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RESEARCH ARTICLE

Correlations between Gray-White Matter Contrast in Prefrontal Lobe Regions and Cognitive Set-Shifting in Healthy Adults

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Humans have a unique capacity for higher order cognition such as planning and multitasking. These abilities are collectively referred to as executive functions. This study investigates cognitive set-shifting, a type of executive function that involves shifting from one task to another. Advances in neuroimaging have allowed for the structural integrity of specific frontal lobe subregions to be probed with greater resolution. One such measure is the intensity contrast between cortical gray and white matter, with greater contrast indicating better development. This study tested whether the gray-white matter contrast (GWC) in eight subregions of the prefrontal cortex (PFC) was associated with set-shifting abilities in 61 healthy participants. Set-shifting abilities were measured using two neuropsychology tests: Trail Making Test B (TMT-B) and Wisconsin Card Sorting Test-Perseverative Errors (WCST-PE), with a third test, the Boston Naming Test (BNT), used to determine the discriminant validity of set-shifting findings. Cognitive set shifting was significantly correlated with GWC in the left ventrolateral PFC (Broca's area), the left and right middle frontal gyri (dorsolateral PFC), and the left and right superior frontal gyri. These findings indicate that successful set shifting relies on the structural integrity of ventrolateral and dorsolateral PFC, but not the basal orbitofrontal regions.

INTRODUCTION

Executive functions are a set of cognitive processes essential in organizing and monitoring behaviors conducive to the attainment of a goal. There are three core executive functions: working memory (short term memory that is manipulated), response inhibition (self-control) and cognitive flexibility (the ability to think about multiple concepts simultaneously) (Miyake et al., 2000). Some of the basic executive functions, such as working memory and inhibitory control, can be observed early in infants. However, the development of more complex executive functions, including cognitive flexibility (also referred to as "cognitive set shifting"), is what allow adults to complete challenging tasks. Many of these occupational tasks are coordinated and completed in the prefrontal cortex (PFC) (Miskin et al., 2015).

Structurally, the PFC consists of both gray and white matter. Gray matter is mainly comprised of cell bodies, dendrites and unmyelinated axons (Budday et al., 2015). It enables muscle movement by directing motor stimuli to neurons in the central nervous system (CNS) and contains glial cells (astrocytes, oligodendrocytes, etc.), which are responsible for providing nutrients and support to neurons. White matter is tissue made mostly of neuronal axons that are insulated by a lipid sheath known as myelin. Myelin allows for saltatory conduction, enabling the brain to send action potentials at higher speeds. Thus, gray- and white-matter regions complement each other and work together to relay impulses efficiently and quickly.

Brain lesion studies suggest that the PFC plays an important role in executive functioning (Bissonette, Powell, & Roesch, 2013), but the specific regions within the PFC that are relevant have yet to be fully identified. This project used quantitative magnetic resonance imaging (qMRI) to obtain grey-white matter contrast (GWC as a measurement of prefrontal lobe brain structure integrity. The less contrast there is, the more blurring occurs at the junction between the cortical gray matter and adjacent white matter. Blurring can occur when neurons designated for gray matter get stuck in the white matter during cortical development. GWC is measured by computing a ratio of signal intensity values in the gray matter above the gray-white junction to signal intensity values in the white matter below. It was chosen as a measure of cortical structural integrity due to previous findings that it is linearly related to decreased language function bilaterally in the temporal, parietal and frontal regions and that it is a mediator of group differences in cognitive performance between patients with epilepsy and healthy controls (Blackmon et al., 2014). While the ratio of grey matter to white matter volume has proven to be a useful brain image modality, previous studies mostly used this for the investigations involving brain aging and Alzheimer's disease (Taki, Thyreau, Kinomura, Sato, & Goto, 2011).

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This study analyzes cognitive performance based on cognitive set shifting, which involves alternating between one task and another. An example is switching back and forth from solving a math problem to answering an email. Shifting from one activity to another can be difficult for some people, especially if the tasks require close attention. Difficulty in shifting between tasks is known as cognitive rigidity, which can be an indication of many different human psychiatric disorders and a lack of sufficient executive function (Chan, Shum, Toulopoulou, & Chen, 2008). Difficulty in set-shifting is often noticed in conditions such as autism spectrum disorder, Alzheimer's dementia, major depression disorder and other neuropsychiatric conditions (Elliott, 2003). On the other hand, cognitive flexibility enables individuals to focus their attention on a number of different tasks.

Neuropsychological tests have been shown to be useful in assessing higher order functioning (Lezak, Howieson, Bilger, & Tranel, 2012). In this study, two neuropsychological tests were used to assess set-shifting abilities: Trail Making Test-B (TMT-B) (created by the Army for the Individual Tests of General Ability) and the Wisconsin Card Sorting Test Perseverative Errors (WCST-PE) .

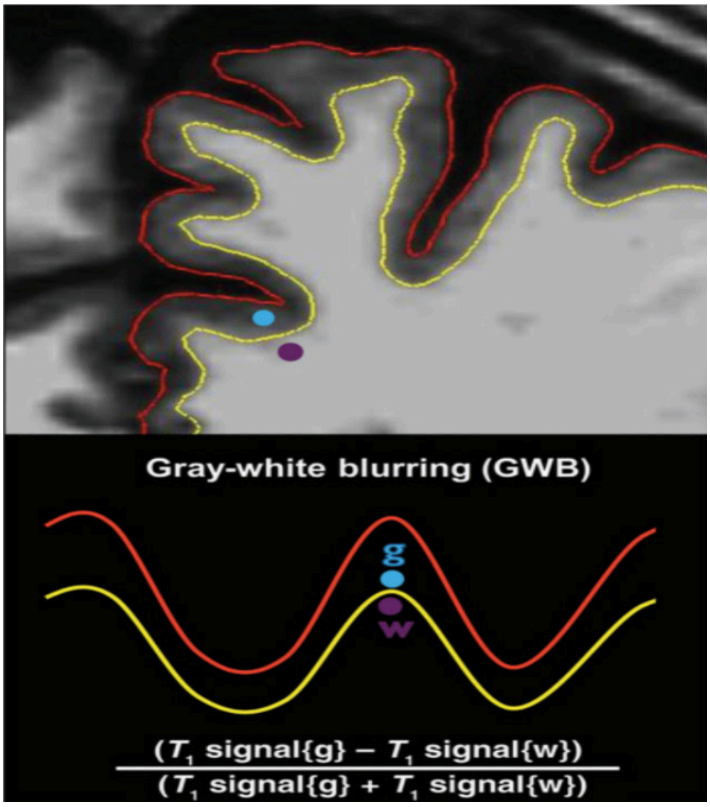

Figure 1. Computing GWB: Sampling points on T1-weighted MPRAGE image with gray-white (GW) junction surface (yellow line) and pial surface (red line). The blue dot represents the sampling location of the gray matter intensity value at 0.5mm into the gray matter relative to the GW junction. The purple dot shows the sampling location of the white matter intensity value at 0.5mm into the white matter relative to the GW junction (adapted from Blackmon et al., 2014).

The TMT-B requires participants to connect dots that are labeled either numerically or alphabetically in an ascending alphanumeric fashion. WCST-PE requires participants to hold in mind three different criteria: shape, number and color, as they try to find the rule set by the test proctor. In both TMT-B and WCST-PE, having to switch between more than one category of thought requires participants to tap into their executive functioning skills. Struggling with these set-shifting tasks may signify problems with participants' PFC and executive functioning abilities (Bissonette et al., 2013).

Previous studies have demonstrated a correlation between GWC in the PFC and decreased cognitive functioning, but the specific subregions within the PFC are yet to be fully elucidated. This investigation used both qMRI and neuropsychological measures to investigate which PFC subregions have the strongest relationships with cognitive set shifting. Specifically, this study explored the correlation between healthy participants' TMT-B and WCST-PE scores and average GWC in eight regions of interest (ROI): the left (Broca's area) and right ventrolateral PFC, the left and right middle frontal gyri (dorsolateral PFC), the left and right superior frontal lobes, and the left and right orbitofrontal cortices (OFC). The OFC was used as a negative control as it is known to function in reward and emotion processing, but not in set shifting (Kringelbach, 2004).

The following hypotheses were tested in this investigation: 1) there will be a positive correlation of GWC of the left- and right-hemisphere superior frontal gyri with TMT-B and WCST-PE scores (higher scores indicate worse cognitive set-shifting abilities); 2) there will be no correlation of GWC in the left or right orbitofrontal cortex (OFC) with TMT-B and WCST-PE scores; 3) there will be a positive correlation of GWC of the left ventrolateral PFC with TMT-B and WCST-PE scores; 4) there will be a positive correlation of GWC in the left and right middle frontal gyri (dorsolateral PFC) with TMT-B and WCST-PE scores; and 5) there will be no correlations of GWC in any of the prefrontal lobe brain regions with performance on the BNT. This study will potentially pinpoint the exact area of the brain that malfunctions in people who struggle with set-shifting, for example, those who are affected with autism, Down's syndrome and attention deficit hyperactivity disorder (ADHD)

METHODS AND MATERIALS

Ethics Statement

The study had current approval by the Institutional Review Board (IRB) at New York University and was conducted in accordance to the Declaration of Helsinki (1964, 2008). All subjects participated voluntarily were given detailed information about the study and gave written consent before participating in the study.

Participants

61 healthy adults (31 males/30 females) with no history of neurological disease, psychiatric illness, developmental learning disorders or traumatic brain injury volunteered to take a series of tests to measure their cognitive set-shifting abilities and to undergo MRI scanning at the New York University Center for Brain Imaging.

Their ages ranged from 15 to 70 years at the time of scanning (M = 31.94 years, SD = 13.34). Group education levels were similar across subjects (M = 15.96 years, SD = 1.91). There were 56 right-handed participants, 4 left-handed participants and 1 ambidextrous participant.

MRI Scanning

Imaging was performed at the NYU Center for Brain Imaging on a 3T head-only MRI scanner (Siemens, New York). Image acquisition included a conventional three-plane localizer and two T1-weighted gradient-echo sequence (MPRAGE) volumes (TE = 3.25ms, TR = 2530ms, TI = 1.100ms, flip angle = 7°, FOV = 256mm, voxel size = 1×1×1.33mm). Acquisition parameters were optimized for increased gray-white matter image contrast.

Gray-White Matter Contrast (GWC)

GWC values were obtained by sampling T1 image intensity contrast at both 0.5mm above and below the gray-white interface with trilinear interpolation. These values were used to create a ratio score: (gray - white)/(gray + white) (Figure 1). Four main processes were involved: (1) segmentation of the white matter; (2) patchwork of the gray-white matter surfaces; (3) inflation of the folded surface; and (4) automatic correction of topological defects (Dale, Fischl, & Sereno, 1999). GWC values ranged from -1 to 0, where scores closer to zero represent higher degrees of blurring around the gray-white inner surface. Mean GWC values were extracted for each participant for each of the following ROIs: the left (Broca's) and right ventrolateral PFC, the left and right middle frontal gyri (dorsolateral PFC), the left and right superior frontal gyri, and the left and right orbitofrontal cortices (OFC). Images were further processed with the FreeSurfer (4.0.2) software package (http://surfer.nmr.mgh.harvard.edu). Mean signed curvature was estimated at each vertex using standard FreeSurfer, giving a measure of the "sharpness" of cortical folding, differentiating between gyral and sulcal regions.

Cognitive Assessments

1. Trail Making Test B (TMT-B)

TMT-B was designed to test an individual's set-shifting ability through a task that involves connecting dots in an alphanumeric manner (Figure 2). As this test involves continually switching between the letters and numbers very quickly, it has been shown to be effective in determining cognitive set-shifting ability. The participant is given a sheet of paper with both numerically and alphabetically labeled dots, and the goal is to connect them as quickly as possible in ascending order (1-A-2-B-3-C…, etc.). Scoring is based on the time it takes for the participant to complete the test. Longer times of test completion are represented by higher scores, indicating lower performance in the test and, thus, poorer set-shift-

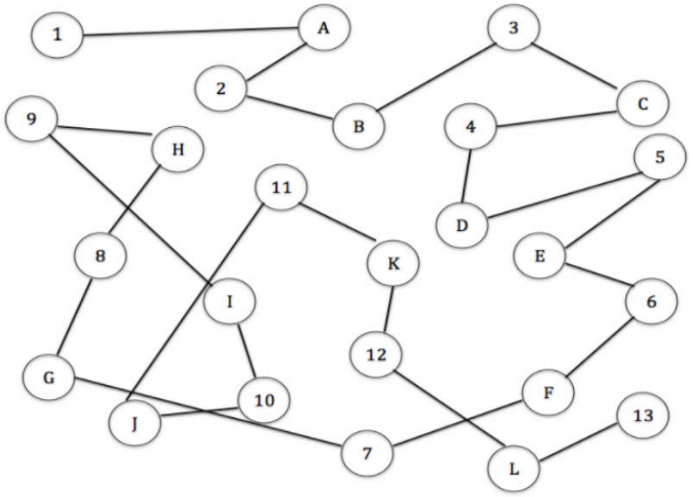

Figure 2. Example of Trail Making Test-B. Participants trace a sequence alternating between numbers and letters in ascending order (set-shifting).

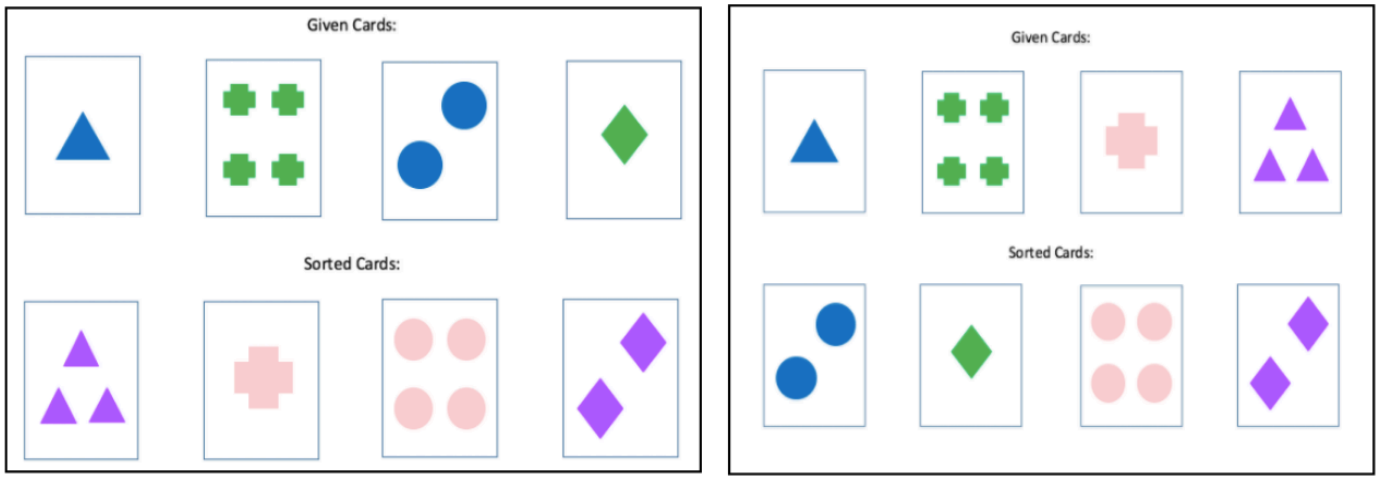

Figure 3. Reproduction of cards used for the Wisconsin Card Sorting Test-Perservative Errors (WCST-PE). Participants match their cards with other cards according to a hidden rule determined by the test proctor.

ing ability (Spreen & Strauss, 1991).

2. *Wisconsin Card Sorting Test-Perseverative Errors (WCST-PE)*

The WCST-PE was designed to test cognitive set-shifting abilities by having the participant match cards according to concealed rules set by a test conductor (Figure 3). The test conductor places four cards in a line in front of the participant and then sets a concealed organizational rule based on color, pattern, number or type of shape. The participant is given several stimulus cards with images of various shapes, colors and numbers, and has to place each in one of the four piles set by the test conductor. Through trial and error, the participant attempts to place the cards into the piles according to the hidden rule. The test conductor only tells the participant whether the match is correct or incorrect. Once the participant correctly identifies the rule, the test proctor changes it without telling the participant. For instance, the rule can change from matching color to matching shape. Scoring is based on the participant's number of perseverative errors: the number of times the participant puts down a card not in line with the conductor's current rule, but consistent with a previously successful rule. In other words, these errors reflect difficulty in switching from a previously successful rule to a new rule. Higher numbers of perseverative errors on this task indicate higher total scores and poorer test performance (Spreen et al., 2006).

3. *Boston Naming Test (BNT)*

The BNT was the only non-set-shifting test administered and was used to measure a type of language ability known as word retrieval. The test consists of 60 pictures of various objects shown to the participant in order of increasing difficulty (high- to low-frequency objects) (Figure 4). Each participant is given a time limit of 20s to correctly name all 60 images. If the participant fails to give the correct response, the examiner may give the participant the initial sound of the target word. The examiner scores each item + or – according to the scoring procedures (max score = 60). Higher scores indicate better performance in this test (Spreen et al., 1991). The Boston Naming Test (BNT) was used as a measure of discriminant validity to determine whether PFC findings are specific to cognitive set-shifting abilities and not cognitive functioning in general. The BNT is considered a measure of language ability that does not rely on PFC to the same extent as executive functioning measures (Lezak et al., 2012). Thus, the BNT was used as a negative control to ensure that GWC in PFC subregions were correlated only with set-shifting abilities.

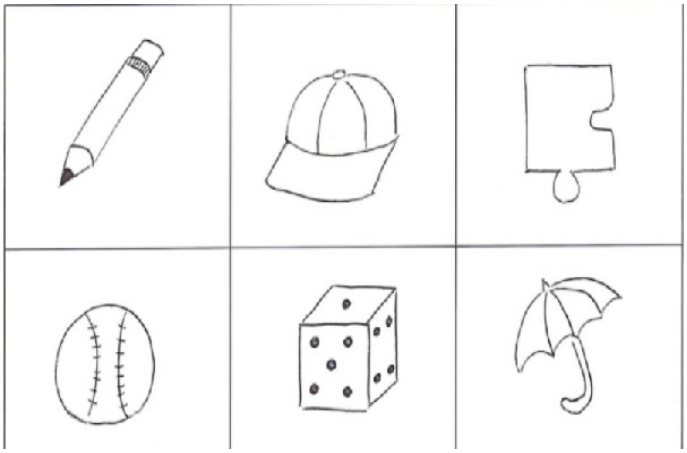

Figure 4. Reproduction of 6 images used for the Boston Naming Test (BNT). Participants are given 20 seconds to identify each individual object.

Statistical Analysis

GWC averages from each participant were calculated for the eight PFC regions of interest. TMT-B, WCST-PE and BNT test scores were available for each participant. Two-tailed Pearson correlation r-tests were run between mean GWC values in each ROI and scores from each neuropsychological test. Results were evaluated for statistical significance using a threshold of $p < .05$. This threshold was adjusted to account for multiple comparisons using the Bonferroni correction, requiring division of the p-value threshold by the number of tests administered for each dependent variable. Given that eight different ROIs were tested for each dependent variable, the p-value of .05 was divided by eight to determine a Bonferroni threshold of $p < .00625$.

RESULTS

Five regions were found to have GWC values significantly correlated with at least one set-shifting test (Figures 5-7). All significant correlations were positive and linear; increased GWC was associated with increased set-shifting scores, indicating worse performance. Out of the eight PFC subregions, four regions had GWC values that were significantly correlated with WCST-PE scores (M = 8.4 perseverative errors, SD = 6.3): the left superior frontal gyrus, right superior frontal gyrus, left middle frontal gyrus (dorsolateral PFC) and left ventrolateral PFC (Broca's). In addition, four regions had GWCs that were significantly correlated with TMT-B scores (M = 71.1 seconds, SD = 41.2): the left ventrolateral PFC (Broca's), right middle frontal gyrus (dorsolateral PFC), left superior frontal gyrus and the right superior frontal gyrus. No correlations were found between the Boston Naming Test scores (BNT) (M = 53.2 correct identifications, SD = 5.0) and any of the eight PFC subregions (M GWC of all eight ROIs = -0.13, SD = 0.011). Table 4 shows the mean GWC of all eight ROIs and the standard deviation.

GWC and Trail Making Test B (TMT-B)

Correlations between GWC values from the eight PFC subregions and each participant's TMT-B score were analyzed. GWC values in four regions were found to have significant correlations with TMT-B performance after adjustment for multiple comparisons: the left ventrolateral PFC (Broca's area) (r = .36, p = .005), the right middle frontal gyrus (dorsolateral PFC) (r = .39, p = .002), the left superior frontal gyrus (r = .40, p = .002) and the right su-

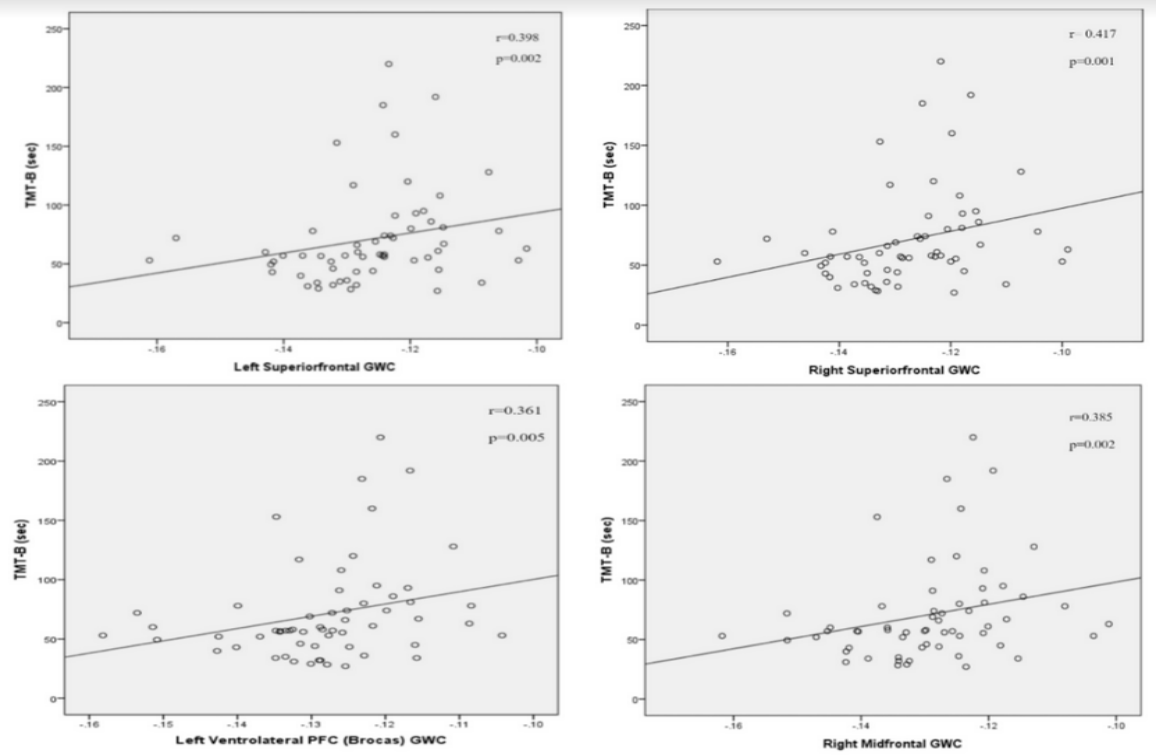

Figure 5. The scatter plots show the relationship between the time for the participants to complete TMT-B. (A) left superior frontal gyrus, (B) right superior frontal gyrus, (B) left ventrolateral gyrus, and (D) right middle frontal gyrus GWB. Longer time for TMT-B completion reflects poorer performance and greater values for GWB.

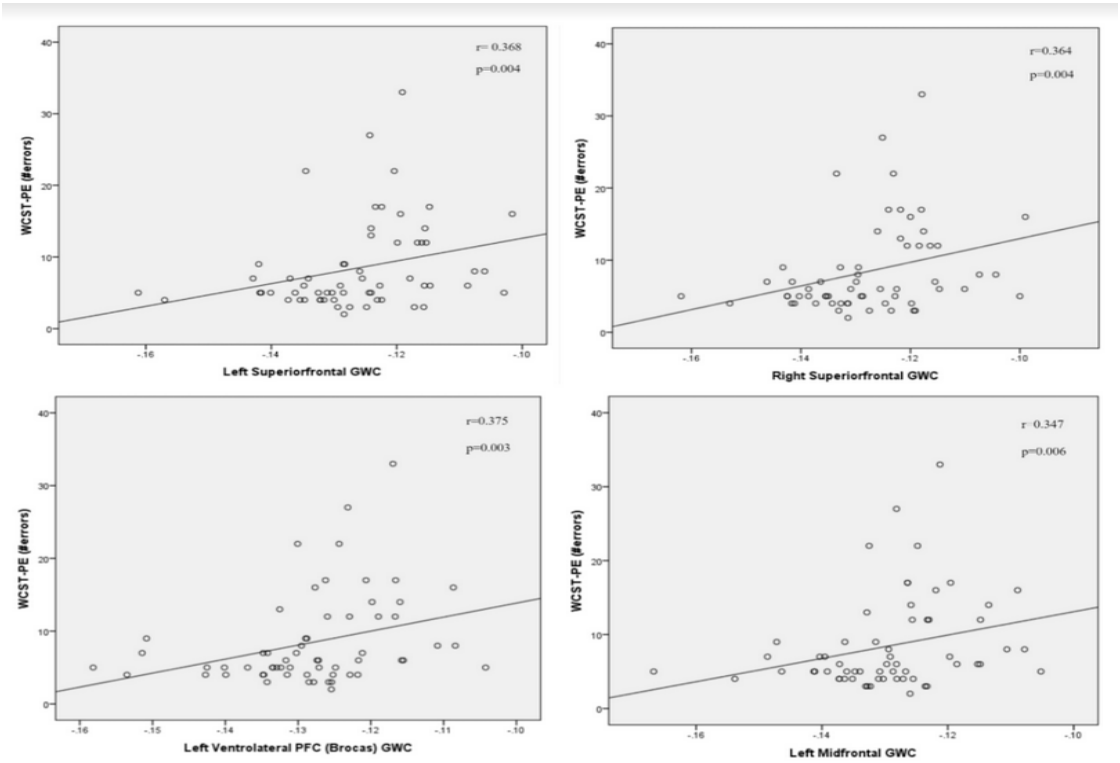

Figure 6. The scatter plots show the relationship between the time for the participants to complete WCST-PE. (A) left superior frontal gyrus, (B) right superior frontal gyrus, (C) left ventrolateral gyrus, and (D) left middle frontal gyrus GWB. Greater number of errors on WCST-PE reflects poorer performance and greater values for GWB.

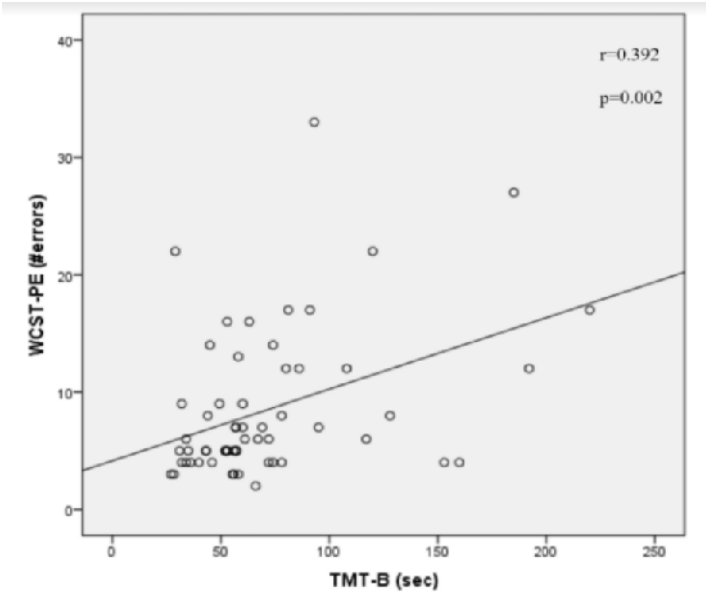

Figure 7. The scatterplot shows the relationship between the number of participants' WCST preservative errors and their time to complete TMT-B. Greater number of errors on WCST-PE reflects poorer performance and longer time for TMT-B completion reflects poorer performance.

Table 1. Correlation coefficients *r* and *p*-values for correlations between GWC of all brain regions tested with TMT-B and WCST-PE neuropsychological test performance. Values with asterisks are significant after Bonferroni correction for multiple comparisons.

PFC Region GWC	TMT- B	WCST-PE	BNT
Left Ventrolateral Gyrus	$r = 0.36$	$r = 0.38$	$r = 0.079$
	$p = 0.005$*	$p = 0.003$*	$p = 0.547$
Left Middle Frontal Gyrus	$r = 0.34$	$r = 0.35$	$r = 0.075$
	$p = 0.007$	$p = 0.006$*	$p = 0.570$
Left Superior Frontal Gyrus	$r = 0.40$	$r = 0.37$	$r = 0.066$
	$p = 0.002$*	$p = 0.004$*	$p = 0.618$
Left Orbitofrontal Cortex	$r = 0.13$	$r = 0.27$	$r = 0.121$
	$p = 0.341$	$p = 0.038$	$p = 0.355$
Right Ventrolateral Gyrus	$r = 0.33$	$r = 0.27$	$r = 0.089$
	$p = 0.009$	$p = 0.039$	$p = 0.501$
Right Middle Frontal Gyrus	$r = 0.39$	$r = 0.33$	$r = 0.041$
	$p = 0.002$*	$p = 0.009$	$p = 0.754$
Right Superior Frontal Gyrus	$r = 0.42$	$r = 0.36$	$r = 0.064$
	$p = 0.001$*	$p = 0.004$*	$p = 0.625$
Right Orbitofrontal Gyrus	$r = 0.17$	$r = 0.24$	$r = 0.027$
	$p = 0.190$	$p = 0.067$	$p = 0.836$

Table 2. Mean and standard deviation of demographics: age at time of scan, age at time of neuropsychology examination, and years of education of all the subjects.

	Age at Time of Scan	Age at Time of Neuropsych	Years of Education
Mean	31.9	33.4	15.9
Standard Deviation	13.3	13.2	1.9

Table 3. Correlations between the three neuropsychology tests; values with asterisks are significant after Bonferroni correction for multiple comparisons.

	WCST-PE	BNT
TMT-B	$r = 0.39$	$r = 0.22$
	$p = 0.002$*	$p = 0.088$
BNT	$r = 0.15$	----
	$p = 0.266$	----

perior frontal gyrus ($r = .42$, $p = .001$). GWC values from the four remaining ROIs did not have significant correlations with TMT-B performance after adjustment for multiple comparisons: the right ventrolateral PFC ($r = .33$, $p = .009$), left middle frontal gyrus ($r = .34$, $p = .007$), left orbitofrontal cortex ($r = .13$, $p = .341$) and right orbitofrontal cortex ($r = .17$, $p = .190$) (Figure 5).

GWC and Wisconsin Card Sorting Test-Perseverative Errors (WCST-PE)

Correlations between GWC values from the eight PFC subregions and each participant's WCST-PE score were analyzed. GWC values in four regions were found to have significant correlations with WCST-PE performance after adjustment for multiple comparisons: the left ventrolateral gyrus (Broca's area) ($r = .38$, $p = .003$), the left middle frontal gyrus ($r = .35$, $p = .006$), the left superior frontal gyrus ($r = .37$, $p = .004$) and the right superior frontal gyrus ($r = .36$, $p = .004$). GWC values from the four remaining ROIs did not have significant correlations with WCST-PE performance after adjustment for multiple comparisons: right ventrolateral PFC ($r = .27$, $p = .039$), right middle frontal gyrus ($r = .33$, $p = .009$), left orbitofrontal cortex ($r = .27$, $p = .038$) and right orbitofrontal cortex ($r = .24$, $p = .067$) (Figure 6).

GWC and Boston Naming Test (BNT)

There were no significant correlations between GWC values from the eight ROIs and BNT performance: the left ventrolateral gyrus (Broca's area) ($p = .547$), left middle frontal gyrus ($p = .570$), left superior frontal gyrus ($p = .618$), right superior frontal gyrus ($p = .625$), right ventrolateral gyrus ($p = .501$), right middle frontal gyrus ($p = .754$), left orbitofrontal cortex ($p = .355$), and right orbitofrontal cortex ($p = .836$) (Table 3).

TMT-B & WCST-PE and BNT

It was found that TMT-B performance was significantly correlated with WCST-PE performance (r = .392, p = .002) (Figure 7). Both TMT-B performance (p = .088) and WCST-PE performance (p = .266) were not significantly correlated with BNT.

DISCUSSION

Correlations between PFC GWC and set-shifting abilities were analyzed in 61 healthy participants. This study tested for five factors: 1) a positive correlation of GWC in the left and right hemisphere superior frontal gyri with TMT-B and WCST-PE test scores; 2) no correlation of GWC in the left or right OFC with TMT-B and WCST-PE test scores; 3) a positive correlation of GWC in the left ventrolateral PFC with TMT-B and WCST-PE test scores; 4) a positive correlation of GWC in the left and right middle frontal gyri (dorsolateral PFC) with performance TMT-B and WCST-PE test scores; and 5) no correlations of GWC in any PFC region with performance on the BNT. The results are consistent with these hypotheses. One slight incongruence between our hypotheses and results is that the left and right middle frontal gyri (dorsolateral PFC) were split in their correlations with set-shifting performance. GWC in the left middle frontal gyrus was correlated with only WCST-PE scores, whereas GWC from the right middle frontal gyrus was correlated with only TMT-B scores. These findings suggest that set shifting is not controlled by the entire PFC, but by certain PFC subregions instead, and that different types of set shifting are correlated with different patterns of PFC subregion involvement.

Few existing studies map PFC subregions to specific functions. One domain of cognition that is thought to be localized to the PFC is a set of processes known as executive functions. This study focused on a type of executive function known as set shifting, or the ability to alternate between two or more tasks. There are multiple types of set shifting that vary based on the additional component of processes involved (i.e., visual or motor). Some studies have localized set-shifting ability to the frontal parietal area; however, findings have been inconsistent due to methodological differences across studies (Pa et al., 2010). The effects of these differences are particularly amplified in studies of higher-order cognition due to the vast and relatively unknown networks involved. In order to maintain a narrower focus, this study concentrated on a few subregions within the PFC and just two types of set shifting. Although this decreased the scope of the study, it allowed for a more thorough analysis of a brain region previously implicated in set-shifting abilities, and the Desikan parcellation method allowed for increased localization specificity. Previous functional neuroimaging studies have found that lateral frontal lobe areas are most vital to set shifting (Pa et al., 2010). This study analyzed six lateral frontal lobe areas and two orbital frontal lobe areas. Orbital regions of the frontal lobe have not been found to correlate with set-shifting ability and thus served as negative controls in the set shifting correlation analyses (Bissonette et al., 2013).

GWC was used to measure the structural integrity of the PFC regions, as it is a marker of cortical development and myelin density. Interruptions during normal brain development can cause neurons to get stuck in the white matter during neuronal migration, resulting in increased GWC. Blurring of gray and white matter in certain brain regions has been correlated with decreased performance on neuropsychological tests of cognitive performance, such as the Wechsler Adult Intelligence Scale (WAIS), Boston Naming Test (BNT) and Controlled Oral Word Association (FAS and CFL) (Blackmon et al., 2011). Moreover, correlations between PFC structures and set shifting have been found in certain animals such as monkeys, rats, and mice (Bissonette et al., 2013). Expanding upon these works, this study demonstrates how set shifting is associated with GWC in different PFC regions in healthy adults.

Both the set-shifting neuropsychological tests used, TMT-B and WCST-PE, require attention, working memory, visual search and executive-functioning abilities to varying extents (Fujiki et al., 2013). Higher TMT-B scores reflect difficulty in switching mental sets between sequencing numbers and letters, whereas higher WCST-PE scores reflect difficulty in relinquishing a previously established rule set that is no longer successful (Pa et al., 2010). Participants who had greater GWC in their left and right superior frontal gyri, left and right middle frontal gyri (dorsolateral PFC) and left ventrolateral PFC all displayed increased performance on either TMT-B or WCST-PE.

Left and Right Hemisphere Superior Frontal Gyri GWC Associations with TMT-B and WCST-PE Performance

Preexisting studies have tied the left superior frontal region to a different executive function, working memory (du Boisgueheneuc et al., 2006), and the right superior frontal region to self-focused reappraisal abilities (Falquez et al., 2014). The positive correlation between the participants' GWC values of both the left and right superior frontal gyri to both TMT-B and WCST-PE scores indicate that these regions are essential to set shifting.

Left (Broca's) and Right Ventrolateral PFC GWC Associations with TMT-B and WCST-PE Performance

The left ventrolateral PFC is part of Broca's area, which normally associated with speech production. Studies have shown that the left ventrolateral PFC is also essential to working memory (Thothathiri, Schwartz, & Thompson-Schill, 2010). The right ventrolateral PFC, on the other hand, is associated with motor inhibition (Levy, & Wagner, 2011) but no other executive functions. This previous research is consistent with findings from the current study: the left ventrolateral PFC was correlated with both TMT-B and WCST-PE, whereas the right ventrolateral PFC was correlated with neither.

Left and Right Middle Frontal Gyri (Dorsolateral PFC) GWC Associations with TMT-B and WCST-PE Performance

The right middle frontal gyrus has been associated with reorienting attention from exogenous to endogenous attentional control (Japee, Holiday, Satyshur, Mukai, & Ungerleider, 2015), whereas the role of the left middle frontal gyrus is largely unknown. The

mid frontal region in this study had split results with each hemisphere's GWC correlating with only one of the two tests. The left middle frontal region had a significant association with WCST-PE, while the right middle frontal region had a significant association with TMT-B. The right middle frontal gyrus' significant correlation with TMT-B might signify that the right middle frontal gyrus controls functions that TMT-B specifically tests, such as visual attention and graphomotor control. In contrast, the left middle frontal gyrus was significantly correlated with WCST-PE, which suggests that this brain region controls functions that the WCST-PE tests, such as cognitive response inhibition and generation of novel problem-solving strategies.

Left and Right Orbitofrontal Cortex (OFC) GWC Associations with TMT-B and WCST-PE Performance

The OFC is known to be essential in processing rewards and punishments (Kringelbach, 2004). The OFC contains the secondary taste cortex, secondary olfactory receptors and tertiary olfactory receptors (Rolls, 2004). No previous studies have tied the orbitofrontal cortex to set shifting, and as expected there were no correlations between the left or right OFC with either test.

PFC GWC Associations with the BNT

The Boston Naming Test was used to establish discriminant validity by demonstrating that GWC in prefrontal regions is correlated with cognitive set shifting specifically and not cognitive functioning in general. The fact that the two cognitive set shifting measures were not correlated with the BNT provides support that the BNT is an independent measure of cognitive function unrelated to cognitive set shifting. Prior studies have demonstrated that intact performance on the BNT requires temporal lobe integrity, rather than frontal lobe (Loring et al., 2008). Results from current study confirmed this as no PFC regions correlate with the BNT. It is unclear whether GWC in temporal lobe regions is correlated with BNT scores; however, this would be a valuable hypothesis to test in future studies. Most regions tested in this study have no correlation with speech production or speech comprehension except for the left superior frontal gyrus, and, as expected, GWC in these areas did not correlate with the BNT. Even the left superior frontal gyrus did not correlate with the BNT, which supports the theories that slow deterioration of Broca's area can trigger compensatory mechanisms from surrounding areas (Plaza, Gatignol, Leroy, & Duffau, 2009). Since GWC is not an abrupt occurrence, neural plasticity is able to compensate for the deterioration of function.

Neuropsychology Test Associations (TMT-B, WCST-PE, BNT)

Since both TMT-B and WCST-PE test for set shifting, their correlation was highly significant as expected. However, the difference between the tests could be observed in the mid frontal gyrus. The two tests assessed different cognitive functions in addition to set-shifting ability. Using cards with pictures of various colors and shapes, WCST-PE tested response inhibition and novel problem solving as the participant had to inhibit a prior response pattern that was no longer successful and use trial and error to solve for the hidden rule. TMT-B, on the other hand, evaluated sequencing and visual attention when the participant had to connect dots in alphanumerical order. Both TMT-B and WCST-PE did not correlate significantly with BNT since BNT measures confrontational word retrieval whereas both TMT-B and WCST-PE focus mainly on executive functioning.

Although this study was conducted methodically with the use of the same scanner, processing steps and neuropsychological tests in each participant, the research could have been improved in several ways. One way would be to consider measures of frontal white matter integrity such as those acquired from diffusion tensor imaging. Numerous studies have shown the impact of white-matter hyperintensities and compromised fiber tracts on impaired set-shifting performance among other executive function abilities (Perry et al., 2009). This study was conducted in 61 participants, a population which could have possibly restricted the generalizability of the findings to patient populations and limited the amount of variance in the data, so further studies may benefit from a larger sample size. Also, there was a wide range of ages among the participants, which should be restricted in future studies.

The next steps would be to develop treatment options for people with executive dysfunctions. Currently, there are no specific medications that help people struggling with these problems. As cognitive set-shifting deficits may be related to certain behaviors of those diagnosed with autism spectrum and individuals diagnosed with ADHD, this research could be essential in developing treatments for these conditions. Future directions for similar research need to focus on whether white-matter integrity in the PFC subregions show a similar pattern of results in repeated trials. Moreover, this study tested not only set-shifting ability, but also other skills sets such as sequencing and working memory. Controlling for component processes to isolate set-shifting ability could have led to confounding interactions between component processes (Pa et al., 2010). In addition, instead of using a test to assess set-shifting ability along with component processes simultaneously, an alternative test, the Design Fluency (DF) test, could be used to assess solely set-shifting abilities. In the Design Fluency test, participants first connect filled dots while avoiding the empty dots and then connect the empty dots while avoiding the filled dots. The test breaks down into three different criteria: elimination of extraneous component processes, generation of original ideas and provision for the allowance of the participant to focus on set shifting. Future tests should determine whether this test is correlated with TMT-B and WCST-PE and show a similar pattern of correlations with GWC in PFC subregions.

CONCLUSION

In sum, this study demonstrates a positive correlation between cognitive set-shifting ability and GWC in specific parts of the PFC. This investigation tested eight different PFC regions that previous studies have marked as controls of the set-shifting abilities, or that can be useful in verifying some hypotheses which were made prior to this study. Our experimental method--using WCST-PE, TMT-B and BNT--showed that GWC in circumscribed regions of the PFC

correlated with WCST-PE and TMT-B. WCST-PE correlated with GWC values in the left ventrolateral gyrus (Broca's), the left and right superior frontal gyrus, and the left mid frontal gyrus. TMT-B correlated with the left ventrolateral gyrus (Broca's), the left and right superior frontal gyrus, and the right mid frontal gyrus. The right ventrolateral gyrus (Broca's) and the left and right OFC were not correlated with any of the tests. This study will provide opportunities for future research to target the specific areas of the prefrontal cortex that are inhibited in people who struggle with set shifting. As a result of these findings, potential treatments can be designed to aid individuals with disorders such as autism, Down's syndrome and ADHD that impair set-shifting abilities.

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