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Abstract

Cognitive flexibility, or the ability to change behavior or cognitive action appropriately in response to context shifts, is crucial to college-level learning, as it is needed for solving problems that require a transfer of familiar knowledge to novel concepts. Cognitive flexibility is known to involve neural areas concentrated in the frontal lobes, such as the inferior and superior frontal gyri and the anterior cingulate cortex, but the activation of this network is typically weaker in the ADHD population. In academic settings, individuals with ADHD tend to perform below healthy peers, have lower GPAs, are more likely to be on academic probation, and have decreased motivation. While most of these downfalls are attributed to attentional deficits, no investigations have been done to assess any effects of cognitive flexibility on academic performance. Therefore, this study used the Wisconsin Card Sorting Task (WCST) in the fMRI to assess cognitive flexibility in college students with and without ADHD and compared task performance to academic performance to determine if there is any relationship. We found that the ADHD group presented more perseverative errors on the WCST, and this performance was negatively correlated to GPA, suggesting that cognitive flexibility deficits impair academic performance. We also observed decreased activation of the anterior cingulate cortex and inferior and superior frontal gyri in subjects with ADHD as compared to controls, suggesting a possible neural network involved in these behavioral deficits.

Cognitive Flexibility and Academic Performance in College Students with ADHD: An fMRI Study

In 1962, cognitive flexibility was defined as the ability of an individual to change their behavior or cognitive action appropriately in response to environmental or context shifts (Scott, 1962). Such cognitive flexibility is crucial to college-level learning, as it is needed for solving problems that require a transfer of familiar knowledge to novel concepts (Spiro et al., 1987). In a study on teaching practices, Spiro and colleagues (1987) state that memorization is not an effective learning tool, as it does not allow for application during context shifts. They also suggested that effective problem solving relies on having a varied understanding of a single concept and urged teachers to present students with a repertoire of perspectives when teaching (Spiro et al., 1987). With this understanding, cognitive flexibility is critical for succeeding in higher education such as the intense academic environment of college.

The neural substrates involved in cognitive flexibility are highly concentrated in the frontal lobe and basal ganglia. A human study by Eslinger and Grattan (1993) observed the impact lesions in different areas of the brain had on two separate types of cognitive flexibility: reactive and spontaneous. “Reactive” flexibility refers to the ability to shift a cognitive response according to a change in context, while “spontaneous” flexibility is the constant flow of ideas spontaneously sought in response to an open-ended question (Eslinger & Grattan, 1993). They observed 40 subjects on reactive and spontaneous flexibility tests (10 with frontal lobe lesions, 10 with basal ganglia lesions, 10 with posterior lesions, and 10 with no lesions) to determine which general areas of the brain are most critical for each type of cognitive flexibility. Reactive flexibility was tested with the Wisconsin Card Sorting Test (WCST), which requires a shift in response when context rules change unannounced (Berg, 1948). Spontaneous flexibility was

tested with the Alternate Uses Test (AUT), which requires subjects to spontaneously create new uses of common objects (e.g., how would you use a newspaper besides for reading?).

Their results indicated that frontal lobe (FL) lesions significantly impaired both types of flexibility more so than the other lesion groups, with FL lesion subjects presenting an average of 64.9 perseverative errors (errors caused by not shifting response type when a context rule changes) on the WCST (control = 26.6) and only 1.5 alternate uses on the AUT (control = 12.7) (Eslinger and Grattan, 1993). Basal ganglia (BG) lesion subjects also exhibited more perseverative errors in the WCST (BG lesion subjects average = 52.6 errors) but were not significantly different from controls on the AUT, and posterior lesion subjects did not differ from controls on either task. These results indicate that the frontal lobe is necessary for both types of cognitive flexibility while the basal ganglia are only implicated in reactive flexibility (Eslinger & Grattan, 1993).

Further studies, summarized in a meta-analysis by Buchshaum and colleagues (2005), found that performance on the WCST was associated with activation of many of the neural areas in the frontal lobes and basal ganglia, including the anterior cingulate, prefrontal cortices, and insula (Buchsbaum, Greer, Chang, & Berman, 2005). A more detailed study by Monchi et al. (2001) analyzed neural activation using fMRI during six defined events during the WCST: receiving correct or incorrect feedback during test trials, sorting during test trials after a rule shift or after learning the rule, and matching during control trials. When subjects needed to sort cards after negative feedback surrounding rule shifts (when cognitive flexibility is necessary), they observed increased activation of the left putamen and left posterior regions of the PFC, posterior parietal cortex (BA 7), and right lateral premotor cortex (BA 6) (Monchi et al., 2001).

Cognitive Flexibility and Academics in ADHD

Cognitive flexibility deficits have been observed in individuals with Attention Deficit/Hyperactivity Disorder (ADHD; Tsuchiya, Oki, Yahara, & Fujieda, 2005) and may contribute to academic underachievement in students with ADHD. ADHD is characterized by age-inappropriate symptoms of impulsivity, hyperactivity, and inattention (American Psychiatric Association, 2013). It is estimated to occur in 3-7% of school-aged children and persists during adolescence and adulthood in 50-65% of cases (Weiss & Hechtman, 1993). Symptoms are often more noticeable in children due to disruptive behaviors and profound learning delays, while young adults exhibit more subtle cognitive and social deficits (Birchwood & Daley, 2012).

Observational studies on college students with ADHD have shown that they tend to perform below healthy peers, have lower GPAs, are more likely to be on academic probation, and have decreased motivation (Birchwood & Daley, 2012; Schwanz et al., 2007). Schwanz, Palm, and Brallier (2007) compared hyperactivity, impulsivity, and inattention levels to academic performance in college students with ADHD. They observed that inattention is the most significant predictor of academic struggles (as measured by GPA) in both ADHD and control populations, and that the size of this effect is equal to the effect of cognitive ability (Schwanz et al., 2007). This suggests that the attentional deficits in ADHD are related to academic underachievement, however, other factors, such as deficits in cognitive flexibility have not been investigated.

Cognitive flexibility deficits in ADHD are significant, with one study reporting that subjects with ADHD had more perseverative errors on the WCST than subjects with high-functioning autism, suggesting impairments in cognitive flexibility are more severe in ADHD than in high-functioning autism (Tsuchiya, Oki, Yahara, & Fujieda, 2005). A clinical study by

Schmitz et al. (2002) examined ADHD deficits seen in the three specific subtypes as defined by the DSM-IV: inattentive, hyperactive, and combined type (meaning both inattentive and hyperactive; American Psychiatric Association, 2013; Schmitz et al., 2002). The researchers assessed 30 adolescents (3 groups of 10, one for each subtype of ADHD) for cognitive flexibility using the WCST and observed that both ADHD-inattentive and ADHD-combined type had more total errors and a lower overall score than controls.

Interestingly, the ADHD-hyperactive type group performed similar to controls on all measures of executive function in this study, suggesting that the inattentiveness is a critical factor in cognitive performance, as was suggested by Schwanz and colleagues (Schmitz et al., 2002; Schwanz et al., 2007). Many similar studies have reported deficits in cognitive flexibility in ADHD populations (King, Colla, Brass, Heuser, & von Cramon, 2007; Schmitz et al., 2002; Tannock, Schachar, & Logan, 1995), but few have utilized neuroimaging to determine neural correlates of the deficits and none have related this deficit to academic performance.

In one imaging study, adults with persisting childhood ADHD performed similarly to controls (did not exhibit more errors) on cognitive switching tasks that required attention and cognitive flexibility (Cubillo et al., 2010). However, during these switch-tasks, subjects with ADHD exhibited lower levels of brain activation than controls in many areas: bilateral inferior frontal cortices, caudate, cingulate cortex, putamen, insula, and inferior parietal cortices. Cubillo et al. (2010) also reported significantly decreased functional connectivity between the thalamus and posterior cingulate in subjects with ADHD compared to controls. The authors suggested that adults were able to compensate for childhood deficits in some way, accounting for the matched task performance (Cubillo et al., 2010). This was an interesting finding because, while the

authors presented data suggesting a less-active neural network for cognitive flexibility in subjects with ADHD, there was no evidence for impaired function.

Deficits in cognitive flexibility have also been reported in animal models of ADHD using similar set-shifting tasks adapted for T-mazes and radial arm mazes. Kantak and colleagues (2008) used a common rat model of ADHD, spontaneous hypertensive rats (SHRs), and observed performance on a set-shifting task utilizing extradimensional shifts in SHRs and control rats that were either treated with a vehicle solution or with methylphenidate (Kantak et al., 2008). This set-shifting task used a radial arm maze in which the rats first learned to either choose an arm based on a visual cue or based on its own turn bias. To respond properly to the visual cue, the rats had to first enter the arm that was marked by a card with black and white stripes in order to gain a food reward. To respond properly to the turn bias condition, the rats had to first enter the arm opposite of the arm they chose most often during habituation to gain a food reward. Then, to assess set-shifting, after the rats learned the proper behavior in their first condition, the set was shifted and they had to respond according to the second condition (e.g., a rat first responded to the visual cue, but after learning that response, they had to respond to the bias condition in order to gain their reward).

Prior to methylphenidate or vehicle treatment, all SHRs exhibited more errors on the set-shifting task and needed more trials to learn the proper behavior than the control rats. These results provide more evidence for deficits in cognitive flexibility in the ADHD population. However, after treatment, only the SHRs treated with the vehicle solution exhibited this increase in errors, and the methylphenidate-treated SHRs performed comparatively to control rats. This suggests that the methylphenidate treatment, a common medication used to treat ADHD, was

effective at improving performance on the task and thus improving cognitive flexibility in the SHRs (Kantak et al., 2008).

Cognitive Flexibility and Methylphenidate

As previously mentioned, methylphenidate is a common medication prescribed to improve symptom management in individuals with ADHD. The previous rat study (Kantak et al., 2008) reported an improvement in cognitive flexibility in the rats treated with methylphenidate, and this improvement is also seen in humans. A study by Tannock, Schachar, and Logan (1995) administered varying doses of methylphenidate to subjects with ADHD to assess the effects of the medication on a change paradigm task. During this task, subjects responded with a fixed behavior (e.g., pushing a button) when given a signal. However, occasionally the signal would be followed by a second signal, and the subjects were required to inhibit that first behavior and instead do something else (e.g., moving an item). The researchers found that methylphenidate improved performance on this task (subjects were more reliably able to inhibit the first response and shift their behavior) in smaller doses, but larger doses did not affect task performance (Tannock, Schachar, & Logan, 1995). This suggests that proper doses of methylphenidate can improve cognitive flexibility functions in individuals with ADHD, but an improper dose (too high) may not provide any benefit to the individual.

A separate study by Rubia and colleagues (2011) used a stop-signal task in an fMRI scanner to assess the effects of methylphenidate on neural activation during error processing in boys with ADHD. While the stop-signal task does not directly assess cognitive flexibility, it can isolate the necessary network for error processing, which is a critical skill needed to be able to accurately adjust a response during rule shifts in flexibility tasks. In this study, subjects with ADHD were given either a clinical dose of methylphenidate or placebo before completing the

stop-signal task. During the task, subjects needed to respond to a visual cue by pressing a button. Throughout the task, the visual cue would be followed unpredictably by an auditory cue that signaled the subjects to inhibit that response, but the task is programmed such that all subjects will make errors on roughly 50% of these stop trials (Rubia et al., 2011).

The researchers observed decreased neural activation in the placebo-treated subjects with ADHD in many areas, including the anterior cingulate cortex, prefrontal areas such as the dorsomedial frontal cortex, and parts of the parietal lobe. However, subjects with ADHD who received methylphenidate treatment exhibited similar activation levels as the control subjects, indicating that methylphenidate treatment was able to normalize brain activations during cognitive tasks (Rubia et al., 2011). Such effects of methylphenidate could contribute to the amelioration of deficits seen in ADHD while medicated, but these effects are not long-lasting and constant medication is necessary.

Contradictions in the ADHD Literature

Other studies in both animal models and human subjects with ADHD have reported no deficits in cognitive flexibility. According to a familial study by Rommelse and colleagues (2007), children with ADHD and their unaffected siblings did not present evidence for deficits in cognitive flexibility. Subjects with ADHD were neither slower nor less accurate than control subjects when cognitive flexibility was assessed. The authors suggested that executive function deficits seen in ADHD may be due to deficits in lower order cognitive functions such as attention rather than directly affecting the higher order functions such as cognitive flexibility (Rommelse et al., 2007). This lack of finding where other studies have observed deficits in cognitive flexibility may be a result of the simpler flexibility paradigm used in this study in which the problem-solving rule is known to the subject and constant throughout the entire test, with

changes of context being signaled. Assessments such as the WCST require multiple problem-solving rules to be retained by the subject with context changes and rule shifts being unannounced. Complex paradigms such as this may require a higher level of cognitive flexibility that is impaired in subjects with ADHD, consistent with the overwhelming literature reporting cognitive flexibility deficits in ADHD. It may be argued that these tasks are particularly relevant to young adult college students with ADHD, who are in an academic environment requiring a high level of cognitive flexibility.

However, a recent animal study of ADHD not only reported a lack of cognitive flexibility deficits but also reported better set-shifting performance (the ability to change a response due to change in reward) in the ADHD model (Chess, Raymond, Gardner-Morse, Stefani, & Green, 2011). Spontaneously hypertensive rats (SHR; a rodent model of ADHD) were given a set-shifting test (which models closely the WCST for humans) utilizing a T-maze and food rewards. The T-maze had either smooth or rough arms that were either dark or light colors. Rats were rewarded for choosing the arm of a specific type (e.g., dark arm), and this was done repeatedly until they learned that response. However, after removing rats from the maze and allowing them the rest, the experimenters then administered an extradimensional shift after which the rats were rewarded for choosing the arm of a different type (e.g., rough arm). Surprisingly, the SHRs were faster at set shifting (learning to choose the rough arm) than control rats, contradicting the reported deficits in cognitive flexibility in ADHD.

The authors suggested this could be due to a memory deficit, where the SHRs forget the rule in set 1. To investigate this, the authors tested the extradimensional shift without a temporal delay to mitigate any memory requirements of the task. As expected, SHRs exhibited perseverative errors in arm choice when the unannounced shift in rule occurred (Chess et al.,

2011). Therefore, it is possible that SHRs were able to perform better than control rats in the first experiment because they had forgotten the first rule and began by trial and error, while the control rats still retained the first rule and had to extinguish that response before learning the new rule. Therefore, the results of the second experiment with no time delay are consistent with models suggesting cognitive flexibility deficits in ADHD.

The Current Study

In order to address contradictions in the literature and the few studies on the brain substrates responsible for cognitive flexibility deficits, we tested college students with and without ADHD on the WCST during fMRI brain imaging. As previously mentioned, the WCST is a hallmark assessment for executive function and cognitive flexibility. Because cognitive flexibility may be critical for academic performance, we collected GPA and academic-related information from ADHD and control subjects in order to examine relationships between cognitive flexibility and academic performance between groups.

With these measures, we tested three specific hypotheses:

1) subjects with ADHD will exhibit more perseverative errors on the WCST,

2) subjects with ADHD will have decreased activation in the neural network for cognitive flexibility (including prefrontal cortex and the basal ganglia) compared to controls, suggesting a neural mechanism for this deficit, and

3) the number of perseverative errors will be negatively correlated with GPA.

If these hypotheses are supported by the data, such results could then suggest potential neural correlates of the cognitive flexibility deficits in ADHD and link these deficits to GPA, providing another contributing factor to the decreased academic performance seen in the ADHD population.

Methods

Study Design

The current study was a between-subject, cross-sectional study that examined cognitive flexibility and academic performance in college students with and without ADHD. We compared cortical activation patterns during performance of the WCST in the fMRI scanner to identify neural correlates of cognitive flexibility between ADHD and controls.

Subjects

Thirteen (10 female and 3 male) non-smoking full-time college students (age 18-22) at the University of Vermont (UVM) participated in this study in two groups, ADHD (4 female and 0 male) and control (6 female and 3 male). Prior to study participation, subjects completed a phone screen where the following eligibility criteria were assessed: non-smoking status, full-time enrollment at UVM, meeting MRI safety requirements, right-handedness, and either having a formal diagnosis of ADHD or being a non-ADHD control. Non-smoking status, assessed via self-report, was defined as never regularly using tobacco products and having less than 100 cigarettes in their lifetime. Full-time enrollment was assessed via self-report, and class standing was recorded. A metal screening was completed in which subjects were asked if they had any of multiple implants or metallic devices. ADHD diagnosis was determined by self-report of prior diagnosis by a medical practitioner. ADHD symptoms were later characterized using the Conners' Adult ADHD Rating Scale (CAARS) to confirm ADHD phenotype (Conners, Erhardt, & Sparrow, 1998). Clinically significant symptoms are defined as having a *t* score above 65 (clinical status) on the Total ADHD Symptom subscale of this measure. A summary of subject characteristics is presented in Table 1.

If female, subjects reported whether they were or were not pregnant (this report was confirmed with a urine pregnancy test prior to MRI scanning). Subjects were excluded if they had MRI safety contraindications, were smokers, were left-handed, were pregnant, or were not full-time students at UVM. All ADHD subjects were required to abstain from using any prescribed ADHD medication on the day of their study visit. Upon successful completion of a phone screen, a study day visit was scheduled.

Study Day Procedures

Study days were scheduled either as one, 3.5-hour study visit or two, 2-hour visits. Subjects checked in to the University of Vermont Medical Center's Clinical Research Center (CRC). Informed consent was obtained before beginning the assessment battery, mock scanner training, and urine pregnancy test (for females). Upon providing informed consent, subjects completed several self-report and interview-style assessments. They were then trained on the control condition of the WCST in the mock scanner. Lastly, subjects completed the WCST (as part of a larger battery that included research measures for a colleague's separate ADHD study) in the MRI at the UVM MRI Center for Biomedical Imaging. Upon completion of the 60 minute scan, subjects were given $50 compensation and discharged from the CRC.

Assessment battery. Assessments to measure demographics, estimated full scale intelligence quotient (IQ), ADHD symptoms, and clinical presentations were administered at the CRC. The following tests were administered as part of a larger test battery in no fixed order:

1. CNRU Demographic, Medical, and Metal History Form: This is a self-report measure of demographics, academic history (including cumulative GPA), and medical history as pertaining to safety for the MRI.

2. Wechsler Abbreviated Scale of Intelligence (WASI): This is an interview-style assessment of IQ in which the subjects completed the Vocabulary and Matrix Reasoning subtests. Subjects were first asked to provide definitions for words that progressively increase in difficulty. Subjects then completed a series of patterns during which they chose an image from 5 possibilities that would complete the larger pattern. These two sub-tests of the WASI provide a valid estimate of IQ (Wechsler, 1999).
3. Achenbach Adult Self-Report (ASR): This is a self-report questionnaire consisting of 126 items rated on a 0-2 scale, with 0 meaning not true and 2 meaning often or always true. Subjects were asked to rate items as they apply to the past 6 months. The items represent 8 syndrome scales that are consistent across age, informant, and culture within the age range of 18-59 and provide a general measurement of adaptive functioning (Achenbach & Rescorla, 2003).
4. Conners' Adult ADHD Rating Scale (CARRS): Subjects completed the long version of this self-report questionnaire, rating the 64 items on a 0-3 scale, with 0 being never and 3 being always. The 64 items provide a generalized measure of ADHD phenotype (not diagnostic in nature; Conners, Erhardt, & Sparrow, 1998).

Cognitive flexibility task. A computerized version of the WCST was programmed and administered using EPrime software (Psychology Software Tools, Pittsburgh, PA). During scanning, the computer display was projected onto a mirror inside the fMRI scanner. The layout of the task is presented in Figure 1. It consisted of two test blocks in which rules (color, shape, or number) were used to sort cards. These blocks were separated by a block of control trials during which the subject matched identical cards. Each block contained 48 trials. On each trial, a test

card was presented in the lower center of the screen, and the subjects were instructed to choose one of the four reference cards that matched the test card according to the sorting rule (e.g., if the test card was red and the sorting rule was color, they would choose the red reference card). Subjects had 4 seconds to sort a test card with a reference card and received 1sec of feedback. Subjects used two handheld response triggers with two buttons per hand (one for the thumbs and index fingers) in order to sort the cards. See Supplemental Materials for the task instructions provided to the subjects.

During test blocks, subjects were not told the current sorting rule. Subjects needed to rely on "Correct" or "Incorrect" feedback after each sorting and adapt accordingly to determine the new rule. Each test block contained 6 unannounced rule changes occurring randomly every 7-10 cards. The control block consisted of 48 test cards that exactly matched one of the reference cards (see example in Figure 1). Subjects matched the cards and received neutral feedback ("+"). Perseverative errors are the hallmark measurement of cognitive flexibility deficits in this study and were defined as any incorrect sorting after a rule shift that is consistent with the rule preceding the shift.

fMRI Procedure

Functional imaging acquisition parameters. The reference scan was a spoiled gradient, T1-weighted volumetric sequence which was obtained along an axial oblique plane parallel to the AC-PC line using 4 mm slice thickness, no gap, TR 2000 ms, TE 35 ms, flip angle 90 degrees, and 1 NSA, which provides the reference for future slice selection within Talairach space. For the fMRI sequences, a single-shot, gradient-echo, echoplanar pulse sequence was used. Resolution was 3.75 mm x 3.75 mm. Thirty-three contiguous slices of 4 mm thickness and no gap were obtained in the axial oblique plane, parallel to the AC-PC line using a FOV of 240

mm x 240 mm and a matrix size of 64x64. Field map correction for magnetic inhomogeneities was accomplished by acquiring images with offset TE at the end of the functional series. During pre-processing, reconstruction included adjustment of the functional image series for bandpass asymmetry correction, field map, and unwarping to remove spatial artifacts.

Scanning procedure. The order of scans was as follows: T1 for high-resolution anatomical images (5min), T2 for a safety clinical screen by a neuroradiologist (7min), and WCST task completion (~13min).

Experimental event periods. In order to study patterns of activation during the WCST, three task conditions were identified (events 2, 4, and 6 outlined by Monchi et al., 2001). Event 2 ("sort") was defined as the 3 test trials preceding the trial of a rule shift, from onset of the third sorting image to offset of the feedback display immediately preceding the rule-shift. Event 4 ("shift") was defined as the 3 test trials immediately following a rule shift, starting from onset of "Incorrect" feedback on the trial of the rule shift and ending on offset of feedback on the third trial after the rule shift. Event 6 ("match") was defined as the display duration of matching images of roughly half of the control trials. See Figure 2 for a representation of these 3 events.

Data Analysis

A series of *t*-tests were run to examine the effects of group on performance on the WCST, and to compare demographic and behavioral reports between the two groups.

fMRI analysis. After volume realignment, preprocessing in BrainVoyager software comprised of a correction for slice x time errors and spatial (8 mm full-width half-maximum isotropic Gaussian kernel) as well as temporal (high pass filter: 5 cycles/run) smoothing was completed. Anatomical and functional images were co-registered and normalized to Talairach space. Statistical analysis was performed by multiple linear regression of the signal time course

at each voxel. The expected blood oxygen level-dependent (BOLD) signal change for each different task condition (switching, sorting and matching) was modeled by a canonical hemodynamic response function. In the first step, voxel-wise statistical maps were generated, and predictor estimates and b-weights were generated for each subject. In the second step, group analyses of these individual contrasts were performed with *t*-tests. We adjusted for multiple corrections by first setting a $p < 0.005$ false discovery rate (FDR)-corrected, and then applying a voxel-size cluster correction. This correction was generated using 1000 Monte-Carlo simulations to estimate the cluster size that exceeded an alpha level of $p < 0.05$.

Analysis of experimental events. In order to determine the neural networks necessary for set shifting and performance on the WCST between groups, the following contrasts were analyzed:

1) shift minus match between control and ADHD – This contrast yields brain activity specific to cognitive flexibility that differs between groups.

2) shift minus sort between control and ADHD – This contrast was used to examine neural activity related to the working memory demands of the task between groups, and

3) total task (all three events, control minus ADHD) – This contrast was used to capture total task demands (attention, working memory and cognitive flexibility) between groups.

Academic correlation analysis. The relationship between perseverative errors on the WCST and academic performance (GPA) was examined using a correlation analysis in SPSS.

Results

Groups did not differ by age ($p = 0.332$), IQ ($p = 0.770$), or GPA ($p = 0.099$). As expected, the ADHD group exhibited significantly higher CAARS Total ADHD scores ($p < 0.001$) and higher AD/H problem scores ($p < 0.01$) on the ASR. Group characteristics are

presented in Table 2. It is important to note that all analyses excluded 1 subject with ADHD, thus leaving an ADHD group size of 3. The subject was excluded because they reported needing glasses in the scanner after task completion and could not read the instructions properly. The performance data were also unable to be analyzed due to rules remaining unlearned and therefore not assessing cognitive flexibility.

Performance on Test Measures

Group performance comparisons on the WCST are presented in Table 3. WCST performance data were analyzed by group using a *t*-test. The ADHD and control groups did not differ in total errors ($F(1) = 4.418$, $p = 0.062$), test reaction time ($F(1) = 0.213$, $p = 0.654$), CTRL reaction time ($F(1) = 0.172$, $p = 0.687$), or number of trials before learning the next rule after a rule shift ($F(1) = 3.340$, $p = 0.098$). However, ADHD and control groups differed significantly on number of perseverative errors ($F(1) = 6.845$, $p = 0.026$), with the ADHD group exhibiting more perseverative errors than controls.

Neural Activation Analysis

Analysis of between-group effects during the shift minus match conditions revealed significant differences ($p < 0.005$ cluster corrected) between control and ADHD activation in many areas: subjects with ADHD had decreased activation of the right superior frontal gyrus (Brodmann Area (BA) 10), right middle occipital gyrus (BA 18), and left middle and inferior frontal gyri (BAs 10 and 47) compared to control subjects; subjects with ADHD also exhibited increased activation of the right superior temporal gyrus (BA 38), right parahippocampal gyrus (BA 36), and left fusiform gyrus (BA 18) compared to control subjects. Imaging analysis of the shift–match conditions is presented in Figure 3.

There were no significant differences in neural activation between groups in the shift minus sort condition. The total task comparison between groups revealed a significant difference ($p < 0.005$) in activation of the anterior cingulate cortex (BA 32; ACC) in which the control group exhibited increased activation as compared to the ADHD group. Total task activation is presented in Figure 4. An outline of all significant differences ($p < 0.005$ cluster corrected) in neural areas used in both conditions is presented in Table 4.

Academic Correlation Analysis

Analysis of the relationship between perseveration errors and GPA across all subjects revealed a significant correlation of -0.641 ($p = 0.025$) (see Figure 5).

Discussion

This study examined the neural correlates of cognitive flexibility in college students with and without ADHD using the WCST during fMRI scanning. Further, we investigated the relationship between cognitive flexibility and academic performance. ADHD and control groups were not significantly different on IQ or GPA, indicating no gross cognitive differences between groups. However, as hypothesized, the ADHD group exhibited significantly more perseverative errors on the WCST than controls, suggesting a deficit in cognitive flexibility. Because there were no significant differences in total errors or rules unlearned between the two groups, we can conclude that the perseverative errors seen in the ADHD group were due to cognitive flexibility deficits and not a lack of understanding or other impairments associated with the task.

The fMRI analysis of the WCST identified a potential network accounting for these deficits in the ADHD population. Neural activity during the contrast of shift trials – match trials, during which artifacts and unrelated activations caused by the task (i.e., motor responses when sorting cards, working memory demands, etc.) were removed by the subtraction, revealed

differences between the groups. Consistent with our hypothesis, control subjects exhibited higher activation levels in several of the neural areas related to cognitive flexibility, including the right superior frontal gyrus (SFG) and left middle and inferior frontal gyri (MFG and IFG). While several brain areas were found to be different between groups during both the contrast of sort – match and switch – match conditions, increased activation of the IFG was only found in the switch – match contrast. We therefore determined that IFG activation is unique to the difference between ADHD and control groups on shift trials, indicating a specific role in cognitive flexibility.

Other studies on the neural correlates of cognitive flexibility have identified increased activation of the IFG during the WCST, especially in relation to rule shifting (Konishi et al., 1998; Monchi et al., 2001). Konishi and colleagues (1998) isolated shift-related fMRI activity using temporal transient signals and observed consistent and reproducible activation of the IFG in all subjects. The IFG is involved in processes such as response inhibition and may be involved in the active maintenance of working memory (Cohen et al., 1997). Decreased activation of this area in subjects with ADHD may account for deficits during rule shifting, as working memory needs to be continuously updated in order to remember the current sorting rule and adjust performance after negative feedback. However, while the IFG is consistently reported as activated during set shifting, no theory as to its direct involvement in cognitive flexibility has been established.

Activation of the SFG is also consistently reported in the literature, and one theory states that the SFG is involved in selecting task-relevant information (i.e., incorrect feedback) from task-irrelevant information (i.e., the previous sorting rule) (Sohn et al., 2000). According to this theory, decreased activation of the SFG in subjects with ADHD could account for an increase in

perseverative errors, as a successful rule shift requires responding to important information such as feedback and a shift in the current behavior.

However, a different explanation was proposed in the same year and suggested a task-dependent network rather than independent involvement of the SFG. A study by Stuss and colleagues (2000) reported a significant increase in perseveration errors on the WCST in subjects with lesions to the right prefrontal areas, including the SFG, as compared to those with lesions to the left prefrontal cortex (PFC). Since the subjects with superior PFC lesions performed similarly to subjects with dorsolateral PFC lesions, they suggested that the superior PFC may be functionally continuous with the dorsolateral PFC, a region known to be involved in many executive functioning processes, including cognitive flexibility (Stuss et al., 2000). This could provide an explanation for the increase in SFG activation in controls during a rule shift. Similarly, since subjects with ADHD had lower levels of SFG activation, this could impair the suggested network with the dorsolateral PFC and thus inhibit cognitive flexibility processes, accounting for the increase in perseverative errors. Further research is needed in this area, as an understanding of the existence of this potential network could provide novel insight for investigating cognitive flexibility and other executive function deficits seen across many different disorders.

We also observed consistent increased activation of areas in the temporal lobe in the control group compared to the ADHD group. While most research reports frontal lobe and basal ganglia areas as implicated in cognitive flexibility, the temporal lobes also play an important role. A primate study by Muhammad, Wallis, and Miller (2006) reported consistent increased activation of the inferior temporal lobe and suggested it played a role in rule recognition. By using electroencephalography (EEG) recordings, the researchers were also able to assess

connectivity between the inferior temporal lobe and prefrontal cortical areas. They observed early encoding in the temporal lobe that was then later reflected in the PFC and suggested that rule and stimuli information were being encoded by the temporal lobe and then communicated to the PFC (Muhammad, Wallis, & Miller, 2011). Therefore, the temporal lobe may be involved in identifying the current rules and altering PFC responses to the task. Decreased activation in the temporal reported in our study could be contributing to the increase in perseverative errors seen in the ADHD group, as it could indicate an impaired ability to identify rules and update the current cognitive set.

We also observed an increase in ACC activation in control subjects compared to ADHD over the total task (switch, sort and match combined), consistent with the overwhelming literature implicating the ACC as a critical structure for performance on the WCST. A study by Lie and colleagues (2006) observed neural activations involved in uninstructed rule shifts as compared to instructed rule shifts in the WCST, allowing a direct assessment of cognitive flexibility associated with spontaneous and non-signaled changes in context. As the task increased in complexity (no shift < signaled shifts < non-signaled shifts), a successive increase in ACC activity was observed (Lie, Specht, Marshall, & Fink, 2006). They suggested this increase in ACC activity is related to increased task demands (such as changing behavior after rule-shifts), as the ACC has been consistently implicated in response selection, attentional control, and error detection (Gehrig et al., 1993; Lie, Specgt, Marshall, & Fink, 2006), all necessary skills to respond appropriately to a rule shift. The ACC has also been consistently reported as hypoactivated in subjects with ADHD as compared to controls on many tasks of attention, impulsivity, and cognitive flexibility (Cubillo et al., 2010).

It is interesting that our analyses did not find significant differences between group ACC activation on the shift minus match condition, as the ACC is increasingly used during rule-shifting (Lie, Specht, Marshall, & Fink, 2006). This could be due to the current study's small sample size, leading to decreased power. A larger sample may have found differences between groups on the switch condition, as is consistent with the literature. However, the difference seen on the total task comparison in this study suggests that the ACC was hypoactivated in subjects with ADHD and might partially account for the decreased task performance.

Research on methylphenidate effects on neural activation levels during cognitive flexibility measures also supports the identification of hypoactivations and the possible relationship to cognitive deficits seen in students with ADHD. Studies have shown that methylphenidate treatment normalizes neural activation levels in subjects with ADHD during cognitive tasks (Rubia et al., 2011). This normalization of activation is also often accompanied by an improvement in task performance. While such fMRI studies can only identify the possible location and activation levels of the neural network involved in such tasks and cannot identify in detail how these networks are functioning, they indicate a relationship between decreased activation levels and decreased performance in ADHD, as we have also observed in our study.

In addition to the WCST performance and neural network analyses, we were also able to identify a significant negative correlation ($p = 0.025$) between perseverative errors and GPA. This indicates that cognitive flexibility is related to college-level academic experiences, with deficits in cognitive flexibility leading to decreased academic performance. This is the first study to examine such a relationship, though other researchers have identified the importance of flexible cognitive sets (Spiro et al., 1987). An educational study by Spiro and colleagues stated that cognitive skills such as cognitive flexibility were crucial to developing effective problem-

solving skills, as familiar knowledge is consistently being related to novel concepts in the academic setting. However, whether it was directly related to academic performance, as our results suggest, was previously unknown. Our data supports the observational claims made by Spiro and colleagues (1987) and could be applied to current research on teaching practices.

The results of this study should be interpreted cautiously, as this study had a small sample size. Future efforts should prolong the recruitment and data collection processes, as a large population was available for this study but time allotments only accommodated a sample size of 12 subjects. A larger sample size might allow for a more detailed neural network to be established and include some other key structures identified in the literature (such as the ACC).

Future studies should also examine any differences in performance that might be observed between being trained on the WCST and not having previously practiced the test blocks. The current study only trained subjects on the control block to allow for acquisition of the correct motor response for sorting the cards in the fMRI scanner. Subjects were told the three sorting rules and given verbal training, but they did not practice before data collection. We used this approach to more accurately model academic experiences in which learning events and skill assessments are typically happening simultaneously. However, there remains a possibility that increases in perseverative errors seen in subjects with ADHD were due to learning deficits associated with ADHD. While our subjects reported no learning disabilities and did not exhibit any performance differences besides perseverative errors on the WCST from controls, a simple study comparing the performance of two groups, one allowed to practice the task and one only verbally trained, could determine if performance is impacted by any learning effects.

Future studies should also use more sensitive procedures to identify the neural network of these cognitive flexibility deficits in more detail. While fMRI provides a measurement of neural

activation during a task using the blood oxygen-level dependent (BOLD) signal, it cannot provide any detail beyond general increased or decreased activation levels of different areas at different time points. Once the general network is identified, other studies using techniques such as diffusion tensor imaging (DTI) could examine whether these hypoactivations are due to a loss of track integrity. DTI could also help identify how the structures implicated in this task are interacting. More sensitive studies using EEG might also be able to identify the roles of specific cell types and how they might be contributing to the differences in the neural activations between ADHD and controls.

In summary, this study identified cognitive flexibility deficits in a college ADHD population and found a possible neural network contributing to these deficits. We also connected cognitive flexibility to academic performance across both groups. These results highlight the importance of understanding the impacts an ADHD diagnosis has on cognitive and executive functions, as it can lead to more difficulties in achieving academic success. Continuing this work by addressing the discussed limitations could lead to a greater understanding of the ADHD diagnosis, the cognitive flexibility deficits seen in students with ADHD, and the relation to academic performance. This information could potentially facilitate development of new educational interventions to improve the academic abilities of students with ADHD.

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Tables

Table 1
Summary Characteristics of Subjects

	Age (years)			GPA (4-pt scale)			WASI (FSIQ)			CAARS G t score		
	Mean *(SD)*	Min	Max	Mean *(SD)*	Min	Max	Mean *(SD)*	Min	Max	Mean *(SD)*	Min	Max
CTRL	20.67 *(0.87)*	19	22	3.43 *(0.4)*	2.77	3.99	120 *(10.25)*	101	131	43.44 *(8.23)*	34	55
ADHD	20.5 *(1.91)*	18	22	2.95 *(0.42)*	2.45	3.45	116 *(6.95)*	109	124	76 *(12.99)*	60	88

FSIQ=Full Scale Intelligence Quotient; CAARS G=Measures total ADHD symptoms/phenotype

Table 1. Summary Characteristics of Subjects

	CTRL (n=9)	ADHD (n=3)	B/w Group p-value*
Age	20.67 *(0.87)*	20.00 *(2.00)*	0.418
GPA	3.43 *(0.39)*	2.92 *(0.50)*	0.099
IQ	120.00 *(10.25)*	118 *(7.94)*	0.770
ADHD Symptoms**	43.44 *(8.23)*	72 *(12.53)*	0.001

*Analyzed using *t*-tests
**CAARS subtest G

Table 2. Statistical Analysis of Subject Demographic & Academic Information, Mean *(SD)*.
The ADHD and control groups did not differ on age ($p = 0.418$), IQ ($p = 0.77$), or GPA ($p = 0.099$), but the ADHD group exhibited higher scores on both the CAARS subtest G ($p = 0.001$) and the AD/H problems on the ASR ($p = 0.011$).

	CTRL	ADHD	B/W Group p-value*
Test RT	1494.43 *(252.34)*	1565.09 *(92.60)*	0.654
CTRL RT	915.68 *(164.72)*	962.06 *(179.39)*	0.687
TrialsToLRN	1.53 *(0.87)*	2.22 *(1.06)*	0.098
Total Errors	26.22 *(6.02)*	37.00 *(12.29)*	0.062
P_Errors	2.11 *(1.80)*	5.67 *(2.87)*	0.026

*Analyzed using *t*-tests

Table 3. Statistical Analysis of Performance on the WCST, Mean *(SD)*.
ADHD and control groups did not differ on total errors ($p = 0.062$), test trial reaction time ($p = 0.654$), control trial reaction time ($p = 0.687$), or the number of trials it took to learn the next rule after a rule shift ($p = 0.098$). The ADHD group had significantly more perseverative errors on the WCST than did the control group ($p = 0.026$).

Shift - Match					
CTRL > ADHD					
Laterality	**Cluster**	**BA**	***X***	***Y***	***Z***
Right	SFG	10	27.49	52.77	-2.47
Right	Middle Occipital Gyrus	18	14.39	-90.4	15.71
Left	Middle Frontal Gyrus	10	-29.2	51.4	-7.18
Left	IFG	47	-49.8	19.59	-6.65
ADHD > CTRL					
Laterality	**Cluster**	**BA**	***X***	***Y***	***Z***
Right	Superior Temporal Gyrus	38	41.81	14.66	-24.01
Right	Parahippocampal Gyrus	36	32.1	-31.6	-19.93
Left	Fusiform Gyrus	18	-25	-93	-15.24

Table 4. Differences in Neural Activity Between Groups in Shift Minus Match.
Table 4 represents the significant differences ($p < 0.005$) in activation of clusters between groups during the shift minus match condition, therefore including trials in which cognitive flexibility is necessary.

Sort - Match					
CTRL > ADHD					
Laterality	**Cluster**	**BA**	***X***	***Y***	***Z***
Right	Sub-Gyral Temporal Lobe		40.86	-9.24	-6.67
Right	SFG	10	27.49	53.43	-2.45
ADHD > CTRL					
Laterality	**Cluster**	**BA**	***X***	***Y***	***Z***
Right	Superior Temporal Gyrus	38	41.24	14.84	-24.3
Right	Parrahippocampal Gyrus	36	32.75	-31.8	-21.6

Table 5. Differences in Neural Activity Between Groups in Sort Minus Match.
Table 5 represents the significant differences ($p < 0.005$) in activation of clusters between groups during the sort minus match condition, therefore not including trials requiring cognitive flexibility.

Figures

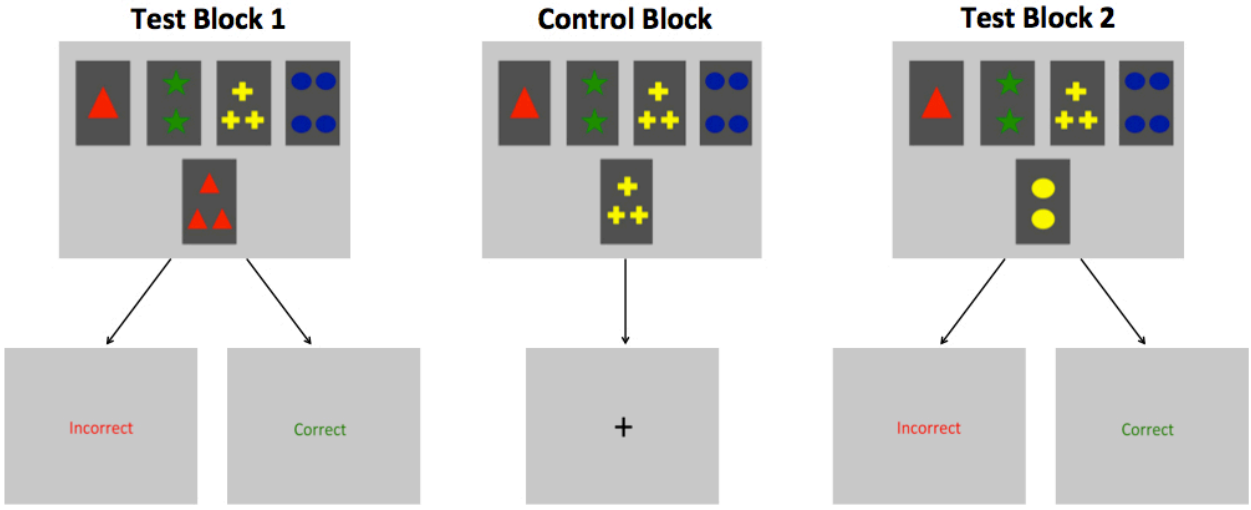


Figure 1. Layout of the WCST.

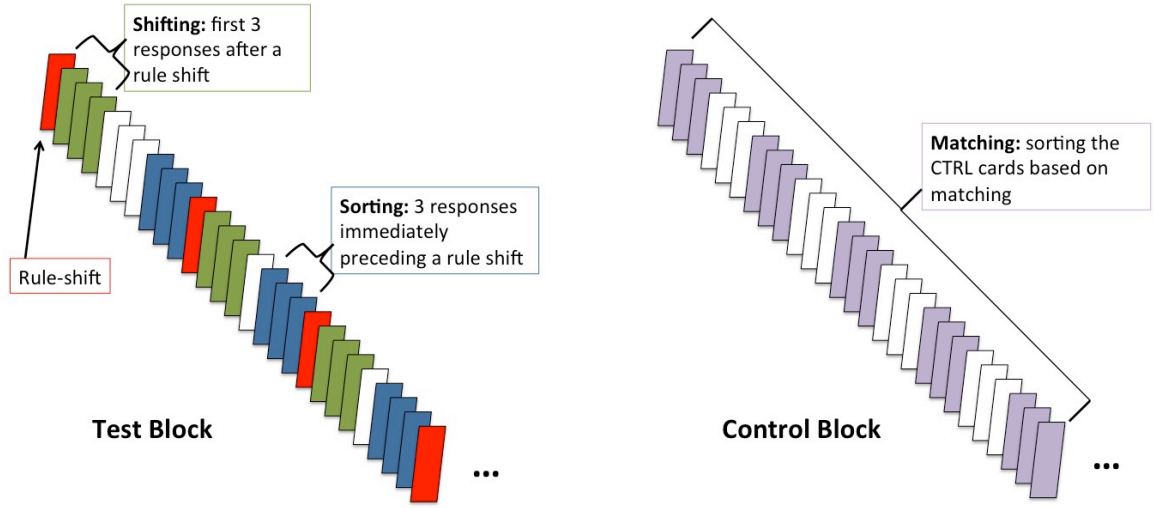


Figure 2. Experimental Event Definitions.
Event 2 was considered the "sorting" event, which consisted of the three test trials immediately preceding a rule shift. During this event, subjects were sorting test cards based on a rule known to them. Event 4 was considered the "shifting" event, which consisted of the three test trials immediately following a rule shift. During this event, subjects needed to use cognitive flexibility in order to adjust their response until they determined the new rule. Event 6 was considered the "matching" event, which consisted of a series of 3-trial blocks taken from the control block. This event allowed us to extract irrelevant artifacts during task completion (i.e. motor responses when pushing the response buttons).

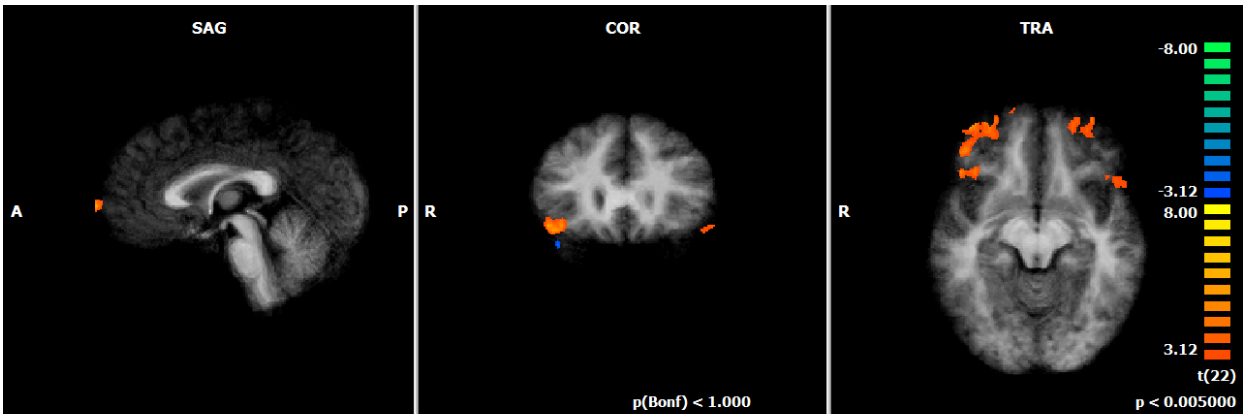


Figure 3. Shift Minus Match Differences with CTRL > ADHD.
The control group exhibited increased activation ($p < 0.005$) of the right superior frontal gyrus (BA 10), right middle occipital gyrus (BA 18), left middle frontal gyrus, and left inferior frontal gyrus during shifting events in the WCST.

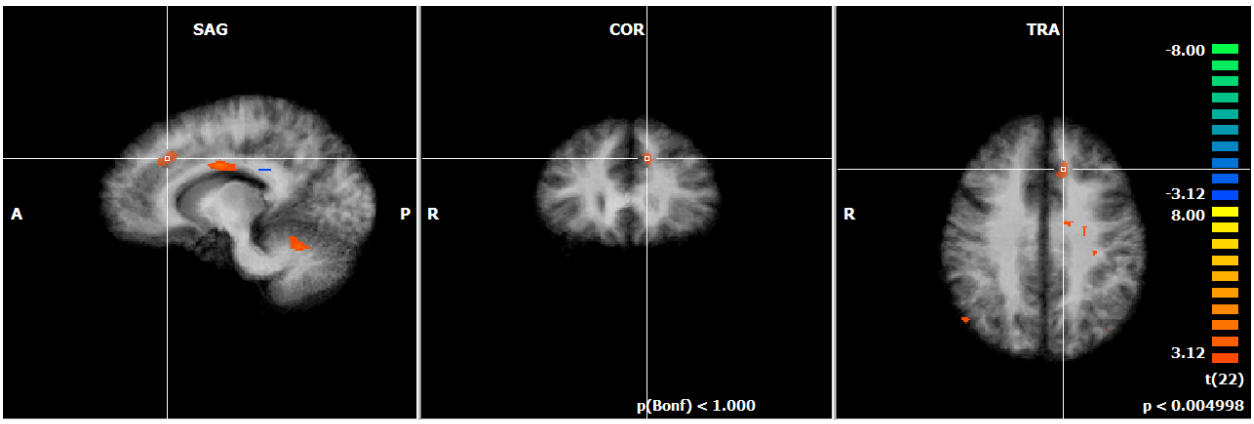


Figure 4. Total Task ACC Activation with CTRL > ADHD.
The control group exhibited increased activation as compared to the ADHD group in the total task comparison ($p < 0.005$). The crosshairs highlight the significant activations

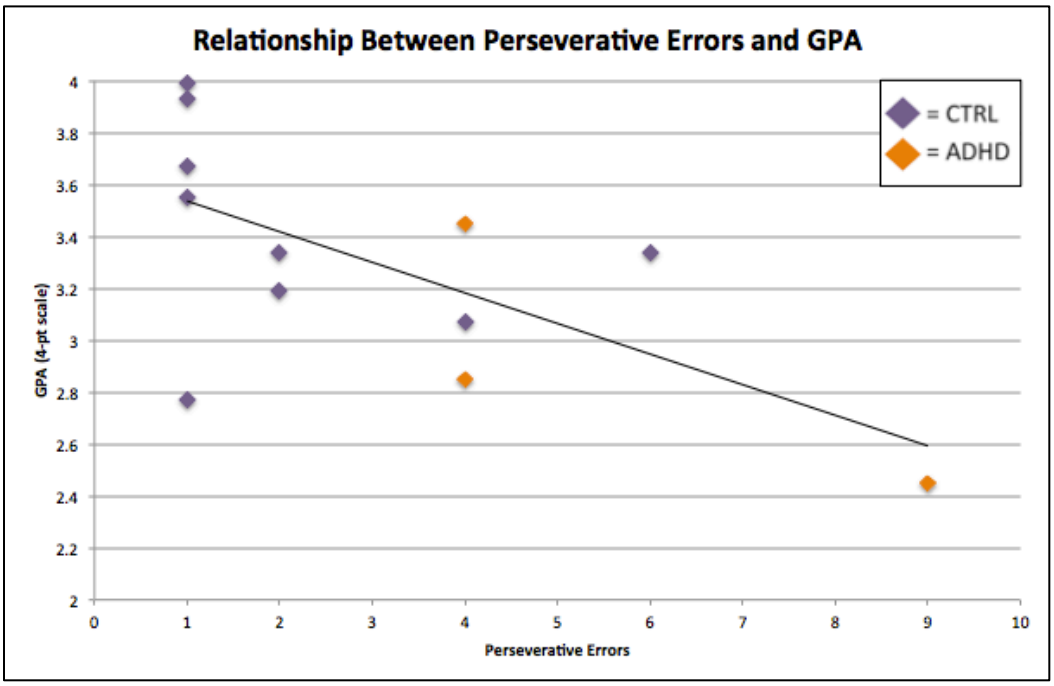


Figure 5. Correlation Between GPA and Perseverative Errors on the WCST.
GPA and perseverative errors were negatively correlated (r = -0.641), indicating a lower GPA (lower academic performance) is associated with more perseverative errors (increased deficits in cognitive flexibility).

Supplemental Materials

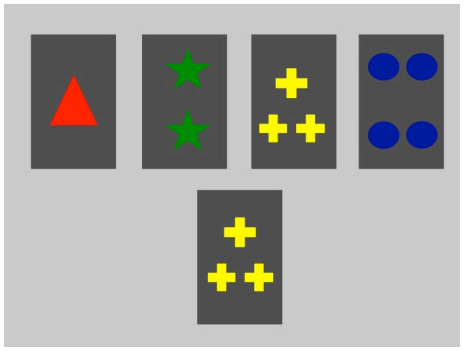
Supplemental Materials 1: Task instructions given to subjects at the MRI mock scanner for task training before practicing the control block of the WCST.
Test block instructions were abbreviated and repeated before data collection at the fMRI.

"*The first task you will be doing in the real scanner is called the Wisconsin Card Sorting Task, where you are asked to sort cards based on different contexts and rules. You will be doing two different types of trials in this task. Let's start with the easiest.*

Control Trial Instructions:

During a matching trial, the test card will exactly match one of the reference cards, like this (show example control trial image). *Your job is to sort the test card with the reference card that matches it exactly.*

- Show example control image.



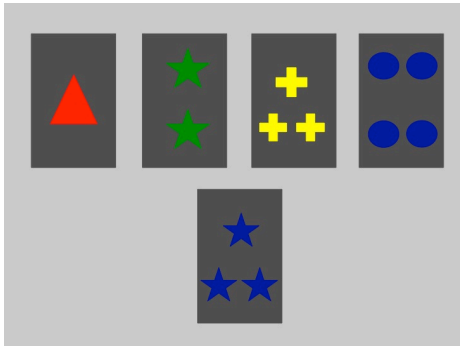
So for this one, where would you sort this card? (**Correct match = reference card C** → If they get it right, *"good job.*") (If they get it wrong, "*Remember, for this part of the task, you are matching the cards. Look for the card that is the same as this test card.*")

Let's move on to the other kind of trial.

Test Trial Instructions:

During a rule trial, the test card will NOT match one of the reference cards. Your job is to figure out what the current "sorting rule" is, but you will not be told the rule. You have to figure it out. The three possible rules are: sort by COLOR, sort by SHAPE, and sort by NUMBER of shapes.

- Show example test image.



*So for this one, if the rule is **COLOR**, where would you sort this card?*

(**Correct match = reference card D →** If they get it right, "*good job. Let's do the next one*." If they get it wrong, "*Remember, for COLOR, you match to the reference card that has the same color as the test card. The other things like shape and number don't matter. Only one rule at a time. So where would you match this card for COLOR*?")

*Okay. If the rule is **SHAPE**, where would you sort this card?*

(**Correct match = reference card B →** If they get it right, "*good job. Let's do the next one*." If they get it wrong, "*Remember, for SHAPE, you match to the reference card that has the same shape as the test card. The other things like color and number don't matter. Only one rule at a time. So where would you match this card for SHAPE?*")

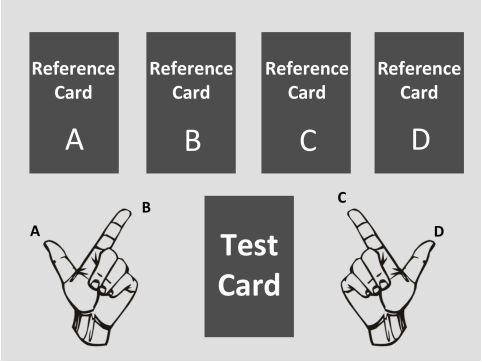
*Okay, last one. If the rule is **NUMBER** of shapes, where would you sort this card?*

(**Correct match = reference card C →** If they get it right, "*good job. Let's go on*." If they get it wrong, "*Remember, for NUMBER, you match to the reference card that has the same number of shapes as the test card. The other things like color and shape type don't matter. Only one rule at a time. So where would you match this card for NUMBER?*")

Great. During a rule trial, the rule will change unannounced. You will have to figure out what the new rule is. Do you have any questions so far?

How to match in the scanner:

Now, you will have to make your choices on where to sort the test card inside the fMRI scanner. In order to do this, you will have two handheld objects that look like this (show picture), *one for each hand, with keys for your thumb and index finger. You will have to match to the reference cards as shown here* (show sorting image).



If you want to sort the test card with the first reference card, you would push the button on your left thumb. If you want to sort the test card with the second reference card, you would push the button on your left index finger. If you want to sort the test card with the third reference card, you would push the button on your right index finger. And if you want to sort the test card with the last reference card, you would push the button on your right thumb. Do you understand how to choose where to sort the test cards?

Okay. Do you have any questions before we go into the mock scanner?"