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

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CHAPTER 2.

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

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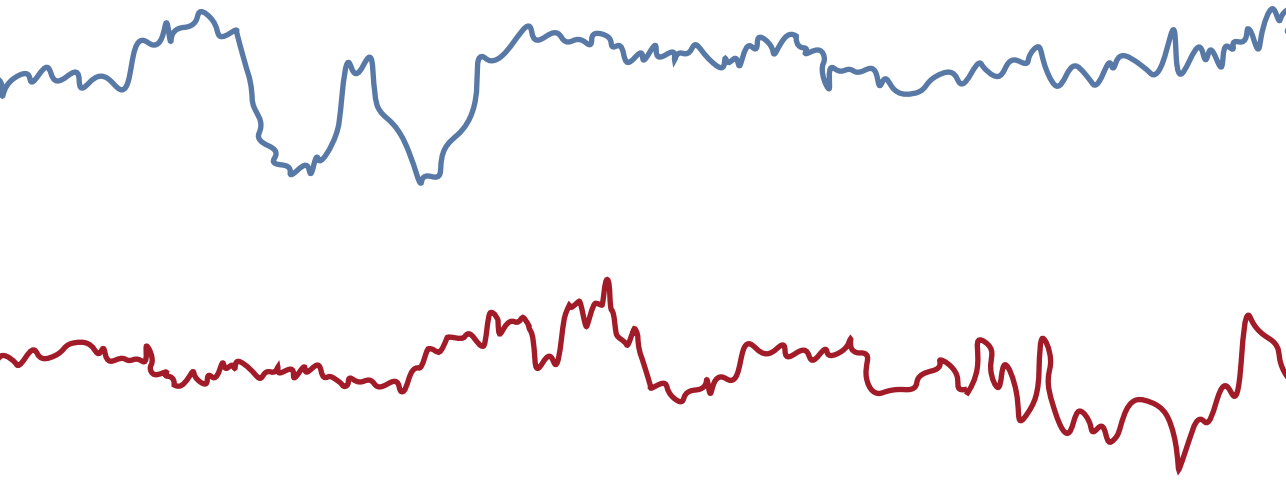

ABSTRACT

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.

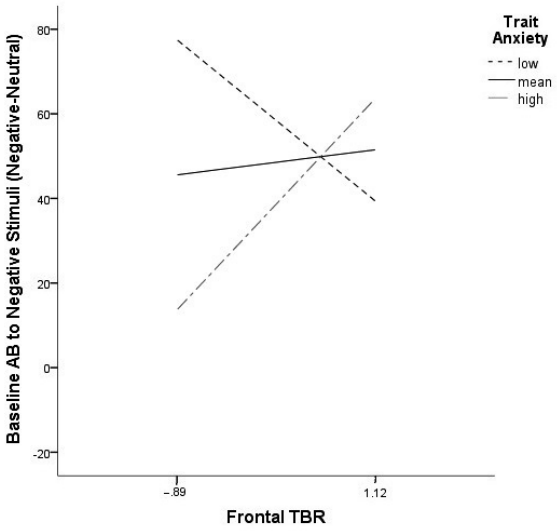

Figure 2.1. Simple slopes for the moderation of trait anxiety on the effect of Ln-normalized frontal EEG on negative interference (AB = attentional bias) in the PEST baseline results frontal TBR = Log-normalized theta/beta ratio.

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.

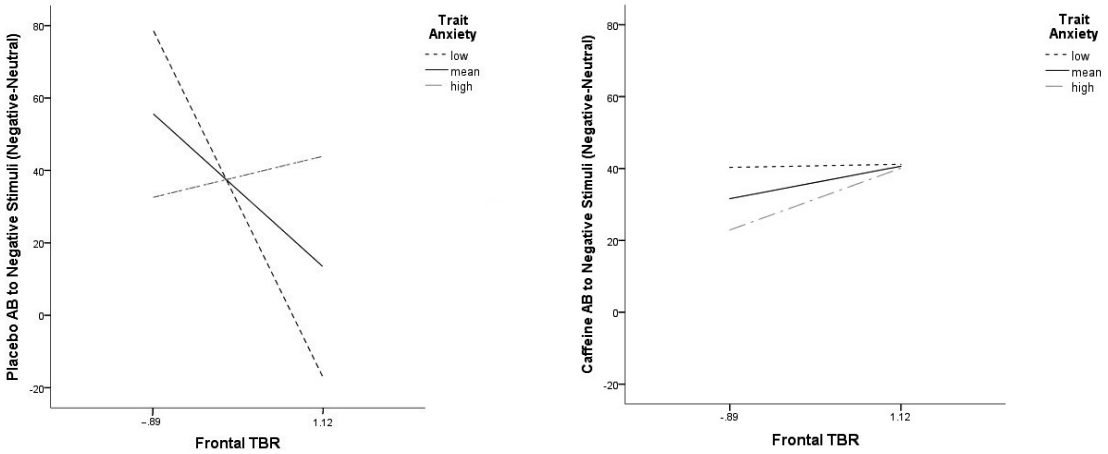

Figure 2.2ab. Simple slopes for the moderation of STAI-t on the effect of Ln-normalized frontal EEG on negative interference in the EST after consumption of placebo (a:left) or caffeine (b:right). Frontal TBR = Ln-normalized frontal theta/beta ratio. In the placebo condition, increased frontal TBR was 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.

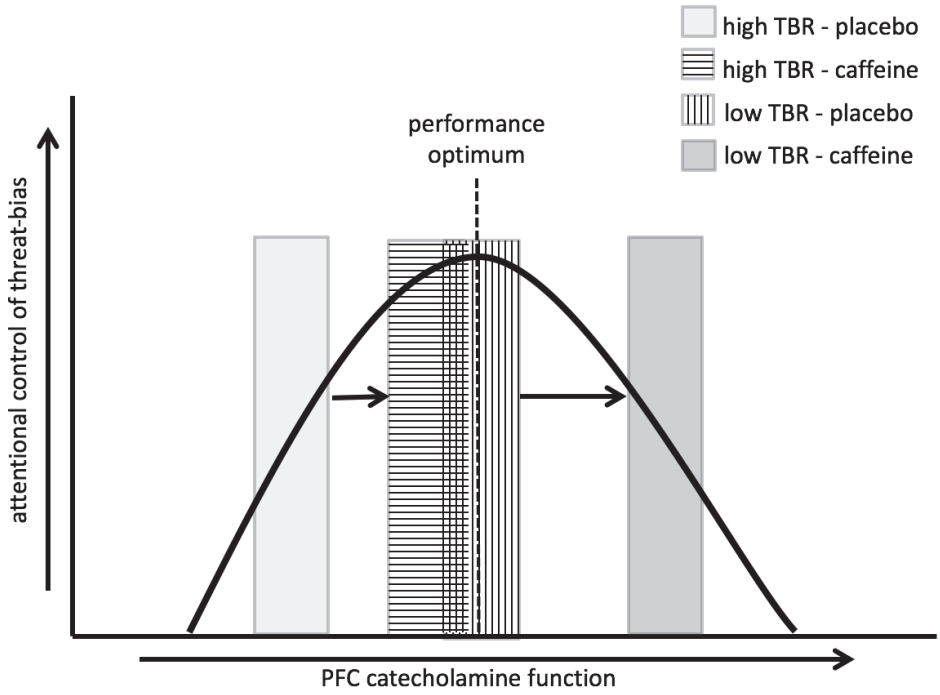

Figure 2.3. The hypothesized inverted U-shape relation between TBR as an indicator of (catecholamine) PFC function and PFC-mediated attentional control (AC) of threat bias and effects of caffeine thereon, as based on the theoretical model of Arnsten (2006; 2009a). Gray-patterned planes represent TBR – 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.

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