Journal of
Emerging Investigators

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

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Summary

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 measure of brain structural integrity is the intensity contrast between cortical gray and white matter (GWC), with greater contrast indicating better development. This study tested whether GWC in 8 subregions of the Prefrontal Cortex (PFC) was associated with set-shifting abilities in 61 healthy controls. 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.

Received: December 11, 2016; **Accepted:** August 10, 2017; **Published:** January 10, 2018

Introduction

Executive functions are a set of cognitive processes essential in organizing and monitoring behaviors conducive to the attainment of a goal. There are 3 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) (2). Some of the most basic executive functions, such as working memory and inhibitory control, can be observed early in infants. Further development of more complex executive functions, including cognitive flexibility, allows adults to complete challenging tasks. Many of these occupational tasks are coordinated and completed in the prefrontal cortex (PFC) (3). Brain-lesion studies suggest that the PFC plays an important role in executive functioning (4), but the specific regions within the PFC that are relevant have yet to be fully characterized.

This investigation used both qMRI and neuropsychological measures to investigate which PFC subregions have the strongest relationships with a task known as cognitive set-shifting. Cognitive set-shifting involves alternating between one task and another, such as solving a math problem and 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, and has been noted in conditions such as autism spectrum disorder, Alzheimer's dementia, major depression disorder, and other neuropsychiatric conditions (7). More generally, difficulty in set-shifting can indicate a deficiency in executive function (6). Conversely, enhanced cognitive flexibility enables individuals to focus their attention on a number of different tasks, allowing them to switch gears when necessary.

Structurally, the PFC contains both gray and white matter. Gray matter is mainly comprised of cell bodies, dendrites, and unmyelinated axons (5). It enables muscle movement by directing motor stimuli to neurons in the central nervous system (CNS) and contains glial cells 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 neurons to send faster action potentials. Gray and white matter regions complement each other, working together to relay impulses quickly and efficiently.

Gray-white matter contrast (GWC) measures the intensity of contrast between gray and white matter (**Figure 1**). GWC is determined by computing the ratio of signal intensity values in the gray matter above the gray-white junction to signal intensity values in the white matter below (9). 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. These measures act as a mediator group to calculate differences in cognitive performance between patients with epilepsy and healthy controls (9).

We explored the correlation between set-shifting abilities and scores and average GWC in eight prefrontal regions: 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 orbitofrontal regions were chosen as negative controls because orbital regions of the frontal lobe have not been found to correlate with set-shifting ability (4). Two neuropsychological tests were used to assess set-shifting abilities: Trail Making Test-B (TMT-B) and the Wisconsin Card Sorting Test Perseverative Errors (WCST-PE).

We hypothesized that as GWC increased, study participants would demonstrate lower scores on TMT-B and WCST-PE tests indicating better cognitive set-shifting skills. Furthermore, we predicted that there would be a positive correlation of GWC of the left-and right-hemisphere superior frontal gyri with TMT-B and WCST-PE scores. In addition, there would be no correlation of GWC in the left or right orbitofrontal cortex (OFC) with TMT-B and WCST-PE scores. There would also be a positive correlation of GWC of the left ventrolateral PFC with TMT-B and WCST-PE scores, GWC in the left and right middle frontal gyri (dorsolateral PFC) with TMT-B and WCST-PE scores, and no correlations of GWC in any of the prefrontal lobe brain regions with performance on the BNT.

We found that 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.

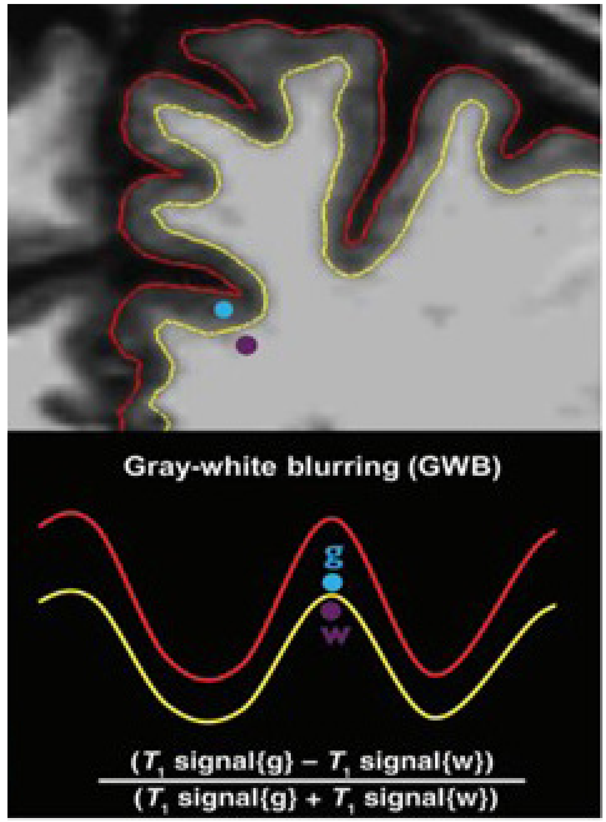

Figure 1: The Gray/White Matter Junction. This figure shows a T1-weighted MPRAGE image with the yellow line representing gray-white (GW) junction and a red line representing pial surface. The blue and purple dots represent the location of the gray matter and white matter respectively. Both gray and white matter intensity valued at 0.5mm relative to the GW junction.

Results

In the present study, two neuropsychological tests were used to assess set-shifting abilities: Trail Making Test-B (TMT-B) and the Wisconsin Card Sorting Test Perseverative Errors (WCST-PE). TMT-B involves connecting dots in an alphanumeric sequence and continually switching between letters and numbers (**Figure 2**). It has been shown to be effective in determining cognitive set-shifting ability. In WCST, the participant is given several stimulus cards of various images and has to place each in one of the four piles set by the test conductor (**Figure 3**). Scoring is based on the participant's number of perseverative errors. These errors reflect difficulty in switching from a previously successful rule to a new rule. Higher numbers of perseverative errors on this task indicate poorer set-shifting ability. Both set-shifting tests used, TMT-B and WCST-PE, require attention, working memory, visual search, and executive-functioning abilities to varying extents (9).

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 (8). This test requires participants to name images of various items that are presented to them on cards (**Figure 4**). As a language measure, it relies on functions localized in the temporal lobe. Thus, the BNT was used as a negative control to ensure that gray-white contrast (GWC) in PFC subregions were correlated only with set-shifting abilities.

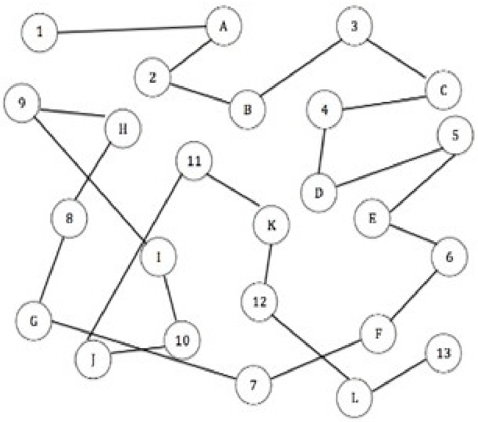

Figure 2: TMT-B Test. Example of Trail Making Test-B reproduc-tion. Participants trace a sequence alternating between numbers and letters in ascending order (set-shifting).

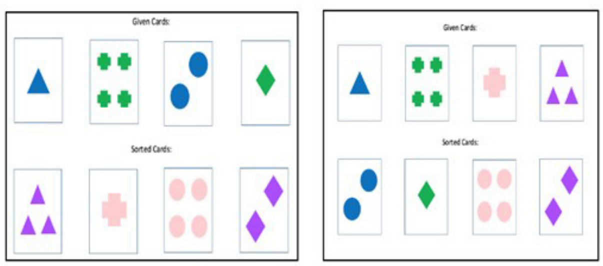

Figure 3: WCST-PE Test. Reproduction of cards used for the Wisconsin Card Sorting Test-Perseverative Errors (WCST-PE). Participants match their cards with other cards according to a hidden rule determined by the test proctor. On the left hand side, cards were sorted by shape. On the right hand side, cards were sorted by color. Both tests are required for this examination.

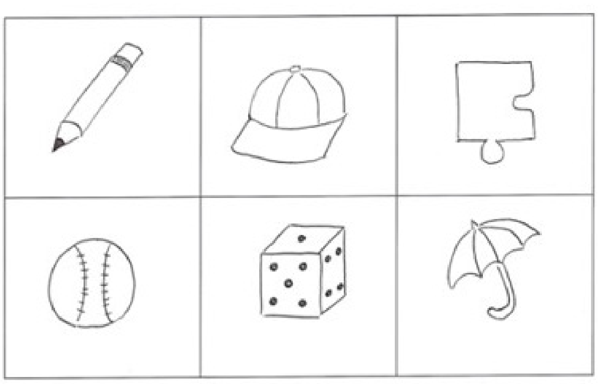

Figure 4: Boston Naming Test. Reproduction of 6 images used for the Boston Naming Test. Participants are given 20 seconds to identify each individual object. The objects are from the left to right top, a pencil, a cap, and a puzzle piece, and left to right bottom, a baseball, a die, and an umbrella.

Five regions were found to have GWC values significantly correlated with at least one set-shifting test (**Figure 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) (**Figure 5**). 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 (**Figure 6**). No correlations were found between the Boston Naming Test (BNT) scores (M = 53.2 correct identifications, SD = 5.0) and any of the eight PFC subregions (M GWC of all eight ROIs = -0.13).

GWC and Trailmaking Test B (TMT-B)

Correlations between GWC values from the eight PFC subregions and each person's TMT-B score were analyzed (**Figure 6**). 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 = 0.36, p = 0.005), the right middle frontal gyrus (dorsolateral PFC) (r = 0.39, p = 0.002), the left superior frontal gyrus (r = 0.40, p = 0.002), and the right superior frontal gyrus (r = 0.42, p = 0.001). All p values less than 0.05 were significant and the r-values closer to a value of 1.0 represented a stronger correlation. 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 = 0.33, p = 0.009), left middle frontal gyrus (r = 0.34, p = 0.007), left orbitofrontal cortex (r = 0.13, p = 0.341), and right orbitofrontal cortex (r = 0.17, p = 0.190) (Table 1).

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

Correlations between GWC values from the eight PFC subregions and each person's WCST-PE score were analyzed (**Figure 5**). 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 = 0.38, p = 0.003), the left middle frontal gyrus (r = 0.35, p = 0.006), the left superior frontal gyrus (r = 0.37, p = 0.004), and the right superior frontal gyrus (r = 0.36, p = 0.004). 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 = 0.27, p = 0.039), right middle frontal gyrus (r = 0.33, p = 0.009), left orbitofrontal cortex (r = 0.27, p = 0.038), and right orbitofrontal cortex (r = 0.24, p = 0.067) (Table 2).

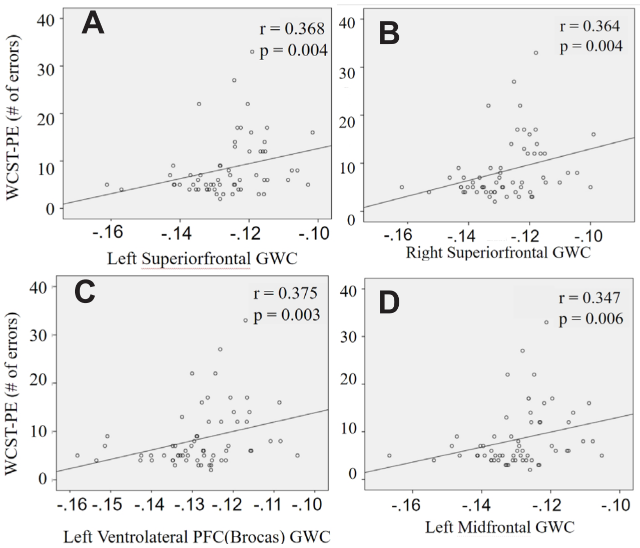

Figure 5: WCST Errors. The scatter plots show the relationship between the number of participants' WCST preservative errors and their (A) left superior frontal gyrus, (B) right superior frontal gyrus, (C) left ventrolateral PFC, (D) left middle frontal gyrus, and GWC. Greater number of errors on WCST-PE reflects poorer performance and greater values for GWC blurring.

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 = 0.547), left middle frontal gyrus (p = 0.570), left superior frontal gyrus (p = 0.618), right superior frontal gyrus (p = 0.625), right ventrolateral gyrus (p = 0.501), right middle frontal gyrus (p = 0.754), left orbitofrontal cortex (p = 0.355), and right orbitofrontal cortex (p = 0.836) (Table 2). In summation, PFC GWC was not associated with language-fluency abilities. This supports the hypothesis that GWC in PFC subregions is associated with set-shifting ability specifically and not cognitive functions in general.

TMT-B & WCST-PE and BNT

It was found that TMT-B performance was significantly correlated with WCST-PE performance (r = 0.392, p = 0.002) (**Figure 7**). Both TMT-B performance (p = 0.088) and WCST-PE performance (p = 0.266) were not significantly correlated with BNT. This supports an assumption from this study that TMT-B and WCST-PE are both measuring the same construct (set-shifting ability), whereas BNT is measuring a different construct (naming ability).

Discussion

Few studies have mapped PFC subregions to specific functions. One domain of cognition 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 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 (12). The effects of these differences are particularly amplified in studies of higher-order cognition, due to the vast and relatively unknown networks involved. 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 ((3). 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 (4).

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. Contrast of gray and white matter in certain brain regions has been correlated with decreased performance on neuropsychological tests

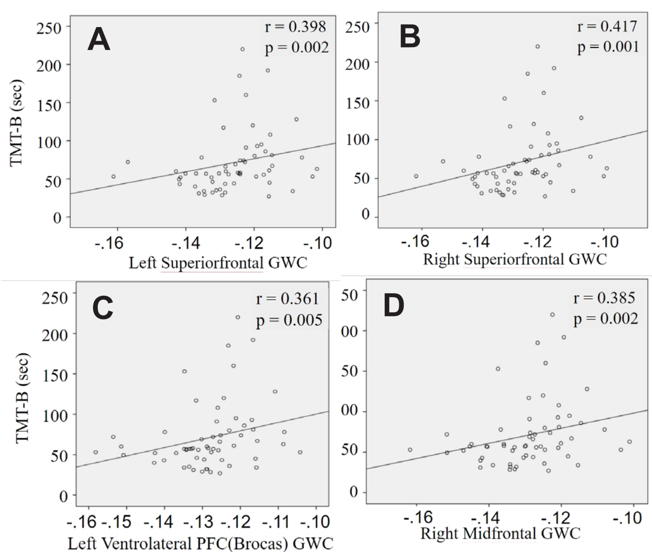

Figure 6: TMT-B Timing. The scatter plots show the relationship between the time for the participants to complete TMT-B and their (A) left superior frontal gyrus, (B) right superior frontal gyrus, (C) left ventrolateral gyrus, and (D) right middle frontal gyrus GWC. Longer time for TMT-B completion reflects poorer performance and greater values for GWC.

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

Table 2: Correlations between the Three Neuropsych Tests. * = significant after Bonferroni correction for multiple comparisons.

of cognitive performance, such as the Wechsler Adult Intelligence Scale (WAIS), Boston Naming Test (BNT), and Controlled Oral Word Association (FAS and CFL) (1). Moreover, correlations between PFC structures and set-shifting have been found in certain animals such as monkeys, rats, and mice (2). Expanding upon these works, this study demonstrates how set-shifting is associated with GWC in different PFC regions in healthy adults.

Both set-shifting tests used, TMT-B and WCST-PE, require attention, working memory, visual search, and executive-functioning abilities to varying extents (9). 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 (12). 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.

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. Unexpectedly, 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 instead by certain PFC subregions, and, further, that different types of set-shifting are correlated with different patterns of PFC subregion involvement.

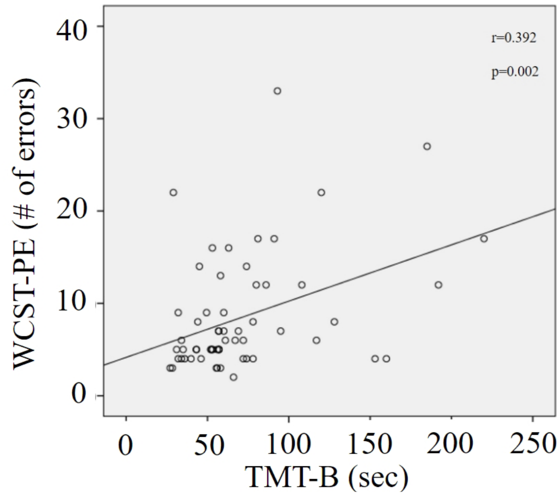

Figure 7: Correlation between Participant WCST-PE and TMB-B. The scatterplot shows the relationship between the number of participants' WCST perseverative errors and their time to complete TMT-B. Greater number of errors on WCST-PE reflects poorer performance and longer time for TMT-B completion reflects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

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

Previous studies have tied the left superior frontal region to a different executive function, working memory (9), and the right superior frontal region to self-focused reappraisal abilities (12). The current study built on these trials by tying human GWC values of both the left and right superior frontal gyri to both TMT-B and WCST-PE performance/set-shifting abilities.

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, normally associated with speech production. Studies have shown that the left ventrolateral PFC is also essential to working memory (13). The right ventrolateral PFC, on the other hand, is associated with motor inhibition (14) 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 middle frontal region 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

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

Table 3: Correlation Coefficients r and p-values for correlations between GWC of all brain regions tested with TMT-B and WCST-PE neuropsychological test performance. * = significant after Bonferroni correction for multiple comparisons.

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 indicates 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 thought to be essential in processing reward and punishment (14). The OFC contains the secondary taste cortex, secondary olfactory receptors, and tertiary olfactory receptors (15). These don't have any correlation with executive functioning and set-shifting, and as expected there were no correlations of 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, rather than frontal lobe, integrity (16) . Results from the current study suggest that the relationship between GWC in PFC subregions and neuropsychological test performance is specific to cognitive set-shifting. 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 theories that slow deterioration of Broca's area can trigger compensatory mechanisms from surrounding areas (17). Given that GWC does not happen abruptly, 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. Even though the tests were significantly correlated, subtle differences exist between the tests, and this difference 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 numerical order. Neither TMT-B nor WCST-PE correlated significantly with BNT, since BNT measures

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

Table 3: 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.

confrontational word retrieval while TMT-B and WCST-PE focus mainly on executive functioning.

Materials and Methods

Participants

For this study, 61 healthy adults (31 male/30 female) 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. They ranged from 15 to 70 years of age at the time of scanning (M = 31.94 years, SD = 13.34) (Table 3). 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 Siemens Allegra head-only MRI scanner. Image acquisition included a conventional three-plane localizer and two T1-weighted gradient-echo sequence (MPRAGE) volumes (TE = 3.25 ms, TR = 2530 ms, TI = 1.100 ms, flip angle = 7°, FOV = 256mm, voxel size = 1 X 1 X 1.33 mm). 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 0.5 mm above and below the gray-white interface with trilinear interpolation. These values were used to create a ratio score:

$$\frac{\text{Gray - White}}{\text{Gray + White}}$$

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 (10). GWC values ranged from -1 to 0, where scores closer to zero represent higher degrees of contrast around the gray-white inner surface. Mean GWC values were extracted for each participant for each of the following regions of interest (ROI): 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

Trail Making Test-B (TMT-B)

TMT-B is designed to test an individual's set-shifting ability through a task that involves changing the rule for connecting dots (**Figure 2**). 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 on this test and thus poorer set-shifting ability (11).

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

The WCST-PE is 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 tells the participant only whether the match is correct or incorrect. Once the participant correctly identifies the rule, the test proctor changes it without telling the participant. 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. 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 (11).

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 20 seconds to correctly name all 60 images. If the patient fails to give the correct response, the examiner may give the patient 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 on this test (11).

Statistical Analysis

GWC averages from each healthy control were calculated for the 8 PFC regions of interest. TMT-B, WCST-PE, and BNT test scores were available for each healthy control. Two-tailed Pearson correlation r-tests were run between mean GWC values in each region of interest (ROI) and scores from each neuropsychological test. Results were evaluated for statistical significance using a threshold of $p < 0.05$. This threshold was adjusted to account for multiple correlations using the Bonferroni correction and to control the false discovery rate (FDR). Bonferroni correction required 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 0.05 was divided by eight to determine a Bonferroni threshold of $p < 0.00625$. The Bonferroni correction equation is $(1 - \alpha')k = 1 - \alpha$ where k represents the number of individual tests performed and α represents the overall significance level of the individual tests.

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.

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