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Gray matter correlates of set-shifting among neurodegenerative disease, mild cognitive impairment, and healthy older adults

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Abstract

There is increasing recognition that set-shifting, a form of cognitive control, is mediated by different neural structures. However, these regions have not yet been carefully identified as many studies do not account for the influence of component processes (e.g., motor speed). We investigated gray matter correlates of set-shifting while controlling for component processes. Using the Design Fluency (DF), Trail Making Test (TMT), and Color Word Interference (CWI) subtests from the Delis-Kaplan Executive Function System (D-KEFS), we investigated the correlation between set-shifting performance and gray matter volume in 160 subjects with neurodegenerative disease, mild cognitive impairment, and healthy older adults using voxel-based morphometry. All three set-shifting tasks correlated with multiple, widespread gray matter regions. After controlling for the component processes, set-shifting performance correlated with focal regions in prefrontal and posterior parietal cortices. We also identified bilateral prefrontal cortex and the right posterior parietal lobe as common sites for set-shifting across the three tasks. There was a high degree of multicollinearity between the set-shifting conditions and the component processes of TMT and CWI, suggesting DF may better isolate set-shifting regions. Overall, these findings highlight the neuroanatomical correlates of set-shifting and the importance of controlling for component processes when investigating complex cognitive tasks. (*JINS*, 2010, *16,* 640–650.)

Keywords: D-KEFS, Design fluency, Trail making test, Color word interference, Executive function, Voxel-based morphometry

INTRODUCTION

Set-shifting is a higher-level cognitive ability that requires individuals to shift attention or response patterns based on different rules. Several neuropsychological tests are used to evaluate set-shifting, including tasks that require individuals to alternate between types of stimuli based on explicit rules on a trial-by-trial basis (e.g., Trail Making Test; Reitan & Wolfson, 1985) and tasks that require individuals to switch between response patterns based on changing schedules of reinforcement after multiple trials (e.g., Wisconsin Card Sorting Test, WCST; Heaton, Chelune, Talley, Kay, & Curtis, 1993). These higher-level cognitive skills are thought to be mediated by a predominantly frontal neural network. Furthermore, performance on tests of set-shifting relies not only on brain regions important for cognitive control, but also on brain regions that mediate other fundamental skills critical to good performance, such as visual scanning or motor speed.

Recently developed tests of set-shifting have emphasized the importance of evaluating and controlling for component processes to isolate set-shifting ability (Delis, Kaplan, & Kramer, 2001). The Delis-Kaplan Executive Function System (D-KEFS) was designed with the intention to move away from the "single achievement score" to a "cognitive process approach" in which fundamental skill performance can be incorporated into an overall assessment of higher-level functions, such as set-shifting. For example, the D-KEFS Design

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Fluency (DF) subtest includes two tests of component processes and one set-shifting condition. In the first component task, the subject is required to generate novel designs by connecting filled dots; this condition measures the ability to generate novel designs using a simple array. In the second component task, the participant is required to connect empty dots while avoiding the filled dots; this condition measures the ability to generate novel designs and avoid irrelevant information on a more complex array. In the set-shifting condition, the individual is required to switch back and forth between connecting filled and empty dots; this condition measures the ability to generate novel designs, avoid irrelevant information, and shift attention between two types of stimuli. By controlling for performance on the component processes, set-shifting ability can be better isolated.

Inferences about the underlying neuroanatomical substrate for set-shifting have come from studying patients with known regional pathology (e.g., focal lesions or relatively focal neurodegenerative diseases) or from studying healthy controls using functional neuroimaging techniques. The bulk of this literature suggests that the frontal lobes play a preeminent role in set-shifting. Performance on set-shifting tests, such as the Trail-Making test, has been found to be impaired in patients with frontal lobe lesions (Aron, Monsell, Sahakian, & Robbins, 2004; Eslinger & Grattan, 1993; Owen, Roberts, Polkey, Sahakian, & Robbins, 1991; Ravizza & Ciranni, 2002; Stuss, Bisschop, Alexander, Levine, Katz, & Izukawa, 2001; Yochim, Baldo, Nelson, & Delis, 2007), frontal lobe epilepsy (McDonald, Delis, Norman, Tecoma, & Iragui-Madozi, 2005), or frontal-striatal dysfunction due to basal ganglia lesions (Eslinger & Grattan, 1993), Parkinson's disease (Cools, Barker, Sahakian, & Robbins, 2001; Ravizza & Ciranni, 2002; Tamura, Kikuchi, Otsuki, Kitagawa, & Tashiro, 2003; Woodward, Bub, & Hunter, 2002), or Huntington's disease (Aron, Watkins, Sahakian, Monsell, Barker, & Robbins, 2003; Lawrence et al., 1998). Functional neuroimaging studies suggest that within the frontal lobes, the lateral regions are most important for shifting set (Aron et al., 2004; Derrfuss, Brass, & von Cramon, 2004; Konishi, hayashi, Uchida, Kikyo, Takahashi, & Miyashita, 2002; Moll, de Oliveira-Souza, Moll, Bramati, & Andreiuolo, 2002; Smith, Taylor, Brammer, & Rubia, 2004), although several studies suggest an important role for the medial frontal lobes (Crone, Wendelken, Donohue, & Bunge, 2006; Rushworth, Hadland, Paus, & Sipila, 2002). While both the right and left frontal lobes are important for set-shifting, some have argued that the left frontal lobe may play a more significant role (Kramer et al., 2007; Mayr, Diedrichsen, Ivry, & Keele, 2006; Moll et al., 2002; Smith et al., 2004; Zakzanis, Mraz, & Graham, 2005).

Although most research suggests that the frontal lobes are important for set-shifting, other brain regions have also been implicated. Patients with nonfrontal cortical lesions often fail the WCST (Anderson, Damasio, Jones, & Tranel, 1991; Barcelo & Santome-Calleja, 2000), and set-shifting deficits have been reported in patients with parietal lesions (Posner, Walker, Friedrich, & Rafal, 1984) or medial temporal lobe dysfunction (Corcoran & Upton, 1993; Strauss, Hunter, & Wada, 1993). Functional neuroimaging studies also suggest that several nonfrontal regions may play a role in set-shifting tasks including the parietal lobes (Asari, Konishi, Jimura, & Miyashita, 2005; Barber & Carter, 2005; Brass, Ullsperger, Knoesche, von Cramon, & Phillips, 2005; Rushworth, Paus, & Sipila, 2001; Wager, Jonides, & Reading, 2004), basal ganglia and their connections to the frontal lobes (Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Monchi, Petrides, Strafella, Worsley, & Doyon, 2006; Nagano-Saito, Leyton, Monchi, Goldberg, He, & Dagher, 2008), temporal lobes (Zakzanis et al., 2005), and the cerebellum (Lie, Specht, Marshall, & Fink, 2006; Schmahmann & Sherman, 1998).

Methodological differences may be one reason why studies have produced varying results. As discussed previously, successful performance on tests of set-shifting relies on a host of other higher-level as well as fundamental cognitive skills that recruit additional brain regions. If these cognitive skills are not independently measured and controlled for, then performance on the shifting condition will be confounded by the integrity of these fundamental cognitive skills and associated brain regions. In addition, even when other cognitive skills have been carefully controlled for, it is not entirely clear whether set-shifting relies on the same brain regions across different tests (e.g., whether shifting on a visuomotor sequencing task relies on the same brain networks as shifting on a color naming and reading task).

Thus, the goal of this study was to evaluate the relationship between gray matter brain volume and set-shifting in a large cohort of patients with neurodegenerative disease, mild cognitive impairment, and healthy older adults. In particular, we aimed to examine the relationship between performance on tests of set-shifting and regional gray matter volume before and after controlling for performance on tests of the component processes. We predicted that before controlling for component processes, set-shifting performance will correlate with diffuse gray matter regions. However, after controlling for component processes, we predicted that set-shifting performance will correlate with more specific and predominantly frontal regions. In addition, we aimed to examine whether there were common gray matter regions across set-shifting tests. Based on the current literature, we predicted that this common region would include dorsolateral prefrontal cortex. To evaluate set-shifting, we selected three clinically available tests from the D-KEFS that include one set-shifting condition and two component processes (i.e., Design Fluency, Trail Making Test, and Color-Word Interference subtests). To examine the relationship between set-shifting performance and gray matter volume, we used voxel-based morphometry (VBM) of brain magnetic resonance imaging (MRI).

METHODS

Participants and Diagnostic Procedure

All participants were recruited through the University of California, San Francisco (UCSF) dementia specialty clinic

and were diagnosed after an extensive clinical evaluation including a detailed history, physical and neurological examination, neuropsychological screening, and study partner interview. The 1-hr neuropsychological screening battery assessed multiple domains of cognition, including memory, executive function, language, and visuospatial skills (Kramer et al., 2003). The interview with the study partner involved the Clinical Dementia Rating (CDR) (Morris, 1993) to assess functional abilities and the Neuropsychiatric Inventory (NPI) (Cummings, 1997) to evaluate behavior. Screening for depression was done using the 30-item Geriatric Depression Scale (GDS) (Yesavage et al., 1983) (self-report) and an interview with the study partner. Diagnosis was determined by consensus involving the neurologist, neuropsychologist, and nurse using only the diagnostic information described above. All participants underwent a high-definition MRI anatomical scan within 120 days of D-KEFS test administration.

We included patients from different diagnostic groups as well as healthy older adults for several reasons. First, inclusion of patients from different diagnostic groups adds greater variance for both task performance and MRI gray matter volume. This increases the statistical power to detect brain–behavior relationships across the whole brain. If we only included controls and patients from a small number of diagnostic groups, we would have more difficulty separating a disease-specific atrophy correlation from a task-specific correlation. Participants included individuals with diagnoses of Alzheimer's disease (AD; $n = 10$), corticobasal degeneration (CBD; $n = 12$), frontotemporal dementia (FTD; $n = 21$), semantic dementia (SD; $n = 14$), amyotrophic lateral sclerosis (ALS; $n = 6$), mild cognitive impairment (MCI; $n = 57$), and healthy older adults (NC; $n = 40$). Patients were diagnosed using published diagnostic criteria (Brooks, 1994; Garbutt et al., 2008; McKeith et al., 2005; McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984; Neary et al., 1998). One patient with PSP was included in the CBD group based on clinical overlap of these two parkinsonian disorders (Kertesz & Munoz, 2004). A research diagnosis of MCI was based on the following criteria: (1) complaint in one or more cognitive domains (i.e., memory, executive function, visuospatial, or language) reported by the participant, informant or clinician; (2) meaningful decline in one or more cognitive domains over a period of at least 1 year; (3) difficulty in the cognitive domain compared with age and education matched peers; (4) absence of dementia (APA, 1994); and (5) the absence of other conditions that could account for cognitive decline (e.g., major depression, substance abuse, hypothyroid). The MCI patients were further subcategorized in amnestic MCI (single or multiple domain) and nonamnestic MCI (single or multiple domain) (Winblad, 2004). The current sample included 6 amnestic single domain MCI, 29 amnestic multiple domain MCI and 22 dysexecutive MCI (Pa et al., 2009). Participants were excluded if they had a current psychiatric illness, history of head trauma with loss of consciousness greater than 10 min, severe sensory deficits, substance abuse, or were taking medications that affect cognition. The study was approved by the UCSF committee on human research. All participants, or their authorized caregivers, provided written informed consent before participating.

Diagnostic Neuropsychological battery

A 1-hr diagnostic neuropsychological battery (Kramer et al., 2003) was used to help diagnose all patients and controls and is reported for descriptive purposes (Table 1). Tests of general cognition included the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). Verbal memory was evaluated using the California Verbal Learning Test (CVLT) (Delis et al., 2001). (The CVLT Long Form was given to the healthy older adults and MCI patients, while the CVLT Short Form was administered to all other patients to mitigate ceiling and floor effects, respectively). Executive function was assessed using the Digit span backward, letter fluency (D words in 1 min), and abstractions (Wechsler, 1997; Kramer et al., 2003). Language was assessed using a 15-item modified Boston Naming Test (BNT) (Kaplan, Goodglass, & Wintraub, 1983). Visuospatial function was assessed using the modified Rey-Osterreith figure copy and Number Location subtest from the Visual Object and Space Perception Battery (VOSP) (Warrington & James, 1991). Nine patients were missing no more than two tests while seven patients were missing three or more tests from diagnostic neuropsychological battery.

D-KEFS Set-Shifting Tasks and Component Processes

We selected the following three subtests from the D-KEFS to investigate set-shifting performance: Design Fluency, Trail Making Test, and Color-Word Interference. Each subtest included a set-shifting condition and two component process conditions. The D-KEFS Design fluency (DF) task requires participants to generate different designs using four straight lines to connect dots. There are five dots in each figure. In the first component condition, participants must connect the filled dots (DF-Filled). This process controls for fluency. In the second component condition, participants must connect the empty dots while avoiding the filled dots (DF-Empty). This process controls for fluency and inhibition. In the set-shifting condition, participants must alternate between filled and empty dots (DF-Switch). We used the total number correct in 60 seconds for each condition as the performance measure.

The D-KEFS Trail Making Test (TMT) is an adaptation of the original TMT test published in 1944 (*Army Individual Test Battery Manual of Directions and Scoring*, 1944) and requires that participants sequentially connect numbers and letters. Each stimulus page contains both numbers and letters. In the first component condition, participants must connect only the numbers (TMT-Numbers). This condition controls for visual scanning, motor speed, and number sequencing. In the second component condition, participants must connect only the letters (TMT-Letters). This conditions controls for visual scanning, motor speed, and verbal skill. In the set-shifting condition,

Table 1. Demographics and Neuropsychological testing

	AD	ALS	CBD	FTD	SD	MCI	Controls
Demographics							
n	10	6	12	21	14	57	40
Age	62.6 (5.4)	62 (10)	62.9 (8.5)	60.8 (7.7)	62.1 (5.9)	69.8 (9.3)	65.2 (8.9)
Education	15.8 (2.7)	17.2 (1.8)	**14.8 (2.9)**	16.8 (2)	15.9 (3.2)	16.8 (2.7)	17.6 (1.9)
Gender (M/F)	6/4	5/1	4/8	17/4	9/5	30/27	20/20
General							
MMSE	**26 (3.1)**	29.2 (2)	**27.3 (2)**	**26.1 (4.4)**	**23.5 (6.2)**	28.4 (1.5)	29.8 (0.5)
CDR-SOB	**3.5 (2.3)**	**3.8 (2.6)**	**3.4 (2.9)**	**6.4 (2.4)**	**3.5 (1.8)**	**1.3 (1)**	0 (0.1)
Memory							
CVLT-SF trials 1-4 (max. 36)	20.5 (5.5)	25.3 (5.6)	24.9 (4.9)	21.6 (5.8)	14.9 (7.7)	—	—
CVLT-SF 10' recall (max. 9)	3.6 (3)	5.7 (3.3)	6.5 (2)	4 (3.1)	2.1 (2.4)	—	—
CVLT-II trials 1-5 (max. 80)	—	—	—	—	—	**40.4 (13.9)**	53.5 (11.6)
CVLT-II 20' recall (max. 16)	—	—	—	—	—	**8.6 (4.4)**	12 (2.9)
Mod Rey recall (max. 17)	**7.1 (6.4)**	10.5 (3.4)	10.3 (3.7)	**7.9 (5.1)**	**6.2 (3.8)**	9.8 (4.2)	12.3 (2.9)
Executive							
Digits backward	**3.9 (1)**	4.7 (1.2)	**3.5 (0.8)**	4.6 (1.6)	4.3 (1.3)	5 (1.1)	5.5 (1.2)
D' words/min.	**10.9 (4.2)**	10.5 (8.1)	**7.6 (3.4)**	**10.8 (8)**	**6.9 (3.3)**	14 (4.9)	16.8 (4.7)
Abstractions (max. 6)	**2.8 (1.9)**	4.5 (1.4)	**3.2 (1.3)**	**2.5 (1.7)**	**1.5 (1.3)**	4.5 (1.5)	5.3 (0.9)
Language							
BNT (max. 15)	13 (2.7)	**10.8 (5.2)**	**14 (1.3)**	**12.7 (3.1)**	**3.6 (3.2)**	13.3 (1.9)	14.7 (0.6)
Animals/min.	**12.1 (4.3)**	19.2 (13.1)	**13 (3.9)**	**12.9 (5.1)**	**6.1 (4.6)**	**16.2 (5.4)**	22.5 (4.9)
Visuospatial							
Mod Rey copy (max. 17)	**13.3 (4)**	14.8 (1.3)	**14.2 (2.6)**	14.6 (4)	15.3 (1.8)	15.6 (1.3)	16.2 (0.9)
VOSP (max. 10)	7.7 (2.9)	9.3 (0.8)	**7.7 (2.5)**	8.2 (2.2)	9.3 (1.1)	8.9 (1.3)	9.4 (0.8)
Set-shifting Tests							
Design Fluency							
Filled Dots	**5 (1.8)**	9.8 (3.7)	**6.8 (3)**	**6 (3.2)**	8 (3)	9.5 (3.4)	10.9 (3.2)
Empty Dots	**4.8 (1.7)**	9.5 (3.1)	**6.5 (3.3)**	**6.2 (3.2)**	**7.6 (2.9)**	**9.8 (3.1)**	11.9 (3.5)
Switching	**2.7 (1.6)**	7.7 (0.8)	**4.1 (2.4)**	**4.2 (3.3)**	**5.9 (3.6)**	**6.5 (2.6)**	8.8 (2.8)
Trail Making Test							
Numbers	**91.1 (36.2)**	50.3 (8.7)	**86.9 (40.4)**	**61 (36.6)**	55 (24.7)	53.2 (24.5)	38.1 (12.4)
Letters	**101.8 (30.9)**	56.8 (14.8)	**101.6 (51.1)**	**67.3 (39.3)**	60.1 (25.2)	52.1 (22.3)	38.8 (14.9)
Switching	**200.4 (62.2)**	103.5 (33.8)	**181.2 (62)**	**147.5 (70.6)**	**141.9 (56.7)**	**117.4 (55.5)**	80.6 (33.2)
Color-Word Interference							
Reading	**39.8 (13.2)**	33 (11.1)	**37.6 (10.9)**	28.4 (8)	**37.5 (17.8)**	24.2 (4.9)	22.2 (5.2)
Interference	**116.5 (37.4)**	88.8 (40)	**94.8 (28.4)**	72.9 (28.2)	**94.3 (37.7)**	**73 (28)**	54.3 (10.3)
Switching	**143.8 (39.6)**	94.7 (42)	**111.3 (36)**	**94.1 (37)**	**105.5 (37.5)**	81.2 (29.7)	63.7 (21.5)

Note. Bold values indicate $p < .05$ vs. controls, analysis of variance with Tukey *post hoc*. Diagnoses: AD = Alzheimer's disease, ALS = amyotrophic lateral sclerosis, CBD = cortical basal degeneration, FTD = frontotemporal dementia, SD = semantic dementia, MCI = mild cognitive impairment. Demographic and Neuropsychological variables: MMSE = Mini Mental State Examination, CDR = Clinical Dementia Rating, CVLT = California Verbal Learning Test, BNT = modified Boston Naming Test, VOSP = Visual Object Spatial Perception. The CVLT-II Long Form was given to Controls and MCI patients, and the CVLT-II Short Form was given to the dementia groups, to mitigate ceiling and floor effects, respectively.

participants must alternate between numbers and letters in sequential order (TMT-Switch). We used the time to complete the task as the performance measure.

The D-KEFS Color-Word Interference (CWI) task is an adaptation of the original Stroop paradigm from 1935 (Stroop, 1935) that requires participants to inhibit an overlearned propensity to read words and instead, identify the ink color of the printed word. In the first component condition, participants must read the words (CWI-Read). This condition controls for reading ability. In the second component condition, participants must say the ink color of the word while inhibiting the propensity to read the word (CWI-Interfere). This controls for inhibition of reading. In the set-shifting condition, participants must alternate between reading the word and saying the ink color (CWI-Switch). We used the time to complete the task as the performance measure.

We excluded 37 participants who performed poorly at ceiling on any of the component processes from any of the three D-KEFS subtests.

Statistical Analysis of Demographics and Neuropsychological Tests

We compared demographic and neuropsychological measures between diagnostic groups using a one-way analysis of variance with Tukey *post hoc* statistics. Significance was assessed at a threshold of $p < .05$, of patient group compared with controls, as indicated by the bolded values in Table 1. We

assessed the relationship between the set-shifting and component process conditions using Pearson product-moment correlation coefficients. The amount of variance explained by the nuisance variables (i.e., age, gender, and MMSE) and component processes was determined using regression analyses. Statistical analyses of behavioral data were conducted using SPSS (version 14.0, Chicago, IL, USA).

Brain MRI Acquisition

Images were collected on a Siemens Vision 1.5 Tesla MRI scanner (Siemens, Iselin, NJ). T1-weighted three-dimensional magnetization prepared rapid acquisition gradient echo (MPRAGE) images were acquired (inhibition time/repetition time/echo time = 300/9.7/4 (ms); flip angle = 15°; field of view 256 × 256 mm^2 with 1.0 × 1.0 mm^2 inplane resolution; 154 partitions with 1.5-mm slice thickness).

MRI Image Preprocessing

Voxel-based morphometry analysis was performed on the T1-weighted images using SPM5 software (Wellcome Department of Imaging Neuroscience, University College London, UK, www.fil.ion.ucl.ac.uk) implemented within Matlab 7.9 (MathWorks, Natick, MA). For the preprocessing steps, we used the DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) toolbox within SPM5. DARTEL uses a nonlinear algorithm which is suggested to achieve better image registration than the parametric approaches used by the unified segmentation process in standard SPM (Ashburner, 2007). In addition, DARTEL has been reported to achieve optimal registration in neurodegenerative diseases (Pereira, Xiong, Acosta-Cabronero, Pengas, Willliams, & Nestor, 2009).

We first segmented the T1-weighted images into gray matter, white matter, and corticospinal fluid. We then imported the gray and white matter images into DARTEL space for preprocessing. We used the segmented gray matter images of each participant to create a study-specific template for warping and normalization. The images underwent a nonlinear transformation using a diffeomorphic registration algorithm (Ashburner, 2007) and were then transformed into MNI (Montreal Neurological Institute) stereotactic space using the default ICBM template. We applied an isotropic Gaussian smoothing kernel of 12 mm FWHM (full width at half maximum) to minimize individual anatomical variability and reduce the chance of false positives (Salmond, Ashburner, Vargha-Khadem, Connelly, Gadian, & Friston, 2002). All images were reviewed before statistical analysis to ensure quality of the segmentation process. The preprocessed images were passed up to voxel-wise statistical comparison.

Statistical Analysis of Brain MRI

We assessed the relationship between performance on the three set-shifting tasks (i.e., DF-Switch, TMT-Switch, CWI-Switch) and gray matter volume by collapsing across diagnostic groups. Investigating the brain regions correlated with set-shifting performance across our entire study sample increased statistical power and variability in our regression analysis.

We conducted a series of multiple regression analyses by hierarchically introducing component processes. Our first analysis consisted of controlling only for the potentially confounding variables of age, gender and MMSE (to control for dementia severity), and total intracranial volume (TIV) (nuisance variables). We then sequentially added in each component process to the statistical model, in a hierarchical manner. We assessed each statistical parametric map at a threshold of $p < .05$, FDR-corrected(false discovery rate) for multiple comparisons.

Using the example of Design Fluency, we first assessed the relationship between DF-Switch and gray matter volume while controlling for the nuisance variables. In the next stepwise analysis, we included the nuisance variables and DF-Filled to control for the first component process (i.e., motor speed). In the last analysis, we included the nuisance variables, DF-Filled, and DF-Empty to control for both component processes (i.e., motor speed and visual complexity). The final analysis identified the gray matter correlates of DF-Switch after accounting for DF-Filled and DF-Empty as control components.

This same procedure was repeated for TMT-Switch and CWI-Switch. Specifically, for TMT-Switch, we began by analyzing the relationship between TMT-Switch and gray matter volume while only controlling for the nuisance variables. In the subsequent analyses, we sequentially added in the component processes of TMT-Numbers and TMT-Letters. For CWI-Switch, we added in the component processes of CWI-Read and CWI-Interfere.

RESULTS

Demographics and Diagnostic Neuropsychological Battery

There were no significant age differences in the patient groups compared with controls. The CBD patients had a significantly lower level of education than controls. The diagnostic neuropsychological test results are presented for descriptive purposes in Table 1. Please note that the AD and ALS patient groups have small sample sizes making it difficult to interpret group differences.

Performance on D-KEFS Subtests

On the D-KEFS Design Fluency tasks, the AD, CBD, and FTD patients scored significantly lower on all measures (DF-Filled, DF-Empty, and DF-Switch) when compared with controls. The SD patients and MCI patients scored significantly lower on the DF-Empty and DF-Switch when compared with controls.

On the D-KEFS Trail Making Test, the AD, CBD, and FTD patients were significantly slower on all measures

(TMT-Numbers, TMT-Letters, and TMT-Switch) compared with controls. SD and MCI patients scored worse than controls on the TMT-Switch condition only.

On the D-KEFS Color-Word Interference tasks, the AD, CBD, and SD patients were significantly slower on CWI-Read when compared with controls. The AD, CBD, SD, and MCI patients were significantly slower on CWI-Interfere when compared with controls. On the CWI-Switch condition, the AD, CBD, FTD, and SD patients were significantly slower than controls.

Relationship Between Component Processes and Set-Shifting Conditions

There were significant associations between the set-shifting conditions and their individual component processes. Across all three tasks, there was a strong relationship between each component condition and the associated set-shifting condition. Performance on the TMT-Switching condition was significantly correlated with the TMT-Numbers ($r = .69$; $p < .001$) and TMT-Letters ($r = .79$; $p < .001$) conditions. Performance on the CWI-Switch condition was significantly correlated with the CWI-Read ($r = .62$; $p < .001$) and CWI-Interfere ($r = .79$; $p < .001$) conditions. Performance on the DF-Switch condition was significantly correlated with the DF-Filled ($r = 0.49$; $p < .001$) and DF-Empty conditions ($r = 0.58$; $p < .001$) conditions. The DF-Switch condition was the least correlated with its component processes. Table 2 shows the amount of variance explained by each component part as it is added into the regression model. In the Trail Making Test and Color Word Interference models, the component processes and nuisance variables account for more than 64% of the variance in the model. In contrast, these factors only account for 43% of the variance in the Design Fluency model.

Relationship Between Set-Shifting and Gray Matter Volume

As discussed above, we used correlation analyses to evaluate the relationship between the D-KEFS subtests and gray matter volume across groups while controlling for potential confounding factors (age, gender, MMSE, and total intracranial volume) and component processes.

Design Fluency (DF)

In the first analysis, without controlling for the component processes, DF-Switch was significantly correlated with the majority of cortical gray matter volume, including bilateral frontal, parietal, temporal, and occipital regions (Figure 1). After adding DF-Filled as a component process into the regression model, there was a relationship between DF-Switch and lateral and medial frontal cortex bilaterally and posterior parietal lobe. After adding both DF-Filled and DF-Empty component conditions into the regression model, DF-Switch was significantly correlated with focal regions in left dorsolateral and ventrolateral prefrontal cortex (Figure 1). These results suggest that performance on the DF-Switch condition, after controlling for the two component processes (DF-Filled, DF-Empty), was associated with frontal–parietal gray matter regions.

Trail Making Test (TMT)

We first investigated the gray matter correlates of TMT-Switch without controlling for the component parts. The gray matter regions that correlated with TMT-Switch performance were diffusely located throughout the brain encompassing frontal, parietal, temporal, and occipital lobes. After introducing TMT-Numbers into the model, TMT-Switch continued to correlate with multiple, but more focal brain regions of bilateral medial prefrontal cortex, dorsolateral prefrontal cortex, temporal lobe, and posterior parietal cortex. After controlling for both TMT-Numbers and TMT-Letters, no brain regions remained significantly correlated. This lack of significant findings may be explained by the high degree of multicollinearity between the component processes and set-shifting task and will be elaborated on in the discussion.

Table 2. Relationship between set-shifting and component processes

Set-shifting task		Variance explained
Design Fluency (DF)	Age, gender, MMSE	24.2%
	Age, gender, MMSE, DF-Filled	38.3%
	Age, gender, MMSE, DF-Filled, DF-Empty	43.2%
Trail Making Test (TMT)	Age, gender, MMSE	22.6%
	Age, gender, MMSE, TMT-Numbers	56.6%
	Age, gender, MMSE, TMT-Numbers, TMT-Letters	**66.9%**
Color Word Interference (CWI)	Age, gender, MMSE	21.6%
	Age, gender, MMSE, CWI-Read	44.2%
	Age, gender, MMSE, CWI-Read, CWI-Interfere	**63.9%**

Note. The amount of explained variance increases, as nuisance variables and component processes are added into the regression analysis. Notably, there is a higher degree of multicollinearity between TMT-Switch and CWI-Switch and their component processes than DF-Switch and its component processes. MMSE = Mini Mental State Examination.

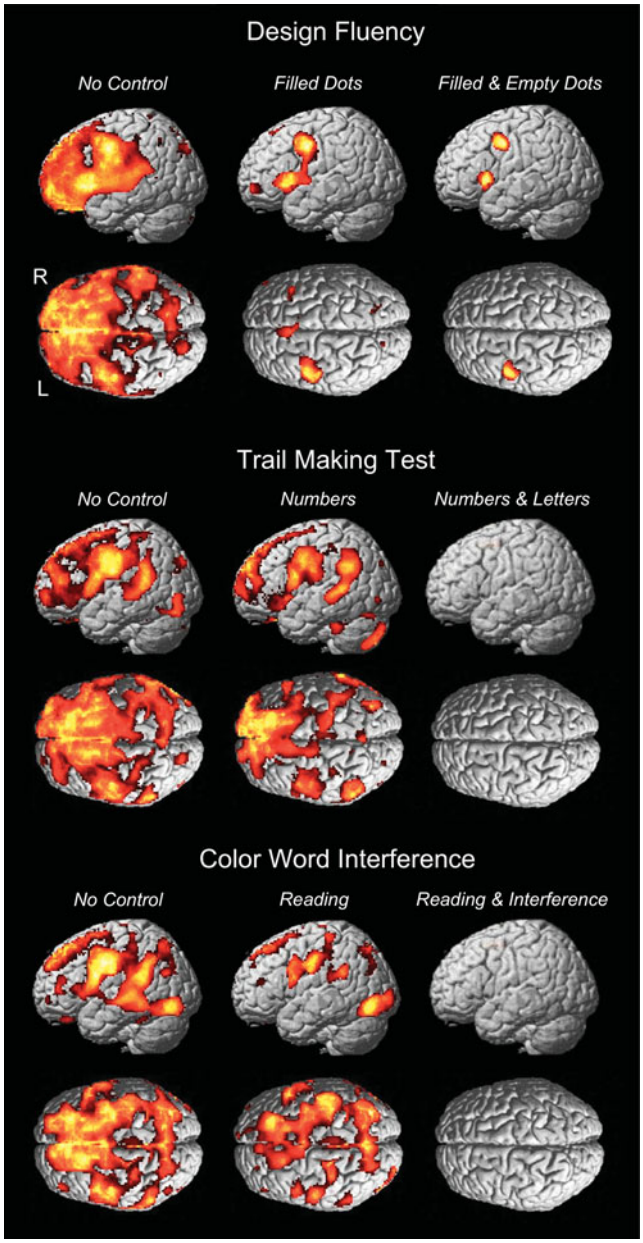

Fig. 1. Gray matter correlates for each Delis-Kaplan Executive Function System set-shifting task Correlations between gray matter volume and set-shifting performance displayed on a rendered brain from each stepwise analysis: 1) without controlling for component processes (left), 2) after controlling for the first component process (middle), and 3) after controlling for both component processes (right). Displayed at $p < .05$, FDR-corrected for multiple comparisons.

Color-Word Interference (CWI)

Similar to the previous tasks, we again found a significant correlation between multiple, diffuse brain regions and performance on the CWI-Switch (when not controlling for the component processes). After controlling for the first component of CWI-Read, CWI-Switch correlated with focal posterior regions of bilateral superior parietal lobule and posterior medial cortex in addition to bilateral prefrontal cortex regions. When both CWI-Interfere and CWI-Read conditions were included in the regression model, there was no significant relationship between CWI-Switch performance and brain volume. Similar to the Trail Making Test final analysis, this result may be explained by the high degree of multicollinearity between the component processes and set-shifting task and will be revisited in the discussion.

Set-Shifting Across the Three Tasks

To illuminate the relationship between set-shifting across tasks and gray matter volume, we overlaid the statistical correlation maps from each D-KEFS subtest (Figure 2). Because no regions remained significant when controlling for both component processes for the Trail Making Test and Color Word Interference, we selected the correlation maps while controlling for the first component process only. This allowed us to investigate common brain regions across the three set-shifting tasks. We found that set-shifting performance across the three switching tasks was correlated with bilateral prefrontal cortex and posterior parietal lobe (Figure 2, shown by the blue arrows).

DISCUSSION

Our results highlight the increased specificity of cortical regions that correlate with set-shifting when controlling for the influence of fundamental processes, such as motor control and visual scanning. In addition, we identify the key gray matter regions of bilateral prefrontal cortex and posterior parietal lobe that correlate across three distinct set-shifting tasks. As a secondary finding, we report the high multicollinearity between the component processes and set-shifting conditions on the Trail Making Test and Color Word Interference tests.

Our neuroimaging findings are consistent with the literature implicating prefrontal function in set-shifting tasks. Multiple patient studies have recognized the impact of frontal lobe lesions on set-shifting performance (McDonald, Delis, Norman, Tecoma, et al., 2005; McDonald, Delis, Norman, Wetter, Tecoma, & Iragui, 2005; Pantelis, Barber, Barnes, Nelson, Owen, & Robbins, 1999; Stuss et al., 2001; Yochim et al., 2007). Disrupted prefrontal lobe function, as measured by increased, aberrant blood flow, has also been implicated in set-shifting impairment in schizophrenia and bipolar patients (Jazbec, Panatelis, Robbins, Weickert, Weinberger, & Goldberg, 2007; McKirdy, Sussmann, Hall, Lawrie, Johnstone, & McIntosh, 2009; Pantelis et al., 1999). In addition, functional neuroimaging studies have identified focal blood oxygenated level dependent (BOLD) or metabolic activity in prefrontal cortex in set-shifting tasks (Horacek et al., 2006; Moll et al., 2002; Zakzanis et al., 2005).

Less evidence has been shown relating posterior parietal cortex to set-shifting performance, as reported in the current study. Methodological differences may be one explanation. Our study is distinct from other structural MRI studies on set-shifting, because we used a voxel-by-voxel approach to identifying gray matter regions involved in set-shifting.

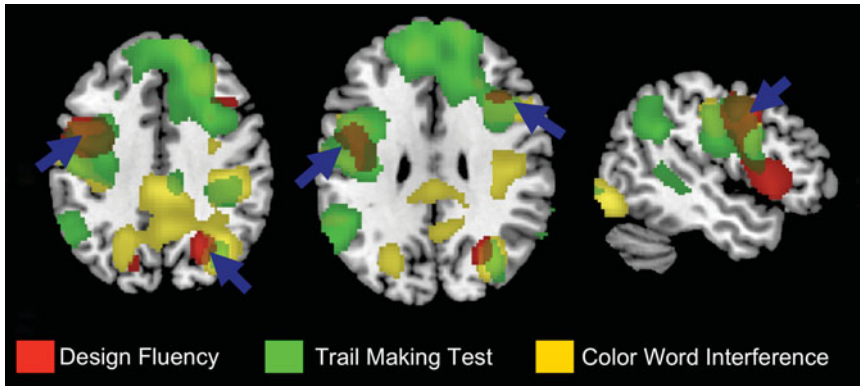

Fig. 2. Common neural correlates across Delis-Kaplan Executive Function System set-shifting tasks. Blue arrows indicate the common regions of overlap across the three set-shifting tasks. Displayed at $p < .05$, FDR-corrected for multiple comparisons.

Previous studies used lobar volume measurements or *a priori* regions of interest in the frontal lobe when probing neural correlates of set-shifting (Kramer et al., 2007; Zimmerman et al., 2006). This is an important distinction because lobar volume measurements may be less sensitive to focal neural correlates (i.e., posterior parietal cortex) of set-shifting. Some functional MRI studies, which conduct statistical analyses on a voxel-by-voxel basis have, however suggested parietal involvement in set-shifting. In fact, one study used a modified verbal form of the Trail Making Test to investigate functional activation (Moll et al., 2002). This study found a task-induced, increase in the BOLD response in left dorsolateral and dorsomedial prefrontal cortex and bilateral intraparietal sulcus. These findings are highly consistent with our current study, and these authors recognize a frontoparietal network in regulating cognitive control and flexibility. Another study aimed at elucidating regions involved in cognitive control also found bilateral lateral posterior parietal cortex activation during a cognitive set-shifting task (Asari et al., 2005). Overall, the findings in the current study are consistent with the role of the prefrontal and parietal cortices in cognitive control, mental flexibility, and task switching.

One recent study sought out the relationship between multiple D-KEFS measures and gray matter density in FTD and CBD patients (Huey et al., 2009). Their study did not specifically investigate set-shifting ability, but rather a set of general higher-order executive functions, and there was only overlapping test with the current study (Trail Making Test). They did not control for the component processes in their study, but used the D-KEFS computed scaled scale, which takes education level into account. In a CBD patient population, it is important to control for component processes that may be compromised due to deficits in basic cognitive functions (e.g., visual scanning, motor control).

Another study sought to identify regions involved in a set of executive function tasks, including a version of the Trail Making Test (shifting condition B) (Newman, Trivedi, Bendlin, Ries, & Johnson, 2007). Gray matter correlates of performance were identified in bilateral prefrontal cortex, among other regions. Importantly, this study was conducted in healthy controls, possibly restricting the generalizability of the findings to patient populations and limiting the amount of variance in the data, as recognized by Newman and colleagues. This study did not control for component processes (i.e., Trail Making Test condition A).

Other studies have highlighted the importance of controlling for component processes when investigating complex cognitive processes. For example, Kramer and colleagues (2007) found that DF-Switch significantly correlated with six lobar volumes (bilateral frontal, parietal, and temporal lobes). However, after controlling for DF-Filled, working memory, and nuisance variables, DF-Switch significantly correlated with the left and right frontal lobes.

To better understand the interplay between cognitive processes, we examined the relationship between the component processes and set-shifting tasks. Although no brain regions were significantly correlated with the Trail Making Test and Color Word Interference analyses after controlling for *both* component processes, this is an interesting result. The high degree of multicollinearity between these set-shifting tasks and their component parts may limit the ability to identify brain regions correlated with set-shifting. It is possible that a significant result would be found in a larger sample size. However, one could still account for fundamental skills (e.g., motor speed, visual scanning) when assessing performance in set-shifting by controlling for one component process (as in the modified version of the Trail Making Test proposed by Reitan and Wolfson (1985).

Identifying a high degree of multicollinearity between component processes and set-shifting may have potential practical applicability for clinicians in assessing set-shifting function. To date, the majority of studies probing set-shifting function use the Trail Making Test as their measures; however, given our current findings, Design Fluency may be a better measure for assessing pure set-shifting ability when controlling for component processes.

Taken together, the results from our study are consistent with the literature suggesting that set-shifting involves a frontal–parietal brain network. One limitation of our study, however, is the lack of consideration for white matter structures involved in set-shifting. Numerous studies have identified the impact of white matter hyperintensities and

compromised fiber tracts on impaired set-shifting performance, among other executive function abilities (Marshall, Hendrickson, Kaufer, Ivanco, & Bohnen, 2006; Perry et al., 2009). The role of white matter regions in set-shifting is an important research area and should be explored in future studies. Another limitation of the study is the applicability of these gray matter correlates on other types of set-shifting tasks. As mentioned previously, the three set-shifting tasks used in this study require subjects to switch stimuli on a trial-by-trial basis. However, other set-shifting tasks require subjects to maintain a rule for a set number of trials (e.g., WCST). Therefore, the brain regions correlated in different types of set-shifting tasks may vary. Lastly, we plan to explore the relationship between surface-based morphometry, cortical thickness, and set-shifting in future studies.

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