

CNTRICS Final Task Selection: Executive Control

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The third meeting of the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) was focused on selecting promising measures for each of the cognitive constructs selected in the first CNTRICS meeting. In the domain of executive control, the 2 constructs of interest were “rule generation and selection” and “dynamic adjustments in control.” CNTRICS received 4 task nominations for each of these constructs, and the breakout group for executive control evaluated the degree to which each of these tasks met prespecified criteria. For rule generation and selection, the breakout group for executive control recommended the intradimensional/extradimensional shift task and the switching Stroop for translation for use in clinical trial contexts in schizophrenia research. For dynamic adjustments in control, the breakout group recommended conflict and error adaptation in the Stroop and the stop signal task for translation for use in clinical trials. This article describes the ways in which each of these tasks met the criteria used by the breakout group to recommend tasks for further development.

Key words: cognition/clinical trials/schizophrenia

Deficits in executive control have long been thought to be one of the hallmark cognitive characteristics of schizophrenia. Executive control processes are those mechanisms that allow individuals to flexibly and dynamically adjust their performance in response to changing environmental demands and changing internal goal states. Numerous empirical studies have shown that individuals with schizo-

phrenia show deficits on tasks designed to measure such executive control processes.¹ Deficits on such executive control tasks are associated with both negative and disorganized symptoms in schizophrenia and those at risk for schizophrenia,^{2–4} and deficits in executive control are associated with poor functional outcome.⁵

Given the prominence of executive control deficits in schizophrenia, it is not surprising that this was one of the cognitive domains upon which both the MATRICS and Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiatives have focused. As described by Kerns et al,⁶ a great deal of basic research in cognitive neuroscience has focused on elucidating the cognitive and neurobiological mechanisms that provide humans with the ability to flexibly shift and adapt their behavior over time and over different internal and external contingencies. As part of the first CNTRICS meeting, it was suggested that 2 components of executive control were ready for immediate translation for development and use in clinical trials in schizophrenia: (1) “rule generation and selection” and (2) “dynamic adjustments in control.” Rule generation and selection was defined as “the processes involved in activating task-related goals or rules based on endogenous or exogenous cues, actively representing them in a highly accessible form, and maintaining this information over an interval during which that information is needed to bias and constrain attention and response selection.”⁷

Dynamic adjustments in control were defined as “the processes involved in detecting the occurrence of conflict or errors in ongoing processing, identifying the type of control adjustments needed, and recruiting additional control processes.”⁷

The goal of the third CNTRICS meeting was to solicit and evaluate nominations for promising tasks that would measure each of the constructs selected in the first CNTRICS meeting (see Carter and Barch⁸ for a full list of all the constructs), including the 2 constructs selected under executive control. Nominations were solicited from both basic and clinical scientists, from both academia and industry. The nominators were asked to provide a description of the task and to provide information on 6 domains relevant to selecting the most promising tasks: (1) cognitive construct validity; (2) neural construct validity; (3) pharmacological sensitivity; (4) reliability; (5) other psychometric characteristics; and (6)

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the availability of animal models. The overview article at the beginning of this special section outlines why and how these specific criteria were selected and discusses the ways in which these criteria were used to select among tasks. In addition, the overview article describes additional criteria that could be used to adjudicate between tasks that appeared similar on the properties described above, such as evidence for impairment in schizophrenia. However, importantly, evidence for impairment in schizophrenia was not considered a requisite feature so as to facilitate the inclusion of potentially promising paradigms that have yet to be studied in schizophrenia. The goal of the current article is to provide a brief summary of the tasks that were nominated, the reasons as to why some tasks were not selected as “recommended for immediate translation” and to provide an overview of the data used to select the tasks. This overview is not meant to be an exhaustive review of the literature on each task, but rather to give the reader a starting point for understanding what each task is, how it is administered, why it was chosen, what the evidence is for construct and neural validity, what challenges the task faces in the translation process, and pointers to the primary literature for further consideration.

Rule Generation and Selection

CNTRICS received 4 initial nominations for the rule generation and selection construct: (1) the 1-2 AX-CPT; (2) the Groton Maze learning test; (3) CANTAB intradimensional/extradimensional (ID/ED) task; and (4) the switching Stroop. The executive control breakout group was tasked with the need to evaluate these nominations. Following animated discussion, the group decided that 2 of these tasks (CANTAB ID/ED and the switching Stroop) should be nominated for further development. Table 1 provides a brief overview of these 4 tasks and a very brief summary of their pros and cons in regards to the selection criteria.

Tasks not Selected as Recommended for Development

In the 1-2 AX-CPT,¹⁴ stimuli are presented one at a time in a sequence and subjects must press one button for a target and another for a nontarget. The stimuli are letters, and subjects are told to look for specific target sequences (eg, A followed by an X). Interleaved with the letters are the numbers “1” or “2.” These numbers instruct the subject to focus on one or another target sequence. For example, if the most recent number was a 1, the target sequence would be an A followed by an X, but if it had been a 2, the target sequence would be a B followed by a Y. This task is designed to test the subject’s ability to generate or select the appropriate rule for responding based on the previously presented number. Performance on this task has been modeled in a neural network model of frontal-basal ganglia interactions and their contribution to working memory.¹⁴ The breakout group felt

that the 1-2 AX-CPT was an interesting and promising task but that it needed more research at both the basic and clinical levels before it was ready for translation. Although there is encouraging pilot imaging work with this task, and pilot work in patients with schizophrenia, neither of these have been published yet.

The Groton Maze learning test¹⁵⁻¹⁷ is one in which subjects must learn a series of hidden mazes based on feedback. Although the breakout group also felt that this was an interesting task, the group felt that it was not clear that it was a specific measure of the construct of interest (rule generation and selection) as poor performance on the Groton Maze learning test could reflect a number of different factors in addition to rule generation and selection, including problems learning from feedback or spatial processing difficulties.

Tasks Recommended for Immediate Translation for Rule Generation and Selection CANTAB ID/ED Task

Description

The CANTAB intra/extradimensional set shift is implemented on a computer-controlled touch screen and takes approximately 7 min to administer, depending on the level of impairment of the individual performing the task (see also www.camcog.com for description and screen shot figure). Two artificial visual perceptual dimensions are used in the test: (1) color-filled shapes and (2) white lines. The simple stimuli in the task are made up of just one of these perceptual dimensions, whereas compound stimuli are made up of both, namely white lines overlying color-filled shapes (see stimuli on www.camcog.com Web site). The subject starts by seeing 2 simple color-filled shapes (presented in 2 of 4 locations on the screen, randomly on each trial) and must learn which one is correct by touching it (simple discrimination stage: SD). Subjects progress through the test by satisfying a set criterion of learning at each stage (6 consecutive correct responses). If at any stage the subject fails to reach this criterion after 50 trials, the test terminates. Computer-provided feedback teaches the subject which stimulus is correct, and after 6 correct responses for the initial simple discrimination stage, there is a reversal (simple discrimination reversal stage: SDR). Following acquisition of this reversal stage (which teaches the subject that different stimuli within a perceptual dimension are relevant to the rule), the subject is asked to complete compound discriminations in which each stimulus now has 2 potentially relevant perceptual features (lines and color-filled shapes), initially with spatially separated (C-D stage) and then superimposed (CD stage) stimuli. The subject then must perform a reversal on the compound discrimination stimuli (compound discrimination reversal: CDR stage) before the stimulus exemplars change for an intradimensional shift. In the intradimensional shift stage, the same dimension of the stimulus

Table 1. Description of Tasks Nominated for Rule Generation and Selection Construct Definition: The Processes Involved in Activating Task-Related Goals or Rules Based on Endogenous or Exogenous Cues, Actively Representing Them in a Highly Accessible Form, and Maintaining This Information Over an Interval During Which That Information Is Needed to Bias and Constrain Attention and Response Selection⁷

Tasks Recommended For Translation

CANTAB ID/ED task

Construct validity

- Supported by both human and animal research
- Designed to decompose the WCST

Neural systems

- Evidence for role of ventro- and dorsolateral prefrontal cortex in extradimensional shifting (rule selection) from human and animal research
- Evidence for role of dopamine and norepinephrine in extradimensional shifting (rule selection) from human and animal research

Pharmacological sensitivity

- Numerous studies in humans and animals showing that ID/ED performance is sensitive to a variety of pharmacological manipulations
- Evidence that modafinil can improve ID/ED performance in schizophrenia

Animal models

- Animal models available for rhesus monkey, marmoset, and rat

Performance in schizophrenia

- Consistent evidence for impairments in extradimensional shifting
- Mixed evidence for impairments in intradimensional shifting

Psychometric data

- Low test-retest reliability
- Practice effects influenced by insight and learning on task over time
- Potential confounds of generalized deficits with differences in discriminating power across conditions

Future directions

- Modifications needed to improve test-retest reliability and to reduce practice effects
- Evaluation of discriminating power across conditions is needed. If not equal, modifications will be needed to improve ability to detect differential deficits

Switching stroop

Construct validity

- Supported by computational modeling and individual differences research
- Is a good measure of rule selection, but not of rule generation

Neural systems

- Evidence from functional neuroimaging on the importance of DLPFC and ACC
- Evidence from lesions studies for importance of DLPFC

Pharmacological sensitivity

- Evidence that dopamine augmentation can improve Stroop performance in schizophrenia, but may not be specific to rule selection

Animal models

- There are rat and primate models of paradigms described as measuring similar constructs
- The degree to which the animal models (especially the rat models) are homologous to the human paradigm is an open question

Performance in schizophrenia

- Evidence for deficits in schizophrenia in the ability to select and apply the appropriate cue on the switching Stroop
- Evidence for reduced DLPFC and ACC activity in schizophrenia during the performance of incongruent Stroop trials

Psychometric data

- Little psychometric data available on test-retest reliability, practice effects, or floor/ceiling effects

Future directions

- Research needed on assessing and improving the psychometric characteristics of the switching Stroop
- Research needed on ways to make the use of the Switch Stroop feasible in clinical trials contexts (eg, task length, standardized administration, enhanced sensitivity to detect deficits, etc.)
- Evaluation of discriminating power across conditions is needed. If not equal, modifications will be needed to improve ability to detect differential deficits
- Evaluation of the homology of putative animal models and development of better animal models if needed

Other nominated tasks

1-2 AX-CPT

Construct validity

- Task modeled in a computational model of prefrontal-basal ganglia contributions to working memory

Neural systems

- No published data

Pharmacological sensitivity

Table 1. Continued

Tasks Recommended For Translation
No published data
Animal models
No published data
Performance in schizophrenia
No published data
Psychometric data
No published data
Groton maze learning task
Construct validity
Not clear that the task selectively measures rule selection or generation as performance may be strongly influenced by the ability to learn from feedback and visual spatial processing abilities
Neural systems
Evidence that performance can elicit feedback-related error negatives in ERP studies ⁹
Pharmacological sensitivity
Evidence that speed and efficiency of performance can be improved ¹⁰
Animal models
Cincinnati Water Maze test in rodents may be an animal homologue ¹¹
Performance in schizophrenia
Evidence for excessive rule-breaking errors in schizophrenia ¹²
Psychometric data
Preliminary evidence of good psychometric characteristics ¹³

remains relevant (eg, lines or shapes), but the specific feature within the dimension that is the target changes (eg, which colored shape). This stage is designed to reinforce perceptual dimension learning and to provide a control for the crucial extradimensional shift stage. For the initial intradimensional shift (IDS stage), color-filled shapes remain the only relevant dimension, then later after intradimensional shift reversal (IDR stage), again there are new stimuli/exemplars for the extradimensional shift (EDS state) in which the white lines become the only relevant dimension. This is followed by the extradimensional reversal stage (EDR), in which subjects must shift between dimensions. There are thus 9 stages in all, designated SD, SDR, C-D, CD, CDR, IDS, IDR, EDS, and EDR. The task has 2 modes: a clinical mode for testing only once and 7 parallel modes for repeated testing. The task has 18 outcome measures, assessing errors, and numbers of trials and stages completed.

From extensive experience with the task, the developers have a number of recommendations for optimal task use. First, although it is feasible to begin the task with lines and shift to shapes, it is recommended that the initial learning be fixed at shape. Second, they recommend, time permitting, that the subjects are screened with a short instructional test (Big circle/little circle discrimination) which tests the subjects' ability to understand what a rule is and to be able to reverse it on command. Third, there is a fixed rubric for the verbal instructions for this test which are minimal but which should be followed closely.

Construct Validity

The theoretical validity of the test was established over 30 years ago and stems from early animal and human learn-

ing theory on discrimination learning, reversal, and dimensional shifting. More recent computational approaches have confirmed for example that reversal learning and extradimensional shifting necessarily engage different processes and have also considered the paradigm in the context of a theory of frontal lobe function based on working memory.¹⁸ The CANTAB test was designed partly to decompose the well-known Wisconsin Card Sort test (WCST) into its constituent parts including a critical extradimensional shift stage that is probably equivalent to a category shift on the WCST. The initial validation study demonstrating cross-species advantage for IDS over EDS performance in humans and marmosets was by Roberts *et al.*¹⁹ There is an extensive and growing bibliography of the ID/ED task, and the reader is referred to www.camcog.com for references and abstracts. The following constitutes a brief overview.

Neural Systems

The neural substrates of the test (or similar variants of it, with changes in the stimuli but not the basic principles of test design) have been defined on the basis of human neuropsychological data in brain damaged patients, functional imaging data (both functional magnetic resonance imaging [fMRI] and positron emission tomography),^{20,21} and animal (monkey, rat, mouse) lesion studies. There is converging evidence that reversal learning implicates orbitofrontal cortex function in humans, monkeys, and rats.^{20,22–27} There is also additional evidence for ventromedial striatal and posterior parietal involvement.^{20,21,28} There is considerable evidence for a role for the primate ventrolateral prefrontal cortex in extradimensional shift learning^{20,22} as well as other posterior cortical

(posterior parietal, temporal) areas. The neuroanatomical dissociation between EDS and reversal learning in marmoset also holds for the rat.²⁹ The precise substrates of discrimination learning and intradimensional shift learning are less clear, but see Rogers et al²¹ for some initial observations.

Pharmacological and Behavioral Manipulation of Task Performance

In humans, there is evidence for double dissociation in effects of indoleamine (serotonin, 5-HT) and catecholamine (dopamine, DA), noradrenaline (NA) manipulations on reversal learning, and extradimensional shifting, respectively, in the ID/ED task. Thus, tryptophan depletion (implicating 5-HT) selectively impairs reversal learning in humans, whereas the catecholamine agent methylphenidate improves extradimensional shifting.^{30,31} Noradrenergic manipulations appear particularly sensitive to human extradimensional shifting performance.³² There is only weak evidence of effects on extradimensional shifting of DA receptor antagonism³³ or L-Dopa medication (in Parkinson's disease).³⁴

In animals, as in humans, there is considerable evidence for an involvement of 5-HT in reversal learning. In marmosets, selective depletion of 5-HT (and not DA) in the orbitofrontal cortex impairs reversal learning.²⁴⁻²⁶ Orbitofrontal 5-HT is also implicated in reversal learning in the rat.³⁵ In monkeys, DA depletion impairs intradimensional shifting but not reversal or extradimensional shifting (which may even be artifactually improved in certain instances).^{36,37} In rats, there is evidence that the noradrenergic system is implicated specifically in the extradimensional shifting.^{38,39} However, there is some evidence in the rat and mouse of involvement of prefrontal cortex (PFC) DA in extradimensional shifting (based on genetic studies with COMT polymorphisms⁴⁰).

In addition, there are, approximately 30 studies of pharmacological effects of drugs, including many candidates for the medication of cognitive deficits in schizophrenia on intradimensional and extradimensional shifting in the rat model to be described below. These drugs include the following: 5-HT₆ receptor antagonist, NA agonist, alpha-7 subunit nicotinic agonist, D1 receptor agonist, PDE inhibitors, and modafinil. Many of these compounds selectively improve extradimensional shifting performance, which may be most closely tied to rule generation and selection. There are also selective demonstrations of effects of stress on extradimensional shifting performance and neuronal morphology in the medial PFC in rats.⁴¹

Animal Models

There are number of different animal models of ID/ED task performance that have been developed. For example, there is a paradigm for rhesus monkeys,⁴² and there have been a number of studies of ID/ED performance in

marmosets.^{19,22} In addition, Birrell and Brown established a rat model based on textures and odors rather than visual stimuli.²⁹ This has been used to establish the neuroanatomical substrates of the task in rats (see above) and for pharmacological studies. It has also been used for models of schizophrenia (eg, chronic PCP treatment, amphetamine sensitization, isolation rearing, MAM pretreatment). A typical study has shown benefit of a PDE inhibitor or modafinil against deficits produced by PCP at the extradimensional shift stage that are not remediated by conventional antipsychotic DA receptor antagonists.⁴³

Performance in Schizophrenia

There have been over 20 studies so far listed in the CANTAB bibliography on the ID/ED test in schizophrenia, beginning with Elliott et al.^{44,45} These studies have been not only in chronic schizophrenia^{46,47} but also in first-episode psychosis.^{48,49} Comparisons with other disorders have included comparisons with bipolar disorder and depression, Alzheimer's, Parkinson's, and Huntington's diseases, OCD and ADHD, neurosurgical patients with damage to the frontal and temporal lobes, as well as amygdalo-hippocampectomy (see CANTAB Web site). An explicit comparison of chronic schizophrenia with frontal and temporal lobe lesions was published by Pantelis et al.⁴⁶ That study showed that people with chronic schizophrenia were severely impaired at both the intradimensional and extradimensional shifting stages, compared with both patients with lateral PFC damage (who were mainly impaired at the extradimensional shifting stage) and temporal lobe lesioned patients (who did not differ from age- and IQ-matched controls). Other studies have shown that people with chronic schizophrenia can also fail at the simple reversal stage or compound discrimination stages.^{44,50} Jazbec et al provided one of the first direct comparisons of ID/ED performance and the WCST in schizophrenia, with significant correlations at the extradimensional shift stage.⁵⁰

In terms of pharmacological treatment, Turner et al⁴⁷ showed, in a double-blind placebo-controlled proof of concept study, that acutely administered modafinil added to conventional antipsychotic medication in schizophrenia improved several aspects of performance including the ID/ED test. This "proof-of-concept" study demonstrated that it was indeed plausible to improve aspects of cognitive function in schizophrenia and was subsequently 'back translated' to show improvement in the rat plus PCP model.⁴³

Psychometric Data

Standardized data on 341 elderly subjects were published in Robbins et al.⁵¹ Performance on the ID/ED test declined quiet sharply in the eldest cohort (>70) especially

at the extradimensional shift stage.⁵¹ There are limited data on test-retest reliability; Lowe and Rabbitt found quite low ($r = 0.4$) test-retest correlations for some variables of the ID/ED test in normal volunteers.⁵² This is not surprising in view of the fact that the WCST has very low test-retest reliability. Thus, significant developmental work is clearly needed to determine how reliability on this test might be improved and what reliability is like in patient groups. In general, this class of tests does depend on insight and/or procedural learning or other forms of practice effects derived from previous experience of the tests, and between-group comparisons are recommended for pharmacological studies to alleviate this problem (as compared with within subject designs that require multiple testing sessions per person). The use of parallel versions of the task may help with this concern but may not entirely reduce the potentially long-acting influence of insight into the basic nature and structure of the task. In addition, the various conditions on the task are not matched for discriminating power, with the conditions that are often most impaired in schizophrenia likely those with the greatest discriminating power (eg, extradimensional shift stages). Thus, work is needed to determine whether greater impairments at the extradimensional shift stage in schizophrenia reflect a specific impairment in generating and/or selecting rules or a generalized deficit that interacts with the psychometric characteristics of this stage of the task.

Future Directions

More analysis of the neural and neurochemical substrates of performance is needed in both humans and animal subjects. Several specific issues require resolution or consolidation, as indicated above. These can be pursued using functional neuroimaging approaches in humans and lesions or neuropharmacological manipulations in experimental animals. Longitudinal studies are also required for schizophrenia, and other studies of pharmacological effects, though proof of concept that ID/ED performance can be enhanced has already been demonstrated. In psychometric terms, more data are required. The test may have to be modified to provide good test-retest reliability. For example, the fixed sequence of testing of the component processes ID shifting and ED shifting may need to be replaced by a version of the test that interleaves the 2 forms of shifting. In addition, research is needed to determine whether deficits on specific stages of the task reflect differential deficits or generalized deficits that reflect the greater discriminating power of the ED compared with the ID, CD, or SD conditions. If ED conditions indeed have greater discriminating power, the test will need to be modified to either match the ID and ED measures on discriminating power or introduce another control (eg, one in which set shifting deficits convey a performance advantage).

The Switching Stroop

Description

The “switching Stroop” is a variation on the classic Stroop task. It was nominated as a measure of the rule generation and selection construct as an example of an asymmetric task-switching paradigm. An asymmetric paradigm is one in which one of the task involves a more prepotent dimensions than another. In such task-switching paradigms, subjects must use the cue to generate and/or select the appropriate rule to govern response selection for the upcoming stimulus. Thus, although this description will focus on the Stroop specifically, it is possible that other asymmetric task-switching paradigms may be just as promising. In the classic Stroop,⁵³ participants are presented with stimuli that vary on 2 dimensions (eg, color words written in different colors). Participants are told to respond to one of the dimensions and to ignore the other. Typically, one of the dimensions is more “prepotent” (ie, word reading), making it more difficult for participants to ignore that dimension and leading to more interference from the prepotent dimension when trying to attend to and respond based on the less dominant dimension (eg, color naming). This typically leads to slower responding and more errors when participants are told to respond on the basis of the less dominant dimension.⁵⁴ To perform the task correctly, especially when responding to the less prepotent dimension, participants need to use task instructions to select the appropriate rule for which stimulus dimension to use for responding. However, standard versions of this task do not sensitively probe the selection or maintenance of rule information. This is because the task is typically kept constant across blocks of trials, so that each trial reinforces the correct response dimension and thus the correct rule. To make the task more sensitive to the ability to select and maintain the appropriate rule, one can vary the task (ie, the dimension to be responded to—word or color) on a trial-by-trial basis⁵⁵ (see figure 1). In such “switching” versions of the Stroop, the subject is cued to the relevant dimension (rule) prior to each trial. This can be done either via an auditory cue or a visual cue. In addition, one can vary the delay (1 vs 5 s) between the task cue and the stimulus. This allows one to assess whether rule maintenance is problematic by comparing performance over a longer rule maintenance delay vs a shorter rule maintenance delay.

In most versions of the Stroop, including the switching Stroop, experimenters typically include 3 types of conditions (see figure 1): (1) congruent, in which the 2 dimensions point to the same response (eg, the word “red” written in red); (2) neutral, in which response relevant information is present in only one dimension (eg, a row of Xs printed in red—see Barch and Carter for discussion of factors influencing choice of neutral condition⁵⁶); and (3) incongruent, in which the 2 dimensions point to different

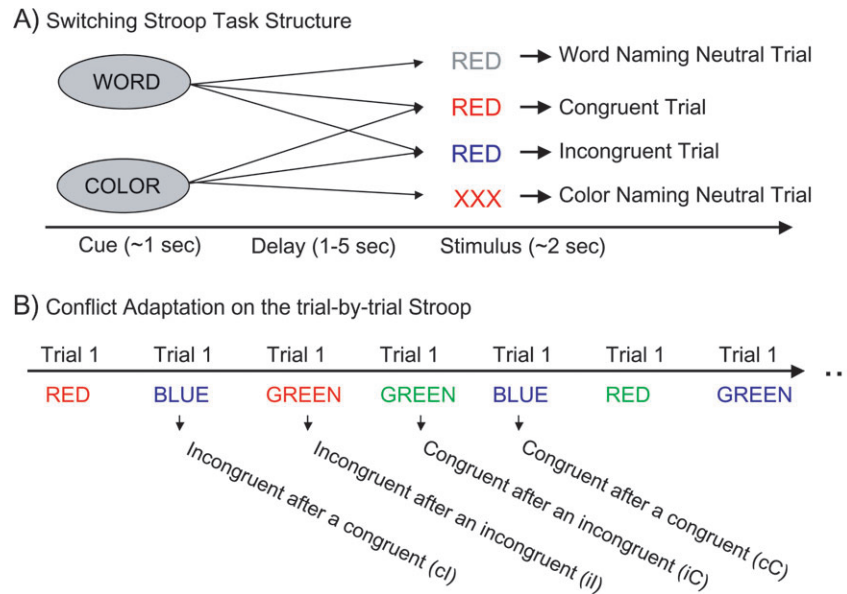


Fig. 1. (A) Illustration of the Structure of the switching Stroop Task. The cue is either to “color” or “word” read and then the stimulus is congruent, neutral, or incongruent. (B) An illustration of trial structure for computing conflict adaptation effects in the trial-by-trial Stroop.

responses (eg, the word red written in blue). In addition, performance on most versions of the Stroop can be measured in terms of either reaction times or errors. Experimenters typically look at one of 3 variables: (1) total Stroop effect (performance in the incongruent condition—performance in the congruent condition); (2) interference (performance in the incongruent condition—performance in the neutral condition); or (3) facilitation (performance in the congruent condition—performance in the neutral condition).

Construct Validity

There is a long history of research on standard versions of the Stroop task that provides evidence for the construct validity of this task as a measure of the ability of an individual to select and apply the appropriate rule for response selection. For example, there is a good deal of computational modeling work demonstrating that performance on the Stroop task across many experimental manipulations, including switching manipulations, can be accounted for by mechanisms that provide for the active selection and maintenance of the appropriate task rule.^{57,58} Such mechanisms have been implemented in connectionist interactive activation models and have been used to make predictions about specific patterns of fMRI data.^{58,59} These models have typically assumed that such task rule representations are stored in prefrontal cortex, maintained through recurrent connections that provide “top-down” support for lateral inhibition mechanisms in relevant processing pathways that allow the less dominant pathway (eg, color naming) to compete successfully with the more dominant pathway (eg, word naming). In addition, there are data suggesting that indi-

vidual differences in the ability to actively maintain representations in working memory predicts individual differences in the ability to select and effect use the appropriate task rule during Stroop task performance.⁶⁰ As with the computational modeling work, these data have been interpreted as reflecting an important role for prefrontally maintained representations in successful Stroop performance. One thing to note with the switching Stroop is that while it is a good measure of the ability to “select” task rules, it is not a good measure of the ability to “generate” rules as the experimenter provides the rule. In addition, there may be some confounding of task-switching demands with rule selection demands in the switching Stroop, given that RTs could also reflect the time it takes to switch from one rule to another (eg, color vs word), as well as the ability to maintain and apply the appropriate rule. Thus, care would need to be taken to dissociate these effects in future work with the switching Stroop.

Neural Systems

There have been only a handful of studies using functional imaging to examine the neural substrates of performance on the switching Stroop. However, these studies have been particularly informative as to the specific roles played by dorsolateral prefrontal cortex (DLPFC) vs anterior cingulate cortex (ACC) in task performance. Specifically, these studies have demonstrated that cue-related activity in DLPFC was enhanced on trials in which the participants were cued to color name as compared with word read, consistent with the hypothesis that greater top-down control to support rule representation is needed on color-naming trials.^{61,62} In contrast,

cue-related anterior cingulate (ACC) activity did not vary as a function of task, but ACC activity was greater on incongruent relative to congruent trials, consistent with a role of for ACC in monitoring for competition during responding.⁶¹

Research has also examined the degree to which lesions to the frontal cortex impair performance on standard versions of the Stroop task, though to our knowledge no such studies have been conducted with switching Stroop tasks. Although the evidence in this regard is mixed, some meta-analytic work suggests that frontal lesions are reliably associated with impaired performance on the Stroop task,⁶³ though it is not clear that such deficits are isolated to conditions in which rule selection and maintenance are most critical (eg, incongruent conditions or color naming specifically).⁶³

Pharmacological and Behavioral Manipulation of Task Performance

A number of different variations on the Stroop task have been used in a range of pharmacological and behavioral manipulation studies. Of most relevance to the current topic are those that involved individuals with schizophrenia. For example, work by Barch and Carter demonstrated that low doses of amphetamine in patients taking stable doses of typical antipsychotics improve reaction times on a standard Stroop task,⁶⁴ though this improvement was found in all conditions, not just the incongruent condition. In addition, research has shown that nicotine administration can improve Stroop interference, with evidence of greater improvements in individuals with schizophrenia than in controls.⁶⁵ Thus, prior research indicates that Stroop performance is amenable to change with pharmacological interventions in individuals with schizophrenia. However, to our knowledge, research has not yet examined the amenability of switching Stroop performance specifically to change via either pharmacological or behavioral manipulations.

Animal Models

A number of paradigms for use in animals have been developed that are designed to capture the type of response competition that requires the type of appropriate rule selection required by the switching Stroop in humans. For example, work in rats has focused on biconditional discrimination tasks that require animals to use contextual information to modify responses to specific stimuli.^{66–68} In addition, paradigms have been developed for monkeys that are designed to mimic critical features of the Stroop task, including the need to selectively attend to one dimension of stimulus and the inclusion of different feature dimensions that provide conflicting response information.^{65,69,70} The degree of homology between the cognitive and neural mechanisms engaged by these paradigms in animals vs humans needs further investiga-

tion. However, these studies provide encouraging evidence of the ability to model “Stroop-like” task performance in animals.

Performance in Schizophrenia

At least one study has specifically examined switching Stroop performance in patients with schizophrenia.⁵⁵ This work used a version of the switching Stroop in which: (1) an auditory cue signaled whether participants should word read or color name, (2) there were 2 different delays between the cue and the onset of the stimulus (1 vs 5 s); and (3) the neutral stimuli for color naming were rows of Xs. The schizophrenia patients showed disproportionate interference in errors compared with controls for color naming as well as a disproportionate total Stroop effect in reaction times compared with controls for color naming (see figure 2). These effects did not interact with delays, suggesting that the magnitude of the impairments was similar for both short and long delays (see figure 2). Functional imaging work with the Stroop has consistently revealed deficits in the activation of DLPFC and ACC in schizophrenia. For example, Kerns *et al*⁷¹ found reduced anterior cingulate activity during incongruent Stroop trials in schizophrenia, Weiss *et al*⁷² found underactivation of DLPFC and anterior cingulate in schizophrenia during performance of a Stroop task, and Yucel *et al*⁷³ found underactivation of paracingulate cortex in schizophrenia. These studies did not use switching Stroop tasks specifically and instead used standard Stroop versions. However, standard Stroop versions do still assess the ability to select and apply the appropriate rule, though they may just not be as sensitive to this process as the switching Stroop. Deficits on the Stroop task are also present in the relatives of individuals with schizophrenia, suggesting that they are associated with vulnerability to the disorder.^{74,75} In addition, recent work has shown reduced DLPFC activity during performance of the Stroop in unaffected first-degree relatives of patients, though intact ACC activity.⁷⁶ However, to our knowledge, the switching Stroop has not been used with relatives of individuals with schizophrenia.

Psychometric Data

There is very little information about any psychometric characteristics of the switching Stroop. Cohen *et al* did report an internal consistency of 0.9 for incongruent color-naming errors at a 5-s cue-probe delay and an internal consistency of 0.53 for color-naming facilitation at a 5-s delay.

Future Directions

There are a number of different important future directions for research on the switching Stroop for use in clinical trial contexts in schizophrenia. As noted above, little is known about the psychometrics of this task, and thus,

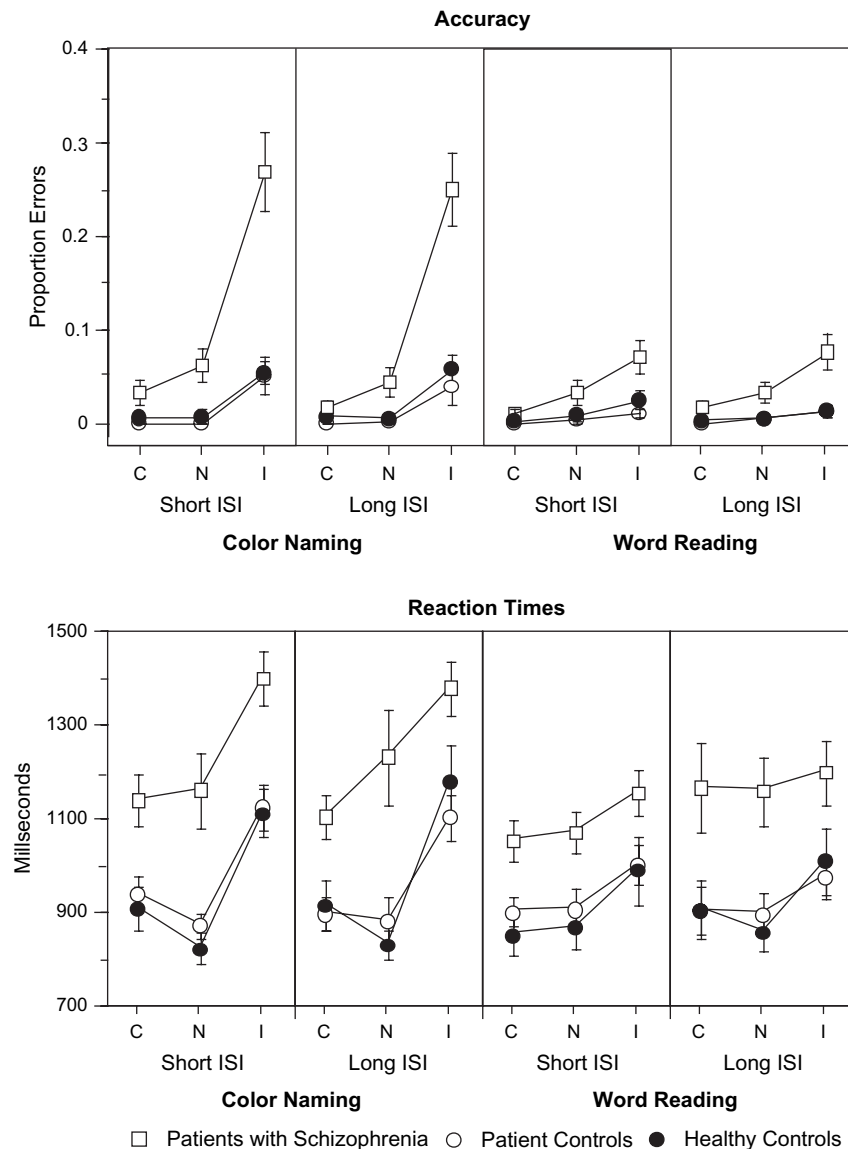


Fig. 2. Stroop Task Accuracy and Reaction Times from Cohen et al.⁵⁵ Reprinted with permission from the American Psychological Association. C = congruent, N = neutral, I = incongruent.

studies examining test-retest reliability, practice effects, floor, and ceiling effect, etc are needed. In addition, research is needed to establish the most sensitive neutral condition to use in studies of schizophrenia. In addition, the ways in which the task has been presented in prior studies involve many trials and a lengthy presentation. This may not be practically feasible in clinical trial contexts. As such, work on ways in which to shorten and enhance the sensitivity of the task is needed. Although standard versions of the Stroop task have been shown to be amenable to pharmacological manipulation, work is needed to demonstrate that performance on the switching Stroop can be enhanced either pharmacologically or behaviorally. In addition, work is needed to establish that the greater deficit on color-naming trial

references a differential deficit rather than a generalized deficit given that the color-naming condition may have greater discriminating power.

Dynamic Adjustments in Control

CNTRICS received 4 initial nominations for the dynamic adjustments in control construct: (1) the attention networks task (ANT); (2) the Simon task; (3) the trial-by-trial Stroop task; and (4) the stop signal task. In the stop signal task, as described below, dynamic adjustments in control are examined by determining how individuals modulate their behavior when given a cue to interpret an ongoing response. In the ANT, the Simon task, and the trial-by-trial Stroop, dynamic adjustments

of control are examined by investigating 2 effects: (1) conflict adaptation⁷⁷ and (2) posterror adjustments.^{78,79} Conflict adaptation is thought to reflect behavioral adjustments following trials with high conflict (eg, incongruent trials) vs those with low conflict (eg, neutral or congruent trials). In other words, participants are faster to respond to an incongruent trial that is preceded by an incongruent trial compared with an incongruent trial preceded by a congruent trial.^{77,80} The interpretation of this result has been that the conflict engendered by the first incongruent trial leads to an upregulation in control that reduces the conflict induced by the next incongruent trial.⁸⁰ Posterror adjustments are thought to reflect a similar process. Participants are typically slower, but more accurate, on trials following errors vs trials following correct responses.^{78,79} This is again thought to reflect an upregulation of control engendered by the awareness (not necessarily “conscious”) of having made an error.

The executive control breakout group felt that all 4 tasks were reasonable measures of the construct of interest. However, the breakout group felt that the ANT, the Simon, and the Stroop were all variations on a theme, with a similar deep structure in terms of assessing dynamic adjustments in control. Of the 3, the breakout group felt that the Stroop version has the largest extant literature in terms of the cognitive and neural bases of dynamic adjustments in control and the largest existing literature in schizophrenia. Thus, the breakout group recommended that the Stroop version be put forth for immediate translation for use in clinical trials in schizophrenia. In addition, the breakout group made a similar recommendation for the stop signal task, given that it measured a somewhat different aspect of dynamic adjustments in control and thus might provide complementary information. Table 2 provides a brief overview of these 4 tasks and a very brief summary of their pros and cons in regards to the selection criteria.

Tasks Recommended for Immediate Translation for Dynamic Adjustments of Control Conflict and Error Adaptation in the Stroop Task

Description

The basic design of a Stroop task was described above under the switching Stroop description. In addition, the basic approach to assessing dynamic adjustments in control in the context of conflict tasks was described above. To clarify, in the Stroop task, a high conflict trial for color naming is an incongruent trial in which the word and the color are different (eg, RED written in blue). A low conflict trial is a congruent trial in which the word and the color are the same (RED written in red). In previous studies, dynamic adjustments in control via conflict adaptation have been studied in the Stroop task by comparing 2 sets of trials (see figure 1B): (1) incongruent

following an incongruent (iI) vs incongruent following a congruent (cI) and (2) congruent following a congruent (cC) vs congruent following an incongruent (iC).^{90–93} Dynamic adjustments in control via posterror adjustments are examined as described above. There are several design aspects that one needs to attend in designing a Stroop study for use in examining dynamic adjustments in control. Most importantly is the need to ensure that the sequences of trials are set up in a way to allow sufficient numbers of the relevant “pairings” of trials, as described above. This may require a pseudorandom trial sequence generation that ensures a lack of predictability on the part of the participants coupled with a sufficient number of trials in each cell.

Construct Validity

The construct validity of conflict and error adaptations as measures of dynamic adjustments in control has been supported from a number of different types of studies. For example, several different computational models have been developed that account for both error and conflict adaptation effects in terms of the detection of conflict and the use of such conflict detection to adjust and regulate the amount of control. These models are framed in terms of control being implemented via active representations of task rules or S-R mappings (potentially housed in prefrontal cortex) that provide feedback over posterior cortical-processing areas,^{94–97} with conflict detection occurring via anterior cingulate (ACC) mechanisms that monitor for the degree of conflict between competing response options. One potential threat to the construct validity of conflict adaptation effects is the degree to which the improvement in performance on iI trials compared with cI trials or on cC vs iC trials can be accounted for by repetition priming instead of increases in cognitive control.⁹⁸ Although it is clear that such repetition priming can facilitate performance on subsequent trials, research has also shown that conflict adaptation effects are present even when no exact repetitions are used in the calculation of such effects.^{90,99,100}

Neural Systems

There is a burgeoning literature on the neural substrates of such conflict adaptation and error adaptation effects as measures of control adjustments, stemming from both ERP and fMRI research in humans. In the evoked response potential (ERP) literature, components such as the error-related negativity (ERN) and the N2 (or N450 during the Stroop task) have been localized to the ACC and have been frequently investigated in the context of conflict and error monitoring and control adjustments. In addition, the conflict-related negativity (CRN) has also been investigated in relationship to conflict monitoring and control adjustments. Further, there is relevant lesion work as well as recent nonhuman

Table 2. Description of Tasks Nominated for Dynamic Adjustments in Control Construct Definition: The Processes Involved in Detecting the Occurrence of Conflict or Errors in Ongoing Processing, Identifying the Type of Control Adjustments Needed, and Recruiting Additional Control Processes⁷

Tasks Recommended For Translation

Conflict and Error Adaptation in the Stroop Task

Construct validity

Supported by computational modeling work and individual differences research

Neural systems

Evidence for the role of ACC in conflict detection and DLPFC in control adjustments from human neuroimaging studies

Mixed evidence for the role of DLPFC in control adjustments from lesion research

Mixed for the role of ACC in conflict detection from lesion research

Pharmacological sensitivity

Consistent evidence that basic ERN effects to errors can be modulated via pharmacological challenges

Mixed evidence on the degree to which behavioral performance adjustments can be manipulated pharmacologically

Evidence for dissociations in the effects of pharmacological manipulations on ERN indices vs behavioral indices

Animal models

Animal models available for monkey and rat, though the degree of homology needs further research

Performance in schizophrenia

Evidence for reduced conflict adaptation and reduced posterror slowing (mixed) in schizophrenia

Evidence for reduced ACC responses to errors and conflict

Psychometric data

Little to none currently available

Future directions

Research needed on assessing and improving the psychometric characteristics of the error and conflict adaptation effects

Research needed on ways to make the use of conflict and error adaptation effects feasible in clinical trials contexts (task length, standardized administration, enhanced sensitivity to detect deficits, etc.)

Evaluation of discriminating power across conditions is needed. If not equal, modifications will be needed to improve ability to detect differential deficits

Evaluation of antipsychotic effects on error and conflict adaptation effects

Stop signal task

Construct validity

Supported by evidence of stopping deficits in populations thought to have impulse control problems, such as ADHD

Neural systems

Evidence from human imaging and lesion studies on the role of inferior frontal gyrus in inhibition

Evidence from human imaging and neurological disorder studies on the role of the subthalamic nucleus in inhibition

Pharmacological sensitivity

Strong evidence that inhibition on the stop signal task is affected by manipulations of catecholamines, which may involve both dopamine and norepinephrine

Animal models

There is a primate model that involves countermanding of eye movements

There is a rodent model that involves an auditory stop signal and button press

Performance in schizophrenia

Evidence for reduced stopping accuracy and elongated stop signal reaction times

Psychometric data

The use of an adaptive stop signal reaction time estimate procedure reduces floor and ceiling effects

Preliminary positive evidence for good test-retest reliability and small practice effects

Future directions

Need to develop better adaptive methods for stop signal reaction time estimation that reduce or eliminate strategy changes on the part of the participant

Need to directly compare different versions of the stop signal task in terms of sensitivity and psychometric characteristics

Need an evaluation of the degree of homology between the human and animal versions

Other nominated tasks

Attention networks task

Construct validity

Evidence from individual differences research and computational modeling

Neural systems

Evidence for activation of the ACC during conflict^{81,82}

Polymorphisms in dopamine receptor 4 and monoamine oxidase A genes were found to be related to differential behavioral conflict response⁸³ as well as differential ACC conflict response in an fMRI study⁸⁴

Pharmacological sensitivity

No published data

Animal models

Animal models available for monkey and rat, though the degree of homology needs further research

Table 2. Continued

Tasks Recommended For Translation
Performance in schizophrenia A selective impairment of ANT conflict processing in schizophrenia has been reported ⁸⁵
Psychometric data Preliminary evidence of good test-retest reliability ⁸⁶
Simon task
Construct validity Behavioral studies have shown robust postconflict and posterror adaptation with this task ⁸⁷
Neural systems Human fMRI studies have linked the ACC to conflict-related activity and subsequent adjustments in control and the DLPFC to supporting those adjustments as for the Stroop ^{88,89} Individuals with lesions to rostral ACC show impaired conflict adaptation on the Simon task 96
Pharmacological sensitivity Unknown
Animal models Animal models available for monkey and rat, though the degree of homology needs further research
Performance in schizophrenia Unknown
Psychometric data Unknown

primate work. Much of this literature suggests that the dorsal anterior cingulate (ACC), via inputs from the mid-brain dopamine system, monitors for and detects conflict.^{80,94,95,97,101} In the discussion below, the term ACC will be used to refer both to activation in fMRI studies and to ERP studies examining the ERN, the N2, and the CRN, given the large literature linking these components to an ACC generator. Although there is some debate as to the precise interpretation of the role of ACC in cognition,¹⁰² it is clear empirically that the ACC is more active on high vs low conflict trials in the Stroop task and that it is more active on cI than iI trials in the Stroop task.^{90,92} Further, the magnitude of ACC activity on trial N predicts the degree of behavioral adjustment on trial N + 1, with greater behavioral adjustments associated with greater ACC activity on the previous trial in the Stroop.⁹⁰ In addition, the ACC is strongly active on error trials in the Stroop, and the degree of ACC activity errors predicts the magnitude of posterror slowing (more ACC → more slowing).^{90,103,104}

The actual implementation of control adjustments following conflict detection has been linked to the function of DLPFC. For example, DLPFC activity is greater on iI than on cI trials, putatively reflecting the increased control necessary to execute conflict adaptation,^{92,105} and the degree of DLPFC activity predicts the degree of conflict adaptation.^{88,90,92,106} Further, the degree of ACC activity on previous high conflict trials predicts the degree of DLPFC activity on the subsequent trial.^{88,90}

The lesion data on the role of ACC and DLPFC in control adjustments is mixed. For example, Fellows and Farah¹⁰⁷ did not find evidence that ACC lesions influenced Stroop performance of posterror slowing. However, recent work by di Pellegrino showed reductions in both conflict adaptation and posterror slowing in ACC lesion

patients.¹⁰⁸ Damage to PFC does seem to reduce the likelihood that individuals will correct their errors, but does not appear to reduce post error slowing, which is not consistent with the hypothesis that DLPFC is necessary for conflict-related adjustments in control.¹⁰⁹

The above discussion perhaps implies more consistency in the literature on the neural substrates of dynamics adjustments of control than would be apparent based on a thorough review of the literature. Although there is a large amount of data to support important roles for DLPFC and ACC in dynamic adjustments of control, there is also conflicting data and data that suggest other roles for ACC in action monitoring^{102,110,111} (for a review, see Carter and van Veen¹¹²). As noted above, some of the open questions involve the degree to which ACC and/or DLPFC function is necessary for dynamic adjustments of control and the degree to which posterror and conflict adaptation effects reflect the same mechanisms. This is still a rich and active area of investigation that is generating much interesting data about the neural substrates of cognitive control.

Pharmacological and Behavioral Manipulation

A number of studies have examined pharmacological influences on the ERN and both conflict adaptation and posterror slowing, with mixed results. For example, benzodiazepines reduce the magnitude of the ERN^{113,114} and show some evidence of reducing the N2 congruency effect on the Stroop.¹¹⁴ Benzodiazepines do not appear to reduce posterror slowing but do reduce the influence of errors on conflict adaptation¹¹⁴ and reduce the number of errors that are corrected.¹¹³ Yohimbine (a selective alpha-2 adrenergic receptor antagonist) increases the ERN but does not change posterror slowing. However,

Yohimbine does lead to fewer errors following errors, another reflection of control adaptation.¹¹⁵ Caffeine also increases the ERN but does not influence posterror slowing.¹¹⁶ In terms of dopaminergic modulation, haldol (a D2 antagonist) consistently reduces the magnitude of the ERN,^{117,118} while amphetamine (indirect dopamine agonist) increases it.¹¹⁸ However, neither appears to influence N2 congruency effects or posterror slowing or conflict adaptation effects.^{114,117,118} Olanzapine reduced the ERN and reduced the degree of posterror slowing.¹¹⁸ Thus, these studies provide strong evidence that basic ERN effects to errors can be modulated via pharmacological challenges, both in terms of enhancement and reduction. However, there is mixed evidence as to the degree to which behavioral performance adjustments can be manipulated pharmacologically and evidence for dissociations in the effects of pharmacological manipulations on ERN indices vs behavioral indices.

Animal Models

A growing number of studies have examined conflict- and error-related processing in nonhuman primate models. These studies indicate that neurons in a number of medial prefrontal regions are modulated in response to errors, including anterior cingulate, supplementary motor regions including the supplementary eye fields, and the superior frontal gyrus.^{119–121} However, it is less clear in monkeys that these regions also signal nonerror-related conflict, with some studies suggesting conflict-related activity¹²² and other not,^{121,123} and the temporal dynamics of the error-related signal may differ from that seen in humans. Some work has also examined the role of DLPFC in conflict adaptation in nonhuman primates. This work demonstrated that lesions to DLPFC reduced postconflict behavioral adjustments, but that lesions to the ACC did not.¹²⁴ There is also recent work in a rat model of posterror slowing. In this study, rats were trained a simple reaction time task, in which they had to hold a lever for a specific period of time. The rats showed longer RTs on trials following an error vs those trials following a correct response. Further, inactivation of dorsal medial PFC reduced the amount of posterror slowing shown by the rats.¹²⁵

Performance in Schizophrenia

A growing number of studies have examined fMRI and ERP measures of error and conflict processing in schizophrenia as well as indices of dynamic adjustments in control. Several studies suggest that individuals with schizophrenia show reduced error-related ACC responses^{71,126–132} as well as reduced posterror slowing^{71,126} on the Stroop task as well as other tasks. However, there is also evidence that patients with schizophrenia can show normal error correction performance even in the context of reduced ACC responses to errors^{127,133} and that the relationship between the

magnitude of the ERN and error-related behaviors is intact in schizophrenia.¹³⁰ Individuals with schizophrenia also show reduced conflict-related ACC activation on the Stroop task^{71,127} as well as reductions in conflict adaptation effects.⁷¹

Psychometric Characteristics

There is little published psychometric data on either ERN or ACC responses to error- or conflict-related processes or behavioral indices of conflict adaptation or posterror slowing.

Future Directions

As noted above, there are still open questions about the specific neural circuits that underlie dynamic adjustments in control and open questions about the degree to which conflict adaptation and posterror changes in behavior reflect the same or dissociable mechanisms. There is also a large need for psychometric research on the conflict adaptation and posterror change measures, as well as for ERN and ACC responses. This includes research on test-retest reliability, practice effects, and floor and ceiling effects. In addition, work is needed to determine the optimal number of trials needed to obtain robust estimate of conflict- and error-related behavioral adjustments. In addition, more information is needed on the degree to which reductions in ACC responses (measured either by fMRI or ERPs) or behavioral indices of dynamic adjustment of control are negatively influenced by either typical or atypical antipsychotics in individuals with schizophrenia.

The Stop Signal Task

Description

The stop signal paradigm measures an individual's ability to interrupt a motor response after it has been initiated. The subject is presented with a primary task that generally involves a 2-choice response, such as deciding which of 2 letters is presented and pressing the appropriate button. On a proportion of trials, the subject is presented with a "stop signal," in which case the subject is instructed to withhold their response if possible (see figure 3). The likelihood of stopping is determined by the delay at which the stop signal is presented; if the signal occurs soon after the stimulus, then the subject is very likely to stop, whereas successful stopping becomes much less likely if the signal occurs later in the trial.

The stop signal paradigm allows one to estimate the time needed to stop a behavior. Although this is not an observable quantity (ie, it is a parameter regarding trials where no behavior was made), it can be estimated from observed behavior if certain assumptions are made. These assumptions comprise the so-called "race model" of the stop signal reaction time.¹³⁴ This model assumes that response production and response inhibition processes race

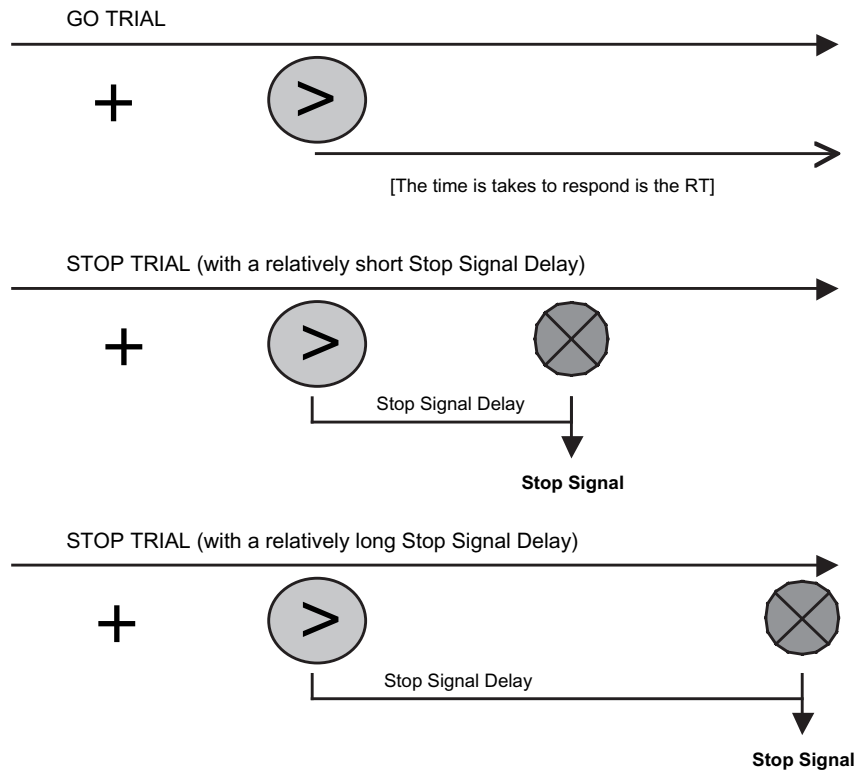


Fig. 3. An Illustration of the Structure of the Stop Signal Task. On each trial, subjects are presented with a stimulus to which they must respond. On some trials they receive a subsequent cue that indicates that they have to stop their response (the stop signal). If the stop signal comes quickly after the initial stimulus, it is a short stop signal delay and it is easier for participants to halt their response. If the stop signal is presented at a longer time following the initial stimulus, it is harder for participants to halt their response.

against one another and that the first one to finish determines whether a response is executed or inhibited. Although the strong assumption of independence is unlikely to be correct,¹³⁵ it nonetheless does a good job of characterizing behavior in the stop signal task.¹³⁶

The goal of the race model is to allow estimation of the stop signal reaction time (SSRT), which is the amount of time needed by the stop process to successfully inhibit a response. There are a number of ways to estimate SSRT;¹³⁴ a commonly used method does this by determining the stop signal delay at which subjects fail to stop on 50% of trials. This value can be estimated either by using an adaptive staircase method to estimate it directly or by evaluating performance at a range of stop signal delay (SSD) values and interpolating to estimate it. Once it is known, then the SSRT can be estimated as, since failing on 50% of trials means that half of the responses are faster than SSRT + and half are slower, which is equivalent to the median RT.

A comprehensive “user’s guide” to the stop signal task was published by Logan and Cowan,¹³⁴ Once the range of SSD values are known, then the SSRT can be estimated, since failing on 50% of trials means that half of the responses are faster than SSRT and half are slower, which is equivalent to the median RT. which should be read closely by any prospective user of the task. It is im-

portant to highlight that this task is highly sensitive to the instructions and feedback that are given to the subject. In particular, many subjects will have the tendency to delay their responses in order to wait for the stop signal. If an adaptive staircase method is used, then this can result in SSD values that do not converge but rather continue increasing across the entire task. When this occurs, it is impossible to obtain an accurate estimate of SSRT because there is no SSD for which the proportion of successful stops is known accurately. These strategies can be reduced by carefully instructing the subjects, and also by providing feedback on go task response time after every block, to ensure that subjects do not slow down on go trials. It is also critical to examine the resulting staircases when adaptive methods are used, to ensure that they have converged to a stable estimate of it. It is particularly useful to use multiple staircases, so that reliability can be assessed across them and so that subjects cannot easily predict changes in SSDs.

One particular issue that has arisen in the literature is whether SSRT should be estimated using adaptive methods or using a set of fixed SSDs. Although more complicated to implement, the adaptive staircase method has a number of benefits. Psychologically, it ensures that subjects with very different levels of inhibitory function exhibit the same proportion of failed inhibitory trials,

which eliminates confounds regarding frustration or error likelihood prediction. Psychometrically, it ensures roughly equal numbers of successful and unsuccessful stop trials, which provides increased power to contrast these conditions; contrast this with the go/no-go paradigm, in which there is generally a very low rate (~10%) of commission errors. Simulation studies¹³⁶ also show that SSRT is more reliably estimated using an adaptive tracking method than using a set of fixed SSDs. The one caution, as noted above, is that adaptive methods may be more likely to lead subjects to adopt waiting strategies; careful instruction and continuous feedback throughout testing can help avoid this problem.

Construct Validity

The stop signal task measures the ability to reactively inhibit a response once it has been initiated. Its construct validity as a measure of control has been demonstrated primarily in the context of impulsivity and behavioral control. In the normal population, SSRT is correlated with real-world impulsivity as measured using paper-and-pencil impulsivity scales.¹³⁷ A large body of research has linked performance on the stop signal task to disorders of impulse control, including attention deficit hyperactivity disorder (ADHD) (reviewed by Lijffijt et al¹³⁸), obsessive-compulsive disorder and trichotillomania,¹³⁹ methamphetamine abuse,¹⁴⁰ and cocaine use.^{141,142}

Neural Systems

Evidence regarding the neural systems supporting stop signal performance in humans comes from both lesion and imaging studies. A study of frontal lesion patients¹⁴³ provided evidence that the right inferior frontal gyrus is critical for stopping in this task; patients with lesions to this area were showed lengthened SSRT values, and SSRT was correlated with the amount of lesion in the region. However, another study found that the medial superior prefrontal cortex (supplementary and pre-supplementary motor areas) is also important for response inhibition.^{144,145} Neuroimaging studies have also implicated both of these prefrontal regions, which show activity on stop trials in comparison to go trials that are correlated across subjects with SSRT.^{146–149} These studies have not generally found activity in right inferior prefrontal or medial superior prefrontal cortex for the comparison of successful vs unsuccessful inhibition; this is predicted by the race model because that model proposes that successful inhibition is primarily driven by the speed of the go process rather than differences in the effectiveness of the stop process.

There is also evidence that basal ganglia regions may be involved in stop signal inhibition, specifically the subthalamic nucleus (STN). Stimulation of the STN in individuals with Parkinson's disease resulted in improved stop signal reaction time.¹⁵⁰ Neuroimaging studies have also found that

STN is activated for successful stop vs go trials and that its activation is also correlated with SSRT across subjects.^{146,147} The role of the STN in stopping is consistent with its excitation of pallidal neurons, which results in thalamic inhibition and cortical deactivation.¹⁵¹ There is also evidence that STN receives direct projections from both of the prefrontal regions implicated in stopping,¹⁴⁷ as part of the "hyperdirect" pathway into the basal ganglia.¹⁵²

Pharmacological or Behavioral Manipulation

There is strong evidence that inhibition on the stop signal task is affected by manipulations of catecholamines. SSRT is improved by methylphenidate in both children¹⁵³ and adults¹⁵⁴ with ADHD. It is likely that this reflects both dopaminergic and noradrenergic effects: SSRT is improved by low doses of cocaine¹⁵⁵ and by specific inhibition of noradrenergic reuptake using atomoxetine¹⁵⁶ and desipramine.¹⁵⁷ There is also evidence for association between stop signal reaction time and genetic polymorphisms in the D4 dopamine receptor and dopamine transporter genes.¹⁵⁸

Animal Models

One of the strong aspects of the stop signal task for translational research is the existence of animal models in both nonhuman primates and rodents. The primate model involves countermanding of eye movements; after fixation on a central point, a lateral stimulus is presented and the animal makes an eye movement to that stimulus. On a small proportion of stop trials, the central fixation point reappears, and the animal is trained to countermand its eye movement on those trials. Extensive work has characterized the neural systems involved in this process (reviewed by Schall et al¹²⁰). This model has provided a great deal of knowledge about how inhibition occurs in eye movements, but there are reasons to believe that the countermanding model may not be applicable to other forms of the stop signal task.

A rodent model of the stop signal paradigm has been developed by Eagle et al.^{159,160} In this paradigm, the rat first presses a button to start the trial and then has to press a second button as the "go" response; on trials when an auditory stop signal is presented, the rat must withhold response in order to obtain reward. Studies using this paradigm have shown that stopping is affected by lesions to the orbitofrontal cortex and STN¹⁶¹ and that it is modulated by *d*-amphetamine,¹⁵⁹ modafinil, and methylphenidate.¹⁶² These results are largely consistent with the human literature and provide strong support for this paradigm as a model system for translational research on response inhibition.

Performance in Schizophrenia

There are relatively limited data on stop signal performance in schizophrenia. Badcock et al¹⁶³ found that

patients with schizophrenia, as well as subjects with other forms of psychosis, exhibited impaired response inhibition (as measured by the slope of inhibition functions because a fixed SSD method was used). Vink *et al.*¹⁶⁴ examined inhibitory control using an adaptation of the stop signal task with a visual stop signal, in patients with schizophrenia and unaffected siblings. SSRT was not estimated, but instead the accuracy of stopping was reported. They found that patients were impaired at stopping, particularly when stop signals became more likely (ie, after a larger number of go trials). Siblings showed a marginally significant effect in the same direction. Bellgrove *et al.*¹⁶⁵ examined stop signal performance in a group of early-onset schizophrenic patients diagnosed as either paranoid or undifferentiated. SSRT was estimated using an adaptive staircase method, with separate SSRT estimates for each hand. The undifferentiated patients exhibited a substantial deficit in SSRT for the left hand; no deficits were observed for the paranoid group. Finally, Enticott *et al.*¹⁶⁶ compared SSRT in schizophrenic inpatients and matched controls and found that schizophrenics showed increased SSRT. Thus, although not conclusive, there is evidence from several studies for deficits in response inhibition in schizophrenic patients and, perhaps more important, in unaffected siblings as well.

Psychometric Characteristics

As noted above, the use of adaptive SSRT estimation methods imbues the stop signal task with desirable psychometric characteristics. By adapting the SSD to each subject to ensure 50% successful inhibition, it prevents ceiling and floor effects (which are problematic in the go/no-go task). In unpublished work (J. R. Cohen & R. A. Poldrack, unpublished), there was no evidence of practice effects in SSRT estimates obtained using adaptive methods. Previous work has also shown that the mean proportion of inhibition, when measured using a fixed set of SSDs, exhibits high test-retest reliability.

Future Directions

Future work on the stop signal task should focus on at least 4 areas. First, a better characterization of response inhibition function across a range of neuropsychiatric disorders is needed, in order to characterize whether there is any specificity to the inhibitory deficits suggested by the existing literature. These studies should also include unaffected relatives, particularly given the potential for antipsychotic drugs to interfere with inhibitory functions. Second, research is needed on ways to develop better adaptive methods for estimation of SSRT and better procedures to prevent strategic adaptations that result in slowing of go response times. Third, work is needed on ways to better delineate different aspects of the stop signal paradigm and their potential effects on reli-

ability and neural systems validity. Relatively little work to date has directly compared different forms of the stop signal task (eg, using visual vs auditory stop signals or using standard vs selective stopping tasks). Fourth, the field needs a better characterization of the genetic architecture of response inhibition. There is evidence from candidate gene studies for association with specific genes, but these await validation by genome-wide association studies.

General Conclusion

The discussion above aimed to present a summary of the data upon which decisions were made at the third CNTRICS meeting in regards to which tasks to nominate for translation into clinical trials. In this selection process and in the descriptions provided above, much emphasis was placed on the evidence regarding construct validity, the neural substrates of the tasks, and the availability of animal models. This emphasis was intentional because the guiding theme of the CNTRICS initiative has been that we need to leverage the advances in cognitive neuroscience to develop better and more effective treatments for cognitive impairment in schizophrenia. One thing that should be clear from the above descriptions though is that much work is needed to make these paradigms—derived from the basic science literature—practical and feasible for use in clinical trials. For some, this process might seem daunting and might lead one to fall back on traditional tasks for which such psychometric and practicality information is already available. However, we would argue strongly that the hard work that lies ahead is well worth it and critically necessary so as to move the field forward. The use of paradigms with a tight grounding in modern theories of human and animal cognitive neuroscience may allow us to pursue a more rationally guided pathway to drug development and testing that has the potential to point the way toward more effective treatment pathways. Yes, it is true that development work for some of these tasks will not end up being successful and some may not “survive” the translation process in a way that allows them to be put to good use in clinical trials. However, even if only some tasks are successfully translated for use in clinical trials, and these paradigms end up improving our ability to design and evaluate effective cognitive treatments, then the whole process will have been worth the time and effort of the many people involved.

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