Determining the Effects of an Acute Bout of Exercise on Executive Function among Individuals with Schizophrenia

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Faculty of Kinesiology and Physical Education
University of Toronto

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Abstract

Objective: To investigate whether one bout of exercise can improve executive function among individuals with schizophrenia. Methods: In this within-subject, counterbalanced experiment, participants with schizophrenia (n=36) either completed a 20-minute bout of moderate intensity exercise on a cycle ergometer or, passively sat for the same time period. Participants completed the Wisconsin Card Sorting Test (WCST) before and after the condition to measure changes in executive function. All participants returned one week later to complete the arm of the study that they did not complete. Results: Due to a significant practice effect, only the WCST scores from the first condition completed by participants were analyzed. There was a significant time by session interaction effect for non-perseverative errors. Post-hoc analyses revealed a significant reduction in non-perseverative errors among the exercise group. Conclusions: An acute bout of exercise may be able to help patients with schizophrenia with select working memory tasks.
Acknowledgments

I would like to express my sincere gratitude to Dr. Guy Faulkner for taking me on as his student, giving me multiple opportunities to get involved in numerous research projects and for giving me the opportunity and support to design my master’s thesis project as how I saw fit. I learned tremendously under your supervision.

I would like to thank Dr. Luc Tremblay for his guidance with the design of my study and the interpretation of my results. The time you devoted to my learning and the critical questions you asked were invaluable.

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1 Overview

Schizophrenia is a serious mental illness, with a significant impact on the quality of life of those who are affected, their families and caregivers. One of the major contributors of poor quality of life in this population is cognitive impairment. Although schizophrenia is a heterogeneous illness, cognitive deficits are almost a uniform characteristic of this illness (Fioravanti, Bianchi, & Cinti, 2012). The following section will provide a background on schizophrenia as a mental illness and common cognitive deficits reported in meta-analyses and systematic reviews. There will be a focus on executive functions, as it is a domain of cognition that is significantly impaired in this population and due to its importance for a number of functional outcomes, such as independent living (Green, Kern, Braff, & Mintz, 2000). Current endeavours to address this problem and their limitations will be explored, with a focus on cognitive remediation therapy, stimulants and pharmaceutical drugs.

1.1 Illness Background

Schizophrenia is a severe mental illness characterized by one or more of the five following characteristics: delusions, hallucinations, disorganized thinking (alogia), disorganized or abnormal motor behaviour (including catatonia) and negative symptoms (American Psychiatric Association, 2013). Schizophrenia is a life-long diagnosis that affects about 1% of the world’s population (Orellana & Slachevsky, 2013). The age of onset of the first symptoms range from late adolescence to early adulthood, with men showing symptoms earlier than women (Castle, Wessely, & Murray, 1993). About 9-13% of people diagnosed with schizophrenia commit suicide (Perenyi & Forlano, 2005). Although this mental illness only affects a small portion of the Canadian population, it has a significant societal and economic burden. The financial cost of addressing the psychological symptoms and physical comorbidities is about US $ 62 million, with variation among countries based on the number of individuals affected (Kitchen, Rofail, Heron, & Sacco, 2012).
Furthermore, the life expectancy of individuals with schizophrenia is lower than the average population by 10-25 years, primarily due to the physical comorbidities that accompany this diagnosis (Laursen, Munk-Olsen, & Vestergaard, 2012). Specifically, cardiovascular disease accounts for 12-46% of all-cause mortality (Bushe, Taylor, & Haukka, 2010; Carney, Jones, & Woolson, 2006). The etiology of cardiovascular disease in this population is varied, ranging from poor lifestyle factors to side effects of antipsychotic medications. Individuals with schizophrenia smoke often (Kelly et al., 2011), eat low-nutritious diets (Ryan, Collins, & Thakore, 2003), and are physically less active (Cohn, Prud’homme, Streiner, Kameh, & Remington, 2004; Daumit et al., 2005; Lindamer et al., 2008). Furthermore, a recent comprehensive review reported that the two main side effects of atypical antipsychotic medications are weight gain and the development of other metabolic risk factors, both of which can occur independently and in concert to lead to cardiovascular disease (Homel, Casey, & Allison, 2002; Meyer et al., 2008). When assessed over a 1-year treatment period, significantly greater weight gain incidence was seen for olanzapine (57%) and risperidone (39%), two common antipsychotic medications used by schizophrenia patients (Parsons et al., 2009). Therefore, both poor lifestyle factors and side effects of antipsychotic medications contribute to cardiovascular disease in this population. One of the other major consequences of poor lifestyle factors and these drug-related side effects is cognitive impairment, potentially mediated by the metabolic risk factors mentioned earlier (Yaffe et al., 2004). However, because cognitive impairment is identifiable before treatment or even the onset of psychosis, the independent nature and role of physical illness post diagnosis on these cognitive deficits is challenging to attribute. In sum, although illness-related symptoms may be adequately managed, the quality of life and functional outcomes of individuals with schizophrenia is still poor, primarily due to cognitive impairment.

1.2 Cognitive Deficits in Schizophrenia

Individuals with schizophrenia have significantly reduced functions in most domains of cognition when compared to the general population (see Table 1). Cognitive function is a broad term used to define and describe a set of mental processes, such as attention, reasoning, problem solving and decision-making. These processes are essential for performing daily activities in order to live autonomously. An extensive review of primary literature by Fioravanti, Bianchi, & Cinti (2012) found deficits in areas of executive function (SMD=-1.10, p<0.01), short-term memory (SMD=-1.05, p<0.01), long-term memory (SMD=-1.14, p<0.01), IQ (SMD=-0.96,
language ($SMD=-0.99, p<0.01$), and reaction time ($SMD=0.99, p<0.01$) when compared to healthy controls. Specifically, within the area of executive function, further evidence was found to support impairments in verbal (cognitive-linguistic) and visual (emotion recognition from eyes) mentalizing tasks (Chung, Barch, & Strube, 2013), cognitive inhibition (Westerhausen, Kompus, & Hugdahl, 2011) and working memory (Forbes, Carrick, McIntosh, & Lawrie, 2009) (see Table 1 for specific effect sizes). Impairments in different types of semantic memory have also been reported, with large effect sizes for naming and verbal fluency (Doughty & Done, 2009).

Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman (2009) found that regardless of age of onset, by the first-episode, schizophrenia patients have medium to large impairments in the majority of neurocognitive functions ($SMD$ from -0.64 to -1.20, $p<0.05$), with severe deficits in immediate verbal memory, processing speed and IQ. Therefore, this suggests that, cognitive deficits precede the onset of the illness. Different cognitive profiles were also found during diagnosis at different points in time throughout the life course. Compared to adult-onset of illness, youth-onset showed larger deficits in executive function, IQ, psychomotor speed of processing and verbal memory (Rajji, Ismail, & Mulsant, 2009). Compared to adult-onset, late-onset of schizophrenia resulted in larger deficits in attention, global cognition, IQ, visuospatial construction, language and working memory (Irani, Kalkstein, Moberg, & Moberg, 2011; Rajji et al., 2009). Patients with schizophrenia also seemed to demonstrate greater deficits in verbal memory and executive function than patients diagnosed with schizoaffective or affective psychosis (Bora, Yucel, & Pantelis, 2009a).

In sum, a wide range of cognitive deficits are found among individuals with schizophrenia, including those in executive function, language, memory, attention and social cognition. Depending on the age-of-onset, different areas of cognitive function seem to be affected with differing severities. However, by first-episode, regardless of age-of-onset, schizophrenia patients already exhibit significant impairments in a range of cognitive functions.
Table 1. Summary of studies using meta-analyses and systematic reviews to evaluate cognitive deficits among individuals diagnosed with schizophrenia (SZ).

<table>
<thead>
<tr>
<th>Article</th>
<th>Disorder</th>
<th># Of Studies</th>
<th>Main Objective</th>
<th>Specific Cognitive Impairment (Effect Sizes)</th>
<th>Use of a Healthy Control (HC) Group/Standardized Tests with Normative Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Bora et al., 2009a)</td>
<td>SZ</td>
<td>31</td>
<td>To directly compare cognitive functioning across SZ, schizoaffective disorder and affective psychosis.</td>
<td>SZ &lt; schizoaffective/affective psychosis on immediate verbal memory ($d=0.42, p&lt;0.01$), IQ ($d=0.37, p&lt;0.01$), verbal working memory ($d=0.31, p=0.02$), and WCST ($d=0.25, p&lt;0.01$) performances for executive function.</td>
<td>No</td>
</tr>
<tr>
<td>(Bora, Yucel, &amp; Pantelis, 2009b)</td>
<td>SZ</td>
<td>36</td>
<td>To understand Theory of Mind (ToM) impairment.</td>
<td>ES for overall ToM and individual tasks were large ($d=0.90-1.08, p&lt;0.01$). In “remitted” patients, ToM less impaired ($d=0.80, p&lt;0.01$) than non-remitted patients ($d=1.21, p&lt;0.01$); general intellectual impairment in SZ contributed to ToM deficit in “remitted” patients.</td>
<td>Yes</td>
</tr>
<tr>
<td>(Chung et al., 2013)</td>
<td>SZ</td>
<td>37</td>
<td>Assessed verbal and visual mentalizing ability in autism spectrum disorder and SZ.</td>
<td>In the SZ group, verbal mentalizing task ($g = 0.99, p&lt;0.01$) and visual mentalizing tasks ($g = 0.73, p&lt;0.01$) showed large deficits.</td>
<td>No</td>
</tr>
<tr>
<td>(Doughty &amp; Done, 2009)</td>
<td>SZ</td>
<td>91</td>
<td>To systematically evaluate whether semantic memory is impaired.</td>
<td>Uneven profile of impairment reported: large ES for tests of naming ($d=-1.45, p&lt;0.05$) and verbal fluency ($d=-1.34, p&lt;0.05$), medium ES for categorisation ($d=-0.49, p&lt;0.05$).</td>
<td>No</td>
</tr>
<tr>
<td>(Fioravanti et al., 2012)</td>
<td>SZ</td>
<td>247</td>
<td>Assessment of neurocognitive impairments in SZ examined through memory deficits, IQ</td>
<td>SZ &lt; HC in all domains and in all different analyses performed within each domain, such as executive function (SMD=-1.10, $p&lt;0.01$), short-term memory (SMD=-1.05, $p&lt;0.01$).</td>
<td>Yes</td>
</tr>
<tr>
<td>Study</td>
<td>Group</td>
<td>Sample Size</td>
<td>Aim</td>
<td>Results</td>
<td></td>
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<tr>
<td>-------</td>
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<td>-------------</td>
<td>-----</td>
<td>---------</td>
<td></td>
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<tr>
<td>(Forbes et al., 2009)</td>
<td>SZ</td>
<td>187</td>
<td>To compare working memory function in SZ and healthy controls.</td>
<td>Statistically significant results present for all working memory measures, indicating large deficits in SZ across all three working memory domains (phonological ($d=0.55-1.14$, $p&lt;0.05$), visuospatial ($d=0.51-1.29$, $p&lt;0.05$) and central executive working memory ($d=0.73-0.92$, $p&lt;0.05$).</td>
<td></td>
</tr>
<tr>
<td>(Irani et al., 2011)</td>
<td>SZ</td>
<td>43</td>
<td>To assess the nature and course of cognitive impairments among older patients with SZ.</td>
<td>Longitudinal changes in global cognition small ($d=-0.097$, $p&lt;0.05$); cross-sectional, baseline assessment of global cognition large ($d=-1.19$, $p&lt;0.05$); IQ ($d=-0.84$, $p&lt;0.05$), language ($d=-1.30$, $p&lt;0.05$), immediate memory ($d=-1.25$, $p&lt;0.05$), executive function ($d=-1.14$, $p&lt;0.05$).</td>
<td></td>
</tr>
<tr>
<td>(Knowles, David, &amp; Reichenberg, 2010)</td>
<td>SZ</td>
<td>47</td>
<td>To analyze processing speed and other cognitive functions in SZ and examine the role of potential moderator variables.</td>
<td>Largest ES for coding task ($g=-1.50$, $p&lt;0.01$), followed by category fluency ($g=-1.31$, $p=0.03$). Important moderators for coding task ES are: publication year, IQ difference from comparison subjects, and chlorpromazine equivalent daily dose. ES=0.8 difference between low and high chlorpromazine equivalent daily dose.</td>
<td></td>
</tr>
<tr>
<td>(Kohler, Walker, Martin, Healey, &amp; Moberg, 2010)</td>
<td>SZ</td>
<td>86</td>
<td>To understand facial emotion perception in SZ.</td>
<td>Large deficit in facial identification and differentiation ($d=-0.91$, $p&lt;0.05$) in SZ, irrespective of task type. Illness-related factors, such as current hospitalization, clinical symptoms and antipsychotic treatments</td>
<td></td>
</tr>
</tbody>
</table>

deterioration, language deficits, executive functioning deficits, and attention deficits

long-term memory (SMD=-1.14, $p<0.01$), IQ (SMD=-0.96, $p<0.01$), language (SMD=-0.99, $p<0.01$), reaction time (SMD=0.99, $p<0.01$).
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Research Question</th>
<th>Findings</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Mesholam-Gately et al., 2009)</td>
<td>FE SZ</td>
<td>47</td>
<td>To provide a meta-analysis of neurocognitive findings from first episode (FE) SZ patients.</td>
<td>FE SZ - medium-to-large impairments across 10 neurocognitive domains (SMD from -0.64 to -1.20, $p&lt;0.05$). Impairments are reliably and broadly present by the FE, approach or match the degree of deficit shown in well-established illness. Largest deficits were found in immediate verbal memory (SMD=-1.20, $p&lt;0.05$), processing speed (SMD=-0.96, $p&lt;0.05$) and executive function (SMD=-0.83, $p&lt;0.05$). Larger IQ impairments in FE compared to premorbid period, but similar to later phases of illness, suggesting deterioration.</td>
<td>Yes</td>
</tr>
<tr>
<td>(Rajji et al., 2009)</td>
<td>SZ</td>
<td>109</td>
<td>To compare cognitive deficits in individuals with youth-onset and late-onset schizophrenia with those in adults with first-episode schizophrenia.</td>
<td>Compared to adults, youth-onset and first-episode SZ demonstrate large deficits ($d \geq 0.8$, $p&lt;0.05$) on almost all cognitive measures. Youth-onset SZ demonstrated larger deficits than those with first-episode SZ on arithmetic, executive function, IQ, psychomotor speed of processing and verbal memory. Late-onset SZ demonstrate minimal deficits on arithmetic, digit symbol coding and vocabulary, but larger ones on attention, fluency, global cognition, IQ and visuospatial construction.</td>
<td>Yes</td>
</tr>
<tr>
<td>(Savla, Vella, Armstrong, Penn, &amp; Twamley, 2013)</td>
<td>SZ</td>
<td>112</td>
<td>Examine the average magnitude of differences between SZ and healthy controls across multiple domains of social cognition.</td>
<td>SZ worse on all domains compared to healthy controls: large effects for social perception ($g = 1.04, p&lt;0.01$), ToM ($g = 0.96, p&lt;0.01$), emotion perception ($g = 0.89, p&lt;0.01$), and emotion processing ($g = 0.88, p&lt;0.01$).</td>
<td>Yes</td>
</tr>
<tr>
<td>(Westerhausen)</td>
<td>SZ</td>
<td>36</td>
<td>Assess a sub-component of executive function (cognitive)</td>
<td>SZ show increased Stroop interference effect both in response time (Mean $g = 0.43$, C.I.</td>
<td>Yes</td>
</tr>
</tbody>
</table>
et al., 2011) inhibition) using the Stroop Color-Word Interference Paradigm. 95%: 0.35–0.52) and accuracy (Mean g = 0.62, C.I. 95%: 0.47-0.77).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Participants</th>
<th>Design</th>
<th>Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stefanopoulou et al., 2009</td>
<td>SZ and affective disorders</td>
<td>53</td>
<td>To conduct a quantitative review of studies on cognitive performance in SZ and affective disorders.</td>
<td>General IQ: SZ &lt; HC (SMD=1.44, p&lt;0.01); National Adult Reading Test: SZ &lt; HC (SMD=0.94, p&lt;0.01), California Verbal Learning Test – Total Free Recall: SZ &lt; HC (SMD=1.32, p&lt;0.01), California Verbal Learning Test – Long Delay Free Recall: SZ &lt; HC (SMD=1.26, p&lt;0.01), Trail Making Test – Part A: SZ &lt; HC (SMD=1.05, p&lt;0.01), Trail Making Test – Part B: SZ &lt; HC (SMD=1.13, p&lt;0.01), Wisconsin Card Sorting Test – Categories Achieved: SZ &lt; HC (SMD=1.14, p&lt;0.01), Wisconsin Card Sorting Test – Perseverative Errors: SZ &lt; HC (SMD=0.84, p&lt;0.01), Controlled Oral Word Association Test: SZ &lt; HC (SMD=1.03, p&lt;0.01). Yes</td>
</tr>
<tr>
<td>Vöhringer et al., 2013</td>
<td>SZ and BD</td>
<td>10</td>
<td>Systematic review of cognitive decline among SZ and BD</td>
<td>Overall, SZ &lt; BD &lt; HC. SZ and BD share similar cognitive impairment profile; SZ with more severe and pervasive cognitive deficits, BD milder and more confined impairment. Yes</td>
</tr>
<tr>
<td>Wang et al., 2013</td>
<td>SZ and BD</td>
<td>13</td>
<td>Systematic evaluation whether semantic inhibition (executive function) is differentially impaired in BD and SZ using the Hayling Sentence Completion Test Performance (HSCT).</td>
<td>SZ &lt; HC (medium-to-large effect sizes, d=0.46-0.94, p&lt;0.01) on all HSCT measures; deficits in SZ and BD were comparable. Yes</td>
</tr>
</tbody>
</table>
1.3 Potential Explanations for Cognitive Deficits

The exact reason why cognitive deficits are a core characteristic of patients with schizophrenia is unknown. Studies with twins and first-degree relatives suggest that genes predisposing some individuals to this illness may affect other heritable traits, like cognitive function (Bilder et al., 2000; Goldman et al., 2008; Greenwood et al., 2007; Toulopoulou et al., 2007). Thus, cognitive impairment would act as the intermediary phenotype between the genetic risk factors for schizophrenia and the illness presentation itself (van Os & Kapur, 2009). Neurochemical hypotheses have also been proposed. For example, poor NMDA receptor activity on GABA inhibitory interneurons in the prefrontal cortex has been associated with poor cognitive performance (Insel, 2010).

Another common view is that schizophrenia is a neurodevelopmental disorder, potentially as a result of abnormal fetal development, obstetric complications or problems during childhood (Cannon, 1996). From this perspective, cognitive impairment is seen as one of the consequential outcomes, where structural brain abnormalities and disconnects between various brain networks are also evident at the time of diagnosis. Environmental factors early in life have also been hypothesized to affect poor neurodevelopment and cognition (Lewis & Levitt, 2002), such as the living environment and maternal drug use. There are also those who propose that cognitive impairment associated with schizophrenia is the result of neurodegeneration. For example, some studies report that among patients with schizophrenia, progressive enlargement of the ventricles and reduction in gray matter volume can be seen over the course of the illness, particularly during the early stages (Davis et al., 1998; Hulshoff Pol et al., 2002; van Haren et al., 2008; Woods et al., 1990). Although schizophrenia neuropathology and explanations for the altered brain morphology may be multifactorial (Kahn & Sommer, 2015), one possible explanation is the side effects of antipsychotics (Navari & Dazzan, 2009). Specifically, typical antipsychotic medications, such as haloperidol, have been show to reduce total brain gray matter to a greater extent than atypical antipsychotic medications, such as olanzapine (Lieberman et al., 2005). It is also possible that reductions in brain volume is due to the natural progression of schizophrenia and that atypical antipsychotics, such as olanzapine and clozapine, work in a facilitative manner, through mechanisms related to synaptic remodeling and neurogenesis, to hinder this progression (Lieberman et al., 2005; Selemon, Lidow, & Goldman-Rakic, 1999).
1.4 Executive Function

Among the many areas of impairment in schizophrenia, executive function has one of the most significant deficits. This is also an area of cognition essential for a number of functional outcomes and autonomous living. Currently, there is no standard definition for executive function. Over the years, researchers have formulated their own definition to describe their interpretation of the processes that are governed by executive function, with common features between many of these definitions. For example, Lezak (1983) defined executive function as having four components: the ability to form goals, plan, carry out goal-directed plans, and perform effectively. All of these behaviours are responsible for “appropriate, socially responsible and effectively self-serving adult behaviour and are necessary to live independently and productively” (Lezak, 1982, pg. 281-285). Elliott (2003) describes executive function as a set of mental processes that are involved in complex cognition, such as solving novel problems, modifying behaviour in the light of new information, generating strategies or sequencing complex actions (Elliott, 2003). When “these systems break down, behaviour becomes poorly controlled, disjointed and disinhibited. Co-ordination, control and goal-orientation are, therefore, at the heart of the concept of executive function” (Elliott, 2003, pg. 50). In sum, executive function is often used to describe the collection of mental processes involved in governing human behaviour in a dynamic fashion according to changing and complex environments in a way that advances one’s own self-interests and is socially acceptable.

1.4.1 Wisconsin Card Sorting Test (WCST)

The Wisconsin Card Sorting Test (WCST) is an extensively used neuropsychological test designed to measure frontal lobe impairments and has a long history as a probe of executive function (Heaton, Chelune, Talley, Kay, & Curtis, 1993). This test is intended to evaluate global executive function as it requires the individual to be able to successfully perform the following skills, among others: strategic planning (via non-perseverative errors), flexibility in thinking (via perseverative errors), formation of goal-oriented behaviour and the minimization of impulsive choices. Please see section 3.3.7 for further details about the WCST.
1.4.2 Performance on the WCST by Schizophrenia Patients

Patients with schizophrenia show deficits in executive function on a wide range of cognitive tests, in particular the WCST. Everett, Lavoie, Gagnon, & Gosselin (2001) conducted a study to directly determine the difference between schizophrenia patients and healthy controls on the WCST. They found that schizophrenia patients had lower performance than healthy controls on all possible sub-analyses of this test (fewer correct categories, more perseverative errors and perseverative responses, more trials to succeed in the first category and lower conceptual level responses). Wobrock et al. (2009) compared executive function in schizophrenia patients to those diagnosed with bipolar disorder and healthy controls through a number of different tests, including the WCST and found that schizophrenia patients performed worse than bipolar patients and healthy controls (Wobrock et al., 2009). Schizophrenia patients had a greater number of perseverative responses, indicating they may have deficits in cognitive flexibility as they had problems detecting changes in the environment. Furthermore, schizophrenia patients with paranoia tend to do worse on the WCST than those without paranoia (Abbruzzese, Ferri, & Scarone, 1996). Specifically, those patients affected with paranoia made more perseverative errors than those without. In other words, these patients continued to sort the cards according to the previous rule, despite negative feedback. In a meta-analysis evaluating the performance of schizophrenia patients to healthy controls on the WCST, the mean weighted effect size was large for the number of categories achieved ($d=0.91$, $p<0.01$), medium for absolute level of perseveration ($d=0.53$, $p<0.01$) and small for perseverative errors ($d=0.18$, $p<0.01$) (Laws, 1999).

In another meta-analysis, Mesholam-Gately et al. (2009) found an overall large deficit in performance on the WCST by first-episode participants compared to healthy controls ($SMD=-0.83$, $p<0.01$). Specific large deficits were also reported for preservative responses ($SMD=-0.99$, $p<0.01$), categories completed ($SMD=-0.84$, $p<0.01$), perseverative errors ($SMD=-0.81$, $p<0.01$), and a medium sized deficit for total errors ($SMD=-0.57$, $p<0.01$) (Mesholam-Gately et al., 2009). In an assessment of 104 participants with schizophrenia, Purdon & Waldie (2001) found similar deficits in the total errors ($M=25.47$, $SD=12.47$), perseverative errors ($M=14.93$, $SD=10.46$), and non-perseverative errors ($M=10.54$, $SD=7.40$).
1.5 Current Attempts at Improving Cognitive Function

1.5.1 Cognitive Remediation Therapy

A number of solutions to address cognitive deficits in this population have been proposed and tested with some success. Cognitive remediation therapies are behavioural interventions aimed at educating and training individuals to develop basic cognitive skills in order to improve functional outcomes in activities of daily, independent living and social situations, such as school and work (Medalia & Choi, 2009). Of the six meta-analyses that were conducted to evaluate some aspect of cognitive remediation among individuals with schizophrenia, five found a moderate to large effect size (Krabbendam & Aleman, 2003; Kurtz, Moberg, Gur, & Gur, 2001; McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007; Suslow, Schonauer, & Arolt, 2001; Twamley, Jeste, & Bellack, 2003). Larger effect sizes were found among studies that targeted improvement on specific, narrow tasks. However, effects were reduced to modest levels when the performance measure was a complex, multi-component daily activity that involved multiple cognitive functions (Medalia & Choi, 2009). These remediation therapies have been reported to be effective for 6 months, especially in the area of executive function, working and verbal memory (Bell, Fiszdon, Greig, Wexler, & Bryson, 2007; Hodge et al., 2010; Hogarty, Greenwald, & Eack, 2006). Furthermore, although schizophrenia is a heterogeneous condition with wide symptom variability, cognitive remediation therapies have been shown to have some success at all levels of illness severity (Bellucci, Glaberman, & Haslam, 2003; Fiszdon, Whelahan, Bryson, Wexler, & Bell, 2005; Gopal, 2005; Kurtz, Moberg, Gur, & Gur, 2004; Medalia, Herlands, & Baginsky, 2003), from patients who are institutionalized (Medalia, Dorn, & Watras-Gans, 2000) to those in vocational rehabilitation programs (Bell et al., 2007; McGurk et al., 2007). There is also evidence to support that cognitive remediation along with other functional outcome related training (e.g. social skills training, job-specific training) would increase the duration of the effect as well as the success rate of the participant at that functional outcome (Bell et al., 2007; Greig, Zito, Wexler, Fiszdon, & Bell, 2007; Spaulding, Reed, Sullivan, Richardson, & Weiler, 1999; Wexler & Bell, 2005).

However, this avenue of cognitive remediation is not without significant limitations. The ability for humans to survive and adapt has been, in part, associated with the ability to acquire information, internalize it and effectively use it in different contexts. In healthy individuals, the
brain can perform this skill with relative ease. However, individuals with schizophrenia cannot flexibly use the knowledge or skills they gain in novel contexts (Bellack, Weinhardt, Gold, & Gearon, 2001; Berger et al., 1993). Cognitive remediation therapies have had limited success in this area (Bell et al., 2007; Kurtz, Seltzer, Fujimoto, Shagan, & Wexler, 2009) and, as a result, additional context- or function-specific training was necessary to reap the rewards of the initial training (Roder, Mueller, Mueser, & Brenner, 2006; Wykes et al., 2007) with modest results at improving functional outcomes (Bell et al., 2007; Hodge et al., 2010; McGurk et al., 2007; Twamley, Savla, Zurhellen, Heaton, & Jeste, 2008). Cognitive remediation therapy is also a time and resource intensive process, where the patients would have to make a commitment to the program. Trained personnel would need to assess the cognitive functions that need to be targeted and, potentially, devise a tailored program for the individual. As such, this does not appear to be a feasible or practical solution that can be made available to every individual with schizophrenia.

1.5.2 Cognition-Enhancing Drugs

Because cognitive impairment is one of the major characteristics of schizophrenia and is a strong predictor of functional outcomes, attempts are also currently made to develop pharmaceutical drugs to improve this deficit. A specific organization, called the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), was developed for this endeavour. The purpose of this organization is to develop and register cognitive-enhancing agents for cognitive impairment associated with schizophrenia (CIAS) (Marder, 2006).

Some research suggests that second generation antipsychotic drugs result in better cognitive outcomes than first generation anti-psychotics, but the overall effect size is small (Breier, 2005; Harvey & Keefe, 2001; Keefe, Silva, Perkins, & Lieberman, 1999). A meta-analysis of 14 randomized controlled trials that assigned participants to either an atypical antipsychotic drug or typical antipsychotic drug control arm found that atypical drugs were slightly better at improving overall cognitive function than the typical drugs (ES=0.24, p<0.01), particularly in the learning and processing speed domains (Woodward, Purdon, Meltzer, & Zald, 2005).

Furthermore, a number of pathways and neurobiological targets have been found to be associated with cognitive function and many of them have been found to be impaired among individuals with schizophrenia. One example is dopamine and its activity at the D1 receptors in
the prefrontal cortex, which has been shown to mediate cognitive processes in this region (Friedman, Temporini, & Davis, 1999). The presence of D1 receptors in schizophrenia patients in the prefrontal cortex is significantly lower than healthy individuals (Okubo et al., 1997). Atypical antipsychotic medications, like risperidone and clozapine, have been shown to increase the levels of dopamine in the prefrontal cortex, but with little success on improvements in cognitive function, particularly working memory and executive function (Friedman et al., 1999). Deficits in cholinergic activity, dysfunctions of glutamatergic neurotransmission and poor norepinephrine activity are other potential mechanisms that may contribute to cognitive impairment among individuals with schizophrenia (Stip, Chouinard, & Boulay, 2005).

Although many drug discovery processes are underway targeting these mechanisms, this is not an available solution for cognitive impairment at the moment. Furthermore, it is not known when these types of drugs will be available or the extent to which they will be effective (Marder, 2006). The cost of developing a new molecular compound in the drug development process costs $1.2 billion (Breier, 2005). In addition, from the time a new molecular compound is discovered to the time it is available for patients is approximately 15 years (Breier, 2005). This is the result of an extensive FDA approval process that requires testing at multiple stages to ensure safety as well as intended drug benefits. Once potential new drugs progress from the laboratory phase to the first clinical testing stage, 90% of them fail to move forward for further clinical testing due to issues concerning toxicology and adverse side effects (Breier, 2005). There is also no validated animal model to reflect the schizophrenia disease state and the associated cognitive impairments in order to test drug efficacy in the laboratory. There is also a lack of basic understanding of the biology of cognition, which slows drug development as it is unclear what should be targeted for the desired effects. Although the idea of developing a drug to address cognitive impairment seems attractive, there are many barriers to its development. As such, waiting for a possible drug solution to help these patients with their cognitive impairment is not practical.

1.5.3 Psychostimulants

Although psychostimulants have been shown to produce some short-term cognitive benefits, their use over the long-term is not without long-term side effects. For example, caffeine is consistently shown to increase alertness, improve sustained attention and support enhanced encoding of new information (Smith, Brice, Nash, Rich, & Nutt, 2003). However, among
sedentary individuals with low levels of physical activity participation, a characteristic which is also reflective of individuals with schizophrenia, caffeine has been linked to poor glucose metabolism and increased insulin resistance (Shearer & Graham, 2014), which is further exacerbated by the consumption of caffeine in caffeinated energy drinks and coffee. These side effects increase the risk of other chronic diseases, such as type 2 diabetes and cardiovascular disease. Amphetamine and methylphenidate are two other psychostimulants commonly used to promote wakefulness and improved attention. However, the short-term effects of these stimulants on cognition among individuals with schizophrenia are limited (Barch & Carter, 2005; Pietrzak, Snyder, & Maruff, 2010). Furthermore, these stimulants have been shown to exacerbate positive symptoms through increased levels of dopamine and noradrenaline (Kapur, 2003). In addition, anxiety/nervousness, insomnia, drug addiction and overdose are possible short and long-term concerns associated with their use. It is also unclear whether these short-term benefits in cognition confer any long-term, cognitive benefits. Therefore, the cost-to-benefit ratio, particularly in the long-term, of these stimulants is high. In light of these limitations, recommending the regular use of these stimulants for short-term, temporary enhancements to cognitive function seems inappropriate.

1.6 Is Exercise a Potential Solution?

In conclusion, although cognitive remediation therapies, cognition-enhancing drugs and psychostimulants appear to be plausible solutions to address cognitive impairments, they also have major limitations. On the other hand, exercise has numerous physical and mental health benefits. It is a modifiable risk factor for a number of metabolic conditions, including cardiovascular disease, diabetes mellitus and obesity. In schizophrenia, exercise has been shown to decrease negative symptoms, and improve mood. In sum, exercise is a non-pharmacological, feasible way to achieve optimal health. But does exercise also confer cognitive health benefits?
Chapter 2 -
Exercise and Cognitive Function

2 Overview

Exercise plays a critical part in achieving and maintaining optimal physical and mental health. There is also evidence to support that exercise may play an important role in maintaining and improving cognitive function. The following section will review the nature of these cognitive benefits, with a focus on an acute bout exercise, from existing meta-analyses and systematic reviews. Potential moderators of this effect will be explored, along with possible theories and biological mechanisms that may explain how an acute bout of exercise may lead to improved cognitive function.

2.1 Acute vs. Chronic Exercise

Both acute and long-term exercise may act in different but complementary ways to improve neurocognitive function (Hopkins, Davis, Vantieghem, Whalen, & Bucci, 2012). Acute exercise is defined as a single bout of exercise performed on a single day which is intense enough to produce any systematic physiological changes in the body, such as increases in heart rate and body temperature (Tomporowski, 2003). Long-term or chronic exercise is defined as exercise performed at least twice a week for four consecutive weeks or greater (Hopkins et al., 2012). In a seminal study by Hopkins et al. (2012), healthy but sedentary young adults were randomly assigned to either (1) 4-week exercise program, with exercise on the final cognitive test day, (2) 4-week exercise program, without exercise on the final cognitive test day, (3) a single bout of exercise on the final cognitive test day, or (4) no intervention (remained sedentary) during study. In a pre-post test of novel object recognition memory, Hopkins et al. (2012) found that only the group that engaged in the 4-week intervention, with the exercise session on the last test day showed improvements in this memory test. Neither group with just the acute or chronic exercise intervention showed improvements, suggesting that both types of exercise may be working differently but together to improve cognitive function. This is also an encouraging finding because multiple acute bouts over a period of time can lead to long-term changes.
2.2 Cognitive Benefits among Healthy Populations

2.2.1 Chronic Exercise

An examination of the effect of regular exercise on cognitive function revealed a number of benefits. Smith et al. (2010) included 29 randomized-control trials (RCTs) in their final analyses and found that individuals assigned to receive the exercise intervention (> 1 month) showed modest improvements in attention and processing speed ($g=0.158, p<0.05$), executive function ($g=0.123, p<0.05$), and memory ($g=0.128, p<0.05$). Two studies examined the effects of chronic exercise among healthy older adults. Angevaren et al. (2008) included 11 RCTs in their analyses and found that exercise interventions had a large effect on motor function (weighted mean difference (WMD)=1.17, $p<0.05$) and auditory attention (WMD=0.52, $p<0.05$). They found moderate effects for information processing speed (standardized mean difference (SMD)=0.26, $p<0.05$) and visual attention (SMD=0.26, $p<0.05$) (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008). Through the inclusion of 15 prospective studies, Sofi et al. (2011) found that older adults who reported low-to-moderate levels of physical activity were significantly protected against cognitive decline (hazard ratio [HR]=0.62, $p<0.05$) at follow-up than those who were not active. Etnier et al. (1997) assessed the effects of both acute and chronic exercise interventions using 134 primary studies of any study design. Overall, the mean effect size among all studies was $g=0.25$ ($p<0.05$). However, analysis of chronic exercise programs revealed a larger effect ($g=0.33$, $p<0.05$) on cognitive function than acute exercise designs ($g=0.16$, $p<0.05$).

2.2.2 Acute Exercise

An examination of existing literature reviews and meta-analyses revealed that an acute bout of exercise improves cognitive function to some extent in the following domains: executive function, attention, working memory, as well as short and long-term memory. McMorris and Hale (2012) evaluated how varying intensities of an acute bout of exercise would affect speed and accuracy on a variety of cognitive functions using 53 within-subject studies. Only timing of the cognitive test (during versus post exercise) had a significant effect on accuracy. A significant effect size was found when testing was done post exercise ($g=0.17$, $p<0.05$), compared to a non-significant effect during exercise (McMorris & Hale, 2012). Speed, as opposed to accuracy, of mental processing accounted for a greater part of the speed-accuracy relationship. Acute
moderate intensity exercise had moderate effects on speed of processing both during \((g=0.48, p<0.05)\) and after \((g=0.53, p<0.05)\) the exercise, compared to non-significant effects found for low and high intensity exercise. Furthermore, when task complexity was accounted for as a moderator, central executive tasks had a larger effect size \((g=0.77, p<0.05)\) than recall and alertness/attention \((g=0.31, p<0.05)\). Therefore, based on this meta-analysis, future research examining similar effects in different populations should target their exercise experimental component to be of moderate intensity and the cognitive test to evaluate executive function post exercise.

In another meta-analysis, McMorris et al. (2011) examined the effects of an acute moderate bout of exercise on both the speed and accuracy of working memory, which is often considered to be a component of executive function. This meta-analysis included 24 within-subject studies. They found a significant reduction in response time \((g=-1.41, p<0.05)\) but a detrimental effect on accuracy \((g=0.40, p<0.05)\) of working memory (McMorris, Sproule, Turner, & Hale, 2011). Cognitive testing both during and after the bout of exercise were collapsed into one category for analysis, masking any differential effect that may have occurred at these two different time points and is, therefore, a major limitation to this study. No significant moderators, such as timing of testing, duration of exercise, gender, or age were found in this meta-analysis. All studies included in this analysis used cycling as the mode of exercise and the cognitive tests relied heavily on central executive functions.

Roig et al. (2013) assessed the effects of both acute and chronic exercise on memory, including 50 studies in the final analysis with the following study designs: RCTs, clinical (non-randomized) controlled trials and within-subject designs. They found that an acute bout of exercise had a moderate effect \((SMD=0.26, p<0.05)\), while chronic exercise had a small effect \((SMD=0.15, p<0.05)\) on short-term memory (Roig, Nordbrandt, Geertsen, & Nielsen, 2013). They also reported that acute exercise had moderate-to-large effect \((SMD=0.52, p<0.05)\) on long-term memory, whereas chronic exercise had insignificant effects \((SMD=0.07, p=0.51)\) on long-term memory. When subtype of memory was analyzed as a moderator, they found that acute exercise improved visual-spatial short-term memory \((SMD=0.30, p<0.05)\) as well as verbal-auditory \((SMD=0.54, p<0.05)\) and procedural \((SMD=0.40, p<0.05)\) long-term memory. Furthermore, time of coding relative to the acute exercise was not significant, although encoding post exercise \((SMD=0.52, p<0.05)\) showed improved long-term memory. Retention did not act
as a moderator between acute exercise and short-term memory, but it did predict success of long-term memory after a long delay period post exercise. Walking was the most effective mode of acute exercise for short-term memory (SMD=0.78, p<0.05), however only two studies were included in this analysis. An acute bout of cycling was effective for long-term memory (SMD=0.92, p<0.05). Short acute bouts (<20 minutes) (SMD=0.63, p<0.05) in low intensity (<40% heart rate reserve) (SMD=0.57, p<0.05) were reported to be beneficial for short-term memory, whereas short (SMD=0.53, p<0.05) or medium (20-40 minutes) (SMD=0.88, p<0.05) duration bouts of any intensity had larger effects on long-term memory.

Two additional reviews examined if performance on cognitive tests was dependent on when it was administered relative to the acute bout of exercise. With 50 within-subject studies, Lambourne & Tomporowski (2010) found that if the cognitive test is administered during the first 20 minutes of exercise, there was a detrimental effect (g=-0.14, p<0.05) but if the cognitive test is administered after 20 minutes of exercise onset, the performance improved (g=0.20, p<0.05), specifically in the areas of speed of mental processing, memory storage and retrieval. Chang et al. (2012) found that an acute bout of exercise has an overall small, significant effect on cognition regardless of when (i.e. during, immediately following or after a delay) the cognitive test is administered (g=0.10, p<0.05). Specifically, they found that cognitive tasks that evaluate executive function (g=0.19, p<0.05) and attention (g=0.42, p<0.05) immediately after an acute bout of exercise found a significant positive effect size, whereas only executive function (g=0.17, p<0.05) showed a positive effect size when it was assessed after a delay (> 1 minute post exercise). Furthermore, Chang et al. (2012) reported that if cognitive function is assessed immediately after an acute bout of exercise, very light (g=0.15, p<0.05), light (g=0.17, p<0.05), and moderate (g=0.12, p<0.05) intensity exercises were beneficial. However, when cognitive function was examined after a delay, moderate (g=0.20, p<0.05), hard (g=0.27, p<0.05), and very hard (g=0.47, p<0.05) intensities were seen as beneficial (Chang, Labban, Gapin, & Etnier, 2012). Those who were considered low (g=0.17, p<0.05) or high (g=0.22, p<0.05) fit, showed greater improvements if tested immediately after the exercise session and those who were moderate (g=0.20, p<0.05) or high (g=0.33, p<0.05) fit showed better improvements on tests after a delay post exercise. In sum, the evaluation of the effectiveness of various acute exercise parameters on cognitive function in these meta-analyses can inform the design of future acute exercise protocols.
2.2.3 Study Limitations

Nevertheless, the limitations present among the studies examined above, of both chronic and acute nature, need to be considered in light of the results reported. First, there is considerable heterogeneity between the samples of participants included, making the interpretation of the results challenging. Although most reviews reported that only healthy adults (≥ 18 years) were included, this was still a broad and flexible inclusion criterion, with a wide range of “healthy” samples. Many studies also did not account for participant IQ and fitness level on cognitive function among their samples. Second, the heterogeneity of the exercise intervention itself, whether chronic or acute, may have had an influence on cognitive performance. Although most studies mentioned a minimum requirement (e.g. the activation of large muscle groups) needed to be considered an exercise intervention, the meta-analyses and systematic reviews included studies that used interventions with a range of intensities, modalities, durations, and frequencies. Some chronic exercise interventions also included muscle strength training, in addition to cardiovascular exercises as part of the intervention. Therefore, it is difficult to decipher an accurate effect of a specific exercise paradigm when these inclusion criteria are very broad. Therefore, all future reviews should consider more strict inclusion criteria and conduct moderator analyses of how particular parameters of an intervention program (e.g. intensity, duration, and modality) may affect the relationship under study. Methodologically, the inclusion of studies with RCTs or counterbalanced, repeated-measures designs would greatly improve the quality of the study and the strength of the results.

2.3 Current Studies Examining Exercise for Cognitive Improvement in Schizophrenia

Only eight primary articles to date have been published examining the effects of exercise on cognition among individuals with schizophrenia and all eight examined the benefits of regular, long-term exercise only (see Table 2). There are no studies that examine the cognitive benefits from an acute bout of exercise in this population.

Of the eight, three studies examined the effects of yoga and found mixed results about the benefits in a variety of cognitive domains (Behere et al., 2011; Bhatia et al., 2012; Jayaram et al., 2013), not including executive function. In another cross-sectional study, Leutwyler, Hubbard, Jeste, Miller, & Vinogradov (2014) concluded that those who reported higher average daily
minutes of moderate physical activity had better scores on verbal working memory tasks and speed-of-processing tests than those who reported lower average daily minutes.

Two other studies examined the benefits of exercise on cognition through the analyses of brain neurogenesis (Falkai et al., 2013; Pajonk et al., 2010). Pajonk et al. (2010) found a significant 12% relative increase in hippocampal volume among patients with schizophrenia (n=8) and 16% increase among healthy participants (n=8) after three months (3 × 30 minutes/week) of aerobic exercise, with no change found among the control group of schizophrenia participants (n=8) (Pajonk et al., 2010). When cortical changes were evaluated from the same data set of these participants, there was only a significant improvement in gray matter volume among the healthy participants who took part in the exercise program, not among the participants with schizophrenia who took part in the exercise program (Falkai et al., 2013). It is possible that due to greater cognitive stimulation from their environment as well as the exercise they received during these three months, it resulted in greater cortical volume increase among these healthy participants.

A confounding factor among these studies may be the use of atypical antipsychotic treatments. Although hippocampal and overall brain volume loss is prominent during the early stages of the illness, possibly exasperated by typical antipsychotic medications (Ho, Andreasen, Ziebell, Pierson, & Magnotta, 2011; Lieberman et al., 2005), the use of atypical antipsychotics has been shown to reduce this progression (Koolschijn et al., 2010). Even though the majority of participants in the study by Pajonk et al. (2010)/Falkai et al. (2013) were using atypical antipsychotics, there was an even distribution of these participants between the exercise and the control group. Therefore, even with the small sample size, the effects of aerobic exercise was more pronounced and detectable in the hippocampus than in the cortex, above any increases due to atypical antipsychotics.

Two recent studies have elevated the cognitive performance of individuals diagnosed with schizophrenia before and after a chronic exercise program. Oertel-Knochel et al. (2014) assessed the effects of aerobic exercise on cognitive performance and individual psychopathology in major depressive disorder (MDD) and schizophrenia. The sample included 29 schizophrenia patients and 22 MDD patients and they were randomly assigned to one of two intervention groups: cognitive training + aerobic exercise, cognitive training + mental relaxation.
training or a waiting control group (Oertel-Knöchel et al., 2014). The interventions included 12 sessions (3 sessions/week, 4 weeks), where each session lasted 75 minutes (30 minutes of cognitive training + 45 minutes of cardio training or mental relaxation training). All participants were assessed on a battery of cognitive tests before and after the intervention. They found that both groups of patients in both intervention groups showed improvements in visual learning, working memory, and speed of processing. However, improvements were greater among patients who received cognitive training and aerobic exercise than cognitive training and mental relaxation. Furthermore, performances on these cognitive tasks were stronger among patients with schizophrenia than patients with MDD. They also found decreased state anxiety and an increase in subject-reported quality of life.

In the most recent study, Kimhy et al. (2015) examined the effect of aerobic training on aerobic fitness, levels of BDNF and neurocognitive function among individuals with schizophrenia. Thirty-three participants were randomized to receive ‘treatment as usual’ or attend a 12-week exercise program (3 sessions/week, 1 hour/session). Participants who completed the exercise program improved their aerobic fitness by 18% whereas the control group saw no change (-0.5%). Furthermore, the exercise group saw a 15% improvement on the cognitive tests compared to no significant change in the control group (-2.0%). This improvement in the exercise group was of large effect ($d=0.93$, $p=0.03$). Serum-BDNF levels increased by 11% in the exercise group compared to only a 1.9% increase in the control group, although there was no between group difference for this assessment.

In sum, even among the few studies that do look at regular exercise for cognitive improvement in this population, the evidence is mixed and inconclusive. Furthermore, the limited number of studies in this field of exercise and cognition for patients with schizophrenia hinders conclusions from being drawn about incorporating exercise as a possible intervention modality. Therefore, this warrants further research in order to determine the effects of exercise for cognitive enhancement among this population. In particular, research examining immediate and long-term changes from one acute bout of exercise is urgently needed in order to understand this effect at a fundamental, proof-of-concept level and in order to establish a basis from which to build future research.
2.4 Barriers to Exercise

Engaging in regular exercise is not without its own limitations and there are barriers that prevent individuals diagnosed with schizophrenia from fully adopting and maintaining this behaviour as part of their lifestyle. For example, when Johnstone, Nicol, Donaghy, & Lawrie (2009) interviewed 27 schizophrenia outpatients regarding their barriers to exercise, participants reported lack of experience (low self-efficacy), the impact of their illness and the negative side effects of the medications, anxiety and lack of social support as the four biggest barriers. Negative symptoms, such as amotivation and anhedonia, are specifically associated with lower levels of exercise (Vancampfort et al., 2012). In addition, individuals diagnosed with schizophrenia are often of low socioeconomic status. Therefore, there are also barriers associated with the affordability of exercise-related expenses, such as gym memberships, transportation and appropriate fitness attire, including proper walking shoes (Hudson, 2005).

However, the tremendous benefits derived from regular exercise and possible cognitive benefits should encourage stakeholders to work together to address these limitations. This present study is intended to act as a proof-of-concept experiment that will further elucidate and provide evidence of the role of acute exercise on cognitive function.
<table>
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<tr>
<th>Article</th>
<th>Disorder Examined</th>
<th>Type of Study/ Sample Characteristics</th>
<th>Main Objective</th>
<th>Duration/Intensity and Modality of Exercise</th>
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<tr>
<td>(Behere et al., 2011)</td>
<td>SZ</td>
<td>RCT; 66 patients</td>
<td>Effect of yoga (n=27) on facial emotion recognition deficits compared to exercise (n=17) and waitlist group (n=22).</td>
<td>Yoga training via instructor for one month; asked to practice on own at home for next two months.</td>
<td>The yoga group showed a significant improvement (p&lt;0.05) in facial emotion recognition, whereas exercise and control group did not.</td>
<td>Exercise group training via instructor for one month (e.g. Brisk walking, jogging) and asked to practise on own next 2 months; waitlist group</td>
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<tr>
<td>(Bhatia et al., 2012)</td>
<td>SZ</td>
<td>Open, non-randomized trial; 88 patients</td>
<td>Evaluate yoga (n=65) for cognitive domains impaired in SZ.</td>
<td>Prescribed yoga protocol for one hour daily for 21 consecutive days, excluding Sundays.</td>
<td>Yoga group showed improvement in attention as it relates to accuracy of performance (d=0.62, p=0.01) compared to non-significant changes in the control group (d=-0.24, p=0.89), particularly in men.</td>
<td>SZ patients (n=23) who received standard treatment</td>
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<tr>
<td>(Falkai et al., 2013)</td>
<td>SZ</td>
<td>RCT 3-arm MRI study; 16 male SZ patients and 8 healthy controls.</td>
<td>To investigate gray matter density and brain surface expansion using MRI-based cortical pattern matching methods.</td>
<td>3 sessions × 30 minutes/session weekly over 3 months; cycling</td>
<td>Comparing SZ (cycling) to HC (cycling) and SZ (control) before and after 3 months: gray matter density increases in the right frontal and occipital cortex only in HC (p&lt;0.05); no significant</td>
<td>2 Control Groups (Male SZ who played table football and exercising healthy controls).</td>
</tr>
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</table>
To assess effect of yoga on socio-occupational functioning, facial emotion recognition deficits and plasma oxytocin levels.

SZ participants in yoga group (n=15) showed improvements in emotion recognition compared to a waitlist group (n=28) (p<0.05).

SZ patients in a waitlist group.

To examine the impact of aerobic exercise training on cognition, and to examine changes in BDNF levels.

The aerobic exercise group showed a 15.1% improvement on cognitive testing post intervention, compared to baseline (d=0.93, p=0.03). The control group did not show any improvements (-2.0%).

Treatment as Usual

To test whether severity of SZ symptoms and cognition is associated with lower physical activity (PA).

Higher scores on verbal working memory task associated with more average daily minutes of moderate PA (p=0.05); higher scores on speed-of-processing test associated with more average daily steps (p<0.01) and average daily minutes of PA (p<0.01).

No
<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Study Design</th>
<th>Description</th>
<th>Intervention Details</th>
<th>Outcome</th>
<th>Control Group</th>
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<tbody>
<tr>
<td>(Oertel-Knöchel et al., 2014)</td>
<td>SZ</td>
<td>RCT; 29 SZ and 22 MDD patients.</td>
<td>The effects of aerobic training on cognitive performance and symptom severity in psychiatric inpatients</td>
<td>12 sessions (3 times a week) over 4 weeks, lasting each for 75 min (30 min of cognitive training + 45 min of cardio training or mental relaxation training)</td>
<td>An increase in cognitive performance and a reduction in severity of illness across subject groups, with strongest effects found in patients undergoing combined cognitive and aerobic physical training ($d=0.47-0.57$, $p&lt;0.05$).</td>
<td>Waitlist Control Group (10 SZ and 8 MDD patients)</td>
</tr>
<tr>
<td>(Pajonk et al., 2010)</td>
<td>SZ</td>
<td>RCT; 16 SZ patients</td>
<td>To determine whether hippocampal volume would change with exercise among individuals with SZ, and whether this effect would be related to improved aerobic fitness.</td>
<td>3 sessions $\times$ 30 minutes/session weekly over 3 months; cycling</td>
<td>Following exercise, relative hippocampal volume significantly increased in patients (12%) and HC (16%) ($p&lt;0.05$). Change in hippocampal volume in SZ was positively associated with improvements in memory ($r=0.51$, $p&lt;0.05$)</td>
<td>Comparison SZ group (n=8) played tabletop football for 30 minutes, 3 times/week in comparable setting; healthy control subjects (n=8) engaged in the same exercise intervention.</td>
</tr>
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</table>
2.5 Theoretical Explanations

There are multiple plausible explanations to account for the way acute exercise may potentially affect cognitive function. Changes in affect and arousal are the two leading theories that have been used to understand the acute effects of exercise on cognitive function. These explanations employ a number of known biological changes and plausible mechanisms to support their respective views (see Figure 1). However, it is evident that there is overlap among these explanations and many of the proposed mechanisms are likely working together synergistically to produce the characterized cognitive changes. These theories and the biological changes will be explored from both an acute and long-term perspective, as multiple acute bouts of exercise lead to chronic, regular exercise. These acute effects include changes in neurochemicals and neurotransmitters, growth factors and inflammatory markers. With regards to long-term effects, structural changes and improved efficiency in energy metabolism will be examined.

2.5.1 Affect

It is well-established that physical activity improves overall psychological function, such as mood and feelings of well-being, better self-esteem while also reducing anxiety and stress, particularly through steady-state exercise lasting at least 20 minutes (Folkins & Sime, 1981; Tomporowski, 2003). Preliminary evidence also indicates that an acute bout of exercise improves affect among individuals affected by serious mental illness, including schizophrenia (Arbour-Nicitopoulos, Faulkner, Hsin, & Selby, 2011; Vancampfort et al., 2011). Among healthy individuals, positive affective states have been shown to produce better cognitive performance, even when the task is dull and not motivating (Isen, 1999; Mitchell & Phillips, 2007). Specifically, positive mood has been hypothesized to promote improved cognitive flexibility and better strategic planning in new situations, potentially through its effects on the dopaminergic system (Ashby, Isen, & Turken, 1999). In addition, the positive effects on affect from an acute bout of exercise dissipate over time, with the greatest effects seen 0-2 minutes after the completion of exercise \( (d=0.61, 90\% \text{ CrI}: 0.10-1.12) \) to minimal effects detected after 40 minutes \( (d=0.10, 90\% \text{ CrI}: -0.28-0.48) \) (Reed & Ones, 2006). Similarly, the cognitive benefits of acute exercise are reported to be the greatest in the first fifteen minutes post exercise \( (d=0.14, 95\% \text{ C.I.}: 0.10-0.18) \) and then tend to subside over time (Chang et al., 2012). Therefore, exercise-
induced changes in psychological feelings or affect may mediate the changes in cognitive performance.

Among other more complex constructs of affect, basic affect is the most fundamental construct that encompasses the experiential, non-cognitive, component of all valenced responses, including emotions and moods (Ekkekakis & Petruzzello, 2000; Gross, 1998). Furthermore, because the exact nature and scope of the feeling states affected by exercise are not known, particularly in the schizophrenia population, it is desirable to target the most broad, basic constructs. Therefore, Ekkekakis and Petruzzello (2002) propose that basic affect be assessed during and after an acute bout of exercise, instead of specific, pre-identified feeling constructs. Specifically, a dimensional approach to assessment of affect is recommended because psychological states are more “systematically inter-related” than distinct states on their own (Ekkekakis & Petruzzello, 2002). The Circumplex Model of Affect (Figure 2), with two orthogonal dimensions, valence (pleasure/displeasure) and activation (arousal), can be used to assess basic affect in a relatively simple and quick manner (Ekkekakis & Petruzzello, 2000). The two scales used to measure these two dimensions are described in section 3.3.3.1.

Ekkekakis (2003) refers to the varying responses in affect during exercise, based on intensity, as the dual-mode theory. In particular, this theory proposes that there is virtually a universal positive affect with low intensity (below the ventilatory/lactate threshold) exercise and negative affect with high intensity affect. However, there is considerable individual variability in affective response during a moderate intensity bout of exercise (Ekkekakis, Parfitt, & Petruzzello, 2011; Ekkekakis, 2003). Furthermore, this individual variability of affect has been suggested to predict future exercise behavior (Ekkekakis, Parfitt, & Petruzzello, 2011). Specifically, those who report positive changes in affect during a bout of exercise are more likely to continue to engage in regular exercise in the future than those who report negative changes.
Figure 1. Potential biological mechanisms that may mediate the effects of exercise on cognitive function (Cotman, 2007).
Figure 2. The Circumplex Model of Affect.
2.5.2 Arousal Hypotheses

2.5.2.1 Inverted U-Hypothesis/Catastrophe Hypothesis

Based on Yerkes and Dodson’s (1908) performance-arousal theory, Davey (1973) was the first person to offer a theoretical rationale for the acute effect of exercise on cognitive performance. He called this theory the inverted U-hypothesis, where he predicted that cognitive performance would increase with increasing physiological arousal, often measured through intensity, to an optimal point, and then performance levels would start to slowly decline with any further increases in arousal (Davey, 1973; Dodson, 1915). Although most studies that have evaluated exercise-induced arousal found an effect on cognitive performance, it did not follow this inverted U-shape pattern (Tomporowski, 2003). In response to the limited evidence for the inverted U-hypothesis, Gould and Krane (1992) proposed the Catastrophe Hypothesis, where they postulated that there is a complex interaction between physiological arousal and cognitive anxiety. Unlike the inverted U-hypothesis, where there is a steady decline in cognitive function once an optimal point is reached, the Catastrophe Hypothesis proposes a drastic and sharp decline in cognitive function once this optimal point is reached (Gould & Krane, 1992). Under this hypothesis, arousal becomes completely detrimental and overrides any positive effect it may have on cognitive function once this optimal point is reached. Most studies that evaluated these hypotheses have measured arousal physiologically through heart rate, oxygen uptake, and through ratings of perceived exertion.

2.5.2.2 Reticular-Activating Hypofrontality (RAH) Model

Dietrich and Audiffren (2011) proposed the reticular-activating hypofrontality (RAH) model to explain the neurocognitive effects of acute exercise. This model has two sequential processes. First, arousal leads to the activation of the reticular system, which is a set of interconnected nuclei found in the brain stem. This system is responsible for functions such as motor and cardiovascular control, pain modulation, mood regulation and alertness, among other functions (Robbins & Everitt, 2007). This is also the region of the brain where the neurotransmitter serotonin, often responsible for positive mood states, is produced. In sum, this arousal-based system, then, subsequently leads to the activation of the other motor systems, the sympathetic nervous system, and endocrine systems. Dietrich and Audiffren (2011) propose that the
activation of the reticular system also leads to the activation of cortical regions responsible for sensory, attentional and motor processes.

Second, in order to perform these additional functions sufficiently, the brain reallocates its limited metabolic resources away from functions not directly involved in maintaining the bodily movements (Dietrich & Audiffren, 2011). Therefore, there is a deactivation of higher-order cognitive processes, such as executive function, during the exercise session. This is based on the assumption that the brain has a set amount of metabolic resources and greater amounts are required by the motor cortices during the bout of exercise in order to perform specific, dynamic movements, which take away from other less urgent functions and their associated brain regions. This model proposes that the prefrontal cortex, which is responsible for executive function, is specifically affected because this region may not be as vital to perform the short bout of exercise (Dietrich, 2006). This model is supported by the poor performance on cognitive tests that measure executive function during the acute bout of exercise. Furthermore, this model purposes that when the bout of exercise is terminated, the motor cortex activation would return to baseline and the metabolic resources would be restored to the prefrontal cortex. This would be reflected in cognitive performance that is as similar as or better than baseline scores. Furthermore, based on the first postulate of this model, the increased arousal state after the bout of exercise may also enhance cognitive performance.

2.6 Biological Mechanisms

2.6.1 Acute Changes in Neurochemicals/Neurotransmitters

The nervous and endocrine systems play a key role in mediating the physiological response to acute exercise. Specifically, immediately before and during exercise, the hypothalamus and the brainstem activate these systems, which results in the release of catecholamines (McMorris & Hale, 2012). In particular, noradrenalin is produced in the locus coeruleus of the brain stem and postganglionic neurons in the sympathetic nervous system in response to the exercise. This activation eventually leads to the release of other catecholamines from the adrenal glands, specifically adrenalin, and to a lesser extent noradrenaline (Zouhal, Jacob, Delamarche, & Gratas-Delamarche, 2008). Dopamine, a neurotransmitter involved in motivation, reward and motor control, is also increased in the brain as a result of acute exercise (Cooper, 1973). Higher intensity exercise produces greater release of these catecholamines, although exercise duration,
age, nutrition and past physical activity also seem to be contributing factors (Zouhal et al., 2008). Therefore, the activation of the 'sympathoadrenal' system and the release of catecholamines lead to responses related to the 'flight-or-fight' system, such as the stimulation of the cardiac, respiratory, metabolic and thermoregulatory functions (Zouhal et al., 2008). The thalamus conveys the changes to these bodily functions, including those related to pain and glycogen depletion, back to the hypothalamus, which in turn, further increases the release of catecholamines peripherally and possibly centrally to meet the exercise demands (McMorris & Hale, 2012). Other stress hormones, such as adrenocorticotropin hormone (ACTH) and cortisol are also released, which can further enhance the release of catecholamines through the interaction with noradrenaline and dopamine (McMorris & Hale, 2012). Acetylcholine is a neurotransmitter released in the cerebral cortex due to exercise and it enhances neural activity and transmission, further contributing to increased arousal and attention, with possible subsequent improvements in cognitive function (Byun et al., 2014). There is also an increase in serotonin in the central nervous system, a neurotransmitter that plays a key role in regulating mood as well as endorphins, which are neuropeptides responsible for the minimization of pain and promoting feelings of euphoria (Dishman & O’Connor, 2009).

2.6.2 Exercise and Growth Factors

Growth factors also play an important role mediating the effects of aerobic exercise on the brain, specifically cognition. Brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1) and vascular endothelial-derived growth factor (VEGF) are three main growth factors increased as a result of exercise and set in motion a complex and intricate cascade of events that lead to increased plasticity, neurogenesis, and development of capillaries after the completion of the exercise bout (Cotman, Berchtold, & Christie, 2007a). Although these growth factors may be released as a result of one single bout of exercise, their downstream effects occur long after the exercise cessation and multiple bouts of exercise over time are often required to sustain these positive effects. This, in turn, would lead to better brain health and improved cognitive function in the long-term. In addition to up regulating these key growth factors, the reduction in inflammation by exercise also leads to improved growth factor signaling.
2.6.2.1 IGF-1 and VEGF

IGF-1 is a growth factor that plays an important role in many processes, such as enhancing learning, preventing depression, inducing angiogenesis and hippocampal neurogenesis (Ding, Vaynman, Akhavan, Ying, & Gomez-Pinilla, 2006). It also has a role in inducing greater amounts of BDNF signaling in response to exercise (Cotman et al., 2007). An acute bout of exercise increases the levels of peripheral IGF-1 within 1 hour post-exercise, which crosses the blood-brain barrier and can support neurogenesis (Trejo, Carro, & Torres-Aleman, 2001), memory (Ding et al., 2006) and induce angiogenesis (Lopez-Lopez, LeRoith, & Torres-Aleman, 2004). Furthermore, IGF-1 gene expression is also increased in the hippocampus several days after exercise onset. IGF-1 signal transduction eventually converges on the BDNF pathway, with both having the same downstream effect as a result of exercise (Cotman et al., 2007).

Pro-inflammatory cytokines counteract the positive effects of IGF-1, by impairing signal transduction (Strle et al., 2004). Not only does an inflammatory state contribute to insulin resistance (Broussard et al., 2003), but it also hinders glucose metabolism, proper tissue maintenance and cerebrovascular function (Cotman, Berchtold, & Christie, 2007). Impaired or low levels of IGF-1 also increase the risk of cognitive impairment. Exercise directly increasing the levels peripheral IGF-1, which helps restore many of the above mentioned functions, and reduces the levels of the pro-inflammatory cytokines (Petersen & Pedersen, 2005).

VEGF is another growth factor that has important roles for neurogenesis and angiogenesis (Fabel et al., 2003). Exercise increases the peripheral VEGF, which also crosses the blood-brain barrier to carry out its function in promoting increased neurogenesis and angiogenesis (Fabel et al., 2003). IGF and VEGF appear to have similar functions, although there may be some distinction in their mechanism of action. However, this distinction is not clear presently.

2.6.2.2 BDNF

BDNF also plays an important role in overall brain health and cognitive function, with similar responsibilities to IGF-1 and VEGF, such as enhancing learning and memory as well as preventing the onset of depression-like symptoms. Conveniently, acute exercise also up regulates the levels of BDNF in the brain and other regions in the body (Ferris, Williams, & Shen, 2007;
Oliff, Berchtold, Isackson, & Cotman, 1998; Rothman, Griffioen, Wan, & Mattson, 2012; Tang, Chu, Hui, Helmeste, & Law, 2008). BDNF binds to tropomyosin-related kinase-B receptor, which then activates other intracellular signaling cascades, which are critical for neurogenesis and neuroplasticity, and as a result important for learning and memory (McMorris & Hale, 2012). Although BDNF is released from a single bout of exercise, the downstream effects take time and often occur after the exercise bout is over. Exercise also promotes greater IGF-1 uptake, which is required for increased BDNF expression (Carro, Nuñez, Busiguina, & Torres-Aleman, 2000).

Furthermore, it appears that there is an intensity/duration trade off when trying to quantify the ideal acute exercise paradigm needed to promote the up regulation of these growth factors. Ferris et al. (2007) have found that 30 minutes of exercise on a cycle ergometer at ventilatory threshold (Vth) + 10, which is considered to be rated as ‘somewhat hard’ or ‘hard’ in intensity on the Borg’s Scale of Perceived Exertion, resulted in significantly greater levels of serum BDNF compared to base line levels, whereas Vth -20, considered as light intensity exercise on the Borg’s scale, produced no significant increases in BDNF levels (Ferris et al., 2007). Furthermore, BDNF moves across the blood-brain barrier in a bidirectional manner, therefore, any systemic increases from acute exercise also support enhanced brain concentrations as well (Pan, Banks, Fasold, Bluth, & Kastin, 1998). Inflammation also has a detrimental effect on BDNF signaling. As with IGF-1 and VEGF, not only does exercise increase the levels of BDNF, but it also counteracts the effects of pro-inflammatory cytokines (Cotman et al., 2007).

2.6.3 Exercise as an Anti-Inflammatory

2.6.3.1 Inactivity, Obesity and Inflammation

Inactivity creates an environment within the body that increases the risk for developing metabolic syndrome, which is characterized as meeting at least three of the following cardiovascular risk factors: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) levels, hypertension, and hyperglycemia (Yaffe et al., 2004). A key component that promotes or exasperates these risk factors for metabolic syndrome is chronic, low grade, systemic inflammation (Hotamisligil, 2006) and this is a risk factor for cognitive decline (Yaffe, 2007).
Among the five major risk factors, obesity may be playing a significant role. When there is increased energy intake compared to expenditure, it sets in motion the cascade of events required to store this excessive energy for long-term use in adipose tissue, resulting in increased body weight. Excessive weight can lead to increased levels of pro-inflammatory cytokines released from these adipose cells, leading to the development of systemic low grade inflammation (Heilbronn & Campbell, 2008). This type of chronic inflammation is defined as having 2 to 4 times greater levels of circulating pro- and anti-inflammatory markers above those that are seen in healthy individuals (Bruunsgaard, 2005). The presence of these adipose-derived cytokines is also affected by the amount and distribution of adipose tissues in the body (Nimmo, Leggate, Viana, & King, 2013). Systemic inflammatory conditions have been found to also influence central nervous system (CNS) inflammation (Perry, 2004), which also plays a major role in brain health, including cognitive function.

One of the major contributors of obesity is increased sedentary time, where energy expenditure is minimal (≤1.5 METs) (Henson et al., 2013). In particular, individuals at high risk of metabolic syndrome may be affected by sedentary behaviour more than those in the healthy population. For example, Henson et al. (2013) reported that high levels of sedentary time influences inflammatory markers, independent of moderate-to-vigorous physical activity (MVPA), glycaemia and adiposity among individuals at high risk for type 2 diabetes mellitus. Specifically, sedentary time was positively associated with increased levels of C-reactive protein, IL-6, leptin and leptin-adiponectin ratio, after controlling for numerous confounding variables. However, most of these associations were reduced or not present when MVPA was taken into account, except for IL-6.

2.6.3.2 Anti-Inflammatory Effects of Exercise

Exercise, including acute bouts, improves overall immune function in the brain. In particular, exercise has been shown to reduce inflammation, which is important considering it is an important risk factor for cognitive decline (Cotman et al., 2007; Fischer, 2006). Although exercise-induced effects on inflammation may be multifaceted, the following effects on TNF-α will be highlighted.

Adipose tissue contributes to systemic inflammation by producing pro-inflammatory cytokine TNF-α (Petersen & Pedersen, 2005). TNF-α is the primary cytokine leading to insulin
resistance and dyslipidemia. IL-6 is viewed more of a marker of these metabolic symptoms than the cause. However, in response to acute exercise, IL-6 is also released by skeletal muscles in response to contraction and acts in an anti-inflammatory manner (Brandt & Pedersen, 2010). Therefore, IL-6 is produced and released both during a pro-inflammatory state and an anti-inflammatory state. However, when IL-6 is produced in response to acute exercise, it is done in a TNF-α-independent manner. Furthermore, IL-6 produced through this mechanism is thought to promote the increased levels of other anti-inflammatory cytokines, like IL-1ra and IL-10, which inhibit the production of TNF-α (Brandt & Pedersen, 2010).

2.6.4 Improved Structural Integrity

Exercise supports the development of a stronger, more intricate brain structure within the brain, particularly in the hippocampus (van Praag, Christie, Sejnowski, & Gage, 1999). The hippocampus and the regions surrounding the ventricles in the brain have neural progenitor cells that give rise to new neurons and glia throughout one’s life. In particular, these progenitor cells are sensitive to the chemical environment that is created by exercise. For example, the increased levels of growth factors promote the proliferation, differentiation, and survival of these new neurons (Fabel et al., 2003; Trejo et al., 2001).

In addition, exercise enhances synaptic plasticity within the brain, in particular within the hippocampus and to some extent, the cortex. Optimal functioning of synapses is crucial for efficient signal transmission and improved communication within the brain. Specifically, when long-term potentiation (LTP) was measured through electrophysiological means, it was found that exercise reduces the threshold for stimulation of LTP (Farmer et al., 2004). This is indicative that neurons are better primed to encode new information, enhancing learning and memory. Furthermore, increased length and density of dendrites also support the enhanced structural integrity of the brain (Eadie, Redila, & Christie, 2005). At the molecular level, the presence of higher levels of synaptic proteins, neurotransmitter receptors, growth factors, synapsin I, synaptophysin and glutamate support optimal structural integrity in the long-term. In particular, the presence of hippocampal neurogenesis has been reported to be a critical feature in the brain that protects against depression and allows the individual to better cope with stress (Cotman et al., 2007).
2.6.5 Energy Metabolism

Free radicals are produced as a by-product of oxidative respiration in the mitochondria and can damage other components/structures of the cell. Exercise enhances improved tolerance of oxidative stress by enhancing the levels of protective enzymes (Navarro, Gomez, López-Cepero, & Boveris, 2004). Exercise also enhances a number of organelles/structures that play a critical role in energy metabolism. For example, in the hippocampus, where neurogenesis has been consistently found, there are also increased mitochondria and mitochondrial-specific proteins, which lead to an increase in energy production (Bechmann et al., 2002). These improvements in mitochondrial efficacy may be mediated by increased levels of uncoupling protein 2 (UCP2) as a result of long-term exercise (Bechmann et al., 2002). This is a mitochondrial protein that regulates free radical production during oxidative respiration in the neurons within the hippocampus. Specifically, increasing the levels of this protein in mouse models have shown to increase ATP production and decrease superoxide production as well as associated damage from this free radical. The exercise-related benefits on synaptic plasticity are strongly correlated with effective mitochondrial function/plasticity (Dietrich, Andrews, & Horvath, 2008; Vaynman, Ying, Yin, & Gomez-Pinilla, 2006).

Furthermore, in order to maintain optimal function of the brain, as well as to support processes, such as new synaptic connections and neurogenesis, an increase in nutrient and oxygen supply is required by the brain. One way to enhance this transport is through the development of additional capillaries from existing blood vessels (angiogenesis). The process of angiogenesis is largely mediated by IGF and VEGF (Kerr, Steuer, Pochtarev, & Swain, 2010). Furthermore, VEGF has effects on mitotic activity specific to vascular endothelial cells that enhance growth and development from existing capillaries (Lopez-Lopez et al., 2004).

2.6.6 Conclusion

In conclusion, theories related to affect and arousal provide a framework to conceptualize how acute exercise may be mediating improved cognitive function in the brain. In addition, there are a number of biological pathways that are simultaneously targeted during and after an acute bout of exercise that may support these theories. Furthermore, multiple regular bouts of exercise have also been shown to lead to structural brain changes. Therefore, regular acute bouts of exercise
have immediate and long-term desired physiological effects that help maintain optimal brain and cognitive health.
2.7 Study Rationale

Cognitive function, in particular executive function, is critical for optimal quality of life as well as a number of functional outcomes, like completing basic daily tasks and successfully maintaining employment. However, cognitive impairment is virtually a universal and pervasive problem among individuals with schizophrenia. At the moment, there are no short-term, immediate solutions to help those who are affected. Although cognitive remediation therapies have shown some success, they take a long time and do not always translate to improved functional outcomes. Atypical antipsychotics have small, improved effects on cognitive function compared to typical antipsychotics, but also with limited improvements in functional outcomes. Other cognition-enhancing drugs are being tested at the moment but it is unclear if any will provide the desired improvements, without adverse side effects. Although psychostimulants may provide some temporary enhancement to cognitive function, their long-term use is not without significant drawbacks.

Exercise has numerous physical and mental health benefits. It has also been shown to produce improvements in cognitive function among healthy individuals, even from acute bouts. Meta-analyses have shown that 11-20 minutes ($d=0.262, p<0.05$) of moderate, aerobic exercise produces modest improvements in executive function (Chang et al., 2012). Furthermore, there are plausible biological mechanisms that may explain and support these findings. However, there are only a few studies conducted to-date that have evaluated exercise for cognitive improvement among individuals with schizophrenia. All of these studies are long-term, with mixed findings. Therefore, exploring the effects of an acute bout of exercise on cognitive function among individuals with schizophrenia is required to assess this effect at a basic, proof-of-concept level. As a secondary possible outcome, this type of evidence may support the use of acute exercise to temporarily enhance cognitive function for immediate, short-term benefits.

Furthermore, among the healthy population, improvements in cognitive function, particularly executive function, from an acute bout of exercise was greater among individuals who had lower baseline functioning than those who had normal or average results (Pontifex, Hillman, Fernhall, Thompson, & Valentini, 2009; Sibley & Beilock, 2007). Individuals with schizophrenia already have a lower baseline cognitive functioning compared to the healthy individuals. Therefore, it was hypothesized that this population stands to gain greater
improvements in cognitive function than healthy individuals. As such, the primary purpose of this study was to test this proof-of-concept idea with an acute bout of moderate exercise (20 minutes) among a group of patients with schizophrenia. Affect was also evaluated throughout this exercise paradigm to determine its potential mediation on cognition.
Chapter 3 - Methodology

3 Study Overview

Thirty-six outpatients with schizophrenia (18-64 years) from the Centre for Addiction and Mental Health (CAMH) were recruited and participated in a within-subject, counterbalanced experiment, where they completed three sessions (Initial Assessment, Session 1 and Session 2), in a total time span of 1-2 weeks. During the Initial Assessment, participants were introduced to the study, completed baseline questionnaires and completed a cycle ergometer familiarization component. Participants were evaluated using the Wisconsin Card Sorting Test (WCST) for executive function. At Session 1, participants were randomly assigned to complete the experimental or the control arm of the study. Participants assigned to the experimental arm completed a computerized WCST and then engaged in 20 minutes of cycling on the cycle ergometer at a moderate intensity (64-75% of age-estimated maximum heart rate). After cool down, participants completed the same WCST again. Participants in the control group completed the same procedure, except they sat quietly for 20 minutes instead of exercising. Measurements of affect were also assessed throughout both sessions. Participants returned one week after Session 1 to complete the arm of the study that they did not complete.

3.1 Participants

Participants were recruited from the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada for this study. The following inclusion criteria were met by participants: 1) 18-64 years of age, in accordance with the Physical Activity Guidelines set for adults; 2) diagnosed with schizophrenia or schizoaffective disorder; 3) outpatients who have not been hospitalized in the last three months in relation to their psychiatric diagnosis; 4) no changes in the antipsychotic treatment regimen in the last four weeks; 5) be considered fit enough to participate in exercise as assessed by the PAR-Q (Canadian Society of Exercise Physiology, 2000). Participants were, however, excluded if: (1) they have been hospitalized in the past 12 months for angina pectoris, myocardial infarction, or cardiac surgery of any kind; (2) uncontrolled hypertension (defined as blood pressure > 140/90); or 3) currently dependent on or abusing either alcohol or drugs. The
participant age range was set broadly for the purposes of recruitment feasibility. However, because age does affect cognitive performance, it was considered as a covariate in the data analyses.

### 3.2 Sample Size Calculation

The required sample size was calculated theoretically using the G*Power 3.1.9.2 calculator. Sample size was calculated in order to detect a medium effect size with a power of 95% ($p<0.05$) for a repeated measures, within-between interaction ANCOVA. There were two groups (moderate intensity exercise and passive sitting) and each group was evaluated two times using the WCST test, for a total of four assessments per participant across both groups. This particular research design produced a minimum sample size of 36 participants. Anticipating a 25% attrition rate, recruitment was planned for 45 participants.

### 3.3 Measures

#### 3.3.1 Screening Tools

##### 3.3.1.1 Diagnosis

The Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) was used to assess and confirm diagnosis. The data from the MINI were retrieved from a previous study that participants completed in the recent past in order to reduce participant burden.

##### 3.3.1.2 Physical Health

The Physical Activity Readiness Questionnaire (PAR-Q+) (Canadian Society for Exercise Physiology, 2000; see Appendix A) was administered over the phone and in person during the Initial Assessment of the study to determine eligibility. If the participant answered “yes” to any of the questions, they were asked to obtain written consent from their physician to participate in the study.
3.3.2 Sample Descriptors

3.3.2.1 Demographics

Participants were asked to complete a basic demographics questionnaire (see Appendix B) that included questions on age, gender, socioeconomic status and ethnicity. It also included questions about clinical information, such as date of first hospitalization, first antipsychotic and current medications as well as anthropometric measurements.

3.3.2.2 Physical Activity Levels

Participants were asked to complete the International Physical Activity Questionnaire Short Form (IPAQ-SF; see Appendix C) in order to characterize their current physical activity levels. This questionnaire has been shown to be a valid measure of assessing physical activity in the schizophrenia population (Faulkner, Cohn, & Remington, 2006). The results from this questionnaire can also be translated into standard metabolic data, for ease of comparability to other physical activity data.

3.3.2.3 Negative Symptoms

Amotivation is a characteristic negative symptom of schizophrenia that has a high probability of mediating the effects on cognitive performance (Fervaha, Foussias, Agid, & Remington, 2013; Foussias, Agid, Fervaha, & Remington, 2013; van Beilen, van Zomeren, van den Bosch, Withaar, & Bouma, 2005). In order to assess amotivation, the Apathy Evaluation Scale (AES; see Appendix H) was used. This scale consists of 18 questions where the participant responded to each question by circling one of the following responses: “not at all”, “slightly”, “somewhat”, or “a lot”. Previous instrument validation in the psychiatric population indicates that this questionnaire is reliable and has strong construct validity (Marin, Biedrzycki, & Firinciogullari, 1991).

3.3.2.4 Symptom Severity

Brief Psychiatric Rating Scale (BPRS) (Woerner, Mannuzza, & Kane, 1988) and the Clinical Global Impression scale (CGI-S) (Guy, 1976) were used to evaluate symptom severity. The BPRS requires that the interviewer ask the participant probing questions to determine the extent of symptom severity on 18 categories. The CGI-S is a single-item scale that requires the
interviewer to make an overall judgment of the participant’s symptom severity in comparison to other participants with schizophrenia. Because participants in this present study were recruited from a list of participants who participated in a previous study, this information was also drawn from this previous study in order to reduce participant burden.

3.3.2.5 Life Satisfaction

To gauge participants’ global cognitive appraisal of their life satisfaction, a 5-item questionnaire was administered (see Appendix D) (Diener & Emmons, 1985). On a scale from 1 (strongly disagree) to 7 (strongly agree), participants’ indicated their level of agreement with the statements. Scores above 21 indicate some level of satisfaction and scores below 19 indicate some level of dissatisfaction.

3.3.3 Measures Used During Experimental and Control Conditions

3.3.3.1 Measures of Affect

In order to measure changes in affect, the Feeling Scale (FS; see Appendix G) (Hardy & Rejeski, 1989) was used to detect changes in pleasure and the Felt Arousal Scale (FAS; see Appendix F) (Svebak & Murgatroyd, 1985) was used to detect changes in activation. Both of these scales were administered to participants throughout the experimental and the control conditions (see Figure 4). The FS scale ranges from -5 (very bad) to +5 (very good) and asks the participant to rate how they are feeling (pleasure/displeasure). The FAS asks the participant how aroused they feel on a scale ranging from 1 (low arousal) to 6 (high arousal). The instructions provided to the participant describe high arousal as “excitement, anxiety or anger” and low arousal as “relaxation, boredom or calmness”. Finally, the Positive and Negative Affect Schedule (PANAS; see Appendix E) (Watson, Clark, & Tellegen, 1988) was also used to assess affect at the beginning of both Session 1 and Session 2. This scale consists of 20 words that describe 10 positive affect and 10 negative affect states on a 5-point scale, ranging from 1 (very slightly or not at all) to 5 (extremely). This tool was used to cross check if baseline responses on the FS and FAS were similar to the PANAS baselines responses.

3.3.3.2 Daytime Drowsiness

The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS; see Appendix J) item #2 was used to assess day-time drowsiness due to neuroleptics (Day, Wood, Dewey, &
Bentall, 1995). The question states, “How much difficulty do you have staying awake during the day?” and participants rate on a scale from 0 (Not at all) to 4 (Very much).

3.3.3.3 Intrinsic Motivation

Intrinsic motivation was assessed using the Intrinsic Motivation Inventory (IMI; see Appendix K) (Choi, Mogami, & Medalia, 2010). This is the modified scale with 21 questions assessing “Interest/Enjoyment”, “Choice” and “Value/Usefulness” on a scale from 1(Not at all true) to 7(Very true) for a total score out of 147. Questions related to “Effort” and “Pressure/Tension” were not included because they had poor reliability when this inventory was validated (Choi et al., 2010).

3.3.3.4 Exit Interview

After both the moderate intensity exercise and passive sitting sessions, participants took part in a brief exit interview (see Appendix L). Participants were asked how they were feeling subjectively, what they were thinking about during the 20-minute session, and whether they had a plan or strategy to complete the WCST task.

3.3.4 Exercise Intensity

Participants were asked to complete the bout of exercise at 64-75% of their age-estimated maximum heart rate, which is considered as moderate intensity exercise (American College of Sports Medicine, 2010). Maximum heart rate was calculated by subtracting age from 220. During the acute bout of exercise, participants were wearing a chest strapped heart rate monitor in order to continuously assess heart rate. If the participant fell below the target heart rate range, he or she was asked to work harder to reach the intended heart rate.

3.3.5 Safety

If the participant felt unsafe or uncomfortable at any point during the bout of exercise, the session was stopped and the study was terminated. Borg’s Rating of Perceived Exertion Scale (Borg’s RPE; see Appendix I) (Borg, 1998) is a standard measure of perceived exertion and it was used at frequent intervals (every 5 minutes) to ensure that participants were cycling at a comfortable range. Borg’s RPE is a scale from 6 (no exertion at all) to 20 (maximal exertion).
The exercise session was terminated if the participant reported a 15 (hard or heavy) or higher on this scale.

Furthermore, part of the rationale to use a cycle ergometer, as opposed to a treadmill for example, was to reduce the attention demand required to maintain the exercise motion because the participant is in a seated position (Lambourne & Tomporowski, 2010). There was also less impact on the participant’s joints and it involved the same consistent motion, as opposed to a treadmill, which may have greater variability in bodily movements. Thus, this mode of exercise gave the participant more control over the exercise bout and allowed him or her to stop easily if he or she felt unsafe. Lastly, the Athletic Centre at the University of Toronto, where this study was conducted has a Sports Medicine Clinic, where trained professionals were available to assist in the event of an emergency.

3.3.6 WCST

In this present study, the WCST was chosen as the outcome measure. This is a complex executive function task that requires participants to use multiple cognitive domains to sort cards according to undisclosed and periodically changing rules (see full test details below in 3.3.7.1). In this test, participants are evaluated on problem solving, cognitive flexibility, inhibition, attention and working memory (Bellack et al., 2001; Head, Kennedy, Rodrigue, & Raz, 2009; Heaton, Chelune, Talley, Kay, Curtis, 1993). Compared to other cognitive tests, the WCST is one of most widely used tests for executive function in the schizophrenia population where large deficits are consistently reported (Banno et al., 2012; Wobrock et al., 2009). In a meta-analysis evaluating the performance of schizophrenia patients to healthy controls on the WCST, the mean weighted effect size was large for the number of categories achieved ($d=0.91$, $p<0.05$), medium for absolute level of perseveration ($d=0.53$, $p<0.05$) and small for perseverative errors ($d=0.18$, $p<0.05$) (Laws, 1999). Other cognitive tests for executive function, like the Stroop test for cognitive inhibition, is also commonly used with this population and demonstrates a greater Stroop interference than healthy controls (response time, $M (g)=0.43$, C.I. 95%: 0.35–0.52 and accuracy, $M (g)=0.62$, C.I. 95%: 0.47–0.77) (Westerhausen et al., 2011). However, this test was not selected in this present study because it has the added language component, which may influence the results. The Tower of London test is less frequently used as an executive function test, although existing studies do report deficits in the schizophrenia population compared to
healthy controls (Liu, Wang, Wang, & Yang, 2012; Morris, Rushe, Woodruffe, & Murray, 1995; Zhu et al., 2010). The Tower of London test also has significant motor initiation and execution aspect to the test that is independent of planning. In order to account for this factor, a control test would need to be done where the time it takes the participant to touch the intended disk (initiation) and the time it takes to move the disk to the destination place (execution) would need to be calculated (Morris et al., 1995). This test was also not selected.

In sum, the WCST was chosen for three primary reasons. First, this is a common test in the clinical setting and, thus, the results of the proposed study will be comparable to existing literature and will be of relevance to clinicians. Second, due to the high functioning nature of the schizophrenia participants that are expected to take part in this study, the baseline scores are expected to be higher (better) on any cognitive test than those reported in meta-analyses. Because the WCST demonstrates the largest deficits in the literature for a test of executive function within this population, it was expected that the participants who took part in this study would have proportionally poorer baseline performance on this test compared to other cognitive tests. Therefore, due to the expected greater baseline difference, this test was expected to be more sensitive to changes in executive function from exercise than any other test.

### 3.3.6.1 WCST Procedure

During this test, the participant was asked to sort cards into one of four different piles (see Figure 3) (Heaton et al., 1993). Each pile had a different number, colour or shape. The correct answer (sorting) depended on a predetermined rule, which the participant was unaware of. However, the participant was told if they respond correctly to each trial. The rule changed throughout the experiment unannounced to the participant once 10 cards were sorted correctly in a row. The participant was required to sort 64 cards one-at-a-time on the computer.

### 3.3.6.2 Test Version - Short Form

Although the ability of the WCST-64 short form to predict performance on the full WCST-128 test version is mixed (Axelrod, 2002; Vayalakkara, Backhaus, Bradley, Simco, & Golden, 2000), for feasibility purposes, this study used the WCST-64 short form. This test took approximately 15 minutes to complete, whereas the long form would have taken about 30 minutes to complete.
Because the bout of exercise is only 20 minutes and the benefits are only short-lived, the short form was deemed appropriate for this particular context.

3.3.6.3 Mode of Test Administration

In past studies, both manual and computerized tests of the WCST have been administered to participants. The review is mixed regarding the correlation of the manual test results with that of the computerized test results. Artiola & Heaton (1996) found similar results between both modes of testing among 119 neurologically normal individuals. Hellman, Green, Kern, & Christenson (1992) also found no significant differences between these two modes among a small sample of psychiatric patients. However, there have also been reports about the characteristics of the results, such as central tendency and variability, between the computer and manual version not being within a reasonable range (Feldstein et al., 1999). Therefore, Feldstein et al. (1999) propose that the norms provided in the standard manual should not be used to compare computerized test results and recommends the creation of new norms for computerized testing. This study will use the computer version for two reasons. Although both the computer and manual version of the test have been used in the schizophrenia population, the computerized version has gained popularity for ease of administration and scoring in the last decade. Second, this proposed study is intended to assess the change in executive function as a result of an acute bout of exercise. As a result, there is less emphasis placed on the absolute results obtained from this test.

3.3.6.4 WCST Data Output

The WCST produced a number of results, including total number of correct responses out of 64 cards, total number of errors, perseverative errors, non-perseverative errors, categories completed, and number of trials to complete the first category. Although these various outputs are intended to give different perspectives on a participant’s overall, global executive function, perseverative and non-perseverative errors have been associated with distinct cognitive functions. Perseverative and non-perseverative errors together comprise the total number of errors. Perseverative errors are errors made by the participant when he or she continues to sort according to the previous rule, despite negative feedback. Therefore, perseverative errors are indicative of poor cognitive flexibility (Dieci et al., 1997; Li, 2004). Non-perseverative errors comprise of the ‘efficient’ and ‘random’ errors (Barceló & Knight, 2002). Efficient errors are
those errors made by the participant in an effort to determine the new correct rule. Because there are only three possible rules, the number of efficient errors needed to determine the new correct rule by trial-and-error is minimal (Barceló & Knight, 2002). Therefore, the majority of non-perseverative errors comprise of random errors, committed because participants fail to maintain attention, inhibit impulsive responses or if fail to update their working memory (Barceló, 1999; Barceló & Knight, 2002).
Figure 3. A visual representation of the Wisconsin Card Sorting Test (WCST) procedure.
3.4 Study Design

This study was a within-subject, counterbalanced experiment where all participants were randomly assigned to either the experimental or control arm of the study during Session 1. All participants completed the arm of the study that they did not complete one week later during Session 2.

3.5 Procedure

3.5.1 Telephone Recruitment and Screening

Participants who volunteered for a previous study were contacted first, as they have already shown interest in participating in research. Upon telephone contact, participants were informed of the study and asked if they would like to participate. If the participant was interested, the PAR-Q was used to determine eligibility. If the participant met the eligibility requirements, he or she was able to verbally consent to participating in the study and a convenient day and time was booked for the participant to come in for the Initial Assessment. The participant was required to attend three sessions in total: Initial Assessment, Session 1 and Session 2.

3.5.2 Initial Assessment

The PAR-Q was administered again to ensure no changes in responses from the initial telephone contact. During this session, the participant was given all appropriate details about the study verbally and in writing. Once the participant had an opportunity to review the consent form and ask questions, they provided written consent to participate in this study. The participant also completed the demographics questionnaire, IPAQ, the Life Satisfaction Scale, and the Apathy Evaluation Scale. Participants were informed that they must abstain from smoking for two hours prior to completing each of the two experimental conditions (Session 1 and Session 2). Two hours is sufficient time to inhibit any nicotine-related enhancement without inducing any withdrawal symptoms that may negatively impact cognitive function (Hatsukami, Fletcher, Morgan, Keenan, & Amble, 1989; Heishman, Kleykamp, & Singleton, 2010; Heishman, Taylor, & Henningfield, 1994; Hughes, 1991). Participants were also given a familiarization session with the cycle ergometer.
3.5.3 Session One

Upon arrival, participants were asked to complete the PANAS and the LUNSERS. Participants were then instructed to wear the heart rate monitor. Participants then completed the first administration of the WCST. This took approximately 10-15 minutes. Participants were then randomized into either the control or experimental arm of the study. Upon completion of the 20-minute session, participants completed the second administration of the WCST. The FS and FAS scales were administered throughout both conditions (see Figure 4 for specific assessment time points). After the second WCST administration was complete, participants completed the Intrinsic Motivation Scale and took part in the Exit Interview.

3.5.4 Session Two

This test session was completed one week after the first test session. Participants underwent the exact same procedure as outlined above during Session 1, except that they completed the arm of the study that they did not complete the previous week (see Figure 4).

3.5.5 Exercise Experimental Arm

If participants were randomly assigned to complete the acute exercise component, they engaged in 20 minutes of cycling on a cycle ergometer at moderate intensity, as this is the dose, intensity and mode used most commonly in past studies of healthy individuals (Chang et al., 2012; Lambourne & Tomporowski, 2010). Moderate intensity was defined as 64-76% of age-estimated maximum heart rate (American College of Sports Medicine, 2010). Participants were given up to 5 minutes in the warm up period to reach the intended heart rate. Participants then completed 20 minutes at a constant rate and load, followed by a 2-minute cool down period. To assess heart rate, participants wore a heart rate monitor strapped to their chest. Participants were advised that their heart rate must fall within the specified range and that workload will be adjusted in order to reach the minimum heart rate.

3.5.6 Control Arm

Participants were asked to sit quietly for 20 minutes in an empty room by him or herself and not engage in any other activity. Although, this may be considered a long time for participants to be sitting passively, this is a commonly used control condition in the healthy population. Therefore, to maintain consistency, this is also the condition that was used in the control arm. Furthermore,
if participants were asked to engage in any other activity, it may have affected their cognitive processes during this session, which may impact the performance on the WCST.
### Exercise Experimental Arm

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**Figure 4.** General protocols outline for Session 2 and 3. PAR-Q = Physical Activity Readiness Questionnaire; PANAS = Positive and Negative Affect Schedule; AES = Apathy Evaluation Scale; FAS = Felt Arousal Scale; FS = Feeling Scale; RPE = Borg’s Rating of Perceived Exertion; HR = Heart Rate; WCST = Wisconsin Card Sorting Test; Cravings = Desire to Smoke Assessment; LUNERS = Liverpool University Neuroleptic Side Effect Rating Scale (Measure of Sedation); IMS = Intrinsic Motivation Scale; EI = Exit Interview.
3.6 Statistical Analyses

3.6.1 Data Reduction

3.6.1.1 Executive Function

Figure 5 illustrates the how many participants were included in the final analyses. For the examination of acute changes in executive function, participants were excluded if a) they did not achieve a heart rate in the moderate-intensity range (64-76% of age-estimated maximum) at any point during the 20-minute exercise session, and b) did not complete both sessions. The majority of participants (n=30) achieved a heart rate in the lower end of the moderate intensity (64%) by the end of the warm up period. Of the five participants who did not achieve minimum heart rate at the start of the session, three met this minimum target at some point during the 20-minute session. The two participants who failed to achieve minimum heart rate were excluded from all relevant analyses. They were randomized to receive the sitting condition first. Only one participant failed to complete the exercise session once started and she was excluded from all relevant analyses. This participant was also randomized to the sitting condition for her first session. Two participants achieved a difference in total correct responses on the WCST from their baseline to one week post-intervention that was two standard deviation units below the mean and were excluded from all relevant analyses. Of these two participants, one was randomized to receive the exercise condition first and the other was randomized to receive the sitting condition first. Another participant, who was randomized to the exercise condition, was excluded because his baseline scores were below three standard deviations from the mean of the group. Lastly, one participant was excluded because he had poor understanding of the instructions about how to complete the cognitive task. Therefore, this participant, who was randomized to the sitting condition, was excluded from all analyses related to cognitive function. One participant did not have data for the PANAS and was excluded from all cognitive analyses because baseline negative affect was one of the controlling variables.

Therefore, the examination of acute changes in cognition, with the inclusion of both conditions that each participant completed, had a sample size of 28 individuals. In order to examine the possibility of a general practice effect, all participants who completed the study (n=36) were included. In order to minimize the effect of practice, acute changes in executive
Figure 5. An illustration and brief explanation of the number of participants included in the final analyses when the study was conducted and analyzed in a within-subject, counter-balanced manner, where each participant completed both conditions in random order.
Figure 6. An illustration and brief explanation of the number of participants included in the final analyses when the study was analyzed in a between-subject manner, where only the first condition completed by participants were included in the analyses.
function were also analyzed with just the first condition that participants completed in a between-group analyses, where the sample size was 33 individuals (exercise=17, sitting=16). Participants in these analyses were excluded based on the same inclusion/exclusion criteria that were noted above (see Figure 6).

Pearson’s Product Moment correlations were conducted between baseline WCST scores and illness duration, positive affect (PANAS), negative affect (PANAS), BMI, age, daytime drowsiness, amotivation and intrinsic motivation. Only illness duration and negative affect were significantly correlated with baseline WCST total correct scores and they were controlled for in all analyses examining acute changes in executive function.

3.6.1.2 Affect

For the examination of changes in affect (FS and FAS), participants were excluded only if they failed to complete both sessions. Only one participant did not meet this criterion and was excluded from the analyses. Although two participants failed to achieve a heart rate in the moderate-intensity range at any point during the 20-minute exercise session, their rating of perceived exertion during the 20-minute session was in the moderate intensity range. Therefore, these two individuals were included in the final analyses. Therefore, there were 35 participants in the final analyses of affect.

3.6.2 Study Objective 1 - Changes in Executive Function from Acute Exercise

Assumptions of normality, homogeneity of variance, homogeneity of intercorrelations and sphericity were met. Any violation of the assumption of sphericity was corrected for using Greenhouse-Geisser interpretation of the data outputs. Based on the inclusion and exclusion criteria noted above, 29 participants were included in the analyses examining changes in executive function after the exercise bout. Analyses were also conducted to evaluate the acute changes in executive function based solely on the first condition that participants completed in a between-group manner to minimize the influence of any practice effect. There were 33 participants in these latter analyses (exercise=17, sitting=16).
Repeated measures analyses of covariance (ANCOVA) and two-way mixed analyses of covariance (ANCOVA) were then used to assess the impact of the two different interventions (moderate intensity exercise vs. passive sitting) on participants’ scores on the WCST test, across two time periods (pre intervention, post intervention), controlling for illness duration and negative affect at baseline. Based on the study hypotheses, significant results from these ANCOVAs were followed by Tukey’s Honestly Significant Difference (HSD) post-hoc analyses. These study hypotheses predicted that participants who received the exercise intervention would have a greater improvement in their total correct responses on the WCST and related sub-variables (e.g. conceptual level responses, number of categories achieved etc.) than the group who received the passive sitting condition. Furthermore, it was hypothesized that the exercise group would also have a significant reduction in perseverative and non-perseverative errors post exercise compared to baseline as well as compared to the passive sitting group at post testing.

3.6.3 Study Objective 2 - Changes in Affect Before, During and After Exercise Compared to Passive Sitting

Assumptions of normality, homogeneity of variance, homogeneity of intercorrelations were met. Violation of the assumption of sphericity was corrected for using Greenhouse-Geisser interpretation of the data outputs. For the reasons mentioned above, analyses evaluating changes in affect had a sample size of 35 participants.

Repeated measures analyses of variance (ANOVA) were then used to assess the impact of the two different interventions (moderate intensity exercise vs. passive sitting) on participants’ affect, measured via the FS and FAS scales, across five time periods (pre-15 minutes, pre-warm up (pre-2-5 minutes), during-session (0-20 minutes), post-cool down (post-2 min) and post-15 minutes). Significant results from these ANOVAs were followed by Tukey's Honestly Significant Difference (HSD) post-hoc analyses, as they related to the study hypotheses. Namely, that participants would a) see a reduction in valence and an increase in activation during the bout of exercise compared to baseline testing and the passive sitting group and b) an increase in valence and activation post exercise cool-down compared to baseline and the passive sitting group, and that these values would return to near baseline levels after 15 minutes.

Furthermore, because participants in the sitting group did not have values for ‘pre-warm up’ or ‘post cool-down’ time periods as they simply did not apply to this group, values from 0
minutes were replicated for a ‘pre-warm up’ time point and values from 20 minutes were replicated for a ‘post cool-down’ time point only for the purposes of running an ANOVA and the illustration on Figure 11 and 12. The results from the ANOVA were the same with and without these extra time points. For Tukey’s HSD analyses, the replicated time points in the sitting condition were not evaluated.
Chapter 4 - Results

4 Overview

There were no significant changes in the WCST total correct responses or any other subcategories when both sessions completed by participants were included in the analyses. However, there was a significant effect of practice from the first to the fourth administration of the test, regardless of the order in which participants completed the two sessions. Therefore, to minimize the effect of practice, only the first condition completed by participants were analyzed in a between-group, parallel manner. This analysis revealed a significant reduction in non-perseverative errors among the exercise group that was not present in the passive sitting group. These changes in non-perseverative errors were also observed independent of affect. Furthermore, significant changes in valence and activation were found in the exercise group that was not present in the passive sitting group. This section will further explore these results in full detail.

4.1 Participants

A total of 42 participants were recruited from the Centre for Addiction and Mental Health in Toronto. The data from six participants were excluded for multiple reasons: participant was a) unable to see physician to complete the Physical Activity Clearance Form, b) unable to complete the exercise bout, c) decided to drop out of the study for personal, undisclosed reasons. Therefore, for the purposes of the final analyses, 36 participants were included. Based on the inclusion and exclusion criteria noted above in the Data Reduction section (3.6.1), select participants were removed from some or all of the analyses.

In the final sample (n=36), there were 24 men and 12 women, representing a similar gender proportion in the general population (Diflorio & Jones, 2010; McGrath, Saha, Chant, & Welham, 2008) with a large range in age (22-65 years; [M=45, SD=12.87]; see Table 3). Although this was an ethnically diverse sample, the majority of participants self-identified as “white” (55.6%). Furthermore, the majority of participants were unemployed (52.8%) and single (97.2%), although there was a range in education attainment (high school, with no diploma [30.6%], high school, with diploma [30.6%], some level of post-secondary education [38.9%]).
Most participants had a diagnosis of schizophrenia (61.1%), although one third of the sample was diagnosed with schizoaffective disorder (36.1%) (see Table 4). Participants varied in symptom severity from being mildly ill (CGI=3; 44.4%), moderately ill (CGI=4; 38.9%) to markedly ill (CGI=5, 13.9%), which is also echoed by the BPRS (M=35.78, SD=6.99). The majority of participants were either overweight (30.6%) or obese (50%) and were not meeting the recommended physical activity guidelines of 150 minutes of moderate-to-vigorous intensity physical activity (MVPA) per week (66.7%). About half of all participants were smokers (47.2%) and one participant indicated he had problems with substance abuse other than smoking and alcohol. When asked about general life satisfaction, participants reported, on average, neither satisfaction nor dissatisfaction (M=20.49, SD=8.23), with 42% of participants reporting some level of dissatisfaction with their life.

Participants (n=33) in this present study did comparably as poor as the scores reported in the literature for this population. In this current study, during baseline testing, participants sorted only about 59.6% of the cards correctly (M=38.18, SD=12.57) and only completed a few categories (M=2.15, SD=1.62). Participants also made high number of total errors (M=25.82, SD=12.57), perseverative errors (M=13.70, SD=10.33) and non-perseverative errors (M=12.12, SD=7.28). In an assessment of 104 participants with schizophrenia, Purdon & Waldie (2001) found similar baseline correct responses (M=38.24, SD=13.00), incorrect responses (M=25.47, SD=12.47), perseverative errors (M=14.93, SD=10.46), non-perseverative errors (M=10.54, SD=7.40), and total number of categories achieved (M=2.13, SD=1.50). Hartman et al. (2003) reported similar deficits in 28 patients with schizophrenia via perseverative errors (M=13.7, SD=9.7), non-perseverative errors (M=10.7, SD=6.3), and number of categories completed (M=2.2, SD=1.8). These scores are much lower than those of healthy individuals (n=28): perseverative errors (M=6.6, SD=1.7), non-perseverative errors (M=5.5, SD=2.6), categories achieved (M=4.3, SD=0.9) (Hartman, Steketee, Silva, Lanning, & Andersson, 2003).
### Table 3. Summary of demographics (N=36).

<table>
<thead>
<tr>
<th>Category</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: Female</td>
<td>24:12</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>45 (12.87)</td>
</tr>
<tr>
<td>Range</td>
<td>22-65</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>20 (55.6)</td>
</tr>
<tr>
<td>S. Asian</td>
<td>5 (13.9)</td>
</tr>
<tr>
<td>African</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (5.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (5.6)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
</tr>
<tr>
<td>Not employed</td>
<td>19 (52.8)</td>
</tr>
<tr>
<td>Part-time</td>
<td>11 (30.6)</td>
</tr>
<tr>
<td>Retired</td>
<td>5 (13.9)</td>
</tr>
<tr>
<td>Student</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>High school (no diploma)</td>
<td>11 (30.6)</td>
</tr>
<tr>
<td>High school (diploma)</td>
<td>11 (30.6)</td>
</tr>
<tr>
<td>Some post-secondary</td>
<td>14 (38.9)</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>35 (97.2)</td>
</tr>
<tr>
<td>Divorced</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Life Satisfaction Mean (SD)</td>
<td>20.49 (8.23)</td>
</tr>
</tbody>
</table>

*Note: Values are counts and percentages unless otherwise specified.*
Table 4. Clinical and Anthropometric Information (N=36).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>22 (61.1)</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>13 (36.1)</td>
</tr>
<tr>
<td>Psychosis NOS</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Concurrent Substance Abuse/Dependence</td>
<td>1 (2.8)</td>
</tr>
</tbody>
</table>

Symptom Severity

<table>
<thead>
<tr>
<th>BPRS Mean Score (SD)</th>
<th>35.78 (6.99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANAS Mean Score (SD), n=35</td>
<td></td>
</tr>
<tr>
<td>Positive Affect EX</td>
<td>31.66 (8.30)</td>
</tr>
<tr>
<td>Positive Affect CN</td>
<td>32.20 (8.11)</td>
</tr>
<tr>
<td>Negative Affect EX</td>
<td>15.29 (5.67)</td>
</tr>
<tr>
<td>Negative Affect CN</td>
<td>16.20 (7.86)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CGI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>16 (44.4)</td>
</tr>
<tr>
<td>4</td>
<td>14 (38.9)</td>
</tr>
<tr>
<td>5</td>
<td>5 (13.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AES Mean Score (SD)</th>
<th>30.94 (8.10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMI Mean Score (SD)</td>
<td></td>
</tr>
<tr>
<td>Exercise, n=31</td>
<td>97.52 (25.05)</td>
</tr>
<tr>
<td>Sitting, n=33</td>
<td>99.21 (25.11)</td>
</tr>
</tbody>
</table>

| LUNERS Mean Score (SD)            |              |
| Exercise, n=34                    | 0.96 (1.00)  |
| Sitting, n=35                     | 1.31 (1.20)  |

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>30.62 (7.33)</td>
</tr>
<tr>
<td>Normal Weight (BMI&lt;24.9)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>Overweight (BMI=25.0-29.9)</td>
<td>11 (30.6)</td>
</tr>
<tr>
<td>Obese (BMI&gt;30.0)</td>
<td>18 (50)</td>
</tr>
</tbody>
</table>

| Baseline MVPA (weekly minutes)    |        |
| Mean (SD)                         | 203.8 (430.5) |
| Not Meeting National Guidelines   | 24 (66.7)  |
| Meeting National Guidelines       | 12 (33.3)  |

| Smoking Habits                    |        |
| Current Smokers                   | 17 (47.2) |
| Mean (SD) cigarettes/day          | 16.21 (5.96)  |

Note: Values are counts and percentages unless otherwise specified. BPRS = Brief Psychiatric Rating Scale 18-item anchored version, possible scores range from 18-126, with higher scores representing more severe illness; PANAS = Positive and Negative Affect Schedule, possible scores can range from 10-50 separately for both the positive and negative affect, where higher scores indicate higher positive or negative affect; CGI = Clinical Global Impression Severity Scale, possible scores range from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). AES = Apathy Evaluation Scale, possible scores 18-72, with higher values representing greater amotivation; IMI= Intrinsic Motivation Inventory, possible scores range from 21-147, with higher scores representing greater intrinsic motivation; LUNERS = Liverpool University Neuroleptic Side Effect Rating Scale, Item #2 only, possible scores range from 0-4,
where higher scores indicate greater difficulty staying awake during the day; BMI = Body Mass Index; MVPA = moderate-to-vigorous physical activity.
Table 5. Summary of heart rate, Borg Rating of Perceived Exertion, Feeling Scale, and Felt Arousal Scale by time and task (mean, SD).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Time (min):</th>
<th>Pre-15</th>
<th>Pre-Warm Up</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>Post-2</th>
<th>Post-15</th>
<th>Mean During Condition (0-20 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>HR</td>
<td>85.5</td>
<td>(11.2)</td>
<td>83.9</td>
<td>(11.6)</td>
<td>114.7</td>
<td>(14.2)</td>
<td>119.9</td>
<td>(16.6)</td>
<td>123.5</td>
<td>(16.7)</td>
</tr>
<tr>
<td></td>
<td>% Max HR</td>
<td>49.2</td>
<td>(7.9)</td>
<td>48.4</td>
<td>(8.2)</td>
<td>65.7</td>
<td>(7.4)</td>
<td>68.7</td>
<td>(8.9)</td>
<td>70.7</td>
<td>(8.7)</td>
</tr>
<tr>
<td></td>
<td>RPE</td>
<td>7.9</td>
<td>(1.9)</td>
<td>8.5</td>
<td>(2.4)</td>
<td>12.7</td>
<td>(1.8)</td>
<td>12.9</td>
<td>(1.4)</td>
<td>13.5</td>
<td>(1.1)</td>
</tr>
<tr>
<td></td>
<td>FS</td>
<td>2.0</td>
<td>(1.7)</td>
<td>1.7</td>
<td>(1.5)</td>
<td>1.1</td>
<td>(2.2)</td>
<td>1.0</td>
<td>(2.1)</td>
<td>1.0</td>
<td>(2.0)</td>
</tr>
<tr>
<td></td>
<td>FAS</td>
<td>2.2</td>
<td>(1.2)</td>
<td>2.4</td>
<td>(1.1)</td>
<td>3.1</td>
<td>(1.4)</td>
<td>3.4</td>
<td>(1.3)</td>
<td>3.5</td>
<td>(1.2)</td>
</tr>
</tbody>
</table>

| Sitting   | HR          | 84.8 | (11.7)      | 85.9 | (12.8) | 84.5 | (12.0) | 84.3 | (11.6) | 83.5 | (12.0) | 83.4 | (11.8) | 83.0 | (10.8) | 84.3 | (11.7) |
|           | % Max HR    | 48.8 | (7.9)       | 49.5 | (8.8) | 48.6 | (8.1) | 48.5 | (8.0) | 48.1 | (8.2) | 48.0 | (8.1) | 47.8 | (7.7) | 48.5 | (8.1) |
|           | RPE         | 8.5 | (2.3)       | -   | 8.9 | (2.4) | 8.4 | (2.2) | 7.9 | (2.2) | 8.1 | (2.4) | 7.8 | (2.2) | -   | 8.2 | (2.2) | 8.2 | (2.0) |
|           | FS          | 2.4 | (2.0)       | 1.9 | (2.0) | 1.8 | (1.9) | 2.0 | (1.7) | 1.9 | (1.8) | 1.8 | (1.8) | 1.9 | (1.9) | 1.9 | (1.5) |
|           | FAS         | 2.3 | (1.0)       | 2.6 | (1.3) | 1.9 | (1.0) | 1.9 | (0.8) | 2.0 | (1.0) | 1.8 | (0.8) | 2.1 | (1.0) | 2.1 | (0.8) |

*Note: HR = Heart Rate, in beats/minute; %Max HR = Percent of Age Calculated Maximum Heart Rate; FS = Feeling Scale; FAS = Felt Arousal Scale.*
4.2 Manipulation Check to Confirm Moderate Intensity Exercise

Both heart rate and ratings of perceived exertion were used to ensure that participants were exercising at the intended intensity (see Table 5). Once participants reached the lower end of moderate intensity (64% of age-estimated maximum), they were able to choose where in the moderate intensity range (64-76% of the age-estimated maximum) they wanted to be for the duration of the exercise bout. Of the 36 participants, one participant was excluded because she was not able to complete the exercise session. Of the remaining 35 participants, 30 met the minimum required heart rate for moderate intensity at the start of the 20-minute session. Of the remaining five participants, three participants met the minimum heart rate at some point in the exercise session. Two participants did not meet minimum heart rate at all and were excluded from all analyses related to executive function. The inclusion or exclusion of these five participants did not change the outcomes of the cognitive function analyses presented below.

For the purposes of analyzing affect, all participants who completed both sessions were included, including the five participants who did not meet minimum heart rate requirements at the start of the session because their ratings of perceived exertion were in the moderate intensity range (RPE=12-15) while they exercised. Nevertheless, the analyses examining affect with and without these five participants did not change the outcome of the results.

4.3 Study Objective 1- Examining Immediate Changes in Executive Function

4.3.1 Both Conditions

The results of the repeated measures ANCOVA revealed no significant time by session interaction for the total number of correct responses achieved, $F(1, 25)=0.05, p=0.82$, partial $\eta^2=0.00$, observed power=0.06. There was no significant effect of time, $F(1, 25)=1.11, p=0.30$, partial $\eta^2=0.04$, with both sessions showing an improvement on the WCST test (see figure 7). The main effect of session was also not significant, $F(1, 25)=4.04, p=0.06$, partial $\eta^2=0.14$. There was a significant main effect of illness duration, $F(1, 25)=8.08, p=0.01$, partial $\eta^2=0.24$, but not a significant effect for baseline negative affect, $F(1, 25)=1.66, p=0.21$, partial $\eta^2=0.06$. However, there was no significant interaction between illness duration and session $F(1,
25)=0.93, \( p=0.34 \), time \( F(1, 25)=2.72, p=0.11 \), and session by time interaction \( F(1, 25)=0.27, p=0.61 \). There was also no significant interaction between baseline negative affect and session, \( F(1, 25)=1.50, p=0.23 \), time \( F(1, 25)=0.88, p=0.36 \), and session by time interaction \( F(1, 25)=0.00, p=0.98 \).

Similar ANCOVAs were run to examine the influence of moderate intensity exercise and passive sitting on trials to complete the first category, number of categories, conceptual level responses, perseverative errors, and non-perseverative errors. However, no significance emerged in the time by session interaction, time or group analyses (\( ps>0.54 \)).

![Figure 7](image_url)

**Figure 7.** Total correct responses (mean, SD) achieved on the WCST test pre and post session (moderate exercise and passive sitting). Participants completed both sessions, \( n=29 \).

### 4.3.2 Practice Effect

To determine if there was a significant practice effect, a repeated measures ANOVA was conducted to determine the effect of time (first, second, third and fourth administration of the WCST) among all participants (\( n=36 \)) for the total number of correct responses. The analyses revealed a significant effect of time, \( F(3, 33)=4.31, p=0.01 \), partial \( \eta^2=0.28 \), observed power=0.82. For the purposes of conducting post-hoc Tukey’s HSD tests, \( q (4, 105)=3.69 \), an estimate based on \( df=120 \) and HSD=4.27 for \( p=0.05 \). These analyses revealed a significant improvement in total correct responses during the fourth administration (\( M = 42.56, SD = 13.94 \)) compared to baseline testing (first administration: \( M = 36.61, SD = 13.69 \), \( d=0.43 \) (Figure 8).
Examination of the effect of practice. The results from the four administrations of the WCST are plotted in the order that participants (n=36) completed the tests in chronological order, regardless of the order in which the sessions were completed. There was a significant improvement in total correct scores (mean, SD) from the first administration to the fourth administration (p=0.05).

4.3.3 First Condition Only

In order to minimize the effects of practice, the results from the first condition that participants completed were solely analyzed in a between-group, parallel analyses. Results from the two-way mixed ANCOVA, controlling for illness duration and baseline negative affect, revealed no significant interaction between session and time for total correct responses, $F(1, 29) = 0.30$, $p=0.59$, partial $\eta^2=0.01$, observed power=0.08. The main effect of time was also not significant, $F(1, 29) = 0.09$, $p=0.76$, partial $\eta^2=0.00$, with participants in both sessions showing an improvement in the number of correct answers achieved on the WCST test (see figure 9). The main effect of session was not significant, $F(1, 29) = 0.07$, $p=0.80$, partial $\eta^2=0.00$, suggesting no difference between the two conditions. There was a significant main effect of illness duration, $F(1, 29)=12.16$, $p<0.01$, partial $\eta^2=0.30$. However, the time by illness duration interaction was not statistically significant, $F(1, 29)=1.65$, $p=0.21$, partial $\eta^2=0.05$. The main effect of baseline negative affect was not significant, $F (1, 29) = 3.33$, $p=0.08$, partial $\eta^2=0.10$, neither was the time by baseline negative affect, $F (1, 29)=1.93$, $p=0.18$, partial $\eta^2=0.06$. 

**Figure 8.** Examination of the effect of practice. The results from the four administrations of the WCST are plotted in the order that participants (n=36) completed the tests in chronological order, regardless of the order in which the sessions were completed. There was a significant improvement in total correct scores (mean, SD) from the first administration to the fourth administration (p=0.05).
Figure 9. The total correct responses achieved (mean, SD) by participants before and after the first condition they completed, n=33 (exercise=17, sitting=16).

Similar two-way mixed ANCOVAs were run to examine the influence of exercise and sitting on perseverative errors, trials to complete the first category, number of categories and conceptual level responses. No significance emerged in the time by session interaction, time or session analyses ($p$s>0.59).

However, there was a significant time by session interaction effect for non-perseverative errors, $F(1, 29)=11.71$, $p<0.01$, partial $\eta^2=0.29$, observed power=0.91. Because there was a significant correlation between the reduction in non-perseverative errors and an increase in activation post exercise ($r=-0.43$, $p<0.05$), post session FAS scores were included as a covariate in a separate mixed two-way ANCOVA. However, there was no significant relationship between this covariate and changes in non-perseverative errors, once the independent variable (moderate intensity exercise vs. passive sitting) was accounted for, $F (1, 28)=1.32$, $p=0.26$, partial $\eta^2=0.05$.

For the purposes of conducting post-hoc Tukey’s HSD tests on changes in non-perseverative errors, $q (2, 29) = 2.89$ and HSD=1.28 for $p=0.05$. These analyses revealed a significant reduction in non-perseverative errors post exercise (M=7.88, SD=4.48) compared to
baseline (M=12.18, SD=6.99), \( d = -0.73 \). There was no statistically significant difference found in the sitting group post condition (M=12.00, SD=8.72) compared to baseline (M=12.06, SD=7.79), \( d = -0.01 \). There was also a between-group difference at post testing, \( d = -0.59 \) (see Figure 10).

![Figure 10](image)

**Figure 10.** The number of non-perseverative errors (mean, SD) made by participants before and after the first condition completed, \( n=33 \) (exercise=17, sitting=16). There was a significant (*) reduction in the exercise group and between both groups at post-testing (\( p=0.05 \)).

Although the omnibus F test (ANCOVA) revealed no significant changes in total number of errors made by participants, post-hoc Tukey's HSD revealed a significant reduction in total errors among the exercise group (Pre: M=24.88, SD=11.24; Post: M=21.82, SD=13.87), whereas this change was not significant in the passive sitting group (Pre: M=26.81, SD=14.16; Post: M=24.81, SD=13.63). In addition, the changes in perseverative errors were not significant both with the omnibus F test and temporal post-hoc Tukey's HSD analyses among the exercise group (Pre: M=12.71, SD=9.49; Post: M=13.94, SD=12.94) and the passive sitting group (Pre: M=14.75, SD=11.36; Post: M=12.81, SD=9.72).
4.4 Study Objective 2 - Changes in Affect

4.4.1 Potential Mediating Effect of Affect on Executive Function

Changes in affect might be one potential mediating mechanism underpinning changes in executive functioning after a bout of exercise. However, the only correlation that was significant was the association between the reduction in non-perseverative errors and activation post session. However, this was a non-significant covariate once included in the mixed two-way ANCOVA. Given no other significant correlations or group by time differences in the WCST sub-analyses, formal assessment of changes in affect as a mediator was not conducted.

4.4.2 Valence (Feeling Scale)

The results of the repeated measures ANOVA revealed a significant time x session interaction effect, \( F(4, 136) = 2.73, p=0.03, \text{partial } \eta^2=0.07, \) observed power = 0.74. The main effect of time was also statistically significant, \( F(2.66, 90.52) = 3.35, p=0.03, \) Greenhouse-Geisser correction, \( \epsilon=0.67, \text{partial } \eta^2=0.09, \) (see figure 11). The main effect of session was not significant, \( F(1, 34) = 0.21, p=0.65, \text{partial } \eta^2=0.01. \) For the purposes of conducting post-hoc Tukey’s HSD tests, \( q (5, 136)=3.92, \) an estimate based on \( df=120 \) and HSD=0.81. These analyses revealed a significant reduction in valence during exercise (M=1.12, SD=1.69) compared to pre-15 minutes (M=2.00, SD=1.75), \( d=-0.51 \) and a significant improvement in valence post-15 minutes (M=2.49, SD=1.42) compared to the valence reported during the exercise bout, \( d=0.88. \) However, the improvement in valence post 15 minutes compared to pre 15 minutes was not statistically significant, \( p>0.05, d=0.31. \) There was no significant change in valence between any of the three time points (pre-15, during, post-15) in the passive sitting group \( (p>0.05). \) The two groups did not differ from each other significantly at any time point throughout the session \( (p>0.05). \)
Figure 11. Changes in valence (mean, SD) as measured by the Feeling Scale (FS) before, during (0, 5, 10, 15 and 20 minutes) and after participants completed each condition (exercise and passive sitting), n=35. Significant (*) changes are noted above. The two replicated time points in the sitting condition are highlighted in white.

4.4.3 Activation (Felt Arousal Scale)

The results of the repeated measures ANOVA revealed a significant time x session interaction effect, $F(3.02, 102.70) = 16.30, p<0.01$, Greenhouse-Geisser correction, $\varepsilon=0.76$, partial $\eta^2=0.32$, observed power = 1.00. The main effect of time was also statistically significant, $F(4, 136) = 3.44, p=0.01$, partial $\eta^2=0.09$ (see figure 12). The main effect of session was also significant, $F(1, 34) = 16.53, p<0.01$, partial $\eta^2=0.33$. For the purposes of conducting post-hoc Tukey’s HSD tests, $q (5, 136)=3.92$, an estimate based on $df=120$ and HSD=0.57. These analyses revealed a significant increase in activation during the exercise session ($M=3.38, SD=1.15$) compared to pre-15 minutes ($M=2.20, SD=1.18$, $p<0.05$, $d=1.01$ and pre-warm up ($M=2.40, SD=1.12$), $d=0.86$. Activation immediately after cool down ($M=3.03, SD=1.25$) was also significantly higher than pre 15 minutes ($d=0.68$) and pre warm-up scores ($d=0.53$). However, there was also a significant reduction 15 minutes after exercise ($M=2.66, SD=1.31$) compared to activation during exercise, $d=-0.58$. The passive sitting group did not have any significant changes in activation between any of the three time points ($ps>0.05$). Furthermore, the exercise and sitting group only differed from each other during the session (passive sitting: $M=2.09$, $SD=0.82, d=1.32$), although the difference in activation between the two groups post-15 minutes was approaching significance (mean difference=0.51 at $p=0.05; d=0.47$).
Figure 12. Changes in activation (mean, SD) as measured by the Felt Arousal Scale (FAS) before, during (0, 5, 10, 15 and 20 minutes) and after participants completed each condition (exercise and passive sitting), n=35. The significant (*) changes are noted above. There was also a between-group difference during the session (significance not illustrated on the graph). The two replicated time points in the sitting condition are highlighted in white.

4.4.4 Circumplex Model of Affect

A global assessment of basic affect is illustrated in Figure 13, on the circumplex space in a bivariate, orthogonal manner using the Feeling Scale (FS) to measure valence and the Felt Arousal Scale (FAS) to measure activation. Participants in both conditions (moderate exercise and passive sitting) began with low-activation and pleasant affect, which is an indication of calmness and relaxation. While the passive sitting group remained in this space, the exercise group increased in activation and decreased in valence during the exercise session compared to baseline evaluations. Thus, these participants were moving towards the trajectory of negative high activation states (e.g. tense effort). This was followed by a return to slightly higher valence and increased activation after 15 minutes of rest post exercise compared to baseline assessments.
Figure 13. Affective responses to exercise (red, squares) and passive sitting (blue, circles) represented in the circumplex space. The exercise session was assessed at nine time points (Pre-15, Pre-Warm Up (Pre 2-5 min), 0, 5, 15, 20, post cool-down, post 15 minutes) and the passive sitting condition was assessed at seven time points (Pre-15, 0, 5, 15, 20, post 15 minutes). Valence was assessed with the FS scale (Hardy & Rejeski, 1989) and activation with the FAS scale (Svebak & Murgatroyd, 1985), n=35.
Chapter 5 - Discussion

5 Overview

The purpose of this study was to examine if an acute bout of exercise can improve executive function in the short-term. Based on the reported small changes in the healthy population and the already lower baseline functioning in the schizophrenia population, it was hypothesized that there would be at least a medium-sized improvement in the schizophrenia population immediately after moderate intensity exercise compared to passive sitting. When only the first completed condition by participants was examined in a between-group analysis, there was a significant reduction in non-perseverative errors after the bout of exercise, an indication of improved attention, inhibition and working memory. Furthermore, changes in basic affect were also assessed throughout both sessions, where participants reported a reduction in valence and an increase in activation during the exercise session. This section will further review these findings from the study, as well as examine the study strengths, limitations and implications for future research.

5.1 Immediate Changes to Executive Function from Acute Exercise

First, the total correct responses from the WCST were analyzed using data from both sessions that participants completed. This within-subject, repeated-measures analysis showed an improvement after both the exercise (mean change=2.54) and the passive sitting conditions (mean change=2.13) compared to baseline. These improvements were not significant and the effect sizes were negligible (exercise: $d=0.18$; sitting: $d=0.15$). Furthermore, there were no other significant or clinically relevant changes found in any other sub-analyses from the WCST (e.g. perseverative errors, non-perseverative errors, conceptual level responses, number of categories completed). These findings are counter to our initial hypothesis, where it was predicted that the exercise group would have a significant improvement on the WCST post testing compared to baseline assessments and the passive sitting condition at post testing. One possible explanation for these null findings may be the effect of practice, as each participant completed the same WCST procedure four times within one week. When the possible influence of practice was
examined, there was a significant improvement from the first administration to the fourth administration, regardless of the order in which the participant completed the two sessions.

Therefore, in order to minimize this effect of practice, only the WCST scores (pre and post administration) from the first session (moderate intensity exercise or passive sitting) completed by participants were examined in a between-subject, parallel manner. No significant changes were found in the total correct responses achieved or any of the other sub-analyses of the WCST, other than non-perseverative errors, where the exercise group showed a significant reduction post session.

Non-perseverative errors are made up of ‘efficient’ and ‘random’ errors. When the rule has changed, participants are “forced to make non-perseverative errors early in the [new] WCST series in order to find the new sorting rule. This is a very efficient trial-and-error process in normal subjects, who can keep track of past incorrect rules to obtain quickly the new correct rule…[these errors] imply an efficient use of recent contextual information to optimize set shifting…[Therefore], an ‘efficient’ error was defined as a shift to the wrong category in the second trial” where there are no subsequent errors in that series (Barceló & Knight, 2002, pg. 350, 353). However, the ‘random’ errors are those non-perseverative errors “that involve a shift in set, but also an inefficient use of past contextual information. [They] are defined as a shift to a wrong category different from the one chosen in the previous trial and are compatible with other errors earlier or later in that series. They indicate that the subject has not kept track of all previously discarded categories” (Barceló & Knight, 2002, pg. 350, 353). Because ‘efficient’ errors only comprise of the second incorrect sorting once a rule has changed, they only make up a small portion of the total number of non-perseverative errors. Therefore, the majority of the non-perseverative errors comprise of ‘random’ errors, where higher scores reflect poor attention, inhibition (Barceló, 1999) and working memory (Barceló & Knight, 2002).

Using a between-subject analysis examining data from the first condition completed by participants, this study demonstrated a significant reduction in non-perseverative errors by the exercise group (Pre: M=12.18, SD=6.99; Post: M=7.88, SD=4.48), compared to the passive sitting group (Pre: M=12.06, SD=7.79; Post: M=12.00, SD=8.72). There was also a significant between-group difference on this variable post administration of the WCST test. Furthermore, the total number of errors made by a participant is equal to the sum of the perseverative and non-
perseverative errors. Although the omnibus F test (ANCOVA) revealed no significant changes in total number of errors made by participants, post-hoc Tukey's HSD revealed a significant reduction in total errors among the exercise group (Pre: M=24.88, SD=11.24; Post: M=21.82, SD=13.87), whereas this change was not significant in the passive sitting group (Pre: M=26.81, SD=14.16; Post: M=24.81, SD=13.63). In addition, the changes in perseverative errors were not significant both with the omnibus F test and temporal post-hoc Tukey's HSD analyses among the exercise group (Pre: M=12.71, SD=9.49; Post: M=13.94, SD=12.94) and the passive sitting group (Pre: M=14.75, SD=11.36; Post: M=12.81, SD=9.72). In sum, these different types of analyses point to the conclusion that there was a significant, medium-to-large finding \((d=-0.73)\) that participants had better attention, improved inhibition and overall better working memory after exercise compared to participants who sat passively in this particular context of novel rule identification and maintenance, once participants have realized that the rule has changed. From a proof-of-concept perspective, these results provide an initial demonstration that an acute bout of exercise does confer immediate benefits in select types of cognitive domains. Therefore, participants may be able to use acute bouts of exercise to improve their day-to-day functioning.

Nevertheless, the other null findings may be due to two possible explanations. First, there may not be any acute changes in overall executive function or all types of cognitive functions classified under executive function. All participants included in the WCST analyses were exercising at moderate intensity for 20 minutes, objectively measured with a heart rate monitor. Based on previous studies, this bout of exercise was appropriate to induce the necessary physiological changes needed to confer the improvements in cognitive function seen in healthy adults (Brisswalter, Collardeau, & René, 2002; Tomporowski, 2003). Because there were only changes in non-perseverative errors, it is possible that the immediate physiological changes induced by one bout of exercise do not significantly alter all aspects of executive function that the WCST is intended to evaluate among individuals with schizophrenia.

Second, due to study limitations, other changes in executive function may have gone undetected. For example, when only the first condition was examined, the sample size was reduced to half of the original value and there may not have been enough power to detect these other changes. There was also considerable variability in the scores between participants, as evidenced by the large standard deviations. These two limitations, among others to be discussed later, may be masking any other effects of exercise that could have occurred.
5.2 Changes in Affect Before, During and After Exercise

This study also evaluated affect throughout both the moderate intensity exercise and the passive sitting session because an improvement in affect may also mediate improved cognitive function (Tomporowski, 2003). However, there was only one significant correlation between post session activation and changes in non-perseverative errors. This relationship was not significant once included in the mixed two-way ANCOVA. Therefore, these reductions in non-perseverative errors seem to have occurred independent of changes in affect. Nevertheless, irrespective of the impact on cognitive functioning, changes in affect during and after a bout of exercise are important to explore given links between affect and well-being, and potential future exercise participation.

The within-subject, repeated measures analysis produced a significant time by session interaction effect for valence that was of moderate effect size (partial $\eta^2=0.08$). Participants generally experienced a significant reduction in valence during the exercise session compared to baseline assessment, which later rebounded after 15 minutes. Valence, however, was not significantly different 15 minutes post session between the exercise and passive sitting groups. These findings support the initial hypothesis of the study, predicting a reduction in valence during the exercise session and a rebound to similar or higher levels after a period of rest, when compared to pre-exercise.

Consistent again with the initial hypothesis, the within-subject, repeated measures analysis produced a significant time by session interaction effect for activation that was of large effect size (partial $\eta^2=0.29$). There was a significant increase in activation during the exercise session compared to baseline assessments, which remained significantly higher after a period of cool down (post 2 minutes) when compared to baseline values. Although not significant, activation post 15 minutes of exercise was still greater than pre exercise and after passive sitting. Only activation during the session was significantly different between the exercise and passive sitting conditions. These findings are consistent with what is reported in the literature, where activation increases during exercise and subsides over time once the exercise session is over, as seen after 15 minutes (Ekkekakis et al., 2011; Ekkekakis & Petruzzello, 1999).
When these measures of affect were plotted on the circumplex model to assess global changes in basic affect, participants in the sitting condition remained, generally, in the same space, a region within the low activation, pleasant affect quadrant, throughout the session. Participants in the exercise session started off in the same quadrant as the passive sitting group. However, during the exercise session, there was a significant movement towards the high activation, unpleasant affect quadrant. The assessment of basic affect before, during and after exercise as well as passive sitting, with subsequent illustration on a circumplex model was instrumental in characterizing the absence of anhedonia in this exercise context, a construct that is often implicated as a core feature of schizophrenia (Andreasen, 1982; Blanchard & Cohen, 2006).

Furthermore, the noted variability in valence reported by participants during exercise is consistent with the inter-individual variability in exercise-related pleasure reported among healthy participants during moderate intensity exercise (Ekkekakis, Hall, & Petruzzello, 2005; Kwan & Bryan, 2010; Williams et al., 2008). Specifically, of the 35 participants who completed the exercise session, 25.7% experienced a reduction in valence, 25.7% experienced no change in valence and 48.6% experienced an increase in valence during the exercise session when compared to valence before the start of the session. Furthermore, only 20% of these participants reported a negative valence (FS<0) during the bout of exercise, whereas 20% reported a 'neutral' valence (FS=0) and 60% reported a positive valence (FS≥1). In addition to other considerations that may lead an individual to engage in regular physical activity, enjoyment plays a critical factor, such that those who report pleasurable feelings during moderate intensity exercise are more likely to engage in future physical activity (Ekkekakis et al., 2011). This study suggests that, at the very least, individuals with schizophrenia are able to experience the same pleasurable feelings post-exercise as otherwise healthy individuals. Further research is required to examine if the affective responses to exercise predicts physical activity behavior in this population.

5.3 Strengths and Limitations

This is the first study to examine if improvements in cognitive function, particularly executive function, are possible with one bout of moderate intensity exercise among individuals diagnosed with schizophrenia. As such, this is the first study to test the benefits of exercise at a fundamental, proof-of-concept level. These findings suggest there may be some potential in
further developing this line of inquiry into exercise and cognitive functioning in schizophrenia. This is also the first study to report significant changes in basic affect among participants with schizophrenia on the circumplex model with a large sample of participants. This latter finding was critical to support the lack of anhedonia among individuals with schizophrenia, at the very least, in the context of exercise. Lastly, this study tested one potential mechanism, changes in affect, which might explain cognitive improvements. Results suggest that improvements were independent of changes in affect. While this does not rule out affect as a mechanism, it does suggest that other mechanisms should be considered in future research.

In addition to the novelty of these research questions, there are several methodological strengths to this study. First, all participants were required to exercise at moderate intensity for 20 minutes, excluding warm-up and cool-down periods. Therefore, participants received an exercise dose, both in duration and intensity, that was, theoretically sufficient to produce meaningful physiological changes (Brisswalter et al., 2002). This exercise dose was also feasible for participants to accomplish in one session. Second, participants were given sufficient time to reach the lower end of their moderate intensity heart rate (64% of age-estimated maximum) during the warm-up period and in most cases (83.3%), participants reached this lower level before the 20-minute session began. Therefore, a reasonable effort was made to ensure this quality control measure was in place and that participants exercised at the intended heart rate for the same duration.

Another major strength to this study is that participants were able to choose where in the moderate intensity range they wanted to be once their 20-minute session began. This is a critical added value to this experiment because previous research shows that when participants are given some level of autonomy over their exercise program, they are more likely to enjoy the exercise session and are able to persist even if they find it challenging to continue (Ekkekakis, 2009). Lastly, this experiment was designed in a within-subject manner to minimize the inter-individual variability and the large heterogeneity inherent in this population.

However, there are a few limitations that may explain the other null findings in executive function from this one acute bout of exercise. First, although the WCST test may be ideal to determine how well an individual's executive function is working from a clinical assessment perspective, it may not be sensitive to detect changes, particularly if they are small. During the
design of this research protocol, the WCST was selected, in part, because there was some evidence to support acute changes via this test among individuals with schizophrenia (Goldberg, Bigelow, Weinberger, Daniel, & Kleinman, 1991; Siegel et al., 1996). Second, even though there are 64 cards, this is still a very much a categorical assessment with four possible choices, where there is a 25% chance of randomly guessing the correct response. Furthermore, this test is only able to detect changes on a card-by-card basis, and does not have the ability to detect changes on a finer, smaller interval. This may be due to the fact that the WCST is used to assess executive function globally, by evaluating multiple, higher-level cognitive functions simultaneously. Therefore, any benefits to lower level cognitive functions may have gone undetected by this test.

Third, the influence of practice had a significant impact. The WCST was initially developed as a clinical assessment to detect damage to or abnormal function of the prefrontal cortex (Nyhus & Barceló, 2009). It was not intended to be used across multiple time points, particularly four times within a week. However, these multiple assessments were deemed appropriate at the initial conceptualization of this study because it was assumed that the effect of practice would not be problematic due to the poor reported baseline cognitive performance among individuals with schizophrenia, particularly on the WCST, and that any effect due to practice would be negligible. However, this was not the case in the present sample. Therefore, in order to minimize this impact, only the first condition completed by participants was evaluated, in a between-subject, parallel analysis. The presence of a ceiling effect was also evident for 25% of the participants who scored 50 out of the 64 cards (78%) correctly during the first, baseline administration of the test. Although participants in this study, in general, performed as poorly as those reported in the literature (Hartman et al., 2003; Purdon & Waldie, 2001), there was considerable heterogeneity in this sample and a select number of participants had high baseline scores. Therefore, the WCST limited these participants in demonstrating the extent of their improvement, if one was present, after the bout of exercise.

There was also no cognitive test familiarization component included as part of the initial recruitment session. As illustrated by Bryan & Harter (1897), there is significant learning/familiarization that occurs during the initial stages of acquisition that eventually plateaus. In this particular study, examining improvement in telegraphic language (letters/minute), they saw the greatest rate of improvement during the first 4-8 weeks, in a 40-
week examination period. Therefore, familiarization to the cognitive test may have accounted for the large learning effect that occurs between these two initial assessment time points.

Another limitation in this present study stems from the large heterogeneity among the participants who were enrolled. Understanding that there is considerable variability in this population at the onset of study, an attempt was made to minimize this factor to include only participants who scored 3, 4, or 5 on the CGI scale, excluding participants who were considered ‘normal’ and ‘borderline, mentally ill’ and those who were considered very ill (‘severely ill’ and ‘among the most severely ill patients’) based on this scale. However, it became apparent during the study that illness severity was not correlated with cognitive impairment ($r=-0.01$, $p=0.98$). Therefore, selecting participants based on their symptom severity did not translate to having participants with similar baseline cognitive functions. Participants also varied in fitness level and baseline heart rate, which influenced how long they stayed in the warm-up phase and, thus, the length of the entire exercise session. For example, some participants were able to achieve target heart rate and maintain it throughout the session possibly because they were more fit or because the duration and dose of their antipsychotic medication led to a higher baseline heart rate (tachycardia) than would normally be expected for someone of the same age. Therefore, these participants may not have been working hard enough for the influence of exercise to have any meaningful physiological changes, and subsequent cognitive changes.

Furthermore, although participants were asked not to smoke or drink coffee two hours before each session, some participants did not follow through with this request and this may have influenced the results. Blood glucose may have had an impact on the participants’ ability to perform the exercise session and their subsequent performance on the WCST afterwards. Anecdotally, some participants mentioned that they did not have sufficient food intake earlier in the day, before the start of the exercise session. In addition, even though participants were given sufficient notification to dress appropriately for the exercise session and were informed that they have the option of changing into different attire in a private changing room on site, the majority of participants completed the exercise session in clothing not conducive for exercise. For example, it was common to see participants complete the exercise session in jeans and improper foot wear. After some struggle, some participants even chose to complete the exercise session bare foot.
5.4 Future Implications

In light of the limitations noted above, a future study revisiting a similar research paradigm needs to include a test that is sensitive to the effects of acute exercise. In order to do this, it is important to determine whether changes are possible with basic cognitive functions before targeting larger, multifaceted cognitive functions, such as executive function. Success on the WCST depended on a number of different, higher-level cognitive functions working together optimally, including working memory, set shifting and planning (Head et al., 2009). Therefore, when presented with null findings on most types of analyses related to the WCST, it is challenging to interpret the results as it is difficult to decipher whether there were no changes in all of these functions, one or a few of these functions or the ability of these functions to work together in an ‘executive’ manner for optimal performance on the test. Therefore, a test that is salient at assessing small changes in one particular cognitive domain would be more appropriate for this research question.

Furthermore, future studies examining acute changes in cognitive function should consider an outcome measure that will minimize the impact of learning and practice. Most available cognitive tests today were designed to primarily detect impairments, not changes in cognition from a particular treatment or intervention. Even the existing tests that are validated to be used in a repeated-measures fashion are often done so with large time intervals between testing, such as the schizophrenia MATRICS battery. If another within-subject, counter-balanced study were to be performed, a longer interval between the two conditions can also reduce the effect of practice. The selected test should also be flexible enough to accommodate participants with varying baseline functions, including participants who score high, so that the test is able to detect improvements from baseline, regardless of where that baseline is, thus reducing the possibility of a ceiling effect.

In this regard, the Stroop task may be a particularly useful outcome measure to employ in future examinations of acute exercise on cognitive function. The Stroop task primarily evaluates cognitive inhibition, which is defined as “the stopping or overriding of a mental process, in whole or in part, with or without intention” (MacLeod, 2007, pg. 5). The Stroop task consists of two separate experiments. The first experiment evaluates the effect of interfering visual colour stimuli on reading the word of the colour and the second experiment evaluates the effect of interfering word stimuli on naming the colour of the word (Stroop, 1935). Both experiments
include a neutral condition, where participants just read the word of the colour printed in black (experiment 1) or name the colour of a particular shape/object (experiment 2). The difference in time to complete the trial between each of the two conditions and their respective neutral condition is taken as the outcome measure. Therefore, poor ability to inhibit irrelevant stimuli would result in a greater time difference.

The Stroop task may be a particularly meaningful test to use in this acute research paradigm because significant short-term changes have been demonstrated using this outcome measure among individuals with schizophrenia with other treatment modalities. For example, Barch and Carter (2005) examined the acute effects of amphetamines on cognitive function, via the Stroop task both among participants who were diagnosed with schizophrenia (n=10) and those who were healthy (n=22), in a within-subject research design. There was a small-to-medium improvement in the schizophrenia group with amphetamines compared to the placebo (congruent reaction time, $d=0.47$; incongruent reaction time, $d=0.38$) (Barch & Carter, 2005). However, only a small improvement was reported among the healthy participants compared to placebo (congruent reaction time, $d=0.27$; incongruent reaction time, $d=0.26$). Furthermore, the cognitive effects of an acute bout exercise have been demonstrated in other population groups via the Stroop task, such as older adults (Hyodo et al., 2012) and older adults with depression (Vasques, Moraes, Silveira, Deslandes, & Laks, 2011). In particular, a recent meta-analysis has demonstrated that the classical card version of the Stroop task where multiple trials are presented simultaneously has greater discriminatory potential and is able to produce larger effect sizes ($M(g)=0.60$, C.I. 95%: 0.48–0.71) than the single trial version ($M(g)=0.19$, C.I. 95%: 0.06–0.32) (Westerhausen, Kompus, & Hugdahl, 2011). This may be due to greater cognitive resources required to focus on one stimulus at a time when there are multiple stimuli presented. This simultaneous assessment of attention as well as inhibition is similar to the cognitive functions assessed by the non-perseverative errors. Therefore, the use of the Stroop task would be a great way to confirm the findings from this study.

Another basic, proof-of-concept avenue for future exploration is the potential role of exercise to enhance learning and support memory consolidation. In this present study, the effect of practice was an interesting and unexpected finding, which was sustained in the long-term, one week later. Considering that a moderate bout of exercise of short duration is sufficient to induce various physiological changes, including the increase in circulating neurochemicals and
neurotransmitters (Brisswalter et al., 2002; Tomporowski, 2003) and is responsible for the small, but significant acute changes in cognition among healthy adults (Labban & Etnier, 2011), it may also play a facilitative role for long-term memory after the completion of the exercise. In fact, these elevated neurochemicals are still present in the body post exercise, particularly BDNF, and may support enhanced memory consolidation (Winter et al., 2007). This idea of exercise-induced memory enhancement is supported by a meta-analysis by Roig et al., (2013), who found a significant, medium-to-large effect (SMD=0.52, p<0.01) of one acute bout of exercise on long-term memory among healthy individuals. Furthermore, sleep is known to play a critical role in consolidating memory (Snigdha, de Rivera, Milgram, & Cotman, 2014; Stickgold & Walker, 2007), and participants may have enhanced long-term memory the following day or anytime thereafter.

In addition, there is evidence to support that participants with schizophrenia have the potential to learn and benefit from additional training or instruction (Rempfer, Hamera, Brown, & Bothwell, 2006). Furthermore, these learning effects have been shown to have a small-to-moderate effect on general problem solving ability (Bellack et al., 2001) and last at least 2-4 weeks (Metz, Johnson, Pliskin, & Luchins, 1994; Vollema, Geurtsen, & van Voorst, 1995). As well, long-term studies have demonstrated that cognitive training with physical exercise was superior to cognitive training coupled with mental relaxation (Oertel-Knöchel et al., 2014) or treatment as usual (Kimhy et al., 2015). These converging pieces of evidence raise the question as to whether and to what extent one acute bout of exercise influences long-term memory among individuals with schizophrenia. This research question has scientific implications, as it would demonstrate, at a fundamental level, how well exercise could enhance learning and memory in the long term. It may also have clinical implications, as it may provide evidence in support of the use of exercise in a complementary fashion within rehabilitation programs and psychosocial therapies, in order to optimize outcomes.

Lastly, irrespective of any short or long-term cognitive changes that may result from acute exercise, this study was able to demonstrate improved positive affect and increased activation/alertness post exercise compared to baseline. Anecdotally, during the exit interview after the exercise session, participants noted that engaging in exercise helped them focus better and got them out of their ‘head’ in order to concentrate on the task at hand. Therefore, there is also subjective evidence that participants were able to think more clearly after the exercise.
session. Considering that the role of psychological therapies, particularly cognitive behavioural therapy, is to help participants address their feelings and their patterns of thinking, exercise, particularly acute exercise, may be a great complementary strategy to incorporate into these types of programs, where participants can take part in an exercise session prior to their therapy session for maximum gains, as participants may be able to derive more value due to improved focus and concentration, in addition to any possible short-term and long-term cognitive gains.
Chapter 6 - Conclusions

6 Conclusions

Cognitive deficits are a core feature of schizophrenia and these deficits are usually present before the onset of symptoms or formal diagnosis. Although the symptoms related to their diagnoses may be managed, it is cognitive impairment that may be central to poor functional and community outcomes. As such, addressing the issue of cognitive impairment continues to be a central focus of schizophrenia research. Various avenues are being explored as possible ways of improving this impairment, including the development of new drugs and psychosocial programs, such as cognitive behavioural therapy.

In healthy adults, exercise has demonstrated cognitive benefits both in the short and long term, in addition to the numerous physical and mental health benefits. These known benefits warrant the exploration of exercise as a means to support and enhance cognitive function among individuals with schizophrenia. However, there is only limited research exploring this effect. Among the eight studies that have examined exercise for cognitive improvement, all were long-term chronic studies, with various methodological qualities. Furthermore, there was often no clear rationale for the described exercise intervention, with a wide range of findings. Therefore, the purpose of this study was intended to act as a proof-of-concept experiment by examining the acute changes in executive function from one exercise session to determine the extent of the improvement seen from a single dose of exercise. A successful demonstration of an improvement would provide the basis for the evaluation of chronic exercise programs and the systematic evaluation of long-term changes in cognition in this population.

There was a significant reduction in non-perseverative errors among the exercise group, suggesting that exercise may facilitate improved attention, inhibition and overall working memory in this population. Therefore, at a fundamental, proof-of-concept level, this study was able to demonstrate that one acute bout of exercise can produce changes in these types of cognitive functions among individuals with schizophrenia. This study was also able to demonstrate that participants with schizophrenia are able to experience changes in affect related to exercise similar to their healthy counterparts. Therefore, individuals with schizophrenia can
benefit from receiving support from their health and community care providers to incorporate short bouts of exercise into their day to promote short-term improvements in affect. Nevertheless, in light of the limitations of the WCST to detect other acute changes, this research paradigm should be re-examined with the proposed changes noted above.
**Abbreviations**

BD=Bipolar Disorder; GABA=gamma-Aminobutyric acid; IQ=Intelligence quotient;
NMDA=N-Methyl-D-aspartic acid; SMD=Standard Mean Difference; RCT=Randomized Control Trial
References


Appendices

Appendix A - Physical Activity Readiness Questionnaire

PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

Regular physical activity is fun and healthy, and more people should become more physically active every day of the week. Being more physically active is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

SECTION 1 - GENERAL HEALTH

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.

1. Has your doctor ever said that you have a heart condition OR high blood pressure?

2. Do you feel pain in your chest at rest, during your daily activities of living, OR when you do physical activity?

3. Do you lose balance because of dizziness OR have you lost consciousness in the last 12 months? Please answer NO if your dizziness was associated with over-breathing (including during vigorous exercise).

4. Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?

5. Are you currently taking prescribed medications for a chronic medical condition?

6. Do you have a bone or joint problem that could be made worse by becoming more physically active? Please answer NO if you had a joint problem in the past, but it does not limit your current ability to be physically active. For example, knee, ankle, shoulder or other.

7. Has your doctor ever said that you should only do medically supervised physical activity?

If you answered NO to all of the questions above, you are cleared for physical activity.

Go to Section 3 to sign the form. You do not need to complete Section 2.

Start becoming much more physically active – start slowly and build up gradually.

1. Follow the Canadian Physical Activity Guidelines for your age (www.csep.ca/guidelines).

2. You may take part in a health and fitness appraisal.

3. If you have any further questions, contact a qualified exercise professional such as a CSEP Certified Exercise Physiologist* (CSEP-CEP) or CSEP Certified Personal Trainer* (CSEP-CPT).

4. If you are over the age of 45 yrs. and NOT accustomed to regular vigorous physical activity, please consult a qualified exercise professional (CSEP-CEP) before engaging in maximal effort exercise.

If you answered YES to one or more of the questions above, please GO TO SECTION 2.

Delay becoming more active if:

1. You are not feeling well because of a temporary illness such as a cold or fever – wait until you feel better.

2. You are pregnant – talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the PARmed-X for Pregnancy before becoming more physically active OR

3. Your health changes – please answer the questions on Section 2 of this document and/or talk to your doctor or qualified exercise professional (CSEP-CEP or CSEP-CPT) before continuing with any physical activity programme.
<table>
<thead>
<tr>
<th>Section 2 - Chronic Medical Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please read the questions below carefully and answer each one honestly: check YES or NO.</td>
</tr>
<tr>
<td>1. Do you have Arthritis, Osteoporosis, or Back Problems?</td>
</tr>
<tr>
<td>1a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)</td>
</tr>
<tr>
<td>1b. Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylosis/pars defect (a crack in the bony ring on the back of the spinal column)?</td>
</tr>
<tr>
<td>1c. Have you had steroid injections or taken steroid tablets regularly for more than 3 months?</td>
</tr>
<tr>
<td>2. Do you have Cancer of any kind?</td>
</tr>
<tr>
<td>2a. Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and neck?</td>
</tr>
<tr>
<td>2b. Are you currently receiving cancer therapy (such as chemotherapy or radiotherapy)?</td>
</tr>
<tr>
<td>3. Do you have Heart Disease or Cardiovascular Disease? This includes Coronary Artery Disease, High Blood Pressure, Heart Failure, Diagnosed Abnormality of Heart Rhythm</td>
</tr>
<tr>
<td>3a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)</td>
</tr>
<tr>
<td>3b. Do you have an irregular heart beat that requires medical management? (e.g., atrial fibrillation, premature ventricular contraction)</td>
</tr>
<tr>
<td>3c. Do you have chronic heart failure?</td>
</tr>
<tr>
<td>3d. Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer YES if you do not know your resting blood pressure)</td>
</tr>
<tr>
<td>3e. Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?</td>
</tr>
<tr>
<td>4. Do you have any Metabolic Conditions? This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes</td>
</tr>
<tr>
<td>4a. Is your blood sugar often above 13.0 mmol/l? (Answer YES if you are not sure)</td>
</tr>
<tr>
<td>4b. Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, and the sensation in your toes and feet?</td>
</tr>
<tr>
<td>4c. Do you have other metabolic conditions (such as thyroid disorders, pregnancy-related diabetes, chronic kidney disease, liver problems)?</td>
</tr>
<tr>
<td>5. Do you have any Mental Health Problems or Learning Difficulties? This includes Alzheimer’s, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome)</td>
</tr>
<tr>
<td>5a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)</td>
</tr>
<tr>
<td>5b. Do you also have back problems affecting nerves or muscles?</td>
</tr>
<tr>
<td>Question</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>6. Do you have a Respiratory Disease?</strong></td>
</tr>
<tr>
<td>*This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary</td>
</tr>
<tr>
<td><em>High Blood Pressure</em></td>
</tr>
<tr>
<td>6a. Do you have difficulty controlling your condition with medications</td>
</tr>
<tr>
<td>or other physician-prescribed therapies? (Answer NO if you are not</td>
</tr>
<tr>
<td>currently taking medications or other treatments)</td>
</tr>
<tr>
<td>6b. Has your doctor ever said your blood oxygen level is low at rest</td>
</tr>
<tr>
<td>or during exercise and/or that you require supplemental oxygen therapy?</td>
</tr>
<tr>
<td>6c. If asthmatic, do you currently have symptoms of chest tightness,</td>
</tr>
<tr>
<td>wheezing, laboured breathing, consistent cough (more than 2 days/week),</td>
</tr>
<tr>
<td>or have you used your rescue medication more than twice in the last</td>
</tr>
<tr>
<td>week?</td>
</tr>
<tr>
<td>6d. Has your doctor ever said you have high blood pressure in the</td>
</tr>
<tr>
<td>blood vessels of your lungs?</td>
</tr>
<tr>
<td><strong>7. Do you have a Spinal Cord Injury?</strong></td>
</tr>
<tr>
<td><em>This includes Tetraplegia and Paraplegia</em></td>
</tr>
<tr>
<td>7a. Do you have difficulty controlling your condition with medications</td>
</tr>
<tr>
<td>or other physician-prescribed therapies? (Answer NO if you are not</td>
</tr>
<tr>
<td>currently taking medications or other treatments)</td>
</tr>
<tr>
<td>7b. Do you commonly exhibit low resting blood pressure significant</td>
</tr>
<tr>
<td>enough to cause dizziness, light-headedness, and/or fainting?</td>
</tr>
<tr>
<td>7c. Has your physician indicated that you exhibit sudden bouts of high</td>
</tr>
<tr>
<td>blood pressure (known as Autonomic Dysreflexia)?</td>
</tr>
<tr>
<td><strong>8. Have you had a Stroke?</strong></td>
</tr>
<tr>
<td><em>This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event</em></td>
</tr>
<tr>
<td>8a. Do you have difficulty controlling your condition with medications</td>
</tr>
<tr>
<td>or other physician-prescribed therapies? (Answer NO if you are not</td>
</tr>
<tr>
<td>currently taking medications or other treatments)</td>
</tr>
<tr>
<td>8b. Do you have any impairment in walking or mobility?</td>
</tr>
<tr>
<td>8c. Have you experienced a stroke or impairment in nerves or muscles in</td>
</tr>
<tr>
<td>the past 6 months?</td>
</tr>
<tr>
<td>**9. Do you have any other medical condition not listed above or do you</td>
</tr>
<tr>
<td>live with two chronic conditions?</td>
</tr>
<tr>
<td>9a. Have you experienced a blackout, fainted, or lost consciousness as</td>
</tr>
<tr>
<td>a result of a head injury within the last 12 months OR have you had a</td>
</tr>
<tr>
<td>diagnosed concussion within the last 12 months?</td>
</tr>
<tr>
<td>9b. Do you have a medical condition that is not listed</td>
</tr>
<tr>
<td>(such as epilepsy, neurological conditions, kidney problems)?</td>
</tr>
<tr>
<td>9c. Do you currently live with two chronic conditions?</td>
</tr>
</tbody>
</table>

Please proceed to Page 4 for recommendations for your current medical condition and sign this document.
PAR-Q+

If you answered NO to all of the follow-up questions about your medical condition, you are ready to become more physically active:

› It is advised that you consult a qualified exercise professional (e.g., a CSEP-CEP or CSEP-CPT) to help you develop a safe and effective physical activity plan to meet your health needs.
› You are encouraged to start slowly and build up gradually - 20-60 min. of low-to moderate-intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
› As you progress, you should aim to accumulate 150 minutes or more of moderate-intensity physical activity per week.
› If you are over the age of 45 yrs. and NOT accustomed to regular vigorous physical activity, please consult a qualified exercise professional (CSEP-CEP) before engaging in maximal effort exercise.

If you answered YES to one or more of the follow-up questions about your medical condition:

› You should seek further information from a licensed health care professional before becoming more physically active or engaging in a fitness appraisal and/or visit a or qualified exercise professional (CSEP-CEP) for further information.

Delay becoming more active if:

› You are not feeling well because of a temporary illness such as a cold or fever - wait until you feel better.
› You are pregnant - talk to your health care practitioners, your physician, a qualified exercise professional, and/or complete the PARmed-X for Pregnancy before becoming more physically active OR
› Your health changes - please talk to your doctor or qualified exercise professional (CSEP-CEP) before continuing with any physical activity programme.

SECTION 3 - DECLARATION

› You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
› The Canadian Society for Exercise Physiology, the PAR-Q+ Collaboration, and their agents assume no liability for persons who undertake physical activity. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.
› If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.
› Please read and sign the declaration below:

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that a Trustee (such as my employer, community/fitness centre, health care provider, or other designee) may retain a copy of this form for their records. In these instances, the Trustee will be required to adhere to local, national, and international guidelines regarding the storage of personal health information ensuring that they maintain the privacy of the information and do not misuse or wrongfully disclose such information.

NAME ___________________________________________ DATE ____________________________

SIGNATURE______________________________________ WITNESS_________________________

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _______________________________________

For more information, please contact:
Canadian Society for Exercise Physiology
www.csep.ca

KEY REFERENCES

The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+ Collaboration chaired by Dr. Darren R. Warburton with Dr. Norman Glenhill, Dr. Veronica Janssens, and Dr. Donald C. McKeenie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or BC Ministry of Health Services.
Appendix B - Demographics

Date: ______________________  ID: _______________

**Age (yrs):** ______________________

**Sex:** Male  □  Female  □

**Ethnicity:**
- African  □
- Aboriginal  □
- Asian  □
- S. Asian  □
- Hispanic  □
- White  □

**Living Arrangements:**
- Independent  □
- Group (meals provided)  □
- With Family  □
- Group (no meals provided)  □

**Employment Status:**
- Full-time  □
- Part-time  □
- Not employed  □
- Student  □
- Retired  □
- Other: ______________________  □

**Educational Attainment:**
- High school (no diploma)  □
- High school (diploma)  □
- Postsecondary  □
- Other: ______________________  □

**Marital Status:** Single  □
- Married  □
- Separated  □
- Divorced  □

**Diagnosis (MINI)**

*Plus chart review:*
- Schizophrenia  □
- Schizoaffective  □
- Psychosis NOS  □
- Other  □
- Specify: ______________________

Substance Abuse: Yes  □
- No  □
**Psychiatric History:**
Date of first hospitalization (dd/mm/yy): _________________________

Date of first antipsychotic rx (dd/mm/yy): _________________________

**Smoking:** Number of cigarettes/day _____  Years as a regular smoker ______

**Medication:**

I. **Current antipsychotic:**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose (mg)</th>
<th>Duration: (mth)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

II. **Concomitant Psychiatric:**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose (mg)</th>
<th>Duration: (mth)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

III. **Concomitant Medical:**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose (mg)</th>
<th>Duration: (mth)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Measurements:**

Height (cms): _________________________

Weight (kgs): _________________________

Waist circumference (cms): _________________________
Appendix C - International Physical Activity Questionnaire

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the vigorous activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

1. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?
   
   _____ days per week

   ☐ No vigorous physical activities ➔ Skip to question 3

2. How much time did you usually spend doing vigorous physical activities on one of those days?

   _____ minutes per day

   ☐ Don’t know/Not sure

Think about all the moderate activities that you did in the last 7 days. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, brisk walking, bicycling at a regular pace, or doubles tennis? Do not include walking casually.

   _____ days per week

   ☐ No moderate physical activities ➔ Skip to question 5

4. How much time did you usually spend doing moderate physical activities on one of those days?
The last question is about the time you spent sitting on weekdays during the last 7 days. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

5. During the last 7 days, how much time did you spend sitting on a week day?

_____ hours and _____ minutes per day

☐ Don’t know/Not sure
Appendix D - Life Satisfaction Scale

DIRECTIONS: Below are five statements with which you may agree or disagree. Using the 1-7 scale below, indicate your agreement with each item by placing the appropriate number in the line preceding that item. Please be open and honest in your responding.

1 = Strongly Disagree
2 = Disagree
3 = Slightly Disagree
4 = Neither Agree or Disagree
5 = Slightly Agree
6 = Agree
7 = Strongly Agree

______ 1. In most ways my life is close to my ideal.
______ 2. The conditions of my life are excellent.
______ 3. I am satisfied with life.
______ 4. So far I have gotten the important things I want in life.
______ 5. If I could live my life over, I would change almost nothing.
Appendix E - The Positive and Negative Affect Schedule

Worksheet 3.1  The Positive and Negative Affect Schedule (PANAS; Watson et al., 1988)

PANAS Questionnaire
This scale consists of a number of words that describe different feelings and emotions. Read each item and then list the number from the scale below next to each word. **Indicate to what extent you feel this way right now, that is, at the present moment OR indicate the extent you have felt this way over the past week** (circle the instructions you followed when taking this measure)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Interested</td>
<td>11. Irritable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Distressed</td>
<td>12. Alert</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Excited</td>
<td>13. Ashamed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Upset</td>
<td>14. Inspired</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Strong</td>
<td>15. Nervous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Guilty</td>
<td>16. Determined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Scared</td>
<td>17. Attentive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Hostile</td>
<td>18. Jittery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Enthusiastic</td>
<td>19. Active</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Proud</td>
<td>20. Afraid</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Scoring Instructions:
Positive Affect Score: Add the scores on items 1, 3, 5, 9, 10, 12, 14, 16, 17, and 19. Scores can range from 10 – 50, with higher scores representing higher levels of positive affect. Mean Scores: Momentary = 29.7 (SD = 7.9); Weekly = 33.3 (SD = 7.2)

Negative Affect Score: Add the scores on items 2, 4, 6, 7, 8, 11, 13, 15, 18, and 20. Scores can range from 10 – 50, with lower scores representing lower levels of negative affect. Mean Score: Momentary = 14.8 (SD = 5.4); Weekly = 17.4 (SD = 6.2)

Appendix F - Felt Arousal Scale (FAS)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FELT AROUSAL SCALE (FAS)</strong></td>
<td>(Svebak &amp; Murgatroyd, 1985)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimate here how aroused you actually feel. Do this by circling the appropriate number. By “arousal” we meant how “worked-up” you feel. You might experience high arousal in one of a variety of ways, for example as excitement or anxiety or anger. Low arousal might also be experienced by you in one of a number of different ways, for example as relaxation or boredom or calmness.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>LOW AROUSAL</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>HIGH AROUSAL</td>
<td></td>
</tr>
</tbody>
</table>
Appendix G - Feeling Scale (FS)

<table>
<thead>
<tr>
<th>Feeling Scale (FS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Hardy &amp; Rejeski, 1989)</td>
</tr>
</tbody>
</table>

While participating in exercise, it is common to experience changes in mood. Some individuals find exercise pleasurable, whereas others find it to be unpleasant. Additionally, feeling may fluctuate across time. That is, one might feel good and bad a number of times during exercise. Scientists have developed this scale to measure such responses.

| +5  | Very good |
| +4  |           |
| +3  | Good      |
| +2  |           |
| +1  | Fairly good |
| 0   | Neutral   |
| -1  | Fairly bad |
| -2  |           |
| -3  | Bad       |
| -4  |           |
| -5  | Very bad  |
Appendix H - Apathy Evaluation Scale

Apathy Evaluation Scale (Self-rated)

Name: ____________________________ Date: ___/___/___

For each statement, circle the answer that best describes the subject's thoughts, feelings, and activity in the past 4 weeks.

1. I am interested in things.
   - NOT AT ALL
   - SLIGHTLY
   - SOMEWHAT
   - A LOT

2. I get things done during the day.
   - NOT AT ALL
   - SLIGHTLY
   - SOMEWHAT
   - A LOT

3. Getting things started on my own is important to me.
   - NOT AT ALL
   - SLIGHTLY
   - SOMEWHAT
   - A LOT

4. I am interested in having new experiences.
   - NOT AT ALL
   - SLIGHTLY
   - SOMEWHAT
   - A LOT

5. I am interested in learning new things.
   - NOT AT ALL
   - SLIGHTLY
   - SOMEWHAT
   - A LOT

6. I put little effort into anything.
   - NOT AT ALL
   - SLIGHTLY
   - SOMEWHAT
   - A LOT

7. I approach life with intensity.
   - NOT AT ALL
   - SLIGHTLY
   - SOMEWHAT
   - A LOT

8. Seeing a job through to the end is important to me.
   - NOT AT ALL
   - SLIGHTLY
   - SOMEWHAT
   - A LOT

9. I spend time doing things that interest me.
   - NOT AT ALL
   - SLIGHTLY
   - SOMEWHAT
   - A LOT
10. Someone has to tell me what to do each day.

   NOT AT ALL    SLIGHTLY    SOMEWHAT    A LOT

11. I am less concerned about my problems than I should be.

   NOT AT ALL    SLIGHTLY    SOMEWHAT    A LOT

12. I have friends.

   NOT AT ALL    SLIGHTLY    SOMEWHAT    A LOT

13. Getting together with friends is important to me.

   NOT AT ALL    SLIGHTLY    SOMEWHAT    A LOT

14. When something good happens, I get excited.

   NOT AT ALL    SLIGHTLY    SOMEWHAT    A LOT

15. I have an accurate understanding of my problems.

   NOT AT ALL    SLIGHTLY    SOMEWHAT    A LOT

16. Getting things done during the day is important to me.

   NOT AT ALL    SLIGHTLY    SOMEWHAT    A LOT

17. I have initiative.

   NOT AT ALL    SLIGHTLY    SOMEWHAT    A LOT

18. I have motivation.

   NOT AT ALL    SLIGHTLY    SOMEWHAT    A LOT

The Apathy Evaluation Scale was developed by Robert S. Marin, M.D. Development and validation studies are described in RS Marin, RC Biedrzycki, S Firinciogullari: “Reliability and Validity of the Apathy Evaluation Scale.” Psychiatry Research. 38:143-162, 1991
Appendix I - Borg's Rating of Perceived Exertion

While doing physical activity, we want you to rate your perception of exertion. This feeling should reflect how heavy and strenuous the exercise feels to you, combining all sensations and feelings of physical stress, effort, and fatigue. Do not concern yourself with any one factor such as leg pain or shortness of breath, but try to focus on your total feeling of exertion.

Look at the rating scale below while you are engaging in an activity; it ranges from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion." Choose the number from below that best describes your level of exertion. This will give you a good idea of the intensity level of your activity, and you can use this information to speed up or slow down your movements to reach your desired range.

Try to appraise your feeling of exertion as honestly as possible, without thinking about what the actual physical load is. Your own feeling of effort and exertion is important, not how it compares to other people's. Look at the scales and the expressions and then give a number.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>No exertion at all</td>
</tr>
<tr>
<td>7</td>
<td>Extremely light</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Very light</td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Light</td>
</tr>
<tr>
<td>12</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Somewhat hard</td>
</tr>
<tr>
<td>14</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Hard (heavy)</td>
</tr>
<tr>
<td>16</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Very hard</td>
</tr>
<tr>
<td>18</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Extremely hard</td>
</tr>
<tr>
<td>20</td>
<td>Maximal exertion</td>
</tr>
</tbody>
</table>

9 corresponds to "very light" exercise. For a healthy person, it is like walking slowly at his or her own pace for some minutes.

13 on the scale is "somewhat hard" exercise, but it still feels OK to continue.

17 "very hard" is very strenuous. A healthy person can still go on, but he or she really has to push him- or herself. It feels very heavy, and the person is very tired.

19 on the scale is an extremely strenuous exercise level. For most people this is the most strenuous exercise they have ever experienced.
Appendix J - Liverpool University Neuroleptic Side Effect Rating Scale (Item #2)

**LUNSERS**

<table>
<thead>
<tr>
<th>Difficulty staying awake during the day</th>
<th>Not at all</th>
<th>Very little</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

Appendix K - Intrinsic Motivation Inventory

**Activity Scale**

For each of the following statements, please indicate how true it was for you in regards to completing today's cognitive testing.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at True</th>
<th>Somewhat True</th>
<th>Very True</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I enjoyed doing this activity very much</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. This activity was fun to do</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. I think this is a boring activity</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. I would describe this activity as very interesting</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. I thought this activity was quite enjoyable</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. I was thinking about how much I enjoyed it</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. This activity does not hold my attention at all</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. I believe I have some choice about doing this activity</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. I felt like it was not my own choice to do this task</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. I really did not have a choice to do this activity</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. I feel like I have to do this</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. I did this activity because I wanted to</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. I had a choice to do this activity or not</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. I did this activity because I had to</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. I believe this activity could be of some value to me</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. I think that doing this activity is useful</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. I think this is important to do</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. I would be willing to do this again</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. I think doing this activity could help me</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. I believe doing this activity could be beneficial to me</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. I think this is an important activity</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix L - Exit Interview

After Session 2 and 3

1. How do you feel now compared to when you began the session?
2. What were you thinking about during this session?
3. Did you have a strategy for completing the cognitive task? If so, what was it?
Addendum

"onions, white mushrooms, garlic bread"
-G.F.