fMRI Investigation of an Experimental Executive Function Measure:

Comparison of the Texas Card Sorting Test

to the Wisconsin Card Sorting Test

in Healthy Adults

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For Grandma Bea, whose love taught me to soar.

For my parents,
who instilled in me the values of
hard work, education, and integrity.

For Matt, whose heartprint changed my soul forever.

fMRI Investigation of an Experimental Executive Function Measure: Comparison of the Texas Card Sorting Test to the Wisconsin Card Sorting Test in Healthy Adults

by

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DISSERTATION

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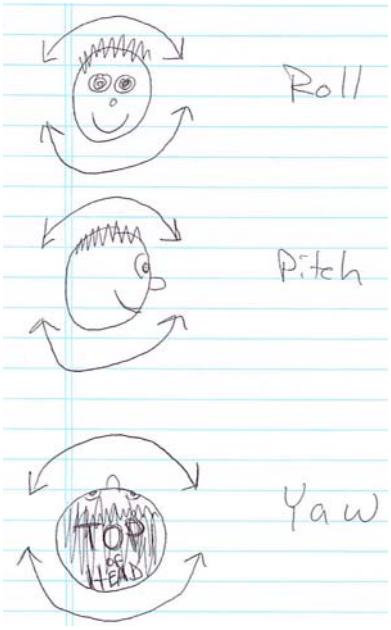

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Although executive functioning is one of the most studied constructs in neuropsychology, it remains one of the most elusive and enigmatic skill sets to measure and understand. The Wisconsin Card Sorting Test (WCST) is commonly used to assess executive functioning, though it has been criticized for its lengthy administration time and negative feedback component. The Texas Card Sorting Test (TCST) was developed as a problem-solving measure to be applied in linguistically diverse samples, and does not have the limitations of the WCST. The

overall purpose of the present study was to validate the TCST as a measure of frontal and subcortical function, and to compare the TCST to the WCST.

Twenty-five healthy volunteers underwent functional magnetic resonance imaging (fMRI) while performing computerized versions of the WCST and TCST. Significant activations during the TCST were observed in the prefrontal cortex (BA 6, 9, 44-47), the basal ganglia, bilateral parietal areas (BA 7 & 39), left cingulate gyrus (BA 24, 31, & 32), right superior temporal areas (BA 41 & 22), left parahippocampal and middle temporal gyri, and right occipital lobe (BA 18 & 19). Compared to the WCST, the TCST showed increased activity bilaterally in the frontal lobe (BA 6 & 47), right frontal areas (BA 10 & 11), the caudate, right superior temporal lobe (BA 38, 41, 42), right temporal lobe (BA 22 & 34), and left occipital lobe (BA 19 & 31). Behaviorally, no significant correlations were seen between the WCST and TCST performance variables.

This research supports the TCST as a measure of frontal-subcortical function. The TCST appears to be particularly sensitive to orbitofrontal/caudate circuitry as well as superior temporal areas, with greater activation overall observed in right cerebral areas. Given the lack of correlation on behavioral performance variables and the distinct differences in neural correlates, the TCST may assess cognitive processes that are different from the WCST. The TCST has promising potential as a clinical neuropsychological instrument.

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LIST OF ABBREVIATIONS

AC	Anterior Cingulate
BA	Brodmann's Area
BOLD	Blood Oxygen Level Dependent
DLPFC	Dorsolateral Prefrontal Cortex
EF	Executive Functions
FDR	False Discovery Rate
fMRI	Functional Magnetic Resonance Imaging
MNI	Montreal Neurologic Institute
MRI	Magnetic Resonance Imaging
OF	Orbital Frontal or Orbitofrontal
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
rCBF	Regional Cerebral Blood Flow
ROI	Region(s) of Interest
SPECT	Single Photon Emission Computed Tomography
SPM	Statistical Parametric Map or Statistical Parametric Mapping
T-CTL	Texas Card Sorting Test Control Task
TCST	Texas Card Sorting Test
W-CTL	Wisconsin Card Sorting Test Control Task
WCST	Wisconsin Card Sorting Test

INTRODUCTION

Executive functions, among the most intriguing neuropsychological conundrums, are described as the most complex processes driving human cognition and behaviors (Fuster, 1999, p. 309). The executive functions (EF) include response inhibition, planning, strategy development, mental flexibility, problem solving, self/affect regulation, integration and interpretation of cognitive processes over time, sequencing, and working memory (Archibald & Kerns, 1999; Barkley, 2004; Lezak, Howieson, Loring, Hannay, & Fischer, 2004). Intact executive functioning is crucial for everyday problem solving, coping with novel situations, directing purposeful activity, adapting flexibly to changing environmental contingencies, and successful incorporation of feedback. Research studies have implicated aspects of person perception, social interactions, and theory of mind constructs as executive functioning domains (Archibald et al., 1999; Channon & Watts, 2003; Macrae, Bodenhausen, Schloerscheidt, & Milne, 1999; Rowe, Bullock, Polkey, & Morris, 2001). Neuroanatomically, executive functions are generally associated with the frontal lobes, and more specifically, prefrontal cortex and frontal-subcortical circuitry (Alexander, DeLong, & Strick, 1986; Chow & Cummings, 1999).

Dysfunction of executive systems is linked to a myriad of disorders. Executive functioning deficits of varying severity have been documented in childhood disorders such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorders, conduct disorders, phenylketonuria, and Tourette's syndrome (Archibald et al., 1999; Barkley, 2004; Bebko & Ricciuti, 2000; Brocki & Bohlin, 2004; Pennington & Ozonoff, 1996).

Executive impairment is also implicated in brain tumors, stroke, traumatic brain injury, schizophrenia, and major depression (Hobson & Leeds, 2001). Furthermore, evidence from empirical studies suggests that some degree of executive functioning decline is associated with normal aging (Amieva, Phillips, & Della, 2003; Bryan & Luszcz, 2000), and determining the degree of symptoms related to executive dysfunction facilitates detection and characterization of various types of dementia (e.g., Parkinson's disease, Alzheimer's disease, frontotemporal dementias, and other subcortical neurodegenerative diseases). Ecologically, a poignant aspect of executive functioning research is that impairment is associated with compromised independence and difficulties in many facets of daily life (Cahn-Weiner, Boyle, & Malloy, 2002). As Lezak et al. (2004) remarked,

> When executive functions are impaired, the individual may no longer be capable of satisfactory self-care, of performing remunerative or useful work independently, or of maintaining normal social relationships regardless of how well-preserved the cognitive capacities are . . . Impairments in executive functions tend to show up globally, affecting all aspects of behavior. (p. 35)

Thus, understanding normal executive functioning and associated brain circuitry is essential for accurately deciphering executive disruption and understanding the roles of executive dysfunction in psychological, neurological, and behavioral disorders across the lifespan.

Measuring and operationally defining EF is an extreme challenge because the construct encompasses a panoply of abilities requiring integration and interaction

among multiple cognitive domains and brain systems. Thus, as Archibald and Kerns (1999) emphasized, neuropsychology has had limited success in creating specific and sensitive measures of executive functioning. Lesion research has validated several “frontal” tests (i.e., Wisconsin Card Sorting Test, Stroop Test, Verbal Fluency, and Auditory Consonant Trigrams) based on patients with pre-frontal lesions exhibiting a greater degree of impairment than patients with non-frontal damage (Boone, Ponton, Gorsuch, Gonzalez, & Miller, 1998; Jurado, Mataro, Verger, Bartumeus, & Junque, 2000; Lombardi et al., 1999; Milner, 1963; Pujol et al., 2001; Stuss et al., 1998; Tucha, Smely, & Lange, 1999). Clinically, one of the most widely used, traditional measures of frontal lobe functioning has been the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993), and factor analysis studies have indicated that the WCST appears to measure several aspects of executive functioning, such as mental flexibility, problem solving efficiency, and ability to adapt behavior to changing contingencies (Boone et al., 1998; Golden, Kushner, Lee, & McMorrow, 1998). However, the literature has not universally supported the WCST as a reliable indicator of frontal lobe dysfunction (Anderson, Damasio, Jones, & Tranel, 1991; Lombardi et al., 1999; Robinson, Heaton, Lehman, & Stilson, 1980). Despite the controversy present in the literature regarding the specificity and sensitivity of the WCST to frontal lobe damage, it continues to be one of the major instruments used in clinical neuropsychological test batteries to assess frontal lobe integrity. Neuroimaging studies have attempted to further elucidate WCST specificity and sensitivity issues by analyzing brain

activation patterns during the WCST, and these studies generally agree the WCST elicits prefrontal cortex activation (Goldberg, Berman, Mohr, & Weinberger, 1990; Ragland et al., 1998; Ragland et al., 1997; Volz et al., 1997). However, reported samples, methodologies, and results vary and are laden with contradictions and inconsistencies. One potential reason for the variable reports of the WCST's sensitivity to frontal lobe damage may be the limited research available on the involvement and function of subcortical structures during the executive processes involved in successful WCST performance (Lombardi et al., 1999). Thus, identifying brain regions the WCST taps and the implications of poor performance or unusual brain activation patterns requires a solid understanding of the subcortical and cortical brain circuitry underlying WCST performance in normal individuals.

Although the WCST is a standard test used to assess mental flexibility and problem solving, it has been criticized for its lengthy administration time, as normal subjects require 20-30 minutes to complete the test (Heaton et al., 1993). Another criticism of the test is its use of negative feedback (i.e., the subject is told "incorrect" or "wrong" when they match a card incorrectly). The use of negative feedback may be perceived as aversive and frustrating by some patient populations, or even by some normal subjects. Thus, alternative measures of executive functioning without the weaknesses of the WCST may prove valuable to clinicians.

Although other available measures of executive functioning do not utilize negative feedback and are briefer than the WCST (i.e., Stroop, California Card Sorting Test, Delis Kaplan Executive Function System), these measures use English

verbal stimuli. Thus, the use of these tests of executive function is restricted in populations with limited language skills or where English is a second language. The Texas Card Sorting Test (TCST) was developed as a new, briefer nonverbal measure of problem solving and cognitive flexibility designed to address these concerns (Kaltreider, Vertovec, Saine, & Cullum, 1999). The TCST is brief (10 minutes for normal subjects to complete), does not use negative feedback, and utilizes nonverbal stimuli. Thus, in theory, the TCST may be a promising alternative to the WCST as a measure of problem solving and mental flexibility, and may also be effective in populations with limited English or language deficiencies. Utilizing functional brain imaging is one innovative way to validate the TCST as a measure that engages executive brain systems, as no normative data on healthy controls exists.

The purpose of the present study was to utilize functional magnetic resonance imaging (fMRI) to investigate the validity of the TCST as a frontal-subcortical measure. Another major objective of this research was to compare activation patterns and behavioral data between the WCST and the TCST to determine whether the TCST is a viable alternative to the WCST, or whether it measures yet another facet of the enigmatic executive functions. An additional focus of this project was to examine the involvement of subcortical and cerebellar structures during the WCST and the TCST in a normal sample. Finally, subjects' perception of frustration during the WCST and the TCST were explored.

LITERATURE REVIEW

Definition of Executive Functioning

Developmental and cognitive psychologists describe executive functions (EFs) as metacognitive processes, which are loosely defined as “cognition about cognition” (Flavell, Miller, & Miller, 1993, p. 150). These processes include the analysis, selection, implementation, regulation, and monitoring of cognitive strategies (Souchay, Isingrini, Clarys, Taconnat, & Eustache, 2004; Torgesen, 1994). Conceptualized as an information processing view, this perspective highlights EFs as necessary for efficient learning, academic success, developing a healthy self-concept, and for future-oriented thinking and goal setting (Lyon & Krasnegor, 1996, p.369). Within this model, EFs are measured indirectly through learning behaviors by measuring strategy choice, utilization, and modification. The ultimate purpose of this model is to improve goal attainment and problem solving, leading to increased adaptive behavioral responses (Lyon et al., 1996).

One major behavioral approach to modeling EF was contributed by Steven Hayes and utilized relational frame theory (RFT; Lyon et al., 1996). Recently, Hayes and Fox (2004) described RFT as an empirically based theory primarily focused on stimulus relationships in humans. Simply stated, someone who learns that A = B and A = C will derive B = C, even though this relationship is never explicitly stated. Hayes and Fox emphasized that the equivalence of B = C is unanticipated as these two events have not been previously grouped together and

reinforcement has not occurred for pairing them. Hayes and Fox also stipulate that their model is not limited to equivalencies; rather, if A > B and B > C, than most people would derive that A > C, where > could represent any comparative relationship (i.e., bigger than, greater than, faster than, etc.). Thus, novel stimuli can be made more or less reinforcing depending on whether they are interpreted to be "more than," "less than," or "equal to." Hayes and Fox suggest that the psychological ramifications of these relational frames can explain complex phenomena such as behavior regulation, rule understanding, development of perspective-taking, sense of self, and powerful emotional responses due to environmental stimuli (Hayes & Fox, 2004). A computational model presented by Kimberg and Farah (1993) explained performances on motor sequencing, the Stroop task, the WCST, and a contextual memory task by diminishing associations among the goal, stimuli, and knowledge-based working memory components (essentially manipulating the A, B, and C relationships). Thus, their work may provide preliminary empirical support for an explanation of RFT contributions to executive functioning.

Barkley's (2004) model of EF incorporates evidence from a broad spectrum of disciplines including behavioral theory, developmental psychology, neuropsychology, and neuroimaging studies. Initial conceptualizations of his theory were influenced by Bronowski's seminal work (1976) on delayed response processes. Barkley put forth behavioral inhibition as the governing force behind four major categories of EFs. He proposed that behavioral inhibition allows individuals to

inhibit precipitous responses, interrupt an ongoing response, and control interference. The four basic classes of EFs Barkley described are: 1) nonverbal working memory, 2) internalization of speech (verbal working memory), 3) self-regulation, and 4) reconstitution (commonly known in neuropsychology as flexibility, generativity, and/or fluency). Barkley's model has a unique evolutionary bent; he proposed that the four EFs developed by a common process and were publicly observable or external at one time. Then with maturity, those outward behaviors were suppressed and internalized for more adaptive behavior control. As Barkley (2004) succinctly stated, "With maturation, the individual progressively comes to be guided more by covert representations that permit self-control, deferred gratification, and goal-directed actions toward conjectured social futures" (p.309). Barkley's model emphasized precise, behaviorally driven operational definitions of EFs in order to generate testable hypotheses.

Similar to Barkley, Denckla (1996) conceptualized the evolution of a child to an adult as the gradual development of executive functions. Denckla suggested that the imprecise definitions of EF and frontal-lobe functioning often lead to inappropriate overlapping of the two terms. She further acknowledged the difficulty of contextually separating EF from prefrontal-subcortical brain circuitry. According to Denckla, clinicians further promote the inconsistent slippage between EF and frontal-lobe functioning, as they are prone to use EF as an abbreviated clinical nomenclature to capture the deficits of certain patient populations, and thus may incorrectly use frontal functions synonymously with EF. Denckla advocated thinking

of the EF as control processes, rather than cognitive psychology's preferred meta processing way of thinking. She suggests that there are three main EF theoretical contexts. They are:

> . . . 1) historic linkage to prefrontal (especially dorsolateral regions and their subcortical domain-general interconnected regions; 2) clinical convenience, the need to capture distinctive features of certain patients; and 3) developmental, in that child becomes adult largely in terms describable under the EF umbrella and isomorphic with brain circuitry dovetailing with context number one. (Denckla, 1996, p. 265)

She stated that the fundamentals of her conceptualization of EF involve response delay and inhibition, and that EF can be measured through four main processes she termed ISIS, which stands for Initiate, Sustain, Inhibit, and Shift. Similar to other theorists, she incorporated working memory, the future-oriented aspect of EF, and the mediating roles of language and intelligence.

Welsh and Pennington (1988) offer a slightly different neuropsychological perspective, though they primarily emphasize that EFs are critical for achieving future-oriented goals and successful problem resolution. Significant components of their approach to the EFs include adequate sequencing of future action plans, retaining plans/programs on-line until carried out, inhibiting/delaying irrelevant actions, and developing the capability to mentally represent the current task/problem and the desired future outcome (Eslinger, 1996; Welsh & Pennington, 1988). Welsh and Pennington further suggested that the EF concept is similar to

cognitive psychology's model of a central processing system. Pennington's approach to EF and his foreshadowing of these functions as central executive operations highlighted working memory as critical to efficient problem solving, goal attainment, and adapting to novel contexts.

In a similar vein, Kolb and Whishaw (2003) described EF as "control systems that implement different behavioral strategies in response to both internal and external cues" (p. 395), and they emphasized that EFs are crucial for the temporal organization of behavior. However, they hastened to add that "in recent years, it has become fashionable to refer to these temporal systems as *executive functions*, although we do not want to read too much into this label" (p. 395). Lezak et al. (2004) succinctly defined EF as consisting "of those capacities that enable a person to engage successfully in independent, purposive, self-serving behavior" (p. 35).

Although theorists disagree on semantics, conceptual similarity clearly exists among the various EF models and definitions. However, their variability makes operationalization and interpretation of EF empirical studies challenging (Wecker, Kramer, Wisniewski, Delis, & Kaplan, 2000). The above definitions demonstrate the breadth of functions under the EF rubric. Many studies have attempted to parcel out the specific cognitive operations of EF through factor analysis (Bentler, 1985). For instance, Miyake et al. (2000) proposed three basic functions (shifting, updating, and inhibition) based on an extensive review of the literature and applying a sophisticated latent variable factor analysis to reported results. Boone et al. (1998) found three factors they labeled cognitive flexibility, processing speed, and divided

attention/short-term memory when analyzing four common tests of executive functioning (i.e., WCST, Stroop Test, Verbal Fluency, and Auditory Consonant Trigrams). Robbins (1998) reported that the three main aspects of EF are planning, working memory, and response control/attentional shifting. Lezak et al. (2004) included volition, planning, purposive action, and effective performance as the primary components of EF. Thus, similar to the enigmatic EF construct, much variability exists among the literature on defining its key features. As the present study looks at performance on problem solving measures (WCST and TCST), it will focus on the strategy generation, mental flexibility, and effective performance aspects of executive functioning.

Strategy generation is the ability to rapidly produce a variety of viable solutions to a particular problem. Individuals with mental flexibility are able to cope with novel situations and problem solve successfully as they can switch solutions or strategies to adjust efficiently to changing environments. Mental flexibility is the ability to adapt as required. Effective performance looks at the efficiency of problem solving, usually through error analysis. Aspects of effective performance include analyzing whether the individual had difficulty staying on task, was perseverative (i.e., had difficulty switching and/or terminating an activity), and/or was inefficient in hypothesis testing of alternative solutions. Errors may also indicate guessing or using overly-complex strategies (Goldstein & Green, 1995; Lezak et al., 2004).

Clearly, executive functions and their associated processes are extremely complex, and theoretical, operational definitions of these constructs remain elusive.

However, with the development of sophisticated technologies to analyze and explore neuroanatomical regions and connections, scientists have new tools to explore the complicated executive functions, their processes, and the underlying neurocircuitry.

Neuroanatomical Models of Executive Functioning

Prefrontal Cortex

As mentioned previously, the terms “frontal lobe functions” and “executive functions” are often erroneously used interchangeably. In fact, patients without frontal lesions may exhibit symptoms of executive dysfunction (Andres & van der Linden, 2002; Goldstein, Obrzut, John, Ledakis, & Armstrong, 2004; Pujol et al., 2001). Thus, the difficulty of defining and measuring executive function has impeded the exploration of its physiological correlates (D'Esposito & Grossman, 1996). However, the frontal lobes, and especially the prefrontal cortex (PFC), are compelling suspects in the executive function arena (Bamdad, Ryan, & Warden, 2003; Pennington et al., 1996; Rezai et al., 1993).

Fuster (2002) argued that temporal organization of actions to achieve goals was the most compelling role of the prefrontal cortex (PFC). He stressed the integrative role of the prefrontal cortex, and noted that the extensive, diverse array of connections within the PFC and to other areas of the brain support its critical role in brain circuitry and multiple brain systems. Fuster pointed out that routine, automatic, or over-learned behavioral sequences do not engage the PFC, whereas sequences with cross-temporal contingencies, and/or ambiguities activate the PFC (Fuster, 2001). According to his theory, temporal integration is served by attention, working memory, and preparatory set. He argues that it is the temporal integration of the PFC that is fundamental to engaging in complex and/or novel language and

behavior. Harrington, Haaland, and Knight (1998) investigated the role of the cerebral cortex in timing with focal left or right hemisphere lesion patients and controls. Lesion and control subjects performed two time perception tasks. One was a duration perception task, where paired tones were presented either 300 or 600 milliseconds apart. The other task was a frequency perception task, which controlled for time-independent processes shared by both tasks. When frequency perception deficits were controlled, only the right hemisphere-lesioned patients showed time perception deficits. Thus, their research implicated a right hemisphere prefrontal-inferior parietal network in timing, providing some support for Fuster's assertion that a critical function of the PFC is temporal operations.

Goldman-Rakic's seminal research with monkeys was a major contributor to the prefrontal cortex puzzle. She asserted that the prefrontal cortex serves a working memory function, by temporarily holding on-line stimulus representations until a response is indicated. Goldman-Rakic used creative electrophysiological techniques to demonstrate that selected prefrontal cortical neurons only fire during the delay between stimulus presentation and response (Goldman-Rakic, 1990). She was devoted to understanding the neural basis of learning and memory, and the intricate relationship of these cognitive processes to the prefrontal cortex. Goldman-Rakic argued that the dorsolateral prefrontal cortex generically processed "on-line" information to support other cognitive functions, and further promoted the idea that the prefrontal cortex was intricately connected with limbic, motor, and sensory areas of the brain in order to integrate attention, memory, motor, and affective facets of

behavior (Goldman-Rakic, 1996; Goldman-Rakic, 1998; Levy & Goldman-Rakic, 2000). She described the concept of a “memory field” in which the same neuron consistently coded a specific visuospatial coordinate. Goldman-Rakic tested this idea in non-human primates, and found that temporarily inactivating the neuron during the delay between a stimulus and response led to a significant increase in errors in memory performance. Thus, she argued, “the finding that neuronal firing is content-specific and directly associated with accurate recall provides a dramatic example of compartmentalized and constrained architecture for memory processing equivalent to that observed in sensory systems” (Goldman-Rakic, 1998, p.92). Further, Goldman-Rakic emphasized that information, not process, was encoded in prefrontal cortex, and that prefrontal cortex could be thought of as an integrated network of areas, with each area having a specialized function. According to her model, networks are functionally integrated by domain. For example, prefrontal areas involved in spatial working memory are linked with posterior parietal cortex, whereas feature working memory areas are interconnected with the temporal lobe. Thus, each domain has local and external networks with sensory, memory, motor, and motivational control elements.

A review by D’Esposito and Grossman (1996) posits that executive functions are dependent on working memory, and they highlight that imaging studies have consistently shown activation of the dorsolateral PFC with tasks that require information to be manipulated and/or monitored. D’Esposito and Grossman further found in their own imaging studies that the PFC was not differentially activated when

increasing task difficulty; rather, dorsolateral PFC activation was only found during dual-task processing (D'Esposito et al., 1995; D'Esposito & Grossman, 1996). However, this result has not been replicated; other researchers have found PFC activation during single task performance, but have not found increased PFC activation during dual task processing (Andres, 2003; Collette & Van der Linden, 2002). Collette and Van der Linden suggested research using single tasks which do not require PFC involvement might help resolve these contradictory results. Andres (2003) proposed that the differing results highlight the involvement of neural networks in dual-task processing, and that in addition to prefrontal cortex, parietal, temporal, and hippocampal areas are also involved.

D'Esposito and Grossman's review (1996) succinctly described two proposed systems thought to be subserved by PFC. Consistent with Goldman-Rakic et al.'s work, D'Esposito and Grossman asserted that imaging studies have shown that memory for location was activated dorsally to memory for faces. This is similar with nonhuman primate research that has found dorsal areas involved in the temporary storage of "where" information, whereas ventral areas appear to be primarily responsible for "what" information. Thus, they argue that the neurophysiological basis of working memory likely involves networks of specific brain regions, though the PFC is thought to play a crucial role. Further work by D'Esposito and Postle (1999) concluded that simple verbal and spatial span performance was not dependent on PFC integrity; however, delayed-response tasks with and without distraction were dependent on specific areas of the PFC. Verbal delayed response

performance was impaired with left ventrolateral PFC lesions (Brodmann's areas 44 and 45). Spatial delayed-response performance was impaired with dorsolateral lesions to areas 9, 46, and possibly 8, and was especially notable with right hemisphere damage. Impaired performance with distraction during delayed-response tasks was found with lesions to Brodmann's areas 9 and 46, regardless of information type. Thus, PFC appears to contribute to delayed-response performance aspects of working memory, and left/right PFC hemispheric differences are beginning to emerge in the imaging data.

Baddeley proposed that working memory is one of the key functions of the prefrontal cortex. His basic cognitive model of working memory, proposed over 30 years ago (Baddeley & Hitch, 1974), has been seminally influential in neuroimaging and cognitive research. Baddeley and Hitch suggested a three-component model of working memory, which is comprised of a central executive (CE) and two slave systems, the visuospatial sketchpad and phonological loop. The initial conceptualization of the central executive component of this model was based heavily on the work of Norman and Shallice (1986).

Norman and Shallice argued there were two subsystems that control activity monitoring. One subsystem is the contention scheduler, which controls routine, semi-automatic processes. The second mechanism is the supervisory attention system (SAS), which consciously controls action and can supersede the contention scheduler when necessary. Norman and Shallice proposed that the SAS is integrated with anterior brain systems that include a large knowledge base

composed of memory units (Miller & Cummings, 1999). Baddeley (2003) initially adopted this model of attentional control for his central executive component, since conceptualizing attention as two systems posed a plausible explanation for attention and action deficits seen in everyday life and in patients with frontal lobe lesions. Automatically driving to work instead of to the supermarket on Saturday morning could be evidence for an implicit attention control schema, as routine simply guides behavior without conscious interference. Evidence for the SAS came primarily from patients with frontal lobe lesions, as their deficits in perseveration and distractibility could be attributed to an impaired SAS. Baddeley (2003) emphasized the contrast between automatic and supervisory control. He cited the vast spectrum of social psychology research which revealed that routine and embedded schema can influence behavior implicitly, without conscious awareness of the individual. He further argued that the SAS concept dovetails with Baumeister's self-control/self-monitoring concept, which allegedly influences inhibition of inappropriate behavior, academic performance, and adequate social and emotional adjustment.

Baddeley has used research from neuroimaging studies to provide functional anatomical locations for his multi-component model of working memory, which now includes an episodic buffer, defined as "a limited capacity store that binds together information to form integrated episodes. It is assumed to be attentionally controlled by the executive and to be accessible to conscious awareness" (p. 836). Baddeley presented the buffer as an entirely separate subsystem, but suggested it could be regarded as simply the storage component of the central executive. He visualizes

the central executive as engaging multiple brain regions in a functionally coherent network, with emphasis on the dorsolateral prefrontal cortex (Garavan, Ross, Li, & Stein, 2000). Some researchers propose that the WCST engages all components of Baddeley's working memory system (Berman et al., 1995; Paulesu, Frith, & Frackowiak, 1993), thus making it an ideal task for further imaging validation of Baddeley's model.

Garavan et al. (2000) point out that convergent activation of the right middle frontal gyrus and left inferior parietal lobule has been reported by various EF researchers, despite the use of different tasks and methods. Even though similar locations have been found to be activated during EF tasks, Garavan et al. suggest that process, rather than location, captures the concept of Baddeley's central executive. Whether central executive functions are subserved by brain storage locations versus a brain circuitry process is still in debate, though a landmark review paper by Smith and Jonides (1999) indicated support for both theoretical positions (executive processes and information storage location modalities). Thus, additional illumination of the neural substrates of the central executive requires further investigation.

Although certainly enticing, Baddeley's central executive model is not without its critics. Towse and Houston-Price (2001), in a delightfully facetious critique of the theory, suggest that the central executive story is nothing more than a Cinderella fairy-tale, with researchers futilely attempting to make the slipper fit. They conclude:

> From one perspective, this means that *there are rather few competing models* to the central executive, because, although there are serious problems with the various conceptions of the central executive, the prospects for any overarching explanation for the processes of cognitive control do not look promising. Thus, as described here, *the main weakness* of the central executive concept lies in its attempt to be all things to all tasks, in its insistence on being a pervasive influence . . . It should also be apparent that we conclude that the *future* of the central executive is less than rosy. We suggest that it is time to give up on this theoretical fantasy, at least in the form it is often used. Indeed, once the central executive slipper is finally discarded, accepting it was but a temporary creation, theoretical life might take on a new purpose and renewed vigor. (p. 255-256)

Collette and Van der Linden (2002) further critique the central executive in their review, especially as it relates to neuroimaging studies of the model. They underscore the problems pointed out by Towse and Houston-Price, with the first major problem being that a number of poorly understood cognitive functions are attributed to the CE, thus further contributing to its methodological and theoretical problems. Secondly, executive tasks are not pure; thus, ability on non-executive elements of the task can contaminate the measurement of so-called executive function. Collette and Van der Linden stressed that specificity of EF and control tasks in central executive neuroimaging research is crucial to disentangling its true nature.

Although theories of the primary functions of the PFC are heterogeneous, the PFC is certainly an intriguing contributor to and coordinator of complex cognitive, motor, sensory, behavioral, social, emotional, and integrative functions. Like Goldberg aptly states, it is "the brain's CEO" (as quoted in Lezak et al., 2004). As a key player in executive systems, the PFC and its associated brain circuits are essential for adequate understanding of executive functioning processes.

Frontal-subcortical Circuits

In their landmark paper, Alexander, Delong, and Strick (1986) introduced the concept of five major parallel but functionally segregated circuits linking the basal ganglia and cerebral cortex. These circuits include: 1) the motor circuit, 2) the oculomotor circuit, 3) the dorsolateral prefrontal circuit, 4) the lateral orbitofrontal circuit, and 5) the anterior cingulate circuit. Alexander, Delong, and Strick postulated that these five basal ganglia–thalamocortical circuits appeared to involve separate parts of the frontal lobe. They originate in the frontal lobes and project sequentially to the caudate, putamen, or ventral striatum, to the globus pallidus and substantia nigra, and then to specific thalamic nuclei, with a final link back to the frontal lobe (See Figure 1; Chow & Cummings, 1999; Lichter & Cummings, 2001). Each circuit has a direct and indirect pathway which ultimately projects to the thalamus. These five circuits are incredibly anatomically segregated, even though they share common structures (Lichter & Cummings, 2001).

Figure 1: Basic organization of frontal-subcortical circuits.

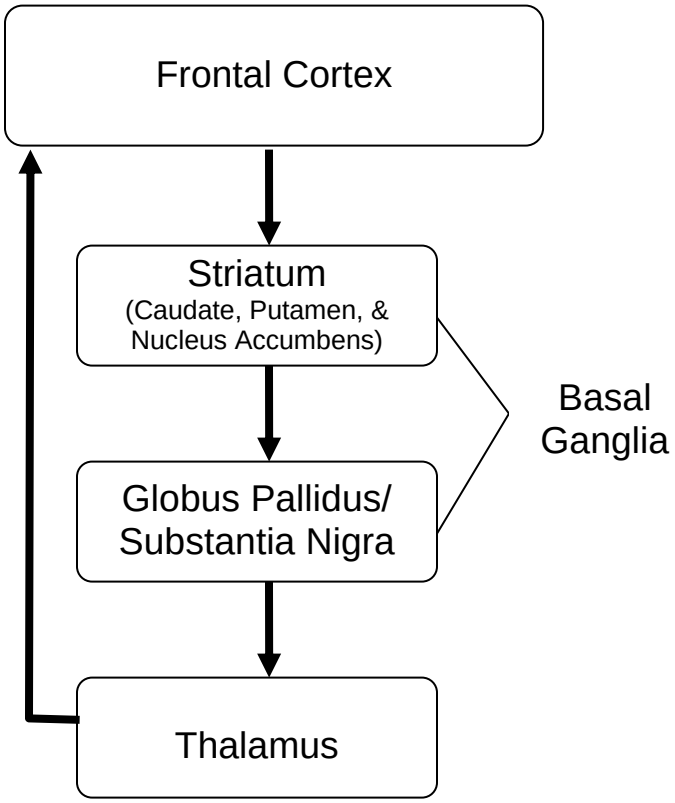


Figure 1. Basic organization of frontal-subcortical circuits that include the frontal cortex, the basal ganglia, and the thalamus.

Middleton and Strick (2001) identified two other frontal-subcortical circuits which they labeled the medial orbitofrontal circuit and the inferotemporal/posterior parietal circuit. They also point out that the seven frontal-subcortical circuits are composed of multiple subcircuits, and that the basal ganglia have many more output connections/targets than previously thought. In addition, they emphasized that basal ganglia output is not restricted to the frontal lobe; anatomical efferents have been identified in the inferotemporal cortex and possibly in the posterior parietal cortex. Mori, Wakana, Nagae-Poetscher, and van Zijl's (2005) pioneering work on developing an atlas of human white matter tracts further elucidate frontal-subcortical circuitry. Mori et al. reconstructed the corticothalamic fibers and cerebellum fibers, which reveal in intricate detail the connections between the frontal-subcortical circuits and their associated fiber tracts proposed by Middleton and Strict. The identification of frontal-subcortical circuitry changed science's understanding of the spectrum of neurological and psychiatric disorders, as pathology could be analyzed and understood within the framework of frontal-subcortical dysfunction. This review will focus on the three frontal-subcortical circuits associated with neurobehavioral syndromes.

The dorsolateral prefrontal (DLPF) circuit has been associated with executive functions, and classic symptoms of dorsolateral frontal-subcortical circuit dysfunction include poor organizational strategies, reduced verbal and design fluency, stimulus-bound behavior, motor programming deficits, and impaired set shifting and maintenance (Chow & Cummings, 1999; Lichter & Cummings, 2001). Thus, integrity

of the DLPF cortex is critical to aspects of WCST performance such as sustaining attention, generating strategies, and mental flexibility. Lombardi et al. (1999) studied the relationship of regional brain metabolism to perseverative responding on the WCST in patients with a history of closed-head injury. They found that decreased metabolism in the right dorsolateral prefrontal cortex and caudate nucleus was associated with increased perseverative responding on the WCST, and the authors suggest that right DLPF function is required for adequate performance on the WCST. A study by Monchi, Petrides, Petre, Worsley, and Dagher (2001) identified distinct neural DLPF circuits during different stages of the WCST using an event-related fMRI paradigm. Thus, neuroimaging data appear to substantiate the DLPF circuitry in WCST performance.

In contrast, WCST performance is often normal in patients with orbital frontal (OF) impairment (Lichter et al., 2001; Stuss et al., 2000). Rather, personality changes and emotional lability are the hallmarks of orbital frontal circuitry dysfunction. According to Lichter and Cummings (2001), lesions appear to sever frontal supervisory circuits from limbic input, which results in unchecked, inappropriate behavior and emotional outbursts. Patients may make inappropriate jokes, refrain from inhibiting sexual remarks/behavior, and may be extremely impulsive. They often lack social discretion and judgment skills. Although patients with impaired OF circuitry often perform normally on the WCST and other measures of executive functions, there is often a great discrepancy between their normal test

performances and their reported dysfunction on activities of daily living and social interactions (Chow & Cummings, 1999).

The anterior cingulate (AC) circuit mediates motivational behavior. Abulia and akinetic mutism can occur with anterior cingulate cortex dysfunction. Akinetic mutism is described by Lichter and Cummings (2001) as a "wakeful state of profound apathy, with indifference to pain, thirst, or hunger; absence of motor or psychic initiative, manifested by lack of spontaneous movement; absent verbalization; and failure to respond to questions or commands" (p. 13). Abulia is a less profound form of apathy, and is characterized by reduced spontaneity, especially noted in speech and movement.

Basal Ganglia and Cerebellum

The basal ganglia and cerebellum were traditionally viewed as motor structures, and their role in cognition and other higher order processes was not generally widely accepted until the late 20th century (Ravizza & Ivry, 2001). The basal ganglia, situated at the base of the cerebral hemispheres, generally include the caudate, putamen, globus pallidus, amygdala, subthalamic nucleus, substantia nigra, and other subcortical structures (Kolb & Wishaw, 2003; Lezak et al., 2004). Middleton and Strick (2000b) emphasized that a major feature of the basal ganglia is that they consist of various "input structures" (the caudate, putamen, and ventral striatum) that receive information directly from the cortex and "output structures" (internal segment of globus pallidus, substantia nigra, and ventral pallidum) that project back to the cortex via the thalamus. Thus, the basal ganglia participate in a

number of cerebral cortex loops, and have the potential to influence diverse aspects of cognition and behavior. Middleton and Strick suggested that the anatomical evidence for detailed connections between the basal ganglia and at least nine major areas of cortex support its involvement in non-motor functions. In addition, single cell recording studies provide support that parts of the basal ganglia are more related to sensory or cognitive functions than to motor operations. Finally, lesion studies and studies of patients with known basal ganglia dysfunction (Parkinson's disease, Huntington's disease, etc.) indicated that in some cases, cognitive or sensory disturbances are present without gross motor dysfunction.

However, relatively few brain imaging studies have been able to analyze basal ganglia function, due perhaps to the small size of some of the nuclei and their location deep within the brain and near the ventricles. Positron emission tomography (PET) studies by Jueptner et al. showed differential activation in the basal ganglia using variations of a motor sequencing task (Jueptner et al., 1997; Jueptner, Frith, Brooks, Frackowiak, & Passingham, 1997). The sensorimotor portions of the putamen had increased activation during the automatic performance of previously learned sequences, and learning of new sequences was correlated with increased activity in the dorsolateral caudate, rostrodorsal portions of the globus pallidus, and the ventral anterior nucleus of the thalamus. A PET study by Owen et al. (1998) using a difficult planning task (Tower of London), a spatial working memory task, and simple visually guided movements found activation of the globus

pallidus during the spatial working memory and planning task in normal individuals, but not in individuals with Parkinson's disease.

A quantitative MR study (Stratta et al., 1997) measuring volumes of striatal structures (caudate, putamen, and nucleus accumbens) in individuals with schizophrenia found that poor WCST performers had reduced striatal complex and caudate nucleus volumes relative to controls. Specifically, significant volume reductions were observed in the left caudate nucleus and putamen and in the right striatum. Although this study divided the schizophrenic group into poor and good WCST performance, it did not similarly delve into the WCST performance in the control sample. Thus, little is known about basal ganglia neuromorphological variables and their impact on cognitive performance in normal individuals. One event-related fMRI study (Monchi, Petrides, Petre, Worsley, & Dagher, 2001) found significant activation patterns involving the caudate and putamen during the WCST in a sample of healthy individuals, and their results indicated the basal ganglia had particular importance in selecting relevant actions in response to feedback and determining attentional set.

Even though basal ganglia circuit dysfunction occurs in multiple neuropsychiatric disorders (e.g., schizophrenia, obsessive-compulsive disorder, depression, Tourette's syndrome, autism, attention deficit disorder, Huntington's disease, Parkinson's disease), an understanding of normal basal ganglia function is still largely unknown, and preliminary studies such as Monchi et al. (2001) and Stratta et al. (1997) have not yet been replicated. Thus, imaging basal ganglia

activation during various cognitive tasks in normal individuals would be illuminating (Middleton & Strick, 2000b). One of the purposes of this study will be to analyze basal ganglia activation patterns during the WCST in normal individuals.

Although the motor functions of the cerebellum have long been documented, its complex contributions to cognitive, sensory, and emotional processing are just beginning to be appreciated. Middleton and Strick's (2000a) approach using retrograde transneuronal transport of the herpes simplex virus type 1 (HSV1) in primates has clearly shown cerebellar output connections to the primary motor cortex, premotor cortex, frontal eye fields, prefrontal cortex, parietal lobe, and inferotemporal cortex (via the thalamus), with many areas left unexplored. Hoshi, Tremblay, Feger, Carras & Strick's recent work (2005) also emphasized the anatomical connections between the cerebellum and basal ganglia. A contemporary study by Allen et al. (2005) further supported the connectivity of the cerebellum and striatum using functional connectivity analyses during a resting fMRI scan.

Neuroimaging studies and lesion studies provide support for non-motor cerebellar functions, including working memory, spatial processing, selective attention, shifting attention, prediction and preparation of action, linguistic processing, word generation, and memory and learning (Allen, Buxton, Wong, & Courchesne, 1997; Chen & Desmond, 2005; Courchesne & Allen, 1997; Gottwald, Wilde, Mihajlovic, & Mehdorn, 2004; Harrington, Lee, Boyd, Rapcsak, & Knight, 2004; Mandolesi, Leggio, Graziano, Neri, & Petrosini, 2001). Lesion studies have shown that cerebellar dysfunction significantly disrupts problem solving, abstract

reasoning, verbal fluency, attention, emotional modulation, and visuospatial abilities (Lezak et al., 2004; Middleton & Strick, 2000a). Thus, the cerebellum is another important player in the frontal-subcortical brain circuitry thought to subserve executive functions.

Clearly, the components of frontal-subcortical circuitry are very complex, and their integrative and unique contributions to cognitive, emotional, and social functions are largely enigmatic. Although unraveling the web of frontal-subcortical circuits is beyond the scope of this project, one focus of this study is to carefully analyze prefrontal cortex, cerebellar, and basal ganglia activation patterns during strategy generation, mental flexibility, and effective performance of the Wisconsin Card Sorting and Texas Card Sorting tests.

Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test (WCST) was created by Grant and Berg in the late 1940's as a measure of abstract reasoning and the ability to shift mental sets in response to changing rules and conditions (Grant & Berg, 1948; Heaton et al., 1993). It is one of the most frequently used neuropsychological instruments in assessing executive functioning and/or problem solving abilities. The most common form of the test consists of 4 stimulus cards and 128 response cards (2 identical decks of 64 cards each) that differ by color (red, green, yellow, or blue), shape (triangles, stars, crosses, and circles), and number of stimuli per card (1, 2, 3, or 4). Clients are told they must match each of the 128 response cards to one of the four stimulus cards, however they think it matches (see Figure 1). The client is not told which category or sorting principle to use to match the cards, but is given yes/no feedback after each card has been placed. After 10 cards have been placed correctly, the examiner covertly switches the rule of matching the cards. Thus, the client must effectively utilize examiner feedback in order to determine the new relevant category sorting principle. The test is discontinued after six complete category sorts or after 128 responses.

Figure 2. Wisconsin Card Sorting Test (WCST)

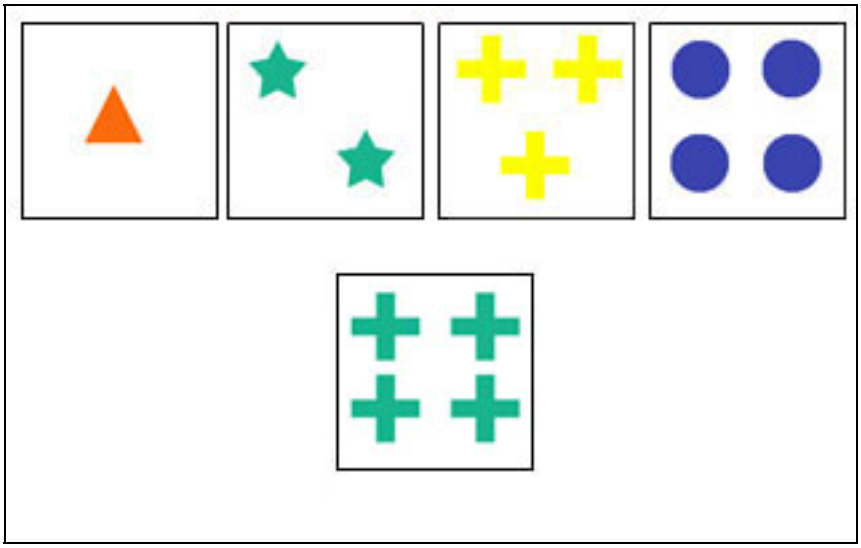


Figure 2. The Wisconsin Card Sorting Test (WCST). The four stimulus cards are depicted with a sample response card.

WCST Lesion Studies

Milner (1963) completed one of the first seminal studies of the WCST. She analyzed data from epilepsy patients who had undergone brain surgery for seizure amelioration, and found that patients with dorsolateral frontal lobe lesions completed significantly fewer categories and made more perseverative responses. A follow-up study of these patients showed that those with left frontal lesions had more lasting and consistent impairment on WCST performance than those with right frontal lesions. Drewe (1974) found that patients with frontal lesions made significantly more perseverative errors, and consistent with Milner's findings, left frontal patients were more impaired overall. However, Drewe's lesion patients were from diverse populations (stroke, head injuries, tumors). Nelson (1976) simplified the WCST, removing ambiguous cards from the response deck (i.e., cards that could be matched to more than one stimulus, such as shape and number). No differences between right or left frontal lesions were found on the measures of WCST performance in this study; however, simplifying the response deck may have removed these potential differences. This early work measuring WCST performance in lesion patients solidified its indication as a sensitive measure of frontal lobe functioning in neuropsychological clinical practice.

As more data accumulated, more controversy appeared in the literature over the specificity, sensitivity, and utility of the WCST. Robinson, Heaton, Lehman, and Stilson (1980) found that frontal lesion patients had significantly more perseverative errors than nonfrontal groups. Their data also indicated that right frontal lesioned

individuals were significantly more impaired on the WCST. However, despite the sensitivity of the WCST to frontal lesions found in their study, Robinson et al. cautioned against using the test to discriminate focal frontal lesions from diffuse lesions, as overall impairment in these groups was equal.

Mountain and Snow (1993) reviewed six articles that investigated the performance of normal controls versus patients with frontal lesions. They found some evidence that patients with frontal lesions tended to have more perseverative errors than patients with nonfrontal lesions and controls, but stated that the overall evidence that frontal patients perform more poorly than nonfrontal patients was weak, especially when other performance variables were analyzed, such as other types of errors and categories completed. Mountain and Snow also investigated the available WCST literature on frontal versus nonfrontal damage. Five of the studies showed more perseverative errors in patients with frontal lobe damage, and four other studies found no difference. Two studies indicated that fewer categories were achieved by patients with frontal damage, but most studies that reported category data showed no difference between the groups. As mentioned earlier, differences between right and left frontal damage remained controversial, with no clear trend. Finally, Mountain and Snow reported, “The evidence in support of the sensitivity of the WCST to dorsolateral lesions is much weaker than clinical lore would lead one to suspect” (1993, p. 115), as their review concluded there was only weak evidence that patients with dorsolateral frontal lesions performed worse than patients with non-dorsolateral lesions.

A landmark paper by Anderson, Damasio, Jones, and Tranel (1991) used MR and CT anatomical lesion data to examine the specificity and sensitivity of the WCST, and found no significant differences in WCST performance between patients with frontal versus nonfrontal damage. However, lesion locations for the subjects in their nonfrontal group varied across thalamic, basal ganglia, temporal, parietal, and occipital locations, which may have confounded these results. Also, given the importance of the thalamus and basal ganglia in prefrontal cortex brain circuitry, it is possible that lesions in these locations interrupted circuits that are critical to adequate WCST performance, which could possibly account for a significant portion of the equivalency between the frontal and nonfrontal groups in Anderson et al.'s data.

In a more recent study, Stuss et al. (2000) also used MR and CT to confirm that their subjects had focal lesions confined to frontal, striatal, or nonfrontal areas. They administered the WCST in three sequential conditions. First, the WCST was given according to standard procedures, except all participants were administered the complete 128 response cards to control for stimulus exposure. Following that, participants were informed of the three ways to sort the cards correctly. Then one deck of 64 cards was administered. Last, participants were reminded of the three sorting criteria, and then were asked to sort by color. After 10 correct sorts, the examiner said, "Now I'm changing how you sort beginning with the next card," and this warning was repeated each time the sorting rule changed, but the correct sorting category was not mentioned. Their analysis of the data indicated that the two

dorsolateral frontal groups and the superior medial groups were significantly impaired compared to the control group. In general, performance improved with instructions for most of the variables measured. One interesting finding was that the inferior medial frontal group had significantly more losses of set in the second condition, when the subjects were told the correct sorting rules. Set loss did not improve in the right dorsal lateral group, even with the additional instructions and support. Stuss et al.'s study revealed functional dissociations between superior and inferior medial regions and between dorsolateral and orbitofrontal/inferior medial areas. The differences observed between his lesion groups on WCST performance with and without verbal instructions may open the door for further studies involving brain plasticity, recovery of function, and development of more effective cognitive rehabilitation strategies.

Goldstein and his collaborators used frontal and nonfrontal low grade tumor patients to further study executive functioning as measured by the WCST (Goldstein et al., 2004). They did not find any significant differences between frontal, nonfrontal, and normal controls on number of categories achieved or perseverative errors. They hypothesized that right frontal patients would have worse performance than left frontal patients, but their data revealed the opposite, as left frontal patients achieved fewer categories and were more perseverative.

Demakis (2003) performed two meta-analyses of WCST studies hoping to clarify sensitivity and specificity issues and the role of various moderator variables (e.g., etiology, lesion location, chronicity, and differing administration procedures).

He compared participants with frontal lobe damage to those with nonfrontal damage, and then analyzed differences between right and left frontal patients. Demakis found that frontal patients were more impaired than nonfrontal patients, with the most severe impairments resulting from dorsolateral damage. However, he did not find any significant left versus right performance differences. Time since injury may have confounded the data, as a larger effect size was observed for patients tested within one year of injury compared with those tested after one year, possibly indicating the WCST is more sensitive to acute versus chronic damage. Administration method was another significant moderator; Nelson's method (where ambiguous cards are removed from the response deck) appeared to enhance performance of frontal patients. Thus, Demakis' research highlighted the necessity of understanding moderator variables in order to interpret WCST performance/results accurately.

In summary, the literature reviewed here (see Table 1) indicates support for utilizing the WCST variables of perseverative errors and number of categories achieved to discriminate frontal versus nonfrontal patients, with the caveats that poor performance may also indicate more diffuse damage or may be related to brain disruption in other components of frontal-subcortical circuitry. Sensitivity and specificity of other WCST performance variables have been largely unexplored or unreported in the current literature. Surprisingly, there appears to be little empirical support for the idea that people with dorsolateral prefrontal cortex lesions perform worse than patients with other frontal or nonfrontal lesions. Finally, left frontal

versus right frontal differences have yet to be clarified. As many of the above authors have noted, variability in the sample characteristics, administration procedures, and the variables measured across studies has contributed to the lack of consistent findings in the lesion literature.

Table 1

Brain Lesion and WCST Performance Data

Author(s)/Date	**Brief Study Description**	**WCST Variables**	**Frontal vs. Nonfrontal**	**DL Findings**	**Left vs. Right**
Milner 1963	94 epilepsy pts. 71 tested pre- and post-operatively; 23 post-operatively only	Categories Psv errors	Dorsolateral lesions worse than orbitofrontal, inferior frontal, and posterior cerebral lesions	↓ categories, ↑ psv	Left more impaired
Drewe 1974	91 pts with unilateral lesions, including left frontal, right frontal, left nonfrontal, and right nonfrontal pts	Categories Psv errors Unique errors Total errors	Frontal ↓ categories, ↑ psv errors Left frontals ↑ overall errors & psv errors Medial frontal lesions ↓ categories	Reported medial frontal areas perhaps more critical to WCST performance than DL areas	Left frontal lesions most impaired
Nelson 1976	53 pts with unilateral cerebral lesions, controls were 32 inpatients with extra-cerebral lesions (spinal lesions, peripheral neuropathy, and carpal tunnel syndrome) and 8 friends/relatives of outpatients	Errors Categories Psv errors	Frontal ↓ categories and ↑ psv	Not reported	No difference
Robinson et al. 1980	107 pts with cerebral lesions (right frontal, left frontal, right nonfrontal, left nonfrontal, right or left hemisphere) and 123 normal controls	Psv responses	Frontal worse; ↑ psv responses, but did not discriminate well between frontal and diffuse brain damage	Not reported	Right more impaired

Table 1, Continued

Brain Lesion and WCST Performance Data

Author(s)/Date	**Brief Study Description**	**WCST Variables**	**Frontal vs. Nonfrontal**	**DL Findings**	**Left vs. Right**
Anderson et al. 1991	91 stroke and tumor pts with single focal brain lesions	Errors Psv errors Categories	No difference	Not reported	No difference
Mountain & Snow 1992	Literature review of available published WCST studies	Categories Psv errors	Frontal lesions vs. normal controls: 2 studies found no difference in categories achieved, most studies (6) supported ↑ psv in frontal pts Frontal vs. nonfrontal lesions: 5 studies found ↑ psv in frontal pts; 4 studies found no difference	One study found DL worse than other areas, one found the opposite, and one found no difference	Right more impaired than left with frontal lesions plus other structures
Stuss et al. 2000	46 pts with single focal lesions (35 frontal, 11 nonfrontal) and 16 normal controls. Lesion patients separated into RDL, LDL, SM, IM, RNF, and LNF groups	Categories PPC PPR Set Loss	Frontal ↓ categories achieved, ↑ psv errors	DL group most consistent impairment; RDL ↑ # of set loss	Not reported, except RDL ↑ # of set loss than LDL
Demakis 2003	Meta-analysis of the literature of frontal vs. nonfrontal patients and left frontal versus right frontal performance on WCST	Categories Psv	Frontal ↓ categories, ↑ Psv compared to nonfrontal	N/A	No difference

Table 1, Continued

Brain Lesion and WCST Performance Literature Data

Author(s)/Date	**Brief Study Description**	**WCST Variables**	**Frontal vs. Nonfrontal**	**DL Findings**	**Left vs. Right**
Goldstein et al. 2004	45 low-grade brain tumor pts (frontal, nonfrontal, left frontal, right frontal), 63 normal controls	Categories Psv errors	No significant differences	Not Reported	Left frontal more impaired than right frontal group

Note. Abbreviations found in the table include: ↑ = increased; ↓ = decreased; DL = Dorsolateral (L = Left, R = Right); IM = Inferior Medial; L= Left; LNF = Left Nonfrontal; PPC = Perseveration of the preceding criterion; PPR = Perseveration of the preceding response; Psv = Perseverative; Pts = Patients; R = Right; RNF= Right Nonfrontal; SM = Superior Medial.

WCST Functional Neuroimaging Studies

While lesion studies can be an informative initial probe into understanding the functions of neural circuitry, they have a major limitation. They cannot indicate which brain areas are involved in normal task performance; rather, they only highlight which regions of the brain hinder or completely inhibit task performance (Berman et al., 1995). Functional brain imaging avoids some of the problems inherent to lesion studies, and provides a way of studying cognitive processes in healthy individuals with intact brains, as well as analyzing neurologically compromised groups. Thus, with the emergence of functional neuroimaging, the capability to detect mental activity in vivo during the performance of cognitive tasks like the WCST became possible. Although a broad literature on the neural correlates of the WCST is available, only key articles pertaining to WCST activation in normal individuals are reviewed here, since this project will analyze WCST imaging data from normal participants.

SPECT Imaging Studies. An early SPECT (single photon emission computed tomography) study by Rezai et al. (1993) found that the WCST produced a significant localized flow to the left lateral frontal region. However, as they used SPECT, an important limitation of the study was poor spatial resolution, and no high-resolution anatomical images were obtained. The authors proposed that exploratory mapping from their study implicated hippocampal, temporal, parietal, and thalamic areas, but due to the poor spatial resolution, they could not be definite. Rezai et al. (1993) concluded that the WCST primarily activated left dorsolateral prefrontal

cortex areas. Kawasaki et al. (1993), in a SPECT study of normal controls and patients with schizophrenia, also found that left lateral prefrontal blood flow significantly increased during the WCST compared to rest. A more recent study (Catafau et al., 1998) found significant regional cerebral blood flow (rCBF) increases in the left inferior cingulate and the left posterior frontal region. In 9 of the 13 subjects, rCBF ratios were slightly higher during WCST performance in the prefrontal cortex (bilaterally) and in the right inferior cingulate, but the authors interpreted this as not statistically significant. Catafau et al.'s study highlighted the potential role of the inferior cingulate cortex in the WCST, and implicated attentional mechanisms as a significant variable in the WCST.

As with the lesion data, other SPECT studies found contradictory results. Cantor-Graae, Warkentin, Franzen, and Risberg (1993) measured rCBF of 22 healthy volunteers during the WCST compared to a simpler matching baseline task. They found no significant prefrontal flow increases during WCST performance. Marenco et al. (1993) compared SPECT rCBF during the WCST to that during a sensorimotor baseline task. In their study, significant rCBF increases were seen in the right anterior dorsolateral prefrontal and left occipital cortices during WCST performance. A reduction of rCBF was found in the left pararolandic region. Further, performance correlated significantly with rCBF in medial frontal regions (positive for left medial prefrontal areas, negative for right medial prefrontal areas). Tien, Schlaepfer, Orr, and Pearlson (1998) put a slightly different spin on WCST imaging; they pre-trained five normal subjects on the WCST prior to imaging. Their

data revealed increased rCBF in bilateral inferior frontal, right middle frontal, and right inferior parietal cortices. Decreases were observed in hippocampi, temporal cortex, and anterior cingulate and caudate. No significant changes in rCBF were reported for the dorsolateral prefrontal cortices.

Many imaging studies have compared WCST performance in normal controls to patients with schizophrenia, and information on WCST neural activation in normal controls is often embedded in the schizophrenia literature. One SPECT study comparing schizophrenics and controls (Parellada et al., 1998) revealed the control group had significant increases in rCBF in the superior and inferior prefrontal regions. Liu, Tam, Xie, and Zhao (2002) reported that for both normal controls and schizophrenics, there was an overall right prefrontal and temporal increase in rCBF compared to the left. For a summary of SPECT results during the WCST task reported in this review, please see Table 2.

Table 2

SPECT Activation in Normal Controls During the WCST

Author(s)/Date	**Brief Study Description**	**ROIs**	**Results ↓/↑ rCBF During WCST**	**DL Findings**
Rezai et al. 1993	13 Normal Controls, M/F Computerized WCST vs. Resting Baseline	Anterior Frontal Lateral Frontal Mesial Frontal Parietal Occipital	Small ↑ left DLPFC Larger ↑ in posterior areas (most likely hippocampal, parietotemporal, & thalamic)	↑ Left DLPFC
Kawasaki et al. 1993	10 Normal Controls & 10 Schizophrenics, M only WCST vs. Resting Baseline	44 ROIs	↑ Left DLPFC ↑ Left medial prefrontal cortex positively correlated with number of unique errors	↑ Left DLPFC
Cantor-Graae et al. 1993	22 Normal Controls, M/F Rest/FAS & WCST/Baseline pairs presented in counterbalanced order between and among pairs Baseline Task: Moving blank cards to designated lit up blank key card pile	Prefrontal Superior Frontal Frontotemporal Temporal Central Parietotemporal Occipital	Asymmetry in rCBF shown with ↑ left superior frontal area, left temporal area, left central area, and right frontotemporal area No significant prefrontal ↑ observed Low education (< 12 years) correlated with ↑ in right prefrontal cortex FAS elicited greater ↑ in prefrontal activation than WCST	No significant DLPFC ↑

Table 2, Continued

SPECT Activation in Normal Controls During the WCST

Author(s)/Date	**Brief Study Description**	**ROIs**	**Results ↓/↑ rCBF During WCST**	**DL Findings**
Marenco et al. 1993	17 Normal Controls, M/F WCST vs. BAR (matching to sample sensorimotor control task)	Medial Prefrontal Anterior DLPFC Posterior DLPFC Central Temporal Parietal Occipital	↑ Left occipital and right anterior DLPFC # of correct categories and % Psv errors correlated with ↑ left medial prefrontal and ↓ in right medial prefrontal. FMS correlated with ↓ left medial prefrontal ↓ Left and right central (pararolandic) cortex Posterior DLPF region negatively correlated with task difficulty as measured by sensory-motor frequency	↑ Right DLPFC
Tien et al. 1998	5 Normal Controls, M only Prior to imaging, all subjects completed standard computerized WCST WCST vs. Matching to Sample Task	SPM whole brain analysis	↑ Bilateral left inferior frontal gyrus ↑ Right medial and right inferior parietal cortex ↓ Hippocampi, right medial temporal gyrus, right caudate, left insula, and anterior cingulate gyrus	No significant DLPFC changes; perhaps due to task pretraining

Table 2, Continued

SPECT Activation in Normal Controls During the WCST

Author(s)/Date	**Brief Study Description**	**ROIs**	**Results ↓/↑ rCBF During WCST**	**DL Findings**
Catafau et al. 1998	13 Normal Controls, M/F WCST vs. Resting Baseline	Anterior frontal Posterior frontal Inferior cingulate gyrus Superior cingulate gyrus Region/Cerebellar Ratios	↑ Left inferior cingulate and left posterior frontal ↑ Left/right prefrontal cortex and right inferior cingulate slightly higher (not reported as statistically significant) in 9/13 subjects	No significant DLPFC changes
Parellada et al. 1998	15 Normal Controls and 25 acute unmedicated schizophrenics, F only WCST vs. Resting Baseline	Prefrontal Temporal	↑ Inferior and superior prefrontal regions (schizophrenics did not show similar increases) Positive sx of schizophrenia associated with left anterior temporal ↑	Not reported
Liu et al. 2001	12 Normal Controls (11 M and 1 F) and 21 Schizophrenics with negative sx (18 M & 3 F) WCST vs. Resting Baseline	"Profrontal" Temporal	↑ Right/left "prefrontal" and right temporal areas Schizophrenics did not show ↑ left "prefrontal" activation	Bilateral ↑ "prefrontal" areas

Note. Abbreviations found in the table include: ↑ = increased; ↓ = decreased; DL = Dorsolateral; DLPFC = Dorsolateral Prefrontal Cortex; F = Female; FAS = Phonemic word generation task using letters F, A, & S; M= Male; FMS = Failure to Maintain Set; Psv = Perseverative; Pts = Patients; rCBF = Regional Cerebral Blood Flow; ROIs = Region of Interest, SPECT = Single Photon Emission Computed Tomography; SPM = Statistical Parametric Mapping; Sx = symptoms; WCST = Wisconsin Card Sorting Test.

PET Imaging Studies. PET is another technique similar to SPECT used to assess brain activation during cognitive challenges. One of the SPECT studies, which pre-trained individuals on the WCST did not find dorsolateral prefrontal activity, and Berman et al. (1995) addressed this issue in a follow-up PET study. Berman et al. scanned 40 normal controls naïve to the WCST and then re-scanned a subset of 9 of the controls after explaining the rules of the test and training to criterion performance levels. They predicted that if DLPFC activation was due to apprehensiveness, worry, confusion, novelty, anticipation, or rule learning, they would expect DLPFC activation to be significantly less or absent during the second WCST PET scan, as their teaching of the task and training to criterion levels would remove these variables. However, if DLPFC activation was primarily due to working memory, there would be no significant differences between the first and second WCST PET scans, because the trial-to-trial working memory demands of the WCST would remain the same even after rule training.

For the normal group as a whole, robust activations were found in the left and right DLPFC, and major activations were observed in the inferior parietal lobule and visual association cortex when comparing rCBF during the WCST to a sensorimotor control task. Additional areas activated included portions of the mesial, orbital and polar frontal cortex, inferior portions of the temporal lobes, and areas of the cerebellum. Regional cerebral blood flow appeared to be decreased in the superior temporal gyri, mesial aspects of the frontal pole, and somatosensory cortex. For the subjects who were scanned in the naïve and trained conditions, only two areas

showed significant differences; the superior portion of the left middle frontal gyrus and the left putamen showed higher relative activity during the second (post-training) WCST. Their finding appears to support the working memory function of the DLPFC. As subjects were informed on the sorting principles and the rules of the WCST, the increased putamen activation could be due to the changed salience of the task (Pagnoni, Zink, Montague, & Berns, 2002). Additionally, striatal areas are often active in learning conditions and conditions associated with reward, and the learning of the WCST or the changed salience of negative or positive feedback could account for activation differences in the putamen. Clearly, basal ganglia structures play important roles in feedback loops and executive functions; however, our understanding of specific functions of the basal ganglia remains insubstantial, and necessitates further scientific exploration.

Nagahama, Fukuyama, Yamauchi, Matsuzaki et al. (1996) observed similar brain activations as Berman et al. using Nelson's Modified Card Sorting Test (MCST). Increased activation was found in the bilateral DLPFC, inferior parietal lobes, striate cortex, cerebellum, and left occipital cortex. Further PET studies by Nagahama et al. (1998; 1997) replicated their prior results, though these activations were reduced in healthy elderly patients as compared to normal controls. Nagahama and Sadato et al. (1998) also used a Weigl-type task (switching matching strategies from shape and color based on feedback) to determine the neural components involved in set shifting. They found significant activation in the right DLPFC and parieto-occipital cortex during attentional shifts. Their work may partially

explain the lack of consistent findings with right and left DLPFC patients, especially if the right DLPFC proves to be more critical for set shifting than the left DLPFC.

Ragland et al. (1997) were interested in exploring the functional and anatomical relationships between working and declarative memory. They compared WCST performance to a paired-associates task using WCST stimuli. Target cards were paired to key cards, but targets did not match key cards on any dimension. They found more consistent dorsolateral prefrontal activation for the WCST than the paired associates recognition task (PART) and additional orbitofrontal increases and dorsomedial decreases during the PART. For both the WCST and PART, inferior frontal and occipitotemporal regions demonstrated increased activation.

The overlap of activation between the WCST and the PART is remarkable as the tasks were not behaviorally correlated; thus their paper suggested that a frontotemporal network subserved both types of memory function, with components of the network more focused for optimal performance of the differing tasks. This may provide evidence that working memory is not an independent system; rather as Goldman-Rakic asserted, overlap may indicate the reciprocal nature of frontal-subcortical and cortico-cortical pathways connecting prefrontal and temporal association areas. Thus, although the WCST appears to be an independent factor in behavioral and factor analysis studies, this brain activation study suggests the functional anatomy may be strikingly similar between divergent tasks. See Table 3 for a summary of PET activation during the WCST.

Table 3

PET Activation in Normal Controls During the WCST

Author(s)/Date	**Brief Study Description**	**ROIs**	**Results ↓/↑ rCBF During WCST**	**DL Findings**
Berman, et al. 1995	40 NCs, M/F 9 of 40 NCs were re-scanned after training and optimization of WCST performance WCST vs. sensorimotor control task (match to sample)	Anterior cingulate Superior frontal gyrus Middle frontal gyrus Inferior frontal gyrus Superior temporal gyrus Parietal cortex Occipital cortex Caudate nucleus Putamen Thalamus Hippocampus SPM Whole Brain Analysis	↑ bilateral DLPFC & inferior parietal lobule (BA 40, minor BA 7); ↑ left occipital cortex (BA 18 & 19) & inferior portion of right middle frontal gyrus ↓ left frontal pole (BA 10), bilateral somatosensory cortex, left putamen, and left superior temporal gyrus Whole brain analysis revealed ↑ mesial, orbital, and polar frontal cortex, inferior portions of temporal lobe, and areas of cerebellum; ↓ superior temporal gyri, mesial aspects of frontal pole, and somatosensory cortex Repeat (trained) WCST vs. WCST revealed ↑ in superior portion of left middle frontal gyrus and left putamen. Very few frontal lobe pixels ↓ after practice	Bilateral DLPFC activation Trend for ↑ L DLPFC activation when data analyzed individually
Nagahama et al. 1996	18 NCs, M only MCST vs. MTS task (each subject matched to a single color, number, or shape category)	Whole brain analyzed	Compared MCST vs. average of shape, color, and number MTS tasks, finding ↑ bilateral DLPFC, inferior parietal lobes, striate, cerebellum, and left occipital cortex	Bilateral DLPFC

Table 3, Continued

PET Activation in Normal Controls During the WCST

Author(s)/Date	**Brief Study Description**	**ROIs**	**Results ↓/↑ rCBF During WCST**	**DL Findings**
Nagahama et al. 1997	6 young healthy subjects (ages 21-24; M only) and 6 healthy elderly subjects (ages 66-71, 4 M & 2 F) Compared MCST to number matching control task	SPM Whole Brain Analysis	↑ Left DLPFC (BA areas 9, 45, & 46); rostral part of bilateral middle frontal gyri (BA 10), left inferior parietal lobule (BA 40), right intraparietal sulcus and angular gyrus (BA 40 and 39) ↑ bilateral ventral and dorsolateral occipital cortices (BA 18 & 19), left striate cortex (BA 17), right parahippocampal gyrus and left cerebellum Elderly subjects had less extensive activation	Left DLPFC
Nagahama et al. 1998	6 Normal Controls, M only Weigl-type card sort with shifts occurring from 2 to 16 correct responses vs. matching to sample	SPM Whole Brain Analysis	↑ Right DLPFC, inferior frontal gyrus, right parieto-occipital cortex, and left inferior occipital gyrus At lowest # of shifts, ↑ observed in anterior cingulate gyrus At highest # of shifts, ↑ observed in right inferior occipital gyrus and left cerebellum	Right DLPFC implicated in set shifting

Table 3, Continued

PET Activation in Normal Controls During the WCST

Author(s)/Date	**Brief Study Description**	**ROIs**	**Results ↓/↑ rCBF During WCST**	**DL Findings**
Ragland et al. 1997	30 Normal Controls (16 M, 14 F, 23 Caucasian, 6 African American, 1 Asian) Resting baseline, WCST task, and Paired Associates Recognition Test (PART) pairing WCST stimuli to key cards that did not match on any dimension (3 blue circles paired with 1 red triangle).	Superior frontal Dorsolateral prefrontal Dorsomedial prefrontal Inferior frontal Occipitotemporal Midtemporal Inferior temporal Temporal pole Parahippocampal gyrus Hippocampus Amygdala Orbital frontal brain regions	↑ inferior frontal and occipitotemporal regions during WCST & PART WCST vs. PART: ↑ DLPFC PART vs. WCST: ↑ orbital frontal and ↓ dorsomedial prefrontal cortex Top WCST performers: ↑ Dorsal lateral and inferior frontal regions. Top PART performers: ↑ orbitotemporal activation	Bilateral Trend for ↑ left activation

Note. Abbreviations found in the table include: ↑ = increased; ↓ = decreased; BA = Brodmann's Area; DL = Dorsolateral; DLPFC = Dorsolateral Prefrontal Cortex; F = Female; M = Male; MCST = Modified Card Sorting Test; MTS = Matching to sample; NC = Normal Controls; PART = Paired Associates Recognition Test; PET = Positron Emission Tomography; Pts = Patients; rCBF = Regional Cerebral Blood Flow; ROIs = Region of Interest, SPM = Statistical Parametric Mapping; Sx = symptoms; WCST = Wisconsin Card Sorting Test.

fMRI Studies. Functional magnetic resonance imaging (fMRI) is another popular technique used to study neural correlates of cognitive tasks. fMRI is noninvasive and has better spatial resolution than PET or SPECT. Thus, researchers hoped that further understanding of the functional anatomy of mental operations would be possible given fMRI's capability of enhanced spatial resolution.

Initially, researchers simply wanted to validate that task activation patterns found using SPECT and PET methodologies were similar in fMRI paradigms. Thus, an early fMRI study by Volz et al. (1997) using the WCST corroborated right mesial and dorsolateral prefrontal cortex activation, with minor activations detected in the medial thalamic nuclei in normal controls. Mentzel et al. (1998) found similar results in normal individuals; their study revealed mesial and dorsolateral PFC activation, predominantly in the right hemisphere, with additional activation in the basal ganglia and mesial thalamic nuclei.

Researchers soon became concerned that an undefined resting condition was not an adequate control for teasing out cognitive processes underlying the WCST. Riehemann et al. (2001) developed a color card sorting task to attempt to discover brain activations specific to the WCST. Their control task required subjects to sort blank colored cards to a matching colored key card. Riehemann et al. also included rest periods. The WCST compared to rest periods showed activations in the right middle frontal gyrus, left thalamus, right caudate, corpus callosum, left middle frontal gyrus, and left cerebellum. When the WCST was compared to their

control color sorting task, stronger activations were seen in the right middle frontal gyrus, perhaps suggesting that this brain area is specific to performing the WCST.

Konishi et al. (1998) applied a novel event-related fMRI method to further elucidate anatomical localization of processes involved in the WCST. By isolating cognitive shift related signals temporally, they found transient activation of the posterior part of the bilateral inferior frontal sulci, suggesting that inferior frontal areas play a critical role in mental flexibility. Konishi et al. (1999) then attempted to isolate the working memory component of the WCST, again employing an event-related fMRI paradigm. Subjects performed the WCST in the original condition (closely modeled after Heaton's standard administration) and an instruction condition (subjects were informed of new sorting dimension). Subjects were also scanned while performing a version of an N-back task (a test commonly used to assess working memory). Their sophisticated study of transient activation indicated that the same areas in the inferior prefrontal cortex appeared to be involved in working memory and cognitive set shifting. However, it is possible the activation the authors attributed to set shifting and working memory may simply be involved when novelty and/or adaptation to changing contingencies are required, as the tasks they used shared those traits.

Monchi et al. (2001) also used event-related fMRI to look at neural responses to positive or negative feedback during the WCST, and found increases in DLPFC areas during positive and negative feedback. During the reception of negative feedback, increased activation was found in the caudate nucleus, mediodorsal

thalamus, and mid-ventrolateral PFC areas. Increased activity was not observed in the putamen following positive feedback, perhaps implying greater involvement during novel rather than routine actions. Monchi et al.'s work (2001) contrasts with the PET study by Berman et al. (1995), as they found increased left putamen activity in subjects during the WCST after explaining and training to criterion levels. Thus, further investigation is needed to clarify the putamen's role during the WCST. However, Monchi et al.'s study uniquely contributed to the WCST imaging literature in that it quantified and subsequently implicated/differentiated cortical basal ganglia loops during cognitive set shifting and set maintenance.

A recent fMRI study by Lie et al. (2006) hoped to further elucidate the task components and neural correlates of the WCST by incorporating cognitive gradients. They utilized three tasks and a control condition: Task A) similar to the original WCST; Task B) subjects were instructed every 4th trial on which dimension they were matching to; Task C) subjects were instructed before each trial how to match the target card; and HLB) a control condition in which target cards were identical to key cards. Lie and colleagues reported a bilateral frontoparietal network including the anterior cingulate cortex, with greater activation on the left, during their task C (instruction given each trial) condition compared to control (HLB). Task B (instruction every 4th trial) compared to HLB showed increased right prefrontal cortex activity. Task A (the most similar to the original WCST) compared to HLB activated a bilateral frontoparietal network including the striatum, with a further increase of right DLPC activation observed.

Lie et al. further analyzed the data to attempt to elicit specific neural correlates of each of the WCST task conditions by contrasting each task condition (A > B, A > C, and B > C). When contrasting uninstructed set shifts (task A) with instructed set shifts (task B), the authors reported increased activation in the right superior parietal cortex, posterior cingulate cortex, and cerebellum. Lie et al. proposed the A > C contrast would reveal the "cognitive gradient" across the tasks. They suggested that A > C indicated neural activity associated with error detection, utilization of feedback, working memory, and set-shifting. Activation was observed in the anterior cingulate cortex, retrosplenium, cerebellum, bilateral temporoparietal junction, and in the PFC (stronger on the right). Right inferior frontal gyrus activation was found with the B > C contrast. Lie et al. emphasized the importance of the right PFC during the WCST, and their study may be an important preliminary step in determining the neural networks of specific WCST task demands.

Lie et al.'s results may help interpret the disparity among reported results of PFC lateralization during neuroimaging versions of the WCST, as they found right PFC activation increased with task demands. Perhaps some WCST imaging tasks with reduced cognitive load elicit more left PFC activation. Alternatively, perhaps the increased right PFC activation can be explained by novelty or task ordering effects, as condition A was always presented first followed by conditions B then C. See Table 4 for a summary of fMRI activation during the WCST in normal participants.

Table 4

fMRI Activation in Normal Controls During the WCST

Author(s)/Date	**Brief Study Description**	**ROIs**	**Results ↓/↑ BOLD Signal During WCST**	**DL Findings**
Volz et al. 1997 Mentzel et al. 1998	31 NCs (23 M, 8 F) and 13 schizophrenic inpatients (8 M, 5 F) Computerized WCST vs. subject-generated tapping pattern	Dorsomedial PFC Dorsolateral PFC Anterior white matter Frontotemporal Superior temporal lobe Inferior temporal lobe Hippocampus Thalamus Posterior white matter Cerebellum	↑ right mesial and dorsolateral PFC; Minor ↑ observed in medial thalamic nuclei and basal ganglia Schizophrenics missing frontal activation	Right DLPFC
Riehemann et al. 2001	9 healthy controls (3F, 6 M) and 9 neuroleptic-naïve schizophrenic patients. Subjects performed WCST, a colored card sorting control task, and resting baseline	Only 4 10-mm slices of functional data obtained. Slices positioned to cover parts of frontal and temporal lobes, thalamus, hippocampus, and the cerebellum	WCST vs. Rest: ↑ activation in right middle frontal gyrus, left thalamus, right caudate, corpus callosum, and left middle frontal gyrus WCST vs. Control Task: ↑ right middle frontal gyrus In all activated areas, neuroleptic-naïve schizophrenic patients showed a reduction	Not Reported

Table 4, Continued

fMRI Activation in Normal Controls During the WCST

Author(s)/Date	**Brief Study Description**	**ROIs**	**Results ↓/↑ BOLD Signal During WCST**	**DL Findings**
Konishi et al. 1998	Event-related fMRI 7 NCs Computerized WCST performed in 3 conditions: All 3 dimensions (color, form, number), 2 dimensions, and 1 dimension	R inferior frontal sulcus L inferior frontal sulcus R supramarginal gyrus L supramarginal gyrus Anterior cingulate gyrus	Found reproducible transient activation of the posterior part of the bilateral inferior frontal sulci, which increased as the number of dimensions were increased Also found activations in the supramarginal gyri and anterior cingulate cortex, though these areas were less reproducible among the subjects	DLPFC activated, but L/R differences not reported.
Konishi et al. 1999	Event-related fMRI 7 NCs (6 M, 1 F) Computerized WCST, WCST with instructions of which category to sort to, and N-back task	Not reported	Original WCST: Transient activation in bilateral inferior frontal sulci; also observed in instructed WCST, but not as great Inferior prefrontal areas activated during N-back task with significant spatial overlap of areas of activation during original WCST Results suggest that same areas in the inferior prefrontal cortex support set shifting and working memory to promote adaptation to changing contingencies	N/A

Table 4, Continued

fMRI Activation in Normal Controls During the WCST

Author(s)/Date	**Brief Study Description**	**ROIs**	**Results ↓/↑ BOLD Signal During WCST**
Monchi et al. 2001	Event-related fMRI 11 NCs (5 M, 6 F) WCST vs. Control Task (matching 2 identical cards)	Whole brain analysis	*Receiving Negative Feedback:* ↑ bilateral mid-DLPFC, posterior PFC, caudate nucleus, dorsal thalamus; ↑ bilateral activation of rostral anterior cingulate cortex, lateral premotor cortex, posterior parietal cortex, and prestriate cortex ↓ found in medial frontal cortex area, left motor cingulate region, left motor cortex, and bilateral putamen and posterior parietal cortex *Matching After Negative Feedback:* ↑ left putamen and left posterior PFC, parietal cortex, prestriate cortex, and right lateral premotor cortex; ↓ found in right restroplenial cortex *Receiving Positive Feedback:* ↑ right mid-dorsolateral PFC areas, posterior PFC, restroplenial cortex, and left posterior parietal cortex; ↓ found in lateral premotor cortex *Matching After Positive Feedback:* ↑ lateral premotor cortex and left posterior parietal cortex; ↓ right restroplenial cortex and right posterior parietal cortex *Positive Feedback vs. Negative Feedback:* ↑ mid-ventrolateral PFC, caudate nucleus, and mediodorsal thalamus, right prestriate cortex, left lateral premotor cortex, and right posterior parietal cortex

Table 4, Continued

fMRI Activation in Normal Controls During the WCST

Author(s)/Date	**Brief Study Description**	**ROIs**	**Results ↓/↑ BOLD Signal During WCST**
Lie, et al. 2006	Block fMRI of three different WCST variants. 12 NCs (10 M, 2 F) Variant A most similar to traditional WCST. Variant B subjects instructed about dimensional changes every 4 trials. Variant C subjects told how to sort each trial. Control task (HLB) was matching cards identical to key cards	Whole brain analysis	*C > HLB:* ↑ bilateral frontoparietal network including ACC, PFC lateralized to left *B > HLB:* Same as above but ↑ right PFC *A > HLB:* ↑ bilateral frontoparietal network including striatum, further ↑ right PFC *Activations in all 3 tasks:* ↑ bilateral frontoparietal network, ↑ caudal anterior cingulate cortex, ↑ left PFC *A-C*: ↑ anterior cingulate cortex, retrosplenium, cerebellum, bilateral temporoparietal junction, PFC, R > L *A-B:* ↑ Rostral anterior cingulate cortex, bilaterally in temporoparietal junction, retrosplenium, cerebellum, superior parietal cortex *B-C:* ↑ right inferior frontal gyrus

Note. Abbreviations found in the table include: ↑ = increased; ↓ = decreased; ACC = Anterior Cingulate Cortex; BA = Brodmann's Area; BOLD = Bold Oxygen Level Dependent; DL = Dorsolateral; DLPFC = Dorsolateral Prefrontal Cortex; F = Female; fMRI = Functional Magnetic Resonance Imaging; HLB = Higher Level Baseline; M = Male; NC = Normal Controls; Pts = Patients; rCBF = Regional Cerebral Blood Flow; ROIs = Region of Interest, SPM = Statistical Parametric Mapping; Sx = symptoms; WCST = Wisconsin Card Sorting Test.

Other Methodologies. Transcranial Doppler sonography has been applied in normal subjects to explore cerebral hemodynamics during the performance of the WCST. Briefly, Schuepback et al. (2002) found that mean cerebral blood flow velocity increased after category shifts during the WCST, and that cerebral blood flow velocity differences were found among the Tower of Hanoi task, WCST, and a visual control task. Barceló and Gale (1997) used evoked potentials in 15 brain areas and found increased bilateral signal in frontal, temporoparietal, and occipital regions. A magnetoencephalography study (Wang, Kakigi, & Hoshiyama, 2001) analyzed WCST response after feedback signals, and found dorsolateral prefrontal and middle frontal cortex activation, as well as activation in broad frontal areas and parieto-frontal networks throughout the WCST. The WCST has also been studied using near-infrared spectroscopy, and significant bilateral increases in oxygenated hemoglobin were found in the frontal lobes (Fallgatter & Strik, 1998). Thus, it would appear that other imaging modalities support the WCST as activating frontal areas, as well as frontal-parieto-temporal networks.

Summary. As with the lesion literature, the imaging data on the WCST has many inconsistencies, which may be attributed to the variety of methodologies applied when studying activation patterns during the WCST. However, the imaging data provides stronger support for the role of the dorsolateral prefrontal cortex during WCST performance, as activation of the DLPFC is consistently observed across imaging modalities and WCST task variations. Imaging data also implicates frontal-subcortical circuitry involvement, as well as broader parietal-temporal-cortical and

cerebellar networks. The imaging literature also suggests that similar brain areas are involved during the performance of differing executive tasks, even though strong correlations are not found behaviorally or statistically using factor analysis among the tasks. Thus, imaging appears to validate the WCST as a complex measure of frontal-subcortical functioning, as these areas are consistently involved in the execution of the task. Consequently, the WCST should be adequate as a comparison with novel EF tasks predicted to activate similar brain circuitry. Therefore, this study will directly compare brain activation during the WCST and the TCST as a unique way of exploring the convergent validity of two frontal-subcortical EF measures through neuroimaging techniques.

Texas Card Sorting Test

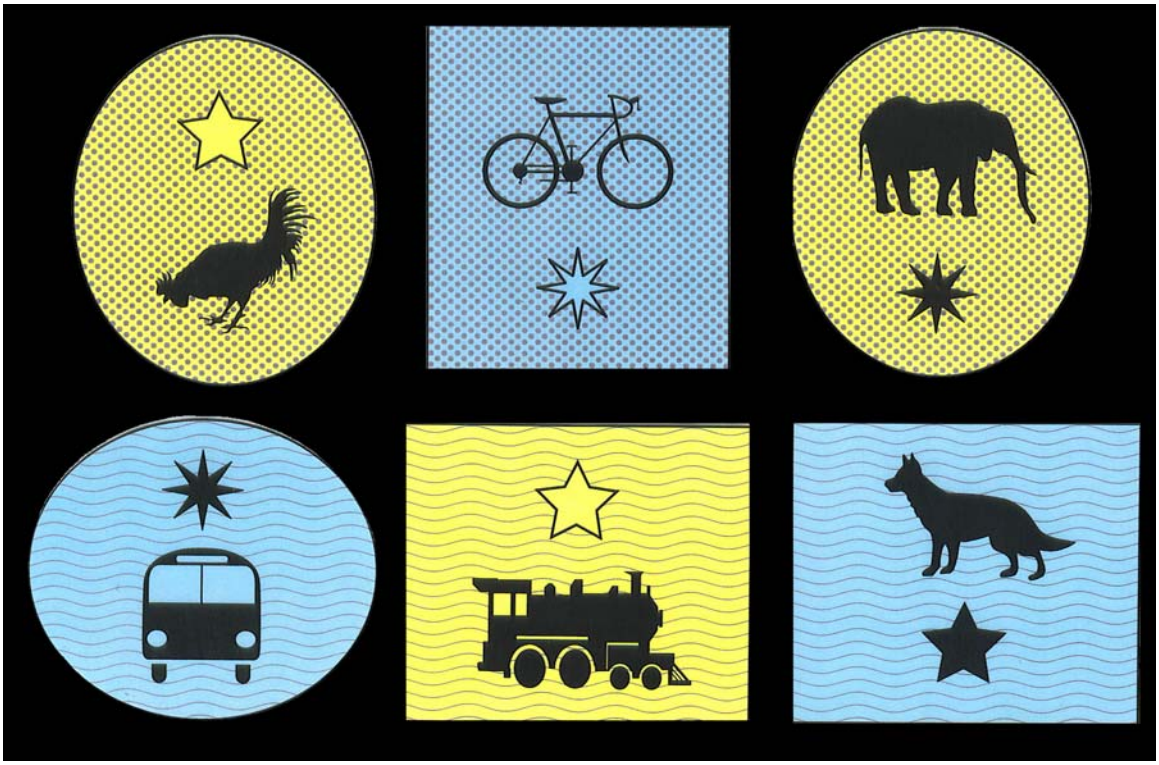
Although the WCST is one of the most popular measures of executive functioning in the clinical arena, it has been criticized for its lengthy administration time and use of negative feedback. While the California Card Sorting Test (now part of the Delis Kaplan Executive Function System; see Delis, Kaplan, & Kramer, 2001) addresses the above issues, it requires verbal responses and relies heavily on knowledge of the English language to adequately generate card-sorting strategies. The Texas Card Sorting Test has the appeal of the California Card Sorting Test, but is a nonverbal measure, and consequently may have more utility in verbally impaired or linguistically diverse populations.

The Texas Card Sorting Test was developed in 1998 in the Neuropsychology laboratory at the University of Texas Southwestern Medical Center at Dallas, and was originally intended to be used in cross-cultural assessments. The test involves sorting cards into groups by shared common dimensions (e.g. color, shape, semantic content, or figure placement; see Figure 3 for a visual depiction of the test). However, the test has only been piloted in two small samples, and normative data do not yet exist. The test was first piloted in 10 Caucasian patients with possible or probable Alzheimer's disease. The TCST total score (composed of the number of correct sorts and the total points from identifying correct sorting principles when the examiner sorted the cards) was significantly correlated with full-scale IQ scores from the Wechsler Adult Intelligence Scales, the Dementia Rating Scale, and WCST perseverative responses. The TCST did not show significant relationships to

measures of language (i.e., verbal fluency, Boston Naming Test). Thus, Kaltreider, Vertovec, Saine, and Cullum (1999) concluded the test showed promise as being sensitive to global cognitive integrity as well as to aspects of executive function. The TCST was more recently piloted using 26 consecutive outpatients presenting with memory complaints (Eisenman, Montague, Lacritz, & Cullum, 2005). Similar to Kaltreider et al.'s findings, Eisenman et al. found that the TCST was significantly correlated with estimated full-scale IQ scores, the Dementia Rating Scale total score, WCST perseverations, and Trail Making Test B. Lower correlations were also observed with category fluency, the Boston Naming Test, measures of visual memory, and simple attention. In contrast to Kaltreider et al., this study also found significant correlations with letter fluency.

Thus, there is limited behavioral data suggesting the TCST is a sensitive measure of executive functioning and that it correlates significantly with the number of WCST perseverative responses. As the TCST overcomes many limitations found in the available measures of executive functioning used by clinicians, one of the major aims of this study will be to further validate the TCST as a viable alternative to the WCST through analyzing behavioral and neuroimaging data in a sample of normal controls.

Figure 3. Original TCST stimuli.



HYPOTHESES

Overall Goal: To investigate the validity of the TCST as a measure of frontal, subcortical, and cerebellar functioning using functional magnetic resonance imaging (fMRI).

Question One: Are frontal, subcortical, and cerebellar circuits activated during the performance of the TCST?

Hypothesis One: Significant activation of the prefrontal cortex, basal ganglia, thalamus, and cerebellum will be observed in healthy volunteers when comparing brain activation during the TCST to a control task.

Exploratory Analysis: Whole brain image analysis will be performed to investigate other areas of brain activation during the TCST compared to a control task.

Question Two: Is there evidence of convergent validity of the TCST when performance variables and fMRI brain activation during the TCST are compared to WCST performance variables and brain activation in a sample of healthy volunteers?

Hypothesis Two: Behavioral performance data from the TCST and WCST will be significantly correlated, indicating convergent validity.

Specific Hypothesis: Number of categories achieved on the WCST will significantly positively correlate with number of correct sorts on the TCST.

Specific Hypothesis: Number of WCST perseverative responses will significantly positively correlate with number of TCST perseverative errors.

Specific Hypothesis: Number of WCST failures to maintain set will significantly correlate with number of TCST set loss errors.

Hypothesis Three: Convergent validity will also be demonstrated when comparing fMRI activation patterns between the WCST and the TCST.

Specific Hypothesis: Prefrontal cortex and thalamic activation patterns between the WCST and the TCST will be similar.

Specific Hypothesis: Differences in basal ganglia activity will be observed when comparing the WCST and the TCST, as performance feedback is not given during the TCST, and feedback is thought to selectively activate specific components of the basal ganglia.

Specific Hypothesis: Cerebellum activation will be significantly different when comparing the WCST and the TCST, as the unpredictability in set shifting is present during the WCST but not during the TCST.

Question Three: Do subjects perceive the WCST as more frustrating than the TCST?

Hypothesis Four: Subjects will report more frustration with the WCST than the TCST as measured by a brief questionnaire following the imaging study.

DESIGN

Participants

Twenty-eight right-handed healthy volunteers, between the ages of 21-40 were recruited for this study. A semi-structured interview was conducted with each volunteer to determine his or her eligibility (see Appendix A for a copy of the interview form). Potential participants were excluded if they had a history of neurological or psychiatric disorder, or general medical illness. Subjects were also excluded if they had any history of alcohol or drug abuse, structural damage to the brain, or any surgical metal or electronic implants that could interfere with MRI evaluation. Selected volunteers were asked to refrain from caffeine, alcohol, and nicotine for four hours prior to scanning. Female participants were asked the date of their last menstrual period and to report whether they were utilizing birth control, as hormonal changes during the menstrual cycle have been reported to significantly affect neural activation (Dietrich et al., 2001; Goldstein et al., 2005). Written informed consent was obtained from each participant.

Cognitive Tasks

An original computerized version of the WCST (created/programmed by Dixie J. Woolston) was administered using Presentation® software (version 9.70, www.neuro-bs.com). During scanning, the computer display was projected onto a mirror in the MRI scanner. Responses were recorded using a four-key button box (FORP, Current Designs).

Four fixed reference squares (analogous to the WCST key cards) were presented in a horizontal row across the top of the screen, displaying one red triangle, two green stars, three yellow crosses, and four blue circles, respectively. On each trial, a new test card was presented in the middle of the screen below the reference cards. Subjects then matched the test card to one of the reference cards. A bell-like tone with a smiley face (positive feedback) was presented if the card matched correctly. If the card did not match correctly, a buzz with a frowning face (negative feedback) was presented (see Figures 4-6). Subjects then used feedback to determine the correct sorting principle, which covertly changed after an unpredictable number of correct sorts; that is, unbeknownst to the examinee, the correct principle was changed pseudo-randomly after 6-10 correct matches. Stimulus timing was response-dependent. Blocks of the WCST task (matching to shape, color, and number) were interspersed with a control task (W-CTL), which consisted of matching a test card that was identical to one of the key stimulus cards, with positive feedback presented after a correct match and negative feedback presented after an incorrect match. See Figure 7 for a sample WCST run.

Figure 4. Sample of WCST imaging task.

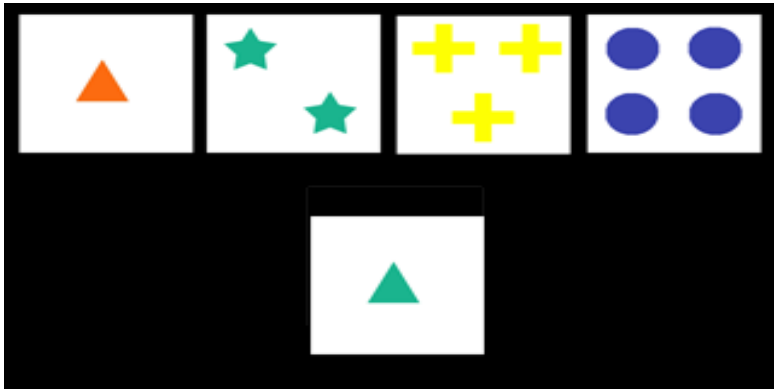


Figure 4. WCST imaging task layout. This figure depicts how the WCST was presented to participants in the scanner. The four key cards are displayed in the top horizontal row, and the subjects pressed buttons 1, 2, 3, or 4 of the response box to select a key card. Sample stimulus cards were presented in the lower half of the screen, as shown here.

Figure 5. WCST positive feedback following a correct match.

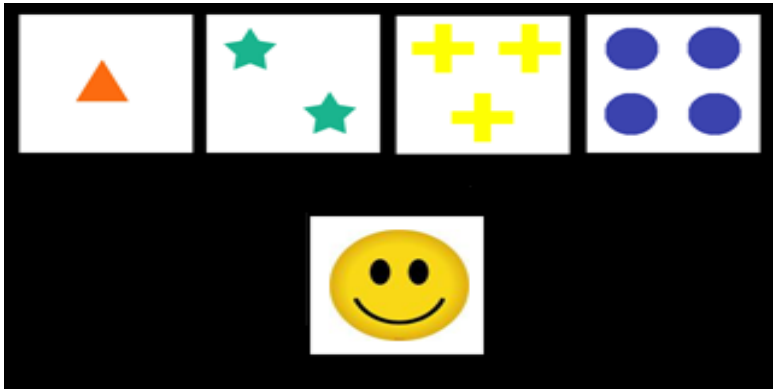


Figure 6. WCST negative feedback following an incorrect match.

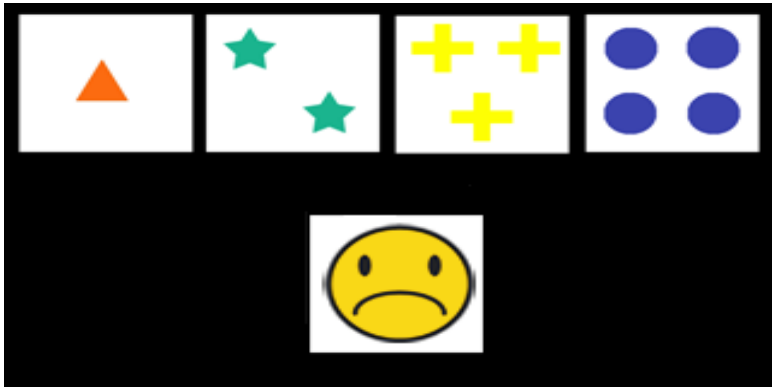


Figure 7. Sample WCST run.

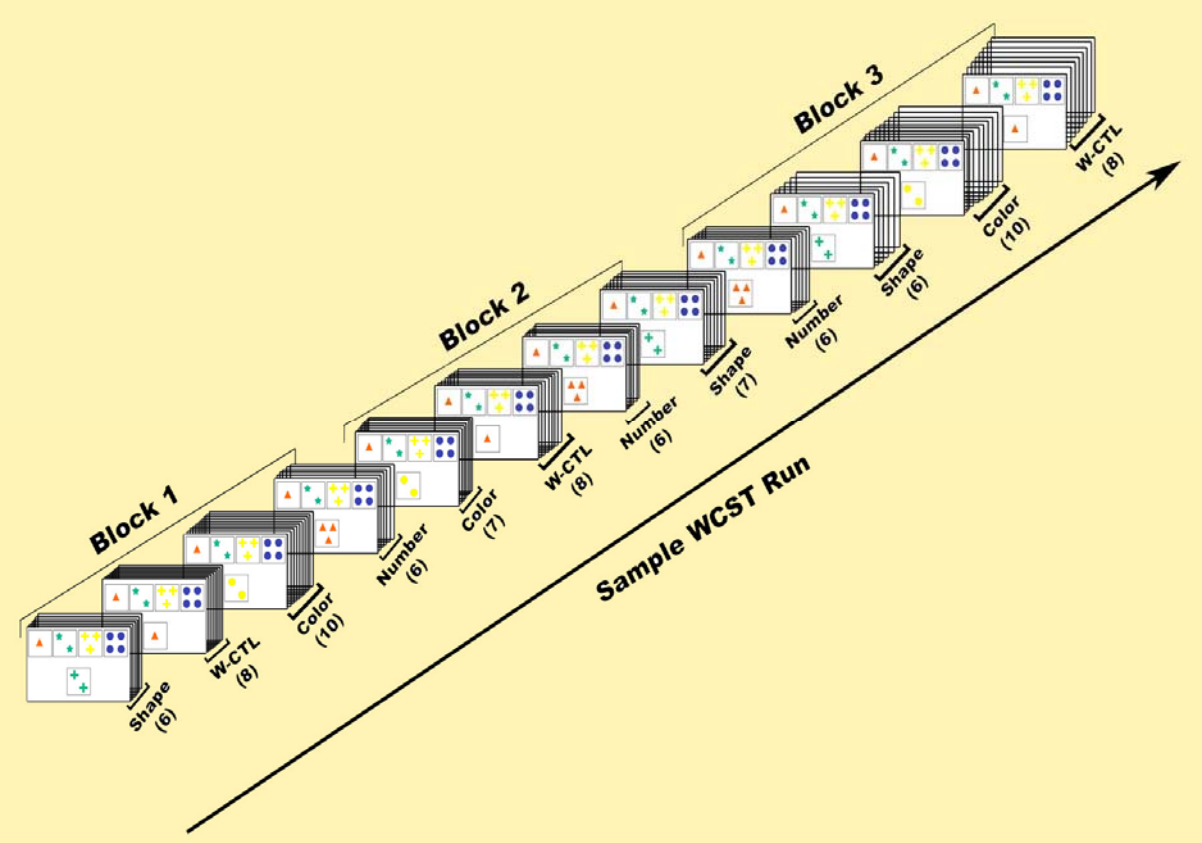


Figure 7. Sample WCST imaging task run. The number in parentheses indicates how many correct card sorts in a row were necessary before moving to the next matching principle.

A computerized version of the TCST (created/programmed by Dixie J. Woolston) was also administered using Presentation® software (version 9.70, www.neuro-bs.com). The 6 stimuli were presented in two horizontal rows (see Figure 8). Examinees were asked to sort each of the 6 cards into two groups of three. Subjects were instructed that each pile should have something in common, that they should work as quickly as they could to make as many sorts as possible, and that each sort should be original (i.e., they should not use the same idea again). During the control task, two different TCST stimuli were each displayed three times, and the examinees were asked to sort identical cards into each group (see Figure 9). As this is an experimental measure, the imaging version of the TCST block was modeled closely after the behavioral version of the TCST. Thus, a 3-minute block of the TCST was followed by a 90-second block of a control sorting task (T-CTL). See Appendix B for specific task instructions.

Figure 8. Computerized TCST task.

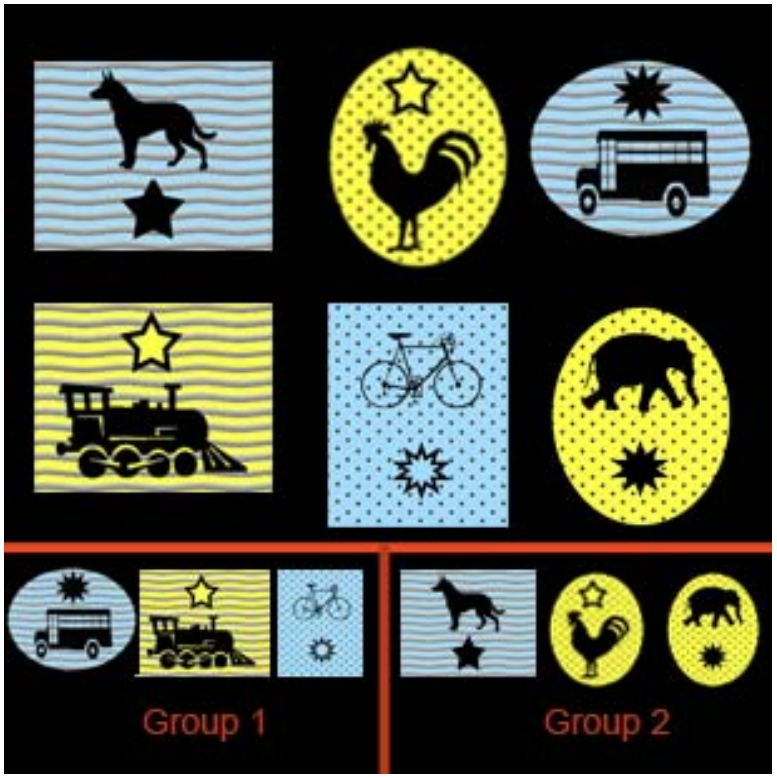


Figure 8. The TCST sorting task. Examinees were asked to sort each of the 6 stimulus cards (top two rows) into two groups with something in common. Depicted above is a sample sort where the subject has sorted the cards into transportation (Group 1) and animals (Group 2).

Figure 9. T-CTL sorting task.

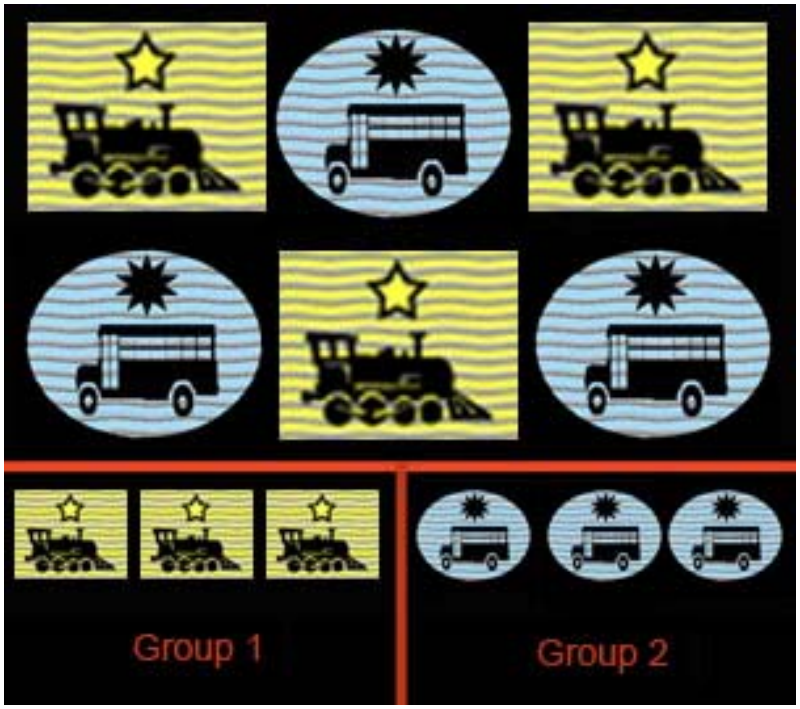


Figure 9. The T-CTL sorting task. This is a sample item from the T-CTL task. Examinees were asked to put identical cards in each group.

For the WCST task, the scanning session consisted of two runs (see Figure 10). Blocks of each of the 4 trial types (WCST trials matching to color, shape, or number and the control task) were presented in random order three times per run. Each run began and ended with a 15-second fixation cross stimulus. During the WCST blocks, the number of correct sorts randomly varied among 6-10 before the sorting principle changed. The control task (matching identical cards) consisted of 8 trials. For the WCST, participants differed on their response time and the number of errors; thus, the total length of each run and the total number of trials individually varied.

The TCST consisted of one run (the TCST for 180 seconds and the T-CTL for 90 seconds; see Figure 11). A 15-second fixation cross stimulus was also presented at the beginning and end of this run. The TCST and T-CTL blocks were always completed last to facilitate the reporting of TCST sorting strategies (see Appendix C for an example of the TCST scoring sheet used for recording sorting principles). Although task duration varied by subject, the total amount of time in the scanner was between 40 and 60 minutes.

Figure 10. WCST task schematic.

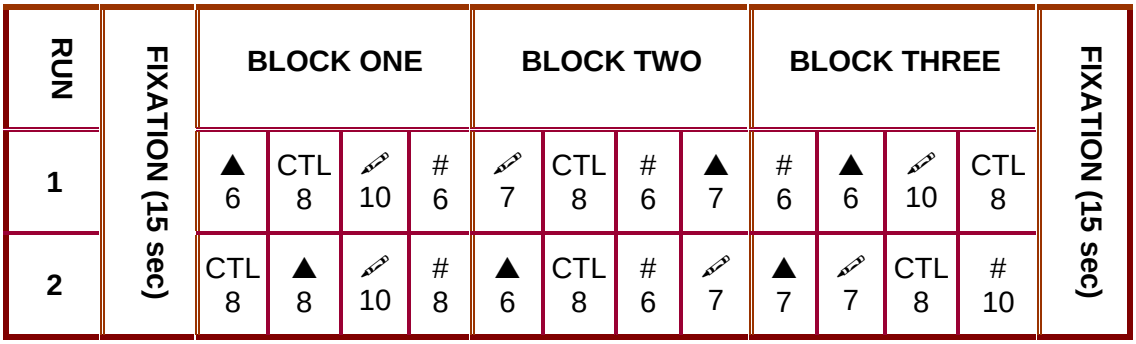
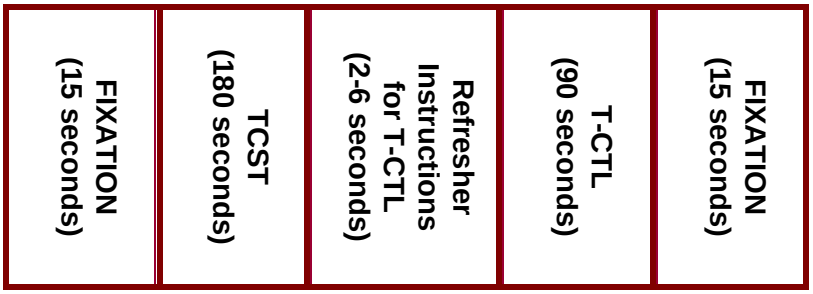


Figure 10. WCST task schematic. Symbol key: ▲ = matching to shape; CTL = W-CTL condition (matching identical cards to the key cards), # = matching to number; ✎ = matching to color. The numbers below each symbol indicate how many correct card sorts in a row (randomly selected among 6-10) were necessary before moving to the next matching principle.

Figure 11. TCST task schematic.



Procedure

Approval to conduct this study was obtained from the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas. Written informed consent was obtained from all participants. (See Appendix D for a copy of the IRB approval letter and Appendix E for a copy of the IRB-approved consent form). As mentioned previously, a brief screening interview was conducted with each potential volunteer to exclude individuals who did not meet inclusion criteria. Subjects were informed of the nature of the study, requirements for participation, and also completed the Wechsler Test of Adult Reading (WTAR) to obtain an estimate of intellectual functioning (The Psychological Corporation, 2001)[1].

Participants were trained on the cognitive tasks using a personal computer before the scanning session. Subjects were then scanned using a Siemens Trio 3 Tesla MR system. After scanning, participants were shown their TCST sorts, and asked to explain the principle behind each sort. Subjects also completed a brief questionnaire to compare frustration levels between the WCST and the TCST (See Appendix F for an example of the post-scan survey/questionnaire). Finally, participants were debriefed and any questions concerning the study were addressed. In compliance with the Health Insurance Portability and Accountability Act (HIPAA) research regulations, all data (paper materials as well as scans) were

[1] The WTAR is an established measure commonly used to estimate intellectual functioning for individuals ages 16 to 89. It consists of asking subjects to read a list of 50 words with irregular pronunciation. It is unique in that it was co-normed with the Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III), making the WTAR an especially effective method for predicting Full-Scale IQ.

numerically coded and identifying information was removed to preserve the privacy of each participant.

Imaging

Magnetic Resonance Imaging (MRI) was performed with a Siemens Trio 3 Tesla scanner (Siemens, AG, Erlangen, Germany) with VB12 software. An MRI Devices*InVivo 8-channels receive-only head coil was used. Each scanning session included a high-resolution T1-weighted three-dimensional volume acquisition for anatomical localization (3D MPRAGE sequence, number of averages = 2, acquisition time = 346 s, TI = 725 ms, TR = 1240 ms, TE = 2.6 ms, bandwidth = 200 Hz/pixel, flip angle = 10°, field of view (FOV) = 240 mm, matrix = 256 X 256, 128 slices, voxel size = 0.94 mm X 0.94 mm X 1.2 mm). A two-dimensional sagittal MRA volume acquisition was also acquired for blood vessel localization (2D FLASH sequence, parallel imaging factor = 2, number of averages = 1, 36 slices, acquisition time = 196 s, TR = 26 ms, TE = 4.2 ms, flip angle = 40°, bandwidth = 180 Hz/pixel, field of view (FOV) = 220 mm, matrix = 256 X 256, 36 slices, voxel size = 0.86 mm X 0.86 mm X 3.5 mm).

Functional MR images were sagitally acquired using echoplanar T2*-weighted images with blood oxygenation level-dependent (BOLD) contrast (40 slices, number of averages = 1, TR = 2000 ms, TE = 25 ms, bandwidth = 2300 Hz/pixel, echo spacing (ES) = 0.54 ms, flip angle (FA) = 80°, field of view = 220 mm, matrix = 64 X 64, voxel size = 3.4 mm X 3.4 mm X 3.4 mm). Functional images were acquired in 3 runs in a single session. The volumes were acquired continuously, and the total

number of volumes varied depending on the subject's performance. The stimulus presentation and the scanning were synchronized at the beginning of each run. The Siemens scanner automatically calculated when the BOLD signal reached steady state and did not acquire the first 3 images after excitations commenced.

Imaging Data Analysis

The data analyses were performed in MATLAB (version 7.0.4, www.mathworks.com) using Statistical Parametric Mapping software (SPM 5, freeware distributed by the Wellcome Department of Imaging Neuroscience at www.fil.ion.ucl.ac.uk/spm/).

Images from each run were realigned (registered to the first image in the series using a 2nd degree B-spline algorithm available in SPM 5), and individual runs exhibiting greater than 1.5 mm in point-to-point translational head motion were rejected (Friston, 2003; Logothetis & Wandell, 2004). As group analyses were performed, after realignment, images were normalized to the Montreal Neurologic Institute template supplied with Statistical Parametric Mapping (SPM), which represents an average of 305 subjects and approximately conforms to the space described in the atlas of Talairach and Tournoux (1988). Functional images were then smoothed using an 8 mm full-width half-maximum (FWHM) isotropic Gaussian kernel (Kiebel & Friston, 2002; Kiebel, Poline, Friston, Holmes, & Worsley, 1999; Poline, Worsley, Evans, & Friston, 1997; Poline, Worsley, Holmes, Frackowiak, & Friston, 1995; Worsley, Poline, Friston, & Evans, 1997; Worsley, Poline, Vandal, & Friston, 1995).

Statistical analyses were performed at the single-subject level using the general linear model with temporal convolution implemented in SPM (Friston et al., 1995; Friston, 2005; Friston, Frith, Frackowiak, & Turner, 1995; Worsley & Friston, 1995; Worsley et al., 1997). In brief, SPM performed a voxel by voxel analysis of variance for each contrast generated. A *t*-statistic was generated for each voxel, and a subsequent image map (an SPM) was displayed. Thus, for each subject, a linear contrast was used to test the relative effect of performing the WCST blocks compared to the W-CTL blocks. SPM *t*-maps (SPMs) were calculated for the WCST versus W-CTL contrast. Resulting maps reflected the differences in activation between the two conditions (WCST > W-CTL) at each voxel location. The TCST block and T-CTL block were also modeled as a single-subject design using the methods described above, and the resulting SPMs reflected differences in activation between the TCST and T-CTL at each voxel location.

Contrast images for each subject were submitted to a second-tier group analysis, using a one-sample *t*-test, and treating subjects as a random effect to obtain group results for TCST > T-CTL and WCST > W-CTL. To determine the differences between TCST and WCST activations, individual contrast images were analyzed using a paired *t*-test. SPMs were thresholded using the False Discovery Rate (FDR, $q < 0.05$, with no extent voxel threshold). FDR is a relatively new approach to the multiple comparisons problem (Benjamini Y. & Hochberg, 1995; Genovese, Lazar, & Nichols, 2002; Laird et al., 2005). FDR controls the expected proportion of false positives among suprathreshold voxels, rather than the probability

of making any false positive errors (such as family-wise error/Bonferroni corrections). Thus, the focus is slightly shifted from traditional multiple comparison correction in that FDR accepts that some predicted positives will be wrong. Thus, an FDR of $q < 0.05$ would suggest that out of 100 activations, on average, 5 are expected to be erroneous. Coordinates for each significant activation (based on normalization to the MNI template) were translated into the corresponding coordinates in Talairach space, using a linear transformation[2]. The transformed MNI coordinates were used to look up grey matter correlates from the Talairach atlas. Anatomical locations of the activations were confirmed by visual inspection of original MNI coordinates on the MNI template.

Statistical Procedures

As mentioned above, SPM was used for all imaging analyses. Non-imaging statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS version 12.0, www.spss.com). A significance level of $p < 0.05$ was adopted for all of the analyses. SPSS was used to examine demographic variables, to analyze Pearson correlation coefficients between TCST and WCST performance variables, and to compute Wilcoxon *T*-tests when analyzing ranked survey data from the two tasks.

The first aim of this study was to determine if frontal, subcortical, and cerebellar circuits were activated during the performance of the TCST versus the T-

[2] This approach was posted to the SPM mailing list in 1998 by Andreas Meyer-Lindenberg, of NIMH. Essentially, the algorithm [x = 0.88x-0.8, y = 0.97y-3.32, and z = 0.05y+0.88z-0.44] was applied to the xyz MNI coordinates to obtain an estimate of the Talairach coordinates.

CTL conditions. To address this aim, a second-tier one-way *t*-test was performed with single contrast images from each subject, parameterizing the effect of interest (TCST > T-CTL). The activation threshold was set to $q < 0.05$ (using FDR to correct for multiple comparisons). SPM generated a list of Montreal Neurological Institute coordinates of all active voxels in the brain that met the multiple comparison criteria. These MNI coordinates were converted into Talairach coordinates using the linear transformation previously referenced. The transformed MNI coordinates were then used to look up the corresponding Brodmann areas in the Talairach atlas and determine the location of the activation.

The second aim of this research was to determine whether the TCST could potentially serve as an alternative to the WCST in tapping prefrontal functioning. Thus, to determine how analogous the TCST and the WCST are, this study investigated the convergent validity of the TCST. If the two tests were similar, it was hypothesized that behavioral performance on the TCST would be correlated with behavioral performance on the WCST. It was also hypothesized that fMRI brain activation would be similar during both measures in a sample of healthy volunteers. A Pearson correlation coefficient was computed between the number of categories achieved on the WCST and the number of correct sorts on the TCST to test the hypothesis that these variables would be positively correlated, with alpha set *a priori* at 0.05. A Pearson correlation coefficient was also computed between the number of perseverative responses during the WCST and the number of perseverative errors during the TCST. Finally, a Pearson correlation coefficient was computed

between the number of WCST failures to maintain set and the number of TCST set loss errors, to test the hypothesis that these variables would be positively correlated, with alpha set *a priori* at .05.

To test the hypothesis that convergent validity would also be demonstrated when comparing fMRI activation patterns between the TCST and the WCST, a second-tier paired *t*-test was performed. In brief, the individual subjects' contrast images that parameterized the effect of interest (TCST/T-CTL and WCST/W-CTL) were submitted to a paired *t*-test group analysis. The contrast was corrected for multiple comparisons (FDR $q < 0.05$), MNI coordinates were transformed to Talairach coordinates using the linear transformation described previously, and Brodmann areas were obtained. It was hypothesized that no significant differences would be found between the two tasks in prefrontal cortex and thalamic areas. It was hypothesized that significant differences in activation would be observed between the two tasks in the basal ganglia and cerebellum.

The third aim of this study was to assess whether subjects found the WCST more frustrating than the TCST. The Wilcoxon *T*-test for two dependent samples was used to test the hypothesis that subjects would report higher frustration levels during the WCST than during the TCST. The Wilcoxon *T*-test is appropriate for two dependent samples with ranked data, which is what the survey contained.

RESULTS

Demographic Characteristics

A total of 28 healthy volunteers were recruited for possible participation in the study; a paper by Desmond and Glover (2002) suggested that at least 24 subjects are necessary to obtain sufficient levels of power in FMRI studies. Three subjects were excluded prior to imaging due to neuromedical history (two were being treated with Zoloft for depression and one met criteria for alcohol abuse). One of the remaining 25 participants reported trouble utilizing the corrective prism lenses during scanning and was subsequently excluded. Out of the remaining 24, 4 were excluded from the TCST analysis and 3 were excluded from the WCST analysis due to excessive movement (greater than 1.5 mm point-to-point) or scanner operator error. Complete data were available for the WCST vs. TCST analysis in 18 participants. The reasons for exclusion are summarized in Table 5.

Of the 24 imaged participants, 15 were men and 9 were women. All participants were right-handed. Their average age was 28 years and average level of education was 17 years. The participants had a mean estimated IQ of 112, ranging from 93 to 120 (population mean = 100; standard deviation = 15). Twenty-one of the participants were Caucasian (87.5%) and three were Hispanic (12.5%). These demographic variables are summarized in Table 6.

Table 5

Excluded Participants

Number of Participants	Reason
3	Did not meet inclusion criteria due to neuromedical history
1	Reported trouble with corrective prism lenses during scan
4	Excluded from TCST analysis as movement during scan was greater than 1.5 mm (3 participants) or scanner operator error (1 participant)
3	Excluded from WCST analysis as movement during scan was greater than 1.5 mm
TOTALS:	23 participants included in behavioral analyses of TCST & WCST 21 participants included in TCST imaging analysis 20 participants included in WCST imaging analysis 18 participants included in WCST vs. TCST imaging analysis

Table 6
Demographic Variables

Variable	**Range**	**Mean**	**Median**	**Standard Deviation**
Age (years)	23-37	28.21	26.50	4.48
Education (years)	16-20	17.04	16.00	1.33
Estimated IQ (WTAR)	93-120	112.17	112.00	5.69
Ethnicity: 21 Caucasian (87.5%), 3 Hispanic (12.5%)				
Gender: 15 Males (62.5%), 9 Females (37.5%)				
Sample Size: (n) = 24				

Hypothesis One

Hypothesis one stated that when comparing the TCST to a control task, significant activation in the prefrontal cortex, basal ganglia, thalamus, and cerebellum would be observed. While significant activation was observed in frontal areas (BA 5-6, 8-9, 11, 44-47) and the basal ganglia (left caudate, right putamen, right globus pallidus), neither significant thalamic nor cerebellar activation was seen in the group results.

As one of the exploratory aims of this research was to investigate other areas of significant brain activation during the TCST, whole brain imaging analysis was also utilized to identify other areas with significant activation. These areas included bilateral parietal areas (BA 7 & 39), left cingulate gyrus (BA 24, 31 & 32), right cingulate gyrus (BA 24), right superior temporal areas (BA 41 & 22), right fusiform gyrus, and left parahippocampal and middle temporal gyrus areas. Significant activation of the right occipital lobe (BA 18 & 19) was also observed. See Figures 12 and 13 and Table 7 for a list of the brain regions activated during the TCST.

Figure 12. TCST versus T-CTL cortical activation in healthy adults.

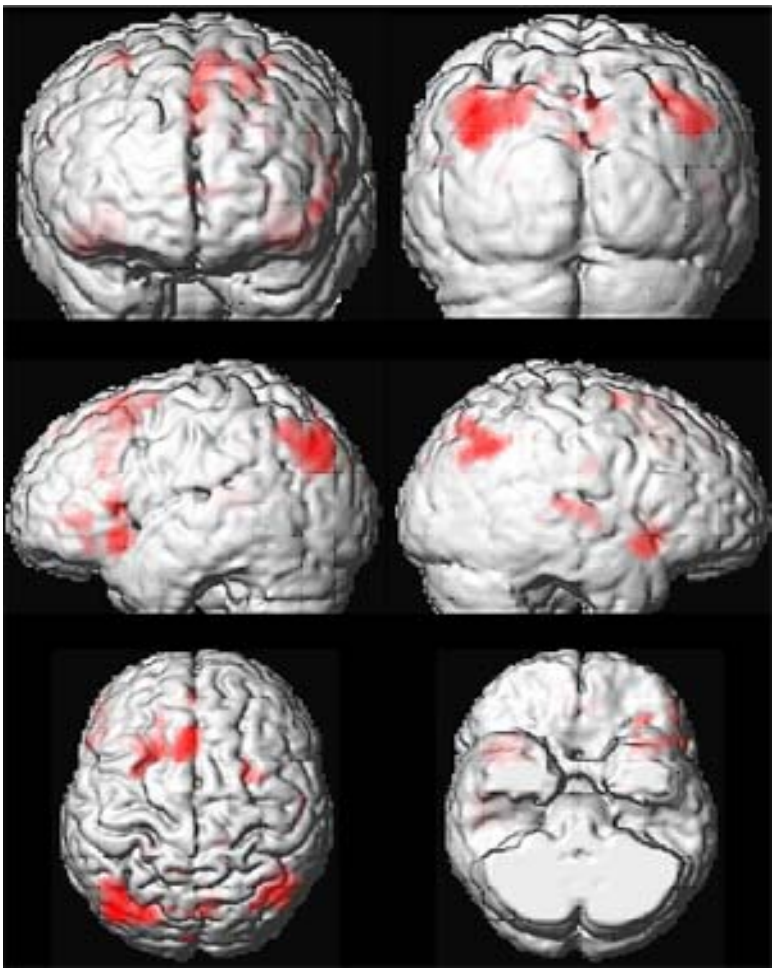
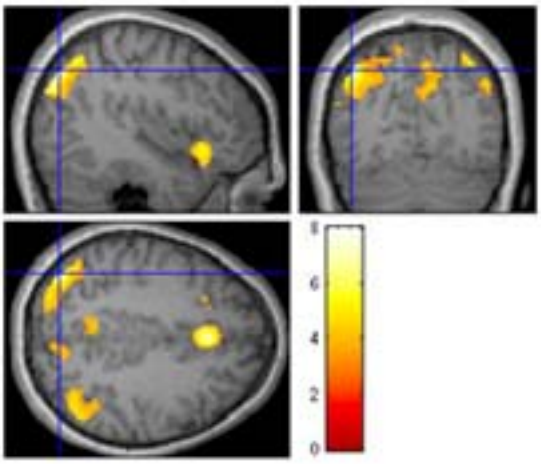


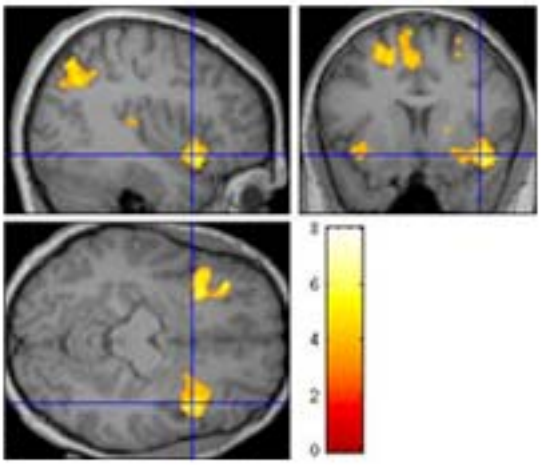
Figure 12. TCST versus T-CTL cortical activation in healthy adults. Cortical regions showing increased blood oxygen level-dependent (BOLD) signal in healthy adults during the TCST compared to the T-CTL condition (FDR $q = 0.05$, no extent voxel threshold).

Figure 13. Significant activation peaks during TCST.

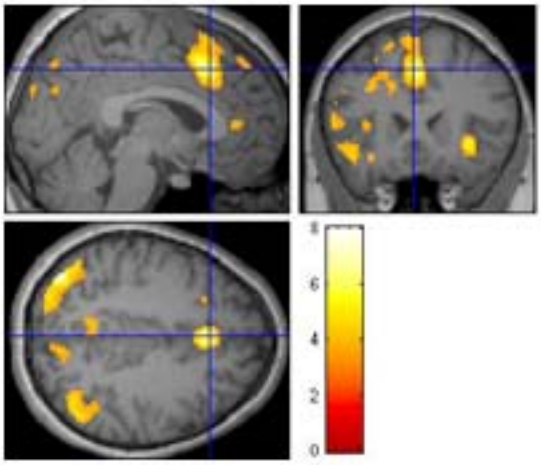
Left Precuneus (BA 7)



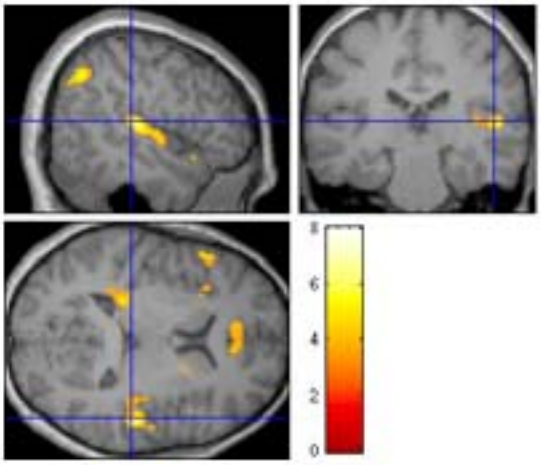
Inferior Frontal (BA 47)



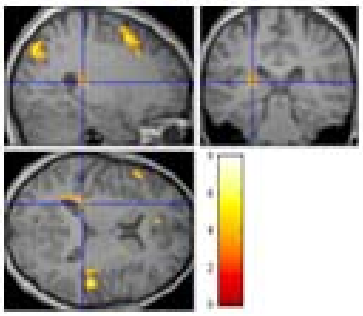
Cingulate (BA 32)



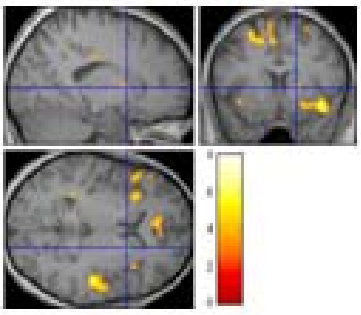
Right Superior Temporal Gyrus (BA 41)



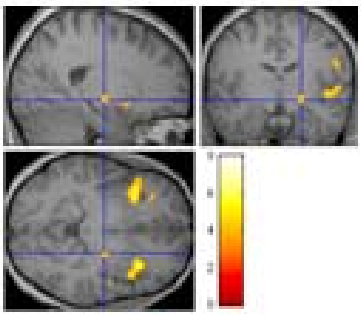
Basal Ganglia



Left Caudate



Right Putamen



Right Globus Pallidus

NOTE: *Left hemisphere is on the left in coronal images.*

Table 7

TCST vs. T-CTL Activation

Location		BA	FDR (*q*)	Threshold (*t*)	Z Value	Cluster Level	MNI Coordinates		
							x	*y*	*z*
Left Parietal Lobe	Precuneus	7	.01	8.03	5.24	1155	-44	-76	44
		31	.02	4.69	3.77	73	-10	-54	42
	Inferior Parietal	39	.01	6.18	4.52		-46	-64	50
		40	.04	3.56	3.08	3	-48	-52	50
	Paracentral Lobule	5	.04	3.69	3.17	11	-24	--42	58
Right Parietal Lobe	Precuneus	7	.01	5.86	4.38	648	36	-74	52
		7	.04	3.66	3.14	7	16	-50	50
	Angular Gyrus	39	.01	5.46	4.19		52	-62	40
	Paracentral Lobule	4	.04	3.68	3.16	9	14	-38	74
	Postcentral Gyrus	3	.04	3.52	3.05	3	20	-36	68
Right Frontal Lobe	Paracentral	5	.04	3.54	3.07	2	20	-34	60
	Middle Frontal	6	.02	4.11	3.43	92	32	2	68
	Inferior Gyrus	47	.01	7.01	4.87	694	42	12	-12
	Insula	13	.01	5.88	4.39		34	22	-6
Left Frontal Lobe	Superior Frontal	8	.03	3.75	3.20	23	-4	50	48
	Middle Gyrus	6	.01	4.88	3.88		-26	10	56
		46	.04	3.55	3.07		-50	36	18
	Inferior Gyrus	47	.01	6.75	4.76	698	-32	18	-10
		11	.01	6.35	4.60		-38	36	-12
		46	.03	3.78	3.22		-48	48	2
		45	.02	4.70	3.78	81	-52	40	0
		44	.02	4.61	3.73	94	-56	20	12
		9	.04	3.64	3.13		-56	22	22

Table 7, Continued

TCST vs. T-CTL Activation

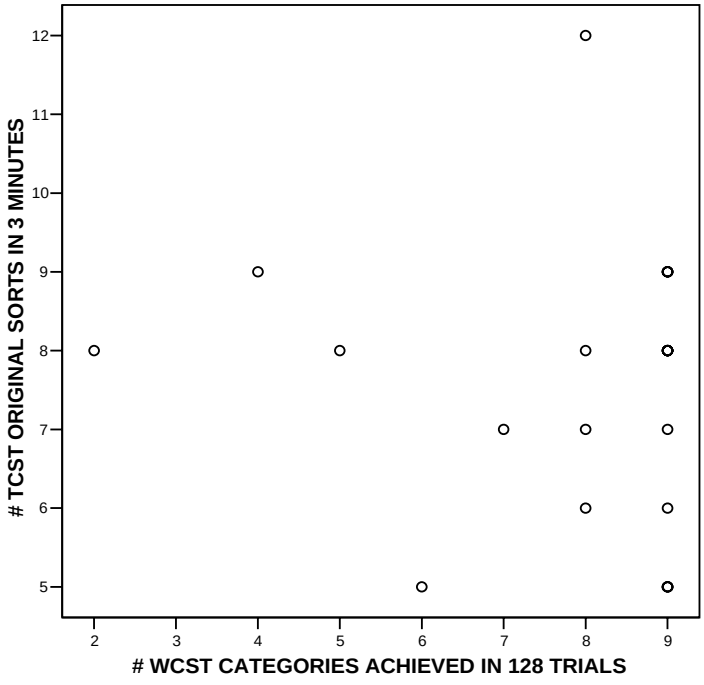
Location	BA	FDR (*q*)	Threshold (*t*)	Z Value	Cluster Level	MNI Coordinates *x*	*y*	*z*
Left Cingulate Gyrus	32	.01	6.92	4.83	1454	-2	24	44
	31	.03	3.95	3.34	24	-22	-42	40
	29					0	-38	24
	24	.01	4.95	3.92		-18	10	52
Right Cingulate Gyrus	24	.02	4.21	3.49		6	42	8
Right Temporal Lobe Superior Gyrus	41	.01	6.38	4.61	381	52	-28	10
	22	.02	4.59	3.72		56	-16	6
Fusiform	20	.05	3.46	3.01		54	-14	-26
Left Temporal Lobe Middle Gyrus	21	.05	3.40	2.97		-64	-20	-8
Parahippocampal Gyrus		.03	4.07	3.41		-32	-52	14
Right Occipital Lobe Superior Gyrus	19	.01	6.94	4.84		44	-82	32
Cuneus	18	.01	5.43	4.17	306	10	-78	34
Right Claustrum		.03	4.01	3.37		38	18	6
Basal Ganglia Left Caudate		.01	4.96	3.92	188	-26	-34	12
Right Putamen		.03	3.96	3.34	16	18	10	6
Right Globus Pallidus		.04	3.73	3.19	7	22	-12	-6

Note. Brodmann areas that were significantly activated during the TCST versus T-CTL one-way *t*-test group analysis (FDR used for multiple comparisons correction, with $q = .05$). Cluster level refers to the number of contiguous voxels; hence, blanks in the table indicate significant individually activated voxels. Height threshold T = 3.36, Degrees of freedom = [1.0, 19.0]. Abbreviations found in the table include: BA = Brodmann's Area; FDR = False Discovery Rate; MNI = Montreal Neurological Institute.

Hypothesis Two

Hypothesis two proposed that behavioral performance data during the TCST and the WCST would be correlated, thereby providing preliminary support for convergent validity of the TCST. Specifically, it was hypothesized that the number of original sorts during the TCST would correlate positively with the number of categories achieved during the entire first WCST run or first 128 trials (whichever came first). A one-tailed Pearson correlation with significance set *a priori* at $p < 0.05$ was used to test this hypothesis. The Pearson correlation coefficient equaled -0.12 with $p = 0.289$. See Figure 14 for a scatter plot of the two variables.

Figure 14. TCST original sorts and WCST categories achieved .



It was also hypothesized that the number of perseverative errors and number of set loss errors on the TCST would correlate positively with the number of WCST perseverative errors and failures to maintain set. The number of perseverative errors between the two measures was not significantly correlated (Pearson correlation coefficient = -0.162 and p = 0.230). However, a weak negative trend was observed in the relationship between TCST and WCST set loss errors (Pearson correlation coefficient = -0.298, p = 0.08). See Figures 15 and 16 for scatterplots of the number of errors on the two measures. Tables 8 and 9 summarize the behavioral test data for the WCST and TCST, respectively.

Figure 15. TCST and WCST perseverations.

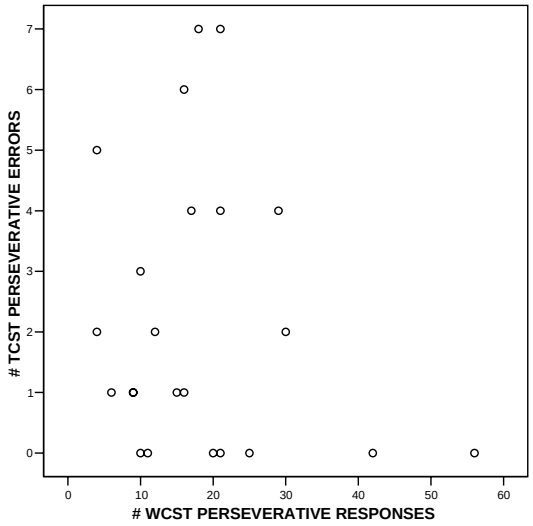


Figure 16. TCST and WCST set loss errors.

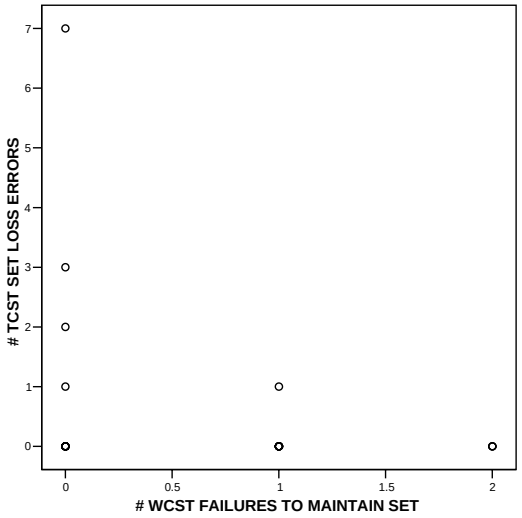


Table 8
WCST Behavioral Performance Variables

Variable	**Range**	**Mean**	**Standard Deviation**
# of Categories Achieved	2-9	7.91	1.91
Perseverative Responses	4-56	18.35	12.23
# of Failures to Maintain Set	0-2	0.61	0.722

NOTE: *WCST behavioral variables were taken from the entire 1st WCST run or 1st 128 trials, whichever came first.*

Table 9
TCST Behavioral Performance Variables

Variable	**Range**	**Mean**	**Standard Deviation**
# of Original Sorts	5-12	7.43	1.78
# of Perseverative Sorts	0-7	2.22	2.34
# Set Loss Errors	0-7	0.61	1.59

Post-hoc one-way analyses of variance (ANOVAs) were conducted to see if gender or IQ significantly impacted WCST and/or TCST behavioral performance variables, with significance levels set to $p = 0.05$. No gender effects were observed on the TCST or WCST variables. Estimated IQ did not vary significantly by gender. To determine if IQ impacted TCST and WCST behavioral performance data, a median split (Estimated FSIQ = 112) was used to divide the sample into relatively lower IQ and relatively higher IQ. None of the TCST variables (number of original sorts, perseverative errors, or set loss errors) or the WCST variables of number of categories achieved and failures to maintain set varied significantly by estimated IQ. However, a significant trend was observed in the relationship between the number of WCST perseverative responses and IQ group ($F = 3.182$, $p = .089$, Partial Eta-Squared = .132). The relatively lower IQ group made more perseverative responses during the first 128 WCST trials than the higher IQ group. See Table 10.

Table 10

TCST and WCST Variables by Gender and Estimated IQ

Variable	Males	Females	Est. IQ > 112	Est. IQ < 112
WCST	Mean (Standard Error)			
# Categories	7.71 (.52)	8.22 (.64)	8.50 (.59)	7.46 (.52)
# Psv Responses	18.86 (3.34)	17.56 (4.17)	13.40 (3.69)*	22.15 (3.24)*
# FMS	.57 (.20)	.67 (.25)	.54 (.20)	.70 (.23)
TCST	Mean (Standard Error)			
# Original Sorts	7.57 (.48)	7.22 (.60)	7.85 (.49)	6.90 (.56)
# Psv Errors	1.93 (.63)	2.67 (.78)	3.00 (.72)	1.62 (.63)
# Set Loss Errors	.93 (.42)	.11 (.52)	.40 (.51)	.77(.45)

NOTE: Means are presented first with the standard error in parentheses. Abbreviations found in the table include: Est. = Estimated; FMS = Failures to Maintain Set; Psv = Perseverative; WCST = Wisconsin Card Sorting Test; TCST = Texas Card Sorting Test. All WCST variables are from 1st WCST run or 1st 128 WCST trials, whichever came first.

* F = 3.182, *p* = .09, Partial Eta-Squared = .13

Hypothesis Three

Hypothesis three specified that the fMRI activation patterns during the TCST and the WCST would be similar. Specifically, it was hypothesized that prefrontal cortex and thalamic activation patterns would be most similar between the two measures. Due to task variation, it was further asserted that the two tasks would show activation differences in the basal ganglia and cerebellum. Consistent with previous data reported in the literature, significant WCST activation was observed in a variety of brain regions, including frontal and parietal areas, the thalamus, and the cerebellum (see Figures 17 and 18 and Table 11).

Figure 17. WCST versus. W-CTL cortical activation.

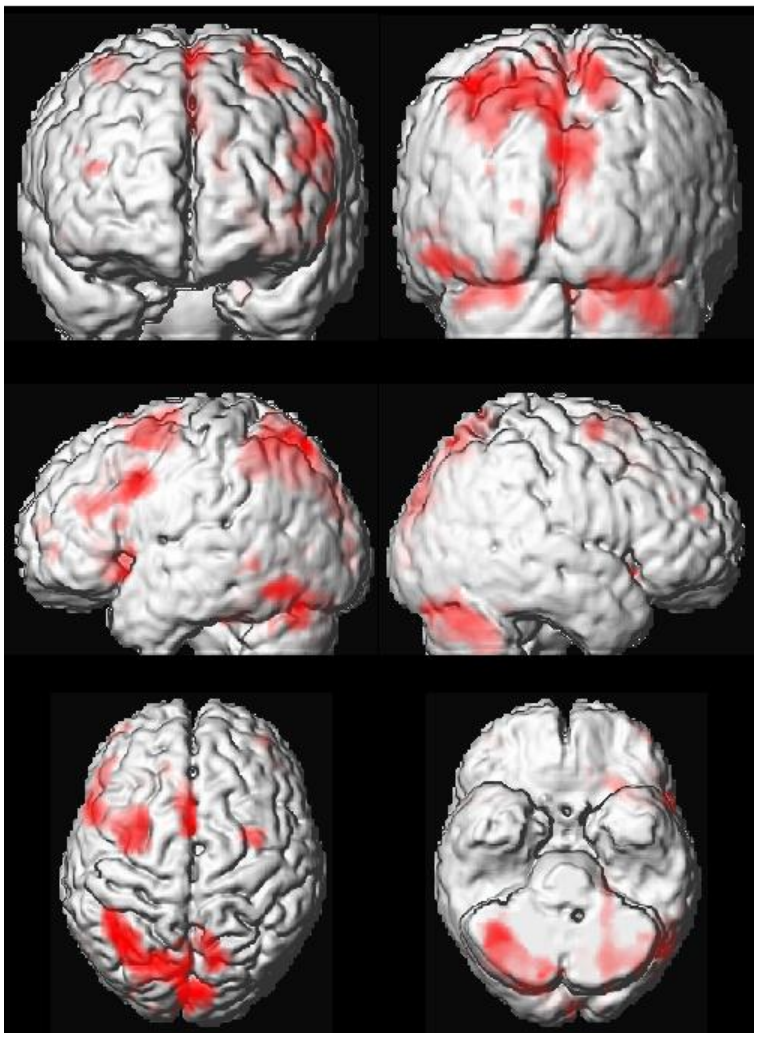
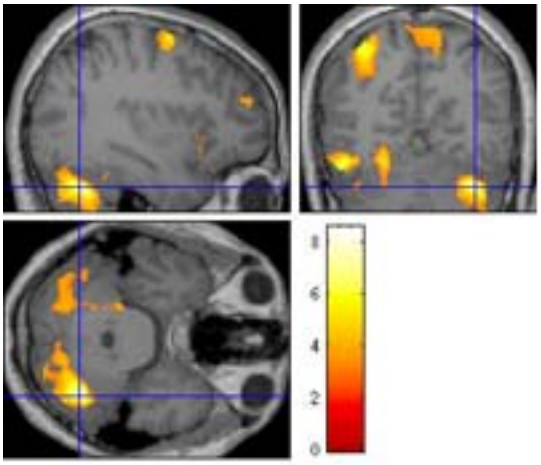


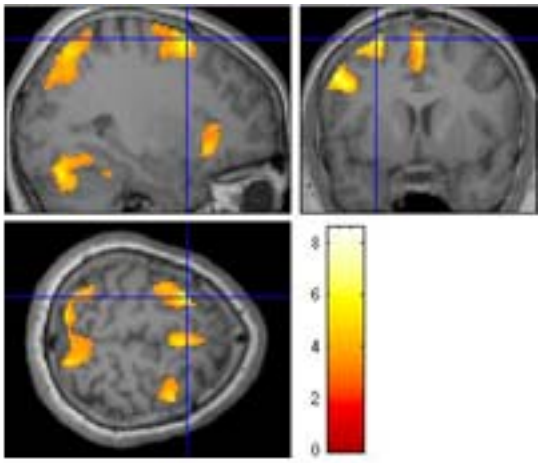
Figure 17. WCST versus. W-CTL cortical activation. Cortical regions showing increased blood oxygen level-dependent (BOLD) signal in healthy adults during the WCST compared to the W-CTL condition (FDR q = 0.05, no extent voxel threshold).

Figure 18. Significant activation peaks during WCST.

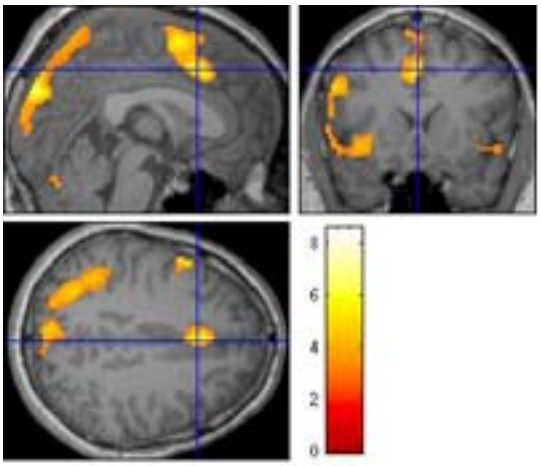
Cerebellum



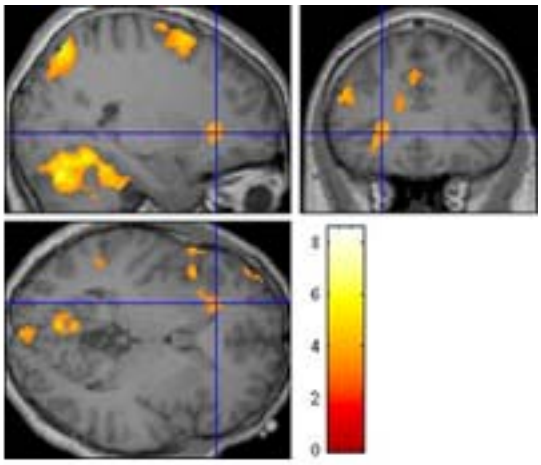
Frontal Areas (BAs 6, 9/10, 46)



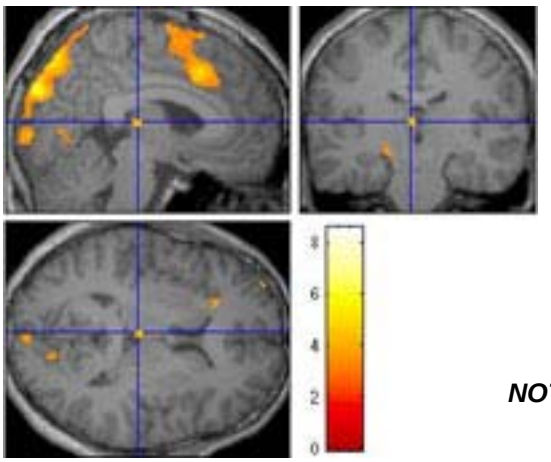
Cingulate (BA 32)



Left Claustrum



Thalamus (Pulvinar)



NOTE: *Left hemisphere is on the left in coronal images.*

Table 11

WCST vs. W-CTL Activation

Location		BA	FDR (*q*)	Threshold (*t*)	Z Value	Cluster Level	MNI Coordinates *x*	*y*	*z*
Right Cerebellum			.00	8.62	5.51	1834	38	-62	-34
Left Cerebellum			.00	7.14	4.98	1713	-24	-76	-26
Left Frontal Lobe	Precentral Gyrus	6	.00	7.00	4.92	686	-54	8	42
	Middle Gyrus	46	.01	4.20	3.51		-50	26	28
	Medial Gyrus	10	.02	3.79	3.25	19	-36	60	10
		32	.01	4.16	3.49		-8	14	50
		6	.00	6.46	4.69	747	-28	8	64
	Sub-Gyral	13	.00	5.10	4.03	564	-30	22	-10
Right Frontal Lobe	Middle Gyrus	6	.00	5.46	4.22	179	38	-2	66
		9	.03	3.64	3.15	5	48	36	28
		10	.02	3.79	3.25	19	-36	60	10
Left Parietal Lobe	Superior	7	.00	6.47	4.70		-38	-60	58
	Precuneus	7	.00	6.59	4.75		-18	-78	56
Left Temporal Lobe	Middle Gyrus	37	.01	4.34	3.60	92	-50	-48	-4
	Fusiform Gyrus	20	.04	3.35	2.95		-64	-42	-8
		19	.05	3.15	2.81	1	-50	-76	-10
	Parahippocampal Gyrus	19	.03	3.61	3.13	18	-20	-24	-10
Right Temporal Lobe	Superior Gyrus	22	.05	3.17	2.82		54	14	-6
Left Occipital Lobe		19	.00	6.76	4.82	3848	-2	-92	32
		18	.01	4.90	3.92		-10	-78	2

Table 11, Continued

WCST vs. W-CTL Activation

Location	BA	FDR (*q*)	Threshold (*t*)	Z Value	Cluster Level	MNI Coordinates		
						x	*y*	*z*
Right Occipital Lobe	17 18	.03 .04	3.65 3.29	3.16 2.91	16 6	10 810	-82 -96	10 -4
Left Limbic Lobe Cingulate Gyrus Parahippocampal Gyrus	32 28	.00 .03	6.38 3.61	4.66 3.13	782 18	0 -20	16 -24	44 -10
Left Insula (Posterior)	13	.01	5.10	4.03	564	-30	22	-10
Right Insula (Posterior)	13	.04	3.33	2.93	21	46	16	-8
Left Claustrum		.01	4.57	3.73		-24	28	2
Right Claustrum		.04	3.21	2.85	2	36	20	-2
Left Thalamus Pulvinar		.04	3.30	2.91	8	-2	-22	12
Right Thalamus Pulvinar Ventral Lateral Nucleus		.03 .03	3.57 3.41	3.10 2.99	4 4	20 12	-28 -8	10 16

Note. Brodmann areas that were significantly activated during the WCST versus W-CTL one-way *t*-test group analysis (FDR used for multiple comparisons correction, with $q = .05$). Cluster level refers to the number of contiguous voxels; hence, blanks in the table indicate significant individually activated voxels. Height threshold T = 3.08, Degrees of freedom = [1.0, 20.0]. Abbreviations found in the table include: BA = Brodmann's Area; FDR = False Discovery Rate; MNI = Montreal Neurological Institute.

Next, to test whether the WCST and TCST showed similar activation patterns in the prefrontal cortex and the thalamus, the TCST/T-CTL and the WCST/W-CTL contrast images were compared (including only those 18 subjects who did not have extraneous movement during ***either*** task). No significant differences were observed between the two tasks in the thalamus, but significant differences in the prefrontal cortex were observed. Specifically, bilateral frontal activation in Brodmann areas 6 and 47 and right prefrontal activation in Brodmann areas 8 and 10 were significantly greater during the TCST than the WCST.

Voxel-wise analysis was also used to determine whether significant differences in activation were seen in the cerebellum and the basal ganglia. No significant differences were present in the cerebellum. However, significantly greater BOLD signal was observed in the caudate (bilaterally) during the TCST.

Unexpectedly, differences were also observed in the right superior temporal lobe (BA 38, 39, 41, and 42) and right medial temporal lobe (BA 34) having significantly greater BOLD signal during the TCST. Bilateral temporal lobe activation was observed in BA 22. Greater left parietal activation was seen in areas 7, 31, and 21. Finally, the left hippocampus and left occipital lobe (BA 19 and 31) had significantly more activation during the TCST. See Figures 19 and 20 and Table 12 for a summary of these results.

Interestingly, when the contrast was looked at in the reverse (i.e., WCST activation > TCST activation), only one cluster of activation (18 voxels located in the left occipital lobe, BA 18) was observed to have more BOLD signal.

Figure 19. Comparison of TCST versus WCST cortical activation .

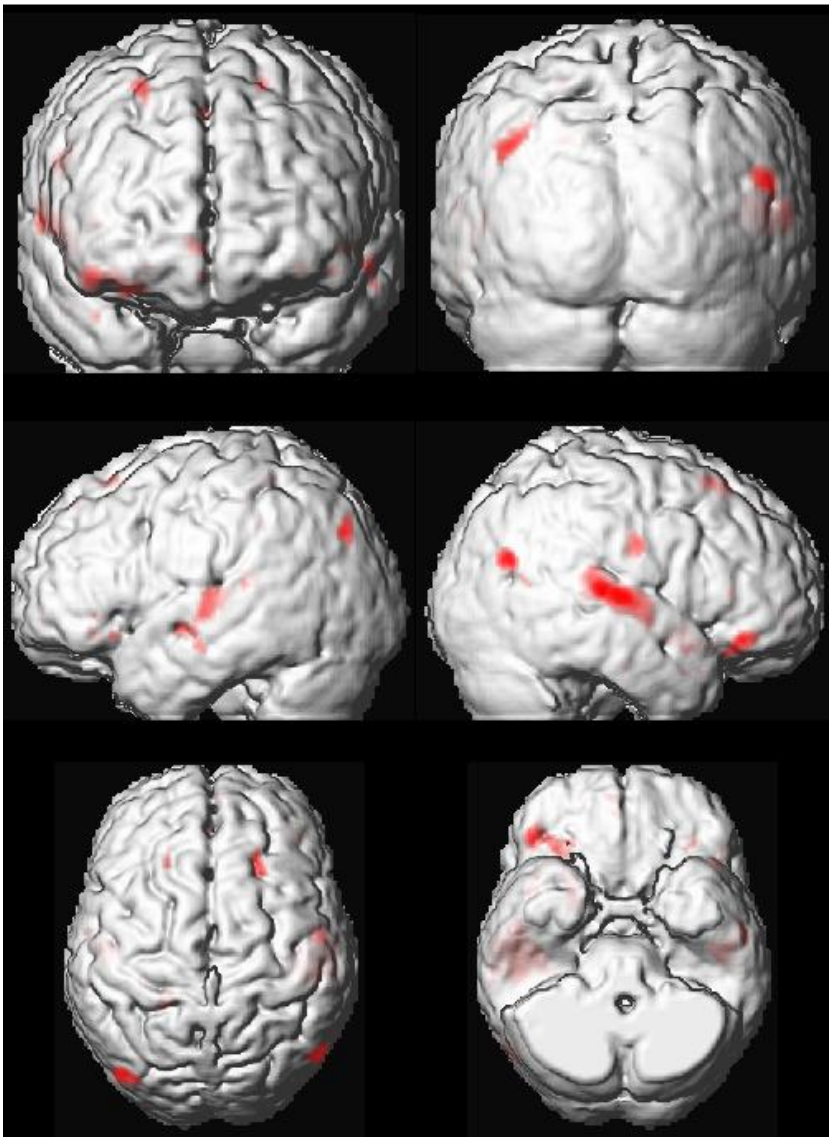
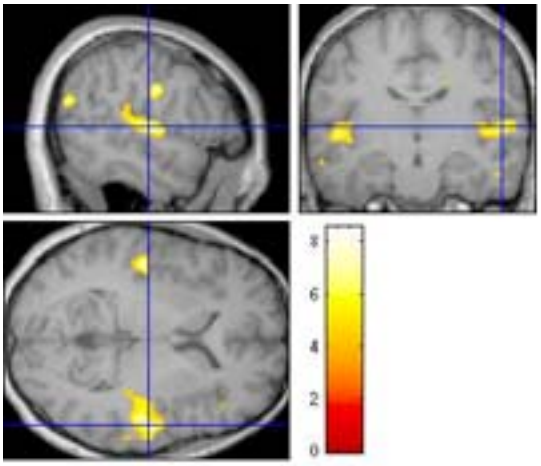


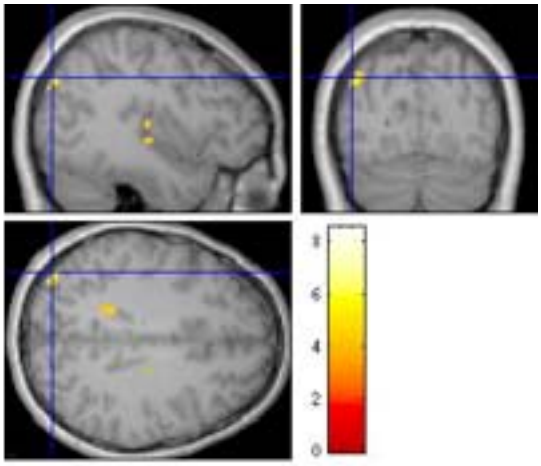
Figure 19. Comparison of TCST and WCST cortical activation. Cortical regions showing significantly increased blood oxygen level-dependent (BOLD) signal in healthy adults during the TCST compared to the WCST (FDR $q = 0.05$, no extent voxel threshold).

Figure 20. Significant activation peaks during TCST compared to WCST.

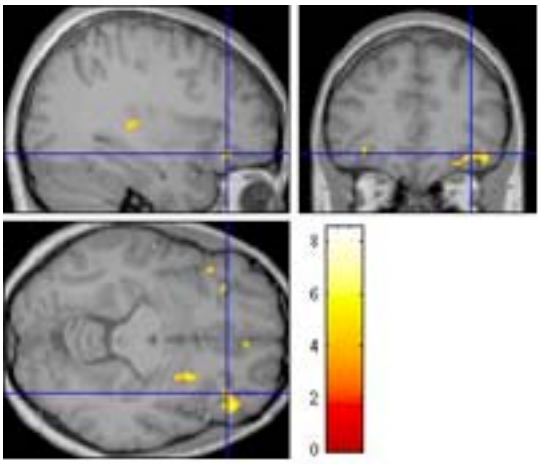
Superior Temporal (BA 22)



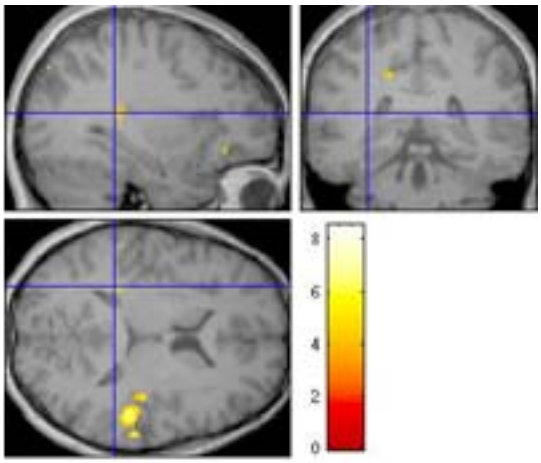
Left Superior Parietal (BA 18)



Orbitofrontal (BA 47)



Left Caudate



NOTE: *Left hemisphere is on the left in coronal images.*

Table 12

TCST Compared to WCST Activation

Location		BA	FDR (*q*)	Threshold (*t*)	Z Value	Cluster Level	MNI Coordinates *x*	*y*	*z*
Right Temporal Lobe	Superior Gyrus	22	.01	8.54	5.26	775	56	-26	6
		41	.01	7.34	4.86		50	-32	14
		42	.01	6.39	4.5		64	-28	12
	Middle Gyrus	34	.01	5.77	4.24	69	24	10	-12
		38	.04	4.32	3.50	3	42	10	-28
		37	.04	4.19	3.43	2	62	-60	12
	Fusiform	39	.01	7.22	4.82	55	56	-70	22
		20	.03	4.60	3.66	2	52	-16	-26
Left Temporal Lobe	Superior Gyrus	22	.01	7.81	5.02	221	-50	-26	6
Left Parietal Lobe	Postcentral Gyrus	21	.02	4.82	3.78		-64	-14	-16
	Precuneus	31	.03	4.61	3.66	18	-20	-40	38
		7	.03	4.55	3.63		-24	-46	62
Right Frontal Lobe	Precentral Gyrus	6	.01	7.68	4.98	56	56	-12	30
		8	.04	4.45	3.57	3	2	42	50
	Inferior Frontal Gyrus	47	.01	6.19	4.42	119	44	40	-12
		45	.04	4.32	3.50	3	42	10	-28
	Subcallosal Gyrus	47	.01	5.30	4.02		32	34	-16
	Medial	10	.03	4.53	3.62	14	4	58	-2
Left Frontal Lobe	Superior Gyrus	6	.02	4.80	3.76	7	-20	26	60
	Inferior Gyrus	47	.03	4.56	3.64	8	-46	26	-10
	Paracentral	5	.05	4.13	3.39	4	-22	-38	52

Table 12, Continued

Summary of TCST Compared to WCST Activation in Healthy Volunteers

Location		BA	FDR (*q*)	Threshold (*t*)	Z Value	Cluster Level	MNI Coordinates *x*	*y*	*z*
Left Occipital Lobe	Superior Gyrus	19	.01	6.27	4.45	53	-44	-80	36
	Precuneus	31	.04	4.27	3.47	2	-10	-62	24
Left Hippocampus			.05	4.07	3.35	1	-34	-40	8
Left Caudate			.03	4.55	3.63	27	-30	-36	18
			.05	4.08	3.36	1	-34	-36	8
Right Caudate Body			.05	4.16	3.41	4	20	-18	36

Note. Brodmann areas that were significantly activated during the TCST versus WCST paired *t*-test group analysis (FDR used for multiple comparisons correction, with $q = .05$). Cluster level refers to the number of contiguous voxels; hence, blanks in the table indicate significant individually activated voxels. Height threshold T = 4.07, Degrees of freedom = [1.0, 17.0]. Abbreviations found in the table include: BA = Brodmann's Area; FDR = False Discovery Rate; MNI = Montreal Neurological Institute.

Hypothesis Four

Hypothesis four stated that subjects would report more frustration during the WCST than the TCST. Overall, 8 subjects reported higher frustration levels during the TCST, 8 subjects reported higher frustration levels during the WCST, and 7 subjects reported equal levels of frustration on both tests. Thus, after a Wilcoxon Signed Ranks Test, no significant differences were found in reported frustration levels during the two tasks ($Z = -0.292$, $p = 0.77$). Subjects also reported when they felt most frustrated (never, beginning, middle, or end) during each task. During the WCST, 6 participants reported no frustration, 4 felt frustrated at the beginning, 10 felt frustrated during the middle, and 3 felt frustrated at the end. During the TCST, 8 participants reported no frustration, 3 felt frustrated at the beginning, and 12 felt frustrated at the end. Thus, during the WCST, more people reported feeling frustrated in the middle of the task, whereas during the TCST more people reported feeling frustrated towards the end. A chi-square analysis indicated that significant differences existed between task type (WCST and TCST) and when individuals reported feeling most frustrated (chi-square = 15.8296, $p < 0.01$, degrees of freedom = 3).

Subjects were also asked to rank their enjoyment levels. Ten subjects ranked the WCST higher than the TCST on enjoyment, 11 subjects rated them equally, and only 2 subjects ranked the TCST as more enjoyable than the WCST. The difference in enjoyment level was significant (Wilcoxon Signed Ranks Test, $Z = -2.496$, $p = .013$), suggesting subjects generally enjoyed the WCST more than the TCST.

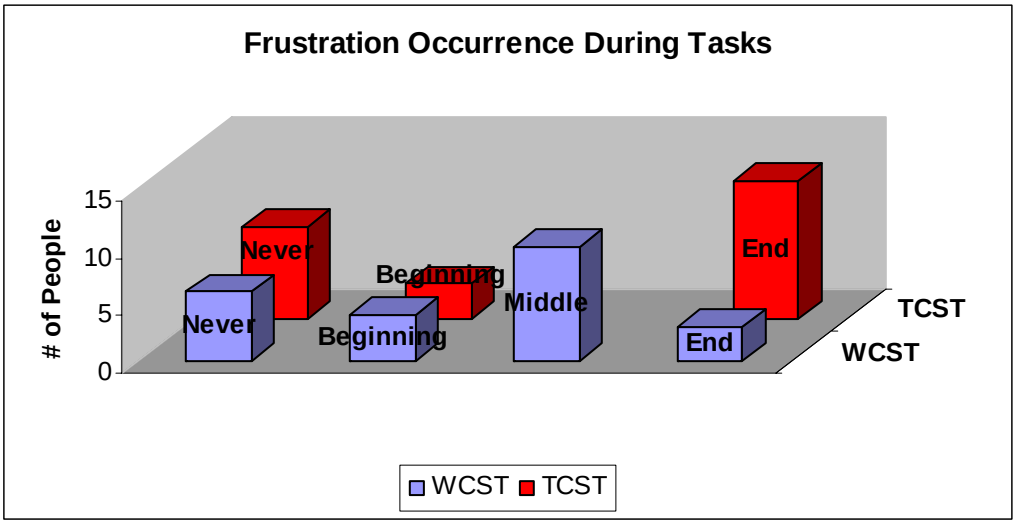
However, when asked which task was their favorite, 12 subjects preferred the TCST and 11 preferred the WCST. A chi-square analysis yielded no significant difference in task preference (p = 0.835). See Table 13 and Figure 21 for a summary of the survey results.

Table 13

Post-Scan Survey Summary

VARIABLE	**TCST > WCST**	**WCST > TCST**	**TIED**	**Z**	***p***
Enjoyment	2	10	11	-2.496	0.013
Frustration	8	8	7	-0.292	0.770
NOTE: Z = Wilcoxon Signed Ranks Test, p = 2-tailed significance.					
Favorite Task*	12	11			
* (chi-square p = .835)					

Figure 21. Frustration occurrence during WCST and TCST.



DISCUSSION

Although executive functioning is one of the most studied constructs in neuropsychology, this group of functions remains one of the most elusive and enigmatic skill sets to measure and understand. Consequently, available assessment instruments are challenged in their capacity to be sensitive and specific measures of executive functions. The WCST is one of the most widely used measures to assess executive functioning, particularly emphasizing mental flexibility, problem solving, and distractibility. The imaging literature has validated the WCST as a task that elicits frontal and subcortical activation, with significant activation peaks seen in the dorsolateral prefrontal cortex and subcortical circuitry (Berman et al., 1995; Monchi et al., 2001; Rezai et al., 1993; Volz et al., 1997). However, the WCST has been criticized for its lengthy administration time and negative feedback component. Other executive function measures overcome the weaknesses of the WCST and appear to activate similar brain pathways, but rely heavily on English verbal stimuli.

The TCST was developed as a potential alternative to the WCST, with the additional benefits of being a briefer measure without the negative feedback component. The overall purpose of the present study was to validate the TCST as a measure of frontal and subcortical function, and to determine if neuroimaging data and behavioral performance data suggested convergent validity between the TCST and the WCST. Thus, healthy volunteers underwent functional magnetic resonance imaging (fMRI) while performing computerized versions of the WCST and TCST to

determine if the TCST could be considered a viable tool for assessing frontal-subcortical functions.

Hypothesis One

The first aim of this study was to determine if the TCST is a measure of frontal, subcortical, and cerebellar functioning using fMRI. Hypothesis one, predicting significant activation in the prefrontal cortex, basal ganglia, thalamus, and cerebellum, was only partially supported. Consistent with literature on executive functioning, (Alexander et al., 1986; D'Esposito et al., 1998; Garavan et al., 2000), significant activation was observed in frontal-striatal areas. Activation was seen in the frontal cortex (BA 6, 9, 44-47) and components of the basal ganglia (left caudate, right putamen, right globus pallidus). However, unlike many of the reported neuroimaging studies on executive functioning, significant activation after the group second-tier group analysis was not observed in the thalamus or cerebellum (Collette et al., 2005; Radanovic, Azambuja, Mansur, Porto, & Scaff, 2003).

In addition to the areas mentioned above, activation was observed in the orbitofrontal cortex bilaterally, though greater activation was observed on the right (BA 47). Extensive neuroimaging research has linked OFC pathways with emotion and reward functions, as well as sensory integration, learning, predicting, and decision making (Kringelbach, 2005; Kringelbach & Rolls, 2004). OFC has also been shown to be involved in response inhibition (Horn, Dolan, Elliott, Deakin, & Woodruff, 2003). Altshuler et al.'s (2005) fMRI research of patients with mania and normal controls found that right lateral OFC was involved in response suppression,

and that patients with mania had less activation in these areas then controls. Thus, their research provides further support for the role of OFC circuitry in inhibition. One possible reason the TCST elicits OFC activation may be that examinees are actively inhibiting previous sorting strategies. Additionally, subjects are required to utilize decision making skills in determining how to sort the cards, and the literature suggests that OFC is crucial to decision making success (Frank & Claus, 2006; Krain, Wilson, Arbuckle, Castellanos, & Milham, 2006; Windmann et al., 2006) However, many fMRI studies specifically designed to study OFC function include feedback and/or rewards/punishments in their task design, so one interesting finding of the present study is that the TCST activates the OFC without utilizing any type of explicit reinforcer.

Basal ganglia activation was observed in the left caudate, right putamen, and right globus pallidus during the TCST. A recent event-related fMRI study by Monchi, Petrides, Strafella, Worsley, and Doyon (2006) indicated that the caudate nucleus and putamen were involved in the planning and execution of self-generated novel actions. The TCST essentially requires the examinee to plan and execute a self-generated novel sort; thus the caudate and putamen activation observed in the present study would be consistent with the basal ganglia findings reported by Monchi et al. (2006). The basal ganglia are also thought to play a role in response inhibition (Kelly et al., 2004). Another study by Manoach et al. provided evidence for frontostriatal neural circuitry participation in appropriate response selection (2003). Thus, basal ganglia activation observed during the TCST would be consistent with

related literature, and could possibly be attributed to the novel response selection requirement of the task as well as the task demands for continual inhibition of previously generated ideas. Middleton and Strick (2000a; 2000b) further postulate that the basal ganglia are involved in higher order aspects of visual processing, which could also be a plausible explanation for the significant basal ganglia activation observed during the TCST.

The orbitofrontal activation in conjunction with the basal ganglia activation is consistent with the lateral orbitofrontal circuit proposed by Alexander, DeLong, and Strick (1986). Lichter and Cummings (2001) reported that one of the major functions of the OF circuit is strategy determination, as well as determining appropriate sociobehavioral responses in the environment.

Unexpectedly, however, no significant group activation was observed in the thalamus during the TCST. This finding is surprising given the vast literature on the thalamus and its role in decision making circuitry and executive functions (Heyder, Suchan, & Daum, 2004; Radanovic et al., 2003). Thalamic activation is consistently reported in a broad spectrum of executive function neuroimaging tasks, and the TCST would definitely fit under the umbrella of the other EF tasks that have reported thalamic activation. It is possible that the TCST elicits thalamus activation, but that activation was undetected in this study due to insufficient power, the application of an overly stringent multiple comparison correction (FDR $q = 0.05$ is a conservative correction in the presence of a positive correlation), task design, or analysis methodology. The TCST imaging study is unusual in that there was only one block

of the TCST and one block of the control condition. Increasing the number of task and control blocks would boost the power of the imaging analyses, and especially aid in detection of activation in subcortical areas. Another possibility is that the thalamus was transiently activated during the generation of novel sorts during the TCST, and the transient activation was undetected due to the block analysis design.

Another surprise in the analysis of the TCST activation was the lack of significant cerebellar activation. This may be partially explained due to task design. As examinees made only 5-12 sorts during the 3 minute TCST block, and those sorts varied in time by individuals across the block, it is possible that there were not enough sorts occurring during the TCST block to demonstrate the cerebellum's role. An event-related analysis of the data, rather than a block analysis, may further illuminate whether the cerebellum has a significant role in TCST performance. In addition, analyzing the data looking at the TCST block versus fixation and the T-CTL block versus fixation may also provide insight to cerebellar functioning during the TCST. The cerebellum is thought to play a key role in predictive and preparatory functions (Courchesne and Allen, 1997), and another possibility for the lack of significant cerebellar activation is that it was too transient to be detected in a three minute task block with an average of 7 original sorts occurring during that block.

In summary, the TCST appears to activate frontal-subcortical circuits with significant peaks of activation occurring in the OFC (right > left) and basal ganglia, This particular circuitry may be selectively activated due to the decision making, response selection, and response inhibition aspects of the TCST. Contrary to

expectations, significant activation was not observed in the thalamus or the cerebellum, and further analyses of the TCST are necessary to clarify these findings.

Exploratory Analysis of TCST Activation

The whole-brain exploratory analysis revealed many other areas of activation in addition to the basal ganglia and the OFC. Parietal centers were bilaterally activated during the TCST (BA 7). A review of the neural substrates of executive functioning in neuroimaging by Collette et al. (2006) found that even among diverse EF tasks, parietal areas appear to be consistently recruited. Thus, the TCST parietal activation found in the present study is consistent with the reported literature of parietal network involvement during EF tasks.

The left cingulate gyrus was also significantly activated during the TCST. The review by Kringelbach et al. (2004) found that the cingulate gyrus and the orbitofrontal cortex are often co-activated in neuroimaging studies, and the results of the present investigation are consistent with Kringelbach's findings. The cingulate gyrus is also activated in tasks of selective attention and inhibition (such as the Stroop). The TCST requires selective visual attention to perceptual details and inhibitory functions; thus, the cingulate gyrus activation observed in the present study is consistent with reported literature and makes sense conceptually for the TCST.

Finally, significant activation was observed in the right superior temporal gyrus (BA 41). There are relatively few available studies on the role of this brain center in cognition. One recent lesion study (Ellison, Schindler, Pattison, & Milner,

2004) found that the superior temporal gyrus appeared to be critical for feature-based visual search tasks. Thus, one possible speculation for the significant cluster of right superior temporal gyral activation is that the generation of novel sorts on the TCST requires more detailed visuoperceptual processing than the T-CTL task. This preliminary conjecture is partially supported by this study's behavioral TCST data which revealed that nearly all of the sorts made by the examinees were perceptually based rather than conceptually based.

Hypothesis Two

The second major purpose of this study was to determine if positive correlations between behavioral performance and similarities in neural activation patterns during the TCST and WCST were present, which would provide evidence of convergent validity of the TCST. Overall, no relationship between the behavioral performance variables measured between the TCST and the WCST was demonstrated. There was no significant correlation between the number of categories achieved/perseverative responses on the WCST and the number of original sorts/perseverative errors on the TCST. An unpredicted trend towards a negative relationship was observed between TCST set loss errors and WCST failures to maintain set, though significant ceiling effects were apparent for both measures.

The limited previous research on the original behavioral version of the TCST did not specify whether correlations existed between categories achieved on the WCST and number of TCST original sorts in neurologically compromised samples.

Possibilities for the lack of correlation between these variables in the present study include a restricted range of WCST categories possible in 128 trials. Theoretically, the same type of ceiling effect does not apply to the TCST, as it has unlimited solutions and the WCST has only 3 viable solutions. In addition, the sample included in the present study was composed of high functioning individuals and may not be representative of the general population, as their mean IQ was in the high average range and they were highly educated. Thus, we may be observing a ceiling effect.

Speculatively, perhaps the lack of correlation between these two variables indicates that generating original sorts on the TCST requires a different type of mental flexibility than the categorical switching between three rules required by the WCST. Conceptually, the TCST appears to require a more creative approach to problem solving, an ability to "think outside the box." The fact that the TCST elicits greater right frontal activity may offer preliminary support for the idea that the number of TCST original sorts might be tapping creativity (Flaherty, 2005; Mendez, 2004; Weinstein & Graves, 2002), whereas WCST card sort generation may simply be measuring a more rote form of mental flexibility.

Perseverative errors on the two measures were not correlated, which was unexpected given that perseverative responses on both the WCST and the TCST appear to reflect mental inflexibility or an inability to generate novel effective problem-solving strategies. However, the task design of the TCST may have prompted artificial perseverative errors, as examinees were required to generate

sorts for the entire three minutes. In the original TCST, examinees have the option to terminate the free sort period at any time and are not required to sustain free sorting for the entire three minutes. Thus, the perseverations on this computerized version of the TCST may be somewhat forced and may not reflect true perseverative thinking. Rather, as subjects are not given feedback on the quality of their sorts during the task, they may have erroneously assumed that perceptual perseverations counted as original ideas if they were able to justify them with slightly different explanations. An example of this would be an examinee who sorted the cards with a wavy line background in group one, and sorted cards with a dotted background in group two. Later on during the test, the examinee may sort the cards with a dotted background in group one, and the wavy background cards into group two, believing that would reflect another viable sort. On the other hand, as direct feedback is given on each trial of the WCST, WCST perseverative trends may be more reflective of an actual inability to respond to feedback and/or generate or switch to an alternative strategy.

Another difference between the TCST and WCST that is relevant here is that the TCST allows subjects to simply cease responding once they've run out of ideas for how to sort the cards, thus avoiding perseverative errors by simply waiting for the time to run out. In contrast, this version of the WCST did not have a time discontinue rule; subjects generally had to keep sorting the cards until they achieved all 9 categories in the block. Thus, it is possible that someone who was very

perseverative on the WCST could choose to simply discontinue sorting the cards on the TCST.

Finally, a surprising trend discovered in the behavioral data analysis was that TCST set loss errors were negatively correlated with WCST failures to maintain set. One explanation is that WCST failures to maintain set appear to be a measure of distractibility/attention or potentially second guessing when changes may occur in the sorting principle. WCST set failures occur when the individual makes an error after five consecutive correct responses. The TCST set loss errors are qualitatively different, as TCST set loss errors occur when an illogical sort is generated. For instance, if an individual sorted the rooster, the dog, and the bike in one group and the elephant, the train, and the bus in another group, and then described the reason for the sort as being “things you can typically have in a house versus things you do not have in a house, this would be an example of a TCST set loss error, as roosters are not typically found in houses. The TCST set loss error may be more indicative of maladaptive perceptual or conceptual thinking than distractibility or second-guessing.

Another potential reason for the trend toward a negative relationship between the set loss errors on the two measures is that a ceiling effect on the WCST failures to maintain set was observed. The maximum number of WCST failures to maintain set was 2, whereas the maximum number of TCST set loss errors was 7. Thus, the restriction of range on the WCST set loss variable may be driving the trend towards

a negative correlation. Without that ceiling effect, the two variables may have appeared unrelated.

Another explanation for the lack of overall correlation between the two measures is that this sample was very high functioning. It is possible that in high functioning, neurologically healthy individuals, the TCST and WCST measures of performance would not be correlated, as frontal-subcortical circuits are most likely intact. However, neurologically impaired populations might show greater correlations in behavioral performance data. In contrast to this expectation, a study carried out by Stuss et al. (2000) of patients with frontal lesions indicated that the inferior medial lesion group was not similar to the dorsolateral lesion group on WCST variables; the inferior medial group's performance more closely approximated that of normal controls. As the TCST appears to activate inferior frontal regions and the WCST activates dorsolateral areas, it may be that the two tasks simply differ in underlying brain circuitry and thus behavioral data would not be expected to correlate.

The fact that hypothesis two was not supported in this study suggests that the cognitive operations underlying effective TCST performance differ from those required for success on the WCST. This further implies that the TCST, rather than being merely an alternative to the WCST, may actually measure unique aspects of executive functioning. The disparate behavioral data provides a preliminary basis for the idea that the neurocircuitry underlying the WCST and the TCST may also be distinct.

Hypothesis Three

It was hypothesized that that the fMRI frontal-subcortical activation patterns (specifically in the thalamus and prefrontal cortex) would be similar during the WCST and the TCST. Our neuroimaging data showed that the TCST activates selected frontal areas more strongly than the WCST, as greater bilateral activation in Brodmann areas 6 and 47 was observed. Right frontal activation in Brodmann areas 10 and 47 was also significantly higher. Additional areas of greater activation were observed in the caudate, right superior temporal lobe (BA 38, 41, 42), right medial temporal lobe (BA 34), bilateral temporal lobe (BA 22), and the left occipital lobe (BA 19 and 31). However, activation differences in the thalamus and cerebellum between the two tasks were not observed.

Brain activity in BA 6 is typically attributed to higher-level motor aspects of a task (Tanaka, Honda, & Sadato, 2005). The finding in this study that BA 6 was more active bilaterally during the TCST than the WCST is intriguing, as the total number of trials involving a motor response was greater during the WCST. Research published by Tanaka et al. (2005) provides preliminary support for BA 6 as an area of specialized cognitive function. They used fMRI and rTMS (virtual lesioning of different areas of BA6) to study the role of BA6 in visual and spatial tasks without a motor component. They reported that both fMRI and rTMS data suggested that medial BA 6 is involved in visual updating, whereas lateral BA 6 appeared to have a stronger role in spatial updating. Work by Picton et al. (2006) with patients with focal frontal lobe lesions compared to age-matched normal controls found that patients

with superior medial lesions, particularly involving BA 6, had an increased number of incorrect responses to a no-go stimulus. Thus, their results suggested that BA 6 plays a significant role in response inhibition. Perhaps the greater BA 6 activity observed when comparing the TCST to the WCST provides additional preliminary evidence of BA 6 involvement in cognitive task demands more salient to the TCST, such as response inhibition and perceptual/conceptual updating.

Activation of inferior frontal cortex was also greater during the TCST than the WCST. Although this area has been reported to be activated when perceiving negative emotional stimuli (i.e., representations of anger) and in reward pathways (generally found in studies using a version of the gambling task), it has also been implicated in fMRI investigations as playing a role in reasoning and problem solving (Goel, Gold, Kapur, & Houle, 1998). In a later work by Goel and Vartanian (2005), they found right inferior frontal activation in a visual-spatial problem solving task, which emphasized hypothesis generation and working memory. Thus, one speculation of why BA 47 activation is greater during the TCST may be that the TCST relies more heavily on perceptual/conceptual reasoning skills, novel card sort generation, and working memory maintenance of previously generated sorts.

Significantly stronger right frontotemporal activation (BA 10, 47, 22, 34, & 39) was also observed on the TCST relative to the WCST. As mentioned previously, these areas are involved in inhibition and decision making. Also, right frontotemporal pathways are more activated in creative processes (Flaherty, 2005; Mashal, Faust, Hendler, & Jung-Beeman, 2005). Flaherty (2005) proposed a

neuroanatomical model of creativity focusing on the interactions between the temporal lobes, frontal lobes, and the limbic system. She argued that right temporal lobe lesions are most likely to generate mania, which might be thought of as uninhibited creative drive. To further support her theory of temporal lobe involvement in creativity, she cited data from frontotemporal dementia patients indicating that a subset of these patients develop compulsive musical or artistic interests, even without a priori artistic interests. This study suggests the TCST may rely more heavily on right frontal circuitry than the WCST. Thus, the greater activation of right frontal areas during the TCST may be due to the increased utilization of inhibitory pathways to suppress previous responses, the increased demands for decision making skills, and the need for creativity to generate novel sorts.

It was also hypothesized that differences in BOLD activation would be observed in the cerebellum and basal ganglia when comparing the WCST and TCST activation. This hypothesis was not fully supported, as significant group differences were not observed in the cerebellum. This finding was unanticipated, as the WCST/W-CTL group analysis revealed the greatest significant peak of activation in the cerebellum, and the TCST/T-CTL group analysis did not have significant cerebellar activation. Exploratory analysis using a more liberal activation threshold (i.e., $p < .001$ with no correction for multiple comparisons) showed greater activation in the cerebellum during the WCST. This suggests that the cerebellar activation differences may have been apparent with greater statistical power (increased

sample size) or when utilizing a less stringent correction for multiple comparisons. Additionally, the lack of significant cerebellar activation when comparing the two tasks may suggest subthreshold cerebellar activation during the TCST.

In terms of the basal ganglia, the caudate showed significantly more activation during the TCST. As mentioned previously, the caudate appears to be involved in novel response selection and response inhibition (Kelly et al., 2004; Monchi, Petrides, Strafella, Worsley, & Doyon, 2006), and these may be more prominent features of the TCST than the WCST (i.e., TCST requires more intense strategy generation and sustained inhibition of previously used card sorting ideas). This is consistent with Monchi et al.'s (2001) conclusion that the caudate nucleus signifies the need for a mental shift, as each original sort on the TCST would signify a need for a mental shift.

In addition, the TCST activated right superior temporal centers (BA 38, 41, and 42) more than the WCST, which, consistent with the TCST > T-CTL contrast, can most likely be attributed to the intense perceptual processing of detailed features of the TCST.

Hypothesis Four

The last aim of this study was to assess whether participants subjectively found the WCST to be a more frustrating task than the TCST. It was predicted that more subjects would report greater levels of frustration during the WCST than during the TCST. This hypothesis was not supported. In fact, the majority of participants reported significantly greater enjoyment levels during the WCST, but no significant

differences in frustration levels or in overall task preference. Interestingly, time of frustration occurrence did vary significantly by task type; during the WCST, more people were frustrated in the middle whereas during the TCST more people were frustrated at the end of the task. Increased frustration at the end of the TCST should be explored, given that subjects tend to generate the most obvious sorts first, so the test becomes progressively more difficult, unlike the WCST.

The difference in time of frustration occurrence may partially explain why no significant difference in frustration levels between tasks were found; perhaps most subjects found the tasks equally frustrating, just at different time points. Interestingly, enjoyment levels were ranked significantly higher during the WCST, perhaps due to the positive feedback component. Given that subjects generally ranked the WCST as more enjoyable, it was surprising that there was no significant difference in overall task preference. However, these were neurologically intact volunteers, and negative feedback may not be experienced as distressing or as frustrating in a high-functioning healthy sample as it would be in cognitively challenged or neurologically impaired populations. Thus, in healthy individuals, the negative feedback component does not seem to increase frustration levels, but future research could measure task enjoyment and frustration in neurologically compromised individuals to determine if the removal of negative feedback is an important consideration for clinical patients.

Limitations

A major weakness of the present study is that the TCST was only presented in one block (again to approximate how the test is administered in a clinical setting), and therefore had less statistical power than the WCST. In contrast, he WCST had up to 18 WCST blocks and 6 control blocks included in the analysis. Thus, it is possible that additional areas involved in the execution of the TCST might have been detected with greater statistical power. However, the significant activation observed when analyzing the TCST > WCST may be even more striking, given that the TCST contrast presumably has much less power that the WCST contrast.

Another significant potential weakness of the present study is the order of task administration. To facilitate recall of TCST sorting strategies, the TCST and T-CTL blocks were always performed last. Thus, the TCST may have been impacted by fatigue or prior exposure to the WCST. One resolution to the order effects problem could be to set up the TCST as an event-related design, with each novel card sort considered a separate event. Then subjects could verbalize their task sorting strategy immediately following each sort, and a random presentation of task order could be implemented.

Another limitation of brain imaging analyses is that each individual brain is unique, and generalizing/warping individual functional activation maps to the anatomical MNI brain template is thus problematic. Specifically, neuroanatomical reviews of the OFC (Kringelbach et al., 2004) indicate that humans have three main sulci types, and this significant variability and individual differences are a

methodological challenge for normalizing individual brains to a template brain. Thus, representations of activation on a brain template may not be representative of the population. Also, as reported in the literature, it is very difficult to image the basal ganglia due to their small size and deep brain location (Middleton et al., 2000a; Middleton et al., 2000b). Although ROI analyses were beyond the scope of this dissertation, further analyses of the data utilizing ROI should be pursued. This would significantly strengthen the interpretation of the results of the group data, and especially facilitate understanding of activation patterns in the cerebellum and smaller subcortical structures like the basal ganglia and thalamus.

Another limitation of this study was that participants were not randomly selected from the population. As the subjects were not compensated, many friends and associates were asked to donate their time for this study. Thus, this sample is not representative of the overall population, and data derived from this study may not apply to neurologically compromised samples. Also, the final sample sizes were somewhat small, and this may have especially impacted the TCST versus WCST analysis, as it only included 18 individuals. The majority of the final participants in this study were Caucasian, and there were more men than women. In addition, the estimated IQ and education levels of this sample were above average for the population. Future studies with larger sample sizes are needed to determine if age, education, gender, IQ, race, and/or other sociodemographic variables introduce confounds or variations on the neural activation patterns or behavioral responses during the TCST and WCST.

In addition, many of the participants were medical students or neuroscience graduate students who had some awareness of the WCST, as it was mentioned during some neuroscience, psychiatry, and/or neurology lectures. Thus, WCST exposure was not completely controlled in the study; however, the literature indicates that exposure to the WCST, pre-training to criterion levels, and/or even learning the exact nature of the task does not significantly change cortical activation patterns, as experts' functional brain activation is not statistically different from that of novices (Berman et al., 1995; Konishi et al., 1999).

Implications/Conclusions

One major implication of this study is that the TCST appears to measure prefrontal and subcortical functioning, and may be a unique measure of EF and problem solving, as it differed in some ways from the WCST. Strengths of the TCST include its brevity, utility with linguistically diverse populations, and the absence of negative feedback. In addition, data from this study suggest that the TCST may be especially sensitive to right frontal lobe functioning, and could thus be particularly valuable in the neuropsychological assessment arena, as there are currently few measures which tap right frontal dysfunction.

The data collected in this study could pave the way for understanding populations with known deficiencies on these tasks. Future research could compare activation patterns of neurologically compromised samples with the normative data collected in this study to further understand brain impairment and dysfunction. The TCST may be a useful measure to explore in right frontal or temporal lobe epilepsy

patients, individuals with frontotemporal dementia, basal ganglia disorders, and/or affective disorders to further establish its sensitivity and specificity as a right frontal-subcortical measure. Further research with the TCST utilizing an extended normal sample more representative of the population could also be illustrative, particularly as the high-functioning sample used in this study may have been vulnerable to ceiling effects. The TCST also has the capability of providing rich amounts of information on conceptual and perceptual types of perseverative errors, which are other areas to explore in future research.

Subsequent analyses of these data might explore functional connectivity to provide further evidence that the TCST and WCST utilize different frontal-subcortical circuitry. Event-related analyses could also be performed to understand the neural correlates underlying the generation of novel sorts on the TCST and performance variables (such as perseverations and set loss errors). Event related analyses of the WCST data could elucidate a more specific understanding of the differences between positive and negative feedback trials and errors (e.g., perseverations, jumping off track, inefficient hypothesis testing). Region of interest analyses could also be explored.

In conclusion, this research supports the TCST as a measure of frontal-subcortical function. The TCST appears particularly sensitive to orbitofrontal/caudate circuitry as well as superior temporal areas, with greater activation overall observed in right hemisphere areas. The TCST may assess cognitive processes that are unique and distinct from the task demands of the

WCST. As some researchers have suggested, utilizing fMRI when evaluating a potential clinical measure may be a way to successfully integrate cognitive neuroscience with assessment to effectively design and develop more sensitive tools for neuropsychologists. This research may serve as an example of the utilization of functional neuroimaging in validating a new clinical cognitive measure. Future research is needed to expand the validity and reliability studies of the TCST. This preliminary study suggests it has promising potential as a clinical neuropsychological instrument.

APPENDIX A

NEUROMEDICAL SCREENING INTERVIEW

Subject # _____ Date: _____

QUESTION	ANSWER	EXCLUSION CRITERIA
1. Age		If not between the ages of 21-40, exclude.
2. If female, are you pregnant?		If pregnant, exclude.
3. Education Level (number of years completed) In what country? In what state?		
4. Where were you born? If not in the U.S., from what country does your family originate?		
5. How long have you lived in the United States?		
6. Do you have vision or hearing problems?		If yes, subject must be able to wear contact lenses in the scanner and/or see/hear adequately to complete task. Also, if color-blind, exclude.
7. Do you have metal implants, like a neurostimulator, pacemaker, or permanent metal retainer?		If yes, exclude.
8. Have you ever fainted, passed out, lost consciousness, or been hospitalized after getting hit in the head in a fight, fall, or car accident?		
9. If you were unconscious, for how long?		If unconscious for > 15 minutes, exclude.
10. Do you currently drink alcohol?		
11. How often do you drink?	_____ 1X/day _____ 1X/week _____ 2X/week _____ More than 2X/week _____ 1X/month _____ 3-4X/year	
12. How much do you usually drink when you drink?	_____ 1-2 drinks _____ 3-4 drinks _____ 5 drinks or more	

Subject # _____ **Date:** _____ **Page 2 of 3**

QUESTION	ANSWER	EXCLUSION CRITERIA
13. How long have you been drinking this amount?	_____ Less than 3 months _____ 3-6 months _____ 7-12 months _____ More than 12 months	Exclude anyone who has been drinking ≥ 5 drinks more than 2X/week for 6 months or longer.
14. Have you used alcohol in the past but are no longer drinking?		
15. If yes, how often did you drink?	_____ 1X/day _____ 1X/week _____ 2X/week _____ More than 2X/week _____ 1X/month _____ 3-4X/year	
16. How much did you usually drink when you used to drink?	_____ 1-2 drinks _____ 3-4 drinks _____ 5 drinks or more	
17. How long did you drink this amount?	_____ Less than 3 months _____ 3-6 months _____ 7-12 months _____ More than 12 months	Exclude anyone who drank ≥5 drinks more than 2X/week for 6 months or longer.
18. Do you currently use any of these drugs?	Cocaine/Crack Marijuana Amphetamines/Meth LSD/PCP Heroin Ecstasy GHB Inhalants (paint, glue, gas) Overuse Prescription Medication	If using any of these drugs, exclude.
19. Have you used any of these drugs in the past but are no longer using them?		
20. Have you ever gotten into fights while drinking or using drugs, or had medical problems because of drinking or drugs?		If yes, exclude.
21. Have you ever been treated for problems with alcohol or drugs?		If yes, exclude.
22. Do you smoke? How much?		
23. Have you ever had a seizure or a convulsion?		If yes, exclude.
24. Do you have or have you ever had any of the following?	Brain surgery Brain tumor Encephalitis Meningitis Multiple Sclerosis PD Syphilis Stroke HD AD Systemic Lupus Erythematosus AIDS/HIV Cancer Aneurysm TIA Epilepsy	If yes to any of these listed conditions, exclude.

Subject # _____ Date: _____ **Page 3 of 3**

QUESTION	ANSWER	EXCLUSION CRITERIA
25. Do you have or have you ever had any of the following?	HTN Diabetes Arteriosclerosis Coronary Heart Attack Pulmonary disease Emphysema Hypoglycemia Thyroid Problems High Cholesterol Chronic Pain/Fatigue Learning Disability	
26. Have you seen visions or other things that other people don't see? Have you heard noises, sounds, or voices that other people don't hear?		If yes, exclude.
27. Have there been times lasting a least a few days when you felt the opposite of depressed, that is when you were very cheerful or high and this felt different than your normal self?		If yes, rule out a manic episode. If prior /current manic episode, exclude.
28. How is your mood? Have you been feeling sad, blue, down, or depressed? For how long have you been feeling this way?		If felt sad, blue, down, or depressed for more than one week, rule out a depressive episode. If experiencing a depressive episode, exclude.
29. Have you ever been exposed to a traumatic event which involved actual/threatened death or serious injury to you or another person?		If yes, rule out PTSD or Acute Stress disorder. If experiencing PTSD or Acute Stress Disorder, exclude.
30. Are you bothered by thoughts that you cannot get out of your mind, such as you might hurt or kill someone you love, contamination by germs or dirt, or that someone you love is hurt? Are you bothered by doing things over and over that you can't resist, such as washing, checking whether the door is locked, the stove is off, or counting excessively?		If yes, rule out OCD. If experiencing OCD, exclude.
31. Have you been worried or anxious about something for longer than 6 months?		
32. Some people have very strong fears of being in certain places or in certain situations. Does being in a closed space make you feel very fearful, anxious, or nervous?		If yes, exclude.
33. Are you/have you been treated for a psychological disorder? If so, what? Are you still experiencing symptoms?		Exclude if the person is currently being treated for Axis I pathology, or if the person was treated in the past for anything other than depression/anxiety.

APPENDIX B

TASK INSTRUCTIONS

Task	Instructions
WCST & W-CTL	This test is a little unusual because I am not allowed to tell you very much about how to do it. You will be asked to match a target card in the middle of the screen to 1 of the 4 key cards at the top of the screen. I cannot tell you how to match the cards, but I will tell you each time whether you are right or wrong. If you are right, you will hear a 'tada' sound and see a smiley face. If you are wrong, you will hear a 'buzz' sound and see a frowney face. If you are wrong, try to get the next card correct. Sometimes, you will see a white cross in the middle of your screen. When you see the cross, please stare at its center until it disappears. There is no time limit on this test.
TCST & T-CTL	For this test, you will see six pictures. I want you to look at them carefully, and sort them into two groups of three cards each. The picture you are sorting will be outlined in white, like the dog in the following example. Press Button 1 to sort the card into Group 1. Press Button 2 to sort the card into Group 2. The three cards should have something in common. There are lots of ways to sort the cards. I want you to find as many different ways as you can. Once you sort the cards one way, DO NOT use the same idea again. Each sort should be ORIGINAL. Work as fast as you can. Like before, sometimes you will see a white cross in the middle of your screen. When you see the cross, please stare at its center until it disappears. Sometimes, you will see 3 copies of 2 different cards. When this happens, put all of the cards that are exactly alike into the same group.

APPENDIX C

TCST SCORING SHEET

Participant #:_____ Age:_____ Ed:_____ RH/LH M/F Race:_____ Date:_____ Page 1/1

Free Sort	Time	Response	Score	Psv Error & Type
Elephant Dog Bus Rooster Train Bike				
Elephant Dog Bus Rooster Train Bike				
Elephant Dog Bus Rooster Train Bike				
Elephant Dog Bus Rooster Train Bike				
Elephant Dog Bus Rooster Train Bike				
Elephant Dog Bus Rooster Train Bike				
Elephant Dog Bus Rooster Train Bike				
Elephant Dog Bus Rooster Train Bike				
Elephant Dog Bus Rooster Train Bike				
Elephant Dog Bus Rooster Train Bike				
Elephant Dog Bus Rooster Train Bike				
Elephant Dog Bus Rooster Train Bike				

KEY:

1 = Square/round card	2 = Yellow/blue card	3 = Animals/transportation	4 = Big/Small object
5 = dot/line background	6 = 10 pt/5 pt star	7 = black/white star	8 = star above/below
Types of Psv Errors:	1 = True Psv	2 = Varied Psv	3 = Concept Psv

APPENDIX D

IRB APPROVAL LETTER

UT SOUTHWESTERN
MEDICAL CENTER

Institutional Review Board

TO: Dixie Woolston
Psychiatry - 9044

FROM: Robert Bash, MD
Institutional Review Board 2 Chairperson
IRB - 8843

DATE: November 3, 2005

RE: **Expedited Approval of Protocol, Consent Form, Participant Surveys, and Recruitment Advertisement**
Acknowledgment of HIPAA Authorization
IRB Number: 092005-067
Title: FMRI Investigation of an Experimental Executive Function Measure: Comparison of the Texas Card Sorting Test to the Wisconsin Card Sorting Test in Healthy Individuals

The Institutional Review Board (IRB) at the University of Texas Southwestern Medical Center has determined that this research is eligible for expedited review in accordance with 45 CFR 46.110(a)-(b)(1), 63 FR 60364, and 63 FR 60353. The IRB Chairman approved the protocol, informed consent document(s), participant surveys, and recruitment advertisement on November 1, 2005. IRB approval of this research lasts until October 5, 2006. If the research continues beyond twelve months, you must apply for updated approval of the protocol one month before the date of expiration noted above. DHHS regulations permit oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. A witness to the oral presentation is required, and the subject must be given copies of the short form document and the summary. **Your approved subject sample size is 25 subjects.**

Important Note: You must use a photocopy of the attached IRB-approved and stamped consent form(s). Use of a copy of any consent form on which the IRB-stamped approval and expiration dates are replaced by typescript or handwriting is prohibited.

When this procedure is used with subjects who do not speak or read English, (1) the oral presentation and the short form written document should be in a language understandable to the subject; (2) the IRB-approved English language informed consent document may serve as the summary; and (3) the witness should be fluent in both English and the language of the subject.

At the time of consent, (1) the short form document should be signed by the subject (or the subject's legally authorized representative); (2) the summary (i.e., the English language informed consent document) should be signed by the person obtaining consent as authorized under the protocol; and (3) the short form document and the summary should be signed by the witness. When the person obtaining consent is assisted by a translator, the translator may serve as the witness.

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www.utsouthwestern.edu

The IRB requires that you report to the Board any unexpected adverse events that occur during the study. In the future, if you require a modification to the protocol, obtain review and approval by the Board prior to implementing any changes except when prompt changes are necessary to eliminate apparent immediate hazards to a subject.

The IRB requires that all personnel who interact with research subjects or who have access to research data identified with the names of subjects receive a copy of the Federal Wide Assurance on file with the Department of Health and Human Services. Document their agreement to comply with the statements therein. Such documentation should be kept with other records of the research, which are subject to review by the IRB. Copies of the Federal Wide Assurance and the Federal regulations governing the participation of human subjects in research (45 CFR 46) are available on the IRB website:
(http://www8.utsouthwestern.edu/utsw/cda/dept31018/files/41623.html)
or from Jan Harrell at irb@utsouthwestern.edu.

If applicable, approval by the appropriate authority at a collaborating facility is required before subjects may be enrolled on this study.

If you have any questions related to this approval or the IRB, you may telephone Jan Harrell at 214.648.9453.

Enc: Consent Form(s)
HIPAA Authorization
Participant Surveys
Recruitment Advertisement
Project Summary
NR1-Exp copy

RB/iw

APPENDIX E

IRB CONSENT FORM

The University of Texas Southwestern Medical Center at Dallas

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research: fMRI Investigation of an Experimental Executive Function Measure: Comparison of the Texas Card Sorting Test to the Wisconsin Card Sorting Test in Healthy Individuals

Sponsor: N/A

Investigators:	Telephone No. (regular office hours)	Telephone No. (other times)
Dixie Woolston, Ph.D. Candidate	214.648.4642	214.686.8467
Greg Allen, Ph.D.	214.648.4641	972.601.9030
Richard Briggs, Ph.D.	214.648.0436	N/A
Patrick Carmack, Ph.D.	214.648.5094	N/A
Kathleen Saine, Ph.D.	214.648.7669	N/A
C. Munro Cullum, PH.D.	214.648.4646	972.317.1680

INVITATION: You are invited to participate in this research because you are a normal volunteer.

Medical research involves offering a plan of care to a group of patients, collecting and studying information about each patient's experience, and using that information to develop the best possible care for future patients.

NUMBER OF PARTICIPANTS: The sponsor plans to include 25 participants in this project.

PURPOSE: The purpose of this research is to study what areas of your brain are involved in problem solving. This research is being done because there are problems with the existing tests used to measure problem solving abilities. We hope to validate a new test of problem solving skills. We still do not clearly understand what parts of your brain are involved during problem solving, and hope to further understand the brain mechanisms involved by utilizing neuroimaging techniques.

PROCEDURES

Screening: The study doctor will ask you questions about your health, medications you take for any health problems, and any surgical procedures you have had.

IRB File Number: 092005-067
Consent Approved: NOV - 1 2005
Consent Expires: OCT - 5 2006

You will undergo tests of intellectual functioning (IQ) and complete problem solving measures. You will also undergo magnetic resonance imaging (MRI) to look at brain activation patterns. These procedures are being done because you are in this research.

Magnetic Resonance Imaging: You will have magnetic resonance imaging (MRI) of your head. For this procedure, you will lie quietly inside a large, doughnut-shaped magnet for about 45 minutes.

Your head will rest in a special helmet-like holder to help you keep your head still.

As the scanning proceeds, we will ask you to pay attention and respond to simple visual stimuli (e.g., colors or shapes). In the final part of the procedure, the MR images will be used to make a picture of your whole brain to act as a map that will show, in accurate detail, where blood flow changes have occurred. This will indicate what parts of your brain were active during problem solving tasks.

POSSIBLE RISKS

The imager makes a loud, banging noise while it is taking pictures. You will be given a set of earplugs to help reduce the noise.

You may experience nervousness from confinement in a tight space (claustrophobia). If you become anxious, you can stop the procedure at any time.

You may experience some discomfort and fatigue from lying still during imaging.

There are no known effects from exposure to magnetic fields.

If you have any metal clips or plates in your body, you should tell the investigator.

MRI may not be appropriate if you are pregnant or are trying to become pregnant.

MRI may not be appropriate if you have permanent eyeliner or eyebrows or any pieces of metal in your body, such as the following:

- heart pacemaker, heart valve replacement, or aortic clips
- metal fragments in your eyes, skin, or elsewhere in your body
- brain clips or pieces of metal used in aneurysm surgery or intercranial bypass
- venous umbrella
- pieces of metal in the body resulting from work as a sheet-metal worker or welder
- clips placed in an internal organ
- prosthetic devices, such as middle ear, eye, joint, or penile implants
- joint replacement.

- hearing aid that cannot be removed
- neurostimulator
- insulin pump
- intrauterine device (IUD)
- shunts or stints
- metal mesh or coil implants
- metal plate, pin, screws, or wires, or any other metal implants

Additional minor risks include psychological discomfort or temporary frustration during the cognitive tasks. This will be monitored and every effort will be made to ensure psychological comfort. In the unlikely event that the tasks become even moderately frustrating, you will be offered the opportunity to discontinue the study. If while doing the MRI we discover a tumor or other health risk, you will be informed and asked to notify your primary care physician.

POSSIBLE BENEFITS

You will not benefit directly from participating in this study, but the results will contribute to our understanding of the neural basis of problem-solving skills in normal individuals. Thus, this data set of problem solving in normal individuals can then be used to compare groups with known problem-solving dysfunction (autism, ADHD, dementia, traumatic brain injuries, etc.) In addition, this study may provide validation for the use of an alternative problem-solving measure in clinical settings.

ALTERNATIVES TO PARTICIPATION IN THIS RESEARCH: You do not have to participate in this research.

Please ask your study doctor as many questions as you wish. The doctor's answers to your questions could help you decide whether to participate in this research or receive the standard care that is currently available for your medical problem.

If you decide to participate in research now, and later change your mind, you may stop your participation in the research then and receive the alternative care.

THE STUDY DOCTOR'S DECISION TO STOP YOUR PARTICIPATION: Your study doctor or the sponsor may stop your participation in this research without your permission under any one of the following conditions:

- Your study doctor believes that participation in the research is no longer safe for you.
- You are unable to keep appointments or to follow your study doctor's instructions.

PROCEDURES AFTER STOPPING PARTICIPATION IN THIS RESEARCH: If you, the study doctor, or the sponsor stops your participation in the research, it is your responsibility to do the following:

- Let your study doctor know immediately that you wish to withdraw from the research.

PAYMENT TO TAKE PART IN THIS RESEARCH: This investigation will not pay subjects for their participation.

COSTS TO YOU: There are no funds available to pay for parking expenses, transportation to and from the research center, lost time away from work and other activities, lost wages, or child care expenses.

COMPENSATION FOR INJURY: Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas. You retain your legal rights during your participation in this research.

VOLUNTARY PARTICIPATION IN RESEARCH: You have the right to agree or refuse to participate in this research. If you decide to participate and later change your mind, you are free to discontinue participation in the research at any time.

Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. Refusal to participate will not affect your legal rights or the quality of health care that you receive at this center. Your status as a medical student, fellow, faculty, or staff in the medical center will not be affected in any way.

NEW INFORMATION: Any new information which becomes available during your participation in the research and may affect your health, safety, or willingness to continue in the research will be given to you.

RECORDS OF YOUR PARTICIPATION IN THIS RESEARCH: You have the right to privacy. Any information about you that is collected for this research will remain confidential as required by law. In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information for Research Purposes," which will contain more specific information about who is authorized to review, use, and/or receive your protected health information for the purposes of this study.

YOUR QUESTIONS: Dixie Woolston is available to answer your questions about this research at 214-648-4646. The Chairman of the IRB is available to answer questions about your rights as a participant in research or to answer your questions about an injury or other complication resulting from your participation in this research. You may telephone the Chairman of the IRB during regular office hours at 214-648-3060.

IRB File Number: 092005-067
Consent Approved: NOV - 1 2005
Consent Expires: OCT - 5 2006

YOU WILL HAVE A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.

Participant's Name (printed)	
Participant's Signature	Date
Legally authorized representative's name (printed)	
Legally authorized representative's Signature	Date
Name (printed) of person obtaining Consent	
Signature of person obtaining consent	Date

IRB File Number: 092005-067
Consent Approved: NOV - 1 2005
Consent Expires: OCT - 6 2006

The University of Texas Southwestern Medical Center at Dallas
Children's Medical Center, Parkland Health & Hospital System
Retina Foundation of the Southwest, Texas Scottish Rite Hospital for Children
The University of Texas Southwestern Moncrief Cancer Center

Authorization for Use and Disclosure of Health Information for Research Purposes

NAME OF RESEARCH PARTICIPANT: _____

1. You agree to let **UT Southwestern Medical Center** share your health information with Dixie Woolston and her staff/dissertation committee at the University of Texas Southwestern Medical Center at Dallas ("Researchers") for the purpose of the following research study: *fMRI investigation of an experimental executive function measure. We will compare brain activation patterns between two executive function tasks: the Wisconsin Card Sorting Test and the Texas Card Sorting Test.*
092005-067
2. You agree to let the Researchers use your health information for this Research Project. You also agree to let the Researchers share your health information with others who may be working with the Researchers on the Research Project ("Recipients") as follows.

- The UT Southwestern Institutional Review Board (IRB). This is a group of people who are responsible for assuring that the rights of participants in research are respected. Members and staff of the IRB at UT Southwestern may review the records of your participation in this research. A representative of the IRB may contact you for information about your experience with this research. If you do not want to answer their questions, you may refuse to do so.

- Representatives of the Office of Human Research Protections (OHRP). The OHRP may oversee the Research Project to confirm compliance with laws, regulations and ethical standards.

3. Whenever possible your health information will be kept confidential. Federal privacy laws may not apply to some institutions outside of UT Southwestern. There is a risk that the Recipients could share your information with others without your permission. UT Southwestern cannot guarantee the confidentiality of your health information after it has been shared with the Recipients.

4. You agree to permit the Researchers to use and share your health information as listed below:

- Physical and mental health history
- MRI of your brain
- Cognitive testing results

5. The Researchers may use your health information to create research data that does not identify you. Research data that does not identify you may be used and shared by the Researchers (for example, in a publication about the results of the Research Project); it may also be used and shared by the Researchers and Recipients for other research purposes not related to the Research Project.

6. This authorization is voluntary. Your health care providers must continue to provide you with health care services even if you choose not to sign this authorization. However, if you choose not to sign this authorization, you cannot take part in this Research Project.

7. This Authorization has no expiration date.

8. If you change your mind and do not want us to collect or share your health information, you may cancel this authorization at any time. If you decide to cancel this authorization, you will no longer be able to take part in the Research Project. The Researchers may still use and share the health information that they have already collected before you canceled the authorization. To cancel this authorization, you must make this request in writing to:

Dixie J. Woolston
5323 Harry Hines Blvd.
Dallas, TX 75390-8846
Phone number: 214.648.4642

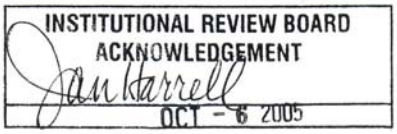
9. A copy of this authorization form will be provided to you.

_____ _____
Signature of Research Participant Date

For Legal Representatives of Research Participants (if applicable):

Printed Name of Legal Representative: _____
Relationship to Research Participant: _____
I certify that I have the legal authority under applicable law to make this Authorization on behalf of the Research Participant identified above. The basis for this legal authority is: _____.
(e.g. parent, legal guardian, person with legal power of attorney, etc.)

_____ _____
Signature of Legal Representative Date

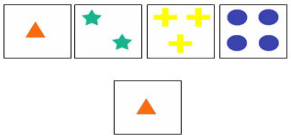


APPENDIX F

POST-SCAN SURVEY

Participant #:_____ Date: _____

You participated in two different types of tasks today. Please fill out this brief survey of your experience of the tasks pictured below.

	None	Little	Somewhat	Much	A Great Deal
Please rate your **enjoyment** level during the task.					
What did you enjoy about the task?					
	Never	Little	Somewhat	Much	A Great Deal
Were you **frustrated** during the task?					
What was frustrating about it? Where your frustration levels worse at the _____ beginning _____ middle _____ end?					
Other Comments:					
EXAMINER USE ONLY *QUALITATIVE REPORT OF PROBLEM SOLVING STYLE DURING WCST* **How did you feel during this task?** **Which task did you like best?**					

Participant #:_____ Date: _____ Page 2/2

	None	Little	Somewhat	Much	A Great Deal
Please rate your **enjoyment** level during the task.					
What did you enjoy about the task?					

	Never	Little	Somewhat	Much	A Great Deal
Were you **frustrated** during the task?					
What was frustrating about it? Where your frustration levels worse at the _____ beginning _____ middle _____ end?					
Other Comments:					

EXAMINER USE ONLY

QUALITATIVE REPORT OF PROBLEM SOLVING STYLE DURING TCST

How did you feel during this task?

Which task did you like best?

THANK YOU VERY MUCH FOR YOUR TIME, COOPERATION, AND EFFORT TODAY.

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Ref Type: Abstract

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VITAE

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