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

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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, Mogoașe, 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.

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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.

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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.

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About the Author

Publications

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