

# Midfrontal Theta Activity in Psychiatric Illness: An Index of Cognitive Vulnerabilities Across Disorders

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## ABSTRACT

There is an urgent need to identify the mechanisms that contribute to atypical thinking and behavior associated with psychiatric illness. Behavioral and brain measures of cognitive control are associated with a variety of psychiatric disorders and conditions as well as daily life functioning. Recognition of the importance of cognitive control in human behavior has led to intensive research into behavioral and neurobiological correlates. Oscillations in the theta band (4–8 Hz) over medial frontal recording sites are becoming increasingly established as a direct neural index of certain aspects of cognitive control. In this review, we point toward evidence that theta acts to coordinate multiple neural processes in disparate brain regions during task processing to optimize behavior. Theta-related signals in human electroencephalography include the N2, the error-related negativity, and measures of theta power in the (time-)frequency domain. We investigate how these theta signals are affected in a wide range of psychiatric conditions with known deficiencies in cognitive control: anxiety, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, and substance abuse. Theta-related control signals and their temporal consistency were found to differ in most patient groups compared with healthy control subjects, suggesting fundamental deficits in reactive and proactive control. Notably, however, clinical studies directly investigating the role of theta in the coordination of goal-directed processes across different brain regions are uncommon and are encouraged in future research. A finer-grained analysis of flexible, subsecond-scale functional networks in psychiatric disorders could contribute to a dimensional understanding of psychopathology.

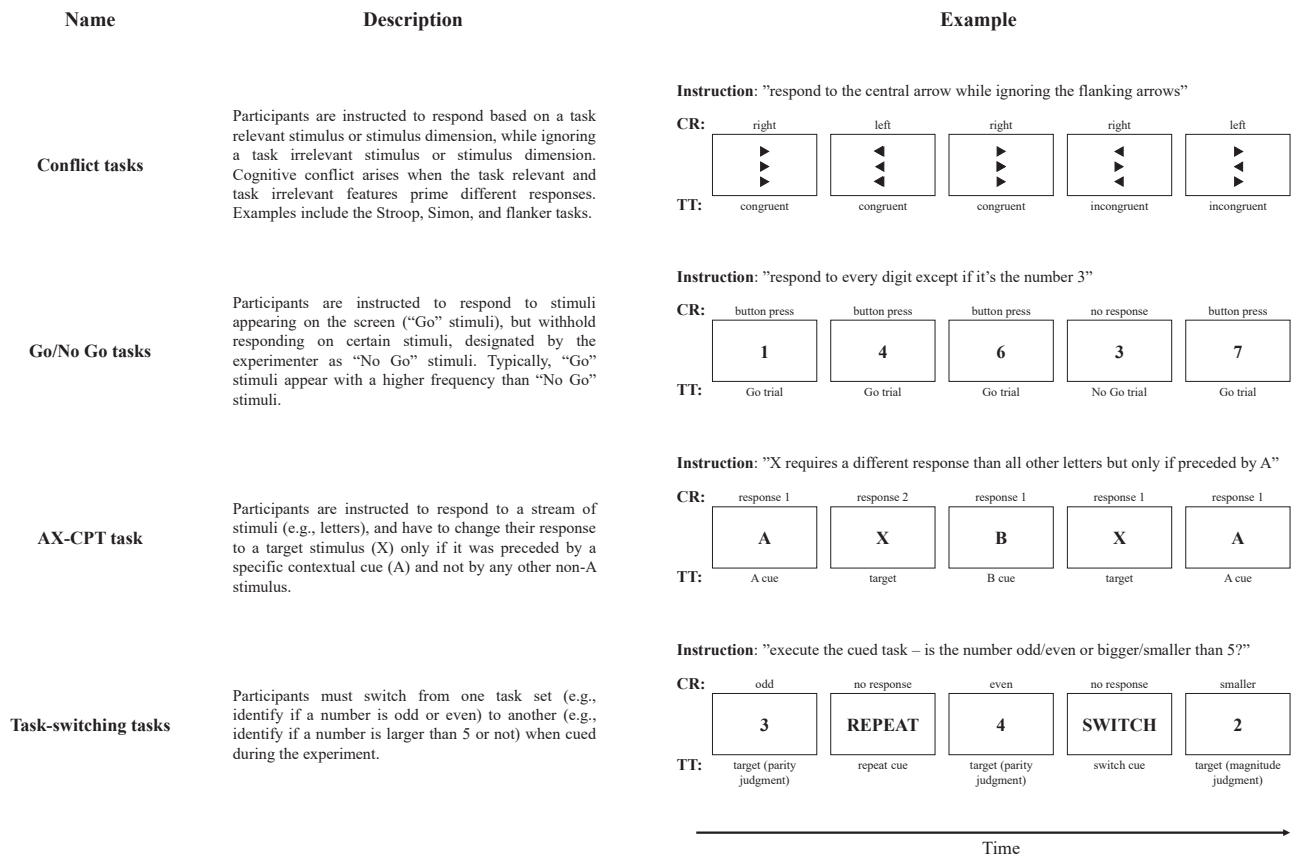
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The capacity to voluntarily guide behavior in a goal-directed fashion is dependent on the ability to accommodate changing internal states and external circumstances and override routine and habitual behavior, when necessary. This allows for the optimization of responses in changing or challenging environments (1,2). Understanding the mechanisms that underlie cognitive control is critical to perceiving why, despite the paramount importance of goal-directed behavior, this ability is often vulnerable to failure. This may be particularly useful for the delineation of specific mental health vulnerabilities in individuals with diagnosed mental illness. Mental disorders are a leading cause of disability and economic burden (3), and there is an urgent need to identify the mechanisms that contribute to associated atypical thinking and behavior (4,5). Deficiencies in behavioral and brain measures of cognitive control are associated with a variety of psychiatric disorders and conditions (6–9) and are predictive of poor daily life functioning (10,11). Individual differences in cognitive control measures positively correlate with personality variables such as emotional resilience and reward sensitivity (12–14), which are increasingly recognized as key indicators of mental health in the general population (15,16).

Recognition of the importance of cognitive control in human behavior has led to intensive research to characterize its

behavioral and neurobiological correlates (17). This research has emerged from a background of investigations of executive function, and while the terms cognitive control and executive function are largely interchangeable in the psychological literature, the former has recently become dominant, possibly because of the association of executive function with older neuropsychological constructs and particular batteries of tasks (18). While no standardized neuropsychological test specifically focuses on cognitive control, numerous experimental paradigms have been designed to capture the associated behavioral processes. Typically, these are speeded reaction time tasks (e.g., Stroop, Simon, Eriksen flanker, go/no-go tasks) involving interference or the need to overcome prepotent response tendencies (Figure 1).

Higher order control over behavior, including executive function, has long been seen as the function of the prefrontal cortex (PFC). Models of various aspects of cognitive control focus on two subdivisions of the PFC, namely, the dorsolateral PFC and the anterior cingulate cortex (6,18–21), which are central to the executive control network of the brain (22). While much is known about the anatomical distribution of cognitive control networks in the brain visualized using functional magnetic resonance imaging (fMRI), the slower time scale of fMRI



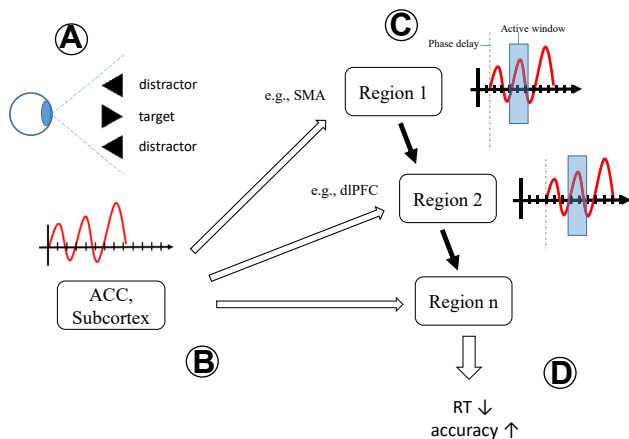
**Figure 1.** Experimental paradigms designed to capture behavioral processes associated with cognitive control. AX-CPT, AX-Continuous Performance Task; CR, correct response; TT, trial type.

makes the inference of associated natural neuronal millisecond phenomena difficult. The high temporal resolution of electroencephalography enables the study of neural activity underlying the rapid processing involved in the fast response selection and cognitive reactivity that is considered the essence of cognitive control. In particular, oscillations in the theta band (4–7 Hz) over medial frontal recording sites (known as midfrontal theta or frontal midline theta [FM $\theta$ ]), potentially reflecting the activation of thalamocortical feedback loops (23), are becoming increasingly established as a direct neural index of certain aspects of cognitive control (2,24,25). Repeated studies show that tasks that emphasize decision making in light of changing internal and external goals elicit frontal-midline neural activity, which manifests as brief bursts of theta oscillations that are time locked and, potentially, phase locked to relevant stimulus presentations (26–28) and/or motor responses (29).

### FUNCTION OF THETA ACTIVITY

Midfrontal theta power increases when information conflicts with or deviates from expectations, such as after cognitive conflict or errors (28,30–32), in contexts that involve uncertainty regarding actions and their associated outcomes (33). As such, an influential model of FM $\theta$  is that it signals the

need for cognitive control (25). More than this, however, theta may be a mechanism for how this need for control is biophysically realized and communicated across different brain regions (25). As with neural oscillations in other frequencies, FM $\theta$  is believed to facilitate information transfer by synchronized phase entrainment (34,35). The crucial role of theta in cognitive control may lie in cross-regional phase synchrony, through creating large-scale and rapidly adaptable functional networks whose main function is to optimize behavior under uncertainty (36,37). Within this model (Figure 2), rhythmic alternation between excitation and inhibition at midfrontal regions creates temporal windows for the transfer of goal-related information to other task-relevant regions, which oscillate at a similar frequency, having temporal windows of similar lengths, but with a phase offset to account for the delay that is due to the transmission time of signals. In this framework, theta provides the channels for control implementation, functioning as a common currency [i.e., theta lingua franca (27)]. Theta is thought to broadcast the need for cognitive control from the anterior cingulate cortex to task-relevant neural networks such as sensory or motor regions (35,38) to allow the brain to act flexibly and rapidly in response to conflict or changing task demands (23,25,39). Data from our own laboratory (unpublished) verifies that independent phase offset theta activity occurs in multiple



**Figure 2.** Midfrontal theta-modulated cognitive control. Here we depict an Eriksen flanker task in a human electroencephalography experimental paradigm. **(A)** The participant is instructed to respond with the left or right mouse button corresponding to the direction of the central target arrow, ignoring the possibly conflicting flanker stimuli above and below. The existence of potentially conflicting stimuli elicits the cognitive control mechanism. **(B)** Converging evidence from animal and human studies supports the hypothesis that the anterior cingulate cortex (ACC) is critical for cognitive control (123,124). Theta oscillations have also been localized to the ACC (37), supplementary motor area (SMA), and pre-SMA (125,126), and data from simultaneous electroencephalography and functional magnetic resonance imaging indicate that theta activity is associated with multiple brain regions, including most of the cingulate (127). **(C)** Local neural activity is known to be modulated by the phase of local field potential oscillations. These preferred theta phases constitute known temporal windows of activity. In this model, phase-offset theta oscillations in local field potential at various brain areas emerge owing to functional coupling between task-relevant regions. **(D)** By synchronizing and coordinating the timing of local activity across multiple regions, performance can be optimized. In the task shown, for example, the central target must be distinguished in the context of the appropriate motor program rule for responding with the appropriate hand. On motor execution, the performance evaluation must be made, and any necessary program adjustments must be made. By biasing the local field potential local active windows to coincide with the output of respective inputs, speed (reaction time [RT]) and accuracy of response can be optimized. Notably, while theta plays a central role in cognitive control by forming short-lived functional networks, faster oscillations, such as alpha and gamma, are also implied to have important functions in the maintenance and setting of goal-relevant representations (128). These spectrally distributed subprocesses might interact through local or interareal cross-frequency coupling, such as phase-amplitude coupling or cross-frequency synchrony (129). A comprehensive neurocognitive theory of control will need to take these phenomena into account as well. dlPFC, dorsolateral prefrontal cortex.

cortical regions, providing support for theta as a fundamental coordinating mechanism (Figure S1).

The critical role of FM $\theta$  in optimal behavioral responding has been underlined by a strong link between increases in theta activity in conflict conditions and improved performance in these conditions, indicative of employment of cognitive control [see (25)]. Studies have shown that, in addition to cognitive control tasks, FM $\theta$  power also increases in tasks that require sentence processing (40), memory encoding and retrieval (41–43), working memory, and short-term memory load (44,45). While ongoing theta activity may be present across multiple conditions, it is specifically altered in response

to current cognitive control demands and tracks with strategic behavioral adjustments (46).

Importantly, for the functional interpretation of theta, numerous studies indicate that trial-to-trial modulation of midline-central theta activity strongly relates to trial-by-trial strategic adjustments in behavior, including posterror, post-conflict, and postpunishment slowing (6,26,47). Single trial analysis allows the neural dynamics to be assessed on a trial-varying basis, thus better reflecting the ongoing flexible adjustments in behavior that cognitive control facilitates. Models of cognitive control differentiate between distinct modes of control: reactive control is a stimulus-driven corrective mechanism, mobilized to optimize behavioral performance in high-conflict situations, whereas proactive control is a more sustained process involved in optimally biasing attention to goal-relevant information (48). Frontoparietal connectivity in theta oscillations may have a critical role in the flexible management of these two modes of cognitive control (46,49). Trial-by-trial analysis indicates that reactive control conditions temporarily activate theta oscillations in the medial frontal cortex (MFC), but that the recruitment of theta oscillations in the dorsolateral PFC allows for the maintenance of information across trials (50).

## EVENT-RELATED MODULATIONS OF THETA ACTIVITY

The study of FM $\theta$  forms a bridge between the investigation of oscillatory activity and that of emergent event-related potentials (ERPs) associated with cognitive control tasks. In general, these ERPs project to the central midline of the scalp from prefrontal areas of the brain and appear during a similar time range (100–350 ms following stimulus/response). The most common ERPs associated with theta are the N2, the error-related negativity (ERN), and the feedback-related negativity (Table 1). In line with the unifying theory of FM $\theta$  as a fundamental cognitive control mechanism used in a wide variety of task contexts, a medial frontal signal derived from independent component analysis related strongly to the ERN, the N2, and the feedback-related negativity recorded during different conditions (51).

ERPs represent activity that is time locked and phase locked to a stimulus or a response (52). Theta-related ERP components are thought to reflect theta oscillations that have become phase locked to an event, either because the event resets the phase of ongoing theta oscillations after the stimulus (or response) event or because the oscillations are elicited de novo by the event itself [see (53 and 54) for more details on phase resetting and evoked models of ERP generation]. The distinction between phase reset and evoked theta is difficult to discern in the time domain using ERPs, as non-phase-aligned prestimulus theta would tend to average to zero in the ERP. Non-phase-aligned prestimulus theta activity can be detected, however, using time-frequency analysis (28,55).

A further benefit of time-frequency analysis is that it enables the estimation of the synchrony of oscillations at different brain regions in a given frequency and the intraregional or interregional interactions between the phase and amplitude of oscillations at different frequencies (55). Thus, time-frequency analysis enables investigation of rapidly changing functional

**Table 1. Properties of Theta-Related Event-Related Potentials Related to Cognitive Control**

Component	Occurrence	Approximate Latency	Relationship With Theta Oscillations
N2	Following signals for need for control, e.g., conflicting stimuli in Stroop, Simon, flanker tasks; or no-go stimuli in go/no-go tasks (33)	250 ms	Reflects phase-locked theta activity (6) generated by the ACC (130)
ERN	Following an incorrect response, typically in speeded paradigms (131), a related response-locked component is the CRN that yields a lower amplitude than the ERN	80 ms	Associated with an increase in theta activity (132) that may be generated by the ACC (130)
FRN	Following signals of loss of value or punishment, e.g., negative feedback, typically in gambling paradigms (133) constructed by subtracting ERPs from two conditions: loss condition potential minus gain condition potential	270 ms	Associated with an increase in theta activity and may be generated by the ACC (134)

All components are negative in polarity and have a frontocentrally maximal scalp distribution. Owing to the relative scarcity of studies focusing on the FRN in the selected disorders, results concerning this component are not discussed at length in the text.

ACC, anterior cingulate cortex; CRN, correct response negativity; ERN, error-related negativity; ERPs, event-related potentials; FRN, feedback-related negativity.

networks during cognition, in terms of both power modulation and phase relationships, which are crucial to assess the role of theta in large-scale cognitive coordination and control.

### ROLE OF THETA DYNAMICS IN PSYCHOPATHOLOGY

The ability to adapt our actions to dynamic environments and adjust information following errors or feedback is a hallmark of healthy goal-directed behavior. Multiple psychiatric disorders, however, are characterized by repetitive and inflexible behavioral patterns or an altered sensitivity to errors or feedback. The proposed critical role of FM $\theta$  oscillations across a variety of tasks and situations and flexibly coordinating these signals across the brain has led to an increased recent focus on its role in the development of psychiatric illness and associated impairments (56). Partly owing to the relative ease of analysis, time-domain trial averaging, as captured by ERPs, has dominated electroencephalography investigations of cognitive control in psychopathology. The ERN, specifically, owing in part to its ubiquity in cognitive control investigations of psychopathology, has been proposed as a transdiagnostic marker of internalizing-externalizing symptoms (57). It is likely that reducing FM $\theta$  to a single functional aspect (e.g., the ERN) limits the full functional significance of its role in psychiatric illness. The purpose of the current narrative review is to synthesize findings of the role of FM $\theta$  in psychopathology in the context of emerging knowledge of its role in brain function. Thus, we also advance hypotheses regarding how differences in FM $\theta$  signals impact behavior in psychiatric illness and propose future directions for basic and applied research. We focus on disorders on the internalizing-externalizing spectrum where research on FM $\theta$  has reached a critical point of sufficient investigation to approach some consensus with replication of key findings: anxiety, obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), and substance abuse (Table S1).

### Anxiety

Collective evidence suggests that anxious individuals show larger frontal-midline theta control signals than nonanxious individuals (33). Meta-analyses indicate that theta-related ERPs (N2, ERN, and feedback-related negativity) are enhanced in highly anxious individuals compared with individuals with low anxiety in nonaffective, cognitive control

tasks (33,58). Findings also indicate that increases in these signals are specific to uncertain situations and predict subsequent behavioral adaptation in the general population (33). Studies employing time-frequency analysis have also identified anxiety-related differences in FM $\theta$  dynamics. Dispositional anxiety was associated with increased theta power during risky decisions in a gambling task (59) and during threat anticipation [albeit in women only (60)]. Individuals with a diagnosis of generalized anxiety disorder have also been found to show enhanced theta-related control signals, both in the time domain (ERN and N2) and in the time-frequency domain [error- and conflict-related theta power (61,62)].

Anxious individuals are more responsive to signals of need for control, but they may be unable to translate these signals into proportionally greater mobilization of control as indicated by impaired behavioral performance (63) or no observable downstream effects of the exaggerated error monitoring (58). According to a cognitive control model of anxiety, anxious individuals are unable to alternate flexibly between proactive and reactive control modes in accordance with changing task demands: the distraction of worries depletes resources needed for active maintenance of task rules and goals (48). As a result, anxious individuals rely more heavily on reactive control. Given the central role of FM $\theta$  in both proactive and reactive control, research has yet to fully leverage the analysis of theta dynamics into specific subprocesses of cognitive control in anxiety disorders. Adequate reactive control does not always relate to improved accuracy: both adaptive and nonadaptive responses can be observed following error detection and posterror slowing (64). A recent study in the general population isolated prerespone and postrespone theta dynamics within the same epochs during an Eriksen flanker task and found that accurate responses were dependent on prerespone theta connectivity between the MFC and the lateral frontal cortex (LFC), whereas posterror behavioral changes (including posterror slowing) were linked to postrespone MFC-LFC connectivity (65). In optimal cognitive control, the MFC interacts with the LFC in a dynamic loop to recruit greater control and improve performance (25,66). Theta connectivity between the MFC and LFC (interchannel phase synchrony/connectivity) has been shown to have a causal role in adaptive task-related behavior, including reaction time variability (RTV) and accuracy (67). Interareal connectivity between the MFC and LFC may be a critical mechanism for the

lack of cognitive flexibility in recruitment of top-down control in anxiety disorders (24). Future work examining the phase connectivity of theta dynamics during response conflict tasks is likely to illuminate differences in subprocesses of cognitive control in anxiety disorders. Trial-by-trial analysis could further test the role of stability in FM $\theta$  in transient control processes versus ongoing control adaptations in anxious individuals and the interplay between them.

### Obsessive-Compulsive Disorder

OCD is characterized by repetitive behaviors that aim to neutralize intrusive thoughts that elicit stress and fear but are time-consuming and lead to significant functional impairments and reduced quality of life (68). People with OCD often report that an action was not performed well or completed and thus another action is required to compensate (69). These symptoms stimulated the first studies of cognitive control in individuals with OCD, which proposed that symptoms, similar to anxiety, are the result of an overactive error monitoring system (70). Complex compulsions may develop when the error signals remain active, thus repeatedly triggering a need for corrective behavior. In support of this, a recent meta-analysis indicated that individuals with OCD consistently show increased amplitude of the ERN across the life span (10–65 years of age) (71). These findings mirror the results of a meta-analysis of fMRI data that indicated hyperactive error-related activity in the anterior cingulate cortex (72). Severity of symptoms has been correlated with ERN amplitude in some studies [e.g. (73)], but an increased ERN has also been shown in subclinical populations (71).

The largest differences with healthy control subjects are found in tasks that emphasize speed over accuracy, as individuals with OCD may fail to downregulate their ERN. A slower, more cautious response strategy in the disorder is consistent with findings of a reduced error rate and slower reaction times (74). Similarly, studies report enhanced amplitudes of the N2 component in conflict monitoring tasks in patients with OCD with slower reaction times during trials with high conflict (75,76). In an approximation of a real-world manifestation of OCD, an increase in FM $\theta$  was observed during provocation of OCD symptoms (77). Furthermore, deep brain stimulation targeting the nucleus accumbens (NAc) was found to attenuate the increase in FM $\theta$  band power. This is in accordance with previous findings that indicate that FM $\theta$  oscillations modulate activity in the NAc (78,79) and builds on extensive fMRI research that indicates a central role of the NAc in OCD [e.g. (80)]. While further work is required, FM $\theta$  may have a central role in the overactive cognitive control system in patients with OCD (81), in agreement with cognitive models of OCD that propose that excessive stimulus habit formation and a failure to suppress irrelevant stimulus-driven behaviors in the disorder are a result of reduced proactive control (72,82).

### Attention-Deficit/Hyperactivity Disorder

One of the defining characteristics of ADHD is ineffective control of behavior in cognitive, emotional, and social domains (83). The amplitude of theta-related ERPs, especially the N2 and the ERN, has been found to be attenuated in individuals

with ADHD compared with healthy control subjects, suggesting deficient error and conflict monitoring (7,84–87). A recent meta-analysis indicates, however, that these findings are not universally agreed upon (88), and it is likely that event-related theta oscillatory measures can provide more insight into inefficiency of cognitive control in individuals with ADHD. A study that identified no differences in the ERN found decreased response-locked intertrial theta phase coherence (a local measure of the degree to which the phase of the signal aligns across trials, independent of amplitude) between participants with ADHD and healthy control subjects (89). Similarly, another study found that ADHD was related to increased variability in phase onset of stimulus-locked FM $\theta$  (6). Both of these studies found that phase consistency in FM $\theta$  was associated with performance, as indexed by RTV. ADHD is characterized by instability in behavior, usually measured in the laboratory as RTV (90) and an impaired ability to regulate speed-accuracy trade-offs (91). Recent studies further showed that event-related amplitude changes in theta predicted RTV (92) and that these findings may extend to phase-independent theta oscillations (93). These findings led to a proposal of dysregulation of theta signaling as a mechanism for failure to implement and optimize task-relevant responding in ADHD (6). A future avenue of research may be to examine the extent to which less consistent FM $\theta$  oscillations in ADHD represent impaired information transfer in the brain and its subsequent effects on the adjustment of behavioral responding. In addition to increased RTV, individuals with ADHD may have absent or delayed posterror slowing (93).

### Substance Abuse

Theoretical models of substance abuse disorders have long implicated impaired cognitive control as a crucial risk factor for, and consequence of, problematic substance use (94). There is evidence to suggest conflict- and error-related hypoactivation in people with substance use disorder, as both the N2 and the ERN are typically attenuated in substance abusers compared with healthy control subjects (95). The ERN has also been found to predict relapse in cocaine users (96). ERN findings in alcohol dependence are more mixed, with some studies reporting an enhanced ERN potentially secondary to comorbid anxiety (97,98) and others reporting an attenuated ERN in line with other types of addictions (99).

Studies examining event-related theta activity in alcohol use disorder (AUD) have more consistent findings. During oddball and go/no-go tasks, reduced FM $\theta$  has been found in participants with active AUD and those with short- and long-term abstinence (100–102). These effects may be a risk factor for AUD, rather than a consequence of the disorder, as reduced FM $\theta$  in early adolescence predicts problematic drinking (103). Family- and twin-based tests of etiology suggest that the relationship between AUD and FM $\theta$  power is best accounted for by genetic influences (104–106), but that specific theta-related alterations may be related to deleterious effects of alcohol abuse in women (107). Future longitudinal research is necessary to examine the potential feedback loops that might exist between theta-related neural changes and alcohol abuse. Reduced FM $\theta$  power may share genetic influences with problematic substance use in general (108). This

study also identified a strong genetic relationship between FM $\theta$  power and inconsistency in responding (RTV), confirming an earlier study in ADHD (6). In line with this, reduced intertrial phase locking of theta is associated with substance use disorder (in addition to general externalizing pathology) (109).

## DISCUSSION

Theta oscillatory dynamics, in both the time and the time-frequency domains, differ in several clinical populations compared with healthy adults during task performance. These theta-related changes provide insight into the fundamental nature of the cognitive subprocesses that are affected in psychiatric illness. The ERN is the most commonly investigated theta-related ERP signal. While an attenuated ERN has been observed in individuals with ADHD and substance abuse, larger ERNs are typically found in anxious individuals and individuals with OCD. These initially seem to point toward a relationship between amplitude of the ERN and internalizing-externalizing pathology. Closer examination of these findings indicate that it may not be that straightforward. Findings in externalizing disorders are more mixed than they initially appear with a recent large meta-analysis on ADHD indicating that both the ERN and the N2 are inconsistently associated with the disorder (88). Furthermore, while OCD and anxiety are associated with enhanced reactive control, as indexed by an increased ERN, investigation of the timing of atypical theta dynamics in conjunction with performance deficits indicates that there are likely effects of impaired proactive control, which may be central to the disabling symptoms of these disorders. In support of this model in anxiety, training and development of proactive control is associated with a reduction in stress in anxious individuals (110) and with avoiding the development of social anxiety in at-risk children (111).

Central to the role of FM $\theta$  in psychopathology may be its role in coordinating brain activity (Figure 2). ADHD, in particular, may be characterized by irregular local phase synchrony in FM $\theta$  oscillations, which strongly relate to variability in behavior across a number of studies [e.g. (6)]. Evidence from disorders outside the internalizing-externalizing spectrum may provide insight into how theta dynamics relate to instability in task engagement. An extensive literature in schizophrenia indicates that neural oscillations may be central to cognitive deficits in schizophrenia (112). Moreover, recent studies have suggested that the dysfunctional activity of the theta band (113,114) and, more specifically, the phase coherence of theta oscillations across trials (115) may underlie reduced cognitive control efficiency in patients with schizophrenia. A recent study found that local, cross-trial phase coherence in the MFC and lateral PFC was specifically reduced in individuals with schizophrenia during periods of increased RTV and increased errors (116). The emerging evidence for atypical phase synchrony in externalizing disorders (ADHD and substance abuse) may translate into less efficient communication across task-relevant networks. However, the extent to which these differences reflect deficient functional coupling between brain regions or interregional information processing is largely unexplored (35,117).

Future work is necessary to unravel these interactions and their dynamics, particularly, during periods of low versus high variability to objectify dynamics of engagement during cognitive control tasks.

FM $\theta$  may have a specific role in provocation and/or management of OCD symptoms, at least partly modulated by the functional connections between the MFC and the NAc (77). Deep brain stimulation of the NAc is emerging as an effective treatment for symptoms of OCD [see (118)], but it is an invasive procedure with potentially serious adverse events (119). Stimulation of the MFC (using transcranial direct current stimulation) synchronized the timing of theta oscillations across trials in patients with schizophrenia and resulted in normalization of their posterror slowing so that their performance was indistinguishable from healthy control subjects (115). Direct stimulation of theta can overwrite its irregular phase synchrony and improve multiple components of adaptive behavior (67). These effects outlast the period of electrical stimulation and were still apparent 40 minutes later. Further work is needed to build on basic and clinical work in FM $\theta$  to determine the applicability of theta modulation as a therapeutic tool for other psychiatric disorders that manifest with severely disabling symptoms, including OCD.

Although the contribution of resting-state studies to clinical neuroscience is unquestionable [e.g. (120)], we excluded these studies from the current review because of the lack of experimental control in these designs. Furthermore, the conflation of 1/f-like aperiodic activity and oscillatory activity that is common in such studies complicates the interpretation of group differences in neural activity (121).

The dimensional approach to understanding psychopathology is clearly expressed in the Research Domain Criteria framework, which focuses on basic dimensions of functioning across a spectrum and not on diagnoses based on heterogeneous clusters of symptoms (5). It may be that the neural and behavioral manifestations of cognitive control can be similarly characterized, from high to low cognitive flexibility, rather than based on functionally discrete single metrics (e.g., ERN). Although FM $\theta$  is unable to capture the full scope of cognitive control deficits in psychopathology, the ubiquity of vulnerabilities related to cognitive control processes indexed by FM $\theta$  signifies its central role in multiple disorders. While there are highly promising initial findings, research of the pathophysiology of psychiatric illness has yet to fully leverage analysis of theta oscillations, particularly of theta-coordinated cognitive networks, in an effort to parse cognitive control at finer levels of detail. Such work could provide a better foundation for the development of neurophysiologically inspired and neurobiologically plausible theories of how cognitive control is implemented by brain circuits in psychopathology to build on the advances in knowledge of the microcircuitry of FM $\theta$  [see (122)]. Interventions that aim to establish intact dynamic FM $\theta$ -related cognition could be powerful for ameliorating the symptoms and broad functional impairments prevalent across psychiatric disorders.

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## ARTICLE INFORMATION

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