Executive Functioning Component Mechanisms and Schizophrenia

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Background: Executive functioning refers to a set of processes involved in complex, goal-directed thought and behavior involving multiple brain regions (e.g., prefrontal cortex, parietal cortex, basal ganglia) and multiple neurotransmitters (e.g., dopamine, glutamate, γ-aminobutyric acid). People with schizophrenia exhibit executive functioning deficits that are associated with treatment-refractory aspects of the disorder. Although there is general consensus about what cognitive tasks involve executive functioning, there is disagreement about the specific cognitive mechanisms that comprise executive functioning.

Methods: This article discusses a number of possible candidate executive functioning mechanisms and provides a summary of the consensus reached by the executive functioning discussion group at the first CNTRICS (Cognitive Neuroscience for Treatment Research to Improve Cognition in Schizophrenia) meeting in Washington, DC.

Results: The consensus was that two constructs have a well-founded basis in basic cognitive neuroscience research and seem to be impaired in schizophrenia: 1) rule generation and selection; and 2) dynamic adjustments in control (i.e., after conflict and errors).

Conclusions: The consensus of the first CNTRICS meeting was that immediate translation of measures of these constructs for use in schizophrenia should be pursued. A number of other constructs (e.g., scheduling, sequencing) could also be very important for schizophrenia and are in need of more basic and more clinical research.

Key Words: Cognition, executive functioning, performance adjustments, rule selection, schizophrenia

People are capable of complex, goal-directed thought and behavior, such as planning future actions, carrying out multi-part tasks, and overcoming habitual responses. Some of the cognitive processes involved in complex thought and behavior have been labeled executive functions (or more recently cognitive control) and involve the ability to dynamically adjust and regulate behavior on the basis of internal representations and feedback from the environment. People with schizophrenia exhibit executive functioning deficits (e.g., 1–3), and these deficits are associated with treatment-refractory symptoms, such as negative symptoms (4,5), and with poor functional outcomes (e.g., 6–8). At the same time, it has long been thought that executive functioning deficits might contribute to many of the other cognitive deficits observed in schizophrenia, such as deficits in working memory and attention (e.g., 9–13). The goal of CNTRICS (Cognitive Neuroscience for Treatment Research to Improve Cognition in Schizophrenia) is to identify cognitive neuroscience constructs and measures that can be used in testing interventions for impaired cognition in schizophrenia. Understanding the nature of executive functioning deficits in schizophrenia and being able to successfully treat these deficits has the potential to greatly improve the lives of people with schizophrenia.

Given that understanding the nature of executive functioning would greatly facilitate our ability to explain why humans are capable of complex thought (14), it is probably not surprising that understanding the specific mechanisms and components of executive functioning has proven challenging. One reason for this challenge is that it is often tempting to resort to concepts and ideas about a homunculus, which tends to get in the way of understanding the specific mechanisms that give rise to the set of behaviors thought likely to reflect executive control (14,15). A second reason for this challenge is that although cognitive neuroscientists tend to agree that some tasks clearly engage executive control (16), there are many such tasks that are used in many different studies. Furthermore, to the extent that researchers have attempted to identify specific aspects of executive functioning (e.g., set-shifting, goal maintenance), it is not necessarily readily clear to what extent any single specific task involves each of the different aspects of executive functioning. For example, consider the frequently used Wisconsin Card Sorting Task (17–19). Poor performance on this task could be due to a variety of cognitive impairments: problems in internally maintaining a task goal or rule; inability to dynamically adjust performance after error feedback; problems updating a previously held rule; difficulty in initially generating a rule to guide performance; problems selecting a particular response; difficulty in developing a strategy to perform the task; and others (for a list of possible executive functions considered by the CNTRICS executive functioning discussion group, see Table 1). Therefore, poor performance on this one task could be accounted for by impairment in a number of possible cognitive mechanisms. This can make it difficult to understand the nature of executive functioning deficits in people with schizophrenia when inferences are drawn on the basis of tasks that might be multicomponential. For example, it is not uncommon for different schizophrenia studies to involve the same set of tasks (e.g., Wisconsin Card Sorting task, verbal fluency, Stroop) and yet to group these tasks in different ways and to report results for presumably different aspects of executive functioning. Ideally, an understanding of basic mechanisms would help to account for interrelationships between different executive functioning tasks.

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Table 1. Candidate Executive Functioning Mechanisms

Mechanisms Recommended for Measurement Development
Goal Maintenance (discussed in working memory paper)
Rule Generation and Selection
Dynamic Adjustments in Control
Mechanisms Recommended for More Basic and More Clinical Research
Response Selection
Scheduling/Planning
Mechanisms Needing More Basic Research
Sequencing
Decision Making (note overlap with emotion/reward processing)
Strategy Development
Dual-Task Performance
Meta-Cognition/Insight

Given the challenges associated with understanding the global construct of executive function, one productive approach has been to try to delineate the specific component processes that make up executive function, rather than treating it as a global domain. There is clear evidence that executive functioning involves multiple components and is not a unidimensional construct (20), with evidence that different executive functioning deficits might be related to different features of schizophrenia (e.g., 21). For example, one influential taxonomy of executive functions suggests that there are at least five key components (22): 1) attention and inhibition, 2) task-management, 3) planning, 4) monitoring, and 5) temporal coding. This list does a good job of capturing our intuitions about the critical functions that executive control needs to manage. However, despite the fact that this list is an excellent starting point, it is not a list of mechanisms that can be tied to specific neural systems. For example, attention itself is a broad construct involving many possible mechanisms (23). Similarly, there are potentially multiple mechanisms that contribute to inhibition (24–26).

To more clearly link executive function mechanisms to neural systems, a number of cognitive neuroscientists have developed biologically plausible models of executive function that begin to specify the mechanisms that are instantiated by the brain and give rise to the list of functions articulated by Smith and Jonides. Several such models exist, including work by O'Reilly, Braver and Cohen (27), Desimone and Duncan (28), and Miller and Cohen (29). It would be premature to say that the field has converged in support of a single model of executive control. However, there are some commonalities and key components of executive function that do feature prominently across many models of executive function. Importantly, these are functions that seem to have the most clearly established links to specific neural systems.

The current article provides a summary of the consensus reached by participants in the CNTRICS discussion group on executive functioning. At the first CNTRICS meeting, a review of basic science research on executive function provided an overview of mechanisms of executive control that have been instantiated across multiple models of executive control and/or that have been linked to specific neural mechanisms. The presentation also highlighted some of the components of executive function that are not yet well understood at the neural level but that feature in many cognitive models of executive control. As described in the article by Carter *et al.* (pages 4–10, in this issue) on the CNTRICS process, this basic science presentation on executive functioning was followed by a group discussion about the degree to which various mechanisms involved in executive control met the criteria (clarity of understanding of cognitive mechanism, ease of measurement in humans, clarity of link to specific neural circuit, ease of use in human imaging studies, strong evidence of impairment in schizophrenia; see Table 1 and 2 in the Carter *et al.* article) identified as being important for selecting mechanisms for immediate translation (for more on the translational objectives of CNTRICS, see article by Carter *et al.*).

This discussion allowed the participants of the CNTRICS executive functioning panel to group mechanisms into three general categories: 1) those recommended for immediate translation; 2) those recommended for more basic and more clinical research; and 3) those recommended for more basic research (see Table 1 for a list of candidate mechanisms considered and the consensus judgment for each construct). Here we briefly review the mechanisms from these different categories, with an emphasis on those two mechanisms selected for immediate translation. As will be described in the following text, the mechanisms chosen for immediate translation are those that feature prominently across models of executive function and that the field agrees are important aspects of executive function. In describing these mechanisms, we focus on the ways in which they met the criteria used to select those components ready for immediate translation.

Constructs Ready for Immediate Translation

Rule Generation and Selection

Clarity of the Understanding of the Cognitive Mechanism. As can be seen in Table 1, there are a number of possible executive functioning candidate mechanisms that have been proposed in the cognitive neuroscience literature. On the basis of cognitive neuroscience models of executive functioning and cognitive control (15,29–31), a critical component mechanism of executive functioning is goal maintenance. Although this construct is discussed in more detail elsewhere in this issue (article by Barch and Smith, pages 11–17, in this issue), given its critical relationship to other aspects of executive functioning, we will discuss it briefly here. Goal maintenance refers to the representation and maintenance of goals or important contextual information (i.e., important task critical information, such as rules, goals, instructions, or intentions) (10,25). Several computational models of executive control (e.g., 27,32) have specified how such goals could influence ongoing processing, by showing how they can be used as a bias signal that alters information flow and competition in other parts of the system. Top-down biasing is thought to be important when needing to overcome automatic but situationally inappropriate responses and when context must be maintained over delays (10,25), with goal maintenance thought to allow for the achievement of goal-directed behavior, such as reaching a particular speech goal (33–34). Therefore, this top-down biasing signal from goal maintenance is thought to play a role in both selective attention (i.e., 28) and in prepotent inhibition (25).

In addition to goal (or rule) maintenance, an important and related construct is rule generation and selection. It has been argued that an important aspect of executive functioning is the ability to dynamically reconfigure itself on a task-by-task basis (35). Hence, people might vary in the quality of their rule representations or in their ability to formulate possible rules across tasks, which could influence executive functioning ability (e.g., 17–19,36–39). Importantly, some recent modeling work has suggested that prefrontal cortex (PFC) rule representations might be influenced by extensive experience across a range of situations (40). From this view, over time and with extensive

experience the PFC develops abstract rule-like representations of task contexts that support generalization of performance to novel task situations and with novel stimuli. This could contribute to performance on a task such as the Wisconsin Card Sorting task which involves the continuous resetting of current rule information. In simulation studies, damage to PFC-like representations disrupted the learning of rule-like representations, producing poor performance on the Stroop and Wisconsin Card Sorting task (40).

At the same time, it is also sometimes necessary to update and select new rule representations in performing a task. As discussed earlier, the ability of the PFC to sustain maintenance of goal or rule information is thought to be an important aspect of executive functioning. However, at the same time, it is also necessary to be able to update appropriately and to change rule information that is being stored in the PFC. One view of rule selection is that it involves a dynamic gating mechanism (14,41–42). When the gate is open, then PFC representations can be updated. However, when the gate is closed, then PFC rule representations are maintained. One possible gating mechanism could involve the neurotransmitter dopamine, with D1 receptor activation associated with stable maintenance and D2 receptor activation associated with rapid updating (14). At the same time, interactions between basal ganglia and PFC might be involved in selective rule updating, with direct pathway "Go" neurons in the basal ganglia resulting in PFC rule updating and indirect pathway "NoGo" neurons resulting in PFC maintenance. Moreover, the gating mechanism is thought to be influenced by reward processing (e.g., lack of rewards might result in updating PFC rules) (40).

Ease of Measurement in Humans. A number of different cognitive tasks have been developed that are thought to measure rule generation and selection. For example, on the Wisconsin Card Sorting task, participants need to generate a sorting rule and then when the sorting rule changes they need to select a new sorting rule (18,19). Similarly, on the Intradimensional Extradimensional shift task participants need to generate a rule and then need to select a new rule that is either from the same dimension (e.g., a different type of shape) or from another dimension (e.g., from shape to color) (43–46). Another task that involves rule selection is the 1-2-AX task (42,47,48). On this task, participants need to maintain a letter cue to know whether to respond to a probe letter as a target or non-target. Moreover, participants also need to periodically select a different rule for when they are supposed to respond to the probe letter as a target.

Clarity of the Link to a Specific Neural Circuit. The computational models developed to elucidate the mechanisms by which rule generation, selection, and maintenance influences cognitive processing have helped to specify the neural systems that support and give rise to goal maintenance. Across a wide variety of models (e.g., 14,15), the consensus has been that rule processing is supported by interactions between prefrontal regions (more specifically dorsolateral regions) and subcortical systems in the basal ganglia. More specifically, many models specify that recurrent sustained activity in dorsolateral PFC (DLPFC) help to support rule information that is used to bias processing in more posterior parts of the systems. Furthermore, it is has been suggested that signals from subcortical regions such as the basal ganglia serve as gating signals that might indicate when rules need to be selected or updated (14,41). A number of models have also begun to specify the neurotransmitter systems that might be particularly important for the maintenance and selection of rule information. For example, some models emphasize the role of dopamine in helping to modulate the gain or signal to noise of rule representations (especially involving D1 receptors) and in helping to cue the need to update rule representations (especially involving D2 receptors) (15,49,50). In addition, it has also been suggested that norepinephrine is important for interference control mechanisms in PFC (51) and that both norepenephrine and N-methyl d-aspartate receptors might be important for rule selection (52–54). The empirical work supporting the development of such models has arisen from both human (10) and animal studies (45,55–57) that have helped to tease apart the neural systems and mechanisms that support different components of rule maintenance and rule selection.

Ease of Use in Human Functional Imaging Studies. A number of functional imaging studies have examined rule generation and selection. In particular, these studies have helped to highlight the role of DLPFC (as well as other regions of PFC and other brain regions) in rule generation and selection with the types of tasks outlined in the preceding text. For example, on the Intradimensional Extradimensional shift task it has been found that shifting to a new dimension is associated with activity in the DLPFC (58). Moreover, a number of studies have found evidence of DLPFC involvement on the Wisconsin Card Sorting task (19,38,59). In addition, on a switching Stroop task it has been found that selecting and maintaining a more difficult rule is associated with activity in the DLPFC (60). Similarly, recent research with a cued Flanker task indicates selective engagement of dorsolateral prefrontal and parietal regions by cues indicating the need to prepare for and overcome conflict (61–62).

Strong Evidence of Impairment in Schizophrenia. Numerous behavioral and imaging studies have shown that individuals with schizophrenia display impairments on a wide variety of tasks that presumably require rule generation and selection. For example, numerous studies have found that individuals with schizophrenia exhibit deficits on the Wisconsin Card Sorting task (3,63), with poor performance on this task being associated with negative and disorganized symptoms and with poor functional outcomes (64–66). Along similar lines, people with schizophrenia also exhibit deficits on the Intradimensional Extradimensional shift task (67). Moreover, people with schizophrenia have also been found to be impaired on the Switching Stroop task, with poor performance associated with increased disorganization symptoms, and with evidence that this is a specific deficit and not due to generalized poor performance (68). Therefore, overall, rule generation and selection seems to be a well-founded cognitive neuroscience construct that can be readily measured in humans and animals, plays an important role in executive functioning ability, and is impaired in schizophrenia.

Dynamic Adjustments in Control

Clarity of the Understanding of the Cognitive Mechanism. Another critical component of executive control is dynamic adjustments in control. Dynamic adjustments in control refers to adjustments in cognitive and behavioral performance on the basis of ongoing performance monitoring (69,70). Several computational models of executive control (e.g., 69–73) have specified how performance monitoring results in cognitive and behavioral adjustments, by specifying what information is monitored and how that information is used to increase control. Performance monitoring is thought to be important to cognition by allowing the cognitive system to rapidly and appropriately increase executive control to meet performance demands (74).

Ease of Measurement in Humans. Most research on dynamic adjustments has used speeded response tasks (e.g., the Stroop) and has examined performance after error trials or after correct trials involving high response conflict (i.e., the simultaneous activation of competing responses). For example, people tend to respond more slowly and accurately after errors (75), which has now been found in many studies (e.g., 71,73,76). After high-conflict trials, participants seem to increase use of controlled processing (77) and are therefore faster and more accurate for the next high-conflict trial, which has now been found in many studies and in multiple selective attention paradigms (78–86).

Clarity of the Link to a Specific Neural Circuit. The consensus among computational models is that the dorsal anterior cingulate cortex (ACC) is critically involved in performance monitoring (e.g., 69–71,73). Computational models specify that the ACC is sensitive to competing motor cortex activation (69). Moreover, these models also have highlighted the role of dopaminergic input to the ACC from other regions that process error information (70,71). For example, it has been proposed that decreased dopaminergic input from the basal ganglia to the ACC results in an error signal (70,71). At the same time, computational models have specified that the ACC provides information to the DLPFC and also to the locus coeruleus (87), regions involved in implementing changes in performance.

Ease of Use in Human Functional Imaging Studies. Human imaging studies have consistently implicated the ACC as an important brain region involved in performance monitoring. Using functional magnetic resonance imaging, positron emission tomography, and electroencephalography, these studies have consistently found evidence that the ACC is active when errors are made (e.g., 73,76,88). Similarly, these studies have also found evidence that the ACC is active during high response conflict trials (e.g., 60,78,83–92). Moreover, brain imaging studies have found evidence for the influence of previous ACC activity on later brain activity associated with performance adjustments (80–86).

Strong Evidence of Impairment in Schizophrenia. A number of studies have provided evidence of impaired performance monitoring in schizophrenia. In particular, many studies have reported reduced ACC activity in people with schizophrenia (involving conventionally large effect size differences), which has been found when making errors or during high-conflict trials, including functional magnetic resonance imaging (e.g., 93–97) and electroencephalography studies (e.g., 98–104). Moreover, there is evidence that impaired performance monitoring is associated with negative and disorganization symptoms (105) and predicts poor executive functioning in schizophrenia (106–107). Therefore, dynamic adjustments in control seems to be a well-founded cognitive neuroscience construct that can be readily measured in humans and animals, plays an important role in executive functioning ability, and is impaired in schizophrenia.

Candidate Executive Functioning Mechanisms Recommended for More Basic and More Clinical Research

In this next section, we provide an overview on a number of potentially very important executive functioning mechanisms that are recommended for more basic and for more clinical research but that the CNTRICS executive functioning discussion group decided were not as clearly ready for immediate translation. For example, in addition to rule generation and selection, another potential computational mechanism involved in executive functioning is "response selection." For example, it has been argued that "willed action" is related to DLPFC activity (108). More recently, it has been argued that freely or randomly selected actions activate the pre-supplementary motor area (109). In contrast, the DLPFC might be active when people pay attention to the selection of action (110,111). At the same time, it is possible that attention to the selection of action might be related to rule maintenance, because top-down biasing by rule representations might be the computational mechanism involved in attention to the selection of responses. For example, it has been found that the same DLPFC region active during maintaining contextual information was also active when selecting a response (34). At the same time, it is known that the basal ganglia play a critical role in action selection (112). In addition, response selection has also been argued to be a central bottleneck in dual task performance and hence might be an important capacity limitation in cognitive processing (113), with—importantly—people with schizophrenia also exhibiting deficits in dual task performance (114). Therefore, it seems that response selection might be an important aspect of executive functioning and might be impaired in schizophrenia. It seems that more basic research on the nature of selection and in how to separately measure selection from other executive functioning constructs is needed in future research. At the same time, future research should also examine whether people with schizophrenia exhibit deficits on specific selection tasks.

Another potentially important mechanism of executive functioning is "scheduling" or planning, such as the planning of multiple steps to reach a particular goal (e.g., 115–117). It is possible that scheduling could overlap with other executive functioning mechanisms. For example, scheduling could involve goal maintenance, because scheduling could involve the maintenance of multiple simultaneous goals (however, we are not aware of direct evidence for this). It is also possible that scheduling could involve rule representation, because it has been found that animals might form abstract representations of multiple actions into a single representation (118). At the same time, there is evidence that scheduling might be somewhat distinct from other executive functioning components. For example, distinct frontopolar activity has been activated specifically during planning, suggesting that there could be unique computational mechanisms associated with planning (i.e., subgoal processing) (119). Future basic research is recommended to identify unique computational mechanisms associated with scheduling (e.g., 120–122).

Other Candidate Executive Functioning Mechanisms Needing More Basic Research

In this next section, we briefly mention several other possible executive functioning mechanisms that might play an important role in executive functioning but that seem to be in need of more basic research. For example, a crucial question is how humans or other animals learn to appropriately sequence actions in contexts that require the coordination of multiple actions, often referred to as behavioral "sequencing." This construct overlaps with scheduling/planning, in that both require the coordination of several components. However, scheduling/planning is often used to refer to more abstract representations governing behavior, with sequencing referring to performing multiple behavioral actions. One question about the nature of sequencing is whether it involves mechanisms distinct from the selection of single re-

sponses. Some evidence that behavioral sequencing might be distinct is that people with basal ganglia dysfunction exhibit greater deficits performing multiple behaviors than on single response tasks (123). However, people with basal ganglia dysfunction are also impaired on single response tasks, and it is possible that this might account for problems with making multiple responses (e.g., after having already made a response, needing to overcome interference from the previous response to select an additional response). Future basic research is recommended to identify unique computational mechanisms associated with behavioral sequencing.

There are a number of other possible executive functioning mechanisms or domains that might be relevant for schizophrenia. However, whether these domains involve unique computational mechanisms or whether they involve combinations of other computational mechanisms (or overlap with other areas of cognition) is unclear. For example, one domain that might be important for executive functioning is "decision making." However, this might involve other more granular executive functioning mechanisms (e.g., rule maintenance, selection) as well as possibly overlapping with other aspects of cognition (e.g., reward processing). Similarly, "strategy development" (which might overlap with rule representation) (40), "dual-task performance" (which has been thought by some to critically depend on response selection processes) (113), and "metacognition" (which might be related although distinct from the concept of insight) could all be important aspects of executive functioning and all might be impaired in schizophrenia (114). Future research is needed to identify specific computational mechanisms involved in these executive functioning domains.

In summary, this article has attempted to provide a summary of the consensus judgment of the executive functioning discussion group at the first CNTRICS meeting. At the same time, it has attempted to provide a brief and selective overview of the state of the field in terms of basic cognitive neuroscience research on specific mechanisms involved in executive function. The discussion of experts from a diverse set of backgrounds at the first CNTRICS meeting achieved a consensus that two constructs involved in executive function were the most ripe for translation: 1) rule generation and selection, and 2) dynamic adjustments of control. In addition, future CNTRICS meetings will take up issues on the psychometric properties of tasks attempting to measure these candidate cognitive mechanisms. At the same time, many other important mechanisms are in need of further basic and clinical research as a precursor to translation.

However, we should note that focusing on rule generation and selection and dynamic adjustments of control as translational foci is not meant to imply that we know all we need to know about these mechanisms. Many important questions about the specific cognitive and neural mechanisms supporting these functions remain and require ongoing basic research. For example, it is not clear how the brain distinguishes between the maintenance of information that constitutes a "rule" versus other types of information, because dorsofrontal and parietal regions can be activated by the maintenance of information we might not necessarily term "rule" information (e.g., 124). As another example, it is unclear how information on the need for changes in control states that are not signaled by increased conflict or errors (e.g., changes in motivational levels, changing priority, reward contingencies) gets communicated or used to modulate ongoing goal maintenance and implementation. A growing body of work on reward and value computations provided by basal ganglia and orbital frontal regions is beginning to address these questions (125–127), but clearly more work is needed in these domains. It is our hope that ongoing basic science work that further clarifies the specific mechanisms of executive control will continue to feed back and enhance our ability to understand and potentially treat abnormalities of executive control that occur in debilitating disorders such as schizophrenia.

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