

**INVESTIGATING BIOMARKERS FOR
ANTIDEPRESSANT EFFICACY VIA COGNITIVE-
BEHAVIORAL ASSESSMENT AND fMRI**

A Thesis
Presented to
The Academic Faculty

by

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In Partial Fulfillment
of the Requirements for the Degree
B.S Neuroscience with the Research Option in the
College of Sciences

Georgia Institute of Technology
May 2019

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ABSTRACT

Although many treatment options have been developed to treat Major Depressive Disorder, the efficacy of these treatment options remain limited. Past studies on antidepressant efficacy have identified a range of cognitive improvements associated with treatments, yet the complexity of these studies and the lack of consistency across paradigms in existing literature hinders the understanding of antidepressant efficacy and highlights the importance of further investigation (Atique- Ur-Rehman & Neill, 2019). Additionally, research has indicated significant trends in anatomical regions and brain networks, but no single biomarker may exist that can be translated across every antidepressant or patient sub-population (Dunlop et al., 2019). Despite the inconsistencies in past results, it is clear that abnormalities in cognition and functional connectivity are important components of the manifestation of depression and further research is necessary to fully understand the mechanisms behind how antidepressants ameliorate these symptoms. The overarching purpose of this research is to investigate a more specific niche of antidepressant research by analyzing cognitive outcomes, specific to working memory and attentional control, and the Citalopram-specific connectivity biomarkers associated with treatment in patients. However, this thesis represents the initial steps of this project by assessing the validity of specific cognitive tasks, known as Antisaccade, Flanker DL, Operation Span, and Symmetry Span, that will be used as the primary behavioral measures of working memory and attention in the depressed subjects. Results demonstrate a consistent relationship across task performance in subjects and reveal multiple statistically significant correlations between average primary measures of the different tasks. This successful validation of these four tasks as appropriate measures of attentional control and working memory is crucial before these tasks can be applied in the future as primary measures of change in cognition in response to the administration of an anti-depressant.

INTRODUCTION

Major Depressive Disorder (MDD) is an incredibly prevalent disease that remains largely unsuccessfully treated and understood. Although an abundance of treatment options have been developed, the efficacy (ability to alleviate depressive symptoms) and impact of these treatment options, such as antidepressant medications and psychotherapy, remain limited. Although the anatomical and functional impacts associated with MDD have been investigated, the symptomatic expressions and effects of the disease are incredibly individual-dependent and lack homogeneity, therefore restricting significant development of treatment efficacy (Arnone, 2019). Clinical treatment of MDD often consists of a “trial and error” approach, where patients must attempt various antidepressants until finding an option that allows for the most significant symptomatic improvement (Dichter et al, 2015).

In addition to significant changes in mood, past research has established an associated decline in various cognitive functions associated with MDD such as executive function, memory, attention and processing ability, but this degeneration and the associated mechanism(s) of action remains largely misunderstood (Atique-Ur-Rehman & Neill, 2019). In addition to these cognitive deficits associated with MDD, research has identified a variety of intrinsic brain networks and neurological pathways that demonstrate impairment or altered activity in depressed patients compared to controls. Yet, no specific concrete pattern has been identified in these impairments of cognitive abilities or changes in functional brain connectivity associated with depression, and therefore, the complexity of the neurological mechanisms behind MDD limits advancement and understanding of the treatment of the disease.

Because of the variability in treatment response in patients, it has proven valuable to investigate potential biomarkers of antidepressant efficacy via various cognitive function assessments and functional Magnetic Resonance Imaging (fMRI). Past studies on antidepressant

efficacy have identified a range of cognitive improvements associated with treatments. (Atique-Ur-Rehman & Neill, 2019). This is primarily a result of the various types of antidepressants that have been investigated, but also a result of the various factors playing a role in the aforementioned studies, such as different cognitive assessments used, varied population demographics, the severity of MDD, length of study, types of control, etc. The complexity of these studies and the lack of consistency across current experimental paradigms further hinders progress towards understanding antidepressant efficacy and highlights the importance of further investigation into these biomarkers.

Furthermore, a wide range of brain regions have shown significant fluctuations in activity and connectivity associated with antidepressant efficacy, but these results aren't consistent across all forms of assessment or even across studies that use similar paradigms (Arnone et al., 2018). Research has indicated significant trends in anatomical regions and networks, but there may be no single biomarker that can be translated across every antidepressant or patient population (Dunlop et al., 2019). Despite this inconsistency, it is clear that abnormalities in neurological functional connectivity is an important component of the manifestation of depression and further research is necessary to fully understand the mechanisms behind how antidepressants impact this network connectivity.

This study aims to better understand the complex mechanisms behind Major Depressive Disorder and mitigate the inconsistency in both past paradigms and results of studies by exploring antidepressant efficacy through cognitive-behavioral assessment and simultaneous functional Magnetic Resonance Imaging. Over an 8-week period of administration of one of the most commonly prescribed and accessible SSRI, known as Citalopram (Celexa), researchers hope to further isolate potential biomarkers associated with treatment efficacy by analyzing the changes from baseline in cognitive-behavioral tasks, specifically in working

memory and attention, and identifying correlations between this change and changes in intrinsic functional connectivity. This work will address the need for further investigation of the wide variety of brain regions across studies implicated as biomarkers for clinical treatment efficacy, potentially specific to Citalopram, in patients with MDD.

LITERATURE REVIEW

The lack of understanding of the pathophysiology of depression itself has diminished the ability to also better understand the clinical efficacy of current anti-depressant therapies. Past research into the therapeutic efficacy of anti-depressants in patients with MDD has identified a variety of potential cognitive-behavioral and functional connectivity improvements associated with treatment administration and decreased depressive symptoms (Arnone, 2019; Atique-Ur-Rehman & Neill, 2019). However, this wide range of improvements across studies recognized as either symptomatic changes resulting from depression or as potential biomarkers for clinical treatment efficacy further highlight the demand for further investigation. Inconsistencies in experimental procedures and the complexity of the neurological mechanisms behind depression establish a need for more exploration of the treatment efficacy, specifically with a more refined experimental direction examining recent implications using previously established methodologies.

Variation in Outcomes Across Therapies

Although providing valuable and comprehensive insight into the complexity of depression, the lack of homogeneity across experimental procedures and methodologies used in current studies investigating anti-depressant efficacy has partially complicated the focus and direction of the research. One key inconsistency across studies is the specific antidepressant type or brand investigated in the research, as there is a wide variety of specific antidepressants that can be prescribed. Recent research indicates that specific classes of antidepressants improve different aspects of cognitive function and this has further complicated the understanding of the interaction between the antidepressant mechanism of action and cognitive outcomes. One of the most commonly prescribed class of antidepressants, Selective Serotonin Reuptake Inhibitors.

(SSRIs), such as Vortioxetine and Citalopram, have been shown to improve processing speed, executive functioning, working memory, and verbal learning in patients with MDD (McIntyre et al., 2018; Zuckerman et al., 2018; Emsley et al., 2018; Lavretsky et al., 2015). Other antidepressant types, such as Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) and non-traditional therapeutic techniques have also shown potential facilitation of cognitive outcomes associated with treatment efficacy (Raskin, 2007; Emsley et al., 2018; Lavretsky et al., 2015). The variability in cognitive improvement across types of therapies implies that specific antidepressants are potentially more effective in improving cognitive impairments in MDD patients, but also that each antidepressant therapy may be limited to improvements in only specific aspects of cognitive function. In combination with the variability in the disease morphology and cognitive symptomatic expression in patients, the inconsistency in therapeutic outcomes exacerbates the need for further investigation of the clinical efficacy of antidepressant therapies.

Variation in Cognitive-Behavioral Tasks Used

Another major discrepancy across studies is the variety of cognitive-behavioral assessments and tasks that have been used, all of which investigate different cognitive mechanisms and therefore indicate different improvements in cognition associated with antidepressant therapies. One of the more common and earlier cognitive behavioral tasks utilized is the Digit-Symbol Substitution Test (DSST) that explores a range of cognitive functions, such as motor speed, executive function, attention, and others, but more importantly has long served as a valid measure of cognitive dysfunction in patients with various psychiatric disorders (Jaeger, 2018). McIntyre and colleague's meta-analysis of 3 independent studies that used this DSST as a primary measure of cognitive function to investigate potential efficacies of the SSRI vortioxetine

indicated significant improvement in cognition (specific to the aforementioned aspects above) independent of change in depressive symptoms across all studies (McIntyre et al., 2016).

Despite this consistency in findings regarding this single type of measure, other studies point to other assessments that could serve as therapeutic efficacy measures as well as different results regarding the DSST. One study that investigated the efficacy measures of Citalopram over an 8-week period by developing a composite cognitive score from multiple tasks (DSST, Stroop, Mini-Mental State Examination (MMSE), Cognition Reflection Test (CRT), Judgement of Line Orientation (JOLO), and Serial Reaction Time Task (SRT)) found only significant improvement in visuospatial functioning and psychomotor speed. However, this increased cognition wasn't significant compared to the placebo group (Culang et al, 2009). Another study later was done by Culang-Reinlieb and colleagues that used another cognitive score composed of a different combination of assessments, but also included SRT, MMSE, and Stroop tasks, primarily found a significant increase in verbal learning from a baseline instead (Culang-Reinlieb et al., 2012).

Investigation using these types of cognitive tasks have been further corroborated by Soczynska's work where treatment using escitalopram was shown to significantly improve verbal learning, nonverbal learning, memory, and global function; however, this was discovered through a different combination of cognitive assessments, such as California Verbal Learning Test (CVLT-II) and Wechsler Memory Scale (Soczynska et al., 2014). The discrepancies across cognitive tasks used and the resulting aspects of cognition implicated in treatment efficacy are further complicated by the results of Shilyansky's research, where the IntegNeuro test battery (consisting of 9 tasks assessing various domains of cognition) was used as the cognitive outcome measure for patients being treated with escitalopram, sertraline or venlafaxine. Yet, despite the very comprehensive approach to measuring cognition, the study reported no significant

improvements in attention, verbal memory, decision speed, working memory, information processing, and motor coordination, while only highlighting some notable improvement in executive function and cognitive flexibility (Shilyansky et al., 2016).

Other Inconsistencies Across Study Paradigms

As seen, this partial insight into the existing research on cognitive biomarkers of antidepressant efficacy displays just the surface of the discrepancies in the cognitive measures used and the results demonstrated by them. However, the inconsistencies across current studies extend beyond just tasks used as primary measures of cognition, as the screening processes, various measures of control and other aspects of experimental design fluctuate greatly from one study to the next. The aforementioned studies, in combination with others, not only vary in the specific antidepressant investigated but also vary in the specific dosage and length of drug administration. While these studies all administered SSRIs and possess the same primary mechanism of action, these antidepressants have been implicated to have different abilities in treating depression and therefore likely exhibit different measurable clinical efficacies across these studies (Marken et al., 2000). Additionally, the complexity of the depressive patient population itself further complicates the consistency across studies and the ability to control for individual differences. Not only does the variation in sample size in investigations have important implications, but specifically inconsistencies in the baseline cognition, age range, mean age, and gender distribution of the studies' samples, as the intersectionality of age, intelligence or gender differences in depression is not fully understood (Arnone, 2019; Atique-Ur-Rehman & Neill, 2019; Salk et al., 2017). Moreover, the disparities in symptomatic manifestation and severity of MDD in the patient population also introduces new confounds into the understanding of treatment efficacy.

The current research demonstrates significant efforts to control for these population demographics; however, the inconsistency of the methodology across studies for approaching the complex population may be further complicating the understanding of anti-depressants. More specifically, studies are seen to employ different screening processes and associated required depressive criteria for sampled subjects. The majority of studies require diagnosis of MDD via the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria and utilize the Montgomery-Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HDRS) as their primary depressive symptomatic outcome measures (Atique-Ur-Rehman & Neill, 2019). Yet, the specific score on these depressive inventories required for selected patients varies greatly across the field and the impact this might have on the symptomatic improvement and efficacy of anti-depressants in sampled patients is unknown. Additionally, the specific DSM-IV criteria for selected subjects vary widely, with some studies requiring only initial onset MDD, others requiring recurrent MDD, and some even allowing both.

Other studies further narrow their pooled population demographics through ways such as including required criteria such as prior suicide attempt/ideation, no other comorbidities (or requiring specific ones), non-psychotic depression, prior inadequate response to antidepressant treatment or combinations of any of these (Atique-Ur-Rehman & Neill, 2019). Furthermore, some researchers included even more complex screening processes by using a safety evaluation component that involves physical examination requirements, measurement of vital signs, evaluation of suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS), and other various clinical laboratory tests (Mahableshwarkar et al., 2018). The inconsistency of screening and sampling techniques across studies further hinders the development of a clear consensus in the current understanding of the implications and efficacy measures of anti-depressants, as the validity and reliability differences between these designs and criteria measures are not known.

The differences in study methodology limit the comparability between studies and this only further demonstrates the growing need for standardization across both the screening and assessment techniques to more effectively evaluate drug efficacy (Arnone et al., 2018).

Variation in fMRI Techniques and Identified Biomarkers

Unfortunately, the complexity of identifying biomarkers of clinical efficacy of antidepressants doesn't end there. An array of functional MRI techniques have been used to identify the presence of biomarkers for antidepressant efficacy through the analysis of the activity of specific regions during resting-state, emotional processing and cognitive task performance (Arnone et al., 2018). Investigations that explored neurological activity during cognitive tasks have revealed that prefrontal regions show “hypoactivity in depressed patients at baseline, but there is improvement in this activity, specifically in areas of the dorsal medial frontal gyrus and the dorsolateral prefrontal cortex,” associated with therapeutic intervention (Arnone et al., 2018; Lemogne et al., 2010). However, Gyurak and colleagues found significant hypoactivity in the dorsolateral prefrontal cortex after 8 weeks of treatment that extended across all 3 randomized groups receiving Escitalopram, Sertraline or Venlafaxine (Gyurak et al., 2016). Other studies using cognitive assessment tools identified decreased activity in the amygdala-hippocampus complex, ventral striatum, and pregenual anterior cingulate cortex associated with treatment intervention and symptomatic improvement in patients (Wagner et al., 2010; López-Solà et al., 2010, Stoy et al., 2012).

However, this wide range of regions displaying significant activity fluctuations identified above isn't consistent when emotional processing tasks or resting states are analyzed instead. Resting-state data across studies have inconsistently reported decreased and increased connectivity from baseline in an array of networks and pathways as a result of treatment

administration, with a trend of decreased activity in functional connectivity following treatment between medial prefrontal regions, dorsomedial and dorsolateral cortices that connect to the default mode network (Arnone et al., 2018; Fu et al., 2015). Additionally, resting-state data across studies has further revealed another noticeable pattern of increased connectivity between limbic and frontal regions (Lai and Wu, 2012; Wang et al., 2015). Emotional tasks reveal more regions of functional connectivity that indicate improvement/change upon treatment administration, such as increased activity (or normalization of activity) in the amygdala, anterior cingulate cortex and a number of other cortical areas and decreased activity in ventrolateral and dorsolateral cortical areas (Godlewska et al., 2016; Delaveau et al., 2016; Victor et al., 2013; Ruhé et al., 2012; Arnone et al., 2012). However, these fluctuations in functional connectivity are highly dependent on the emotional task used and the directionality of the emotional stimuli (positive vs. negative) (Arnone et al., 2018). This review allows only a glimpse into the variability in reported functional connectivity outcomes implicated in the efficacy of SSRI's.

The complexity of identifying cognitive outcomes and functional connectivity biomarkers for treatment efficacy in patients with MDD has been exacerbated by variations in cognitive assessments used, study designs, sample characteristics, and fMRI tasks/methodology across the research. And as a result, there has been a wide range of cognitive outcomes and functional biomarkers implicated in the efficacy of current SSRI therapies, but comparison across these results are strictly limited due to the variations in study paradigms and sample parameters. However, the development of these broad results indicates not only the need for further investigation into the potential efficacy biomarkers for anti-depressants but also the importance of approaching the research with a more refined experimental question beyond just the clinical efficacy of anti-depressants. Therefore, we hope to investigate a more distinct niche of this research by analyzing cognitive outcomes, specific to working memory and attentional

control, and the Citalopram-specific biomarkers associated with treatment in patients with MDD, as this has become one of the more commonly prescribed anti-depressants (National Alliance on Mental Health [NAMI], 2018). Additionally, by adapting methods and study parameters of past studies, this work will ideally produce more generalizable results than research has in the past. This will simultaneously add insight into the understanding of the therapeutic efficacy of Citalopram while contributing more comparable results to aid the current body of knowledge.

METHODS AND MATERIALS

Overview of Project Methodology

The overarching goal of this project is to eventually assess the treatment efficacy of Citalopram on patients with MDD via cognitive-behavioral testing and fMRI; however, it is important that the validity of specific cognitive tasks be investigated in a healthy, control subject group before the tasks are applied as a measure of cognition, specifically working memory and attention, in depressed patients. Therefore, due to time constraints and unforeseen circumstances in project development, the majority of the methodology of this thesis is focused on the assessment of the validity of cognitive tasks that will be used later as the primary behavioral measures of working memory and attention in the depressed subjects. Additionally, it is equally important that this piloted control subject data is used for means of comparison to the behavioral data obtained from patients with MDD in the future. Moving forward, these cognitive behavioral tasks will be used in combination with a separate array of psychometric fMRI tasks to identify potential biomarkers.

The tasks used as the primary behavioral measure of cognition in this study are a combination of some renowned and some relatively novel tasks, known as the Flanker Deadline (DL), Antisaccade, Operation Span, and Symmetry Span tasks, that were specifically developed by Randall Engle and colleagues in the Attention and Working Memory Lab at Georgia Institute of Technology. Antisaccade and Flanker DL tasks specifically assess attentional control, while Operation and Symmetry Span both assess working memory capacity. These tasks not only provide a unique assessment of attention and working memory capacity compared to more commonly used tasks in previous aforementioned literature, but these tasks have been indicated to produce more reliable and valid results, specifically at the individual differences level (Draheim et al., 2019a; Draheim et al., 2019b). Existing and traditional attentional measures, such as the Stroop task, rely on the use of difference scores, specifically reaction time, as a primary measure; and consequently,

researchers argue that this produces unreliable results for individual differences in attentional tasks (Draheim et al., 2019a; Draheim et al., 2019b). However, these different attentional control measures, specifically Antisaccade and Flanker DL, are primarily accuracy-based, rather than based on reaction time difference scores, and collectively have shown to be more reliable and produce stronger intercorrelations and associations to working memory measures. It was theorized that by using these novel tasks that are potentially better equipped to monitor individual differences in cognition and fluid intelligence, this investigation will more effectively assess, compared to previous studies, change in attention and working memory in patients being treated with antidepressants.

Site of Study

This research was conducted within the Cognitive Neuroscience at Tech Research Laboratory at the Center for Advanced Brain Imaging at Georgia Institute of Technology. All cognitive-behavioral testing was administered using E-Prime Psychology Software (Version 3.0.80) via a Lenovo ThinkCentre M93p (Intel® Core i7-4770 Processor) running on Windows Version 7 Enterprise. Any functional connectivity images obtained later will use a 3-Tesla Siemens Prisma-Fit Magnetic Resonance Imaging system equipped with 32 channel head coils.

Participants

6 individuals (age range 18-22, 3 males) participated in the experiment as part of this pilot group. This study was facilitated in accordance with the regulations of the Institutional Review Board at the Georgia Institute of Technology. All participants were voluntary and gave written consent. At the time of consent, participants were administered a safety screening and were informed of each task's instructions. The second component of data collection for this project,

which has not been completed, aims to collect data on around 10-15 patients, diagnosed with MDD. These patients will be prescribed 20 mg of Citalopram daily, over an 8-week period, but will otherwise be administered the same cognitive behavioral procedure (in addition to the fMRI task component) both at baseline and after the 8-week period of taking the drug.

Cognitive-Behavioral Procedure

Subjects performed a comprehensive battery of cognitive-behavioral tasks that assessed different aspects of working memory and attention control, consisting of the aforementioned Antisaccade task, Flicker DL Task, Operation Span task and the Symmetry Span task, in a randomized order. The entire cognitive-behavioral task battery took approximately 60 minutes based on individual subject speed.

Flanker DL task (Figure 1).

For this task, subjects were presented with a black target arrow, pointing to the left or right, that appeared above a fixation cross in the center of the screen. The target arrow was presented in the middle of an array of other arrows flanking to both sides, but subjects were informed to respond only to the direction of the middle arrow. The flanking arrows were either pointing towards the opposite direction of the central target arrow (incongruent) or the same direction as the central arrow target (congruent). Subjects indicated their response to the target arrow by pressing either “z” (target arrow is pointing left) or “/” (target arrow is pointing right). Subjects completed 18 blocks of 18 trials each (a total of 324 trials). Each single block had 6 incongruent trials and 12 congruent trials that were presented in randomized order with an interstimulus interval randomized between 400-700 milliseconds (ms).

However, as opposed to a normal Flanker task used in attention control literature, each trial had a response “deadline” that controlled for the amount of time a subject had to respond to the arrow stimulus (Draheim et al., 2019a; Draheim et al., 2019b). The standard initial deadline for the first block of trials was 1050 ms, and the response deadline was consistent between the congruent and incongruent trials. If the deadline was reached without the subject pressing a response, the stimuli was removed from the screen and subjects were marked as inaccurate for that trial.

Additionally, this response deadline increased or decreased based on the subject’s accuracy. If the subject accurately responded to 15 trials or more within a single block, the response deadline decreased; however, if the subject failed to respond accurately to at least 15 trials, the response deadline was increased. Furthermore, the amount that the response deadline was changed after a block varied depending on the specific block. The first six blocks were either decreased by 90 ms or increased by 270 ms for the following block, depending on the subject’s accuracy as mentioned before. For the last 12 blocks, the response deadlines were either decreased by 30 ms or increased by 90 ms. The differences between subject’s calculated response deadline after the final trial block served as the primary measure of attentional control for this task.

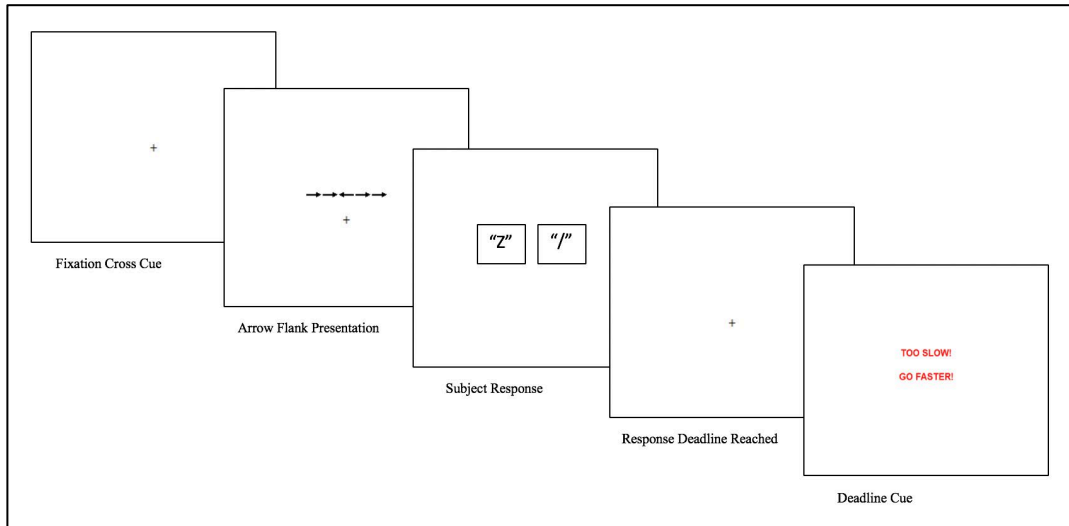


Figure 1. *Trial Sequence for the Flanker DL Task.* This example shows the trial sequence for the Flanker task. After being presented with the fixation cross, the array of arrows appears and the subject identified the direction of the central target arrow by using the “Z” (left) and “/” (right) keys. If the response deadline is reached without indication of an answer, feedback is provided to the subject.

Antisaccade task (Figure 2).

In this task, subjects were first presented with a fixation cross in the center of a grey screen. The fixation cross was presented for a randomized period of time, ranging from 2,000 – 3,000 ms, and then a white asterisk (*) was presented to either the left or right side of the screen as a cue for the target stimulus. Subjects were instructed to quickly look away from the asterisk cue as a black target (either the letter O or Q) would then immediately appear on the opposite side from the asterisk cue. The target is presented for 100 ms and then masked by the pattern “##”, requiring subjects to quickly classify the target and submit a response. The subjects designated their response simply by pressing the “Q” or “O” key on the keyboard as indicated by the target. Once the subjects responded, they were presented with accuracy feedback that was followed by an inter-

stimulus interval of 1,000 ms. Each subject completed a total of 72 trials for this task and overall accuracy was obtained.

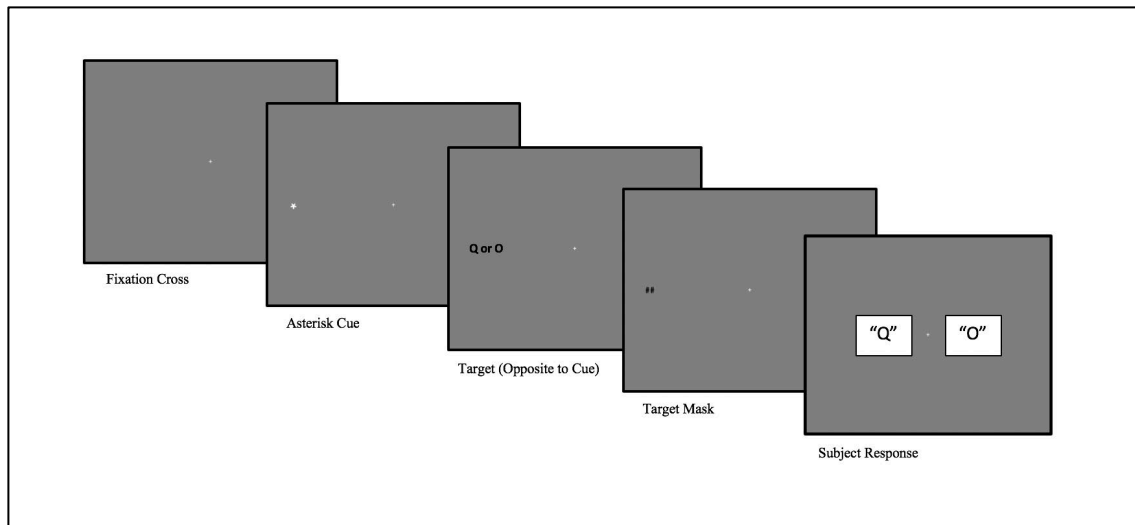


Figure 2. *Trial Sequence for the Antisaccade Task.* This example demonstrates the presentation of the asterisk cue that directed the subject to look at the opposite side of the screen and identify the target, “Q” or “O”. The figure displays the target on the left side of the screen for visual purposes, but in this scenario, the target would actually appear on the right. The subjects indicated their responses via the Q or O keys on a keyboard.

Operation Span task (Figure 3).

For this task, subjects were asked to memorize a series of letters presented to them in between simple math equations that they were required to accurately solve. A simple math equation was presented on the screen first, such as “ $(5 \times 2) - 3$ ”, and the subjects indicated that they had arrived at an answer. Next, a proposed answer was presented on the screen (e.g., “ $(5 \times 2) - 3 = 7$ ” for the previous problem, and the subject indicated whether the answer was correct or not. After indication of their response, a single letter is presented for 800 ms. This process repeated until a variable set of letters had been presented, in which the recall screen appeared and subjects

were required to recall the correct serial order of the presented letters. This was done by selecting from a pool of 12 letters organized in a 4x3 matrix. A blank option was available for subjects to mark a letter that was not memorized, but still receive credit for the letters that were successfully recalled in that particular set. Feedback on accuracy was provided to the subjects for both the math problem and letter recall portions at this point for a period of 2,000 ms.

A total of 14 trials (2 blocks of 7 trials) was completed by each subject, where the set size of letters ranged from 3-8 letters. Each set size was presented once in each of the two blocks in a randomized order. Additionally, subjects were administered practice trials of both the math and letter components of the task independently and then also combined together before real data collection occurred. The set size of the 3 practice blocks (letter recall, math problem-solving, and combined) was 3 letters for each of the trials. Average computing speed was calculated throughout the experiment, and if a subject took a longer time to solve the math problems than their average computed speed plus 2.5xSD, the program would move forward and mark the response as incorrect. This automated speed time as a maximum limit was based on the procedure established by piloting from the Engle Lab at Georgia Tech (Unsworth et al., 2005). Participants were encouraged to keep an 85% accuracy rate or above on the math operations throughout the task.

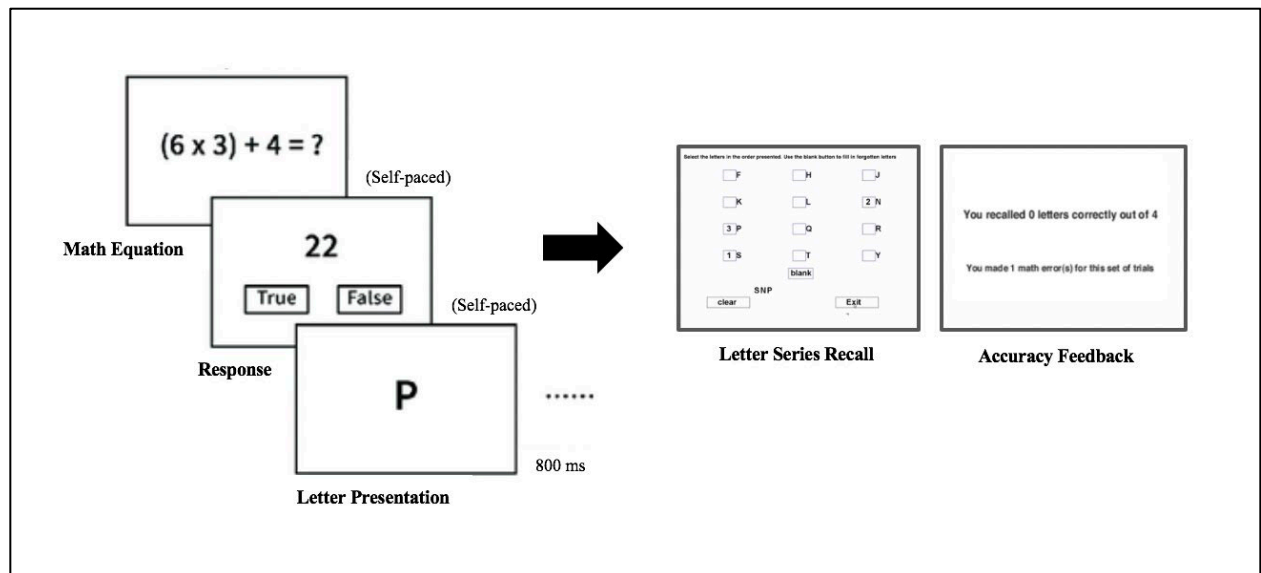


Figure 3. *Trial Sequence for the Operation Span Task (Lee & Cho, 2019).* The figure above displays the alternation between the distractor task (math equation) and the target task (letter presentation). The subject first solved a math problem and confirmed if the presented answer was true or false. After confirming their response, the first “to be memorized” letter was presented for 800 ms. A new math equation was then displayed, and this alternating pattern continued until a variable set of letters were presented. In the figure, 3 letters were presented, and the subject is asked to recall the correct serial order. Accuracy feedback was then provided on both math problems and the letter recall.

Symmetry Span task (Figure 4).

The Symmetry Span task involved a similar paradigm to the aforementioned Operation Span, where a distractor task is interspersed between the goal task to assess working memory capacity. However, the subject was first presented with a distractor shape within a 16x16 matrix of black and white squares, in which they were required to accurately determine if the shape is symmetrical along its vertical axis/midline. Therefore, the symmetry portion of this task is self-paced, similar to the math component portion of Operation Span. After correctly determining the shape’s symmetry, a 4x4 grid was presented to the subjects for 800 ms. The subjects were instructed to remember the spatial location of a red square within this 4x4 grid. This task alternation continued until a randomized number of red square locations had appeared. Upon reaching a designated set size of red square locations, the subjects were asked to recall the locations of the red squares in the correct serial order.

There were a total of 12 trials (2 blocks of 6 trials) for subjects to complete. Set sizes of squares randomly ranged from 2-7, but each set size was presented once in each of the two blocks. Additionally, the practice blocks for this task mirrored the paradigm from the Operation span;

therefore, each individual component was practiced until sufficient accuracy (>85%) was reached, and then a combined practice block was administered. Practice blocks only involved set sizes of red squares ranging from 2-5. Additionally, the average computing speed was also calculated throughout this task, and if a subject took a longer time to solve the symmetry problems than their average computed speed plus 2.5xSD, the program would move forward and mark the response as incorrect.

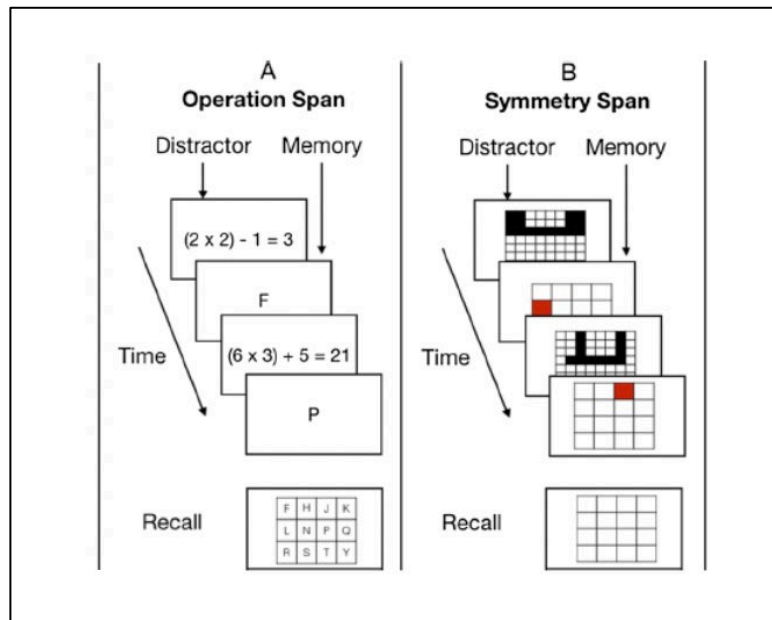


Figure 4. *Difference in Trial Sequence between Operation and Symmetry Span* (Foster et al., 2015). This figure demonstrates the parallels between the Operation and Symmetry Span task sequences. For the Symmetry Span task, the distractor task consisted of identifying if a shape was symmetrical about a vertical midline, and the target task was to memorize the spatial location of a variable set of red squares in the correct serial order. After subjects were asked to recall the set of spatial locations, feedback was provided for both the distractor symmetry task and the memory recall task.

Data Analysis

For each individual task administered, an .edat3 file was automatically exported upon completion of the task by the subject. From here, E-Merge 3.0 was used to merge all subject files for each of 4 tasks administered to create 4 merged files, containing all subject data for each respective task. These files then were analyzed using E-Data Aid 3.0 to determine the primary measures for each subjects' attempt of the 4 tasks (Final Response DL for Flanker DL, Total Accuracy for Antisaccade, and Partial Scan Score for both Operation and Symmetry Span). Any necessary secondary measures, specifically reaction time and accuracy for the distractor tasks in Operation and Symmetry Span, were also analyzed using E-Data Aid 3.0. The necessary primary measure data was imported into Microsoft Excel, which was used to calculate averages and standard error across subjects for each task, as described below in further detail. Microsoft Excel was also used to generate plots.

For Flanker DL, the final response deadline time after the final block for each subject was recorded after each attempt at baseline. Then, the average final response deadline and standard error were calculated across all subjects. For the Antisaccade task, the total number of correctly identified target letters was recorded at the end of all trial blocks. This total number of correct trials was divided by the total value of trials (72) to determine the total Antisaccade accuracy for each subject (%). The average Antisaccade accuracy and standard error were calculated across all subjects. For the Operation and Symmetry Span tasks, the partial span score, which is the total number of items (either letters or spatial locations) that were recalled in the correct serial position, was obtained at baseline. The average symmetry and operation partial scan scores (and respective standard errors) were determined across all subjects as well. Data from subjects who were unable to maintain an 85% accuracy rate on the distractor tasks (math equations and symmetry components) in both the Operation Span and Symmetry Span were removed from the data set. A

Bivariate Pearson Correlation matrix between all 4 tasks' primary measures was performed using the Analyze tool in the IBM SPSS Statistics Data Editor. Pearson correlations calculated were two-tailed and used alpha values of 0.05 to determine the p-values for each correlation in the matrix and their significance. Correlation values between all 4 tasks were automatically reported (total of 6 unique comparisons).

RESULTS

Each of the 4 tasks contained their own respective primary measures (Final Response deadline time for Flanker DL, Total Accuracy Percentage for Antisaccade, and Partial Scan Score for both Operation and Symmetry Span). For the Flanker DL task, the average Final Flanker Response Deadline time obtained across all subjects was 570.00 ± 67.528 ms. The bivariate Pearson Correlation matrix revealed that Flanker DL time was strongly negatively correlated with Symmetry Span partial scores, $r(4) = -.839, p < 0.05$, but only moderately negatively correlated with Antisaccade accuracy, $r(4) = -.679, p = .138$, and Operation Span partial scores, $r(4) = -.637, p = .174$. For the Antisaccade task, the average Total Antisaccade Accuracy across all subjects was $78.94 \pm 7.327\%$. Antisaccade accuracy revealed a strong positive correlation with both Operation Span partial score, $r(4) = .803, p = .055$, and with Symmetry Span partial score, $r(4) = .954, p < .01$. For Operation Span, the average Operation Span partial score, which represents the total number of correctly recalled letters, across all subjects was 67.17 ± 4.324 . For the Symmetry Span task, the average Symmetry Span Partial Score, which represents the total number of correctly recalled spatial locations, across all subjects was 37.67 ± 2.753 . The bivariate Pearson correlation matrix revealed a strong positive correlation of $r(4) = .729, p = .100$ between Operation and Symmetry Span partial scores.

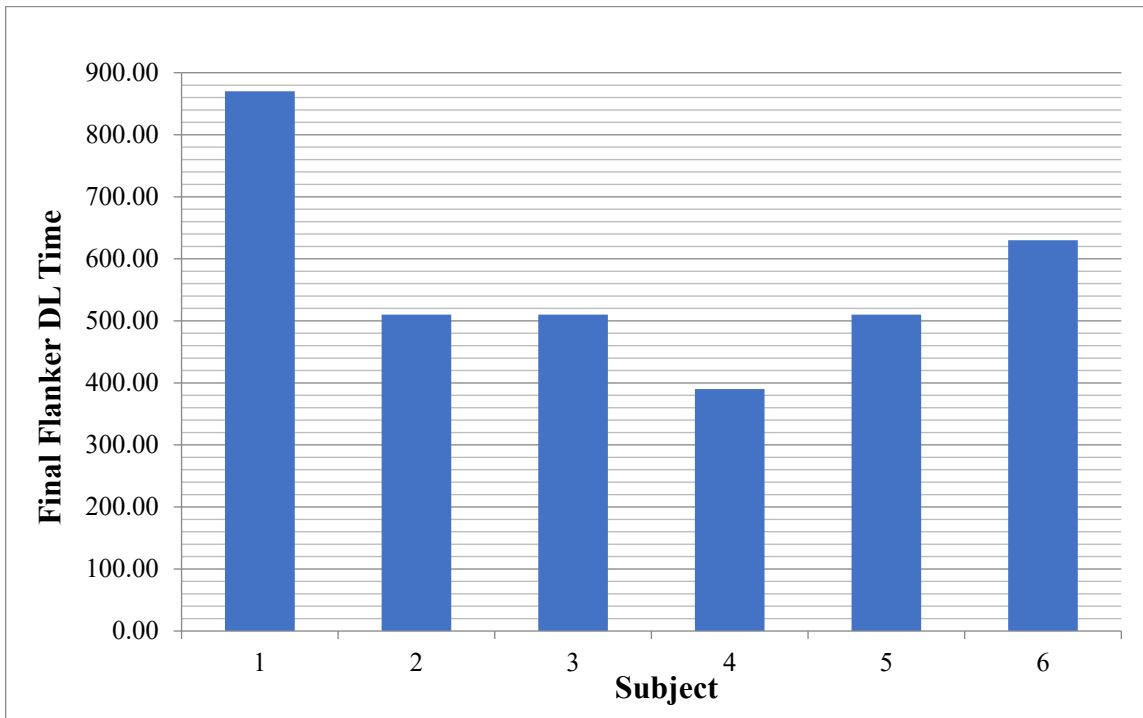


Figure 1. *Final Flanker Response Deadline Time Across Subjects.* This figure displays the final Flanker Response Deadline Time reached by each subject tested. The final Response Deadline Time is the maximum amount of time the subject would be given to respond to the flanker task after the final block of trials were completed. The response time was calculated based on the accuracy of the subjects' responses for the current block and would adjust for the next block of trials based on this accuracy. If the subject accurately responded to 15 trials or more within a single block, the response deadline decreased; however, if the subject failed to respond accurately to at least 15 trials, the response deadline was increased. As mentioned before, the amount that the response deadline was changed after a block varied depending on the specific block. The average Final Response Deadline across all subjects was 570.00 ± 67.528 ms. The bivariate Pearson Correlation matrix revealed for Flanker DL a correlation of $r(n-2) = -.839$, $p < 0.05$ with Symmetry Span, a correlation of $r() = -.679$, $p = .138$ with Antisaccade and $r() = -.637$, $p = .174$ with Operation Span partial score.

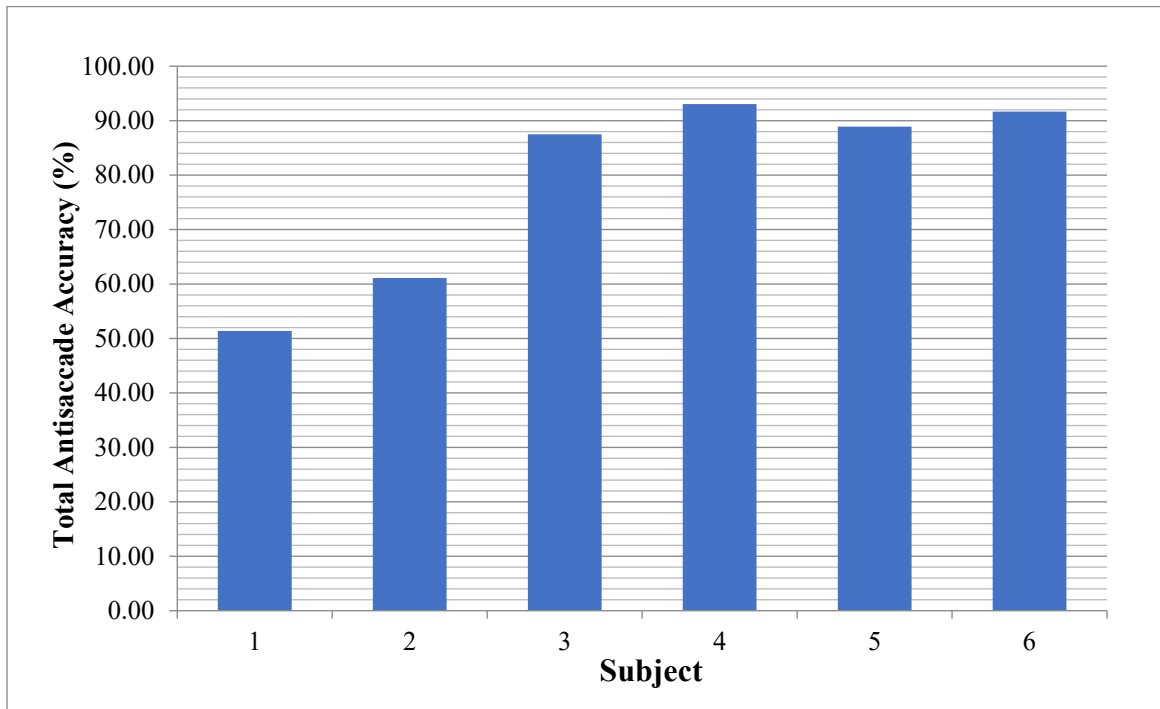


Figure 2. *Total Accuracy for the Antisaccade Task Across Subjects.* This figure shows the total accuracy across all trials (%) in the Antisaccade task for each subject administered the task.

There were a total of 72 trials for this task and subjects' total number of correct responses were divided by this total value of trials to determine the total accuracy (%). The average Total Antisaccade Accuracy across all subjects was $78.94 \pm 7.327\%$. The bivariate Pearson Correlation matrix revealed for Antisaccade a correlation of $r(4) = -.803, p = .055$ with Operation Span, a correlation of $r(4) = -.679, p = .138$ with Flanker DL and $r(4) = .954, p < .01$ with Symmetry Span partial scores.

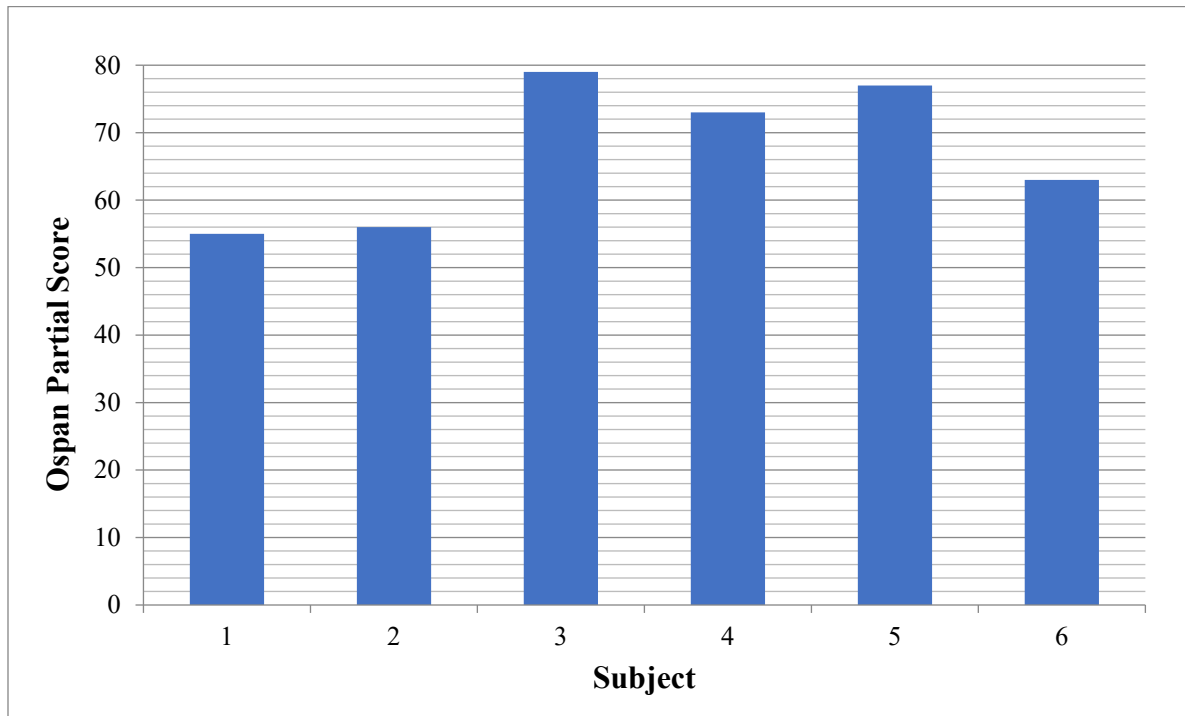


Figure 3. *Operation Span Partial Scores Across All Subjects.* This figure displays the Operation Span partial score for each subject administered the task. The Operation Span partial score is the total number of correctly recalled letters across all trials, despite any mistakes in a single trial. In comparison, an absolute score (not shown) was also obtained for each subject, which requires a stricter criteria by only identifying a response as correct if the entire span of letters in a set were correctly recalled. The partial score includes any letter correctly recalled in the total score, despite if any other letter in that set was incorrectly recalled. The average Operation Span partial score across all subjects was 67.17 ± 4.324 . The bivariate Pearson Correlation matrix revealed for Operation Span partial scores a correlation of $r(4) = -.803, p = .055$ with Antisaccade accuracy, a correlation of $r(4) = -.637, p = .174$ with Flanker DL time and $r(4) = .729, p = .100$ with Symmetry Span partial scores.

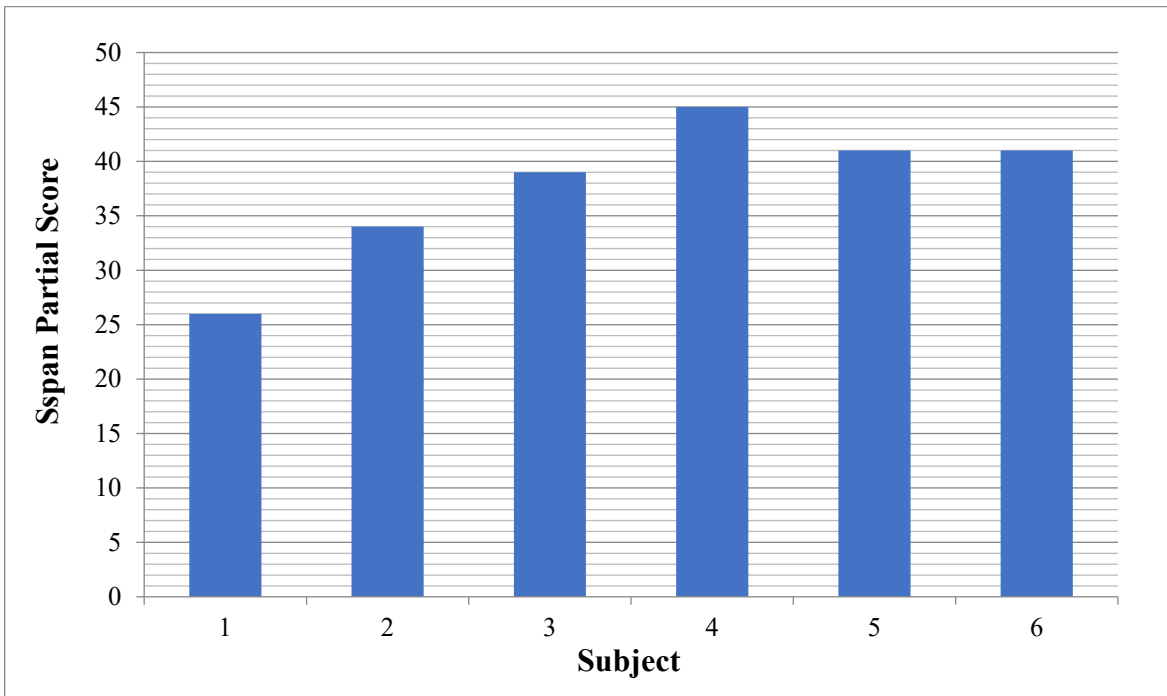


Figure 4. *Symmetry Span Partial Score Across All Subjects.* This figure displays the Symmetry Span Partial Score for each subject administered the task. The Symmetry Span Partial Score is the total number of correctly recalled red square spatial locations across all trials, despite any mistakes in a single trial. In comparison, an absolute score (not shown) was also obtained for each subject, which requires a stricter criteria by only identifying a response as correct if the entire span of spatial locations in a set were correctly recalled. The partial score counts all spatial location correctly recalled towards the total score, despite if any other letter in that set was incorrectly recalled. The average Symmetry Span Partial Score across all subjects was 37.67 ± 2.753 . The bivariate Pearson Correlation matrix revealed for Symmetry Span partial scores a correlation of $r(4) = -.954, p < .01$ with Antisaccade accuracy, a correlation of $r(4) = -.839, p < .05$ with Flanker DL time and $r(4) = .729, p = .100$ with Operation Span partial scores.

DISCUSSION

At first glance, the preliminary results from the 4 tasks demonstrate a consistent trend; subjects that showed higher performance on the attentional tasks (faster Final Flanker response deadline time and higher Antisaccade accuracy) also showed higher performance on the working memory tasks (higher partial span score). More specifically, subjects 1 and 2 consistently showed the lowest performance on all 4 tasks, while subject 4 mostly performed at the highest level across tasks. This trend infers some level of validation of these tasks, as those subjects' who demonstrate lower intelligence or cognition level on one task are consistently doing so on different types of tasks that assess different aspects of cognition. Furthermore, the trend is even consistent across the tasks that test the same cognitive function but vary in methodology. For example, subjects who performed less accurately on the Antisaccade task also demonstrated a slower final response deadline on the Flanker DL task, which both assessed attentional control, but through different paradigms.

The Antisaccade task is often viewed as a “hallmark” measure of attention control in this field, and past research has revealed strong, statistically significant correlations between the Antisaccade task and the Flanker DL task (Draheim et al., 2019a). Furthermore, past work has shown that Antisaccade and Flanker DL are two of the best indicators of attentional control based on reliabilities and intercorrelations and their strong relationship to working memory capacity and fluid intelligence. Our work demonstrated a moderately strong negative correlation of $r = -.679$ ($p = .138$) between the Flanker DL final response deadline (ms) and the Antisaccade total accuracy. Therefore, a relationship seems to exist in which subjects who reached a faster response deadline time on the Flanker DL task were also scoring more accurately on the Antisaccade task. This correlation, although not significant, corresponds to past work and partially supports how both tasks assess processing components of attentional control.

All correlations established between task results were either moderately strong or strong, but the 2 significant correlations found were between Symmetry Span and both Flanker DL ($r = -.839, p < .05$) and Antisaccade ($r(n-2) = .954, p < .01$). Flanker DL and Antisaccade have been indicated to be more strongly correlated with measures of working memory capacity in comparison to other attentional control measures and these significant correlations calculated demonstrate that relationship (Draheim et al., 2019a). However, this same strength of replication is not reflected with Operation Span, another measure of working memory capacity like Symmetry Span. This could suggest that Symmetry and Operation Span measure different aspects or mechanisms of working memory processing, and this variation in paradigm between the 2 tasks allows Symmetry Span to be more strongly correlated with these measures of attentional control.

An empirical test and validation assessment has been previously performed by researchers (Draheim et al., 2019a) on a variety of measures of attentional processing, including the 4 tasks we administered, and comparison of primary measure averages to the values determined in this study is important. The average data values obtained from the 4 tasks here display both consistency and inconsistency with the average standard values determined in this empirical study performed on a sample of 396 subjects. Compared to the average Final Flanker Response Deadline of 570.00 ms we obtained here, Draheim and researchers (2019a) determined a higher average Final Response Deadline of 674.61 ms across all subjects. The average Antisaccade accuracy rate we obtained was 78.84%, and Draheim and researchers demonstrated a substantially close average Antisaccade accuracy of 79.00%. Yet, the Operation and Symmetry Span partial scores obtained by Draheim et al. (2019a) were not as comparable to values found in this work. The Operation Span partial score obtained here was 67.17, while past researchers isolated a smaller value of 55.76. Additionally, while the average Symmetry Span

partial score obtained here was 37.67, the Symmetry Span partial score indicated in this empirical research was also lower, at a value of 27.90 (Draheim et al., 2019a). Although only the Total Antisaccade Accuracy was in close proximity to previously established values, the 3 inconsistent primary measures for the tasks still displayed a consistent trend of higher cognitive performance across the board, i.e. lower response deadline, higher operation span and symmetry span partial scores, compared to the averages demonstrated by past research.

The inconsistency shown between previously established average values and the obtained results could be a consequence of the small sample size used ($n=6$) and the sample size's less accurate representation of the general population. The sampling methods used, such as only assessing Georgia Tech students as control participants, is likely less representative of the average population and could influence the higher (or faster) average values for the Flanker DL, Operation Span, and Symmetry Task. Another limitation of this research is that the Flanker DL and Antisaccade tasks, although reliable, may be demonstrating only task-specific processing within attentional control and could be an incomplete representation of attention. More specifically, although these 2 tasks measure important attention-related processing, these tasks could to some extent measure only specific mechanisms of attention and this could limit the scope of their use as measure of change in cognition in patients with MDD. This also goes for the Operation Span and Symmetry Span tasks, as both could be assessing only a component of working memory processing as limited by their methodological design. Furthermore, uncontrolled extraneous variables, such as task administration fluidity and subject motivation, could impact the level of subject performance and the data collected.

FUTURE DIRECTIONS

The validation of these 4 tasks as appropriate measures of attentional control and working memory is crucial before these tasks can be applied as primary measures of change in cognition in response to the administration of an anti-depressant. Although the validation and proper testing of these tasks in a healthy, control population is an important step, the overall end goal of this project remains to identify biomarkers for Citalopram efficacy using a combination of cognitive-behavioral assessment and functional Magnetic Resonance Imaging. Additionally, it is equally important that this piloted control subject data is used for means of comparison to the behavioral data obtained from patients with MDD in the future. Because some significantly strong correlations between the 4 tasks were obtained, researchers will continue to assess the validity of these tasks and hope to administer them in patients with MDD over an 8-week period to assess change in attentional control and working memory from baseline. Moving forward, these cognitive behavioral tasks will be used in combination with a separate array of psychometric fMRI tasks that have already previously been validated to potentially isolate correlations between changes in cognitive performance and in functional connectivity as a result of anti-depressant administration.

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