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

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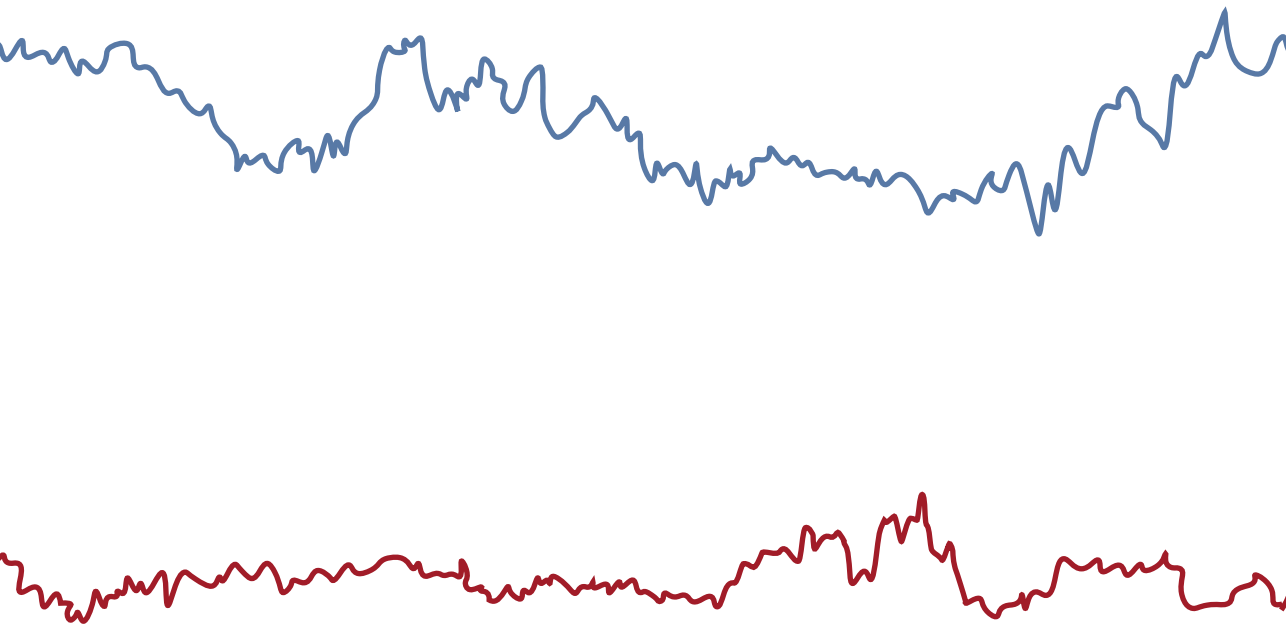
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CHAPTER 4.

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

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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, Hagens, van der Does & Putman, 2018a) and state attentional control (Putman et al., 2014) and with the controlled modulation of threat selective attention (Angelidis, Hagens, van Son, van der Does, & Putman, 2018; van Son et al., 2018a; van Son, Schallbroeck, 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 cingulate 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 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-

Chapter 4

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 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 x 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 hemodynamic 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 *SD*s 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 ($t[25] = 1.62, p = 0.117, d = 0.32$).

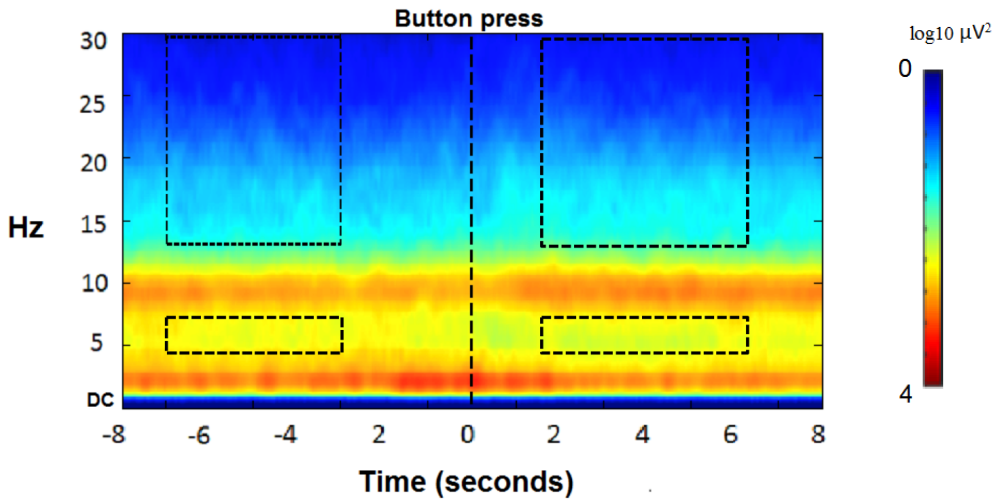


Figure 4.1. ERSP spectral plot of the frontal average (across F3 Fz F4 sites) at 1 Hz frequency resolution, and 62.5 ms time resolution. Rectangular frames highlight the epochs of primary interest corresponding to the two ‘real time’ 2-TR epochs that fall within the pre-defined periods for MW and focussed 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); $t(23) = -0.03, p = 0.90$. 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) \times 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 $F(1,25) = 0.89, p = 0.354, \eta_p^2 = 0.04$, however, there was a main effect for networks, $F(1,25) = 5.78, p = 0.024, \eta_p^2 = 0.19$, with activity greater in ECN than DMN (see **Figure 4.2**). A significant interaction effect was found between time and networks; $F(1,25) = 31.04, p < 0.001, \eta_p^2 = 0.55$. 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.

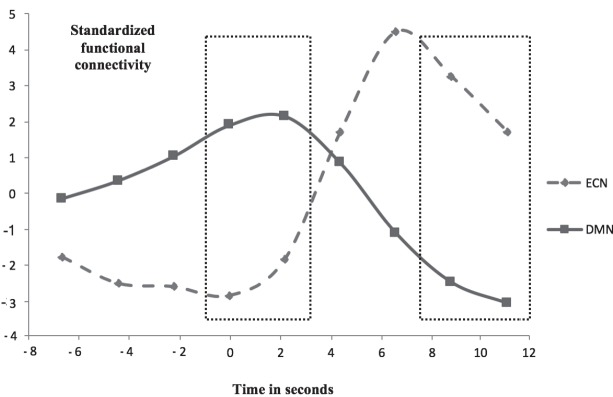


Figure 4.2. Slopes of normalized functional connectivity over time for the executive control network (ECN) and the default mode network (DMN). Rectangular frames highlight the epochs of interest. After correction for the HRF delay, the button press occurs at 6s. The y-axis shows the demeaned beta values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

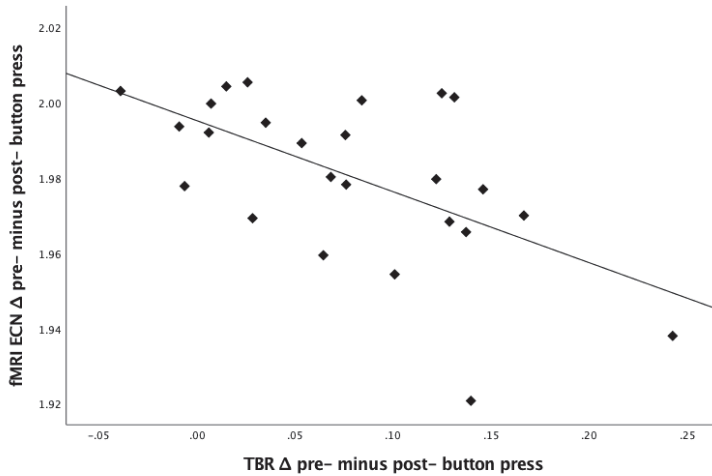


Figure 4.3. Scatterplot of the significant relation between the MW-related changes in frontal EEG theta beta ratio (TBR; x-axis) and the corresponding changes in ECN functional connectivity (y-axis); $r(23) = -0.58, p = 0.002$. Spearman's ranked order correlation (insensitive to outliers) was also significant;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

Chapter 4

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.

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Chapter 4

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