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Assessing Dysfunction Using Refined Cognitive Methods

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Instruments currently being used to assess cognitive dysfunction do not grant us the granularity to pinpoint the specific cognitive impairments associated with various disorders. With the advent of sophisticated neuroimaging methods and lesion data, we are in a better position to understand the component processes of the various psychological functions. Here we describe 2 such functions and elucidate how the same refined cognitive methods that are being used to understand the processes underlying these functions can be applied to exploring dysfunctions associated with various psychological disorders.

Key words: cognitive dysfunction/executive function/frontal lobes

Introduction

Many psychological functions are complex mixes of component processes. Despite the complexity of these psychological functions, however, most instruments aimed at assessing cognitive dysfunction are too coarse to inform what processes are impaired with psychological disorders. For example, it is recognized that long-term memory has at least 3 distinct stages: encoding, storage, and retrieval.[1] Yet oftentimes a single measure of long-term memory, say percentage of items correctly recalled, is used to assess one's long-term memory function. When poor memory performance is observed with this measure, it is difficult to determine what processes are impaired in the individual. This is because a disruption in any 1 of these stages, encoding, storage, or retrieval, would produce a deficit in the percentage of items correctly recalled.

What this example shows is that when a deficit is found on a gross test of performance (e.g., percent correct recall), the specific processes that are down-regulated remain unspecified. If more analytic instruments were available to isolate the specific processes that are impaired, efforts at rehabilitation could be targeted narrowly at these processes. This is especially important for drug interventions for which there may be interest in rehabilitating a single process while leaving other processes undisturbed. Suppose a gross measure, such as percentage of items correctly recalled in a long-term memory experiment, is used to determine a drug's efficacy. If a drug effect is found, it is difficult to determine the locus of that drug's effect. The effect could be at any combination of the various stages of long-term memory. Indeed, the locus of the drug's effect will determine whether that drug is appropriate for a given patient. A patient who has difficulty in long-term memory retrieval would not be well served by a drug that improves encoding. It is clear, then, that refined measures that isolate specific cognitive processes would be beneficial not only to uncovering the origin of cognitive impairments but also to understanding the efficacy of rehabilitation techniques and determining their proper administration.

To better understand long-term memory, and indeed all psychological functions, at least 2 ingredients are needed: (1) a theory of the component processes involved in the psychological function under question (ideally, computational theories that are precise in specifying the role and function of the component processes) and (2) assessment instruments that are capable of isolating processes of interest. These instruments can include refined behavioral tasks, as well as neuroimaging and lesion evidence. Ultimately, a synergy of behavioral, brain, and modeling work will yield a greater understanding of the various psychological functions and provide refined instruments for their assessment.

One class of psychological functions that would be useful to understand is executive functions. Many neuropsychological instruments are targeted at assessing deficits in executive functioning. These functions include the ability to focus attention, shift attention between stimuli, manage multiple tasks, monitor performance, detect conflict between competing processes or responses, and inhibit irrelevant processes or responses.[2] Diagnostic tests, such as the Wisconsin Card Sorting Task[3] and the Trail-Making Task,[4] provide good sensitivity at detecting impairments in 1 or more of these supposed functions. This sensitivity likely derives from the measurement of a collection of processes, some or all of which might be impeded by the deficit under consideration. The downside of this

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sensitivity is a lack of specificity in analysis of the component processes due to the complexity of the assessment instruments. However, specificity of this sort is vital in understanding the deficit involved and prescribing proper rehabilitation.

Here we examine 2 important executive functions that have been the focus of a large amount of research, and we demonstrate how current standard neuropsychological assessment tools are inadequate in identifying cognitive impairments for these functions. We propose that the same advanced tools being used to expand our understanding of these functions can be utilized to assess cognitive dysfunction.

Wisconsin Card Sorting Task

One popular measure of cognitive dysfunction is the Wisconsin Card Sorting Task (WCST).[3] With this task, a subject is required to sort a deck of cards that vary in 3 attributes: color, shape, and numerosity (figure 1). The subject must sort these cards according to 1 of these attributes but must rely on feedback from the experimenter to determine which 1 of the attributes should be the basis of sorting. Additionally, the experimenter changes the sorting rule unexpectedly, requiring subjects to discover and use a new sorting rule.

Embedded in the assessment tool are several processes. First, pattern-matching processes are needed to sort a card to its proper deck. Next, monitoring processes are enlisted to analyze negative or positive feedback. In the case of positive feedback, working memory processes will be needed to store the proper rule. Negative feedback, on the other hand, will require processes that shift attention from the incorrect rule and generate hypotheses to determine the proper rule. Therefore, this task incorporates processes of working memory, attention shifting, hypothesis generation, and pattern matching. When a subject makes an error in this task, any 1 of these processes may be at fault.

There have been some efforts to tease apart these various processes in a neuroimaging setting. One study used a computerized version of the WCST that isolated 4 separate stages: negative feedback, positive feedback, sorting after negative feedback, and sorting after positive feedback.[5] A simple matching condition was included as a control. These stages were chosen based upon a computational model that predicted dissociable contributions from corticostriatal loops during these 4 stages of processing.[6] For our purposes, we will focus on the 2 feedback conditions.

When a subject receives negative feedback, several processes are at work. First, the subject detects the presence of conflict deriving from use of an incorrect rule. Next, this conflict must be resolved by either inhibiting the incorrect rule, switching to a new rule, or both. Consonant with these ideas, Monchi et al. found increased activation in the anterior cingulate cortex, dorsolateral and ventrolateral prefrontal cortex, posterior parietal cortex, basal ganglia, and thalamus for negative feedback relative to a control condition.[5] These areas have been implicated in conflict monitoring,[7] interference resolution,[8] and attention shifting.[9] In contrast, when subjects receive positive feedback, they must maintain the appropriate rule in working memory. This most likely involves verbal

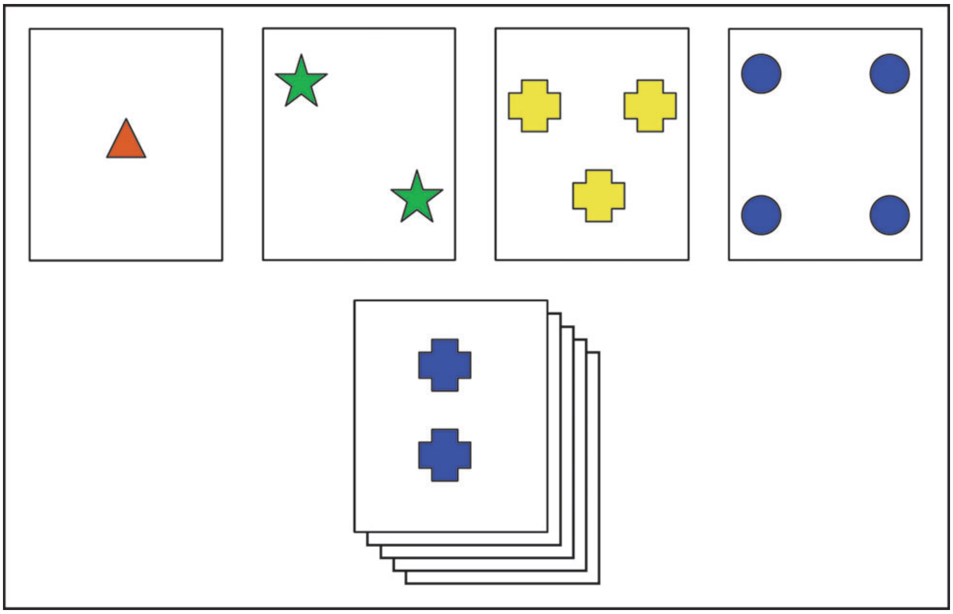

Fig. 1. A representation of the Wisconsin Card Sorting Task. The 4 piles (top) differ with respect to color, shape, and numerosity, and subjects must sort test cards (pile below) into these piles via a certain rule. In this case, if the rule were shape, the test card would be placed with the pile of crosses.

working memory processes, as the subject will often keep the rule in mind in some sort of verbal form. Indeed, when analyzing responses to positive feedback versus a control, Monchi et al.[5] found increased activation in areas typically associated with verbal working memory.[10–11]

Although this study makes nice progress toward decomposing the complexities of the WCST, it cannot precisely inform us about which brain regions are associated with which processes. For example, the regions involved in processing negative feedback may be detecting conflict, resolving interference, switching attention, or any combination of these functions. Indeed, these functions in themselves may also be further decomposed. We begin by analyzing switching processes.

Switching

In the WCST, successful performance depends on the ability to flexibly switch from 1 hypothesis to another. For instance, a subject may have to switch from attending to the color attribute of a stimulus to attending to the shape attribute. Alternatively, subjects may be required to switch between stimuli themselves or between tasks. To investigate whether there is any coherence in brain activations among these various kinds of switches, Wager and colleagues performed a meta-analysis of neuroimaging studies involving switching.[9] This study found that a distinct network of brain regions was consistently activated across different kinds of switches including the intraparietal sulcus, anterior cingulate cortex, premotor cortex (figure 2), and to a lesser degree, dorsolateral and ventrolateral prefrontal cortex and thalamus. Notably, this is much the same network found by Monchi and colleagues for negative feedback in the WCST.[5]

The convergence between the meta-analysis and the study by Monchi et al. suggests that responses to negative feedback may be subsumed under switching. However, this is not the complete story. In the WCST, and indeed in many switching tasks, competing stimuli are present that may induce conflict of 1 sort or another. For example, when switching from sorting by color to sorting by shape, the color and numerosity dimensions of the card are still present, providing a temptation to sort by the incorrect dimension. Processes may be enlisted to suppress these response tendencies so that the correct rule may be selected and used. Unfortunately, from these studies it is unclear what activation is attributable to this conflict resolution and what activation is purely switch related.

To investigate this matter further, Lacey and colleagues examined neural responses to switching with

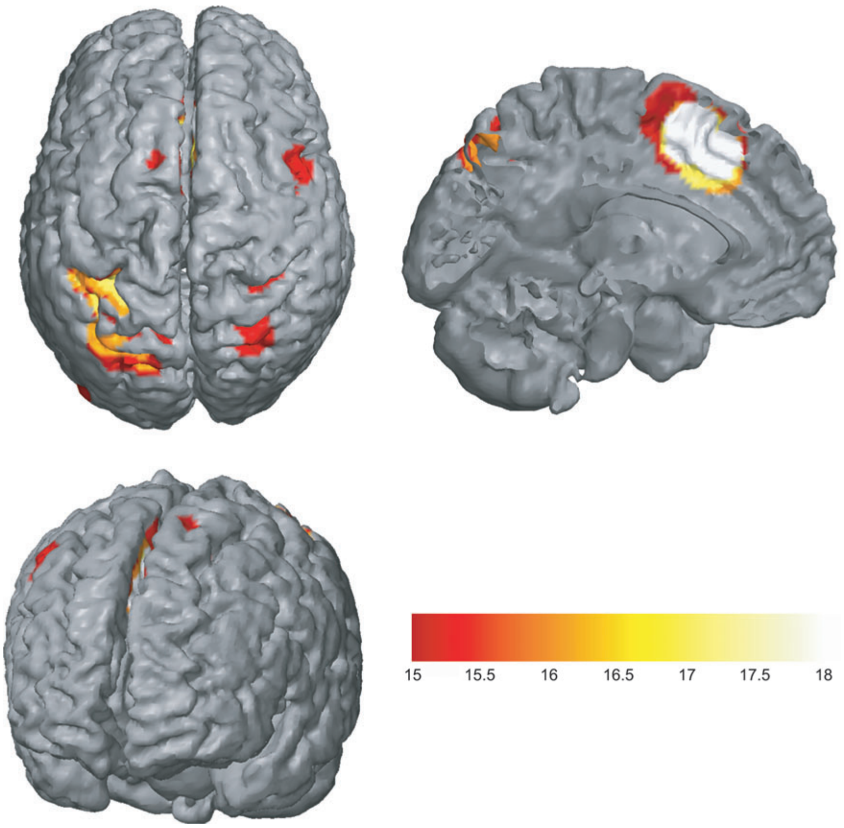

Fig. 2. Renderings of significant switching activation from a meta-analysis of switching tasks.[9] Significant activations are present in the anterior cingulate cortex, premotor cortex, and intraparietal sulcus. Activation in the dorsolateral and ventrolateral prefrontal cortex, as well as the thalamus, is present at a lowered threshold (not pictured).

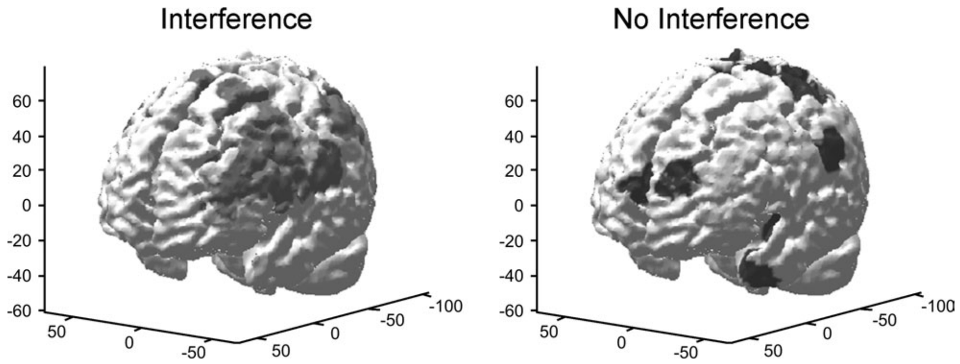

Fig. 3. Activations for interference (left) and noninterference (right) versions of a task-switching paradigm.[13] Both contrasts examine switch- versus non-switch-related activity. Notably, the interference version of the task uniquely activates the dorsolateral prefrontal cortex, whereas the noninterference version shows unique frontopolar activation.[12]

and without the presence of conflict.[12] These researchers adapted a popular switching paradigm that presents subjects with a letter and a digit.[13] The color of the stimuli denotes which stimuli (either the letter or the digit) the subject is required to attend to. When attending to the letter, subjects make a vowel/consonant judgment, and when attending to the digit, they make an odd/even judgment. So in this paradigm, switching occurs when subjects switch from attending to a letter to attending to a digit or vice versa. Embedded in this task is competition from the irrelevant stimulus (i.e., the stimulus that is not to be attended to). To control for this, Lacey and colleagues included a condition where the competing stimulus was a false-font character, thereby eliminating a source of interference from competing task-irrelevant stimuli.

When examining switch-related activity with and without the presence of interference, dissociable neural patterns emerged. Notably, the lateral prefrontal cortex was uniquely activated for switching in the presence of conflict, whereas the frontopolar cortex was uniquely activated for switching without conflict (figure 3). This suggests that much of the lateral prefrontal activation may be attributable to conflict resolution rather than switching per se. Can we further interrogate this conflict-related activation? We turn to this question next.

Interference Resolution

Many clinical symptoms of dysexecutive syndrome and frontal lobe insults involve failures to resolve interference.[14] For example, perseverative behaviors found in schizophrenia and in other pathologies may be the result of failures to resolve interference.[15] One task that has commonly been used to assess the ability to resolve interference is the Stroop Task.[16] In the color word version of this task, subjects are required to name the color of a word while suppressing the tendency to read the word itself. When the color of the word and the word itself denote conflicting responses (e.g., the word *red* printed in green), this conflict must be resolved in order to arrive at the appropriate response. However, even in this simple task, it is often unclear at what processing stage the conflict is resolved. Conflict can be resolved during stimulus processing by ignoring the competing stimulus itself, during response selection by biasing responses toward selecting color information over word information, or at response execution by restraining an inappropriate response in favor of the correct response.[8] Is there reason to believe that these various types of conflict resolution are mediated by different mechanisms, or is interference resolution a unitary construct?

Nee and colleagues conducted a meta-analysis of 6 interference-resolution tasks including the Stroop, flanker, go/no go, stimulus–response compatibility, Simon, and stop-signal tasks to investigate whether there was any coherence among different types of interference resolution.[8] Across the various interference-resolution tasks a network of brain regions including the dorsolateral and ventrolateral prefrontal cortex, premotor cortex, anterior cingulate cortex, and posterior parietal cortex was observed. However, when individual tasks were interrogated it was found that each task preferentially activated a subset of these regions. Other studies have confirmed both common and unique brain regions among interference-resolution tasks.[17–18] Furthermore, correlations among interference-resolution tasks are often quite low,[19–20] and other studies have found behavioral dissociations among different kinds of interference resolution.[21] Therefore there appears to be some controversy regarding whether interference resolution is a unitary or multidimensional construct.

Part of the ambiguity of whether interference resolution is unitary or involves multiple mechanisms is likely due to the complexity of interference-resolution tasks, such as the Stroop Task. What is needed, then, is a task that requires a simple and isolated form of interference resolution. One task that has been widely studied adds a well-controlled form of proactive interference into a popular working memory paradigm.[21–22] In this task,

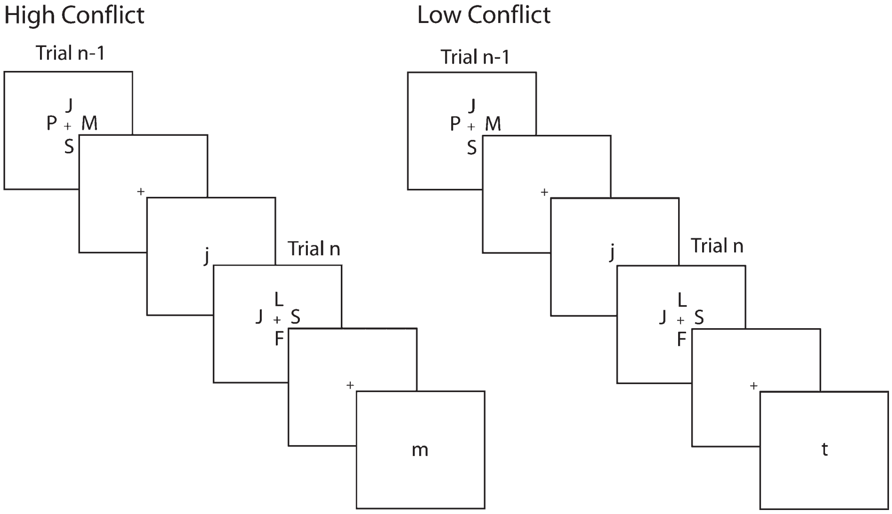

Fig. 4. A schematic of the Recent-Probes task. In the high-conflict condition, a probe that was a member of the target set on the previous trial must now be rejected on the current trial (recent negative). In the low-conflict condition, the negative probe has not occurred recently (nonrecent negative).

subjects are given a small memory set of items (figure 4). After a short retention interval, subjects are given a probe and must determine whether or not the probe was a member of the target set. To introduce conflict, a probe letter may be a member of a recently presented target set, although not included in the current target set (recent negative). In this task, subjects must overcome proactive interference to respond negatively to the target item. We can contrast these recent negatives to probes that have not appeared recently yet also demand a negative response (nonrecent negatives). Comparing recent negatives to nonrecent negatives isolates the conflict-resolution process aimed at reducing proactive interference. In this way, this task provides a simple approach to analyzing a single executive function without being swamped by several other processes.

Studies using this paradigm have found interference effects reflected by increased reaction times and error rates for responses to recent negatives compared to nonrecent negatives.[21, 23] When contrasting brain activation for recent negatives compared to nonrecent negatives, robust activation has been found in the left inferior frontal gyrus (figure 5).[23–24] This activation correlates with behavioral interference effects.[25] Furthermore, elderly subjects show increased behavioral interference effects on this task with a concurrent lack of activation in the left inferior frontal gyrus, furthering the evidence that this region mediates resolution of interference.[25]

Mere correlational data do not provide a causal link between this region and the resolution of proactive interference. Fortunately, lesion data may provide evidence where correlational data are insufficient. A study investigating a patient, R.C., with damage to the left inferior frontal region implicated in this task discovered that R.C. shows a profound behavioral deficit in this task. Compared to controls with frontal damage that does not

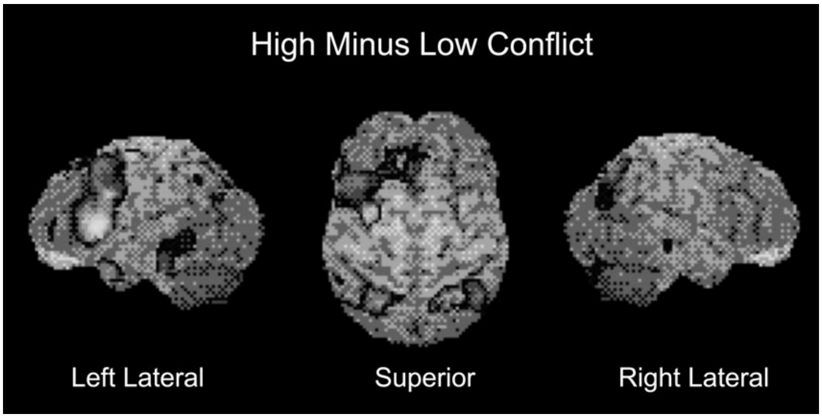

Fig. 5. Activations for recent negative versus nonrecent negative blocks of trials from Jonides et al.[23] The most significant activation can be seen in the left inferior frontal gyrus.

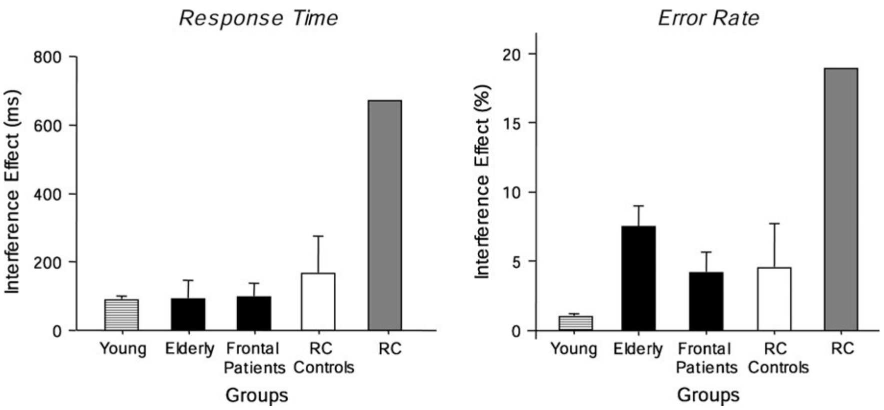

Fig. 6. Behavioral interference effects of patient R.C., with damage to the left inferior frontal gyrus. Compared to those of frontal controls, normal young subjects, and elderly subjects, R.C.'s interference effects are several standard deviations higher.[26] Interference effects did not correlate with the size of the lesion.

include this region, as well as elderly subjects, R.C. is still several standard deviations worse than the norm (figure 6).[26] These effects have also been replicated in another patient, M.L., with similar damage.[27] In sum, there appears to be clear evidence that the left inferior frontal gyrus is implicated in interference resolution. Moreover, this interference resolution appears to be of a specific sort, namely, the resolution of proactive interference in a finely controlled task.

From this example, we can begin to see how it is possible to isolate a particular process, understand the neural underpinnings of that process, and measure what deficits occur when this process is disrupted by combining refined behavioral and neuroimaging techniques, as well as lesion data. However, as we discussed earlier, this is merely 1 kind of interference resolution. Much work is still needed to unpack and discover the neural correlates and behavioral signatures of other types of interference resolution. As research in these areas progresses, so too will our ability to assess and understand cognitive dysfunction.

Conclusion

Returning to the WCST, we can see clearly that we must be precise in dissecting the specific processes that are impaired to identify and rehabilitate deficits. A failure to switch to a new rule and an inability to resolve interference from a highly salient and competing previous rule can both lead to perseveration errors. However, a gross look at this dependent variable is not diagnostic as to which specific function is impaired. In other words, very different psychological and neurobiological dysfunctions can lead to very similar behavioral deficits that will be ambiguous without properly analytic techniques. Therefore it may be more appropriate to separately assess switching, interference resolution, and the other various processes involved to better understand the nature of the deficit. "Classic" tests of executive dysfunction such as the WCST may still hold value in narrowing down which of many processes may be down-regulated, but these would be best followed up with more analytical measures to precisely identify the specific processes of interest.

We have demonstrated that many psychological functions are actually complex mixes of component processes. We have argued that sifting through this complexity to better understand psychological functions is not only a fruitful but also a tenable task. Refined behavioral and neuroimaging techniques combined with lesion data and accurate and precise models will help us further our understanding of psychological functions and grant us the ability to understand what disruptions occur in association with psychological disorders.

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References

1. Baddeley AD. *Human Memory: Theory and Practice*. Boston: Allyn and Bacon; 1998.
2. Smith EE, Jonides J. Storage and executive processes in the frontal lobes. *Science* 1999;283:1657–1661.
3. Milner B. Effects of brain lesions on card sorting. *Arch Neurol* 1963;9:90–100.
4. Reitan RM. *Trail Making Test: Manual for Administration and Scoring*. Tucson: Reitan Neuropsychology Laboratory; 1992.
5. Monchi O, Petrides M, Petre V, Worsley K, Dagher A. Wisconsin Card Sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *J Neurosci* 2001;21(19):7733–7741.
6. Monchi O, Taylor JG, Dagher A. A neural model of working memory processes in normal subjects, Parkinson's disease

and schizophrenia for fMRI design and predictions. *Neural Networks* 2000;13:953–973.

7. Botvinick M, Braver TS, Barch DM, Carter CS, Cohen JD. Conflict monitoring and cognitive control. *Psychol Rev* 2001;108:625–652.
8. Nee DE, Jonides J, Wager TD. A meta-analysis of interference-resolution tasks. Poster presented at the Meeting of the Cognitive Neuroscience Society, San Francisco, April 2004.
9. Wager TD, Reading S, Jonides J. Neuroimaging studies of shifting attention: a meta-analysis. *Neuroimage* 2004;22: 1679–1693.
10. Jonides J, Schumacher EH, Smith EE, et al. Verbal working memory load affects regional brain activation as measured by PET. *J Cognitive Neurosci* 1997;9:462–475.
11. Smith EE, Jonides J, Koeppe RA. Dissociating verbal and spatial working memory using PET. *Cereb Cortex* 1996;6: 11–20.
12. Lacey SC, Sylvester CYC, Jonides J. Dissociating prefrontal and parietal cortices in task-switching. Paper presented at the Meeting of the Society for Neuroscience, New Orleans, November 2003.
13. Rogers RD, Monsell S. Costs of a predictable switch between simple cognitive tasks. *J Exp Psychol Gen* 1995;124(2):207–231.
14. Stuss DT, Knight RT. *Principles of Frontal Lobe Function*. New York: Oxford University Press; 2002.
15. Goldberg E. *The Executive Brain: Frontal Lobes and the Civilized Mind*. New York: Oxford University Press; 2001.
16. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol* 1935;18:643–662.
17. Fan J, Flombaum JI, McCandliss BD, Thomas KM, Posner MI. Cognitive and brain consequences of conflict. *Neuroimage* 2003;18(1):42–57.
18. Wager TD, Sylvester CYC, Lacey SC, Nee DE, Franklin MS, Jonides J. Common and unique components of response inhibition revealed by fMRI. *Neuroimage*; in press.
19. Kramer AF, Humphrey DG, Larish JF, Logan GD, Strayer DL. Aging and inhibition: beyond a unitary view of inhibitory processing in attention. *Psychol Aging* 1994;9: 491–512.
20. Shilling VM, Chetwynd A, Rabbitt PMA. Individual inconsistency across measures of inhibition: an investigation of the construct validity of inhibition in older adults. *Neuropsychologia* 2002;40:605–619.
21. Monsell S. Recency, immediate recognition, and reaction time. *Cognitive Psychol* 1978;10:465–501.
22. Sternberg S. High-speed scanning in human memory. *Science* 1966;153:652–654.
23. Jonides J, Smith EE, Marshuetz C, Koeppe RA, Reuter-Lorenz PA. Inhibition in verbal working memory revealed by brain activation. *P Natl Acad Sci USA* 1998;95:8410–8413.
24. Jonides J, Nee DE. Brain mechanisms of proactive interference in working memory. Submitted MS.
25. Jonides J, Marshuetz C, Smith EE, Reuter-Lorenz PA, Koeppe RA, Hartley A. Age differences in behavior and PET activation reveal differences in interference resolution in verbal working memory. *J Cognitive Neurosci* 2000;12: 188–196.
26. Thompson-Schill SL, Jonides J, Marshuetz C, et al. Effects of frontal lobe damage on interference effects in working memory. *Cognitive Affect Behav Neurosci* 2002;2: 109–120.
27. Hamilton AC, Martin RC. Dissociations among tasks involving inhibition: a singe-case study. *Cognitive Affect Behav Neurosci* 2005;4(1):1–13.