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A neural microcircuit for cognitive conflict detection and signaling

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During human response conflict – competition between multiple conflicting actions when a mistake could be made – a specific pattern of brain electrical activity occurs over the medial frontal cortex (MFC), characterized by modulations of ongoing theta-band (~6 Hz) oscillations and synchronization with task-relevant brain regions. Despite the replicable and robust findings linking MFC theta to conflict processing, the significance of MFC theta for how neural microcircuits actually detect conflict and broadcast that signal is unknown. A neural MFC microcircuit model is proposed for processing conflict and generating theta oscillations. The model makes several novel predictions for the causes and consequences of MFC theta and conflict processing, and may be relevant for understanding the neural implementations of related cognitive processes.

> It is a law of nature we overlook, that intellectual versatility is the compensation for change, danger, and trouble... Nature never appeals to intelligence until habit and instinct are useless. H.G. Wells, *The Time Machine*.

Cognitive control, conflict processing, and the need for biologically inspired theories

Cognitive control refers to the ability to monitor one's actions and the external environment for mistakes, conflicts, and negative performance feedback, and to initiate rapid but flexible action adjustments to optimize goal-directed behavior [1,2]. It is one of the most important sets of cognitive functions for success in a complex and rapidly changing world, and individual differences in these abilities predict real-world outcomes including academic success and career choices [3,4].

The need for cognitive control is perhaps strongest in situations of response conflict, in which multiple competing actions are activated but only one is appropriate and should be selected. Response conflict is epitomized by the well-known Stroop task [5], in which one responds to the color of a font rather than the meaning of the word (e.g., say 'red' when reading the word 'blue'). It is becoming increasingly clear that impaired cognitive control is a hallmark of several disorders ranging from attention deficit hyperactivity disorder (ADHD) to schizophrenia to obsessive-compulsive disorder [6–8].

Psychological and cognitive neuroscience theories of cognitive control abound [9,10], but most extant models are built on abstracted assumptions rather than on neurobiologically plausible foundations. This gap between model assumptions and neurobiology hinders progress in understanding the neural mechanisms underlying (as opposed to correlates of) conflict processing. Many current models that claim to be neurobiological or neurobiologically informed are so in name only, and are better characterized as 'box-and-arrow' models. For example, many cognitive control models have a box labeled 'anterior cingulate cortex,' but there are no neurobiological constraints that make that box resemble the cingulate any more than it could resemble lateral prefrontal cortex, thalamus, or retina. Futhermore, equations of the form $c = wa_1a_2$, which are used in some cognitive control models [11], to compute the amount of conflict as a weighted combination of the activation of two responses cannot be considered biologically informed or constrained any more than a linear regression ($y = mx + b$) is biologically constrained. Other models that include biologically constrained neurons [12] lack sufficient specificity to account for the empirical neurophysiology data described later in this paper.

The box-and-arrow approach of cognitive modeling was an important first step that was necessary to begin integrating cognitive psychology with neuroscience, and this approach has taken us a long way. However, as neuroscientific knowledge has increased over the past decade it has become apparent that the neophrenological 'brain region X performs cognitive process Y' approach is too simplistic to provide deep insights into the neurophysiological mechanisms of cognition. 'Biologically inspired' models that contain little or no biological plausibility may be useful as descriptive models for characterizing task performance or functional magnetic resonance imaging (fMRI) activations, but provide limited insights into the neurophysiological mechanisms of cognitive computations, and cannot easily be integrated into advances in the neuroscientific understanding of how the brain represents, processes, and transmits information. In part this is because many cognitive control theories were developed to fit patterns of behavioral task data or fMRI activations; they were not developed to account for functional, cytoarchitectonic, or physiological properties of the brain [13].

The purpose of this paper is to review recent findings that provide insights into putative neurophysiological mechanisms underlying conflict processing, and to propose

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a model that can account for key features of conflict processing and its neural manifestations in humans, while relying solely on known neurophysiological and biophysical mechanisms. This new model generates precise and testable (and, in a few cases, surprising) hypotheses that may help understand how high-level cognitive processes can be implemented at the level of neural microcircuits and dendritic computations, and what implications those neural microcircuit dynamics might have for the timing of behavior.

Behavioral manifestations of conflict

Response conflict occurs when one response is automatically activated by a task-irrelevant feature (such as the physical location of the stimulus) whereas a different response is activated by the task instructions that often entail arbitrary stimulus–response mappings such as pressing the left-hand button for a purple stimulus. The competition between the fast automatic response and the slow task-relevant response [14] generates conflict, particularly when subjects are encouraged to respond quickly [15]. At a conceptual level, this process can be reasonably approximated as a weighted multiplication of motor activation magnitudes [16]. There are several tasks to manipulate response conflict and measure its effects on behavior, including the Stroop task described above, and the 'Simon task' [17,18] (Figure 1A).

The effects of conflict on behavior depend on the recent trial history of conflict, a phenomenon known as the congruency sequence effect [19]. Though highly replicable, the nature of congruency sequence effects depends on several variables, including the type of task, the duration of the intertrial interval, and instructions such as a speed–accuracy trade-off. In the flankers task, for example, current-trial behavior is less strongly influenced by conflict when the previous trial contained conflict. In spatial conflict tasks such as the Simon task, the conflict effect may even reverse after incongruent trials (Figure 1B). In the Stroop task, negative priming can occur, which means that the response to a stimulus is impaired when that stimulus was ignored in the previous trial. The common theme across these effects is that behavior and brain activity on the current trial are strongly influenced by the congruency of the previous trial.

Although the existence of congruency sequence effects is not debated, the underlying causes remain a contentious issue in the cognitive psychology literature. Sequence effects have variously been attributed to conflict adaptation [11,20], expectations of near-future events [21,22], task- or set-switching costs [23], feature binding or response repetitions [24,25], proactive versus reactive control [26,27], negative affect-induced attention [28], and several other accounts [29]. This debate often involves designing increasingly complicated experiments to rule out increasingly detailed potential alternative explanations. Below it will be argued that a neuroscientific perspective may facilitate a concise and parsimonious explanation for at least part of the congruency sequence effects.

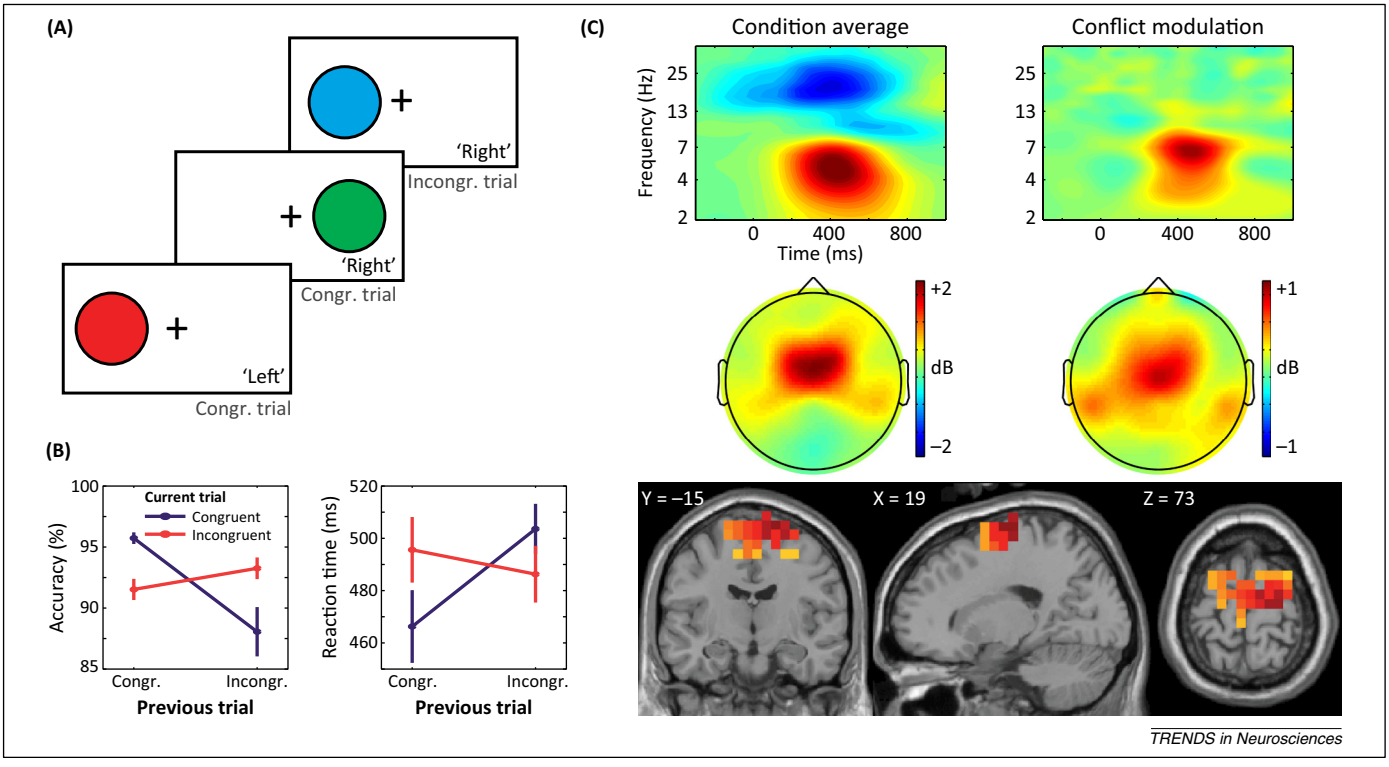

Figure 1. Example conflict task and representative findings. **(A)** The 'Simon task,' in which subjects respond as quickly as possible to the color (task-relevant feature) while ignoring the location (task-irrelevant feature). During 'incongruent' (i.e., high conflict) trials the stimulus is on the opposite side to the required response. This increases reaction times and error rates. **(B)** Typical behavioral findings from the Simon task. The effect of conflict on the current trial depends on the conflict in the previous trial. **(C)** Typical EEG results from the Simon task, showing modulations in non-phase-locked theta-band power over midfrontal scalp electrodes ('conflict modulation' refers to the difference between incongruent and congruent trials). Brain-space estimation algorithms suggest a source of this conflict modulation in or around the supplementary motor area. Panels B and C were adapted, with permission, from [41] and [56], respectively.

Electrophysiological manifestations of conflict processing

Many cognitive control processes have been associated with the MFC. Conflict per se engages the (pre-)supplementary motor area more than the anterior cingulate cortex [30]. Much has been learned about the brain regions involved in cognitive control from studying the fMRI blood oxygen level-dependent (BOLD) response [1,31]. However, due to uncertainties in the precise interpretation of the BOLD response [32–35], findings from electrophysiological investigations provide firmer grounding upon which to develop a neuroscientific account of conflict.

Time-frequency-based data analyses of electroencephalography (EEG) data allow inferences regarding neural oscillations [36], and have revealed that the neural response to conflict is an increase in theta band (4–8 Hz) power over midfrontal electrodes [37–41] (Figure 1C). Despite being a temporally brief response (several hundreds of ms), the conflict-modulated theta power is non-phase-locked to stimulus onset or to button press [42]. This suggests that conflict is processed in the MFC within burst-like dynamics during ongoing endogenous theta oscillations, rather than as an additive stimulus-evoked transient activation or phase reset.

The relationship between midfrontal theta and conflict processing is further strengthened by findings that trial-varying fluctuations in non-phase-locked theta power predict reaction times during conflict trials, a finding that cannot be explained simply as a relationship with manual responses or 'time-on-task' [37,42]. Conflict-modulated midfrontal theta is robust to the type of task and analysis procedure or parameters, is observable in individual subjects, and has high statistical power (>0.9 with only 18 subjects [42]).

As discussed in Box 1, conflict processing entails both the detection of conflict and the broadcasting of that conflict signal to modulate processing in sensory, motor, and attention systems. Evidence suggests that midfrontal theta is a key part of the substrate for this long-range communication: Functional connectivity, measured through a variety of linear and nonlinear analysis techniques (including power correlations and Granger prediction, but mainly phase synchronization), shows theta-band conflict- and control-related electrophysiological coupling between MFC and task-relevant cortical regions including lateral prefrontal, parietal, and motor cortices [37,41,43–47], and between MFC and task-relevant subcortical structures, including the ventral striatum and subthalamic nucleus [44,48]. Because the conflict modulation of theta power is non-phase-locked to stimulus or to response (and thus reflects changes in ongoing theta amplitude rather than phase perturbations), and because conflict-modulated long-range connectivity manifests as phase synchronization, it can be inferred that the theta oscillations in non-MFC brain regions become phase-locked to ongoing MFC theta oscillations.

To summarize, the electrophysiological literature has consistently demonstrated two key conflict-related findings: (i) a brief, non-phase-locked increase in MFC theta power that correlates both with discrete manipulations of conflict (conflict vs no-conflict trial types), and with variable manifestations of conflict (reflected in trial-varying reaction times); (ii) task-relevant brain regions become phase-locked to ongoing MFC theta-band oscillations. To understand how the brain implements conflict processing and related cognitive control functions, we need to understand the significance of MFC theta for underlying physiology and the physiological implementations of neural computations.

Theta is theta is theta?

Memory [49], feedback and feedback-driven learning [50,51], response errors [52], other cognitive control processes [38,53], and quiet resting [54] have also been associated

Box 1. Parameters relevant to conflict processing

Conflict processing

'Conflict' arises when multiple responses are activated but only one can be engaged (see Simon task description in Figure 1A). Conflict is typically studied in terms of competition between two fingers pressing different buttons, but it is possible that competition between other, non-motor-related representations may be processed using similar brain mechanisms (also Box 2). Conflict processing involves three distinct stages: (i) the conflict must be detected, (ii) this conflict signal must be transmitted to other brain regions, and (iii) the transmission must be implemented to adapt behavior. Situations that produce conflict are associated with slower decision-making and increased chance of errors.

Congruency sequence effects (also known as trial sequence effects)

The impact of response conflict on behavioral performance and accompanying brain activity depends on how much conflict has been experienced over the past several seconds. Though a highly replicable effect, many psychological explanations have been proffered, and the issue remains hotly debated.

Electrophysiological oscillations

Neural oscillations are rhythmic (e.g., sinusoid-like) fluctuations in electrical activity. They are observed in the nervous system over an impressive range of spatial scales (from single dendritic branches to the coordinated activity of billions of neurons during sleep) and temporal scales (from <0.01 Hz to 600 Hz), and have been linked to a variety of biological, psychological, and disease-related processes [119]. Oscillations in specific 'bands,' or narrow frequency-ranges (e.g., theta: 4–8 Hz, or alpha: 8–12 Hz) are shaped by combinations of cellular morphology, biophysical properties, and patterns of connectivity. Because of their fundamental and multiscale nature, oscillations are an important feature of brain activity that can help to bridge findings across myriad spatiotemporal scales and analytical techniques.

Laminar structure of the cortex

The neocortex has a remarkably consistent vertical organization that predicts the characteristics of cell types, local and long-range connectivity, and computational functions. Much of the cortex has six layers, although some areas have more or fewer subdivisions. The MFC, for example, contains no layer 4, which is the primary thalamic input layer in many other cortical regions. Developments in neuroscience are showing that interactions within- and across-layers are more important for brain function than was previously thought, and are likely to be of increasing importance to neuroscientific theories of cognition and perception [120].

Columns and microcircuits

In addition to the vertical organization of the cortex, there is also a horizontal organization. Groups of neurons are clustered into columns that are around a millimeter or less in diameter. Columns are one manifestation of a microcircuit – or an ensemble of a few dozen to hundreds of neurons that work together to support one function or set of related functions.

with theta oscillations in the prefrontal cortex. At initial glance this may suggest that theta oscillations serve a single functional purpose that is common to all cognitive processes supported by the prefrontal cortex. Alternatively, it is possible that the intrinsic architecture of the prefrontal cortex supports theta-band rhythmogenesis, and that heterogeneous computations manifest at the macroscopic level as theta-band EEG fluctuations.

Careful inspection of the available data suggests that the latter scenario is more likely. Response errors and feedback learning are conceptually similar to conflict, and are associated with frontal theta [45,50,51,55]. Errors and conflict can be difficult to disambiguate: many errors occur because conflict is experienced. Four key pieces of evidence, however, suggest that errors and conflict reflect distinct neurophysiological mechanisms: (i) the error-related theta comprises both phase-locked and non-phase-locked power [55] whereas conflict-related theta contains only non-phase-locked oscillations [39,42,48]. (ii) Both conflict-related and error-related activity begin before and continue until after the behavioral response, but conflict-related theta peaks before the response whereas error-related activity peaks after the response. (iii) Subtracting conflict-related theta from error-related activity reveals that errors are uniquely associated with delta-band (~2–4 Hz) power; there is little residual error-related theta power after removing that attributable to conflict [43]. (iv) Within-subject brain–behavior correlations show that although conflict-related theta power is positively correlated with reaction times, error-related delta/theta power is negatively correlated with reaction times [43,56]. The theta associated with negative feedback during stimulus–response learning, unlike that associated with conflict, has a strong phase-locked component, as well as a more anterior and somewhat right-lateralized topographical distribution [50,51,57]. Theta oscillations during memory encoding and retrieval are observed in several non-MFC prefrontal regions, as well as in the medial temporal and parietal lobes, and are generally temporally sustained [49,58–63]. Thus, the spatial–temporal characteristics of memory-related theta appear to differ from those associated with response conflict. Although the same M/EEG topographical distribution could be driven by different neural generators, different topographical distributions imply different neural configurations.

Thus, careful consideration of the available evidence indicates that the EEG manifestation of conflict is different from that of other cognitive control processes associated with prefrontal theta (Box 2), and is likely to differ from theta oscillations during resting-state. It is therefore equally striking that EEG signatures of different manifestations of conflict elicit a similar spatial–temporal–frequency pattern, including the main effect of conflict, conflict-related congruency sequence effects, and conflict-related brain–reaction-time correlations. These similarities, and their collective differences with EEG correlates of other cognitive processes, suggest that conflict processing might be implemented by a specialized microcircuit in the MFC that produces theta oscillations measurable with EEG. In the next section, such a microcircuit will be introduced.

Box 2. How specialized might this specialized MFC microcircuit be?

Many neuroscience theories of microcircuit function propose that canonical microcircuits are nearly ubiquitous and roughly homogenous throughout the cortex. Other discussions, as well as empirical data, suggest considerable heterogeneity such that only a few core features of microcircuits are ubiquitously expressed, whereas other features are specific for brain region and function. Is the microcircuit described here responsible only for the type of response conflict experienced in the Stroop or Simon tasks, or is it a generalized canonical microcircuit for cognitive conflict – and how does it interact with circuits for related behaviors such as reinforcement learning [121]?

Cognitive specialization

There are many forms of conflict, such as conflict of emotions, religious or political beliefs, memories, and the conflict (known to all scientists) between theory and data. The section 'Theta is theta is theta?' suggests that response conflict may elicit a spatial–temporal–spectral neural signature that is distinct from that of other related cognitive processes. It is possible that this microcircuit is highly specialized for response conflict, but is recruited during cognitive processes that, although not typical response conflict tasks, nonetheless evoke response conflict. For example, memory retrieval may incite conflict when interference from semantically related memories causes uncertainty as to the correct memory. Perhaps the microcircuit described here is repeated, with slight variations, in other prefrontal cortical areas for processing different types of conflict.

Anatomical/functional specialization

The anatomical and biophysical properties of MFC neurons differ from those of other, particularly sensory, cortical regions. For example, MFC neurons have strong reciprocal excitatory (AMPA-mediated) interconnections, fewer parvalbumin-positive interneurons, theta-band bursting properties, facilitative short-term plasticity, and modulation by dopamine. These properties are not unique to the MFC but are expressed in higher proportion compared to other prefrontal and sensory cortices [83,91,94]. Although this may seem a minor shift, nonlinear interactions in a complex system may result in major qualitative differences. The extent to which these properties optimize the MFC to process conflict is an open question.

A putative neural microcircuit in the MFC for conflict processing

Layers and microcircuits in the MFC

The MFC, similarly to the rest of cortex, is organized in a laminar fashion [64–66], with specific types of cells and patterns of connectivity within and across layers (Figure 2A). However, MFC regions implicated in conflict processing have relatively low cell density and few parvalbumin-positive interneurons [67], and contain no layer 4, which is the primary thalamic input layer. Although there are sparse inputs to layer 3 from the anterior and mediodorsal thalamic nuclei [68,69], it is unlikely that the thalamus plays a significant role in MFC theta oscillations (this can be contrasted, for example, with visual cortex, in which thalamic inputs likely have a strong role in alpha oscillations [70]). Indeed, laminar recordings in humans and non-human primates [46,71–73], analysis of single-cell spike timing [74,75], and the presence of theta-band oscillations in *in vitro* MFC preparations that lack long-range afferents [73] suggest that the MFC produces endogenous theta-band activity.

A microcircuit, similarly to a column, is a small vertically oriented ensemble of neurons that have strong intra-circuit connectivity and work together towards a common computation or set of related computations. Precise boundaries of

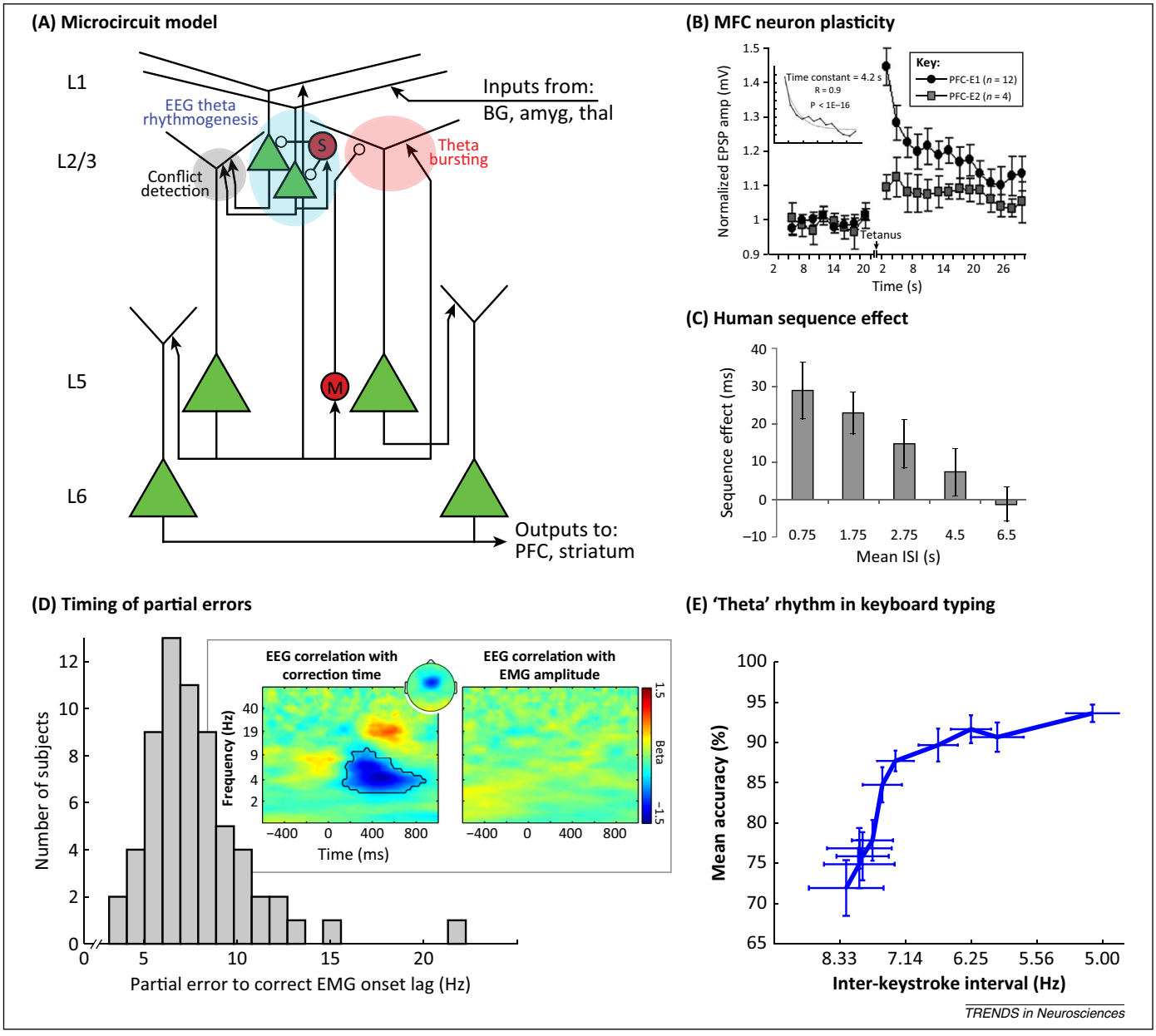

Figure 2. A putative specialized microcircuit in medial frontal cortex (MFC) for conflict processing, and its relationship to behavior. **(A)** Schematic overview of the major components of the microcircuit. Green triangles represent pyramidal cells; red circles represent Martinotti (M) or other somatostatin (S) interneurons. Arrows indicate excitatory connections; open circles indicate inhibitory connections. 'Theta bursting' refers to the empirical observation of short (2–4 cycles) periods of increased theta-band power. Abbreviations: amyg, amygdala; BG, basal ganglia; L, layer; PFC, prefrontal cortex; thal, thalamus. This microcircuit may be <1 mm in diameter. **(B)** Short-term synaptic plasticity in MFC layer 5 pyramidal cells (taken with permission from [83]). Individual layer 5 neurons were stimulated with 15 action potentials at 50 Hz (time 0), and the excitatory postsynaptic potential (EPSP, *y* axis) response to a single action potential was recorded at intervals thereafter (*x* axis). Neurons that express facilitation-dominant synapses ('E1') showed enhanced responses to stimulation with a decay time-constant of 4.2 s. **(C)** The magnitude of the congruency sequence effect in human behavior (that is, the effect of previous trial conflict on current trial behavior; *y* axis) decreases as the inter-stimulus interval (ISI) increases (taken with permission from [93]). It is suggested here that the type of neural plasticity illustrated in panel B may partly underlie the congruency sequence effect and its temporal decay. **(D)** 'Partial errors' refer to situations in which an error response was initiated but corrected before being fully committed. The time-lag between the partial error and the corrected response onset (also known as the correction time; measured through finger electromyography, EMG) was predominantly in the 'theta' band. Trial variations in correction time significantly predicted MFC theta power (faster correction times predicted increased theta), whereas the strength of the muscle response was unrelated to MFC theta (reproduced with permission from [43]). **(E)** Inter-keystroke intervals during keyboard typing show 'theta' rhythmicity over a variety of speed–accuracy trade-off instructions (Figure reproduced and *x* axis labels modified from ms to Hz, with permission, from [114]).

microcircuits may be poorly defined [76] but, in general, MFC deep layer cells provide a vertical anatomical 'bundling' within a microcircuit, and probabilities of synaptic connections within microcircuits are higher than probabilities of connections across microcircuits [66,77,78]. Although there are organizational principles that define a canonical microcircuit [66,79], there is considerable variability of microcircuits within and across brain regions [80,81]. For example, a recent study of neural laminar responses to flashes of light in the primate supplementary eye field [82] found that predictions from the canonical circuit model (based on sensory cortex) were only partly confirmed, with notable differences in the timing and spatial spread of activity. The microcircuit proposed here is thus a specialized MFC microcircuit for conflict processing.

Microcircuits exhibit oscillations and other complex spatiotemporal dynamics, perform computations that could be the basic building-blocks of cognition, and are

studied using computational, *in vitro*, and *in vivo* techniques. They are thus at an optimal spatial scale to bridge neurobiology, systems neuroscience, and cognitive neuroscience because they reflect a scale of functional organization that is larger than a neuron but smaller than a Brodmann area. As described below, each layer contains specialized neuron subtypes and unique patterns of connectivity that produce layer-specific functions. Nevertheless, the functioning within each layer is modulated by functioning in other layers.

Layer 5: conflict detection

Layer 5 is notable for its large pyramidal cells with apical dendrites that terminate in superficial layers. MFC layer 5 pyramidal cells have denser interconnectivity with other layer 5 pyramidal cells within- and across-columns compared to visual cortex [83]. Layer 5 pyramidal cells switch from slow-bursting to regular theta-spiking when driven by input currents [75,84].

Conflict detection is proposed to be implemented as coincidence detection in large layer 5 pyramidal cells (Figure 2A). Detecting temporally coincident synaptic events is one of the known dendritic computations in a neuron's 'toolkit' [85], and can be implemented through a variety of biophysical mechanisms – including voltage-gated NMDA-type glutamate receptor activation or sublinear synaptic summation in combination with a spike threshold. Multiple inputs (e.g., from layer 2/3 neurons, reflecting the activation of left and right hands; see next section) providing simultaneous synaptic input onto the same layer 5 neuron would switch that neuron to a regular theta-band spiking mode, which will then catalyze a chain of reactions that are described in the next sections. The extent to which synaptic inputs are spatially organized on the dendritic tree remains unclear [86], but it appears that afferents to MFC neurons have some dendritic topographical organization [87]. Nonetheless, coincidence detection relies on precise timing of synaptic inputs; recent findings in humans show that the timing of competing motor activations, rather than the amplitude of their corresponding muscle responses, is the crucial determinant of conflict-related theta [43] (Figure 2D).

The hyper-interconnectivity of MFC layer 5 pyramidal cells [83] ensures that activation of a small number of cells will quickly ignite an avalanche of synchronous theta-band spiking in a larger population. However, layer 5 pyramidal cells can also inhibit their neighbors indirectly via Martinotti or other somatostatin-positive inhibitory interneurons [88]. This dynamic would effectively shut down the deep-layer theta rhythmogenesis a few cycles after it begins, and thus may partly cause EEG conflict-related theta power to occur in brief, large-amplitude bursts.

The possibility of being rewarded or punished for accurate performance in conflict tasks modulates conflict-related theta power [89]. This modulation may result from limbic afferents into the MFC [87], and these in turn modulate the gain function of layer 5 pyramidal cells [90].

Layer 5 pyramidal cells express several forms of short-term plasticity, including synaptic augmentation, which means that after a period of intense stimulation the neuron is more reactive to synaptic inputs. Augmentation and other forms of synaptic facilitation are considerably higher in MFC compared to sensory regions (which predominantly show synaptic depression) [83,91], and may further contribute to burst-like responses [92]. In this microcircuit, synaptic augmentation of layer 5 pyramidal cells is hypothesized to be responsible for part of the congruency sequence effects observed after conflict is experienced (Figure 2B,C). When no conflict has been detected for many seconds (e.g., after a congruent trial in the Simon task), the neurons are less excitable and thus require stronger input over a longer period of time to be able to detect and signal coincidence (conflict). This would result in increased theta activity and slower reaction times. By contrast, after a recent conflict is detected, the layer 5 neurons are more excitable, and thus can detect coincidences faster and with less input, leading to overall less theta activity and faster reaction times.

Remarkably, synaptic augmentation in layer 5 pyramidal cells can last up to tens of seconds [91], with a decay time-constant of around 4 s [83]. This is similar to the decay time-constant of the behavioral manifestation of congruency sequence effects (that is, sequence effects decay with longer intertrial intervals) [26,93] (Figure 2B,C). Depending on the specific design features of the cognitive control task, the congruency sequence effect may be driven by a combination of processes such as learning, expectation, response preparation or suppression, selective attention, and conflict adaptation. Synaptic augmentation may be responsible for part of the congruency sequence effect, in combination with additional contributing factors.

Layer 2/3: input integration and theta oscillations

The theta oscillations measured by EEG cannot solely reflect layer 5 theta-band spiking. This is partly because EEG does not measure spiking, and partly because laminar recordings in the MFC of human epilepsy patients during cognitive control tasks show that the task modulations of the local field potential, as well as theta oscillations, are mainly present in superficial layers [46]. Thus, the EEG conflict-related theta may reflect oscillations in layer 2/3.

Layer 2/3 contains pyramidal cells that are generally smaller than those in deeper layers, with branching apical dendrites ideally suited to integrate, filter, and amplify incoming information [66]. Subcortical inputs to layer 2/3 dendrites include the basal ganglia, amygdala, and hippocampus [87], and cortical inputs include lateral prefrontal areas 9 and 46, insula, anterior cingulate, and several regions along the medial and lateral walls of the parietal cortex [94]. The information-integration role of layer 2/3 may be facilitated by afferents synapsing onto clustered regions of the dendrites [95,96]. The diversity of inputs implies that this microcircuit may by modulated by several forms of conflict (e.g., concerning memories or emotions), in addition to motor responses (Box 2).

MFC layer 2/3 can generate oscillations independently of the deeper layers [73], but nevertheless can strongly entrain layer 5 spiking [73,97,98]. Little is known about the primate laminar distribution of oscillatory activity and its relation to cell types, but layer 2/3 presumably contains inhibitory interneurons, such as the somatostatin-positive

interneurons in the mouse [99], which maintain theta rhythmicity under a variety of conditions and chemical environments. Layer 2/3 neurons also receive direct projections from layer 5 [100]. Thus, coincidence detection in layer 5 pyramidal cells would boost the ongoing layer 2/3 oscillations, presumably in service of amplifying the incoming signals from basal ganglia, amygdala, and prefrontal–parietal circuits. This amplification may occur in pulses according to the ongoing theta rhythm. Thus, layer 5 pyramidal cell spiking should be phase-locked to layer 2/3 theta oscillations, but layer 2/3 theta oscillations need not be phase-reset by an external stimulus or response. As with layer 5 interconnectivity, lateral connections from layer 2/3 neurons would marshal neighboring columns to boost overall theta-band activity. Relatively smaller pyramidal cells in layer 2/3 that produce faster oscillations [73,101] may cause conflict- and feedback-modulated theta-alpha coupling, which has been observed in human EEG [102].

Thus, careful consideration of the neuroscientific evidence leads to the novel and perhaps surprising claim that the theta oscillations recorded by EEG do not reflect conflict processing *per se*, but instead reflect the input integration process that leads to the detection of conflict.

Layer 6: long-range conflict signaling

MFC layer 6 contains a variety of output pyramidal cells with long-range projections to the superficial layers of distant cortical regions, such as lateral prefrontal cortex and premotor cortex [103], as well as to subcortical regions including the striatum, subthalamic nucleus, and midbrain dopamine region VTA [104,105] (for conceptual simplicity, layer 5 long-range output cells are functionally grouped into layer 6.)

Conflict-induced theta spiking of layer 5 pyramidal cells would activate these layer 6 output cells, causing theta-band phase-locking between MFC and frontal and subcortical networks, particularly when the long-range efferents synapse onto inhibitory interneurons [64,106]. However, conflict-modulated connectivity is observed with task-relevant brain regions, which shift according to task demands [38,44]. This leads to a homunculus problem – how do MFC layer 6 output cells 'know' to which region the conflict signal should be sent? One possibility is that the signal is transmitted to all target sites, but whether that signal impacts local processing depends on the activity levels at the target site. Such activity-dependent responses are a hallmark of top-down signals and may depend on NMDA receptors [107]. Furthermore, this same output signal will have different computational effects depending on the function of the target circuit. For example, the same output signal could induce the subthalamic nucleus to inhibit motor outputs transiently (which would further slow reaction times during conflict situations) [108], the lateral prefrontal cortex to enhance short-term memory and reactivate goal representations, the motor system to increase the thresholding for responses, and the visual system to increase visual acuity or attention.

Thus, the prediction is that whereas EEG MFC theta power reflects input integration in layer 2/3, EEG inter-regional theta phase synchronization reflects the transmission of the conflict signal from layer 6 to other brain circuits to be used to modify processing. To test this prediction in humans, novel experiment paradigms may be necessary to dissociate the integration of information that leads to a conflict signal (MFC theta oscillations stemming from layer 2/3) from the signaling of that conflict information to other brain systems (phase synchronization with layer 6).

Functional implications of MFC theta for action monitoring and conflict processing

Although research to date has unequivocally shown that human MFC theta oscillations are a marker of conflict processing, it remains unclear what functional role – if any – theta might have in the neural implementations of conflict computations. Modern theories on the role of brain oscillations in computation generally suggest that oscillations form a cyclic temporal reference frame for organizing information processing. In this light, the functional implication is that MFC theta may serve to provide a reference frame for monitoring and adjusting temporally sequenced actions. Because conflict detection relies on precise synaptic input timing, theta oscillations could enforce narrow windows for inputs to synapse onto layer 5 pyramidal cell dendrites. This raises the obvious question: why would theta be used instead of, for example, alpha or gamma? Indeed, neither scalp EEG nor intracranial studies in monkeys show cognitive control modulations of MFC gamma [71,109]. Of course, absence of evidence is not evidence of absence, but the available data suggest that the non-theta frequencies have little or no significant role in the primate MFC neurophysiology underlying conflict and related cognitive control operations.

A speculative answer as to why theta may be the preferred frequency band for conflict computations comes from the curious observation that many everyday and naturalistic behaviors that must be monitored and adjusted comprise temporally sequenced microactions that occur in the 'theta band.' Examples include keyboard typing, saccades, speech (most languages are uttered at a rate of 5–8 syllables per second), and visual–motor coordination [110–114] (note that not all 'theta-band' actions require monitoring and adjusting: giggling and shivering also occur with 'theta' rhythmicity [115,116]). It is tempting to speculate that the human MFC utilizes theta as a dominant speed for action monitoring because human muscle movements and microactions are dominated by 'theta-band' rhythmicity.

An important avenue for future research is therefore to test for a relationship between MFC theta and conflict during real-world behaviors that comprise 'theta-band' microactions. Decades-old computerized cognitive psychology tasks (Stroop, Simon, and flankers) may be poorly suited to test this hypothesis owing to their discrete trials with minimal action requirements that are separated by seconds of inactivity. Indeed, it is possible that the reason why the conflict modulation of theta power is so brief is that these tasks require only one response with few microactions.

The hypothesis that MFC theta provides a temporal reference frame for monitoring and adjusting temporally sequenced actions requires empirical investigation. If unconfirmed, an alternative possibility is that theta

Box 3. Outstanding questions and future directions

Laminar profile of theta oscillations and spiking in primate or human MFC
Many of the predictions outlined in the text are inspired by empirical findings but have not been directly tested. The validity of a neurobiology theory rests on the confirmation of its neurobiological predictions. Future research should build on existing work [46,82] to examine the vertical distribution of cell types, firing rates, and theta-band LFP oscillations in primates as well as in small animals (see below concerning species differences).

Interactions between theta and other neural dynamics during conflict processing
Theta oscillations and neural spiking are but two manifestations of neurophysiological activity. Is the model described here missing important dynamics that support the neural implementation of conflict processing? These dynamics could include activity in other frequency bands such as gamma (but see main text for lack of evidence of a role of higher frequencies in conflict processing), cross-frequency coupling, oscillatory amplitude asymmetries, microstate changes, and peak oscillation frequency fluctuations.

Exogenous modulation of MFC theta
If MFC theta serves an important role in temporally organizing conflict-related computations then externally modulating theta should modulate performance on tasks that require conflict processing or rhythmic action monitoring. Such manipulations could be performed in humans via transcranial electrical or magnetic current stimulation, or in animals using invasive electrical or optical stimulation.

Species differences
Animal models may be crucial to elucidating the neural mechanisms of conflict processing, but species differences in conflict processing exist between monkey and human [122]; to what extent can findings from rodents be generalized to understand human cognitive control? Some cross-species comparisons have been attempted [123], but the results appear to show little similarity between oscillatory signatures in rat versus human MFC (although no quantitative assessments of similarity were provided). Furthermore, if the hypothesis – that human MFC theta is related to microaction 'theta' – is confirmed, it is possible that action monitoring occurs in different frequency bands in different species, according to the speed of species-specific microactions. By contrast, owing to its fundamental nature, the functional and anatomical organization of the microcircuit may more conserved across species, compared to the behavioral or macroscopic EEG manifestations of conflict.

The role of neurochemistry
Dopamine and serotonin are involved in modulating both MFC activity and some aspects of cognitive control such as learning and working memory [2]. Direct empirical tests of theories implicating dopamine in EEG correlates of cognitive control [124] are largely lacking, but the available evidence suggests weak modulatory and perhaps complex roles of dopamine and other monoamines in conflict processing and associated MFC theta oscillations (reviewed in [2]).

Relationship between MFC theta and microaction 'theta'
Many behaviors that must be monitored and adjusted occur with rhythmic microactions in the 'theta' band (main text and Figure 2D,E for examples). Whether and how this rhythmicity is related to theta oscillations in the MFC microcircuit described here is unknown. Testing this hypothesis requires moving beyond the traditional discrete trial-based cognitive tasks, and towards tasks that elicit more naturalistic and real-world behaviors.

Implications for individual differences and brain disorders
Several disorders including ADHD, schizophrenia, and obsessive-compulsive disorder have been associated with aberrant patterns of cognitive control-related MFC theta oscillations. If empirical data confirm the relationship between EEG theta and the microcircuit model that is presented in Figure 2A in main text, will it be possible to infer abnormalities in microcircuit functioning based on patterns of EEG activity?

oscillations are not a necessary component of conflict processing but instead simply reflect the constraints governed by morphological and biophysical properties of MFC neurons and microcircuitry, including dendritic lengths and time-constants of various currents that result in band-pass filtering of synaptic inputs [74]. Conflict-related theta could also result from theta-rhythmic afferent inputs, and thus lack any specific computational role. It is important to stress that whether the theta rhythm proves to be necessary or epiphenomenal for the computations underlying conflict does not affect the use of theta as a sensitive and specific marker of conflict processing in MFC. Theta oscillations have proven highly useful for understanding the organization of human conflict processing, and their use in understanding human brain disorders involving cognitive control dysfunction is only beginning.

Concluding remarks

Multiscale and neurobiologically informed approaches to understanding the neural implementations of cognitive processes are becoming increasingly important, particularly because 'neural correlates of' studies may be approaching a ceiling of neurobiologically relevant insights [117]. As the neuroscientific understanding of how neurons and microcircuits implement computations becomes increasingly well understood, the biological plausibility of cognitive neuroscience theories must be correspondingly increased.

Regardless of how the predictions of this model hold up to empirical testing, the key to theorizing a neurobiologically plausible microcircuit model of conflict was the link between a cognitive process and its electrophysiological oscillatory correlates. Oscillations are one of the few fundamental functional features of the brain that are studied across nearly every spatial and temporal scale in neuroscience, ranging from individual synapses to 'default mode' networks [118]. Understanding the meaning and implications of neural oscillations may prove crucial for linking the multiple scales, species, and methods used in neuroscience (Box 3).

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