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Frontal midline theta reflects anxiety and cognitive control: Meta-analytic evidence

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ABSTRACT

Evidence from imaging and anatomical studies suggests that the midcingulate cortex (MCC) is a dynamic hub lying at the interface of affect and cognition. In particular, this neural system appears to integrate information about conflict and punishment in order to optimize behavior in the face of action-outcome uncertainty. In a series of meta-analyses, we show how recent human electrophysiological research provides compelling evidence that frontal-midline theta signals reflecting MCC activity are moderated by anxiety and predict adaptive behavioral adjustments. These findings underscore the importance of frontal theta activity to a broad spectrum of control operations. We argue that frontal-midline theta provides a neurophysiologically plausible mechanism for optimally adjusting behavior to uncertainty, a hallmark of situations that elicit anxiety and demand cognitive control. These observations compel a new perspective on the mechanisms guiding motivated learning and behavior and provide a framework for understanding the role of the MCC in temperament and psychopathology.

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1. Introduction

The rostral cingulate cortex, the thick belt of cortex encircling the genu and body of the corpus callosum (Fig. 1A), plays a central role in neuroscientific models of emotion and cognition (Etkin et al., 2011; Lindquist et al., 2012; Pessoa, 2008; Shenhav et al., 2013). Work to understand these two basic domains has profoundly influenced contemporary perspectives on more complex psychological phenomena, including psychopathology, pain, social processes, and the nature of executive control (Behrens et al., 2009; Etkin et al., 2011; Grupe and Nitschke, 2013; Iannetti et al., 2013). There is a growing consensus that the dorsal region of the rostral cingulate, the *midcingulate cortex* (MCC), is sensitive to both the elicitation of negative affect and the need for cognitive control, suggesting that the MCC implements a common, domain general process (Botvinick, 2007; Etkin et al., 2011; Pereira et al., 2010; Pessoa, 2008). Indeed, a recent meta-analysis of functional imaging studies demonstrates that the elicitation of both negative affect and cognitive control are associated with activation of an overlapping region in the anterior MCC (Fig. 1B) (Shackman et al., 2011).

This overlap is consistent with anatomical evidence suggesting that the MCC represents a hub where information about pain, threat, and other more abstract forms of potential punishment can be synthesized and used to modulate regions involved in expressing fear and anxiety, executing goal-directed behaviors, and biasing the focus of selective attention (Fig. 1C and D) (Shackman et al., 2011).

Despite this progress, the functional significance of activity in the rostral cingulate remains incompletely understood. The objective of the present review is to highlight recent advances in understanding the adaptive control system that have been made using electrophysiological measures indicative of MCC activity. A key focus will be on investigations characterized by *frontal midline theta* (FM Θ) signals: \sim 4–8 Hz oscillations recorded from sensors on the scalp overlying the MCC. Using meta-analytic techniques to synthesize the human electrophysiology literature, we provide evidence that anxious individuals show larger FM Θ control signals and that larger control signals are, in turn, associated with a more cautious or inhibited response set following errors and punishment. Collectively these observations support the idea that FM Θ reflects a common mechanism, a *lingua franca*, for implementing adaptive control in a variety of contexts involving uncertainty about actions and their motivationally-significant potential outcomes (Cavanagh et al., 2012b). More broadly, they provide a neurobiologically-grounded framework for conceptualizing the

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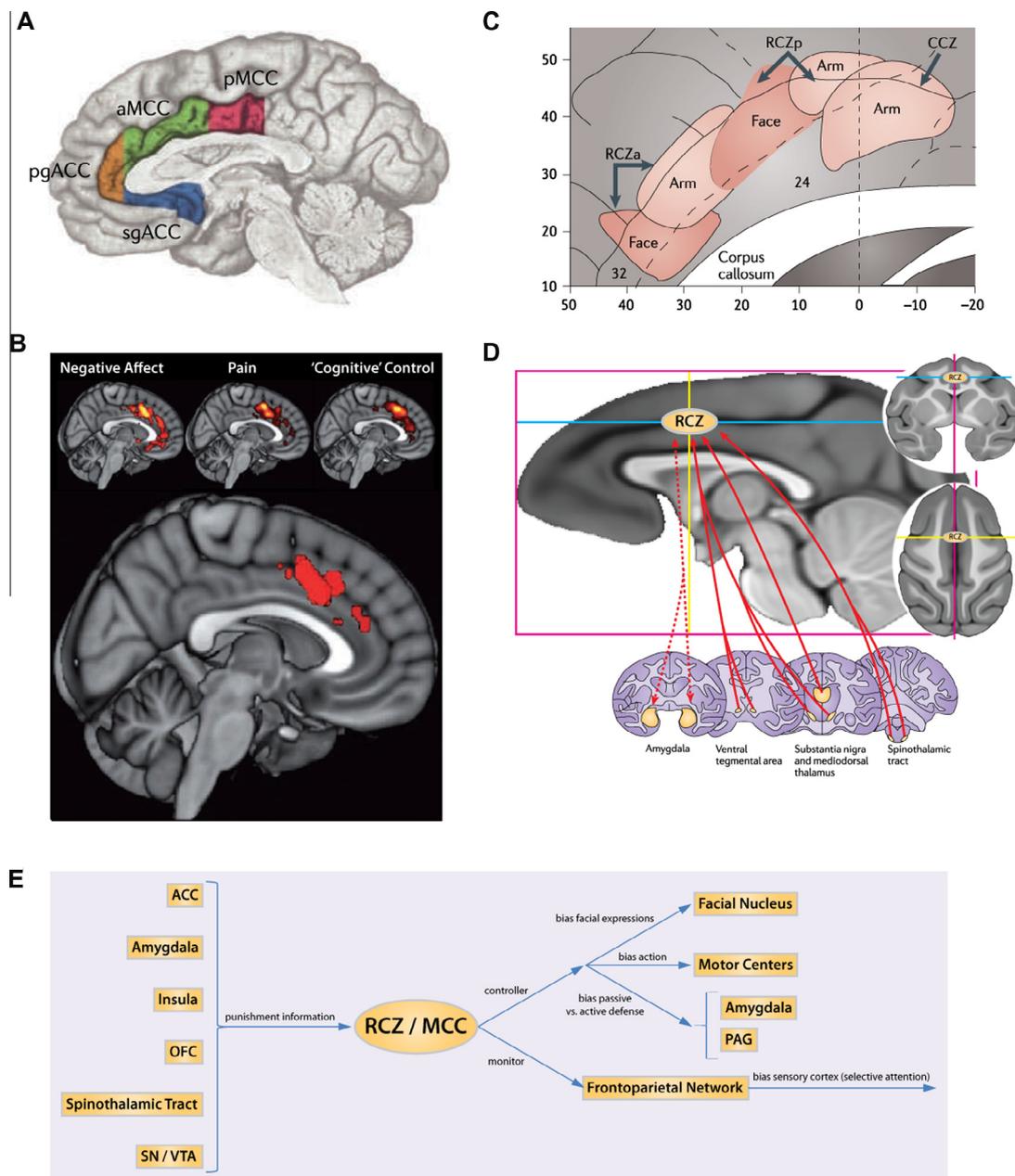


Fig. 1. The Adaptive Control Hypothesis (TACH). In humans and other primates, the rostral cingulate (architectonic areas 24, 25, 32 and 33)—a thick belt of cortex encircling the rostral corpus callosum—is among the most prominent features on the mesial surface of the brain. Much of the constituent gray matter lies buried within the cingulate sulci. (A) The four major subdivisions of the human rostral cingulate. Supracallosal cingulate is designated the midcingulate cortex (MCC) and is divided into anterior (aMCC; green) and posterior (pMCC; magenta) subdivisions. Cingulate territory lying anterior and ventral to the corpus callosum is designated the anterior cingulate cortex (ACC) and is approximately divided into pregenual (pgACC; orange) and subgenual (sgACC; blue) subdivisions by the coronal plane at the anterior tip of the genu. (B) Negative affect, pain and cognitive control activate a common region within aMCC. This map depicts the results of a coordinate-based meta-analysis (CBMA) of 380 activation foci (192 experiments involving >3000 subjects). The upper panel shows thresholded activation likelihood estimate maps for each domain. The lower panel depicts the region of three-way overlap within aMCC (areas 32', a24b/c'). (C) The MCC harbors somatotopically-organized premotor areas. Shown here are provisional locations of the cingulate premotor areas, the rostral and caudal cingulate zones (RCZ, CCZ). Somatotopy in RCZ and CCZ are based on human imaging studies. The cluster identified by the meta-analysis corresponds to the location of RCZ. The abundant projections from aMCC to motor centers would permit it to use information about punishment, feedback and other aversive reinforcers to optimize aversively-motivated instrumental actions. This stands in contrast with other cortical regions, such as the OFC and insula, that lack strong ties with motor centers. (D) Subcortical connectivity of the rhesus homologue to human RCZ. This area receives substantial inputs from the spinothalamic system, which relays nociceptive information from the periphery to RCZ via the mediodorsal nucleus of the thalamus. Dopaminergic inputs to RCZ arise from the substantia nigra and, to a lesser extent, the ventral tegmental area. RCZ projects to the ventral striatum, including the core region of nucleus accumbens, and has robust reciprocal connections with the lateral basal nucleus of the amygdala. Dotted arrows indicate reciprocal connections. (E) The Adaptive Control Hypothesis (TACH). We have previously argued that MCC implements adaptive control by integrating information about punishment arriving from subcortical regions (Panel D), insula, orbitofrontal cortex (OFC) and elsewhere in order to bias responding in situations where the optimal course of action is uncertain or entails competition between alternative courses. Control signals generated in aMCC and directed at the amygdala or periaqueductal gray (PAG) might serve to resolve conflict between passive and active defensive behaviors. Another possibility is that aMCC directly biases aversively-motivated actions through its connections with motor centers, but indirectly biases selective attention through its connections with the frontoparietal network. It is also possible that these different mechanisms are functionally segregated at a finer level of resolution (e.g., intermingled networks) or are organized along overlapping gradients within MCC. Abbreviations: anterior cingulate cortex (ACC), caudal cingulate zone (CCZ), midcingulate cortex (MCC), orbitofrontal cortex (OFC), periaqueductal gray (PAG), rostral cingulate zone (RCZ), substantia nigra (SN), ventral tegmental area (VTA). Panels A–D adapted from (Shackman et al., 2011).

mechanisms that confer increased risk for the development of anxiety and other psychiatric disorders.

1.1. The Adaptive Control Hypothesis (TACH)

On the basis of brain imaging and anatomical evidence, it has been hypothesized that MCC activity reflects control processes that optimize responses made in the face of uncertainties about instrumental actions and their potentially aversive outcomes (Fig. 1E) (Shackman et al., 2011), a perspective that we term *The Adaptive Control Hypothesis* (TACH). Put simply, TACH suggests that anxiety and negative affect tend to involve the same processes described by cognitive control theories in order to solve similar problems (see also Grupe and Nitschke, 2013). We suggest that this is a *domain-general* function of the MCC.

Control processes are engaged when automatic or habitual responses are insufficient to support goal-directed behavior (Botvinick et al., 2001; Norman and Shallice, 1986; Shenhav et al., 2013). This occurs when there is uncertainty about the optimal course of action (e.g., probabilistic learning), when potential actions are associated with the possibility of error or punishment, or when there is competition between alternative courses of action (e.g., flee/freeze, go/no-go). These features are hallmarks of dangerous environments, as in studies of fear, anxiety, and pain (Choi et al., 2010; Steenland et al., 2012). Not surprisingly, optimal instrumental behavior in threatening environments has long been thought to require control processes to monitor risk and generate the biasing signals required to resolve response uncertainty and avoid potentially catastrophic actions (Dehaene et al., 1998; Gray and McNaughton, 2000; Norman and Shallice, 1986; Rushworth and Behrens, 2008). Importantly, a growing body of behavioral and biological evidence indicates that errors, like punishments and other kinds of control prompts, are experienced as unpleasant and facilitate avoidance, reinforcing the possibility that MCC makes a similar contribution to 'cognitive' and 'affective' control (Dreisbach and Fischer, 2012; Kool et al., 2010; Lindström et al., 2013; Schoupe et al., 2012).

1.2. FM Θ reflects signals of the need for control

Neuronal control signals generated within the MCC propagate to the scalp, where they can be measured using well-established electroencephalographic (EEG) techniques. In particular, MCC-related control processes are reflected in a variety of event-related potential (ERP) components elicited by novel information, conflicting stimulus-response requirements, punishing feedback, and the realization of errors (Fig. 2A). For example, the presentation of cue arrays associated with conflicting response options (as in the Eriksen flanker task) elicits the N2, a negative potential that peaks approximately 300 ms after the onset of conflicting cue arrays (for a review, see: Folstein and Van Petten, 2008). Likewise, unexpected punishment elicits a similar signal, the feedback-related negativity (FRN) (for a review, see: Walsh and Anderson, 2011). ERP control signals can also be elicited by endogenous activities (i.e., internal error signals), as with the error-related negativity (ERN), a negative potential peaking approximately 80 ms after the commission of an error (for a review, see: Gehring et al., 2012). While the cerebral generators of these scalp-recorded signals remains a matter of active research, and likely includes contributions from other brain regions (Bonini et al., 2014; Cohen et al., 2008; Emeric et al., 2010), a variety of evidence implicates the MCC as a key generator, including EEG source estimation (Gehring et al., 2012; van Noordt and Segalowitz, 2012; Walsh and Anderson, 2012), EEG-informed fMRI (Becker et al., 2014; Debener et al., 2005; Edwards et al., 2012; Hauser et al., 2014; Huster et al., 2011), MEG (Doñamayor et al., 2011), and invasive recordings in humans and monkeys (Cohen

et al., 2008; Gemba et al., 1986; Tsujimoto et al., 2010, 2006; Wang et al., 2005; Womelsdorf et al., 2010a,b).

Although data derived using these ERP components have played a crucial role in the development of formal models of cognitive control and reinforcement learning (Holroyd and Coles, 2002; Yeung et al., 2004), there are theoretical and methodological advantages to focusing on the spectral characteristics of these signals rather than the separate ERP components. Spectral methods decompose complex signals into different contributions of frequency, power and phase angle over time, each of which can differentially contribute to information representation. Spectral decomposition has revealed that the ERN (errors), FRN (punishment), and N2 (conflict) share a common signature in the theta band (Cavanagh et al., 2009; Luu et al., 2004, 2003; Trujillo and Allen, 2007; Yordanova et al., 2004) (Fig. 2B and C). It was recently proposed that this family of theta signals reflect canonical phase-locked activities that are used for the temporal organization of distributed neuronal ensembles (Cavanagh et al., 2012b). Neural reactions to conflict, punishment, and error manifest as variations of these obligatory theta band phase dynamics, particularly via power increases (Cohen and Donner, 2013). In the context of this common spectral perspective, we refer to this collection of control-sensitive EEG signals as FM Θ . While these ERP components are partially dissociable, emphasizing their common dominant FM Θ processes offers an appropriately broad methodological and theoretical perspective.

2. Meta-analyses of FM Θ support for TACH

As the electrophysiological literature has grown, it is increasingly difficult to integrate new data with extant models of adaptive control and reinforcement learning (Shackman et al., 2011; Shenhav et al., 2013). Meta-analytic techniques provide an important tool for overcoming this challenge. Here we used random-effects meta-analytic techniques (Borenstein et al., 2009) to synthesize the voluminous electrophysiology literature and understand the relationships among FM Θ control signals, dispositional anxiety, and controlled adjustments of behavior.

2.1. Dispositional anxiety

TACH and other models argue that negative emotions, such as anxiety and fear, are tightly integrated with control processes implemented in the MCC (Proudfit et al., 2013; Shackman et al., 2011). This implies that anxiety should systematically covary with differences in control-sensitive electrophysiological signals generated in the MCC. That is, one would expect a substantial degree of functional convergence (i.e., convergent validity; Campbell and Fiske, 1959). Here, we used a random-effects meta-analysis to provide a comprehensive assessment of the evidence for convergence between measures of dispositional anxiety and FM Θ control signals (for more focused meta-analyses, see: Mathews et al., 2012; Moser et al., 2013). The decision to focus on dispositional anxiety was motivated in part by work demonstrating that ERP measures of conflict monitoring and control themselves represent trait-like individual differences (Hämmerer et al., 2013; Leue et al., 2013; Olvet and Hajcak, 2009a,b; Segalowitz et al., 2010; Weinberg and Hajcak, 2011).

2.1.1. Adaptive control of behavior

A central claim of TACH and other prominent models of cognitive control and reinforcement learning is that a circuit centered on the MCC tunes future instrumental behavior in the face of action-outcome uncertainty (Shackman et al., 2011; Shenhav et al., 2013). Despite strong claims, there is inconsistent evidence

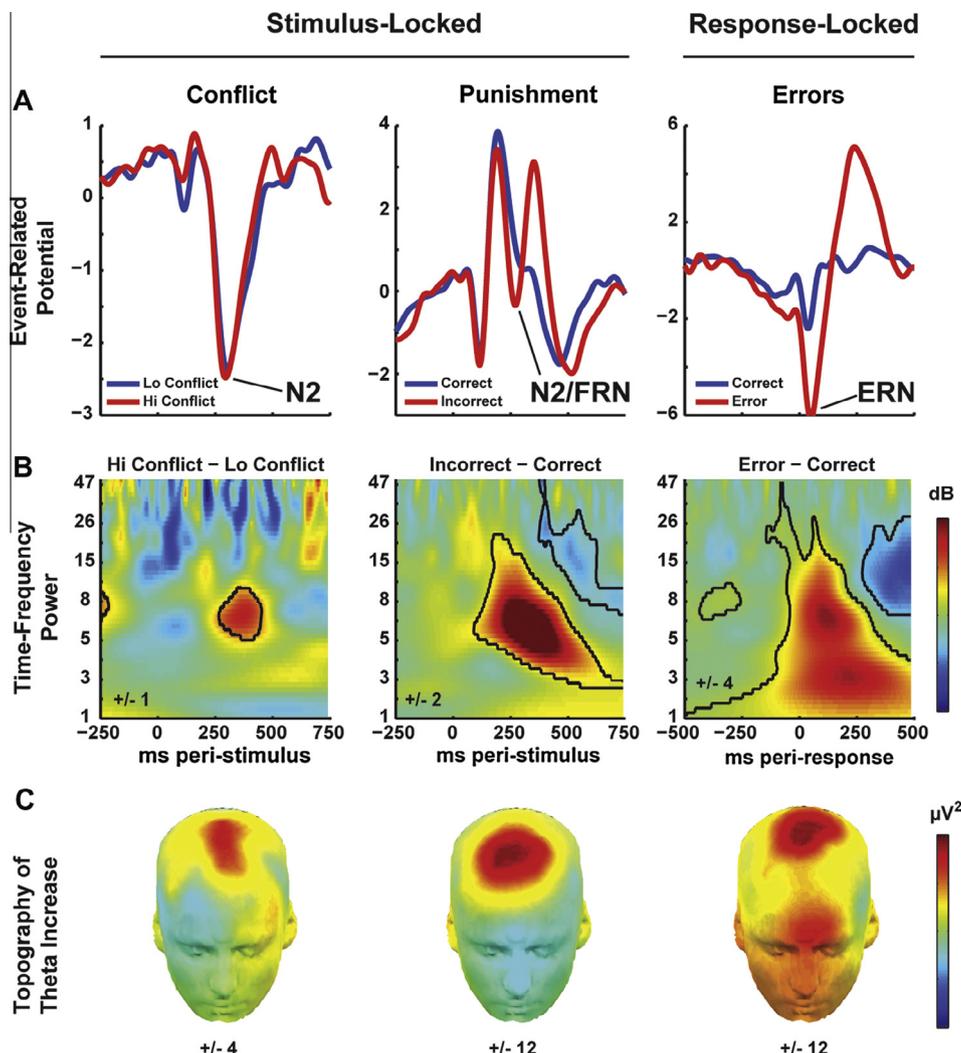


Fig. 2. A variety of events indicating a need for control are associated with a similar neuroelectrical signature in the theta band ($\sim 4\text{--}8$ Hz) over mid-frontal sites. Rows depict different components of the event-related electrophysiological signal, columns show different events associated with increased demands for adaptive control. (A) Event-related potential (ERP) components in the time-domain. N2: an ERP component evoked by exogenous cues of novelty or conflict. **Feedback Related Negativity (FRN)**: An N2-like component evoked by exogenous feedback signaling loss or punishment. **Error Related Negativity (ERN)**: A massive ERP component evoked by commission errors. While these ERP components (i.e., peaks and troughs in the wave) are related to learning and adaptive control, they represent a small fraction of ongoing neural dynamics: signal averaging in the time-domain imposes a substantial reduction in potentially meaningful information. (B) The full spectral dynamics of event-related neuroelectrical activity depicted in time-frequency plots. Here, significant increases in power to conflict, punishment and error are outlined in black, revealing a common feature in the theta band ($\sim 4\text{--}8$ Hz). (C) Scalp topography of event-related theta activity. The distribution of theta power bursts is consistently maximal over the frontal midline. Data and statistical tests from (Cavanagh et al., 2012b).

that MCC activity predicts behavioral adjustments made in response to conflict, errors, punishment, and other prompts for increased top-down control. Here we used random-effects meta-analytic techniques to test whether electrophysiological control signals generated in the MCC (i.e., FM Θ) predict behavioral adjustments following errors and punishments.

2.1.2. Post-error slowing

Errors, like other kinds of punishments, are associated with adaptive changes in subsequent behavior. In particular, errors are associated with a speed/accuracy tradeoff in subsequent behavior, characterized by a slower, more cautious response style on the next trial (Dutilh et al., 2012; Rabbitt, 1966). It is natural to ask whether the amplitude of the ERN predicts the degree of subsequent post-error slowing. Many studies have investigated this question as an inter-individual phenomenon: testing whether subjects with larger error signals slow down more after making mistakes. Studies employing this between-subjects analytic strategy

have revealed inconsistent evidence for a predictive relationship between MCC control signals and behavioral adjustments (see: Weinberg et al., 2011). Moreover, there is evidence that ERN amplitude and post-error slowing are pharmacologically dissociable (for a review, see: Jocham and Ullsperger, 2009), raising the possibility of distinct substrates.

The ambiguity, however, reflects an over-focus on between-subject examinations of individual differences and a failure to examine within-subject trial-to-trial brain-behavior relationships. Trial-by-trial correlations between neural signals and behavior offer the most stringent correlational test of brain-behavior relationships (Lim et al., 2009). Here, we used a random-effects meta-analysis to systematically test whether the magnitude of error-related MCC signals, indexed by the ERN or spectral measures of FM Θ power, predicts post-error slowing. Furthermore, moderation analyses allowed us to assess whether the strength of this relationship is influenced by the use of inter-individual versus intra-individual analytic strategies.

2.1.3. Lose-switch behavior

Adaptation to punishment often involves a ‘lose-switch’ strategy, where alternate behavioral responses are chosen following punishment. Here, we used a third random-effects meta-analysis to test whether the magnitude of feedback-related MCC signals, indexed by the FRN or spectral measures of FM Θ power, predicts the active avoidance of cues associated with punishment (i.e., ‘lose-switch’), as TACH and other control models claim. Yet, not all investigations should be expected to show explicit relationships between punishment signaling and immediate switching. As detailed in Section 4.2.2 below, we predict that this punishment-avoidance relationship should be only be apparent when the task does not involve the long-term integration of stimulus-response-reward relationships, since switching after every punishment would then be maladaptive. Put simply, if the best response in a given state still leads to punishment on 20% of trials, an optimal agent may plan to weather these temporary disappointments in the service of reaping long-term benefits.

2.1.4. General methods

We conducted three independent meta-analyses. The first aimed to test whether dispositional anxiety predicts trait-like individual differences in control-sensitive frontal-midline signals (i.e., ERN, FRN, and N2; no studies employing time-frequency measures of FM Θ were identified). The aim of the other meta-analyses was to test whether these same scalp-recorded neurophysiological measures consistently predict behavioral adjustments following prompts for enhanced control. Specifically, we assessed whether FM Θ signals predict response slowing on trials following commission errors (post-error slowing) and whether FM Θ signals predict the subsequent active avoidance of cues associated with punishment (lose-switch).

2.1.5. Study identification

Pubmed searches were used to generate a pool of potential articles for each meta-analysis (March 2012). Both used the search terms: “(ERN OR “error-related negativity” OR ERSP OR time-frequency OR “event-related spectral perturbation” OR FRN OR “feedback-related negativity” OR N2 OR “frontal theta” OR “midline theta” OR “theta band”).” For the dispositional anxiety meta-analysis, this was combined with the search terms “(anxiety OR anxious OR avoidance OR avoidant OR BIS OR EDA OR electrodermal OR fear* OR FPS OR inhibited OR nervous OR neurotic OR punishment* OR SCR OR “skin conductance” OR STAI OR startle OR stress*)”. This yielded 2204 abstracts. For the remaining meta-analyses, this was combined with the search terms: “(aversive OR conflict OR NoGo OR accuracy OR “post-error” OR “post-response slowing” OR “reaction time” OR “response time” OR Laming OR learning OR “lose-switch” OR probabilistic OR Rabbit)”. This yielded an additional 2467 abstracts.

At least one of the authors read the abstracts and identified a subset for in-depth evaluation. The preliminary review of abstracts was meant to be inclusive; articles were excluded only if the abstract clearly indicated that the article did not meet inclusion/exclusion criteria (e.g., nonhuman sample). This was supplemented by personal communications with investigators aimed at identifying file-drawer, in-press, or in-preparation manuscripts, as well as backward citation checks on articles and reviews chosen for in-depth evaluations. Altogether, 354 reports were comprehensively evaluated by at least one of the authors.

Inclusion criteria for all meta analyses included: (a) English language; (b) use of a cognitive conflict, gambling, or probabilistic learning task, and (c) sufficient statistics from a continuous (e.g., regression) or categorical (e.g., ANOVA on extreme groups) analysis of relations between EEG amplitudes and individual differences in dispositional anxiety or behavioral measures. Studies of develop-

mental or geriatric populations were included. A wide range of self-report and behavioral indexes of dispositional anxiety were included (e.g., behavioral inhibition, harm avoidance, neuroticism, and trait anxiety), consistent with a growing consensus that these measures reflect a broad underlying dimension of anxiety-proneness and anxious distress (Caspi et al., 2005). Exclusion criteria included: (a) the absence of previously unpublished inferential statistics (e.g., reviews); (b) pharmacological manipulations; (c) analyses of data obtained from participants with diagnosed psychopathology or who were explicitly enrolled on the basis of sub-clinical psychopathology. Studies of psychopathology and pharmacology were only included in cases where the authors reported effect sizes separately for psychiatrically-healthy or unmedicated controls and the study otherwise met our inclusion/exclusion criteria. Based on these criteria, 76 studies, incorporating nearly 2300 psychiatrically-healthy subjects, were used in one or more of our meta-analyses.

2.1.6. Effect sizes

To maximize independence, the mean effect size was used in cases where multiple conditions or trait measures were reported. A similar rule was applied in cases where effects for continuous analyses were reported separately for participants with high and low levels of dispositional anxiety (e.g., Meyer et al., 2012). Exceptions were made for cases where the condition manipulation coincided with one of our candidate moderator variables (Olvet and Hajcak, 2009c; West and Travers, 2008) and for two cases where extensive follow-up analyses were performed on a subset of conditions (De Pascalis et al., 2010; Moadab et al., 2010). In cases where multiple conditions or measures were collected, but an effect size was only reported for the single condition or measure that reached significance (Boksem et al., 2008; Pailing and Segalowitz, 2004), that was used. In cases where multiple ERP components were reported, each component was treated as an independent sample (Amodio et al., 2008; Boksem et al., 2006; Moadab et al., 2010).

Reported effect sizes were transformed as necessary to Pearson’s correlation coefficient using the formula:

$$r = (t^2 / (t^2 + df_e)) \quad (1)$$

where $F = t^2$ and df_e = degrees of freedom for the error term, equal to the sample size minus 2 in cases with no additional covariates. Tests in which higher levels of anxiety or larger behavioral adjustments predicted a more negative component (i.e., larger amplitude ERN, FRN, N2) were treated as positive effects. If an effect was reported as nonsignificant but specific information was not provided, the effect size was conservatively assigned a value of $r = 0$ (unbiased estimate). Confidence intervals were transformed from z to r for figures, thus they reflect the likely range of effect size in future studies, and do not directly reflect the confidence range for the statistical test in the sample reported here. Thus, in some cases, significant effects are associated with a 95% confidence interval that, when back-transformed to r , includes 0. Both r and z values are reported below.

2.1.7. Random-effects meta-analyses

Analyses were performed using the *metafor* package (Viechtbauer, 2010) written for R (version 2.14.1; <http://www.R-project.org>). Analyses were performed using Z-transformed correlation coefficients and an approximation to the unbiased estimates of the sampling variances (Hedges, 1989). As described above, effect sizes and 95% confidence intervals were shown in figures as back-transformed correlation coefficients. For omnibus tests, random-effects models were estimated using maximum likelihood (ML). Random-effects models have the advantage of permitting unconditional inferences about the mean effect size in the

population of studies from which the sampled studies are drawn (Borenstein et al., 2009).

2.1.8. Moderator analyses

The potential impact of both categorical and continuous moderator variables was assessed using a series of planned contrasts implemented as ML mixed-effects linear models, one for each candidate moderator variable. Specifically, we tested whether relations with dispositional anxiety were significantly moderated by the kind of control prompt: commission error (ERN), feedback (FRN), or response conflict (N2). Likewise, for the meta-analysis of post-error adjustments, we tested whether the strength of FM Θ -behavior relations differed as a function of being computed across (inter-individual) or within subjects (intra-individual). There were no significant differences in age or sex distributions between the inter- and intra-individual subgroups for this analysis. This contrast could not be performed with adequate reliability for the lose-switch meta-analysis given the limited number of studies employing intra-individual analytic techniques (2/7; 29%).

2.1.9. Evaluation of potential publication bias

Publication bias occurs when positive ('significant') results are more likely to be published than negative ('non-significant') results, leading to an overestimate of the true population effect size. Potential publication biases were first assessed using funnel plots, which depict the effect size as a function of the standard error of the effect (i.e., an index of sample size) and serve as a diagnostic aid for detecting publication bias and other systematic heterogeneities. Absent publication bias, effect sizes are expected to be symmetrically distributed about the mean without regard to standard error; visual evidence of a lower-rightward asymmetry (e.g., smaller studies with larger standard errors tending to report larger effects) is suggestive of publication bias. The robustness of omnibus effect sizes was assessed by computing the Fail-safe N (Rosenthal, 1979) using the *MAc* package (version 1.1; <http://CRAN.R-project.org/package=MAc>) for *R*. This provides an estimate of the number of additional non-significant results that would have to exist for the omnibus estimate of effect size to be rendered non-significant.

3. Meta-analysis results

3.1. Convergence between measures of anxiety and 'cognitive' signals generated in MCC

As shown in Fig. 3A, individuals with higher levels of dispositional anxiety show enhanced frontal-midline control signals when performing standard, emotionally-neutral cognitive control tasks (z -test = 5.38, $p < .01$; mean $z = .26$, CI: .17, .34, mean $r = .26$, CI: -.21, .67). This relationship supports the hypothesis that anxiety and other kinds of negative affect are tightly integrated with cognitive control processes in the MCC (Shackman et al., 2011). The strength of this association was similar to a recent estimate derived solely from the ERN literature (Moser et al., 2013) and did not significantly differ among signals evoked by response conflict (N2), commission errors (ERN), or negative feedback (FRN), z -tests < 1.42 , $ps > .15$), consistent with the idea that these three signals are sensitive to the same underlying FM Θ processes (Cavanagh et al., 2012b).

3.2. FM Θ predicts post-error slowing

As shown in Fig. 3B, larger error signals predict greater response time slowing on the trial following an error (z -test = 4.52, $p < .01$, mean $z = .24$, CI: .14, .34; mean $r = .24$, CI: -.07, .51), providing

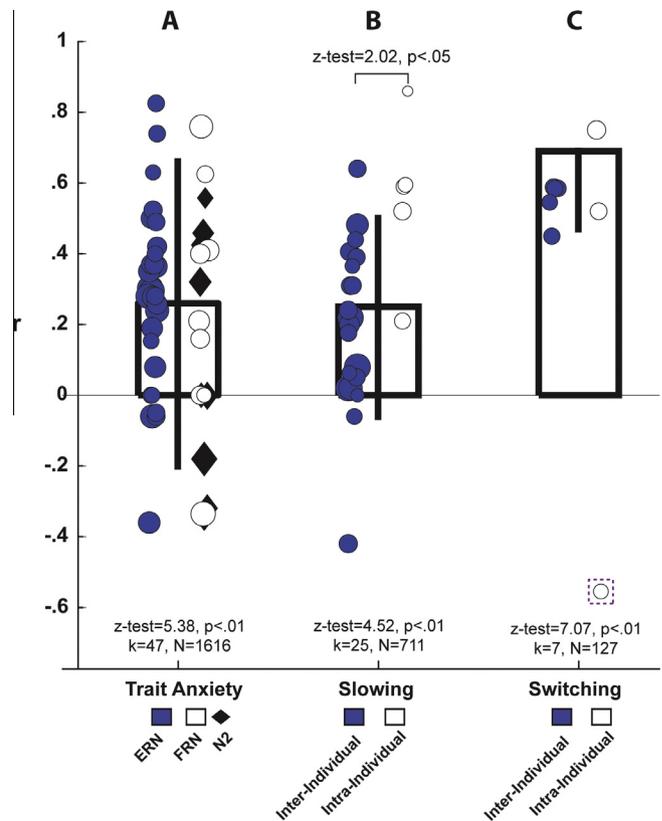


Fig. 3. FM Θ is consistently related to dispositional anxiety and predicts aversively-motivated behavioral adjustments. (A) Individuals characterized by greater dispositional anxiety show larger FM Θ signals in response to conflict, punishment, and error. There was not a significant difference between response-locked error signals (filled circles) and cue-locked signals of punishment (empty circles) or conflict (filled diamonds). (B and C) Larger control signals predict a more cautious or inhibited response set following punishment or errors. (B) Larger error-related FM Θ signals predict greater post-error slowing on the subsequent trial. This was observed both inter-individually (filled circles: individuals with larger error signals showed increased behavioral adjustments) and intra-individually (empty circles: trial-to-trial differences in control signals predicted proportional variation in post-error slowing) analyses. There was a significant moderating effect of this level of analysis, where intra-individual studies had a significantly larger relationship between error signals and response slowing (z -test = 2.02, $p < .05$). (C) Larger FM Θ responses to worse-than-expected feedback predict an increased probability of switching to the alternative among studies employing both inter-individual (filled circles) and intra-individual (empty circles) analytic strategies. The empty circle outlined by a dashed box indicates a study where feedback must be integrated over time and rapid switching would be maladaptive, this study was excluded *a priori* from this meta-analysis on these grounds. Statistics were determined using random-effects meta-analyses (k : number of studies; n : number of participants). Error bars depict the random-effects estimate of the brain-behavior correlations ($\pm 95\%$ CI). Each circle is centered on the correlation of each study, with the size of the circle scaled by the sample size ($10^3 \log_{10}(N)$). Larger numbers indicate a larger absolute relationship (i.e., the sign of the voltage potential is not taken into account).

important evidence that MCC signals serve to regulate behavior in situations where reflexive or habitual actions are inadequate. Moreover, studies assessing the relationship between trial-by-trial fluctuations in the amplitude of MCC error signals and slowing reported significantly stronger brain-behavior relations than those relying on traditional individual differences analyses, z -test = 2.02, $p < .05$. While this moderation analysis is limited by the few studies that have formally investigated trial-to-trial effects, the intra-individual method remains a more direct test of the functional brain-behavior relationship associated with adaptive control. These findings highlight the sensitivity of the intra-individual analytic technique and support the hypothesis that FM Θ signals

support the adaptive regulation of behavior when there is a risk of negative outcomes.

3.3. FM Θ predicts lose-switch behavior

As shown in Fig. 3C, individuals characterized by larger FM Θ amplitudes to punishment were more likely to actively avoid that option on the following trial (z -test = 7.07, $p < .01$; mean $z = .69$, CI: .50, .88; mean $r = .69$, CI: $-.46, .70$). Taken with the post-error slowing results, this indicates that FM Θ signals play an important role in using information about uncertain negative outcomes to optimize avoidance behaviors. While this lose-switch tendency is adaptive for simple decision making and instrumental learning tasks, it is maladaptive when integrating reinforcement history over a longer time period. Consistent with this principle, the only investigation that involved longer-term probabilistic integration yielded a strong negative correlation between FM Θ and subsequent behavior (it was removed *a priori* from the meta-analytic summary; see Section 2.1.3).

3.4. Individual effect sizes, funnel plots and fail-safe N results

Effect sizes for each study incorporated in the meta-analyses are depicted in Figs. 4 and 5. Visual inspection of the funnel plots for each meta-analysis revealed no evidence of publication biases (Fig. 4C). While there is an outlying point in the switching meta-analysis funnel plot, this study had the largest N and largest effect size, and is thus not suggestive of a bias to report findings that capitalize on chance from a small N analysis. While funnel plots are prone to inaccuracy and misinterpretation, especially those with fewer than 10 samples (Lau et al., 2006; Sterne et al., 2011; Terrin et al., 2005), we included them here for all major meta-analyses for completeness. Additional tests of potential publication bias bolster these conclusions, as the results of the fail-safe N analyses show that a substantial number of additional null results (i.e., unpublished or to-be-published studies) would be required for any of the meta-analyses to yield null results (Dispositional Anxiety: 1061; Post-Error Slowing: 204; Lose-Switch: 62). Collectively, these findings demonstrate that the meta-analytic results are robust.

4. Understanding the role of FM Θ in affective, cognitive, and behavioral control

The present results, summarized in Fig. 3, demonstrate that anxious individuals are characterized by heightened FM Θ signals in response to a range of control prompts. The similarity of these relations across signals evoked by high-conflict cues, errors, and negative feedback is consistent with the idea that that FM Θ reflects a common mechanism, a *lingua franca*, implementing adaptive control in a variety of contexts involving uncertainty about actions and their outcomes (Cavanagh et al., 2012b). More broadly, these relations strengthen claims that 'emotional' and 'cognitive' control processes are functionally integrated in the MCC (Shackman et al., 2011). Importantly, the results of the post-error slowing and lose-switch meta-analyses indicate that larger FM Θ signals in response to errors and punishment, in turn, predict a more cautious and avoidant pattern of instrumental behavior on subsequent trials. These observations provide compelling evidence that a circuit centered on the MCC contributes to the adaptive regulation of instrumental behavior in the face of action-outcome uncertainty, a central claim of TACH and other, more computationally-explicit models of cognitive control and reinforcement learning (Shackman et al., 2010; Shenhav et al., 2013).

4.1. Dispositional anxiety and FM Θ

Our meta-analytic results demonstrate that control-sensitive FM Θ signals generated in the MCC are elevated in dispositional anxious individuals. These results provide a novel framework for conceptualizing anxiety. When extreme, dispositional anxiety is a key risk factor for the development of anxiety disorders as well as co-morbid depression and substance abuse (Barlow et al., 2013; Kotov et al., 2010). These psychiatric disorders are highly prevalent, debilitating, and challenging to treat (Bystritsky, 2006; Kessler et al., 2012), underscoring the importance of a deeper understanding of the neural systems that confer liability to dispositional anxiety.

The present results suggest that chronically elevated anxiety partially reflects heightened sensitivity to uncertain punishment and risk (e.g., of error or failure). While the anxious phenotype is complex and multidimensional, there is a growing consensus that elevated reactivity to uncertain threat is a core feature of both the anxiety disorders and trait-like individual differences in anxiety and behavioral inhibition (Barker et al., 2014; Davis et al., 2010; Grupe and Nitschke, 2013; Mushtaq et al., 2011; Reeb-Sutherland et al., 2009). Indeed, elevated anxiety in response to uncertain or ambiguous threat is more discriminative of many anxiety disorders than that elicited by certain threat and prospectively predicts the initial appearance of the disorder (Craske et al., 2012; Davis et al., 2010; Lissek et al., 2005).

Converging lines of pharmacological evidence suggest that anxious individual's exaggerated response to uncertain threat is caused by alterations in the adaptive control network (Fig. 1), consistent with our meta-analytic results. In particular, clinically-effective pharmacological treatments for anxiety and alcohol selectively reduce anxiety elicited by uncertain threat (Bradford et al., 2013; Davis et al., 2010; Gray and McNaughton, 2000; Hefner and Curtin, 2012; Hefner et al., 2013). Importantly, these anxiolytic compounds also attenuate FM Θ signals and weaken behavioral adjustments following control prompts (Bartholow et al., 2012; de Brujin et al., 2004; Easdon et al., 2005; Ridderinkhof et al., 2002; but c.f.: Yeung and Cohen, 2006; Yeung et al., 2007). Together, these findings suggest that a circuit centered on the MCC is an important substrate for the pervasive, over-generalized distress characteristic of anxious individuals.

4.2. FM Θ and the adaptive control of instrumental behavior

Our results also demonstrate that larger error-related FM Θ signals are associated with more cautious or inhibited instrumental responses on subsequent trials. These findings are consistent with the idea that FM Θ reflects the summed activities of cingulate neurons, which have been shown to be modulated by conflict, punishment, error, and behavioral adjustment. This breadth of eliciting circumstances suggests that FM Θ may be interpreted as a generic signal of uncertainty indicating an enhanced need for control (c.f. Miltner et al., 1997). We discuss these ideas in more detail below, arguing that this mechanistic perspective may add to a better understanding of the nature of anxiety.

4.2.1. Cingulate neurons compute the need for control

Cingulate neurons are sensitive to errors (Amiez et al., 2005), and show enhanced and sustained activity following conflict (Sheth et al., 2012) and error (Narayanan and Laubach, 2008; Narayanan et al., 2013). Pharmacological inactivation of cingulate neurons in rats attenuates post-error slowing (Narayanan and Laubach, 2008; Narayanan et al., 2013) and in humans, MCC lesions increase error rates (Devinsky et al., 1995; Milea et al., 2003) and diminish behavioral adjustments following conflict (di Pellegrino et al., 2007; Milea et al., 2003; Sheth et al., 2012). Paral-

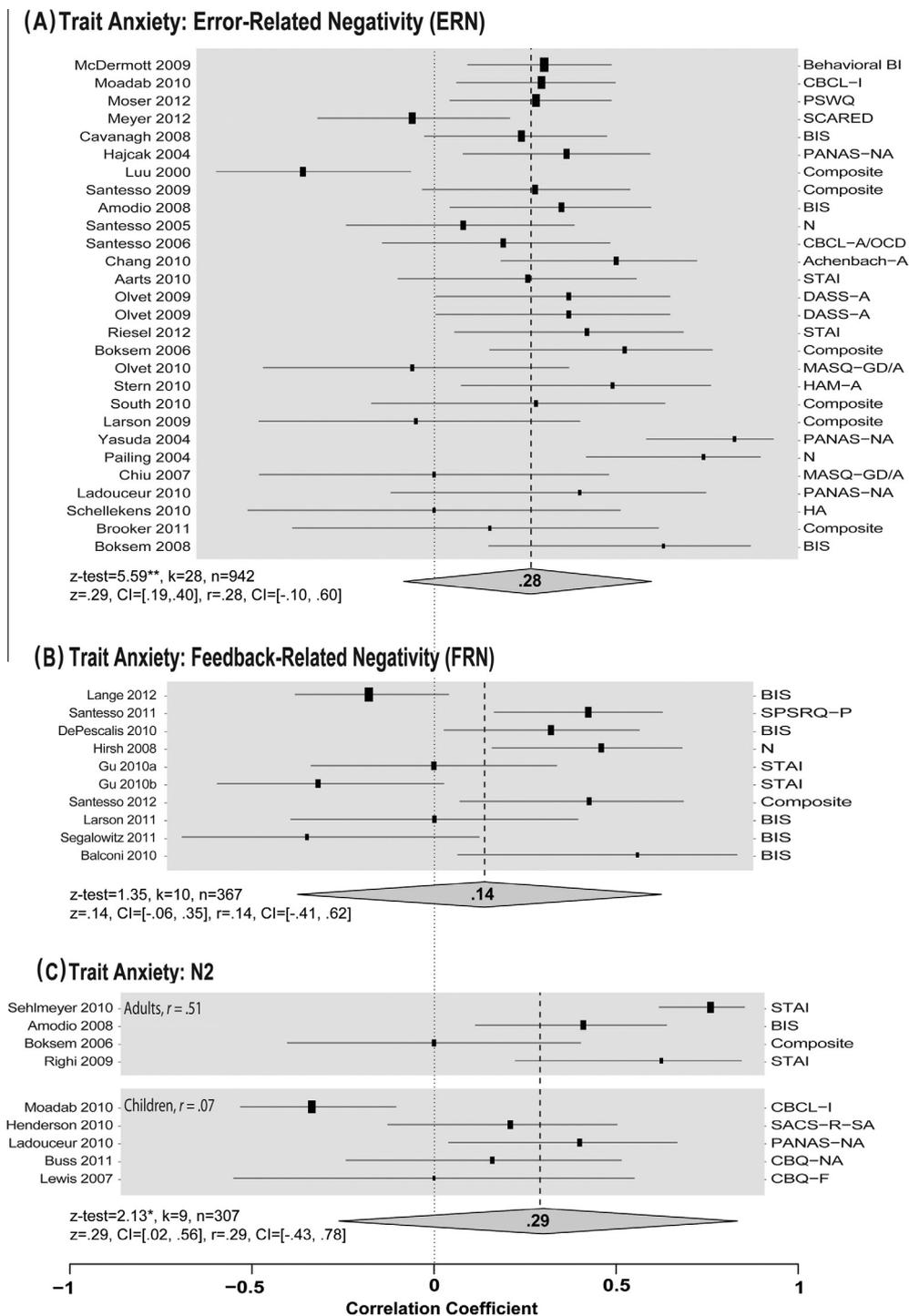


Fig. 4. Forest plots of the relationship between FM θ and trait anxiety (as Pearson's r). Forest plots display each study included in the meta-analysis in descending order of sample size (also indicated by the size of the box). Here the forest plots are separated by the type of eliciting event and specifically associated ERP component (A: error/ERN, B: punishment/FRN, C: conflict/N2). Psychometric instruments used to assess dispositional anxiety are detailed on the right of each plot.

lel effects have been obtained using transcranial direct current stimulation applied to the scalp overlying the frontal-midline (Reinhart and Woodman, 2014). Cingulate neurons also respond to punishments and switch cues, as well the combination of these two features (i.e., lose-switch) in monkeys (Amiez et al., 2005; Ito et al., 2003; Shima and Tanji, 1998) and humans (Williams et al., 2004). When these cells are inhibited (Shima and Tanji, 1998) or lesioned (Kennerley et al., 2006; Rushworth et al., 2007; Williams et al., 2004), lose-switch behavior is hindered and persev-

eration is common. Moreover, glutamatergic agonists applied directly to the ACC in rats have additionally proven both necessary and sufficient for aversive learning, putatively serving as a learning signal (Johansen and Fields, 2004).

Cingulate neurons generate theta band activities (Tsujiimoto et al., 2010, 2006; Wang et al., 2005; Womelsdorf et al., 2010a,b), which are proposed to be detectable on the scalp as FM θ signals. Our meta-analytic results underscore the contribution of such FM θ signals to the active avoidance of potentially aversive

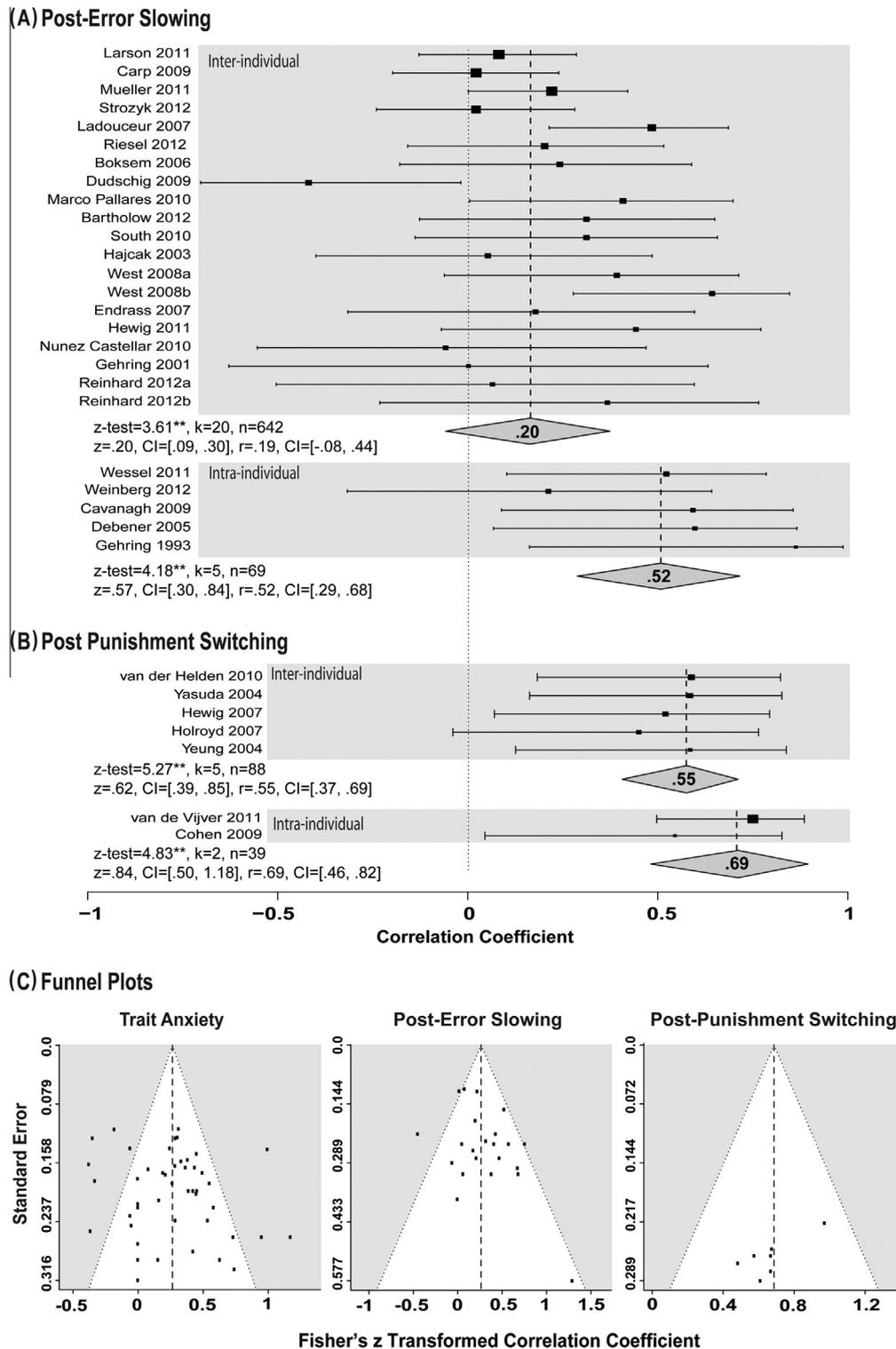


Fig. 5. Forest plots of the relationship between FM Θ and behavioral control (as Pearson's r) and funnel plots. Here the forest plots are separated by the type of eliciting event and specifically associated EEG activity (A: error/ERN and RT slowing, B: punishment/FRN and switching), as well as the distinction between inter- and intra-individual analysis. C) Funnel plots were used to qualitatively assess the presence of publication bias. These plots display the standard error (y -axis) as a function of the effect size (x -axis). The lines of the funnel represent the range where 95% of points are expected to lie in the absence of publication bias. Asymmetrical deviations around the center line also suggest possible publication bias, especially if there are more points in the lower right corner (small N , large effect) but not in the lower left corner (small N , small effect). There was no qualitative evidence for publication bias in any meta analysis.

outcomes. Collectively, these results provide compelling evidence that the MCC, as reflected in FM Θ , serves to regulate instrumental behavior in the face of uncertainty about actions and aversive out-

comes, an axiom of TACH and other prominent models of cognitive control and reinforcement learning (Shackman et al., 2011; Shenhav et al., 2013).

4.2.2. The functional significance of FM Θ signals in adaptive control

Adaptive control requires that an agent form expectations and monitor deviations (prediction errors) or potential deviations (conflict) about the need for control. FM Θ appears to reflect the summed outputs of these processes, providing a plausible neurophysiological mechanism for the realization of the need for control. In contrast to more established models, we argue that FM Θ reflects both prediction errors and conflict due to a common reaction to uncertainty, which signals the need for increased control.

Feedback-related FM Θ signals, in particular, appear to be sensitive to both worse-than-expected (Cavanagh et al., 2010; Chase et al., 2010; Holroyd and Coles, 2002; Ichikawa et al., 2010; Philiastides et al., 2010; Yasuda et al., 2004) and better-than-expected (Baker and Holroyd, 2011; Cavanagh et al., 2012a; Oliveira et al., 2007) outcomes, suggesting that they represent an unsigned prediction error, or simple surprise (Cavanagh et al., 2012a; Hauser et al., 2014; Holroyd et al., 2008; Sallet et al., 2013; Talmi et al., 2013). Yet additional evidence indicates that feedback-related FM Θ signals are not pure measures of surprise or feedback salience, insofar as they are disproportionately enhanced for negatively-valenced outcomes (Cavanagh et al., 2012a), consistent with invasive recordings in the nonhuman primate cingulate (Hayden et al., 2011). The apparent negativity bias of this signal may reflect an innate sensitivity of the MCC to “bad” events (Blair et al., 2006; Bush et al., 2002; Shima and Tanji, 1998; Wrase et al., 2007), or be indicative of a general need for change. While a domain-general perspective suggests that there is no substantive difference between these affective and effective tendencies, it remains an important issue to more precisely determine the information content of FM Θ signals. Developing a deeper understanding of the functional significance of these signals will require that investigators employ new tasks: most of the studies described in this review relied on tasks that confound valence- and behavioral-specific information (i.e., win-stay/lose-switch).

The theoretical perspective advanced here suggests that these FM Θ measures may be most useful when interpreted in the context of how uncertainty/prediction error signals relate to adaptive control. We anticipated in Section 2.1.3 that FM Θ signals will only predict rapid behavioral adaptation in cases where larger prediction errors would be expected to lead to rapid adaptation, as with conflict-induced slowing or punishment-induced switching. However, this relationship would not necessarily hold during exploration or hypothesis testing, as in long-term probabilistic or reversal learning.

4.2.3. Relationships between avoidance and anxiety as informed by FM Θ

From a translational perspective, these observations provide a foundation for understanding the neurocognitive mechanisms that underlie the maladaptive behavioral profile—excessive behavioral inhibition and heightened avoidance—that characterizes anxious individuals (Grupe and Nitschke, 2013). For example, inflated expectations about punishment magnitude or likelihood would explain enhanced avoidance of cues and contexts associated with threat and punishment. Likewise, aberrant estimates of prediction error or uncertainty (i.e., learning rate) would retard expectancy adjustments when anticipated punishments do not occur, potentially explaining anxious individuals' difficulties learning to discriminate certain from uncertain threat and associated sustained distress and avoidance. This framework is broadly consistent with evidence that successful phobia treatment is associated with a lasting reduction in MCC activation to phobic cues as well as diminished behavioral avoidance (Hauner et al., 2012).

5. Future challenges

The present results provide robust meta-analytic evidence that dispositionally anxious individuals are characterized by larger FM Θ signals in response to uncertain negative outcomes. Larger control signals, in turn, predict subsequent behavioral adaptation. Nonetheless, it is clear that much work remains to clarify the relationships between anxiety, aversion, FM Θ , and the underlying neural circuitry. Here, we outline several of the most important challenges for future research.

First, while this is compelling evidence that scalp-recorded FM Θ signals reflect generators in the MCC, the lack of a unique solution to the inverse problem dictates that other brain areas, particularly those in the adaptive control network, are also likely to contribute to these signals (Agam et al., 2011; Emeric et al., 2010; Luu et al., 2003). Clarifying the neuronal sources of the FM Θ is particularly important for bridging the gap separating invasive work in nonhuman species from correlative neurophysiological investigations in humans (Narayanan et al., 2013).

Second, while our results demonstrate that larger FM Θ signals are associated with heightened inhibition and enhanced avoidance, it will remain important to critically assess the influence of task demands on the relationship between FM Θ and behavioral adjustment. Errors appear to elicit a somewhat subtle increase in response caution and stimulus attention (Danielmeier and Ullsperger, 2011), whereas punishment in a rapidly adaptive two-alternative forced choice task predicts a clear-cut lose-switch avoidance strategy. The strategic nature of behavioral adjustments thus appear to moderate the size and consistency of observable FM Θ -behavior relationships. Our results suggest that trial-by-trial analyses performed at the level of individual subjects may prove especially sensitive to detecting such relationships.

Third, it will also be useful to clarify whether behavioral adaptation reflects the direct influence of MCC on motor centers or, as some have suggested (Miller and Cohen, 2001), a consequence of MCC triggering top-down control processes implemented in the fronto-parietal network. It has been previously suggested that FM Θ signals underlie the communication and implementation of control via phase synchronous relationships with distal cortical areas (Cavanagh et al., 2009). This technique provides a testable measure of directional influence preceding behavioral adjustments. Fourth, a central challenge will be to determine whether increased MCC control signals are a consequence of amplified punishment-related information arriving from distal brain regions, such as the extended amygdala (Brázdil et al., 2002; Nishijo et al., 2008; Ousdal et al., 2008), or instead reflect local changes in the way that the MCC assesses demands for control and uses it to bias learning and behavior (Fig. 1).

Finally, it will be important to clarify the link between control-sensitive FM Θ signals and the development of psychopathology. Although our results provide clear evidence that dispositionally anxious individuals show amplified FM Θ signals, the clinical significance of this neural marker remains uncertain (Proudfit et al., 2013). Alterations in the ERN, in particular, have been found in patients with a remarkably broad range of diagnoses, including anxiety, obsessive-compulsive, and psychotic disorders (Mathews et al., 2012; Moser et al., 2013; Weinberg et al., 2011). This apparent lack of specificity may partially reflect the influence of transdiagnostic features, such as elevated neuroticism (Foti et al., 2013, 2012), that are shared by many psychiatric disorders (Caspi et al., 2013; Kotov et al., 2010; Tackett et al., 2013). While it is not yet known whether FM Θ plays a role in the etiology of these features, evidence from pharmacological studies indicates that these signals are attenuated by the administration of anxiolytic compounds (Bradford et al., 2013; Davis et al., 2010; Gray and McNaughton,

2000; Hefner and Curtin, 2012; Hefner et al., 2013), suggesting that the MCC-centered adaptive control network (Fig. 1) may be a key site of action (i.e., anxiety). Future work aimed at clarifying the neurobiology of adaptive control and its underlying neurobiology in humans and other animals promises to enhance nosology, improve prognosis, and accelerate the development of novel therapeutic interventions (Borsook et al., 2006; Narayanan et al., 2013; Reinhart and Woodman, 2014).

6. Concluding remarks

Here we have surveyed new evidence that anxiety and cognitive control are anatomically, functionally, and computationally integrated in the MCC. TACH suggests that anxiety and cognitive control often share a common need to determine an optimal course of action in the face of uncertainty about instrumental actions and their potentially aversive consequences. The present meta-analytic results reinforce this claim, demonstrating that anxious individuals show heightened FM \ominus signals in response to punishment and other prompts for increased cognitive control; in turn, elevated FM \ominus signals are associated with more cautious and avoidant instrumental behavior on subsequent trials. These findings suggest that key elements of adaptive control are embodied in FM \ominus activity and contribute to both 'affect' and 'cognition'. This work provides a novel, neurobiologically-grounded framework for deciphering the contribution of adaptive control circuitry to temperament and psychopathology.

Conflict of interest

The authors declare no conflicts of interest.

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