*(3), 697-703.

Delaveau, P., Arruda Sanchez, T., Steffen, R., Deschet, K., Jabourian, M., Perlbarg, V., … Fossati, P. (2017). Default mode and task-positive networks connectivity during the N-Back task in remitted depressed patients with or without emotional residual symptoms. *Human Brain Mapping*, *38*(7), 3491-3501.

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9-21.

Derryberry, D., & Reed, M. A. (2002). Anxiety-related attentional biases and their regulation by attentional control. *Journal of Abnormal Psychology*, *111(2)*, 225-236.

Engel, A. K., & Fries, P. (2010). Beta-band oscillations-signalling the status quo? *Current Opinion in Neurobiology. 20*(2), 156-165.

Gratton, G., Coles, M. G. H., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology, 55*, 468-484.

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences*, *100*(1), 253-258.

Hasenkamp, W., Wilson-Mendenhall, C. D., Duncan, E., & Barsalou, L. W. (2012). Mind wandering and attention during focused meditation: A fine-grained temporal analysis of fluctuating cognitive states. *Neurolmage*, *59*(1), 750-760.

Hermans, E. J., Henckens, M. J. A. G., Joëls, M., & Fernández, G. (2014). Dynamic adaptation of large-scale brain networks in response to acute stressors. *Trends in Neurosciences*, *37*(6), 304-314.

Hirsch, C. R., & Mathews, A. (2012). A cognitive model of pathological worry. *Behaviour Research and Therapy*, *50*(10), 636-646.

Hollins, M., Harper, D., Gallagher, S., Owings, E. W., Lim, P. F., Miller, V., … Maixner, W. (2009). Perceived intensity and unpleasantness of cutaneous and auditory stimuli: An evaluation of the generalized hypervigilance hypothesis. *Pain*, *141*(3), 215-221.

Jap, B. T., Lal, S., Fischer, P., & Bekiaris, E. (2009). Using EEG spectral components to assess algorithms for detecting fatigue. *Expert Systems with Applications*, *36*(2), 2352-2359.

Jenkinson, N., & Brown, P. (2011). New insights into the relationship between dopamine, beta oscillations and motor function. *Trends in Neurosciences*, *34*(12), 611-618.

Jensen, O., & Lisman, J. E. (2005). Hippocampal sequence-encoding driven by a cortical multi-item working memory buffer. *Trends in Neurosciences*, *28*(2), 67-72.

Karapanagiotidis, T., Bernhardt, B. C., Jefferies, E., & Smallwood, J. (2017). Tracking thoughts: Exploring the neural architecture of mental time travel during mind-wandering. *Neurolmage*, *147,* 272-281.

Keune, P. M., Hansen, S., Weber, E., Zapf, F., Habich, J., Muenssinger, J., … Oschmann, P. (2017). Exploring resting-state EEG brain oscillatory activity in relation to cognitive functioning in multiple sclerosis. *Clinical Neurophysiology, 128*(9), 1746-1754.

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: The inhibition-timing hypothesis. *Brain Research Reviews*, *53*(1), 63-88.

Knyazev, G. G. (2007). Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neuroscience and Biobehavioral Reviews*, *31*(3), 377–395.

Loo, S. K., Lenartowicz, A., & Makeig, S. (2016). Research Review: Use of EEG biomarkers in child psychiatry research - Current state and future directions. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 57*(1), 4-17.

Loo, S. K., Teale, P. D., & Reite, M. L. (1999). EEG correlates of methylphenidate response among children with ADHD: A preliminary report. *Biological Psychiatry, 45*(12), 1657-1660.

Lorist, M. M., Bezdan, E., ten Caat, M., Span, M. M., Roerdink, J. B. T. M., & Maurits, N. M. (2009). The influence of mental fatigue and motivation on neural network dynamics; an EEG coherence study. *Brain Research*, *1270*, 95-106.

Lubar, J. F. (1991). Discourse on the development of EEG diagnostics and biofeedback for attention-deficit/hyperactivity disorders. *Biofeedback and Self-Regulation, 16*(3), 201-225.

Marrufo, V., Vaquero, E., Cardoso, M. J., & Gómez, C. M. (2001). Temporal evolution of α and β bands during visual spatial attention. *Cognitive Brain Research, 12*(2), 315-320.

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: The default network and stimulus-independent thought. *Science*, *315*(5810), 393-395.

Massar, S., Kenemans, J. L., & Schutter, D. J. L. G. (2014). Resting-state EEG theta activity and risk learning: sensitivity to reward or punishment? *International Journal of Psychophysiology*, *91*(3), 172–177.

Massar, S., Rossi, V., Schutter, D. J. L. G., & Kenemans, J. L. (2012). Baseline EEG theta/beta ratio and punishment sensitivity as biomarkers for feedback-related negativity (FRN) and risk-taking. *Clinical Neurophysiology, 123*(10), 1958–1965.

Mazoyer, B., Zago, L., Mellet, E., Bricogne, S., Etard, O., Houdé, O., … Tzourio-Mazoyer, N. (2001). Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Research Bulletin*, *54*(3), 287-298.

McVay, J. C., & Kane, M. J. (2009). Conducting the Train of Thought: Working Memory Capacity, Goal Neglect, and Mind Wandering in an Executive-Control Task. *Journal of Experimental Psychology: Learning Memory and Cognition*, *35*(1), 196.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex "Frontal Lobe" Tasks: A Latent Variable Analysis. *Cognitive Psychology*, *41*(1), 49-100.

Mogg, K., & Bradley, B. P. (1998). A cognitive-motivational analysis of anxiety. *Behaviour Research and Therapy*, *36*(9), 809-848.

Mogg, K., & Bradley, B. P. (2016). Anxiety and attention to threat: Cognitive mechanisms and treatment with attention bias modification. *Behaviour Research and Therapy*, *87*, 76-108.

Morillas-Romero, A., Tortella-Feliu, M., Bornas, X., & Putman, P. (2015). Spontaneous EEG theta/beta ratio and delta–beta coupling in relation to attentional network functioning and self-reported attentional control. *Cognitive, Affective and Behavioral Neuroscience*, *15*(3), 598-606.

Nešlehová, J. (2007). On rank correlation measures for non-continuous random variables. *Journal of Multivariate Analysis*, *98*(3), 544-567.

Ottaviani, C., Shahabi, L., Tarvainen, M., Cook, I., Abrams, M., & Shapiro, D. (2015). Cognitive, behavioral, and autonomic correlates of mind wandering and perseverative cognition in major depression. *Frontiers in Neuroscience*, *8*, 433.

Putman, P., van Peer, J., Maimari, I., & van der Werff, S. (2010). EEG theta/beta ratio in relation to fear-modulated response-inhibition, attentional control, and affective traits. *Biological Psychology*, *83*, 73-78.

Putman, P., Verkuil, B., Arias-Garcia, E., Pantazi, I., & Van Schie, C. (2014). EEG theta/beta ratio as a potential biomarker for attentional control and resilience against deleterious effects of stress on attention. *Cognitive, Affective and Behavioral Neuroscience*, *14*, 782-791.

Rood, L., Roelofs, J., Bögels, S. M., Nolen-Hoeksema, S., & Schouten, E. (2009). The influence of emotion-focused rumination and distraction on depressive symptoms in non-clinical youth: A meta-analytic review. *Clinical Psychology Review, 29*(7), 607-616.

Rosanova, M., Casali, A., Bellina, V., Resta, F., Mariotti, M., & Massimini, M. (2009). Natural Frequencies of Human Corticothalamic Circuits. *Journal of Neuroscience*, *29*(24), 7679-7685.

Sari, B. A., Koster, E. H. W., Pourtois, G., & Derakshan, N. (2016). Training working memory to improve attentional control in anxiety: A proof-of-principle study using behavioral and electrophysiological measures. *Biological Psychology*, *121*, 203-212.

Schutter, D. J. L. G., & Knyazev, G. G. (2012). Cross-frequency coupling of brain oscillations in studying motivation and emotion. *Motivation and Emotion*, *36*(1), 46-54.

Schutter, D. J. L. G., & Van Honk, J. (2004). Decoupling of midfrontal delta-beta oscillations after testosterone administration. *International Journal of Psychophysiology, 53*(1), 71–73.

Schutter, D. J. L. G., & Van Honk, J. (2005a). Electrophysiological ratio markers for the balance between reward and punishment. Brain Research. *Cognitive Brain Research*, *24*(3), 685–690.

Schutter, D. J. L. G., & Van Honk, J. (2005b). Electrophysiological ratio markers for the balance between reward and punishment. *Cognitive Brain Research*, *24*(3), 685–690.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., … Greicius, M. D. (2007). Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *Journal of Neuroscience, 27*(9), 2349-2356.

Smallwood, J. (2013). Distinguishing how from why the mind wanders: A process-occurrence framework for self-generated mental activity. *Psychological Bulletin*, *139*(3), 519.

Smallwood, J., Beach, E., Schooler, J. W., & Handy, T. C. (2008). Going AWOL in the brain: Mind wandering reduces cortical analysis of external events. *Journal of Cognitive Neuroscience*, *20*(3), 458-469.

Smallwood, J., Nind, L., & O'Connor, R. C. (2009). When is your head at? An exploration of the factors associated with the temporal focus of the wandering mind. *Consciousness and Cognition*, *18*(1), 118-125.

Smallwood, J., & Schooler, J. W. (2006). The restless mind. *Psychological Bulletin*, *132*(6), 946.

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., … Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences*, *106*(31), 13040-13045.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). STAI manual for the state-trait anxiety inventory. *Self-Evaluation Questionnaire*, Palo Alto, CA: Consulting Psychologists Press.

Stawarczyk, D., Majerus, S., Maquet, P., & D'Argembeau, A. (2011). Neural correlates of ongoing conscious experience: Both task-unrelatedness and stimulus-independence are related to default network activity. *PLoS ONE*, *6*(2), e16997.

Tortella-Feliu, M., Morillas-Romero, A., Balle, M., Llabrés, J., Bornas, X., & Putman, P. (2014). Spontaneous EEG activity and spontaneous emotion regulation. *International Journal of Psychophysiology*, *94*(3), 365-372.

Unsworth, N., & McMillan, B. D. (2014). Similarities and differences between mind-wandering and external distraction: A latent variable analysis of lapses of attention and their relation to cognitive abilities. *Acta Psychologica*, *150*, 14-25.

Valentino, D. A., Arruda, J. E., & Gold, S. M. (1993). Comparison of QEEG and response accuracy in good vs poorer performers during a vigilance task. *International Journal of Psychophysiology*, *15*(2), 123-133.

van Son, Angelidis, A., Hagenaars, M.A., van der Does, W., Putman, P. (2018a). Early and late dot-probe attentional bias to mild and high threat pictures: Relations with EEG theta/beta ratio, self- reported trait attentional control, and trait anxiety. *Psychophysiology*, e13274.

van Son, D., Schalbroeck, R., Angelidis, A., van der Wee, N. J. A., van der Does, W., & Putman, P. (2018b). Acute effects of caffeine on threat-selective attention: moderation by anxiety and EEG theta/beta ratio. *Biological Psychology*, *136*, 100-110.

van Son, D., De Blasio, F. M., Fogarty, J. S., Angelidis, A., Barry, R. J., & Putman, P. (2018c). Frontal EEG theta/beta ratio during mind wandering episodes. *Biological Psychology*.

Ward, A. M., Schultz, A. P., Huijbers, W., Van Dijk, K. R. A., Hedden, T., & Sperling, R. A. (2014). The parahippocampal gyrus links the default-mode cortical network with the medial temporal lobe memory system. *Human Brain Mapping, 35*(3), 1061-1073.

Weymar, M., Keil, A., & Hamm, A. O. (2014). Timing the fearful brain: Unspecific hypervigilance and spatial attention in early visual perception. *Social Cognitive and Affective Neuroscience*, *9*(5), 723-729.

Wischnewski, M., Zerr, P., & Schutter, D. J. L. G. (2016). Effects of Theta Transcranial Alternating Current Stimulation Over the Frontal Cortex on Reversal Learning. *Brain Stimulation*, *9*(5), 705-711.

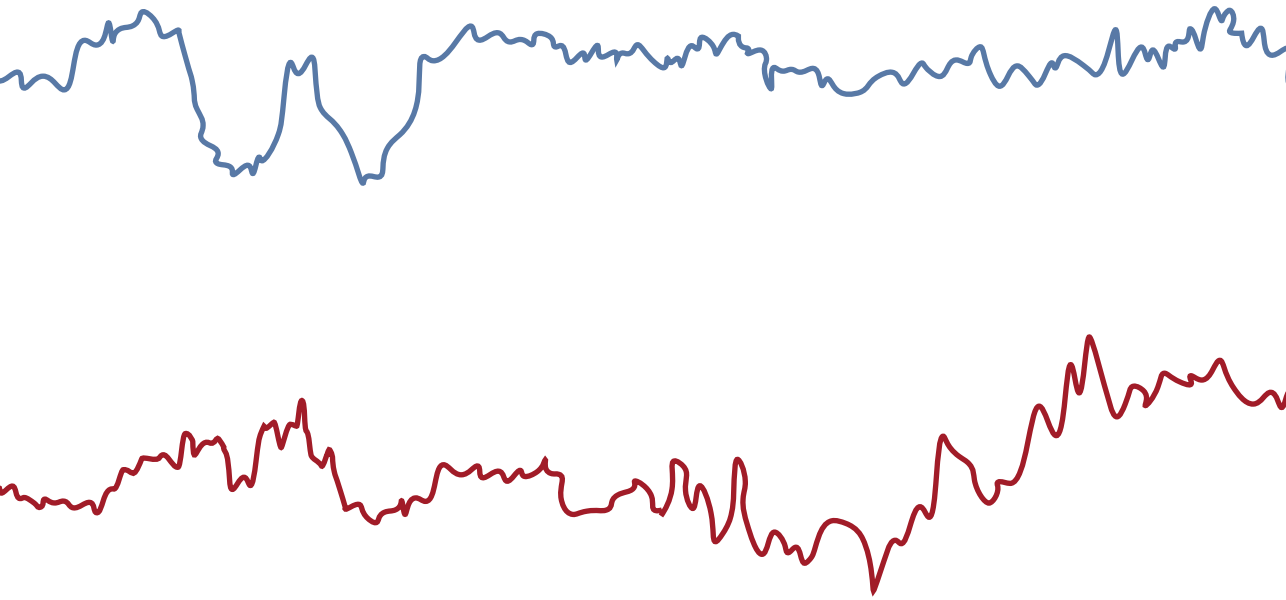
Wolfe, C. D., & Bell, M. A. (2004). Working Memory and Inhibitory Control in Early Childhood: Contributions from Physiology, Temperament, and Language. *Developmental Psychobiology*, *44*(1), 68-83.

Wróbel, A. (2000). Beta activity: A carrier for visual attention. *Acta Neurobiologiae Experimentalis*, *60*(2), 247-260.

CHAPTER 5.

EEG Theta/Beta Ratio Neurofeedback Training in Healthy Females

Dana van Son, Willem van der Does, Guido P.H. Band, Peter Putman.



ABSTRACT

Background: a growing number of studies suggest that EEG theta/beta ratio (TBR) is inversely related to executive cognitive control. Neurofeedback training aimed at reducing TBR (TBR NFT) might provide a tool to study causality in this relation and might enhance human performance.

Goal: to investigate whether TBR NFT lowers TBR in healthy participants

Method: Twelve healthy female participants were assigned (single blind) to one of three groups. Groups differed on baseline durations and one group received only sham NFT. TBR NFT consisted of eight or fourteen 25-minutes sessions.

Results: No evidence was found that TBR NFT had any effect on TBR.

Conclusions: The current TBR NFT protocol is ineffective. This replicates a previous study with a different protocol. TBR NFT may not be effective in healthy participants.

Resting state encephalographic (EEG) signals are composed of different frequency components, many of which are found to be relatively stable over time (Williams, Simms, Clark, Paul, Rowe & Gordon, 2005). Specific spectrum components reflect functional neural activity as an electrophysiological correlate with certain behaviors (Hofman & Schutter, 2012; Sutton & Davidson, 2000). For example, the ratio between activity in the theta band (4-7 Hz) and activity in the beta band (13-30 Hz), called theta/beta ratio (TBR), has been related to different aspects of cognitive control and motivated decision making (Schutter & van Honk 2005a; Massar, Rossi, Schutter & Kenemans, 2012; Massar, Kenemans & Schutter, 2014), to attentional control in healthy young adults (Putman, van Peer, Maimari & van der Werff, 2010; Putman, Verkuil, Arias-Garcia, Pantazi & van Schie, 2014; Angelidis, Schakel, van der Does & Putman., 2016) and to reversal learning (Wischnewski, Zerr & Schutter, 2016). Additionally, a higher baseline TBR was found to correlate to a stronger decline in cognitive control after stress-induction (Putman et al., 2014). TBR has a high test-retest reliability and predicts attentional control scores over a one-week interval (Angelidis et al., 2016). All in all, TBR is likely a stable electrophysiological marker of executive control.

Attentional control refers to the capacity to efficiently choose where to pay attention to (Posner & Petersen, 1990). When attentional control fails, attentional bias towards threat can be the result. This may happen when stress or anxiety prioritizes the processing of mildly threatening distracters. In other words, during anxious states, bottom-up processing of threatening distracters is facilitated, while top-down executive functions are inhibited (Derakshan & Eysenck, 2009). Furthermore, executive control can be decreased by distracting thoughts that accompany stress or anxiety, impairing working memory (Coy, O'Brien, Tabaczynski, Northern, Carels, 2011; Eysenck, Derakshan, Santos, Calvo, 2007). This is in line with the widely accepted idea that test anxiety causes divided attention, leading to for example lower academic performance (Hembree, 1988; Duty Christian , Loftus, Zappi, 2016).

TBR was found to be related to trait attentional control (Putman et al., 2010; Putman et al., 2014; Angelidis, Schakel & van der Does & Putman, 2016), to resilience to the effects of stress on task performance (Putman et al., 2014), to down regulation of negative affect (Tortella-Feliu , Morillas-Romero, Balle, Llabrés, Bornas, Putman, 2014) and to regulation of automatic attentional bias to threat; (Angelidis, Hagenaars, van der Does, van Son & Putman, 2018). The study of TBR is therefore potentially interesting for a range of phenomena, conditions and applications, such as stress-cognition interactions, anxious psychopathology or human performance enhancement. Experimentally manipulating TBR could give further insights in causal relations between this EEG marker, cognitive control and stress effects, as well as possibly pave the way for future development of interventions.

A method to induce changes in TBR is neurofeedback training (NFT). NFT is a procedure in which participants may implicitly learn to gain control over particular aspects of their EEG signal. Providing online feedback on people's EEG spectrum while asking them indirectly to increase or decrease power in certain frequency bands (e.g. by keeping a video running) can eventually lead to the ability to do this (Vernon, 2005). An increasing number of studies have reported positive effects of NFT in neurological and psychological disorders (Marzbani et al., 2016) as well as areas like performance enhancement (for a review, see Gruzelier, 2014a) optimized performance in sports (Graczyk et al., 2014), cognitive control (Keizer, Verment & Hommel, 2010), and

situations with counterproductive interactions between stress and cognition, such as music performance under stressful conditions (Egner & Gruzelier, 2003). NFT has also been applied for reducing symptoms of Attention Deficit Hyperactivity Disorder (ADHD). ADHD has very often been associated with high TBR (for review and meta-analysis, see Arns et al., 2013; Barry, Clarke & Johnstone, 2003) and NFT targeting TBR has been found to successfully reduce TBR and ADHD-related symptoms in individuals diagnosed with ADHD (e.g. hyperactivity, impaired attention; e.g. Butnik, 2005; Leins et al., 2007; Lubar et al., 1995; Kouijzer, de Moor, Gerrits, Congedo and van Schie, 2009; Janssen, Bink, Weeda, Geladé, van Mourik, Maras & Oosterlaan, 2016; for a review see Vernon, 2005).

The study of the potential beneficial effects of TBR-reducing NFT seems warranted given the abovementioned relations between TBR and various psychological regulatory constructs. However, because we believe it is imperative to first ascertain that indeed reliable changes in TBR by NFT can be observed, we selected healthy participants with mildly elevated TBR. We aimed to investigate whether NFT induces changes in TBR in people with mildly elevated TBR but who do not have a clinical diagnosis of psychopathology. The primary outcome measure of this study was changes in the targeted EEG parameters. These changes are likely easier to detect and more consistent than changes at the more multifaceted and complex behavioral level.

Doppelmayr and Weber (2011) previously investigated whether a TBR NFT protocol exerts the intended effects on the EEG spectrum level in healthy individuals, not selected on TBR level. The effect of the NFT TBR training on its trained EEG indices was compared to the effect of an NFT protocol training the 'Sensori- Motor Rhythms' (SMR; 12-15 Hz) and a sham-NFT with daily changing frequency bands. Healthy individuals who received the SMR training protocol were able to significantly modulate their EEG in the trained frequency band, whereas individuals who received the TBR or sham protocol were not. To our knowledge, this is the only study to date that directly investigated TBR NFT in healthy individuals by primarily looking at the direct effects on the EEG parameters of interest. We aimed to replicate and extend Doppelmayr and Weber's findings by testing in an independent study again if TBR can be changed.

Our hypothesis that a TBR NFT can induce changes in EEG for individuals with mildly elevated TBR has not been studied extensively yet. Subjecting participants from this population to a very lengthy active NFT TBR training is demanding on the participants and could potentially cause unknown side effects. The best approach would be to study a small sample in depth, by thoroughly inspecting effects of active-NFT in each individual per session. We therefore employed a multiple baseline case series design. This design was chosen in order to closely examine any possible change in TBR at the level of the studied individuals so as not to overlook possible leads to increase NFT effectiveness and to minimize the chance of prematurely ruling out potential effectiveness of NFT for our purposes. A multiple baseline case series design involves the measurement of multiple persons both before and after an intervention (Watson & Workman, 1981). In this design the start of the intervention is varied sequentially across individuals or small groups of individuals. During the baseline phase before intervention, the behavior or measure of interest is measured a number of times to observe its natural variation over time. When a change only takes place shortly after a specific intervention is introduced and not following a different intervention, the change can be attributed to the intervention (Baer et al., 1968; Kinugasa et al., 2004; Koehler &

Levin, 2000). A frequently used method in a case series design is visual inspection, which provides a reliable alternative for statistical tests for detecting changes by intervention, when sample sizes are too small for good statistical power (Fisher et al., 2003).

There are other, mainly ethical benefits to the smaller number of sessions required for a case series design. First of all, executing a controlled study with large sample sizes (see Cohen et al., 2014) places a lot of burden on the test-participants and implies a big investment of societal resources that may not be warranted yet. Additionally, nothing is known about possible negative side-effects in our intended population although the literature does suggest that such effects might exist. Low TBR for example has been related to low approach-driven or hedonically motivated behavior as measured with the IOWA gambling task (which has been associated with depression and anxiety; Cella, Dymond & Cooper, 2010; Massar et al., 2012; Massar et al., 2014; Mueller, Nquyen, Ray, Borkovec, 2009; Schutter & van Honk, 2005) and as measured with the self-report BIS/BAS scale (Putman et al., 2010; Carver & White, 1994). Also, two studies (Putman et al., 2010; Angelidis et al., 2016) demonstrate a negative association between TBR and self-reported negative, anxious affect as measured with the State-Trait Anxiety Inventory (STAI-State; Spielberger, 1983; van der Ploeg, Defares & Spielberger, 1980). Finally, one study (Enriquez-Geppert et al., 2014) has reported beneficial effects of working memory performance of a theta-only upregulation using NFT in healthy participants. All in all, at this stage of TBR NFT research in healthy adults, where side effects are not yet thoroughly investigated but cannot be ruled out, applying this intervention in a large group of participants and over a long time period is not yet defensible.

We assessed whether NFT reduces TBR in healthy individuals with mildly elevated TBR. TBR was the primary outcome; self-reported attentional control and state anxiety were assessed as secondary outcomes and to measure potentially unwanted side effects of NFT. A multiple baseline design was used employing various durations of baseline, sham-NFT and active-NFT sessions. We expected to see a reduction of TBR sometime after switching from measurement-only sessions to active treatment. We expected an absence of such measurement-only-controlled changes in a third sham-only group and, finally, we expected that TBR during the final sessions would be clearly lower in the two active NFT groups than in the sham-only group. Our primary interest was changes in TBR within the training sessions but we also looked at changes in TBR during resting state measurements at the start of the sessions (between-sessions changes). Finaly, we performed in-depth exploration of the time course of TBR within and between training sessions, exploiting the case series' benefits of temporally fine grained observation.

Methods

Participants

Twelve female participants (age 19-23 years; $M = 21$; $SD = 1.04$) were included by preselection on elevated resting state frontal TBR from three previous studies from our lab (in which no attempts to change EEG measures were made in any way). Because of the low number of men in these previous studies, only female participants were included in the current study. The preselection was done based on frontal TBR measures obtained from previous studies in our lab in unselected female participants who left contact details for further

study (N = 54). Frontal TBR was chosen as preselection outcome variable since all previous studies had frontal TBR as main outcome variable and this is highly correlated with central TBR (r= 0.902, p<0.001 in the current study). We invited participants with the highest frontal TBR for the current study. Other inclusion criteria were: age between 18 and 24 years; no history of neurologic or psychiatric disorders; no history or current use of drugs other than low to moderate alcohol use or nicotine use and no use of medication that is known to directly influence the central nervous system. Recruitment took place at Leiden University, The Netherlands, between December 2015 and February 2016. All participants signed an informed consent and were free to terminate their participation at any time. For monetary compensation we used an incremental pay-off scheme, including disproportionately larger rewards for longer participation. This pay-off scheme was applied to minimize drop-out from the study. The study was approved by the local ethics review board (CEP16-011413), and pre-registered at ClinicalTrials.gov (NCT02763618).

Design

A single-blind case series multiple baseline design was used with a baseline (measurement-only period) varying prior to training onset and after training offset (**Figure 5.1**). Before the first lab session, the participants were assigned to one of three groups. Care was taken to obtain a more or less equal distribution of frontal TBR levels and age across the groups, but other than that the allocation to one of the three study groups was arbitrary. Allocation was done by the principal investigator who was not involved in the actual testing of the participants and had no contact with them. The experimenters that performed the study were kept blind to this allocation. All participants started with a three-session measurement-only phase with only a resting state EEG measurement. Participants in Group A continued with 14 sessions of active-NFT. Group B received six extra measurement-only sessions before they continued with eight active-NFT sessions. Group C received 14 sham-NFT sessions after the three-session measurement-only phase. A minimum of eight sessions active-NFT was applied because changes were usually seen around five or six 30-minute sessions in studies that found effects on theta frequency (Kao et al., 2014; Enriquez-Geppert et al., 2014). All participants were blind to which group they were in but the experimenters were not blind to this for reasons of practical feasibility. During all sessions, questionnaires for state anxiety and state attentional control were assessed before every EEG measurement, active-NFT or sham-NFT. Our primary outcome variable was changes in frontal TBR within each session while our secondary outcome measurement was changes in frontal TBR between the sessions.

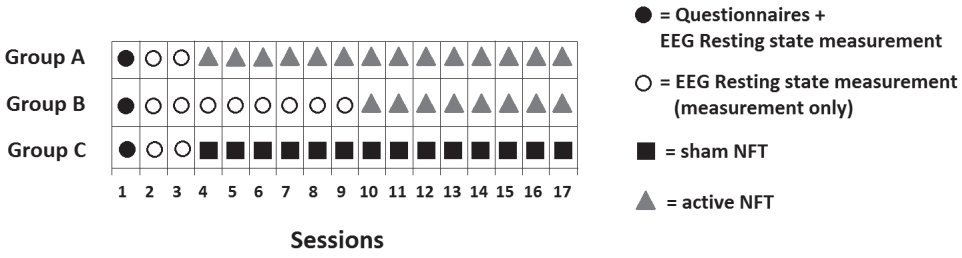


Figure 5.1. *Difference in session course per group.*

Materials

Self-Report Questionnaires. During the first and last session, participants completed the trait version of the State-Trait Anxiety Inventory (STAI-Trait; Spielberger, 1983; van der Ploeg, Defares & Spielberger, 1980) and the Attentional Control Scale (ACS; Derryberry & Reed, 2002). The STAI-Trait assesses trait anxiety (20 items, range 20-80; Cronbach's alpha = 0.89) and participants had to indicate their agreement with items like 'I feel satisfied with myself' and 'I am a steady person' on a four-point Likert scale. The ACS assesses self-reported attentional control in terms of attentional inhibition, attentional focus and the capacity to generate new thoughts (20 items, range 20-80; Cronbach's alpha in present study = 0.85), e.g. 'I can quickly switch from one task to another'. Self-reported state anxiety and state attentional control were measured on every session using the state version of the State-Trait Anxiety Inventory (STAI-State; Spielberger, 1983; van der Ploeg, Defares & Spielberger, 1980) and the state-Attentional Control questionnaire (s-AC; Angelidis & Putman, *manuscript in preparation*). STAI- State measures state anxiety at the moment of participation (20 items, range 20-80, Cronbach's alpha = 0.91) and includes items like 'I am tense'. s-AC measures attentional control at the moment of participation (6 items) and included items like 'I feel very focused' (Cronbach's alpha = 0.84). The Behavioral Activation Scale (BAS; part of the Behavioral Inhibition and Activation Scale; BIS/BAS Carver & White, 1994) was assessed for the personality trait of behavioral activation (Cronbach's alpha = 0.78). The BAS consists of the subscales BAS Reward, BAS Drive and BAS Fun Seeking but we assessed the total BAS score. STAI-t, ACS and BAS were included only to see if their scores changed on these measures on the first session compared to the last session to check for potential unwanted side-effects. STAI-s and s-AC were used to observe possible unwanted side-effects of NFT over time with a greater precision The questionnaires were programmed and presented using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA).

EEG recording and Neurofeedback. The TBR Neurofeedback signal was measured and applied by a NeXus-4 amplifier and recording system with BioTrace Software (Mind Media B.V., The Netherlands). The NeXus-4 amplifier is a DC amplifier in which EEG is sampled at 1024 Hz. One NeXus Ag/AgCl disposable electrode was applied on the participant's scalp between locations Cz and FCz. A ground and a reference electrode were placed

on the jaw and right-ear mastoid respectively. Additionally, nine extra in-cap electrodes (BioSemi, The Netherlands) were added on locations F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, with one reference electrode on the left-ear mastoid, during every session. Data from these electrodes were collected with the Biosemi ActiveTwo DC amplifier. Both devices were active during all measurements, except during the sham-NFT sessions; then both the NeXus and the BioSemi system were attached but only the BioSemi system was active. Each session had a four-minute baseline measurement and a 25-minute measurement-only, active-NFT or sham-NFT. Active and sham neurofeedback were provided by BioTrace Software. Per time window of 15 seconds, individualized thresholds were automatically reset in a way that, based on the previous 15 seconds, the feedback signal would likely indicate successful performance for +/- 80% of the time, resulting in a standardized NFT protocol. Before feedback onset, measurement started 15 seconds earlier to determine the thresholds. When the EEG theta power went below the threshold, and the beta power above its threshold simultaneously, the participant was rewarded by the continuation of a video (a simulation of an airplane flying over a mountainous terrain). If they failed to reach these thresholds, the video stopped. Theta and beta amplitudes were online filtered with a 4 Hz high-pass and 7 Hz low-pass filter for theta and a 13 Hz high-pass and 30 Hz low-pass filter for beta. Online calculation of theta and beta amplitude (=feedback resolution) was done in epochs of 125 milliseconds using a moving time window; at every data sample (sampling rate was 256 per second) calculation was done over the last 125 milliseconds of that sample. These amplitude values were calculated by taking the root mean square (RMS) of the band-pass filtered data. Since online Fast Fourier transformation needs at least 2 seconds to calculate amplitudes; RMS is a representative and practical method of online calculation (Nitschke, Miller and Cook, 1998). Feedback by video continuation therefore appeared continuously when theta and beta were below and above the threshold for 125 milliseconds. The theta and beta amplitudes were visualized in separate bar graphs on the screen, next to the video. A third 'inhibit' bar represented voluntary eye blinks or muscle artifacts. The filter of this inhibit band was set at 2-3 Hz for eyeblinks and above 60 Hz for muscle artifacts. If the amplitude of the eyeblinks or muscle artifacts exceeded its threshold, no feedback was provided. The theta bar was a fluctuating bar in blue and beta a fluctuating bar in red. The participants were instructed which bar (beta) needed to go up above a threshold (small black stripe) and which bar (theta) needed to go down below a threshold, and in this way, they had to keep the video running. No instructions about how to influence their EEG spectrum were given. With respect to this, the participants were only told to 'sit still' and 'not to tense their face or jaws' (to reduce interference from muscle activity and to prevent increased beta activity resulting from such volitional motoric action).

The sham-NFT was a previously recorded active-NFT session of a participant from Group A (received 14 active-NFT sessions). Every participant in Group C (sham-NFT) was matched to another participant in group A and received the active-NFT video per session of their matched participant. That is, participants in Group C at session 4 saw the video and bars moving as if it was caused by their own EEG, however they actually watched the feedback that their matched participant from Group A in session 4 received. In this way, participants receiving sham-NFT were not able to influence the theta or beta bar graphs nor the continuation of the video. By matching every participant in Group C to a real participant in Group A, we kept the sham-NFT realistic for the participants in Group C, providing an accurate 'yoked control' procedure controlling for possible effects of motivation as a result

of the received feedback, for instance.

Procedure

General procedure. Testing took place at Leiden University, between February 2016 until May 2016. All participants visited the lab 17 times. In all sessions, participants received state questionnaires, a four-minute EEG passive baseline resting state measurement followed by either a measurement-only, an active NFT or a sham-NFT (all 25 minutes; for an overview see **Figure 5.1**). Sessions were planned minimally three times a week with a maximum of five times a week. Every session took place on a separate day with a maximum of three days in between. One session approximately took between 60-70 minutes. The complete experiment therefore took 17-20 hours per participant in approximately four weeks. At the end of every session, all participants performed a 10-minute cognitive control task (Bishop, 2009). We included this task to pilot its extensively repeated use in a multiple baseline design for future studies. Results on this task are irrelevant for the current hypotheses and therefore the task and its outcomes will not be further reported.

First session. During the first session, participants were asked to sign an informed consent in which they were informed about the pay-off scheme regarding financial compensation. After signing the informed consent, a questionnaire about general and medical information was completed including questions about drug use and health. Participants started with the STAI-Trait, ACS, BAS, STAI-State and s-AC; in that order. Subsequently, preparation of the EEG equipment started and the participants continued with the four-minute passive baseline measurement followed by a 25 minute 'measurement-only' part.

Session 2 – 16. The second session till the sixteenth session, all maintained the same procedure, except that the fourth session till the sixteenth session could either include a measurement-only, an active NFT plus EEG measurement or sham-NFT plus EEG measurement (see **Figure 5.1**). Participants always started with completing the STAI-State and s-AC. This was followed by the EEG four-minute passive baseline measurement and the 25 minute measurement-only (session 2 and 3 for all groups and 2 – 9 for Group B), active-NFT (session 4 – 16 for Group A and session 10-16 for Group B) or sham-NFT (session 4-16 for Group C).

Last session (17). The last session started with completion of the STAI-Trait, BAS and trait ACS questionnaires, followed again by the STAI-State and s-AC questionnaires, EEG four-minute passive baseline measurement and the 25-minute active NFT or sham-NFT. All participants ended with a funneled debriefing interview. In this interview the participants were asked how they experienced the study, what kind of mental methods they used to become successful in the training, and which experimental group they thought they were in and why. After completing the interview, participants received a financial reward for their participation.

Data Reduction and analysis

Data processing was done using Brain Vision Analyzer V2.0.4 (Brain Products GmbH, Germany). Data was

high-pass filtered at 0.1 Hz, low-pass filtered at 100-Hz and a 50-Hz notch filter was applied. The data was automatically corrected for ocular artifacts (Gratton, Coles & Donchin, 1983) in segments of 4 seconds. Remaining segments containing muscle movements, amplitudes above 200 µV or other artifacts were removed. For offline amplitude calculation, Fast Fourier transformation (Hamming window length 10%) was applied for theta (4-7 Hz) and beta (13-30 Hz) at C3, Cz, and C4 positions. Amplitude values were calculated by taking amplitude spectral density (µV*Hz). Amplitude squared provided the power values. Central theta and beta power was calculated by taking the average of C3, Cz and C4 positions, and central TBR in turn was calculated by dividing central theta power by central beta power. Central TBR was chosen as outcome variable of focus because the NeXus sensor for active-NFT was placed between Cz and FCz positions, however we have exploratively looked at frontal average TBR too, as well as theta, beta, beta 1 (13-20 Hz) and beta 2 (21-30 Hz) separately. All raw data are freely available on (https://tinyurl.com/y948dcsl).

For interpreting the results, primarily visual inspection was used to determine the effectiveness of the active-NFT. If central TBR in Group A would reduce shortly after the introduction of the active-NFT (and after a comparable delay across the four participants) compared to no changes in Group C, the experiment would provide compelling evidence for the effectiveness of active-NFT. The effect would be even more strongly supported if a similar reduction was seen in Group A and B (after an equal number of active-NFT sessions, regardless the longer duration of the baseline). These changes after onset in Group A and Group B are assumed to be absent in Group C, where we expected no changes. The expected change in Group B could be considered as a direct replication of the effect in Group A. Furthermore, we expected differences in central TBR between Group A, B and C at the last session compared to the first session, with Group A showing the strongest reduction in central TBR (after performing the most active-NFT sessions), and Group C showing the weakest reduction in central TBR (no active NFT sessions). Primarily, we expect to see a consistent reduction in central TBR over active-NFT measurements, though we have inspected the four-minute passive baseline measurements as well, despite its smaller chance to detect any effect of active NFT. Also, besides inspecting changes in central TBR over all sessions, we have inspected changes in central TBR at the end of every session (average of last five minutes) and changes over time (25 minutes) within sessions too, since fluctuations might have occurred across the 25 minutes that could remain undetected when only inspecting session averages.

Trait anxiety and self-reported trait attentional control were measured at the start and the end of the study to exploratively relate these measures to possible changes in TBR as indication of potential unwanted side-effects. State anxiety and state-AC were assessed during every session to allow closer observation of such potential side effects.

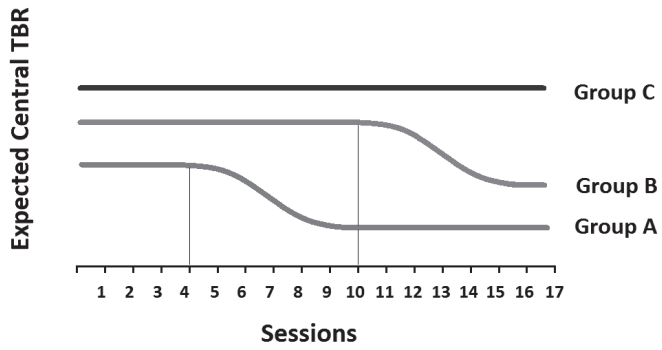


Figure 5.2. Expected pattern of central TBR per group. Central TBR in Group A and B was expected to reduce some time after onset of active-NFT (session 4 for Group A and session 10 for Group B). The reduction is expected to be relatively constant between individuals. Central TBR in Group C was not expected to show any change over time because sham-NFT was introduced in session 4 instead of active-NFT. The thin black line represents the point of active-NFT introduction for Group A and Group B.

Results

Participants

Twelve participants were selected, and all completed the 17 sessions (for a flow diagram of participant selection, see Figure 5.3). Age, baseline TBR and questionnaire scores per participant and per group during the first session are summarized in Table 3 The first baseline measurement of the selected 12 participants in the current study showed a frontal TBR of $M = 1.51$, $SD = 0.76$, median = 1.43). Although this was somewhat lower than their frontal TBR during their pre-selection measurement ($M = 1.68$, $SD = 0.55$, median = 1.47), it was still noticeably higher than the frontal TBR that was observed in the N=56 unselected sample that the preselection was based on ($M = 1.26$, $SD = 0.54$, median = 1.13) and represented the 45^{th}-88^{th} percentile score of this unselected sample. In sum, also at the time of testing, the sample had elevated frontal TBR.

	Age	Pre-selection TBR	ACS score	STAI trait score	BAS total score
Group A	*M* = 20.5 ± 1	*M* = 1.74 ± 0.81	*M* = 55.5 ± 5.97	*M* = 37 ± 2.16	*M* = 43 ± 4.54
Participant 2	21	1.72	48	37	37
4	21	1.19	58	36	42
5	19	2.89	54	35	46
10	21	1.15	62	40	47
Group B	*M* = 21.25 ± 1.25	*M* = 1.80 ± 0.51	*M* = 50.5 ± 11	*M* = 45.25 ± 9.78	*M* = 38 ± 7.48
Participant 1	21	2.50	45	36	36
7	21	1.36	45	56	38
8	20	1.88	45	51	30
11	23	1.48	67	38	48
Group C	*M* = 21.25 ± 0.96	*M* = 1.5 ± 0.32	*M* = 53.75 ± 7.89	*M* = 35 ± 4.08	*M* = 44.5 ± 3.42
Participant 3	21	1.93	50	38	44
6	20	1.44	57	39	46
9	22	1.16	63	32	40
12	22	1.47	45	31	48
Total Mean	*M* = 21 ± 1.04	*M* = 1.51 ±0.55	*M* = 53.25 ± 8.02	*M* = 39.10 ± 7.31	*M* = 41.83 ± 5.70

Table 3. Demographic information of all participants and means per group. Note TBR = frontal theta/beta ratio; M = mean, ± is standard deviation.

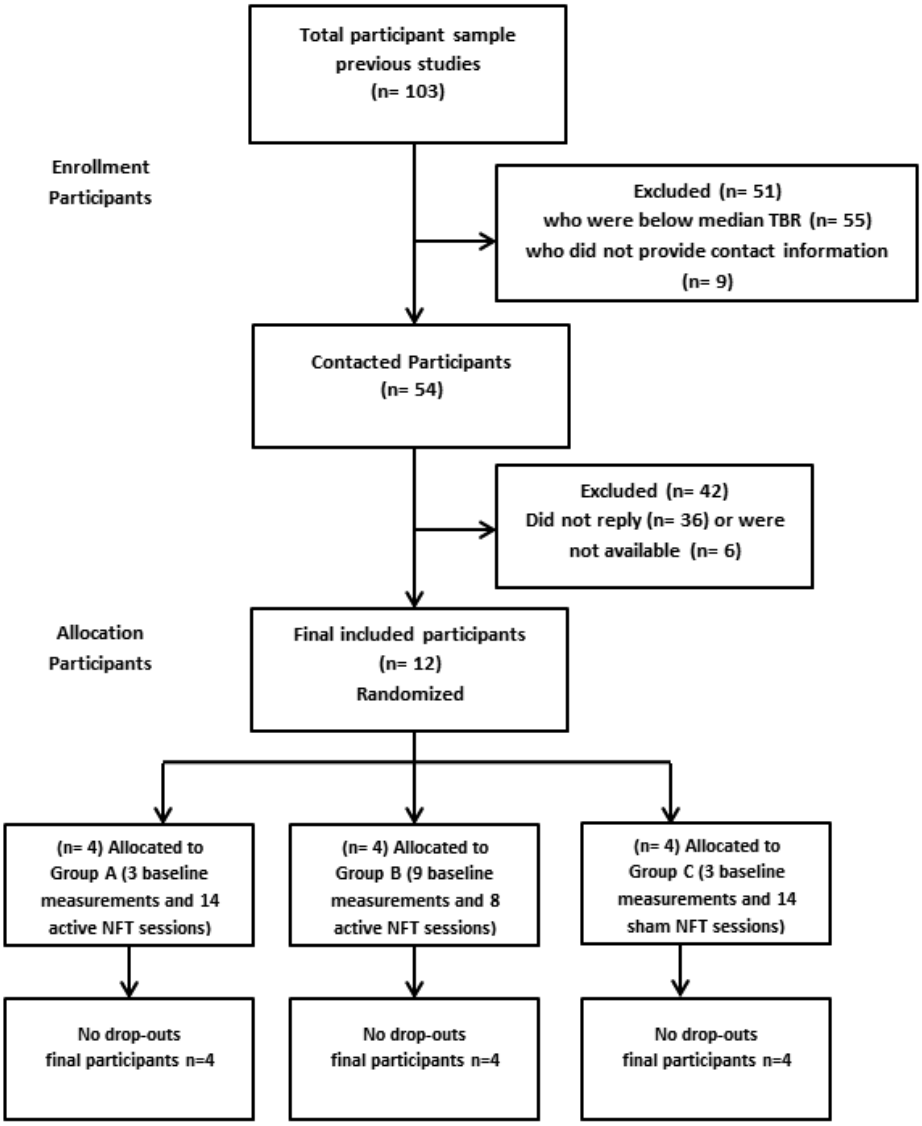
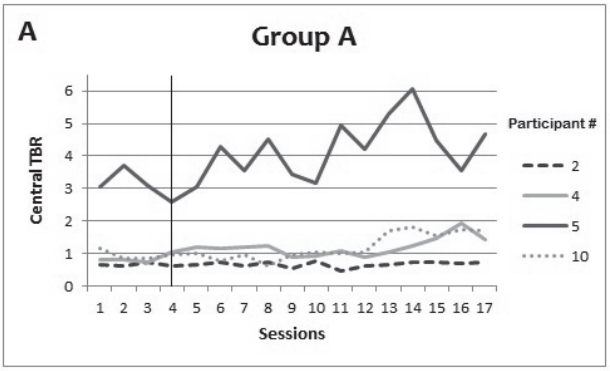
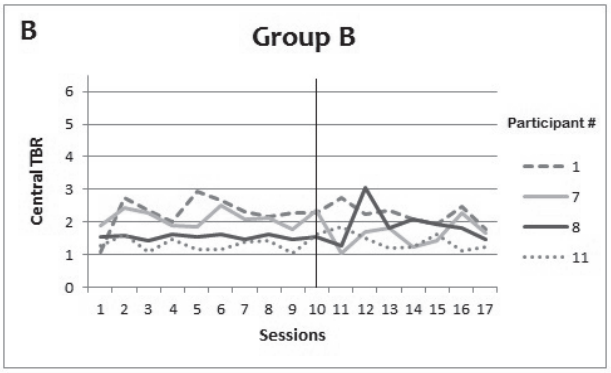


Figure 5.3. Flow diagram of participant recruitment and testing





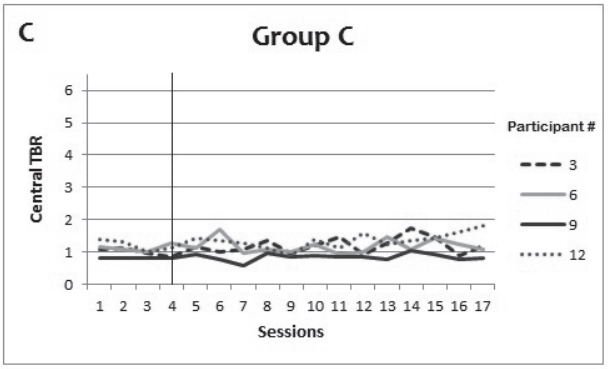


Figure 5.4(ABC). Central TBR averages per 4 minute baseline measurement per participant (lines) in group A, B and C. The thin black vertical lines represent when the active or sham NFT started.

Passive baseline between sessions

Each session started with a four-minute passive baseline measurement. Figure 5.4 shows the pattern of the average central TBR on the four-minute passive baseline per participant. A vertical line indicates the start of active-NFT or sham-NFT. We hypothesized that central TBR would reduce after the onset of active-NFT (in Group A and Group B) but would not show a consistent decrease or increase after the onset of sham-NFT (in Group C).

Visual inspection provided no support for such pattern. Passive baseline central TBR did not consistently change during the study, although some apparently random fluctuations between sessions were observed. This was invariably the case for all participants in both Groups A and B. No consistent increase or decrease of baseline central TBR was observed at any point in time in all participants. None of the participants that received sham-NFT showed a consistent decrease or increase after the onset of sham-NFT (Group C).

Average TBR during the active training phase of the sessions

Next, we inspected the pattern of average central TBR on the 25-minute measurements (measurement-only, active-NFT or sham NFT). This pattern was visually inspected per participant and by calculating the average central TBR per session per participant (**Figure 5.5**). No consistent increase or decrease was observed in any participant across sessions on central TBR after active-NFT onset compared to the measurement-only or the sham-NFT sessions (nor for any other EEG parameter; see online data repository). Additionally, no group differences were observed between Group A, B, and C in central TBR pattern over sessions.

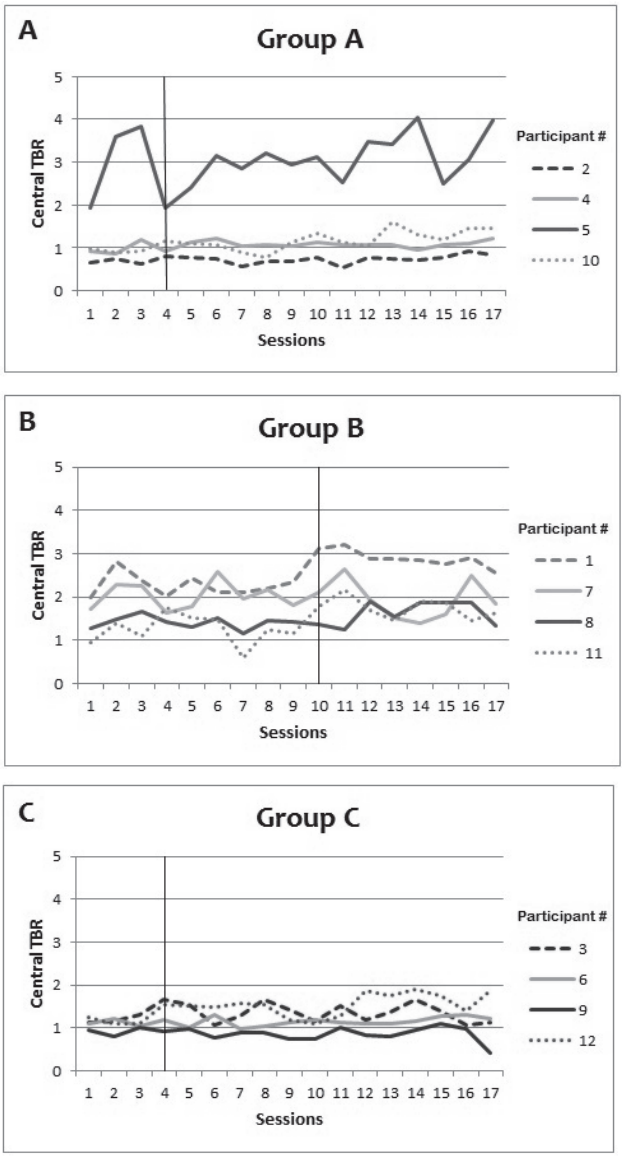


Figure 5.5(ABC). *Central TBR averages during the 25-minute sessions of measurement only or active NFT or sham NFT training for Groups A, B and C.*

Last five minutes of training phase

The possibility exists that calculating an average over a longer period of time will obscure any delayed within-session effects of active-NFT. In other words, active-NFT might reduce central TBR at the end of sessions only, for example because the learning-process takes time. To check for this possibility, we explored changes between sessions in average central TBR during the last five minutes of every session. Figure 5.6A, B, and C show

the pattern of the central TBR over sessions per participant of the averaged final 5 minutes. No clear differences between measurement-only, active-NFT and sham-NFT sessions became visible.

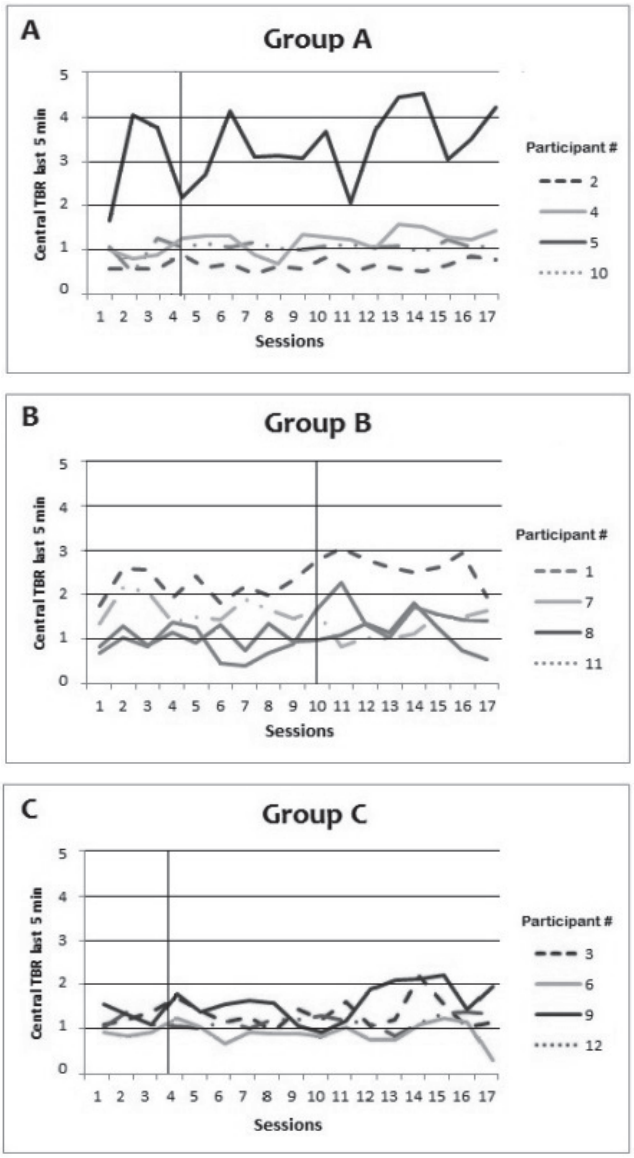


Figure 5.6(ABC). *Central TBR averages of last 5 minutes per measurement-only/active/sham NFT session per participant in Group A, B, or C.*

Inspection per case

Finally, we examined whether any consistent change in central TBR could be detected within the sessions. We calculated the average central TBR per minute for every session and plotted these over time (25 minutes on the x-axis) for each session and participant. All plots are available online (https://tinyurl.com/y948dcsl). Developments of central TBR over time were compared within sessions between measurement-only, active-NFT and sham NFT conditions. The effect of active-NFT might for example have been driven by motivation, or inhibited by fatigue, factors that are likely a function of the duration of a session and that are different for each session and participant. Visual inspection did not reveal any clear change over central TBR within the active-NFT sessions. We here present some detailed data for one of the 'best cases', showing some kind of change in central TBR/active-NFT effect. This concerns two out of four participants in Group B, in whom central TBR seemed to decrease within some active-NFT sessions compared to the measurement-only sessions. Here, we present these detailed data only for participant 7 (**Figure 5.7C and 7D. See https://tinyurl.com/y948dcsl for all data of all participants)**. The reduction in central TBR occurred in sessions 10 and 13 but not anymore in sessions 15 or 17. Furthermore, central TBR always started at approximately the same value in all active NFT sessions of participant 7. The data therefore do not show any transfer of a learning process caused by the active-NFT intervention.

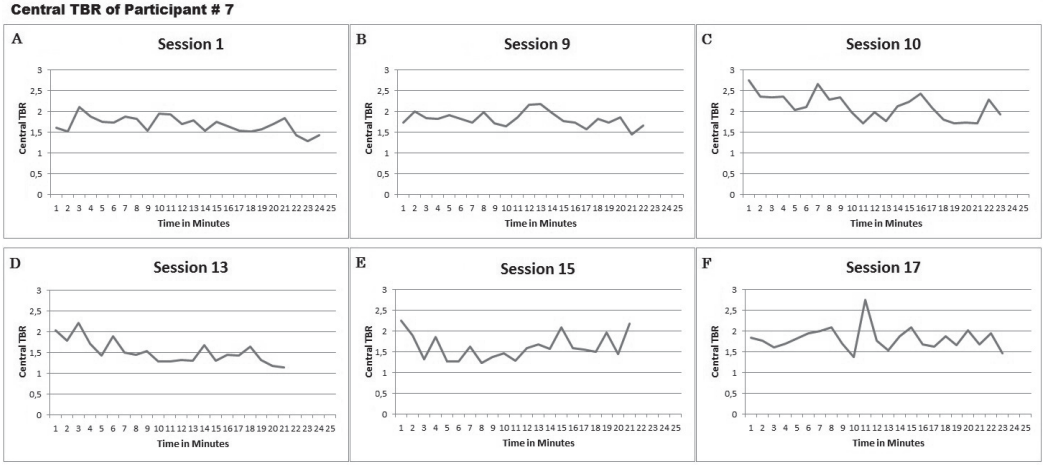


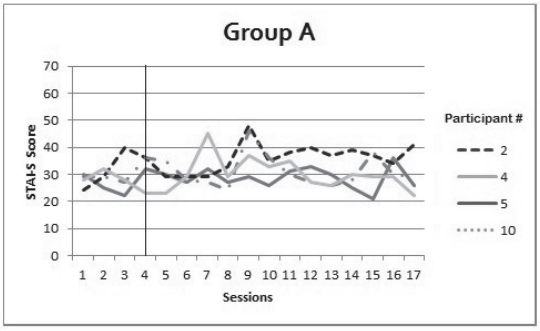
Figure 5.7(ABCDEF). Central TBR over time for participant 7 within; session 1 (A) session 9 as the last measurement-only session (B), session 10 as the first active NFT session (C), session 13 and 15 as two in between active NFT sessions (D and E) and session 17 as the last session (F).

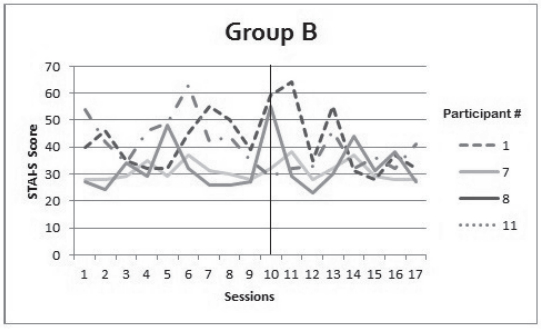
State anxiety and state AC over time

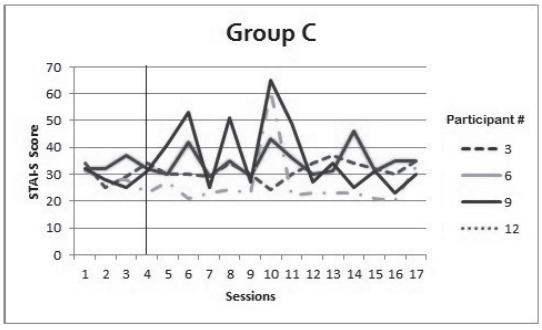
To check for potential adverse effects, scores on STAI-s and s-AC were plotted for all participants over all

sessions and visually inspected for changes over time. The plots show that for all three groups, STAI-s and s-AC did not show any consistent increase or decrease over sessions (Figure 5.8A B.). Active-NFT sessions therefore did not seem to induce any unwanted effects on state anxiety or state attentional control. Finally, scores on trait anxiety, ACS and BAS scores did not show any changes as measured on the first session compared to the last session. These plots can be found online via https://tinyurl.com/y948dcsl. No adverse effects were observed nor reported by the participants.

A) State-Anxiety







B) State AC

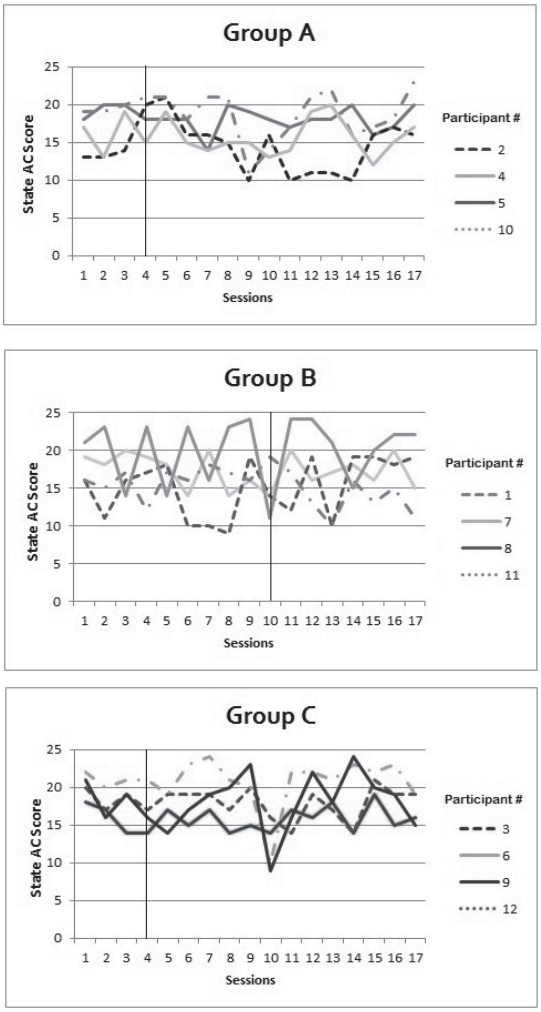


Figure 5.8(AB). Scores on state anxiety (A) and state attentional control (B) per session per participant in Group A, B or C.

Motivation and debriefing

All participants generally reported to be motivated performing the NFT over all sessions ($M = 3.35$; range 1-4 with 4 being most motivated), although for all three Groups (A, B and C) there was a small drop in motivation between the 10th and the 12th session. Motivation returned to their initial level after the 12th session. All participants received a funneled debriefing interview after the final session of the study, and it became clear that two out of the four participants that received sham-NFT (Group C) were not sure whether they were in the sham-

controlled group (60% chance of being in the sham controlled group) whilst the two other participants in Group C thought that they had received an active-NFT (70% chance).

Discussion

In this study we aimed to reduce central TBR with NFT in healthy individuals with elevated TBR. The results indicate that active-NFT did not alter TBR in any way. No consistent within-session change of TBR was found on either the passive baseline measurement or 25-minute active training measurement nor was there any evidence of between-session change. This suggests that the active-NFT did not induce any changes in EEG measurements of interest. State anxiety and state attentional control did not show a consistent change after active-NFT onset either. All participants reported to remain motivated performing the active- or sham-NFT however, and participants that received sham-NFT indicated that they believed to have received an active-NFT.

The present study was a first step towards intervention studies in a healthy population with elevated TBR. We expected that NFT would reduce TBR in healthy participants. Changes in EEG were the primary outcome, as these changes are likely easier to detect and more consistent than changes at the more multifaceted and complex behavioral level. We used a multiple baseline case series design for a detailed study of all NFT effects.

Our finding that active-NFT did not induce any consistent reduction or increase in TBR in healthy individuals is in line with the results of Doppelmayr and Weber (2011) who performed a randomized controlled trial in 14 healthy participants. Thirty active-NFT sessions did not induce changes in EEG TBR or the separate theta or beta frequency bands. Their results do not provide explanation why the active-NFT did not alter TBR. Possibly, some changes were simply not detected because TBR changes were not inspected within-sessions. By using a multiple baseline case series design, we provide a detailed view of what precisely happened with EEG TBR over time after the onset of active-NFT over sessions, as well as a precise view of TBR changes within active NFT sessions, over the course of 25 minutes. None of our detailed observations provided any evidence that active-NFT had an effect on the primary outcome variable, the EEG spectrum level of TBR, replicating the results of Doppelmayr and Weber (2011).

In particular, we had the ability to visually inspect what exactly happened with TBR over time on different levels of the data, between all participants and all conditions. First of all, we inspected the passive baseline measurement, which was done in four minutes before every 25-minute active measurement. No consistent decrease or increase of TBR was found in any of the participants. Yet, the passive baseline measurement was no main outcome variable because a longitudinal change in TBR was found to be more difficult to achieve than a direct change in TBR (van Doren et al., 2016). The main outcome measure was average TBR over time per session, for which we expected a consistent decrease in central TBR with a comparable lag after the first active-NFT session for the two active NFT groups. No such decrease or any other consistent change in central TBR was observed, making it unlikely that with our NFT procedures, TBR can be reduced in healthy participants. If any NFT induced changes would not transfer between sessions and take a long time within-sessions to occur, then reduced TBR might have been only visible at the end of the session, but no consistent

change in central TBR was observed in any of the participants in the last-five-minute averages either. Finally, it might have been possible that non-linear fluctuations in TBR occurred over the 25-minute active measurement, which would remain undetected when solely inspecting session averages. Only two participants in Group B showed the least bit of evidence of consistent reduction in TBR over time within the first few active NFT sessions. It became clear however that in their fifth active-NFT session this apparent TBR reduction was no longer discernable and again from this session onwards no consistent change in TBR was observed. Detailed analyses of data per case therefore did not show a transfer of learning caused by the active-NFT intervention in any way.

State anxiety and state attentional control were included for prudent use of an intervention like active-NFT of which no details on its side effects in a healthy population are known yet. The aim was to check carefully if state anxiety did not increase and state attentional control did not decrease. Plots of STAI-s and s-AC scores for all participants over all sessions were visually inspected on changes over time and no consistent change in either state anxiety or state attentional control was observed. We advise future studies to monitor unwanted effects on anxiety, attentional control and hedonically motivated behavior, as existing literature provides some reasons for concern (Massar et al., 2012; Massar et al., 2014; Putman et al., 2010; Angelidis et al., 2016). Similar arguments remain for the question if TBR down-training might actually reduce working memory in healthy participants (see Enriquez-Geppert et al. (2014)). Regarding the main research purposes of our study, the data does not provide any evidence for active-NFT causing changes to the EEG spectrum. We were purely interested in reducing TBR and to assess whether the NFT manipulation can be considered successful in doing this. Janssen et al. (2016) aimed to down-train TBR with NFT in children diagnosed with ADHD, and found no effects of NFT after 30 sessions on theta, however they found a significant increase in beta over sessions. These authors noted that this increase in beta activity was possibly a result of volitional motoric action as some participants reported to occasionally apply this during the active-NFT and cortical beta power is associated with motor control (Hammond et al., 2001).

When debriefing our participants, almost all indicated having used a different 'technique' to reduce the theta and increase the beta band, ranging from counting to imagining music. Neurofeedback is generally seen as an operant conditioning process (Kamiya, 2011; Strehl, 2014). However, other aspects like skill learning ability and motivation turned out to have a strong influence too (Roberts et al., 1989; Hofmann et al., 2012; Strehl, 2014). There seems to be a strong impact of feedback reinforcement, application of trial and error and transferring learned skills into everyday life (Abikoff, 2009; Mazur, 2002) making any effect of NFT dependent on individual differences. Also, it should be taken into account that the single-blind nature of this study might involuntarily have affected the interaction between the experimenter and participant. However, the instructions that the experimenters provided were standardized and no signs of such experimenter effects were reported by the participants in the debriefing. Moreover, it should be mentioned that our sample is not generalizable to the entire population in terms of age and gender, as we have measured female university students between 19 and 24 years old with elevated TBR (with respect to their previous study samples) only.

A few methodological choices in our study must be highlighted here, in order to best interpret the data and to increase the informative value of this report's null findings. Firstly, the use of automatic threshold regulation might not correspond to the prerequisites of shaping a learning process (Gruzelier, 2014c). It is

reasoned that not all individuals learn at the same speed, and the above-mentioned individual differences may also play a role. Manually adjusted thresholds, usually by a trained clinician, is suggested as a solution to this potential problem (Bazanova et al., 2007; Bazanova & Vernon, 2014; Klimesh, 1999) but has obvious experimental-methodological drawbacks. However, positive findings for successful regulation of beta or theta activity have been reported for other studies that did not use manual threshold adjustment. For instance, Lubar et al. (1995) used an automatic threshold scheme. Leins et al. (2007) used a reward method that automatically changed every 15 sessions. Fuchs et al, (2003) also used automatic thresholds when applying SMR/beta ratio neurofeedback in children diagnosed with ADHD. Neurofeedback training significantly reduced ADHD related behavioral problems. In their study, the thresholds were set to accept the signal 70% of the time, which is similar to the protocol as used in the current study. Since these studies did report changes in EEG activity, it seems unlikely that our null findings result from our use of that method. In general, no studies have been conducted that directly compared automatic thresholding to manual thresholding when using NFT, making it difficult to draw firm conclusions on this issue that go beyond simple observation (Gruzelier, 2014c).

Secondly, our protocol used a 'continuous' video feedback procedure. It has been argued that entertaining feedback might strengthen reinforcement associated with the stimulus rather than a specific brain-behavior response, suggesting that discrete feedback (e.g., earning points) might be more effective on the long-term (Egner & Sterman, 2006). However, Butnik (2005) described cases in which children diagnosed with ADHD successfully reduce or increase the targeted frequency bands when being submitted to video-neurofeedback trainings. Furthermore, Kouijzer et al. (2009) successfully reduced excessive theta power when applying video feedback in children with autism spectrum disorders. No studies have compared the effectiveness of continuous vs. discrete feedback.

Thirdly, the number of sessions used in NFT varies widely in the literature, and is usually dependent on the trained population as well as the specific protocol that is used (for a review see Enriquez-Geppert, Huster and Hermann, 2017). Reiner et al. (2014) found posterior theta to change already after one session, followed by some studies that observed clear changes in alpha after only one neurofeedback training (Escolano et al., 2014; Ros et al., 2014; Xiong et al., 2014). Also, Enriquez-Geppert et al. (2014) found frontal-midline theta to change after eight sessions of NFT, making it difficult to explain the absence of changes in theta after 14 training sessions in the current study. The duration of a single session is usually between 20-40 minutes, dependent on the participant's ability to focus on the training, which varies across health status and age (see Gruzelier, 2014c and Enriquez-Geppert, Huster and Hermann, 2017 for systematic reviews). For these reasons and because of the complete lack of EEG change throughout the entire duration of our study, it seems unlikely that we would have observed effects after more sessions.

Fourthly, we opted to select participants with elevated TBR scores, because such participants might respond better to the training. Although mean TBR had decreased somewhat between the pre-selection measurement and the start of the current study some six months later (regression to the mean may have occurred), their TBR was still clearly above the TBR as observed in the unselected samples. For potential application of TBR NFT to increase cognitive performance, we had chosen to study the effectiveness of TBR in

individuals with a mildly elevated TBR, also because it is not unlikely (though undocumented) that such participants might respond better to the training. Nevertheless, future studies might refrain from such a pre-selection, which can possibly contribute to the generalizability of study outcomes.

In summary, we found no evidence that TBR-targeted NFT affects TBR in healthy participants. Although it is possible that different NFT protocols may lead to different results, the present findings indicate that NFT, as implemented in the current study (using automatic thresholds, video feedback with a maximum of 14 sessions), does not affect TBR. The current study had several methodically strong features; a case series multiple baseline design that allowed us to inspect all EEG data per participant per session in detail, and control for unknown side effects. A sham controlled NFT group was included that, according to the funneled debriefing, let the participants believe that they received an active-NFT. We cannot identify convincing procedural limitations of our study that might serve to adequately explain the lack of positive result and thus consider these results a valid null-finding. These results are relevant given recent publications on TBR and its relation to executive cognitive control and affect regulation (Schutter et al., 2005; Jap, Lal, Fischer, & Bekiaris, 2009; Massar et al., 2014; Wischnewski et al., 2016; Tortella-Feliu et al., 2014; Angelidis et al., 2016) in healthy adults. The present results, which replicate and extend previous results by Doppelmayr and Weber (2011), suggest that TBR-targeted NFT will not likely provide a tool to study causality of the relations between cognitive control and affect regulation. Futhermore, TBR NFT does not seem to be a promising candidate for human performance enhancement in these functional areas.

References

Abikoff, H. (2009). ADHD psychosocial treatments: Generalization reconsidered. *Journal of Attention Disorders*, *13*(3), 207-210.

Angelidis, A., van der Does, W., Schakel, L., & Putman, P. (2016). Frontal EEG theta/beta ratio as an electrophysiological marker for attentional control and its test-retest reliability. *Biological psychology*, *121*, 49-52.

Angelidis, A., Hagenaars, M., van Son, D., van der Does, W., & Putman, P. (2018). Do not look away! Spontaneous frontal EEG theta/beta ratio as a marker for cognitive control over attention to mild and high threat. *Biological psychology, 135,* 8-17.

Arns, M., Conners, C. K., & Kraemer, H. C. (2013). A decade of EEG theta/beta ratio research in ADHD: a meta-analysis. *Journal of Attention Disorders, 17*(5), 374-383.

Baer, D. M., Wolf, M. M., & Risley, T. R. (1968). Some current dimensions of applied behavior analysis. *Journal of applied behavior analysis*, *1*(1), 91-97.

Barry, R. J., Clarke, A. R., & Johnstone, S. J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clinical neurophysiology*, *114*(2), 171-183.

Bazanova, O. M., Verevkin, E. G., & Shtark, M. B. (2007). Biofeedback in optimizing psychomotor reactivity: II. The dynamics of segmental α-activity characteristics. *Human Physiology*, *33*(6), 695-700.

Bazanova, O. M., & Vernon, D. (2014). Interpreting EEG alpha activity. *Neuroscience & Biobehavioral Reviews*, *44*, 94-110.

Bink, M., van Nieuwenhuizen, C., Popma, A., Bongers, I. L., & van Boxtel, G. J. (2015). Behavioral effects of neurofeedback in adolescents with ADHD: a randomized controlled trial. *European child & adolescent psychiatry*, *24*(9), 1035-1048.

Bishop, S. J. (2009). Trait anxiety and impoverished prefrontal control of attention. *Nature neuroscience*, *12*(1), 92-98.

Butnik, S. M. (2005). Neurofeedback in adolescents and adults with attention deficit hyperactivity disorder. *Journal of Clinical Psychology*, *61*(5), 621-625.

Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. *Journal of personality and social psychology*, *67*(2), 319.

Cella, M., Dymond, S., & Cooper, A. (2010). Impaired flexible decision-making in major depressive disorder. *Journal of Affective Disorders*, *124* (1), 207-210.

Cohen, L. L., Feinstein, A., Masuda, A., & Vowles, K. E. (2013). Single-case research design in pediatric psychology: Considerations regarding data analysis. *Journal of pediatric psychology*, *39*(2), 124-137.

Coy, B., O'Brien, W. H., Tabaczynski, T., Northern, J., & Carels, R. (2011). Associations between evaluation anxiety, cognitive interference and performance on working memory tasks. *Applied Cognitive Psychology*, *25*(5), 823-832.

Derakshan, N., & Eysenck, M. W. (2009). Anxiety, processing efficiency, and cognitive performance: New developments from attentional control theory. *European Psychologist*, *14*(2), 168-176.

Derryberry, D., & Reed, M. A. (2002). Anxiety-related attentional biases and their regulation by attentional control. *Journal of abnormal psychology*, *111*(2), 225.

Desmond, J. E., & Glover, G. H. (2002). Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. *Journal of neuroscience methods*, *118*(2), 115-128.

Doppelmayr, M., & Weber, E. (2011). Effects of SMR and theta/beta neurofeedback on reaction times, spatial abilities, and creativity. *Journal of Neurotherapy*, *15*(2), 115-129.

Duty, S. M., Christian, L., Loftus, J., & Zappi, V. (2016). Is Cognitive Test-Taking Anxiety Associated With Academic Performance Among Nursing Students?. *Nurse educator*, *41*(2), 70-74.

Egner, T., & Gruzelier, J. H. (2003). Ecological validity of neurofeedback: Modulation of slow wave EEG enhances musical performance. *Neuroreport*, *14*(9), 1221-1224.

Egner, T., & Sterman, M. B. (2006). Neurofeedback treatment of epilepsy: from basic rationale to practical application. *Expert Review of Neurotherapeutics*, *6*(2), 247-257.

Enriquez-Geppert, S., Huster, R. J., & Herrmann, C. S. (2017). EEG-neurofeedback as a tool to modulate cognition and behavior: a review tutorial. *Frontiers in human neuroscience*, *11*.

Enriquez-Geppert, S., Huster, R. J., Scharfenort, R., Mokom, Z. N., Zimmermann, J., & Herrmann, C. S. (2014). Modulation of frontal-midline theta by neurofeedback. *Biological psychology*, *95*, 59-69.

Escolano, C., Navarro-Gil, M., Garcia-Campayo, J., & Minguez, J. (2014). The Effects of a Single Session of Upper Alpha Neurofeedback for Cognitive Enhancement: A Sham-Controlled Study. *Applied psychophysiology and biofeedback*, 1-10.

Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: attentional control theory. *Emotion*, *7*(2), 336.

Fisher, W. W., Kelley, M. E., & Lomas, J. E. (2003). Visual aids and structured criteria for improving visual inspection and interpretation of single-case designs. *Journal of applied behavior analysis*, *36*(3), 387-406.

Fuchs, T., Birbaumer, N., Lutzenberger, W., Gruzelier, J. H., & Kaiser, J. (2003). Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: a comparison with methylphenidate. *Applied psychophysiology and biofeedback*, *28*(1), 1-12.

Graczyk, M., Pachalska, M., Ziolkowski, A., Manko, G., Lukaszewska, B., Kochanowicz, K., ... & Kropotow, I. D. (2014). Neurofeedback training for peak performance. *Annals of Agricultural and Environmental Medicine*, *21*(4).

Gratton, G., Coles, M. G., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and clinical neurophysiology*, *55*(4), 468-484.

Gruzelier, J. H. (2014a). EEG-neurofeedback for optimising performance. I(a): a review of cognitive and affective outcome in healthy participants. *Neuroscience & Biobehavioral Reviews*, *44*, 124-141.

Gruzelier, J. H. (2014c). EEG-neurofeedback for optimising performance. III(c): a review of methodological and theoretical considerations. *Neuroscience & Biobehavioral Reviews*, *44*, 159-182.

Hammond, D. C., Stockdale, S., Hoffman, D., Ayers, M. E., & Nash, J. (2001). Adverse reactions and potential iatrogenic effects in neurofeedback training. *Journal of Neurotherapy*, *4*(4), 57-69.

Hembree, R. (1988). Correlates, causes, effects, and treatment of test anxiety. *Review of educational research*, *58*(1), 47-77.

Hofmann, W., Schmeichel, B. J., & Baddeley, A. D. (2012). Executive functions and self-regulation. *Trends in cognitive sciences*, *16*(3), 174-180.

Hofman, D., & Schutter, D. J. (2011). Asymmetrical frontal resting-state beta oscillations predict trait aggressive tendencies and behavioral inhibition. *Social cognitive and affective neuroscience*, *7*(7), 850-857.

Janssen, T. W., Bink, M., Geladé, K., Mourik, R., Maras, A., & Oosterlaan, J. (2016). A randomized controlled trial into the effects of neurofeedback, methylphenidate, and physical activity on EEG power spectra in children with ADHD. *Journal of Child Psychology and Psychiatry*, *57*(5), 633-644.

Jap, B. T., Lal, S., Fischer, P., & Bekiaris, E. (2009). Using EEG spectral components to assess algorithms for detecting fatigue. *Expert Systems with Applications*, *36*(2), 2352-2359.

Kao, S. C., Huang, C. J., & Hung, T. M. (2014). Neurofeedback training reduces frontal midline theta and improves putting performance in expert golfers. *Journal of Applied Sport Psychology*, *26*(3), 271-286.

Kamiya, J. (2011). The first communications about operant conditioning of the EEG. *Journal of Neurotherapy*, *15*(1), 65-73.

Kouijzer, M. E., de Moor, J. M., Gerrits, B. J., Congedo, M., & van Schie, H. T. (2009). Neurofeedback improves executive functioning in children with autism spectrum disorders. *Research in Autism Spectrum Disorders*, *3*(1), 145-162.

Keizer, A. W., Verment, R. S., & Hommel, B. (2010). Enhancing cognitive control through neurofeedback: A role of gamma-band activity in managing episodic retrieval. *Neuroimage*, *49*(4), 3404-3413.

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain research reviews*, *29*(2-3), 169-195.

Koehler, M. J., & Levin, J. R. (2000). RegRand: Statistical software for the multiple-baseline design. *Behavior Research Methods*, *32*(2), 367-371.

Kinugasa, T., Cerin, E., & Hooper, S. (2004). Single-subject research designs and data analyses for assessing elite athletes' conditioning. *Sports medicine*, *34*(15), 1035-1050.

Leins, U., Goth, G., Hinterberger, T., Klinger, C., Rumpf, N., & Strehl, U. (2007). Neurofeedback for children with ADHD: a comparison of SCP and Theta/Beta protocols. *Applied psychophysiology and biofeedback*, *32*(2), 73-88.

Lubar, J. F., Swartwood, M. O., Swartwood, J. N., & O'Donnell, P. H. (1995). Evaluation of the effectiveness of EEG neurofeedback training for ADHD in a clinical setting as measured by changes in TOVA scores, behavioral ratings, and WISC-R performance. *Applied Psychophysiology and Biofeedback*, *20*(1), 83-99.

Massar, S. A. A., Rossi, V., Schutter, D. J. L. G., & Kenemans, J. L. (2012). Baseline EEG theta/beta ratio and punishment sensitivity as biomarkers for feedback-related negativity (FRN) and risk-taking. *Clinical Neurophysiology*, *123*(10), 1958-1965.

Massar, S. A., Kenemans, J. L., & Schutter, D. J. (2014). Resting-state EEG theta activity and risk learning: sensitivity to reward or punishment? *International Journal of Psychophysiology*, *91*(3), 172-177.

Marzbani, H., Marateb, H. R., & Mansourian, M. (2016). Neurofeedback: a comprehensive review on system design, methodology and clinical applications. *Basic and clinical neuroscience*, *7*(2), 143.

Mazur, J. E. (2015). Learning and behavior. Psychology Press.

McVay, J. C., & Kane, M. J. (2009). Conducting the train of thought: working memory capacity, goal neglect, and mind wandering in an executive-control task. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *35*(1), 196.

Mueller, E. M., Nguyen, J., Ray, W. J., & Borkovec, T. D. (2010). Future-oriented decision-making in Generalized Anxiety Disorder is evident across different versions of the Iowa Gambling Task. *Journal of Behavior Therapy and Experimental Psychiatry*, *41*(2), 165-171.

Murphy, K., & Garavan, H. (2004). An empirical investigation into the number of subjects required for an event-related fMRI study. *Neuroimage*, *22*(2), 879-885.

Nitschke, J. B., Miller, G. A., & Cook, E. W. (1998). Digital filtering in EEG/ERP analysis: Some technical and empirical comparisons. *Behavior Research Methods*, *30*(1), 54-67.

Ogrim, G., Kropotov, J., & Hestad, K. (2012). The QEEG theta/beta ratio in ADHD and normal controls: Sensitivity, specificity, and behavioral correlates. *Psychiatry Res*, *198*, 482-488.

Putman, P., van Peer, J., Maimari, I., & van der Werff, S. (2010). EEG theta/beta ratio in relation to fear-modulated response-inhibition, attentional control, and affective traits. *Biological psychology*, *83*(2), 73-78.

Putman, P., Verkuil, B., Arias-Garcia, E., Pantazi, I., & van Schie, C. (2014). EEG theta/beta ratio as a potential biomarker for attentional control and resilience against deleterious effects of stress on attention. *Cognitive, Affective, & Behavioral Neuroscience*, *14*(2), 782-791.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual review of neuroscience*, *13*(1), 25-42.

Roberts, L. E., Birbaumer, N., Rockstroh, B., Lutzenberger, W., & Elbert, T. (1989). Self-Report During Feedback Regulation of Slow Cortical Potentials. *Psychophysiology*, *26*(4), 392-403.

Ros, T., Munneke, M. A. M., Parkinson, L. A., & Gruzelier, J. H. (2014). Neurofeedback facilitation of implicit motor learning. *Biological psychology*, *95*, 54-58.

Schneider, W., Eschman, A., & Zuccolotto, A. (2002). *E-Prime: User's guide*. Psychology Software Incorporated.

Schutter, D. J., & Van Honk, J. (2005). Electrophysiological ratio markers for the balance between reward and punishment. *Cognitive Brain Research*, *24*(3), 685-690.

Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., Jacobs, G. A. (1983). Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: *Consulting Psychologists Press*.

Stawarczyk, D., Majerus, S., Maquet, P., & D'Argembeau, A. (2011). Neural correlates of ongoing conscious experience: both task-unrelatedness and stimulus-independence are related to default network activity. *PloS one*, *6*(2), e16997.

Strehl, U. (2014). What learning theories can teach us in designing neurofeedback treatments. *Frontiers in human neuroscience*, *8*.

Sutton, S. K., & Davidson, R. J. (2000). Prefrontal brain electrical asymmetry predicts the evaluation of affective stimuli. *Neuropsychologia*, *38*(13), 1723-1733.

Xiong, S., Cheng, C., Wu, X., Guo, X., Yao, L., & Zhang, J. (2014). Working memory training using EEG neurofeedback in normal young adults. *Bio-medical materials and engineering*, *24*(6), 3637-3644.

Tortella-Feliu, M., Morillas-Romero, A., Balle, M., Llabrés, J., Bornas, X., & Putman, P. (2014). Spontaneous EEG activity and spontaneous emotion regulation. *International Journal of Psychophysiology*, *94* (3), 365-372.

Van der Ploeg, H. M., & Defares, P. B. (1980). ZBV: handleiding bij de zelf-beoordelings vragenlijst: een Nederlandstalige bewerking van Spielberger state-trait anxiety inventory STAI-Y.

Van Doren, J., Heinrich, H., Bezold, M., Reuter, N., Kratz, O., Horndasch, S., ... & Studer, P. (2017). Theta/beta neurofeedback in children with ADHD: feasibility of a short-term setting and plasticity effects. *International Journal of Psychophysiology*, *112*, 80-88.

Vernon, D. J. (2005). Can neurofeedback training enhance performance? An evaluation of the evidence with implications for future research. *Applied psychophysiology and biofeedback*, *30*(4), 347.

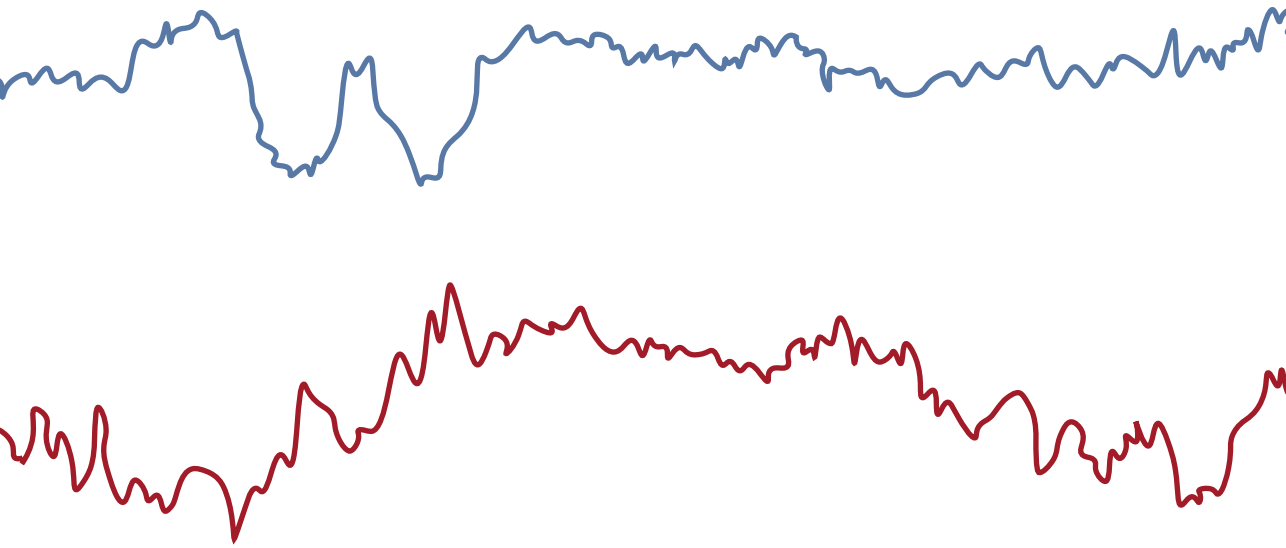
Watson, P. J., & Workman, E. A. (1981). The non-concurrent multiple baseline across-individuals design: An extension of the traditional multiple baseline design. *Journal of Behavior Therapy and Experimental Psychiatry*, *12*(3), 257-259.

Williams, L. M., Simms, E., Clark, C. R., Paul, R. H., Rowe, D., & Gordon, E. (2005). The test-retest reliability of a standardized neurocognitive and neurophysiological test battery: "neuromarker". *International Journal of Neuroscience*, *115*(12), 1605-1630.

Wischnewski, M., Zerr, P., & Schutter, D. J. (2016). Effects of theta transcranial alternating current stimulation over the frontal cortex on reversal learning. *Brain stimulation*, *9*(5), 705-711.

Chapter 6

GENERAL DISCUSSION



The aim of this thesis was to further investigate on the role of attentional processes in anxiety. To this end we measured and/or manipulated EEG theta/beta ratio (TBR), self-reported attentional control, trait anxiety, catecholamines, functional connectivity, and selective attention to varying levels of threat. The studies were carried out in healthy samples. In the first chapter we described that high TBR (low control) was associated with more attention to mild than to high threat, independent of trait anxiety or probe-delay in a visual-spatial attention task. Lower self-reported attentional control also predicted more attention to mild than to high threat, but only after longer stimulus delays. In Chapter 2, we reported that at baseline and after placebo administration, high TBR was related to low threat-bias in a modified emotional Stroop task in low trait-anxious people. Caffeine had opposite effects on threat-bias in high and low TBR in low trait-anxious people. In the third chapter, it became clear that frontal TBR is significantly higher during mind wandering (MW) episodes than focused periods, suggesting that previously reported relationships between TBR and attentional control may be related to MW. The fourth chapter moreover reported that this effect of controlled versus uncontrolled thought was also found for functional connectivity of the 'executive control network', which was in turn correlated to the controlled versus uncontrolled thought effect on TBR. This provides indications of the neuropsychological functional nature of TBR, which remained a 'black box' till now. Finally, the fifth chapter reported no evidence that TBR is affected by a form of neurofeedback training.

These findings will be further discussed below in which the possible applicability and usefulness of TBR will be illustrated.

Attentional threat-biases

To correctly interpret our results on attentional threat bias and TBR, it can be helpful to briefly describe the neural networks and connections involved in threat bias again. Anxiety and attentional biases depend on multiple processes. Firstly, exposure to acute threat induces fear and vigilance, and prompts a reallocation of resources to a so-called 'salience network'. This happens at the cost of the executive control network (Hermans, Henckens, Joels, & Fernandez, 2014). Salience network activation includes bottom-up detection and attentional processing of salient and threat-related stimuli, which are mediated by, for example, the anterior cingulate cortex (ACC) and the amygdala (Bishop, 2008). When the threat subsides, resource allocation to both the salience and executive control network reverses, normalizing emotional reactivity and enhancing higher-order cognitive processes that are important for long-term survival. Top-down attentional control and inhibition of stimulus-driven attention involves, for example, activation of the dorsal ACC and (dorso-) lateral prefrontal cortex (DLPFC; Bishop, 2008; Hermans et al., 2014). The (DL)PFC is involved in working memory and executive cognitive processes like attentional control (see e.g., Arnsten & Rubia, 2012; Arnsten, 2006). Importantly, anxiety and stress also directly disrupt (DL)PFC function and therewith top-down executive (attentional) control (Bishop, 2008; Hermans et al., 2014; Arnsten, 2011). Thus, multiple cognitive functions, organised as coordinated systems or networks, underpin salience-driven and top-down processing. Disruption of these systems underlie anxiety, and threat-related attentional biases.

Before starting this research, we hypothesized that TBR, as a marker for attentional control, plays a role in

the disrupted interplay between top-down and bottom-up processes. Using this physiological marker could possibly be useful in current treatment consideration for certain mental disorders, since 'outbalanced' neural system functions as described above have been identified in various mental illnesses. The bottom-up cognitive processes (such as perception and pre-attentive perceptual biasing) can in that case interfere with top- down processes (e.g., cognitive control, and metacognitive appraisal). In major depression for example, impairments in executive function and processing speed related to aberrant activity in prefrontal and limbic system networks are for example associated with affect dysregulation (Bowie, Gupta, & Holshausen, 2013; Rive, van Rooijen, Veltman, Phillips, Schene, & Ruhé, 2013) and abnormal biasing of attention to negative cognitions (Etkin & Schatzberg, 2011). Increased knowledge of top-down attentional control and bottom-up processes could therefore possibly aid further clinical research. TBR as a marker for attentional control and moderator for attentional threat biases can be valuable in these studies as demonstrated in the current thesis. Also, as described in Chapter 2, individual differences in TBR and baseline executive function might determine catecholamine functioning and threat processing, and hence forms an important feature when investigating neural underpinnings of psychopathology.

Inconsistencies in threat-bias-research

Multiple theoretical models exist on the role of threat related attentional processes in pathological anxiety (e.g. Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Armstrong & Olatunji, 2012; Cisler, Bacon, & Williams, 2009; Cisler & Koster, 2010; Mathews, & MacLeod, 2005; Teachman, Joormann, Steinman & Gotlib, 2012; van Bockstaele, Verschuere, Tibboel, De Houwer, Crombez, & Koster, 2014; Weierich, Treat, & Hollingworth, 2008). These models indicate that anxiety disorders are associated with automatic processing biases for threatening information (e.g. Bar-Haim et al., 2007; Teachman et al., 2012). However, certain aspects (e.g. individual differences) have not been addressed in the models, while these are possibly vital ingredients for our understanding of threat processing (e.g. see Mogg & Bradley, 1998; 2016). Examples of these aspects are; subjective threat valence, attentional control and attentional avoidance (van Bockstaele et al., 2014; Fox, Russo, Bowles, & Dutton, 2001; Derryberry and Reed, 2002; Eysenck, Derakshan, Santos, & Calvo, 2007). The importance of these aspects is also supported by the current findings of our lab. This will be further discussed below.

In Chapter 1 we manipulated threat value in a dot-probe task (cf. Angelidis, Hagenaars, van Son, van der Does, & Putman, 2018). Our findings on the effects of TBR on threat biases were threat-level dependent. The level (mild or high) or type of valence (positive or negative) had an impact on threat bias (Angelidis et al., 2018; van Son et al., 2018a [Chapter 1]; 2018b [Chapter 2]). This indicates that threat processing and a physiological marker of attentional control (TBR) are related to participant's 'subjective value' or how vigilant participants are for these stimuli. This is in agreement with findings by Mogg and colleagues (1987) and Mogg and Bradley (2016), who also stated that attentional bias towards threat may be opposed by mechanisms of avoidance, and that individual differences in cognitive control are crucial in the actual manifestation of threat-bias toward or away from threat (Mogg, Weinman & Mathews, 1987; Mogg & Bradley, 2016).

Regarding attentional avoidance, the 'vigilance-avoidance hypothesis' was introduced some decades

ago (Mogg et al., 1987): this hypothesis stated that the initial attentional bias towards threat in healthy adults may be followed by avoidance, which possibly reflects an attempt to reduce subjective discomfort or danger (e.g., avoiding threat). While avoidant attention strategies may reduce immediate stress, they may be detrimental when used long-term, by refraining from coping with the actual threat and thus maintaining anxiety. Bardeen and Daniel (2017) for example found that trauma-exposed participants with high post-traumatic stress symptoms, who habitually shifted attention from threatening stimuli to neutral stimuli, showed reduced distress in the short term but maintained and even increased post-traumatic stress symptoms in the long term. Later, also other models indicated that attentional bias towards threat may be opposed by mechanisms of avoidance and that individual differences in cognitive control are crucial in the actual manifestation of threat-bias towards or away from threat (e.g. Algom, Chajut & Lev, 2004; Bar-Haim et al., 2007; Eysenck et al., 2007; Mogg et al., 1987; Mogg & Bradley, 1998; 2016). Whether participants direct attention towards or away from a stimulus, depends on whether stimuli are highly or mildly threatening, which is also supported by our studies (Angelidis et al., 2018; van Son et al., 2018a). This altogether indicates that threat value or vigilance to threat, and attentional avoidance, are important aspects when investigating attentional bias to threat, and it is therefore troublesome that these mechanisms have not always been incorporated in threat bias studies.

Attentional control

Attentional control in general as well seems a partly neglected factor in attentional threat bias literature (for an overview see van Bockstaele et al., 2014). Like attentional control, TBR seemed to affect and moderate threat selective attention and emotional processes (Angelidis et al., 2018; van Son et al., 2018a; 2018b), as examined by a dot probe task and an emotional threat interference task. This finding strengthens the assumption of functional overlap of TBR and attentional control. The role of attentional control in automatic emotional and cognitive top-down processes as described in the chapters of this thesis, among others, encompasses the framework as proposed by Mogg and Bradley, (1998; 2016) and as later described by Bardeen, Daniel, Hinnant & Orcutt, (2017). We thus suggest that TBR, as a marker of attentional control, is associated with regulating automatic-stimulus salient processes and that it supports goal directed behavior (Angelidis et al., 2018; van Son et al., 2018a, 2018b; Mogg & Bradley, 1998; Miyake & Friedman, 2012) since findings of the first two studies in this thesis support this assumption. Besides threat value or vigilance to threat, attentional control hence seems another important factor when investigating attentional bias to threat which should be taken into account in future studies studying threat biases.

Furthermore, our results as described in Chapter 2 also indicate that besides that attentional control plays an important role in threat processing, the interaction between caffeine and the TBR-related threat-interference effect, is likely catecholamine-mediated.

Namely, performance on the Pictorial Emotional Stroop Task (*PEST*) in participants with low TBR/better attentional control after caffeine, resembled more the baseline/placebo performance of participants with less attentional control. Performance of people with higher TBR/less attentional control resembled more the baseline/placebo performance of people with better attentional control after caffeine administration (van Son et al., 2018b [Chapter

2]). These findings fit with the established model of inverted U-shape relations between prefrontal catecholamine activity and cognitive attentional control (Arnsten, 2006; Arnsten, 2009a; Cools and D'Esposito, 2011). Our results moreover showed that baseline TBR (as a marker for attentional control) of low anxious individuals, had a significant direct relation with responding in the *PEST*, and this was clearly influenced by caffeine administration. This pattern of responding is just as the predicted moderation of caffeine's effects by baseline TBR. It was already found that lower TBR is related to better executive (attentional) control (Angelidis, van der Does, Schakel, & Putman, 2016; Barry, Clarke, & Johnstone, 2003; Keune, Hansen, Weber, Zapf, Habich, Muenssinger, Wolf, et al., 2017), and better top-down control over the automatic attentional processing of salient threatening stimuli (Putman, van Peer, Maimari, & van der Werff, 2010; Angelidis et al., 2018; van Son et al., 2018a). It can be speculated that such basal prefrontal attentional control is regulated by prefrontal catecholamine levels (Arnsten, 2006; Hermans et al., 2014). Indeed, the TBR-moderated responding pattern fitted with the established model of inverted U-shape relations between prefrontal catecholamine activity and cognitive attentional control (Arnsten, 2006; Arnsten, 2009a; Cools and D'Esposito, 2011). This finding stresses the importance of TBR in such relations and TBRs possible applicability in future studies to the effects of catecholamine. Accordingly, attentional control can be considered to be an essential factor in threat processes, and the inverted U-shape relation between TBR and threat interference highlights the importance of also taking baseline executive function into consideration when studying such processes.

Attentional stages

Threat processing thus seems rather complex and to depend on a variety of aspects, of which threat value, attentional avoidance and attentional control are examples which have not consistently been incorporated in the past literature. However, their importance has now been further demonstrated by our current studies. Another factor that has scarcely been integrated in threat processing models and related to attentional control are the attentional stages of threat processing. The nature of attentional bias is thought to depend on the stage of information processing (Cisler & Koster, 2010). Information processing is commonly conceptualized in two stages, automatic and strategic processing stages (Shiffrin & Schneider, 1977; Cisler & Koster, 2010). Automatic (early) processing generally refers to processing that is effortless, capacity free, unintentional, and outside of conscious control, whereas strategic (later) processing generally refers to processing that is effortful, capacity-limited, intentional, and dependent on conscious control (Shiffrin & Schneider, 1977). The expectation that cue-target delay would affect threat processing originates from the assumption that the cognitive control mechanisms that regulate automatic attention away from threat (attentional avoidance) occur at later – strategic stages of attentional processing (Derryberry & Reed, 2002; Cisler & Koster, 2010; Mogg & Bradley, 1998; 2016). We therefore expected that TBR would be more strongly related to the attentional bias effect in late compared to early attentional stages. The results as described in Chapter 1 and the results of Angelidis et al., (2018) do not support this notion. We do not have a clear explanation for the absence of a delay effect for TBR, but the presence of this effect for attentional control, especially considering the positive relation between self-reported attentional control and TBR as found in this study. Whether attentional stages play a role in the TBR – threat bias relation thus

remains inconclusive, however it might as well be the case that the short cue target delay was too short for sufficient emotional-attentional processing. Another option is that both the automatic and the strategic attentional stages when applying a dot-probe task (Cisler & Koster, 2010) are not differently affected by TBR. Future studies should investigate this matter and manipulate shorter cue target delays compared to longer cue target delays when investigating the role of TBR in attentional stages in a dot-probe task.

Nevertheless, an effect of self-assessed attentional control on cue target delay was found, indicating that attentional stages are imperative for investigating threat processes. Attentional stages are therefore advised to be taken into account when studying the effects of attentional control in threat processing and should be further investigated to consider how threat selective attention should be manipulated. Measuring the time-course of attention remains however notoriously difficult (see also Mogg & Bradley, 2016). Different methods such as emotional cueing tasks (Koster, Crombez, Verschuere, Vanvolsem, & De Houwer, 2007), event-related potential tasks (Harrewijn, Schmidt, Westenberg, Tang, & van der Molen, 2017), non-spatial emotional-attention tasks such as interference tasks (Clarke, MacLeod, & Guastella, 2013) or serial presentation tasks (Peers & Lawrence, 2009) are advised to be used for future studies to more accurately assess the time-course (stages) of selective attention, attentional avoidance and attentional control.

Application of attentional bias (attentional bias modification [ABM] trainings)

Altogether, the now repeatedly mentioned framework of Mogg and Bradley (1998; 2016) was the first important model to signal that essential aspects have not been included when studying threat processing. The Mogg and Bradley framework together with the vigilance-avoidance hypothesis also indicate implications for research that applies the attentional bias theories; mainly attentional bias modification (ABM) trainings. In ABM, attentional biases are conceptualized as the tendency to allocate attention to threat-related information rather than non-threat information (MacLeod & Mathews, 2012; MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). ABM trainings therefore aim to train attention away from threat (attentional avoidance) and to direct attention towards non-threat. Recent reviews and meta-analyses however, conclude that conventional ABM trainings have inconsistent effects on anxiety and attentional-bias (e.g. Heeren, Mogoaşe, Philippot, & McNally, 2015; Mogg & Bradley, 2016; 2018; van Bockstaele et al., 2014; Mogg, Waters & Bradley, 2017; Macleod & Grafton, 2016). The degree of effectiveness of ABM may be dependent on individual differences, which will be further discussed in this paragraph. One limitation of ABM-threat-avoidance trainings for example is that not all anxious individuals show an attentional bias towards threat (e.g., Dudeney, Sharpe, & Hunt, 2015; Salum, Mogg, Bradley, Gadelha, Pan, Tamanaha et al., 2013; van Bockstaele et al., 2014; Waters, Bradley & Mogg, 2014) since attentional biases depend on individual differences in the perception of subjective threat (e.g. how threatening a certain stimulus is). Mogg and Bradley (1998) already suggested that attentional biases in anxiety are highly dependent on stimulus threat-value or threat-level. Results as described in Chapter 1 and 2 confirm the effect of threat-level and valence in threat-processing, which suggest implications for ABM as ABM does not always manipulate different levels of threat or does not take perception of subjective threat into account (van Bockstaele et al., 2014; Waters et al., 2014).

Some ABM trainings instruct to direct attention away from threat (MacLeod & Clarke, 2015) with the goal to induce automatic threat avoidance by repeated practice, rather than using effortful controlled strategies. Because not all anxious individuals show an attentional bias to threat, another limitation of ABM training is that not all individuals should receive a threat avoidance training as some individuals are already threat avoidant (van Bockstaele et al., 2014). As found by the first studies of this thesis (van Son et al., 2018a [Chapter 1]; 2018b [Chapter 2]) and others (e.g. Angelidis et al., 2018; Mogg et al., 1987; Algom et al., 2004; Bar-Haim et al., 2007; Eysenck et al., 2007), avoidant attentional strategies seem to influence threat processing, possibly in a maladaptive way. Attentional avoidance may be detrimental when applied long-term, and might even maintain anxiety (Bradley, Mogg, & Lee, 1997; Wald et al., 2011). Among others, our studies therefore implicate that ABM may not be beneficial for reducing anxiety; even though attentional biases might be reduced, attentional avoidance can be more strongly introduced resulting in such avoidant habituation. This problem however does not apply to all types of ABM trainings; ABM-positive search training for example is potentially suitable for threat avoiding individuals as it uses a visual search task which presents arrays of pictures, and in each array, one picture is positive and the others are negative. Participants are instructed to search for the positive image and ignore the others (e.g. Dandeneau, Baldwin, Baccus, Sakellaropoulo & Pruessner, 2007). It would be interesting to investigate the role of TBR in threat processing in such positive search trainings as these trainings are not specifically subject to the avoidance-implication of ABM.

Also, individual differences in attentional control are not incorporated in ABM trainings, however now our (Angelidis et al., 2018; van Son et al., 2018a; 2018b) and several other studies (Bardeen et al., 2017; Mogg & Bradley, 1998; 2016; Eysenck et al., 2007) argue that attentional control is a critical factor in threat processing. Basanovic and colleagues, (2017) moreover found that attentional bias change by ABM was dependent on individual differences in two facets of attentional control, control of attentional inhibition and control of attentional selectivity (Basanovic, Notebaert, Grafton, Hirsch, & Clarke, 2017). Besides that, we can argue that the stages of attentional processes are an important aspect for the role of attentional control in threat processing as well (e.g. Ohman, 1993, 1994; Whalen, 1998; Derryberry and Reed, 2002; Bardeen & Orcut, 2011), which most ABM trainings also do not take into account.

In sum, ABM aims to reduce anxiety by reducing threat biases but should take several individual differences into account. Subjective threat value, attentional control and severity of anxiety symptoms for example vary among anxious individuals and can influence ABM training outcome. Research on ABM may advance by assessing or training other cognitive variables in the framework, for example threat evaluation/appraisal, attentional control, and threat avoidance.

Theta/beta ratio

While TBR was first found to be related to AD(H)D (see Barry et al., 2003; Arns, Conners, & Kraemer, 2013, for reviews), non-clinical research further clarified its cognitive functional significance. High TBR in a healthy sample correlated with sub-optimal performance on a motivated decision-making task (Schutter & van Honk, 2005; Massar et al., 2012; Massar et al., 2014). Later, TBR in healthy people was found to be negatively related to

modulation of response inhibition in an emotional go/no-go task (Putman et al., 2010) and down-regulation of negative affect (Tortella-Feliu, Morillas-Romero, Balle, Llabrés, Bornas, & Putman, 2014), which both require prefrontal cortical executive control. Studies from our lab then reported negative correlations between self-reported trait (Putman et al., 2010; Putman, Verkuil, Arias-Garcia, Pantazi, & van Schie, 2014; Angelidis et al., 2016; van Son et al., 2018a) and state attentional control (Putman et al., 2014) in healthy samples. TBR also correlated negatively to objectively measured attentional control in multiple sclerosis patients with clinically impaired attention (Keune et al., 2017). Most recently, again in healthy participants, studies from our lab showed that TBR correlates negatively to controlled moderation of threat selective attention (Angelidis, et al., 2018; van Son et al., 2018a; 2018b). Together, these studies in non-AD(H)D samples demonstrate that TBR is negatively related to a variety of psychological functions that require prefrontal executive regulation of subcortically mediated emotional and motivational processes. TBR therewith remains an interesting marker when studying a variety of functions like emotional/threat processing and executive control. The functions TBR is related to can however be both dependent of the EEG theta or beta frequency band, as TBR logically consists of these two. It might therefore be helpful to briefly re-evaluate the functions these two bands are related to.

Correlates of Beta

Beta was found to be involved in behavioural inhibition (Brown, 2007; Engel & Fries, 2010) and inhibitory motoric processes (Baker, 2007; Jenkinson & Brown, 2011). It has been suggested that beta oscillations provide a mechanism for sequential encoding of processed items in working memory and for retrieval from long-term memory (Jensen & Lisman, 2005; Rosanova, Casali, Bellina, Resta, Mariotti & Massimini, 2009). Several studies found beta activity to be related to visual attention (e.g. Marrufo, Vaquero, Cardoso, & Gomez, 2001; Wróbel, 2000). Beta was for example found to decrease in elderly who showed lower performance during a visual attentional task (Gola, Magnuski, Szumska & Wróbel, 2013). Beta band activity furthermore seems to be related to cognitive control, more specifically, the maintenance of sensorimotor or cognitive states (Engel & Fries, 2010). In their review, Engel and Fries (2010) propose beta activity to be associated with endogenous top-down influences during cognitive tasks. Tempo-parietal regions have been implied to be involved in the salience network which regulates automatic attentional processes (bottom-up) as compared to the top-down executive control network (Hermans et al., 2014). Subcortical regions seem to connect directly to these tempo-parietal regions in the salience network, whilst the executive control network mainly has connections between the dorso-lateral PFC and, for example, the frontal eye field (Hermans et al., 2014). Considering that beta activity has a strong coherence between frontal and parietal regions during top-down compared to bottom-up visual attention (Buschman & Miller, 2007; 2009; Engel & Fries, 2010) it can be speculated that beta activity is to some extent related to the establishment of reciprocal control of bottom-up and top-down processes. Altogether, beta seems to be related to executive control related processes and possibly maintains prefrontal control over bottom-up automatic processes.

Correlates of Theta

Theta activity on the other hand has been associated with subjective sleepiness (Strijkstra, Beersma, Drayer, Halbesma, & Daan, 2003), decreased vigilance (e.g. Daniel, 1967; Belyavin, & Wright, 1987) and mental fatigue (e.g. Wascher, Rasch, Sänger, Hoffmann, Schneider, Rinkenauer et al., 2014). One study, for example, asked participants to drive for two hours in a driving simulator without any road stimuli, resulting in a significant increase of theta activity over time (Lal & Craig, 2002). Theta activity particularly persists in subcortical areas like the hippocampus, which is involved in memory processes (Buzsáki, 2006; O'Keefe, & Recce, 1993; Squire, Stark & Clark, 2004), and scalp- recorded EEG theta activity might represent volume conducted hippocampal activity (Buzsáki, 2006). Also, theta has been related to thalamic and anterior cingulate activity (Asada, Fukuda, Tsunoda, Yamaguchi, & Tonoike, 1999; Vertes, Albo, & Di Prisco, 2001). It was found that rhythmically synchronized theta activity in these limbic regions together with the amygdala was measured during confrontation with conditioned fear stimuli and expression of freezing behaviour in mice (Seidenbecher, Laxmi, Stork, & Pape, 2003). Hence, EEG theta activity might be generated in limbic structures involved in a brain network subserving more 'bottom-up' automatic attention as opposed to more cortically mediated executive control (Hermans et al., 2014). Moreover, theta activity over the midfrontal cortex was found to reflect a computation used for realizing the need for cognitive control (Cavanagh & Frank 2014). Altogether, the literature on beta and theta activity supports the conjecture that TBR reflects an interplay between top-down executive control (beta) and activity in limbic, partially subcortical areas (theta; Klimesch, Sauseng, & Hanslmayr, 2007; Knyazev, 2007; Schutter & van Honk, 2005). This all fits with above outlined functional correlates of TBR, which again indicates that TBR represents processes related to executive control and threat selective attention. In our first studies, TBR has however always been measured offline as baseline resting state. Its specific 'online' correlates and to which brain area-functionality TBR is related, was not yet investigated. We therefore decided to conduct additional studies to further clarify the relations between TBR, its dynamic relation to states of increased/decreased cognitive control and the brain networks TBR might be involved with.

TBR and mind wandering

We hypothesized that resting state TBR reflects mind wandering (MW), which would support the previously found relations between TBR and bottom up/ top-down (executive control) functions. As described in Chapter 3 and 4, high frontal TBR was indeed related to mind wandering (MW). These findings confirm and extend the findings of Braboszcz and Delorme (2011), and show that phasic changes in TBR are associated to a variation of mental state between uncontrolled MW and focused attention, or perhaps meta-cognitive vigilance. Since MW is thought to represent a state of reduced cognitive control (McVay & Kane, 2009; Unsworth & McMillan, 2014), our results again support the conjecture that baseline TBR represents relative activation of top-down (prefrontal) cortical versus more bottom-up and subcortical processes. Whereas associations between resting state TBR and psychological functions previously remained unclear, we suggest that people with less cognitive control experience more frequent and/or more profound states of uncontrolled thought during the typical EEG measurements of several minutes at rest, as individual differences between mind wandering and TBR seem to be

related (Chapter 3; Braboszcz & Delorme, 2011). The often-observed negative correlation between TBR and ACS was however unexpectedly not observed. The observed positive correlation between MW-related high-TBR and resting state TBR might however support the likelihood of this hypothesis and future studies should retest this TBR – ACS relation in the context of controlled versus uncontrolled thought.

An important negative consequence of MW emerges through its association with mood. Using experience ratings of more than 2000 participants, Killingsworth and Gilbert (2010) observed that MW episodes were followed by lowered mood. Similarly, worry is also seen as a form of MW, and inducing negative mood in participants increased MW and worry simultaneously (Smallwood, Fitzgerald, Miles, Phillips, 2009; Ottaviani, Shahabi, Tarvainen, Cook, Abrams & Shapiro, 2015). In addition, the association between negative affect and worry has been documented in individuals with depressive disorders, who excessively ruminate about past failures (e.g. Watkins & Teasdale, 2001; Nolen-Hoeksema, Wisco, Lyubomirsky, 2008). Anxious people, for example, worry a lot, which is usually accompanied by biased internal activation of threatening cognitions in working memory, and shares mechanisms with biased attention (Hirsch & Mathews, 2012). This in turn fits with findings that fear-derived automatic bottom-up processes also involve overlapping DMN regions such as the angular gyrus and the inferior frontal gyrus (Sreenivas, Boehm, & Linden, 2012) and moreover the joint activity of the medial PFC and amygdala (Kim, Sohn, & Jeong, 2011). Altogether, it can be suggested that TBR is related to brain networks that are functionally involved in MW, worry and fear evoked bottom-up processes, including their interplay with executive functions. These findings underline the importance of TBR in executive functions and its possible applicability when investigating these. TBR may be used as a marker of MW-related changes in brain activity and can be very useful in general for the study of MW (Smallwood & Schooler, 2006) and inattention (Jap, Lal, Fischer, & Bekiaris, 2009; Lorist, Bezdan, ten Caat, Span, Roerdink, & Maurits, 2009), specifically in anxious samples. To our knowledge, no studies to date have investigated the involvement of TBR in negative-MW or worry in anxious individuals, which can possibly aid further study of these populations.

TBR and the executive control network

Frontal TBR's connections to certain psychological functions thus became clearer over the years, however, our MW study using fMRI (Chapter 4) was the first to directly relate online measured frontal TBR to task-dependent brain network activity. We found that controlled versus uncontrolled thought related changes in frontal TBR were associated with controlled versus uncontrolled thought related changes in functional connectivity in the executive control network (ECN). The ECN covers several medial-frontal areas including the dorsolateral PFC (dl-PFC), anterior cingulate cortex (ACC) and the para-cingulate cortex. Miyake and colleagues (2000) identified three cognitive functions covering executive control: inhibition, shifting and the updating of working memory representations (Miyake, Friedman, Emerson, Witzki, Howerter, & Wager, 2000). Several theoretical considerations and empirical research suggest that these three executive control functions are likely to be supported by overlapping, yet somewhat distinct brain systems (Miyake & Friedman, 2012; Herd, Hazy, Chatham, Brant, & Friedman, 2014). In line with our findings described in Chapter 4, functional MRI studies showed that the ability to maintain a task goal and inhibit potential distractors is thought to rely on areas of

lateral prefrontal cortex, extending from the mid dl-PFC (Banich, 2009, Herd, Banich, & O'Reilly, 2006; Reineberg, Andrews-Hanna, Depue, Friedman, & Banich, 2015), potentially including the ACC as well (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008). Our finding that the controlled versus uncontrolled thought related changes were correlated for ECN and TBR, fits with previous explanations of TBR reflecting voluntary top-down processes of executive control (including attentional control), mediated by (dorso-lateral) PFC, over bottom-up processes from limbic areas, such as the ACC, hippocampus and amygdala (Angelidis et al., 2016; 2018; Bishop, 2008; Knyazev, 2007; Schutter & Knyazev, 2012) as these areas are similarly involved in executive control functions.

We moreover found functional connectivity in the DMN to be higher during MW compared to on-task periods (Chapter 4). The DMN includes the posterior cingulate, medial PFC and the angular gyrus, and functional activity and connectivity within this network was found to be high during task unrelated thoughts (Stawarczyk, Majerus, Maquet, & D'Argembeau, 2011) and also to directly relate to MW (Karapanagiotidis, Bernhardt, Jefferies, & Smallwood, 2017; Smallwood, Beach, Schooler, & Handy, 2008). In line with our findings, a recent study of Delaveau and colleagues (2017) found that rumination in depressed out-patients was accompanied by activity in the DMN, but this rumination was also related to a reduced functional connectivity between the DMN and the so called 'task positive network' (Delaveau, Arruda Sanchez, Steffen, Deschet, Jabourian, Perlbarg et al., 2017). The task positive network is a network functionally related to the ECN and involved working memory processes and attention directed to the external world, which could in turn be linked to TBR as TBR seems to represent executive control.

In summary, we found direct empirical relations between MW-related frontal TBR and a MW-related functional connectivity between the ECN and TBR. This strongly underlines the already suggested relations of TBR with top-down executive vs bottom-up automatic processes and its brain networks involved. Our findings generate hypotheses about how TBR is related to psychiatric symptoms, in particular anxiety and avoidance, and more firmly establishes frontal TBR as a useful tool in the study of executive control in normal as well as abnormal psychology.

Manipulating EEG theta/beta ratio

In Chapter 5 we reported that Neurofeedback training (NFT) did not alter TBR in any way. This was unexpected, given that past studies using NFT targeting TBR successfully reduced TBR and ADHD-related symptoms in individuals diagnosed with ADHD (e.g. hyperactivity, impaired attention; e.g. Leins, Goth, Hinterberger, Klinger, Rumpf, & Strehl, 2007; Lubar, Swartwood, Swartwood, & O'Donnell, 1995; Janssen, Bink, Weeda, Geladé, van Mourik, Maras & Oosterlaan, 2017). However, no study to date yet investigated whether NFT induces changes in TBR in people with mildly elevated TBR but who do not have a clinical diagnosis of psychopathology. Our results are somewhat comparable to Doppelmayr and Weber, (2011) who performed a randomized controlled trial with a total of 14 healthy participants receiving active-NFT on TBR. After 30 active-NFT sessions no change in EEG TBR or the separate theta or beta frequency bands was found. Their results however do not provide explanation why the active-NFT did not alter TBR and neither did ours.

Besides NFT, neuromodulation approaches, such as transcranial magnetic stimulation, transcranial direct/alternating current stimulation (tDCS/tACS), and vagal nerve stimulation, can potentially enhance cognition by modulating neuronal excitability (Miniussi, Cappa, Cohen, Floel, Fregni, Nitsche, Oliveri et al., 2008). It has been suggested that the effects of brain stimulation may be determined by the initial neural activation state (Silvanto, Muggleton, & Walsh, 2008); thus, manipulating neural activation states may allow one to selectively enhance activity in a given neural circuit. Wischnewski, Zerr and Schutter (2016) used tACS to stimulate theta which resulted in an enhancement of working memory, decreased frontal and central TBR and increased flexible implicit reversal learning in motivated decision making (Wischnewski et al., 2016). Also, as mentioned before, our results of Chapter 2 indicate a relation between TBR and catecholamine functioning suggesting that pharmacological manipulations could as well modulate TBR, which should be further investigated. Such neuromodulation techniques altogether seem more promising for studying whether changing TBR can be used as a clinical tool in anxiety disorders or when studying causal relations of TBR.

Another possible manipulation method might be derived from cognitive trainings. Cognitive training aims to enhance learning and adaptive neuroplastic changes in an individual's neural system through controlled learning events (e.g. Keshavan, Vinogradov, Rumsey, Sherrill & Wagner, 2014). Sari and colleagues (2016) for example used an adaptive working memory training to improve attentional control in anxious individuals. They found that the training improved attentional control and lowered resting state TBR, and training related gains were associated with lower levels of trait anxiety (Sari, Koster, Pourtois, & Derakshan, 2016). Cognitive trainings can therefore have beneficial effects on attentional control and cognitive performance that may protect against emotional vulnerability in individuals at risk of developing clinical anxiety. Again, as already noted, anxious individuals show more problematic top-down regulated executive control over salient thoughts or stimuli, which is in line with the findings of Sari et al., (2016). Growing knowledge of the specific processing anomalies, developmental features, and distributed neural circuits that characterize TBR as a measure of executive control, might aid further development and applicability of TBR-neuromodulation techniques and cognitive training approaches, for example anxiety disorder treatment.

Clinical relevance

Throughout this thesis it already became clear that TBR is a conceivably interesting tool for clinical research. Chapter 2 for example, described that individual differences in TBR and thus baseline executive function might determine catecholamine functioning and threat processing, and is considerably important when investigating neural underpinnings of psychopathology. Chapter 3 and 4 described the involvement of TBR in MW and suggested possible involvement of TBR in 'negative MW' or worry in anxious individuals, which can possibly provide valuable information for treatment development in these samples. TBR may be used as a marker of MW-related changes in brain activity and can be useful for the study of MW and inattention. Also, as anxious populations often have disturbed top-down cognitive control over salient stimuli (as well as depressed patients as described previously), and our results indicate that TBR represents just that process, the assumption was raised that TBR could provide a marker of individuals' vulnerability to such reduced top-down control over salient

stimuli. Modulation of TBR (reduction) might still be expected to improve top-down executive control, however our neurofeedback study for example did not provide any evidence for this, and different neuromodulation techniques should be further tested.

TBR and Anxiety

An important consideration when studying potential clinical applicability of TBR is that the relation between TBR and anxiety is still unresolved. Studies from our lab have repeatedly found that TBR is related to self-reported attentional control (Putman et al., 2010; Putman et al., 2014; Angelidis et al., 2016; van Son et al., 2018a). However, two studies from our lab also reported a negative relation between TBR and self-reported anxious affect (Putman et al., 2010; Angelidis et al., 2016). This is rather paradoxical, as a robust negative association between attentional control and anxiety is generally assumed (e.g. Derryberry & Reed, 2002; Mogg & Bradley, 1998; 2016; Mogg et al., 1987), leading to the assumption that independent functional processes are responsible for these two associations (TBR and attentional control versus TBR and anxiety). Research done by Schutter & van Honk, (2005) suggests that TBR might not represent overall PFC regulated inhibition of subcortical processes, but rather reflects the inhibition of specifically approach-motivated decision making (Schutter & van Honk, 2005; replicated by Massar et al., 2012; Massar et al., 2014). Anhedonia (thus not approach-driven), or unpleasant emotional states however relate to anxiety (e.g. Gilbert, Allan, Brough, Melley, & Miles, 2002), which possibly supports the negative relation between TBR and anxiety. Hence, we can speculate that TBR does not solely reflect executive control over the processing of negative information (as in Chapter 1 & 2), but also approach-motivation related processes, perhaps originating from other neural sources that also produces TBR as measured by EEG. If this applies, high TBR should not be perceived only as some form of impairment from a psychopathological viewpoint. One could theorize for example that patients suffering from PTSD or depression have increased TBR since their expected reduced executive control (Lanius, Vermetten, Loewenstein, Brand, Schmahl, Bremner & Spiegel, 2010, Vasterling, Duke, Brailey, Constans, Allain & Sutker, 2002), but considering their lack of hedonic/approach motivation, not increased but reduced TBR should be expected. Applying manipulations like transcranial alternating/direct current stimulation or neurofeedback in these patient samples should therefore be avoided before the exact systems behind TBR are investigated and clarified. Our paradoxical findings thus suggest that TBR might result from different neural sources and further (fMRI) research is necessary to investigate this before TBR can be a candidate for, for example, more applied research into affective psychopathology.

Final conclusions

We conclude that attentional control has an important role in threat processing. The electrophysiological marker of executive control, frontal TBR, may be a useful approximation of individual differences in baseline prefrontal catecholamine function. Increased frontal TBR is also related to mind wandering and as such further supports the notion that low TBR reflects brain processes involved in executive control processes. The current findings contribute to the understanding of the functional relation between frontal TBR and executive cognitive functions. We did not find any evidence that TBR-targeted neurofeedback training affects

TBR in healthy participants. Although it is not impossible that NFT could work with other parameters than we investigated, we suggest that it may be more fruitful to investigate other neuromodulation techniques. Cognitive training effects on TBR might also further be investigated. In conclusion, the studies as conducted for this thesis are notable for providing a somewhat clearer picture of what online frontal TBR represents on a behavioural and neural level. Our results further support the notion that low TBR reflects connectivity in brain networks involved in executive control processes. Although our findings might have established a strong groundwork for further exploration of frontal TBR and its representations, it remains important for future studies to replicate and extend our findings and further investigate, for example, the paradoxical relation between TBR and anxiety as just discussed, before considering more direct (clinical) application.

References

Algom, D., Chajut, E., & Lev, S. (2004). A rational look at the emotional stroop phenomenon: a generic slowdown, not a stroop effect. *Journal of experimental psychology: General, 133*(3), 323.

Angelidis, A., van der Does, W., Schakel, L., & Putman, P. (2016). Frontal EEG theta/beta ratio as an electrophysiological marker for attentional control and its test-retest reliability. *Biological Psychology, 121(Pt A),* 49-52.

Angelidis, A., Hagenaars, M., van Son, D., van der Does, W., & Putman, P. (2018). Do not look away! Spontaneous frontal EEG theta/beta ratio as a marker for cognitive control over attention to mild and high threat. *Biological psychology, 135,* 8-17.

Armstrong, T., & Olatunji, B. O. (2012). Eye tracking of attention in the affective disorders: A meta-analytic review and synthesis. *Clinical psychology review, 32*(8), 704-723.

Arnsten, A. F. (2009a). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature reviews. Neuroscience, 10*(6), 410.

Arnsten, A. F. T. (2011). Catecholamine influences on dorsolateral prefrontal cortical networks. *Biological Psychiatry, 69*, 89-99.

Arnsten, A. F. T. (2006). Stimulants: Therapeutic actions in ADHD *Neuropsychopharmacology*, *31*, 2376-2383.

Arnsten, A. F., and Rubia, K. (2012). Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(4), 356-367.

Arns, M., Conners, C. K., & Kraemer, H. C. (2013). A decade of EEG Theta/Beta Ratio Research in ADHD: a meta-analysis. *Journal of Attentional Disorders, 17*(5), 374-383.

Asada, H., Fukuda, Y., Tsunoda, S., Yamaguchi, M., & Tonoike, M. (1999). Frontal midline theta rhythms reflect alternative activation of prefrontal cortex and anterior cingulate cortex in humans. *Neuroscience letters, 274*(1), 29-32.

Baker, S. N. (2007). Oscillatory interactions between sensorimotor cortex and the periphery. *Current opinion in neurobiology, 17*(6), 649-655.

Banich, M. T. (2009). Executive function: The search for an integrated account. *Current directions in psychological science, 18* (2), 89-94.

Bardeen, J. R., & Orcutt, H. K. (2011). Attentional control as a moderator of the relationship between posttraumatic stress symptoms and attentional threat bias. *Journal of Anxiety Disorders, 25*(8), 1008-1018.

Bardeen, J. R., Daniel, T. A., Hinnant, J. B., & Orcutt, H. K. (2017). Emotion dysregulation and threat-related attention bias variability. *Motivation and Emotion, 41*(3), 402-409.

Bardeen, J. R., & Daniel, T. A. (2017). A longitudinal examination of the role of attentional control in the relationship between posttraumatic stress and threat-related attentional bias: An eye-tracking study. *Behaviour research and therapy, 99,* 67-77.

Barry, R. J., Clarke, A. R., & Johnstone, S. J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clinical neurophysiology, 114*(2), 171-183.

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & Van Ijzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychological bulletin, 133*(1), 1.

Basanovic, J., Notebaert, L., Grafton, B., Hirsch, C. R., & Clarke, P. J. (2017). Attentional control predicts change in bias in response to attentional bias modification. *Behaviour research and therapy, 99*, 47-56.

Belyavin, A., & Wright, N. A. (1987). Changes in electrical activity of the brain with vigilance. *Electroencephalography and clinical Neurophysiology, 66*(2), 137-144.

Bishop, S. J. (2008). Neural mechanisms underlying selective attention to threat. *Ann N Y Acad Sci, 1129*, 141-152.

Bowie, C. R., Gupta, M., Holshausen, K., Jokic, R., Best, M., & Milev, R. (2013). Cognitive remediation for treatment-resistant depression: effects on cognition and functioning and the role of online homework. *The Journal of nervous and mental disease, 201*(8), 680-685.

Braboszcz, C., & Delorme, A. (2011). Lost in thoughts: neural markers of low alertness during mind wandering. *Neuroimage, 54*(4), 3040-3047.

Bradley, B. P., Mogg, K., & Lee, S. C. (1997). Attentional biases for negative information in induced and naturally occurring dysphoria. *Behaviour research and therapy, 35*(10), 911-927.

Brown, P. (2007). Abnormal oscillatory synchronisation in the motor system leads to impaired movement. *Current opinion in neurobiology, 17*(6), 656-664.

Buschman, T. J., & Miller, E. K. (2007). Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science, 315*(5820), 1860-1862.

Buschman, T. J., & Miller, E. K. (2009). Serial, covert shifts of attention during visual search are reflected by the frontal eye fields and correlated with population oscillations. *Neuron, 63*(3), 386-396.

Buzsáki, G. (2006). Rhythms of the Brain. New York: Oxford Univ. Press. pp 448.

Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. *Trends in cognitive sciences, 18*(8), 414-421.

Cisler, J. M., & Koster, E. H. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clin Psychol Rev, 30*(2), 203-216. doi:10.1016/j.cpr.2009.11.003

Cisler, J. M., Bacon, A. K., & Williams, N. L. (2009). Phenomenological characteristics of attentional biases towards threat: A critical review. *Cognitive therapy and research, 33*(2), 221-234.

Clarke, P. J., MacLeod, C., & Guastella, A. J. (2013). Assessing the role of spatial engagement and disengagement of attention in anxiety-linked attentional bias: a critique of current paradigms and suggestions for future research directions. *Anxiety, Stress & Coping, 26*(1), 1-19.

Cools, R., & D'Esposito, M. (2011). Inverted-U–shaped dopamine actions on human working memory and cognitive control. *Biological psychiatry, 69*(12), e113-e125.

Dandeneau, S. D., Baldwin, M. W., Baccus, J. R., Sakellaropoulo, M., & Pruessner, J. C. (2007). Cutting stress off at the pass: Reducing vigilance and responsiveness to social threat by manipulating attention. *Journal of Personality and Social Psychology, 93*(4), 651.

Daniel, R. S. (1967). Alpha and theta EEG in vigilance. *Perceptual and Motor Skills, 25*(3), 697-703.

Delaveau, P., Arruda Sanchez, T., Steffen, R., Deschet, K., Jabourian, M., Perlbarg, V., ... & Fossati, P. (2017). Default mode and task-positive networks connectivity during the N-Back task in remitted depressed patients with or without emotional residual symptoms. *Human brain mapping, 38*(7), 3491-3501.

Derryberry, D., & Reed, M. A. (2002). Anxiety-related attentional biases and their regulation by attentional control. *Journal of Abnormal Psychology, 111*(2), 225-236.

Doppelmayr, M., & Weber, E. (2011). Effects of SMR and theta/beta neurofeedback on reaction times, spatial abilities, and creativity. *Journal of Neurotherapy, 15*(2), 115-129.

Dosenbach, N. U., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-networks architecture of top-down control. *Trends in cognitive sciences, 12*(3), 99-105.

Dudeney, J., Sharpe, L., & Hunt, C. (2015). Attentional bias towards threatening stimuli in children with anxiety: A meta-analysis. *Clinical psychology review, 40*, 66-75.

Engel, A. K., & Fries, P. (2010). Beta-band oscillations—signalling the status quo? *Current opinion in neurobiology, 20*(2), 156-165.

Etkin, A., & Schatzberg, A. F. (2011). Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in generalized anxiety and major depressive disorders. *American Journal of Psychiatry, 168*(9), 968-978.

Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: attentional control theory. *Emotion, 7*(2), 336.

Fox, E., Russo, R., Bowles, R., & Dutton, K. (2001). Do threatening stimuli draw or hold visual attention in subclinical anxiety? *Journal of Experimental Psychology: General, 130*(4), 681.

Gilbert, P., Allan, S., Brough, S., Melley, S., & Miles, J. N. V. (2002). Relationship of anhedonia and anxiety to social rank, defeat and entrapment. *Journal of affective disorders, 71*(1-3), 141-151.

Gola, M., Magnuski, M., Szumska, I., & Wróbel, A. (2013). EEG beta band activity is related to attention and attentional deficits in the visual performance of elderly subjects. *International Journal of Psychophysiology, 89*(3), 334-341.

Harrewijn, A., Schmidt, L. A., Westenberg, P. M., & Tang, A. (2017). Electrocortical measures of information processing biases in social anxiety disorder: A review. *Biological psychology*, 129, 324-348.

Herd, S. A., Banich, M. T., & O'Reilly, R. C. (2006). Neural mechanisms of cognitive control: An integrative model of Stroop task performance and fMRI data. *Journal of cognitive neuroscience, 18*(1), 22-32.

Herd, S. A., Hazy, T. E., Chatham, C. H., Brant, A. M., & Friedman, N. P. (2014). A neural network model of individual differences in task switching abilities. *Neuropsychologia, 62*, 375-389.

Heeren, A., Mogoaşe, C., Philippot, P., & McNally, R. J. (2015). Attention bias modification for social anxiety: a systematic review and meta-analysis. *Clinical psychology review, 40*, 76-90.

Hermans, E. J., Henckens, M. J., Joels, M., & Fernandez, G. (2014). Dynamic adaptation of large-scale brain networks in response to acute stressors. *Trends Neurosci, 37*(6), 304-314. doi:10.1016/j.tins.2014.03.006

Hirsch, C. R., & Mathews, A. (2012). A cognitive model of pathological worry. *Behaviour Research and Therapy, 50*(10), 636-646.

Janssen, T. W., Bink, M., Weeda, W. D., Geladé, K., van Mourik, R., Maras, A., & Oosterlaan, J. (2017). Learning curves of theta/beta neurofeedback in children with ADHD. *European child & adolescent psychiatry, 26*(5), 573-582.

Jap, B. T., Lal, S., Fischer, P., & Bekiaris, E. (2009). Using EEG spectral components to assess algorithms for detecting fatigue. *Expert Systems with Applications, 36*(2), 2352-2359.

Jenkinson, N., & Brown, P. (2011). New insights into the relationship between dopamine, beta oscillations and motor function. *Trends in neurosciences, 34*(12), 611-618.

Jensen, O., & Lisman, J. E. (2005). Hippocampal sequence-encoding driven by a cortical multi-item working memory buffer. *Trends in neurosciences, 28*(2), 67-72.

Karapanagiotidis, T., Bernhardt, B. C., Jefferies, E., & Smallwood, J. (2017). Tracking thoughts: Exploring the neural architecture of mental time travel during mind-wandering. *Neuroimage, 147*, 272-281.

Keshavan, M. S., Vinogradov, S., Rumsey, J., Sherrill, J., & Wagner, A. (2014). Cognitive training in mental disorders: update and future directions. *American Journal of Psychiatry, 171*(5), 510-522.

Keune, P. M. , Hansen, A., Weber, E., Zapf, F., Habich, J., Muenssinger, J., Wolf, S., Schonenberg, M., Oschmann, P. (2017). Exploring neurophysiologic monitoring parameters and cognitive functioning in multiple sclerosis (MS): resting-state brain oscillatory activity and attention performance. *Clinical neurophysiology, 128*(9), 1746-1754.

Killingsworth, M. A., & Gilbert, D. T. (2010). A wandering mind is an unhappy mind. *Science, 330*(6006), 932-932.

Kim, Y.-T., Sohn, H., Jeong, J., (2011). Delayed transition from ambiguous to risky decision making in alcohol dependence during Iowa Gambling Task. *Psychiatry Res. 190,* 297–303.

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition–timing hypothesis. *Brain research reviews, 53*(1), 63-88.

Knyazev, G. G. (2007). Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neuroscience and Biobehavioral Reviews, 31*(3), 377-395.

Koster, E. H., Crombez, G., Verschuere, B., Vanvolsem, P., & De Houwer, J. (2007). A time-course analysis of attentional cueing by threatening scenes. *Experimental Psychology, 54*(2), 161-171.

Lal, S. K., & Craig, A. (2002). Driver fatigue: electroencephalography and psychological assessment. *Psychophysiology, 39*(3), 313-321.

Lanius, R. A., Vermetten, E., Loewenstein, R. J., Brand, B., Schmahl, C., Bremner, J. D., & Spiegel, D. (2010). Emotion modulation in PTSD: Clinical and neurobiological evidence for a dissociative subtype. *American Journal of Psychiatry, 167*(6), 640-647.

Leins, U., Goth, G., Hinterberger, T., Klinger, C., Rumpf, N., & Strehl, U. (2007). Neurofeedback for children with ADHD: a comparison of SCP and Theta/Beta protocols. *Applied psychophysiology and biofeedback, 32*(2), 73-88.

Lorist, M. M., Bezdan, E., ten Caat, M., Span, M. M., Roerdink, J. B., & Maurits, N. M. (2009). The influence of mental fatigue and motivation on neural network dynamics; an EEG coherence study. *Brain Research, 1270*, 95-106.

Lubar, J. F., Swartwood, M. O., Swartwood, J. N., & O'Donnell, P. H. (1995). Evaluation of the effectiveness of EEG neurofeedback training for ADHD in a clinical setting as measured by changes in TOVA scores, behavioral ratings, and WISC-R performance. *Applied Psychophysiology and Biofeedback, 20*(1), 83-99.

MacLeod, C., & Clarke, P. J. (2015). The attentional bias modification approach to anxiety intervention. *Clinical Psychological Science, 3*(1), 58-78.

MacLeod, C., & Grafton, B. (2016). Anxiety-linked attentional bias and its modification: illustrating the importance of distinguishing processes and procedures in experimental psychopathology research. *Behaviour Research and Therapy, 86*, 68-86.

MacLeod, C., & Mathews, A. (2012). Cognitive bias modification approaches to anxiety. *Annual review of clinical psychology, 8*, 189-217.

MacLeod, C., Rutherford, E., Campbell, L., Ebsworthy, G., & Holker, L. (2002). Selective attention and emotional vulnerability: assessing the causal basis of their association through the experimental manipulation of attentional bias. *Journal of abnormal psychology, 111*(1), 107.

McVay, J. C., & Kane, M. J. (2009). Conducting the train of thought: working memory capacity, goal neglect, and mind wandering in an executive-control task. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 35*(1), 196.

Marrufo, M. V., Vaquero, E., Cardoso, M. J., & Gomez, C. M. (2001). Temporal evolution of α and β bands during visual spatial attention. *Cognitive Brain Research, 12*(2), 315-320.

Massar, S. A., Kenemans, J. L., & Schutter, D. J. (2014). Resting-state EEG theta activity and risk learning: sensitivity to reward or punishment? *Int J Psychophysiol, 91*(3), 172-177. doi:10.1016/j.ijpsycho.2013.10.013

Massar, S. A., Rossi, V., Schutter, D. J., & Kenemans, J. L. (2012). Baseline EEG theta/beta ratio and punishment sensitivity as biomarkers for feedback-related negativity (FRN) and risk-taking. *Clin Neurophysiol, 123*(10), 1958-1965. doi:10.1016/j.clinph.2012.03.005

Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology,(1)*, 167-195.

Miniussi, C., Cappa, S. F., Cohen, L. G., Floel, A., Fregni, F., Nitsche, M. A., ... & Walsh, V. (2008). Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. *Brain stimulation, 1*(4), 326-336.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive psychology, 41*(1), 49-100.

Miyake, A., & Friedman, N. P. (2012). The nature and organization of individual differences in executive functions: Four general conclusions. *Current directions in psychological science, 21*(1), 8-14.

Mogg, K., & Bradley, B. P. (1998). A cognitive-motivational analysis of anxiety. *Behaviour Research and Therapy, 36*(9), 809-848. doi:10.1016/s0005-7967(98)00063-1

Mogg, K., & Bradley, B. P. (2016). Anxiety and attention to threat: Cognitive mechanisms and treatment with attention bias modification. *Behav Res Ther, 87*, 76-108.

Mogg, K., & Bradley, B. P. (2018). Anxiety and threat-related attention: Cognitive-motivational framework and treatment. *Trends in cognitive sciences*.

Mogg, K., Waters, A. M., & Bradley, B. P. (2017). Attention bias modification (ABM): Review of effects of multisession ABM training on anxiety and threat-related attention in high-anxious individuals. *Clinical Psychological Science, 5*(4), 698-717.

Mogg, K., Weinman, J., & Mathews, A. (1987). Memory Bias in Clinical Anxiety. *Journal of Abnormal Psychology, 96*(2), 94-98. doi:Doi 10.1037//0021-843x.96.2.94

Nolen-Hoeksema, S., Wisco, B. E., & Lyubomirsky, S. (2008). Rethinking rumination. *Perspectives on psychological science, 3*(5), 400-424.

Ohman, A. (1993). Fear and anxiety as emotional phenomena: Clinical phenomenology, evolutionary perspectives, and information-processing mechanisms. In M. Lewis, & J. M. Haviland (Eds.), Handbook of emotions (pp. 511e536). New York: Guilford Press.

Ohman, A. (1994). The psychophysiology of emotion: Evolutionary and nonconscious origins. In G. d'Ydewalle, P. Eelen, & P. Bertelsen (Eds.), International perspectives on psychological science (Vol. 1, pp. 197e226). Hillsdale, NJ: Erlbaum. The state of the art.

O'Keefe, J., & Recce, M. L. (1993). Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus, 3*(3), 317-330.

Ottaviani, C., Shahabi, L., Tarvainen, M., Cook, I., Abrams, M., & Shapiro, D. (2015). Cognitive, behavioral, and autonomic correlates of mind wandering and perseverative cognition in major depression. *Frontiers in neuroscience, 8*, 433.

Peers, P. V., & Lawrence, A. D. (2009). Attentional control of emotional distraction in rapid serial visual presentation. *Emotion, 9*(1), 140-145. doi:10.1037/a0014507

Putman, P., van Peer, J., Maimari, I., & van der Werff, S. (2010). EEG theta/beta ratio in relation to fear-modulated response-inhibition, attentional control, and affective traits. *Biological Psychology, 83*(2), 73-78. doi:10.1016/j.biopsycho.2009.10.008

Putman, P., Verkuil, B., Arias-Garcia, E., Pantazi, I., & van Schie, C. (2014). EEG theta/beta ratio as a potential biomarker for attentional control and resilience against deleterious effects of stress on attention. *Cognitive Affective & Behavioral Neuroscience, 14*(2), 782-791.

Reineberg, A. E., Andrews-Hanna, J. R., Depue, B. E., Friedman, N. P., & Banich, M. T. (2015). Resting-state networks predict individual differences in common and specific aspects of executive function. *Neuroimage, 104*, 69-78.

Rive, M. M., van Rooijen, G., Veltman, D. J., Phillips, M. L., Schene, A. H., & Ruhé, H. G. (2013). Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies. *Neuroscience & Biobehavioral Reviews, 37*(10), 2529-2553.

Rosanova, M., Casali, A., Bellina, V., Resta, F., Mariotti, M., & Massimini, M. (2009). Natural frequencies of human corticothalamic circuits. *Journal of Neuroscience, 29*(24), 7679-7685.

Salum, G. A., Mogg, K., Bradley, B. P., Gadelha, A., Pan, P., Tamanaha, A. C., ... & do Rosario, M. C. (2013). Threat bias in attention orienting: evidence of specificity in a large community-based study. *Psychological Medicine, 43*(4), 733-745.

Sari, B. A., Koster, E. H., Pourtois, G., & Derakshan, N. (2016). Training working memory to improve attentional control in anxiety: A proof-of-principle study using behavioral and electrophysiological measures. Biological Psychology, 121, 203-212.

Schutter, D. J., & Knyazev, G. G. (2012). Cross-frequency coupling of brain oscillations in studying motivation and emotion. *Motiv Emot, 36*(1), 46-54. doi:10.1007/s11031-011-9237-6

Schutter, D. J. L. G., & Van Honk, J. (2005). Electrophysiological ratio markers for the balance between reward and punishment. *Cognitive Brain Research, 24*(3), 685-690. doi:10.1016/j.cogbrainres.2005.04.002.

Seidenbecher, T., Laxmi, T. R., Stork, O., & Pape, H. C. (2003). Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. *Science, 301*(5634), 846-850.

Smallwood, J., Fitzgerald, A., Miles, L. K., & Phillips, L. H. (2009). Shifting moods, wandering minds: negative moods lead the mind to wander. *Emotion, 9*(2), 271.

Smallwood, J., & Schooler, J. W. (2006). The restless mind. *Psychological bulletin, 132*(6), 946.

Smallwood, J., Beach, E., Schooler, J. W., & Handy, T. C. (2008). Going AWOL in the brain: Mind wandering reduces cortical analysis of external events. *Journal of cognitive neuroscience, 20*(3), 458-469.

Shiffrin, R. M., & Schneider, W. (1977). Controlled and automatic human information processing: II. Perceptual learning, automatic attending and a general theory. *Psychological review, 84*(2), 127.

Silvanto, J., Muggleton, N., & Walsh, V. (2008). State-dependency in brain stimulation studies of perception and cognition. *Trends in cognitive sciences, 12*(12), 447-454.

Sreenivas, S., Boehm, S. G., & Linden, D. E. J. (2012). Emotional faces and the default mode network. *Neuroscience letters, 506*(2), 229-234.

Stawarczyk, D., Majerus, S., Maquet, P., & D'Argembeau, A. (2011). Neural correlates of ongoing conscious experience: both task-unrelatedness and stimulus-independence are related to default network activity. *PloS one, 6*(2), e16997.

Strijkstra, A. M., Beersma, D. G., Drayer, B., Halbesma, N., & Daan, S. (2003). Subjective sleepiness correlates negatively with global alpha (8–12 Hz) and positively with central frontal theta (4–8 Hz) frequencies in the human resting awake electroencephalogram. *Neuroscience letters, 340*(1), 17-20.

Squire, L. R., Stark, C. E., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience,* 27, 279-306.

Teachman, B. A., Joormann, J., Steinman, S. A., & Gotlib, I. H. (2012). Automaticity in anxiety disorders and major depressive disorder. *Clinical psychology review, 32*(6), 575-603.

Tortella-Feliu, M., Morillas-Romero, A., Balle, M., Llabrés, J., Bornas, X., & Putman, P. (2014). Spontaneous EEG activity and spontaneous emotion regulation. International Journal of *Psychophysiology, 94*(3), 365-372.

Unsworth, N., & McMillan, B. D. (2014). Similarities and differences between mind-wandering and external distraction: A latent variable analysis of lapses of attention and their relation to cognitive abilities. *Acta Psychologica, 150*, 14-25.

van Bockstaele, B., Verschuere, B., Tibboel, H., De Houwer, J., Crombez, G., & Koster, E. H. (2014). A review of current evidence for the causal impact of attentional bias on fear and anxiety. *Psychological bulletin, 140*(3), 682.

van Son, D., Angelidis, A., Hagenaars, M. A., van der Does, W., & Putman, P. (2018a). Early and late dot-probe attentional bias to mild and high threat pictures: Relations with EEG theta/beta ratio, self-reported trait attentional control, and trait anxiety. *Psychophysiology*, e13274.

van Son, D., Schalbroeck, R., Angelidis, A., van der Wee, N. J., van der Does, W., & Putman, P. (2018b). Acute effects of caffeine on threat-selective attention: moderation by anxiety and EEG theta/beta ratio. *Biological psychology, 136*, 100-110.

Vasterling, J. J., Duke, L. M., Brailey, K., Constans, J. I., Allain Jr, A. N., & Sutker, P. B. (2002). Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology, 16*(1), 5.

Vertes, R. P., Albo, Z., & Di Prisco, G. V. (2001). Theta-rhythmically firing neurons in the anterior thalamus: implications for mnemonic functions of Papez's circuit. *Neuroscience, 104*(3), 619-625.

Watkins, E. D., & Teasdale, J. D. (2001). Rumination and overgeneral memory in depression: effects of self-focus and analytic thinking. *Journal of abnormal psychology, 110*(2), 353.

Wald, I., Shechner, T., Bitton, S., Holoshitz, Y., Charney, D. S., Muller, D., ... & Bar-Haim, Y. (2011). Attention bias away from threat during life threatening danger predicts PTSD symptoms at one-year follow-up. *Depression and anxiety, 28*(5), 406-411.

Waters, A. M., Bradley, B. P., & Mogg, K. (2014). Biased attention to threat in paediatric anxiety disorders (generalized anxiety disorder, social phobia, specific phobia, separation anxiety disorder) as a function of 'distress' versus 'fear'diagnostic categorization. *Psychological medicine, 44*(3), 607-616.

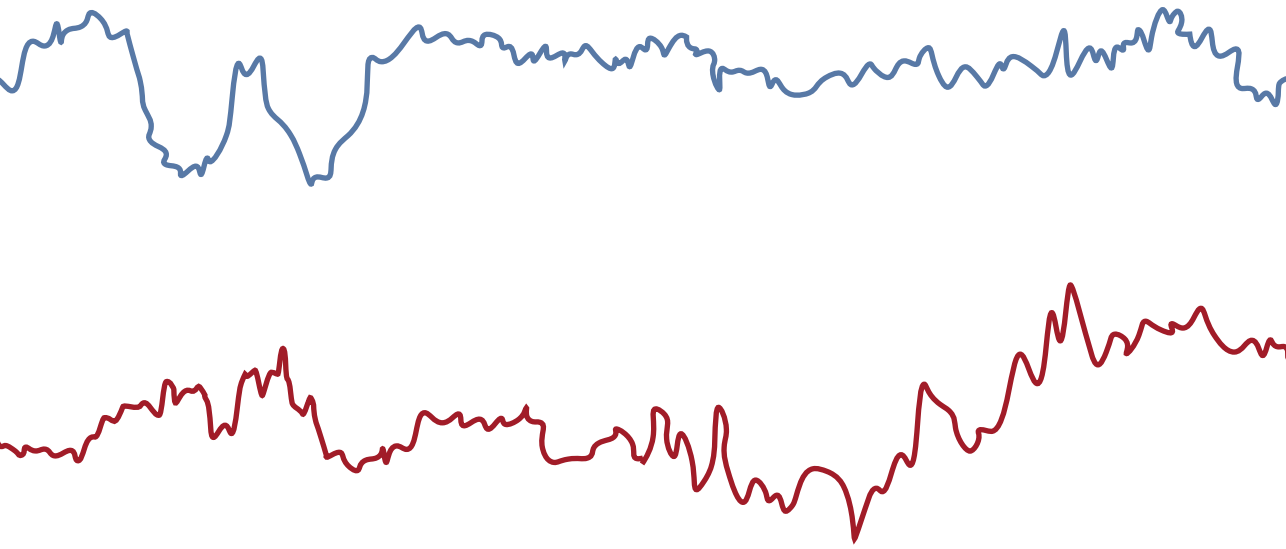
Wascher, E., Rasch, B., Sänger, J., Hoffmann, S., Schneider, D., Rinkenauer, G., ... & Gutberlet, I. (2014). Frontal theta activity reflects distinct aspects of mental fatigue. *Biological psychology, 96*, 57-65.

Weierich, M. R., Treat, T. A., & Hollingworth, A. (2008). Theories and measurement of visual attentional processing in anxiety. *Cognition and Emotion, 22*(6), 985-1018.

Whalen, P. J. (1998). Fear, vigilance, and ambiguity: Initial neuroimaging studies of the human amygdala. *Current directions in psychological science, 7*(6), 177-188.

Wischnewski, M., Zerr, P., & Schutter, D. J. (2016). Effects of theta transcranial alternating current stimulation over the frontal cortex on reversal learning. *Brain stimulation, 9*(5), 705-711.

Wróbel, A. (2000). Beta activity: a carrier for visual attention. *Acta neurobiologiae experimentalis, 60*(2), 247-260.



NEDERLANDSE SAMENVATTING

Introductie

Elektro-encefalografie (EEG) is een techniek om neurale activiteit (synchroon vuren van neuronen) te meten. De verhouding tussen de (lage) theta en (hoge) beta frequentie-banden als frontaal gemeten in een EEG tijdens rust (ook wel de 'theta/beta ratio' of TBR genoemd) bleek eerder gekoppeld te zijn aan een veelvoorkomende psychische stoornis, ADHD (attention deficit hyperactivity disorder). Later werd TBR ook gekoppeld aan andere psychologische functies zoals cognitieve-emotionele processen, vaak afhankelijk van uitvoerende (executieve)-cognitieve controle. Een hogere TBR was specifiek gerelateerd aan een lagere aandachts-controle in meerdere studies. TBR werd ook in verband gebracht met emotionele processen in bijvoorbeeld een respons- remming (inhibitie) taak. Deze gevonden relaties tussen TBR en aandacht-emotionele processen suggereren dat TBR zou kunnen dienen als unieke voorspeller voor uitvoerende controle over emotionele informatie. Door TBR verder te onderzoeken kan er aldus waardevolle informatie verzameld worden, die mogelijk toepasbaar is voor stoornissen met een emotie-problematiek, aangezien deze stoornissen vaak gekenmerkt worden door een verstoorde aandacht voor dreigende informatie en problemen met uitvoerende controle. Het is bekend dat de rol van aandachts-controle en de invloed van deze op de verwerking van en aandacht voor dreigende prikkels (stimuli), bij angststoornissen, niet onderschat mag worden (Mogg & Bradley, 2016). TBR is daarom een interessante variabele in verschillend psychologisch onderzoek.

Doel van het promotieonderzoek

Gezien de mogelijke interessante rol van TBR als marker voor aandachts-controle in zowel gezonde als klinische populaties, hebben we verschillende onderzoeken met gezonde proefpersonen opgezet en uitgevoerd om de relatie van TBR met aandachts-controle en de selectieve aandacht voor dreigende prikkels verder te bestuderen. We hebben onder andere het niveau van dreiging van stimuli gevarieerd, net als tijds-stadia van aandacht, processen die onder invloed van neurotransmitters staan (catecholamines) en ongecontroleerde gedachten (gedachtedwalingen) experimenten. Verder is er getest of TBR te manipuleren is in gezonde volwassen proefpersonen met behulp van een neurofeedback training.

Hoofdstuk 1

In een eerdere studie door Angelidis en collega's werd gevonden dat EEG theta/beta ratio (TBR) gekoppeld was aan een zogenaamde aandacht 'bias' voor mild-dreigende prikkels vergeleken met hoog-dreigende prikkels in een aandachtstaak (dot-probe task). Deze relatie was verweven met angstigheid als persoonlijkheids-trek. De relatie bleek onafhankelijk te zijn van tijd-stadia van aandacht, die aangepast werden in de taak, bij het zien van een 'target' (een puntje dat in beeld verschijnt) met een vertraging van 200 of 500 ms. Het doel van de huidige studie was het herhalen en bevestigen van deze resultaten van Angelidis et al., en daarbij opnieuw het effect van tijds-stadia van aandacht te onderzoeken, ditmaal met kortere target verschijningsvertragingen van 80 en 200 ms. Daarnaast werd er een negatieve relatie verwacht tussen TBR en aandachts-controle. TBR werd gemeten in rust

bij 53 gezonde proefpersonen. Ook werden zelf-gerapporteerde aandachts-controle en angstigheid als persoonlijkheids-trek gemeten. De proefpersonen voerden na deze metingen eenzelfde dot-probe taak uit als in Angelidis et al., maar dit keer met kortere target vertragingen. In de dot-probe taak moesten de proefpersonen aangeven met een knop links en rechts, of het 'target' (een zwart puntje) respectievelijk links of rechts verscheen. Het target verscheen altijd onder één van twee gecentreerde plaatjes. Deze plaatjes bevatte bij één van de twee dreigende en bij de andere neutrale informatie. De dreigende informatie kon een milde dreiging zijn (bijvoorbeeld een spin of slang) of een hoge dreiging (afbeelding van ernstig lichamelijke letsels). De aandachts-bias werd gemeten door de reactietijd van 'target onder dreiging' af te trekken van 'target onder neutraal'. De reactietijd wordt namelijk verwacht sneller te zijn wanneer het target onder dreigende informatie zit dan wanneer deze zich onder neutrale informatie bevindt. De resultaten gaven aan dat verhoogde TBR meer aandachts-bias voorspelde naar prikkels met een milde dreiging, vergeleken met de prikkels met een hoge dreiging. Hetzelfde effect was gevonden voor aandachts-controle, wat alleen het geval was bij een target vertraging van 200 ms. De TBR en aandachts-controle effecten waren onafhankelijk van angstigheid als persoonlijkheids-trek. TBR hing verder negatief samen met aandachts-controle. Concluderend lijkt het modulerende effect van TBR en aandachts-controle op een aandachts-bias voor mild-dreigende prikkels herhaald te zijn, maar dit keer was er geen interactie-effect gevonden met angstigheid als persoonlijkheids-trek. Het effect van aandachts-controle lijkt daarnaast enkel van toepassing in een later tijd-stadium van aandacht.

Hoofdstuk 2

Aangezien in eerder onderzoek is gevonden dat EEG theta/beta ratio (TBR) de prefrontaal-gereguleerde processen als aandachts-controle weerspiegelt, en daarnaast dat TBR een aandachts-bias voor dreigende informatie beïnvloedt, zou cafeïne als werkzame stof een invloed kunnen hebben op TBR. Een lage dosis cafeïne versterkt namelijk aandachts-controle door een verhoogde werking van zogenaamde catecholamines in de prefrontale cortex (PFC), afhankelijk van iemands basale-catecholamine niveau in de PFC. Ons doel was om te testen of cafeïne ook invloed heeft op een aandachts-bias voor dreigende informatie en of deze relatie daarnaast wordt geregeld door TBR en/of angstigheid als persoonlijkheids-trek. Veertig gezonde vrouwelijke proefpersonen bezochten het lab driemaal met steeds een week ertussen. Tijdens de eerste sessie werd TBR gemeten en er werd een interferentie taak met positieve en dreigende informatie uitgevoerd. Tijdens de tweede en derde sessie werd er (dubbelblind) 30 minuten voor het starten van de sessie 200 mg cafeïne of een placebo toegediend. De tweede en derde sessie waren verder exact gelijk aan de eerste sessie. Wanneer de proefpersoon de tweede sessie cafeïne toegediend kreeg was dit de derde sessie placebo en andersom, zodat alle proefpersonen beide substanties voor één van de sessies kregen. De resultaten gaven aan dat een verhoogde TBR gekoppeld was aan een lagere aandachts-bias voor dreigende prikkels. Dit was alleen het geval voor proefpersonen met een lage score voor angstigheid als persoonlijkheids-trek, en in de eerste sessie of na placebo toediening. Dit effect was niet aanwezig voor positieve prikkels. Na toediening van cafeïne leek dit effect te zijn omgedraaid; een verhoogde TBR was gekoppeld aan een hogere aandachts-bias voor dreigende prikkels, onafhankelijk van angstigheid als persoonlijkheids-trek. Cafeïne veroorzaakte verder geen verandering in TBR. Deze resultaten suggereren dat,

aangezien cafeïne catecholamine niveaus verhoogt, individuen met een lage TBR eerder een negatieve invloed (meer aandachts-bias) ondervinden van cafeïne, en individuen met een verhoogde TBR eerder een positieve invloed (minder aandachts-bias) ondervinden van cafeïne. TBR lijkt daarmee indirect gekoppeld te zijn aan basale catecholamine niveaus in de PFC. De resultaten versterken opnieuw de aanname dat TBR aandachts-controle weerspiegelt en benadrukken dat het belangrijk is basale aandachts-controle mee te nemen bij onderzoek naar effecten van cafeïne op prestatie.

Hoofdstuk 3

Naast de eerder gevonden relatie tussen EEG theta/beta ratio (TBR) en aandachts-controle was een verhoogde TBR (hogere theta, lagere beta) ook gekoppeld aan ongecontroleerde gedachten (gedachtedwalingen), vergeleken met 'gecontroleerde gedachten', ofwel tijdens gefocuste aandacht (Braboszcz & Delorme, 2011). Dit suggereert dat de eerder gevonden relatie tussen TBR en aandachts-controle eventueel verklaard zou kunnen worden door ongecontroleerde gedachten van individuen met een lagere aandachts-controle tijdens de EEG-meting in rust. Het doel van dit onderzoek was het herhalen en bevestigen van de eerder gevonden relatie tussen TBR en gedachtedwalingen, en of deze relatie op zijn beurt gekoppeld is aan aandachts-controle. Zesentwintig gezonde proefpersonen voerden een ademhalings-tel taak uit van 40 minuten. TBR was gemeten in rust vóór deze taak en daarnaast werd TBR tijdens de taak 'actueel' gemeten. Tijdens de ademhalings-tel taak gaven proefpersonen aan wanneer de gedachten afdwaalden van het tellen van ademhalingen door op een knop te drukken. De resultaten gaven aan dat TBR significant hoger was tijdens periodes van gedachtedwalingen (vóór de knop-druk) vergeleken met periodes van gefocuste aandacht (na de knop-druk). De relatie tussen TBR en aandachts-controle werd echter niet gevonden. Wij concluderen daarom dat verhoogde TBR een verlaagde controle over gedachtedwalingen lijkt te weerspiegelen.

Hoofdstuk 4

Eerder onderzoek heeft nu laten zien dat EEG theta/beta ratio (TBR) samenhangt met aandachts-controle en ongecontroleerde gedachten (gedachtedwalingen). Gedachtedwalingen zijn daarnaast ook gekoppeld aan verminderde activiteit in het zogenoemde 'executieve controle netwerk' (ECN) een prefrontaal brein-netwerk dat betrokken is bij cognitieve/aandacht controle. Ook zijn gedachtedwalingen gekoppeld aan een toegenomen activiteit in het zogenoemde 'default mode-netwerk' (DMN); dit is een brein-netwerk dat vaak actief is tijdens rust. Het is daarom mogelijk dat een verhoogde TBR gekoppeld is aan een verhoogde mate van gedachtedwalingen wat zelf weer gekoppeld is aan verandering in activiteit in het ECN en DMN. Dit is echter nog niet eerder onderzocht. Deze studie had daarom als doel de relaties te onderzoeken tussen TBR tijdens rust en tijdens gerapporteerde gedachtedwalingen ten opzichte van gefocuste aandacht. Daarnaast werd gekeken of deze relaties op hun beurt correleerden met functionele verbinding (connectiviteit) binnen het ECN en DMN. Achtendertig gezonde proefpersonen voerden twee keer een ademhalings-tel taak uit van 40 minuten; tijdens een eerste sessie terwijl TBR actueel werd gemeten en tijdens een tweede sessie terwijl functionele 'magnetic resonance imaging' (MRI) actueel werd gemeten. TBR werd ook gemeten in rust. Tijdens de ademhalings-tel taak

gaven proefpersonen aan wanneer de gedachten afdwaalden van het tellen van ademhalingen door op een knop te drukken. De resultaten gaven aan dat TBR significant hoger was tijdens periodes van gedachtedwalingen (vóór de knop-druk) vergeleken met periodes van gefocuste aandacht (na de knop-druk) en deze verandering was marginaal significant gekoppeld aan TBR tijdens rust. Functionele verbinding binnen het DMN was hoger en binnen het ECN lager tijdens periodes van gedachtedwalingen (voor de knop-druk) vergeleken met periodes van gefocuste aandacht (na de knop-druk). Daarnaast was de verandering in ECN-connectiviteit tijdens gedachtedwalingen ten opzichte van gefocuste aandacht significant gekoppeld aan de verandering in TBR tijdens gedachtedwalingen vergeleken met gefocuste aandacht. Deze resultaten suggereren opnieuw dat TBR aandachts-controle weerspiegelt en geven een eerste indicatie van de neurale-correlaten van TBR.

Hoofdstuk 5.

Neurofeedback is een methode waarin hersenactiviteit (bijvoorbeeld gemeten door EEG) wordt omgezet in beelden of geluiden. Deze beelden of geluiden dienen dan als 'feedback'. Met een neurofeedback training wordt getracht de hersenactiviteit te beïnvloeden met behulp van operante (werkzame)-conditionering. Met bijvoorbeeld videobeelden of een computerspel wordt door middel van beloning getraind de hersenactiviteit boven of onder een gestelde drempel te houden. De aanpassing van EEG theta/beta ratio (TBR) door neurofeedback training is eerder onderzocht. Aanpassing van TBR zou sterk kunnen bijdragen aan onderzoek naar de oorzaak van de eerder gevonden relatie tussen TBR en aandachts-controle. Deze studie had daarom als doel om een algemeen gebruikte TBR neurofeedback training te onderzoeken in twaalf gezonde vrouwelijke proefpersonen, die waren voorgeselecteerd op een hoger dan gemiddeld TBR. Aangezien dit onderzoek bedoeld was als een eerste pilot of TBR daadwerkelijk verandert met neurofeedback training, en bijwerkingen van TBR neurofeedback training niet uitgesloten konden worden, werd er gekozen voor een 'multiple baseline design'. In dit design wordt een manipulatie op verschillende momenten in de tijd aangeboden na periodes van het meten van de te manipuleren variabele als basis. Op deze manier kunnen veranderingen in de gemanipuleerde variabele nauwkeurig bekeken worden voor en na de start van de manipulatie. In deze studie werden de proefpersonen verdeeld over drie groepen van vier proefpersonen. De groepen begonnen allen met drie sessies waarin alleen TBR werd gemeten in rust voor de duur van een neurofeedback training (25 minuten). Na deze drie 'baseline' sessies ging één groep verder met 14 sessies actieve TBR neurofeedback training (geprogrammeerd om TBR te verlagen), één groep kreeg nog zes extra baseline sessies voordat ze verder gingen met acht actieve TBR neurofeedback training sessies, en de laatste groep ging verder met 14 sessies placebo neurofeedback training (niet werkzame voor-opgenomen neurofeedback training). De EEG van beta, theta en TBR werd per minuut per proefpersoon en per groep in detail bekeken. De resultaten gaven geen enkele aanwijzing dat neurofeedback training de TBR verlaagde tijdens, of over de sessies, noch aan het einde van de 14 sessies. Ons onderzoek toont daarmee niet aan dat neurofeedback training TBR verandert in gezonde proefpersonen met een hoger dan gemiddeld TBR.

Discussie

De onderzoeken in dit proefschrift toonden tezamen aan dat de EEG-marker 'theta/beta ratio' (TBR) mogelijk aandachts-controle weerspiegelt. Er is gevonden dat een verhoogde TBR samenhangt met verhoogde aandacht voor 'mild' dreigende prikkels ten opzichte van 'hoog' dreigende prikkels. TBR leek daarnaast indirect gekoppeld te zijn aan basale catecholamine niveaus in de prefrontale-cortex in individuen met een lage score op angstigheid als persoonlijkheidstrek. Er is meerdere keren gevonden dat een verhoogde TBR samenhangt met verlaagde (zelf-gerapporteerde) aandachts-controle. TBR bleek daarnaast hoger tijdens ongecontroleerde gedachten (gedachtedwalingen) vergeleken met gecontroleerde gedachten (gefocuste aandacht). Dit effect was hetzelfde voor functionele verbinding in het 'executieve controle netwerk', wat op zijn beurt weer gekoppeld was aan het ongecontroleerde versus gecontroleerde gedachten- effect van TBR. Ons onderzoek heeft echter niet aan kunnen tonen dat TBR aangepast zou kunnen worden door een neurofeedback training. De bevindingen zoals beschreven in dit proefschrift bieden nieuwe inzichten op de neuropsychologische functie van TBR en ondersteunen het gegeven dat TBR de verbinding weerspiegelt in brein-netwerken van aandachts-controle. Deze bevindingen dragen bij aan een breder begrip van fysiologische weergaven van aandachts-controle en cognitief functioneren. Ondanks dat deze bevindingen al een sterke basis vormen voor wat TBR vertegenwoordigt, blijft toekomstig onderzoek essentieel, met name voor het herhalen en bevestigen van onze bevindingen en het verder uitzoeken van TBR's relaties tot psychologische functies, zowel in gezonde populaties als populaties met een psychopathologische achtergrond.

About the author

Dana van Son was born on May 11th, 1990 in Naarden, The Netherlands, and lived in Almere throughout her childhood where she completed high school at 'Baken Park Lyceum' in 2008. She then started the Bachelor of Psychology at VU University in Amsterdam. After completing her first year, she however switched to the University of Amsterdam (UvA) where she finished her Bachelor's degree (2011) and (Research) Master's degree in Cognitive Psychology (2013). During her Master's, she was involved in research projects on attention trainings and alcohol addiction in the lab of Prof. Wiers, and conducted an internship on fMRI grey and white (brain) matter in gamblers and cocaine addicts at the University of Granada, Spain. After her graduation, she worked as a research assistant in Amsterdam in the same lab of Prof. Wiers, helping out in fMRI projects and attentional trainings for heavy drinkers. In September 2014 she started her PhD project on 'Anxiety and cognitive performance' at Leiden University under the supervision of Dr. Putman and Prof. van der Does. In a series of studies as explained in this dissertation, she explored the role of EEG theta/beta ratio in cognitive/emotional processes. In 2018, she visited the University of Wollongong, Australia, for a three-month collaboration project, conducting EEG time frequency analysis on data collected at Leiden University. Dana now works as workgroup teacher at Leiden University.

Publications

van Son, D., De Blasio, F. M., Fogarty, J. S., Angelidis, A., Barry, R. J., & Putman, P. (2019). Frontal EEG theta/beta ratio during mind wandering episodes. *Biological psychology, 140,* 19-27.

van Son, D., Angelidis, A., Hagenaars, M. A., van der Does, W., & Putman, P. (2018). Early and late dot-probe attentional bias to mild and high threat pictures: Relations with EEG theta/beta ratio, self-reported trait attentional control, and trait anxiety. *Psychophysiology,* e13274.

van Son, D., Schalbroeck, R., Angelidis, A., van der Wee, N. J., van der Does, W., & Putman, P. (2018). Acute effects of caffeine on threat-selective attention: moderation by anxiety and EEG theta/beta ratio. *Biological psychology, 136,* 100-110.

Angelidis, A., Hagenaars, M., **van Son, D.**, van der Does, W., & Putman, P. (2018). Do not look away! Spontaneous frontal EEG theta/beta ratio as a marker for cognitive control over attention to mild and high threat. *Biological psychology, 135*, 8-17.

van Son, D., Wiers, R. W., Catena, A., Perez-Garcia, M., & Verdejo-García, A. (2016). White matter disruptions in male cocaine polysubstance users: Associations with severity of drug use and duration of abstinence. *Drug and alcohol dependence, 168,* 247-254.

Moreno-López, L., Perales, J. C., **van Son, D.**, Albein-Urios, N., Soriano-Mas, C., Martinez-Gonzalez, J. M., ... & Verdejo-García, A. (2015). Cocaine use severity and cerebellar gray matter are associated with reversal learning deficits in cocaine-dependent individuals. *Addiction biology, 20*(3), 546-556.

(Submitted)

van Son, D., de Rover, M., De Blasio, F. M., van der Does, W., Barry, R. J., Putman, P. (2019). *EEG theta/beta ratio co-varies with mind wandering versus controlled thought and their functional brain network connectivity (submitted).*

van Son, D., van der Does, W., Band, G. P. H., Putman, P. (2019). *EEG Theta/Beta Ratio neurofeedback training in healthy females (submitted).*

Hamstra, D. A., Franke, L. K., de Kloet, R., de Rover, M., **van Son, D.**, & van der Does, A. J. W. (2019). *Mineralocorticoid receptor haplotype, not oral contraceptives use, influences resting state EEG theta/beta ratio in healthy women (submitted).*

Acknowledgements (Dankwoord)

Het aantal personen die ik graag zou willen bedanken is aanzienlijk, het was daarom een moeilijke taak een niet al te lang dankwoord te schrijven. Hieronder een aantal personen die ik in het bijzonder wil bedanken.

Allereerst mijn directe promotoren; Willem, je hebt mij goed wegwijs gemaakt in de wereld van de klinische psychologie, waar ik als nieuweling om de hoek kwam kijken. Je hebt mij daarnaast altijd goed advies gegeven en mij uitgedaagd mijn eigen standpunten en wensen te verdedigen. Bedankt voor je goede vertrouwen en steun de afgelopen jaren.

Peter, ik heb ontzettend veel van je geleerd. We hadden af en toe onze verschillen van inzicht maar met jouw grote kennis van het vakgebied en je ervaring kon je me (bijna) altijd overtuigen. Op deze manier hebben we samen een aantal mooie studies kunnen uitvoeren en publiceren. Je hebt mij de mogelijkheid gegeven kennis op te doen van nuttige technieken, en zelfs, al dan na wat twijfels, de mogelijkheid gegeven een hippe nieuwe EEG-analyse techniek te leren in Australië, waarvan ik denk dat de nieuw-gevormde kennis en connecties mij een flinke steun in de toekomst geven. Bedankt voor de leerzame jaren die mij tot beginnend-onderzoeker hebben gevormd.

I would also like to thank Prof. Robert (Bob) Barry for receiving me at the University of Wollongong in Australia to conduct EEG time frequency analysis and to form a new collaboration. I had a never-to-be-forgotten experience working in your lab, boosting my motivation to continue in science as never before. The kind and patient analysis-help of Frances and Jack contributed immensely to my experience, without even counting in our fairy-bread and chocolate-coated liquorice breaks.

Mijn naaste promovendi-collega's van Universiteit Leiden zijn van onbetaalbare waarde geweest. My 'roomie' Angelos, thanks for the nice four-years of sharing together our frustrations, successes, comfort during our broken relationships, mocking the Dutch culture and bureaucracy and your great and kind support during good and bad times. Verder Andreas en Sanne, onze hardloop challenges met shotjes als straf zal ik niet snel vergeten. Sanne opnieuw, en ook Sandy dank dat jullie altijd voor mij klaar stonden en o.a. voor vele leuke uitstapjes, salsa dansjes, borrels en feestjes zorgde. Partypsycho's (men weet zelf wie bedoeld wordt) dank ook voor het maken van de sfeer op deze feestjes tijdens mijn promotie traject. Danielle, ik heb een enorme steun in de rug van je ervaren, onze gesprekken over promotieonderzoek-tegenslagen hebben mij altijd gemotiveerd onvermoeid verder te gaan. Verder dank aan alle andere collega's waar ik mee heb gewerkt, in het bijzonder Charlotte, Melanie, Stephanie, Margit, Lemmy, Lisa, Aleksandrina, Nathan, Milan, Daphne, Kaya, Loes, Mirjam, Dianne, Lisanne, Maartje, and our visiting friend Alfonso, dank ieder van jullie voor de lunches, koffies, de gezellige EPP's, het prettige contact en de leuke sfeer op de afdelingen.

Graag wil ik ook de (voormalige) onderzoekassistenten en studenten bedanken die keihard gewerkt hebben data te verzamelen voor onze studies, en zonder wie dit proefschrift niet tijdig af was gekomen: Akrivi, Anastasia, Alexandros, Cevdet, Daíre, Delia, Fan, Fanni, Jennifer, Joni, Julia, Kristina, Lieke, Marilisa, Mariëlle, Nil, Niamph, Poliniki, Rick, Samantha, Samu, Yiannis en Winglet.

Dan ouders, dankzij jullie als voorbeeld-wetenschappers ben ik met nieuwsgierigheid opgegroeid, en heb geleerd met een kritische maar scherpe blik met informatie om te gaan. Dank voor jullie steun, liefde en vertrouwen. Lieve Lieke, liefste zus, jij blijft nummer één support in zware en goede tijden. Dank dat je mij hebt meegesleept op mooie reizen en uit de sleur haalde door in het knusse Leiden samen onder zussen-praat wat koffie te drinken, bij een feestje aan te sluiten of een rondje singels te rennen.

Lieve Joeri, hoe alles ook is gelopen, ik wil je erg bedanken voor alle jaren van 24/7 steun, aanmoediging en troost. Je hebt mij het grootste deel van mijn promotie-traject doorgeholpen. Als ik weer eens down thuiskwam, triest dat het allemaal niet meer ging, was jij daar om mij nieuwe moed in te spreken. Ik wens je al het goeds in de toekomst.

Lieve familie, tantes, ooms, oma's, opa, vrienden en vriendinnen, ik heb erg veel gehad aan jullie persoonlijke contact, diepgaande gesprekken, gezelligheid en andere support. Reismaatje Laura, ik heb heerlijk met jou kunnen bijkomen in mooie oorden. Verder wil ik in het bijzonder bedanken; Sarah, Fidessa, Fleur, Diana, Maria, Joren, Irma, Emma, Jannet, Rianne1, Rianne2, Vincent, Laura (Muns), Helena, Melle, Bram, Anya, Yentl en mijn hofjesburen.

Als laatste, eerder ook persoonlijk genoemd, maar veel dank aan mijn Paranimfen (Lieke en Laura) voor jullie uitmuntende hulp en inzet voor een onvergetelijke promotie dag!