CHARACTERIZING ELECTROCORTICAL PROFILES DURING TWO COGNITIVE TASKS IN TRANSITIONAL AGED YOUTH WITH AND WITHOUT DEPRESSION

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ABSTRACT

Depression in transitional aged youth (TAY; aged ~16-24yr) has become a major issue of concern, with 14-25% of those aged 12-21yr experiencing at least one episode of depression. As such, the burden of disease of depression in this population is substantial. Depression in TAY is characterized as a chronic, relapsing disorder, with 50-70% of remitted patients developing a subsequent depressive episode within five years. Further, in younger adulthood (~21-38yr) individuals who experience depression do not always show complete functional recovery between episodes and report residual cognitive impairments. However, research examining the neural correlates of putative cognitive impairments in depressed individuals has traditionally focused on adult populations, with more limited research in depressed TAY. One means of characterizing neural profiles during cognitive processing is via electroencephalography (EEG), and event-related potentials (ERPs) extracted from EEG. To date, it is unclear if ERP profiles during tasks tapping into certain cognitive processes known to be altered in depressed adults are comparable in depressed TAY. Greater insight into the neural features of cognitive processes in the context of depression can, ultimately, help in refining intervention and perhaps prevention strategies in depressed youth.

The primary aim of this work was to assess ERP-indexed neural profiles of attention, including novelty orienting, and inhibition via the auditory oddball and visual flanker tasks in depressed, unmedicated TAY (DEP) vs. non-depressed TAY (HC). Specifically, the N2 and P3 ERPs elicited by incongruent and congruent stimuli in a visual flanker task were assessed, as were the P3a and P3b ERPs extracted from an auditory novelty oddball task. Further, behavioural scores on three tasks, measured by the National Institutes of Health (NIH) Toolbox, that tap into similar cognitive processes as the ERP tasks (i.e., executive function, stimulus

evaluation, inhibition, and working memory) were compared between groups using well-validated cognitive tests. Finally, correlations were carried out on the entire sample's cognition scores and ERP measures, as well as the DEP group's clinical scores and ERP measures to explore the relation between behavioural and neural features.

A significant difference was found between groups for the early P3a (eP3a) latency elicited by unexpected novel sounds in the oddball task; the DEP group had a significantly shorter latency than the HC group. For the flanker task, group differences were found for N2 amplitude to incongruent flanker stimuli, wherein the DEP group showed significantly higher amplitudes than the HC group. No group differences were found between composite scores of three NIH Toolbox tasks assessed. Correlations revealed a positive relation between the Dimensional Change Card Sort test (NIH Card Sort task), generally regarded as a test of executive function, and P3 amplitude to both congruent and incongruent stimuli on the ERP Flanker task. Second, a positive relation existed between the Flanker Inhibitory Control and Attention task (NIH Flanker) and P3 latency on the ERP Flanker task.

This study failed to replicate previous reports of reduced ERP amplitudes and increased latencies of the oddball and flanker tasks in a depressed adult populations population. However, they contribute to our limited knowledge on the effects of depression in youth on cognitive processes and associated neuronal profiles. Indeed, the data suggest that non-severely depressed and unmedicated young people exhibited more efficient cortical processing to novelty orienting than matched controls, perhaps reflecting a hyper-vigilant state. Further, depressed TAY appeared to exhibit more pronounced cortical resource allocation to processes implicated in inhibition. Across all participants, we were also able to demonstrate a relation between better executive function and increased cortical resource allocation to attentive processes, and greater

behavioural inhibition being associated with longer cortical processes of attention. Collectively, these data inform our understanding of the neural processes in young people with depression; such insight may aid in more refined intervention and prevention strategies in the future.

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LEGEND

BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory
CSSRS	Columbia Suicide Severity Rating Scale
DEP	Depressed Group
EEG	Electroencephalography
eP3a	Early P3a
ERP	Event-related potential
$HAMD_{24}$	Hamilton Depression Rating Scale, 24-item version
HC	Healthy Control
IQR	Interquartile Range
lP3a	Late P3a
MADRS	Montgomery-Äsberg Depression Rating Scale
MDD	Major Depressive Disorder
MINI	Mini International Neuropsychiatric Interview
N2	Negative ERP occurring around 200ms post-stimulus
NIH	National Institutes of Health
NIH Card Sort	NIH Toolbox Dimensional Change Card Sort Test
NIH Flanker	NIH Toolbox Flanker Inhibitory Control and Attention Test
NIH List Sort	NIH Toolbox List Sorting Working Memory Test
RT	Reaction Time
SD	Standard Deviation
TAY	Transitional Aged Youth
tP3a	Total P3a

INTRODUCTION

1.1 Depression in Transitional Aged Youth (TAY)

Depression in transitional aged youth (TAY; aged ~16-24yr) has become the primary contributor to the burden of disease (the human and economic costs as a result of an illness, measured through morbidity, mortality, and other factors) (National Collaborating Centre for Infection Diseases & National Collaborating Centres for Public Health, 2016) in this population and is, therefore, an increasingly prevalent societal concern (Bailey et al., 2018; Gore et al., 2011). It is estimated that 14-25% of adolescents aged 12-21yr experience at least one depression episode before adulthood (Carter et al., 2016; Ryan, 2005; Stikkelbroek et al., 2013), and that, by 18-21yr, the prevalence of major depressive disorder (MDD) is estimated to be as high as 17% (Platt et al., 2017). Much like in adults, depression in TAY is characterized as a chronic, relapsing disorder, with 50-70% of remitted patients developing a subsequent depressive episode within five years (Thapar et al., 2012). Early-onset depression might represent a more severe form of the disorder as it can result in more frequent episodes, increased risk of suicide, more psychosocial impairments, lower educational attainment, higher chance of unemployment, and higher risk of comorbidity with other mental disorders compared to late-onset depression (Baune et al., 2014; Castaneda et al., 2008). These outcomes might be due to the presence of depression disrupting or interfering with the formation of educational, employment, and relational life aspects typical during the TAY life stage. Further, once in younger adulthood (21-38yr; (Baune et al., 2014), individuals who experience depression do not always show complete functional recovery between episodes. For instance, Conradi et al. (2011) reported residual impairments and symptoms in remitted MDD participants such as cognitive problems and lack of energy, among

other depression-associated symptoms (e.g., feelings of worthlessness/guilt, eating disturbances, psychomotor problems); further, at least two depressive symptoms were present at all times. Given the significant long-term impact of depression in youth, compounded with the residual symptoms that might persist into adulthood, greater insight into the disorder earlier in life may provide us with better knowledge in terms of how to prevent and treat depression-associated impairments.

1.2 Cognition in Depression

Research has repeatedly linked depression with impairments in information processing, attention, memory, inhibition, and executive functions; however, most work investigating the cognitive effects of depression has focused on middle-aged or elderly populations or has not considered age as a meaningful variable (Gohier et al., 2009; Lam et al., 2014; Levinson et al., 2010; Reppermund et al., 2009; Rock et al., 2014; Sheehan et al., 2017; Steele et al., 2000). Studies specifically examining potential cognitive deficits in adolescents with depression have yielded varying results; nevertheless, several studies have reported significant deficits in executive function, attention, inhibition, and memory in TAY with MDD (Castaneda et al., 2008; Wagner et al., 2015). A meta-analysis on the cognitive effects of depression in adolescents by Baune et al., (2014) found that three out of seven studies reported deficits in executive function, four out of seven found deficits in working memory, one out of two noted deficits in visual-spatial memory. Finally, four out of seven studies reported reduced psychomotor processing speed in youth with MDD. However, only one out of seven studies examined attention and inhibition; no significant differences between adolescents with and without depression were noted in this study (Baune et al., 2014). Notably, the number of studies in depressed youth is substantially lower than in comparable meta-analyses of cognitive deficits in depression adults

(e.g. Rock et al., 2014). Others studies, including those not included in Baune's 2014 meta-analysis, have reported that unmedicated adolescents and young adults with MDD have attentional and executive function deficits as well as slowed reaction times (RT) across several cognitive tasks (Castaneda et al., 2008; Sommerfeldt et al., 2016). Youth with either current or past depression have also shown episodic memory and working memory deficits (Barch et al., 2019; Castaneda et al., 2008). Finally, some studies have demonstrated a correlation between executive function deficits and depression severity; typically, these studies have shown an impaired ability to process conflict and perform cognitive control processes in adolescents with more severe depression (Maalouf et al., 2011; Sommerfeldt et al., 2016). In summary, the comparatively limited research in TAY with MDD vs. depressed adults most consistently has shown cognitive deficits in domains such as executive function and working memory. Impairment in such domains may have significant impacts on their daily functioning, including education, social functioning, and employment attainment (Castaneda et al., 2008; Sommerfeldt et al., 2016).

One means of broadly categorizing cognition is into the subcategories of *crystallized* and *fluid* cognition (Cattell, 1963). Crystallized cognition encompasses knowledge and skills that are learned throughout life during education and cultural experiences; while fluid cognition involves processing and integrating novel problems and information (Cattell, 1963; Stawski et al., 2013). The National Institutes of Health (NIH) Toolbox® for the Assessment of Neurological and Behavioural Function® measures cognition in these broad categories, as well as in several cognitive subdomains: executive function, episodic memory, language, processing speed, working memory, and attention (Gershon et al., 2013). It is composed of seven tests, which comprise a "crystallized cognition" composite score (Picture Vocabulary test & Oral Reading

Recognition test) and "fluid cognition" composite score (Picture Sequence Memory test, Flanker Inhibitory Control and Attention test, List Sorting Working Memory test, Dimensional Change Card Sort test, and Pattern Comparison Processing Speed test) (Gershon et al., 2013). The Flanker Inhibitory Control and Attention (NIH Flanker, **Figure 1**) and Dimensional Change Card Sort (NIH Card Sort, **Figure 2**) tasks (National Institutes of Health, 2021) are measures of executive function via inhibition and stimulus evaluation and processes, respectively. Meanwhile, the List Sorting Working Memory (NIH List Sort, **Figure 3**) task (National Institutes of Health, 2021) taps into working memory and stimulus evaluation. Lower scores indicate impaired cognitive function in these domains.

The scores of NIH tasks can be compared between individuals with depression to normative population scores provided by the NIH Toolbox, or a healthy sample collected as part of a study, for instance. Kavanaugh et al., (2020) used three tasks (i.e., NIH Flanker, NIH List Sort, and NIH Card Sort) to compare the NIH Toolbox's measures of executive functioning deficits to that of a clinically administered executive functioning test in depressed children and adolescents. They found that the NIH toolbox tasks' measures of executive functioning deficits were comparable to the reported deficits by the clinically-administered measures. This illustrates that there is measurable executive dysfunction in youth with depression; further, this work indicates that the computer-administered NIH Toolbox, particularly the NIH Flanker, List Sort, and Card Sort tasks, are able to capture these deficits. However, this appears to be the only published study examining performance on these three tasks in depressed youth; thus, further validation is needed.

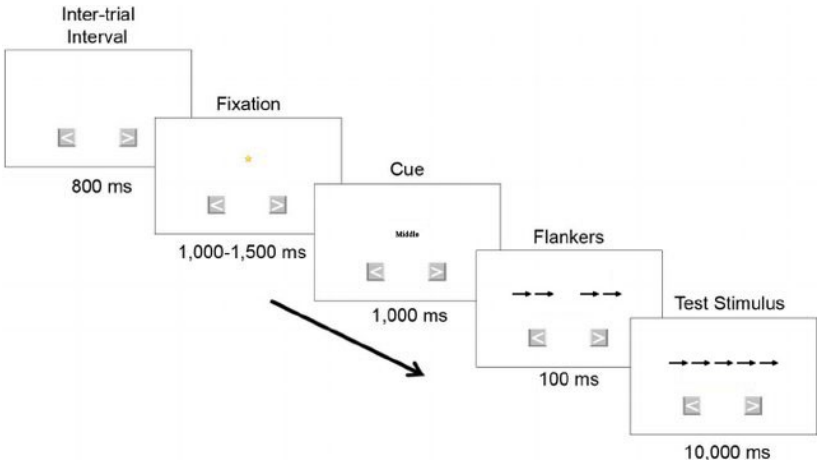

Figure 1. Trial sequence of the National Institutes of Health (NIH) Flanker task. Image adapted from Zelazo et al. (2014)

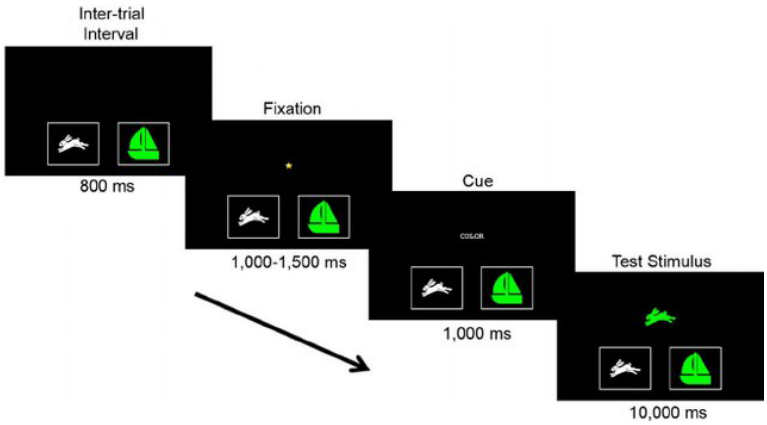

Figure 2. Trial sequence of the National Institutes of Health (NIH) Card Sort task. Image from Zelazo et al. (2014).

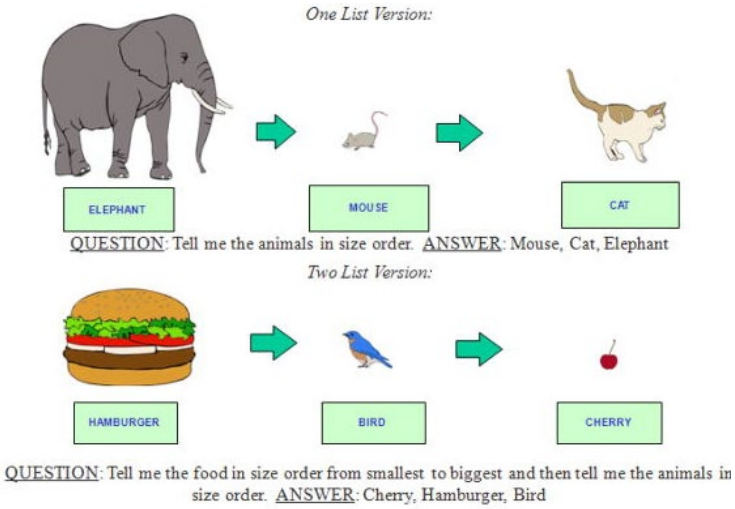

Figure 3. Trial Examples from National Institutes of Health (NIH) List Sort Task. Image from Tulsky et al. (2014).

1.3 Electroencephalogram (EEG) and Event Related Potentials (ERPs)

Electroencephalography (EEG) has been used for decades as a non-invasive method to measure brain electrical activity. Specifically, EEG captures synchronized neuronal activity arising from both inhibitory and excitatory postsynaptic potentials (Fisch & Spehlmann, 1999; Kappenman & Luck, 2016; Melnik et al., 2017). EEGs can measure changes in neuroelectric activity in nearly real-time, picking up voltage fluctuations at the surface of the scalp over just a few milliseconds (Woodman, 2010). By presenting multiple trials of the same stimulus, background EEG activity can be attenuated (Ibanez et al., 2012), and electrocortical activity time-locked to a stimulus is represented via event-related potentials (ERPs, see **Figures 4-6** below). A shorter ERP latency is thought to reflect more efficient cortical processing speed (Sur & Sinha, 2009). ERP amplitude is generally regarded as an index of cortical resource allocation. Early-latency ERPs (emerging <150ms) are often involved in basic visual or auditory processes, such as the P1 or N1 ERPs. The amplitudes of these ERPs are strongly affected by the physical properties of the stimulus, such as tone or volume of auditory stimuli, and the size or shape of visual stimuli (Kiesel et al., 2008). Later-latency components, such as the P3, are somewhat less affected by stimuli physical properties. Instead, later-latency ERPs are likely more influenced by probabilities, expectations, attention, and other higher-order cognitive processes (e.g., stimulus classification) (Sur & Sinha, 2009).

1.3.1 Tasks Tapping into Inhibition and Attention

There are simple tasks tapping into specific cognitive domains which are associated with certain ERPs that can inform us about underlying neural processes. One such task is the flanker task (Eriksen & Eriksen, 1974), which is employed to tap into conflict resolution and inhibitory processes. The traditional version of the task consists of arrows pointing either left or right, with

a central/target arrow pointing in the same (congruent: <<<<<) or opposite (incongruent: <<><<) direction as the flanking arrows (Kopp et al., 1996; Seer et al., 2017). The participant is required to respond to/report the direction of the central arrow. In some studies, the target and flanking stimuli are presented simultaneously (Kałamała et al., 2018); however, delaying the onset of the target stimulus (i.e., first presenting the non-central flaking arrows) is thought to cause a more pronounced flanker interference or facilitation effect due to preparatory mechanisms (Kopp et al., 1996). The flanker task engages frontally governed inhibitory processes by requiring the participant to selectively attend to and focus on the target flanker, and to suppress attentive and cueing information from the distracting flankers (Kałamała et al., 2018; Kopp et al., 1996). Incongruent trials elicit a state of conflict that must be resolved to accurately respond to the direction of the central target stimulus, resulting in slower response times and generally lower accuracy on such trials (Dillon et al., 2015). ERPs that are commonly elicited during this task are discussed in subsequent sections (**Section 1.3.2** and **Section 1.3.3**).

The auditory oddball task is commonly used to study attentional processing and memory updating; associated ERPs can inform us about the neural substrates of these processes. The original auditory oddball design involves two tones: a frequently occurring standard tone, and a less frequently presented target tone (e.g., lower in pitch from the standard), which the participant responds to (Squires et al., 1975). Adaptations of the auditory oddball task involve three sounds: the standard and deviant tones as well as novel, distractor sounds, such as car horns or animal noises (as described in Jaworska & Protzner, 2013); this task tends to be referred to as the "novelty oddball task". Participants are asked to only respond to the target tone while ignoring the standard tone and novel sounds. Similar to the flanker task, the novelty oddball task engages anterior inhibitory processes in order to avoid responding to distracting novel sounds. It

also engages parietal regions involved in attentional processing, and memory updating as the participant actively listens for and responds to the target tone (Nan et al., 2018).

1.3.2 The P3 ERP

The P3 is a positive-deflecting ERP that emerges 300-400ms following an auditory or visual stimulus (Patel & Azzam, 2005), and can be divided into two sub-components: the P3a and P3 (also referred to as the P3b). The P3b (**Figure 4**) is typically evident in parieto-occipital regions at the scalp surface, with its neural generators most frequently being hippocampal and parietal areas, particularly the temporal-parietal junction (Patel & Azzam, 2005). The P3b has been implicated in stimulus recognition, evaluation, and working memory, with a notable increase in its amplitude to infrequent target stimuli (Ibanez et al., 2012; Jaworska & Protzner, 2013; Nan et al., 2018). In the context of the auditory oddball task, for instance, the P3b is elicited by the target stimuli, the amplitude of which typically increases the more infrequent the target stimuli are. The flanker task also elicits the P3, which is thought to reflect conscious, higher-order cognitive processes related to selective attention to the target arrow (Ibanez et al., 2012).

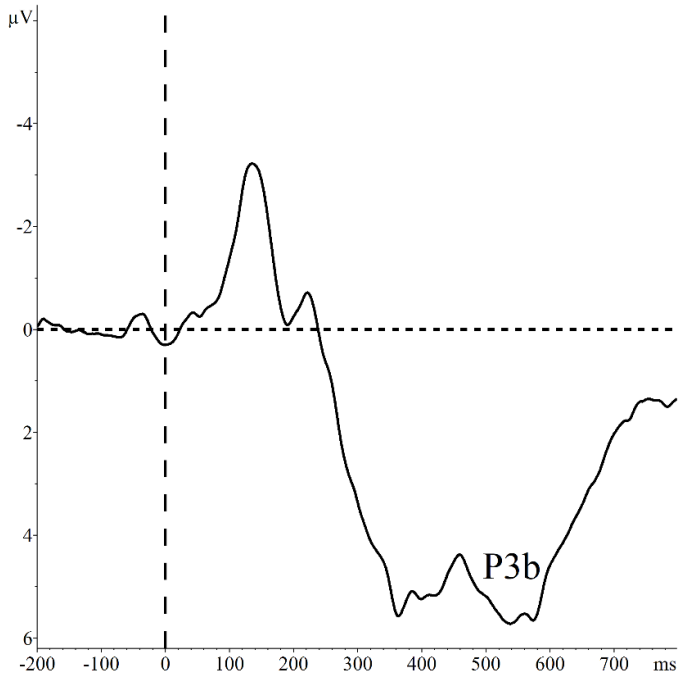

Figure 4. Grand average of the P3b event-related potential (ERP) at site Pz to a novelty auditory task.

The P3a (**Figure 5**) is a frontally-localized variant that is elicited by novel and unexpected stimuli in the environment (e.g., novel sounds in the context of the novelty oddball task) – as such, it is thought to index orienting to novelty and involuntary changes in the environment (Delle-Vigne et al., 2015; Ibanez et al., 2012; Jaworska & Protzner, 2013; Nan et al., 2018; Polich, 2007). Its neural generators tend to be the prefrontal cortex, anterior cingulate cortex (ACC), and the hippocampus (Bruder et al., 2012; Jaworska & Protzner, 2013; Volpe et al., 2007); it typically has a maximum amplitude at frontocentral scalp sites (Jaworska & Protzner, 2013). Further, its latency tends to occur somewhat earlier than the posterior P3b (Bruder et al., 2002). Some previous studies have also further subdivided the P3a into the early P3a (eP3a) and late P3a (lP3a), which have been seen observed in young participants (Correa-Jaraba et al., 2016; Escera et al., 1998, 2001; Mager et al., 2005) and in middle-aged to older adults (Correa-Jaraba et al., 2016, 2018; Mager et al., 2005). One group of researchers suggest

that the eP3a acts as an indicator for violations of regularity by novel stimuli; the lP3a, in turn, reflects attentional orientation and reorientation towards non-target, novel stimuli (Escera et al., 1998, 2001). Correa-Jaraba et al. (2016, 2018), however, proposed that the eP3a may reflect the orienting response to novel stimuli, while the lP3a is a correlate of the evaluation of the novelty of the stimuli.

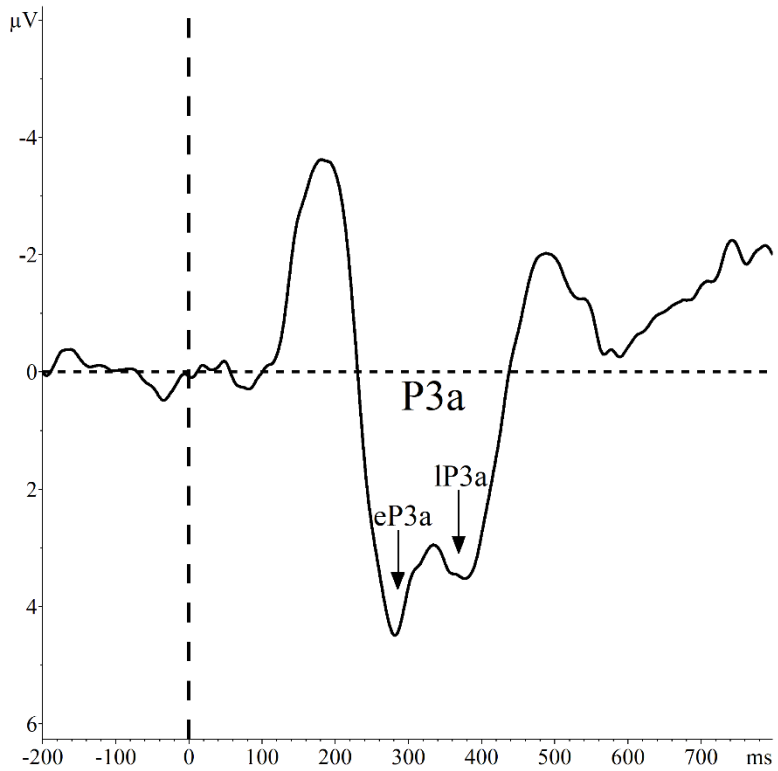

Figure 5. Grand average of the P3a event-related potential (ERP) at site Cz to a novelty auditory task.

1.3.3 The N2 ERP

The N2 (**Figure 6**) is a frontocentral negative peak and its neural generators tend to be the ACC, among other prefrontal cortical regions (Ibanez et al., 2012). N2 onset typically occurs 180-350ms (on average, ~200ms) after a stimulus that deviates from a prior expected stimulus, suggesting that the N2 is involved in stimulus identification (Ibanez et al., 2012; Larson et al.,

2014; Patel & Azzam, 2005). The N2 has been shown to be involved in inhibitory control, interference suppression, and directed forgetting (Downes et al., 2017). Larson et al. (2014) found that the N2 is sensitive to the degree of conflict prompted by a target stimulus, resulting in a larger N2 for incongruent than congruent stimuli. They also found that the N2 is sensitive to the extent to which the individual attends to the distractor (i.e., task-irrelevant information). This supports the idea that the N2 is an early neural index of inhibitory processes, as reflected by larger N2 amplitudes to targets primed by incongruent cues, which also tends to be accompanied by increased N2 latency (Kopp et al., 1996). As such, the amplitude of the N2 during the flanker task is typically larger/more negative in response to an incongruent trial (see **Table 4** below), particularly when preceded by a congruent trial (Kopp et al., 1996; Ligeza et al., 2018; Purmann et al., 2011).

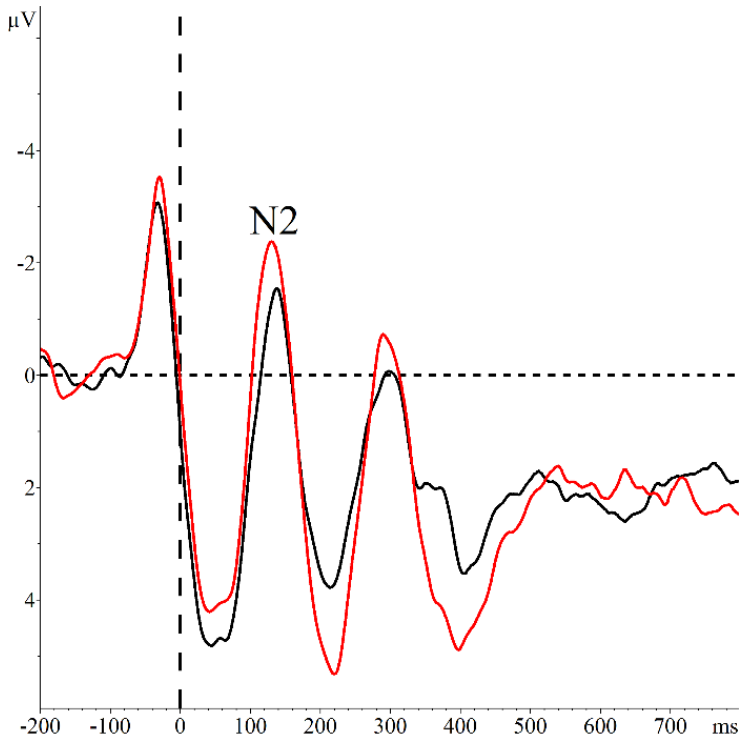

Figure 6. Grand Average of the congruent (black) and incongruent (red) N2 event-related potential (ERP) at site Fz to a visual flanker task.

1.4 Effects of Depression on N2 and P3 ERPs

Much of the work regarding the features of the N2 and P3 in the context of the flanker and oddball tasks, and whether they may be modulated by depression, has focused on adult populations (see **Table 1** for a summary). For instance, a study by Ruchsow et al. (2008) utilized a hybrid flanker and Go/No-Go task to investigate N2 and P3 features in adults with MDD in partial remission versus healthy controls. They found that the central P3 elicited by No-Go stimuli was reduced in patients with MDD, however, the No-Go N2 did not differ. Conversely, Alderman et al. (2015) found a reduced N2 in young adults with MDD using a modified flanker task, suggesting impaired conflict monitoring and inhibition in this group. Kaiser et al., (2003) found that depressed participants performed worse on the Go/No-Go task, and showed a reduction of an early fronto-temporal positivity. However, no group differences existed between healthy controls and depressed participants for the P3 (Kaiser et al., 2003). A meta-analysis by Bruder et al. (2012) found mixed results concerning the N2 in the context of depression; however, more studies than not tend to report reduced N2 amplitudes during visual tasks involving attentive and inhibitory responses in depressed adults. In one notable study, Clawson et al. (2013) found that decreased N2s to conflict adaptation (a cognitive process wherein congruency in previous trials modulates performance in the current trial) were correlated with higher levels of depressive symptoms in university students. This suggests a relationship between depressive symptoms and neural indices of conflict adaptation in TAY/young adults (Clawson et al., 2013).

With respect to the P3 in the context of the flanker task, in particular, Santopetro et al. (2021) found that a reduced P3 amplitude predicted an increase in depressive symptoms at a follow-up visit approximately 9 months later in depressed participants. When compared to

matched healthy controls, adult participants with MDD showed reduced P3 amplitudes during the flanker task (Klawohn et al., 2020). Notably, a study on young adolescent females (aged 8-14yrs) found that reduced P3 amplitude during a flanker task predicted increased depressive symptoms two years later. Additionally, strong relations existed between P3 amplitudes at baseline and anhedonia and negative self-esteem symptoms at a two-year follow-up (Santopetro et al., 2020). In sum, these results suggest that the P3 amplitude in the flanker task might be reduced in the context of depression, though data are not extensive.

Table 1. Summary of literature examining the frontal-central N2 and parieto-central P3 ERPs during flanker or hybrid flanker tasks in depressed (MDD) populations.

Study	Task	N2	P3
Kaiser et al. (2003)	Go/No-Go task	F_1/F_2: No group differences	P_1/P_2: No group differences
Ruchsow et al. (2008)	Hybrid flanker and Go/No-Go task	Central sites: No group differences	Central sites: Reduced amplitudes in MDD during No-Go task
Bruder et al. (2012)	Meta-analysis	Prefrontal sites: Reduced amplitudes in MDD	Central sites: Reduced amplitudes in MDD
Clawson et al. (2013)	Conflict adaptation	FCz/Cz: Reduced amplitude correlated to higher depressive symptoms	N/A
Alderman et al. (2015)	Modified flanker task	Fz, FCz, Cz: Reduced amplitudes in MDD	N/A
Klawohn et al. (2020)	Flanker task	N/A	Pz: Reduced amplitudes in MDD
Santopetro et al. (2020)	Flanker task	N/A	Pz: Reduced amplitude predicted increase in depressive symptoms
Santopetro et al. (2021)	Flanker task	N/A	CP_2/C4: Reduced amplitude predicted increase in depressive symptoms

LEGEND: Orange: no change; Blue: decreases; Yellow: increases; Green: increases and decreases

With respect to the oddball-task elicited P3, data are more extensive in the context of depression, though still relatively scarce in depressed youth in particular (see **Table 2** for a summary). In adults, Kemp et al. (2010) found reduced amplitudes and increased latencies of the P3 in MDD patients with melancholia using the auditory oddball task. On the other hand, (Nan et al., 2018) did not find P3 amplitude group differences in the single modality (i.e., auditory or visual) oddball task, but these differences did emerge in the combined auditory-visual task. The authors also found that P3 latency was greater in the depressed group for both the auditory-only and combined auditory-visual tasks (Nan et al., 2018). Further, adults with melancholic depression showed both a longer P3 latency and reduced P3 amplitude compared to matched controls (Urretavizcaya et al., 2003). Additionally, Feldmann et al. (2018) examined several ERPs using an auditory oddball task in adolescents (13-18yr) and found that P3 latencies in the depressed group were longer compared to the remitted and healthy adolescents, albeit not significantly; no group differences in P3 amplitude existed. (Zhou et al., 2019) found decreased P3 amplitudes and increased P3 latencies in depressed patients (M = 25.57yr) compared with healthy controls. In an earlier study, however, Zhou et al. (2018) found a smaller P3 amplitude, but no difference in latencies in depressed TAY patients (M = 21.36yr). Further, Greimel et al. (2015) found no group differences in P3 amplitudes and latencies between depressed adolescents (M = 14.3yr, range: 11-18yr) and a matched control group. Finally, in adolescent females (M = 16.9yr), Houston et al. (2004) also found no group differences in posterior P3 ERP measures during both a simple oddball task (frequent tone and target tone only) and a novel oddball task (with dog barks as the novel sound). Thus, based on the existing literature, oddball-elicited P3 profiles in depressed versus non-depressed TAY may be comparable to, but more subtle, than those observed in depressed adults (presumably because of ongoing neural plasticity and task

ceiling effects). Further, differences between depressed vs. non-depressed TAY might be more evident in P3 latency; however, this is speculative given the relative scarcity of research in this domain.

Of the above-reviewed studies, none assessed the P3a specifically. Indeed, limited research has examined the P3a in the context of depression (Bruder et al., 2012), and no known studies have examined the eP3a or lP3a sub-divisions. The latter may be beneficial for more precisely characterizing what cognitive functions, and associated electrocortical measures, might be impacted in depressed populations. Jaworska et al. (2013) examined the P3a and P3b in a depressed adult group who went on to be pharmacotherapy treatment responders and non-responders as well as controls, at baseline (i.e., prior to treatment in the depressed cohort). They found that eventual antidepressant non-responders showed smaller P3a and P3b amplitudes than treatment responders and controls at baseline. Interestingly, no difference was found between treatment responders and controls (Jaworska et al., 2013). This parallels some of the above-mentioned work indicating that the P3 is associated with subsequent depression severity and disease emergence (Santopetro et al., 2020, 2021). Further, a study using a two-stimulus oddball task found that patients with depression and comorbid anxiety had smaller early P3 amplitudes (which appeared to be equivalent to the P3a; Bruder et al., 2012) than healthy controls, however, patients with depression and no comorbid anxiety did not differ from controls (Bruder et al., 2002). Additionally, while no group differences on P3a or P3b amplitudes existed between a depressed group and controls on a go/no-go task, Pierson et al. (1996) found that the peak-to-peak measures of N2b-P3a amplitudes were smaller in a subgroup of depressed patients with blunted affect versus healthy participants, suggesting a global reduction in amplitudes in depressed patients during a Go/No-Go task. In young adults (M = 24.1yr), (lv et al., 2010) found

that depressed participants showed a reduced target P3 in the right hemisphere, and a reduced novelty P3 in the fronto-central region during a novelty oddball task when compared to matched controls. Finally, Bruder et al. (2009) found reduced P3a amplitudes during a novelty oddball task in depressed participants compared to controls; but no significant difference in P3b amplitudes. While the literature is both mixed and limited, the P3a amplitude does appear to reduce in depressed cohorts; however, some of the studies mentioned did not use tasks that are best suited for eliciting a novel P3 ERP (Bruder et al., 2002, 2012; Pierson et al., 1996).

Table 2. Summary of literature examining the P3 and P3 subcomponent ERPs during oddball or related tasks in depressed (MDD) populations.

Study	Task	P3	P3a	P3b
Pierson et al. (1996)	Go/No-go task	N/A	Fz: No group differences	Pz: Longer latencies in blunted affect group
Bruder et al. (2002)	Two-stimulus oddball task	N/A	Cz: Reduced amplitudes in MDD	N/A
Urretavizcaya et al. (2003)	Auditory oddball task	Sites $Cz/C_4/C_3$: Reduced amplitudes, longer latencies in MDD	N/A	N/A
Houston et al. (2004)	Simple and novel oddball tasks	Parieto-central & frontal sites: No group differences	N/A	N/A
Bruder et al. (2009)	Novelty oddball task	N/A	Fz/Cz: Reduced amplitudes in MDD	Pz: No group differences
lv et al. (2010)	Novelty oddball task	N/A	FCz/FC_3/ FC_4: Reduced amplitude in MDD	$Pz/P_3/P_4$: Reduced target amplitude in RH* in MDD
Kemp et al. (2010)	Auditory oddball task	Fz/Cz/Pz: Reduced amplitudes, longer latencies in MDD	N/A	N/A
Jaworska et al. (2013)	Novelty oddball task	N/A	Cz: Reduced amplitudes in antidepressant non-responders	Pz: Reduced amplitudes in antidepressant non-responders

Greimel et al. (2015)	Auditory oddball task	Fz/Cz/Pz: No group differences	N/A	N/A
Feldmann et al. (2018)	Auditory oddball task	Parieto-central sites: No group differences (current vs remitted)	N/A	N/A
Nan et al. (2018)	Combined auditory-visual oddball tasks	P_3/P_4: Reduced amplitudes, longer latencies in MDD	N/A	N/A
Zhou et al. (2018)	Auditory oddball task	16 sites: Reduced amplitudes in MDD	N/A	N/A
Zhou et al. (2019)	Auditory oddball task	16 sites: Reduced amplitudes, longer latencies in MDD	N/A	N/A

*RH: Right Hemisphere; LEGEND: Orange: no change; Blue: decreases; Yellow: increases; Green: increases and decreases

Interestingly, numerous studies have found that accuracy on the flanker and oddball tasks tend not to differ between depressed and healthy adults (Alderman et al., 2015; Bange & Bathien, 1998; Chiu & Deldin, 2007; Clawson et al., 2013; Dillon et al., 2015; Greimel et al., 2015; Ruchsow et al., 2008; Santopetro et al., 2020; Zhou et al., 2018). This may be due to the relatively simple nature of these tasks. This also speaks to the notion that electrocortical differences may not necessarily be associated with overt behavioural differences, and may also be an index of neurocompensatory processes that maintain and sustains performance. Results vary, however, in terms of reaction times (RT). While some groups have found no difference in RTs between depressed and healthy participants on the flanker (Chiu & Deldin, 2007; Clawson et al., 2013; Ruchsow et al., 2008) and oddball tasks (Bruder et al., 2012; Feldmann et al., 2018; Greimel et al., 2015; Zhou et al., 2019), others report slower RTs in depressed adult participants on both the flanker (Bange & Bathien, 1998; Dillon et al., 2015; Santopetro et al., 2020) and oddball tasks (Kemp et al., 2010; Nan et al., 2018; Zhou et al., 2018). Slower RTs may reflect an increased focus on errors and reduced performance in response to incongruent or conflict stimuli (Clawson et al., 2013; Holmes & Pizzagalli, 2010). However, when not accompanied by accuracy decrements, they might also reflect a slower accuracy-response trade-off.

Finally, only six studies outlined above included a participant group with a mean age falling between 16 and 24 years, i.e., TAY (Alderman et al., 2015; Clawson et al., 2013; Feldmann et al., 2018; Greimel et al., 2015; Houston et al., 2004; Zhou et al., 2018). Most of these studies in TAY with depression documented reduced N2 and P3 amplitudes and increased P3 latencies in the flanker and oddball tasks, respectively (Alderman et al., 2015; Clawson et al., 2013; Feldmann et al., 2018; Zhou et al., 2018), mirroring some of the ERP deficits seen in adult populations. However, some studies in TAY found no group differences on oddball P3 ERP features (Greimel et al., 2015; Houston et al., 2004). Further, none of the studies assessing auditory oddball have examined the early and late subcomponents of the P3a in depressed youth (or adults), with all existing research looking solely at healthy populations (Correa-Jaraba et al., 2016, 2018; Escera et al., 1998, 2001; Mager et al., 2005). Thus, whether the ERP profiles in depressed TAY are comparable, or perhaps have some unique sub-features, to what has been noted in adult populations warrants further study and replication.

2. OBJECTIVES AND HYPOTHESES

This study was embedded within a larger clinical study aimed at investigating the antidepressant effects of aerobic exercise on TAY with depression. The primary aim of this thesis work was to assess ERP-indexed neural profiles of attention, including novelty orienting, and inhibition during the auditory oddball and visual flanker tasks in depressed, unmedicated TAY (DEP group) vs. non-depressed TAY healthy controls (HC group).

Specifically, as part of our **primary** aims, we assessed:

a) The P3b ERP to target stimuli in the auditory novelty oddball task, which is thought to reflect conscious attentional processes and memory updating. We expected significantly smaller P3b amplitudes and increased latencies in the DEP group vs. the HC group.
b) The amplitude and latency of the P3a to novel (unexpected) sounds in the context of the novelty oddball task were also measured and thought to reflect novelty orienting. The eP3a and lP3a were explored as no previous work has assessed this in the context of depression. It was expected that eP3a, lP3a, and tP3a amplitudes in the DEP group would be significantly smaller, and latencies increased, vs. the HC group.
c) N2 amplitudes and latencies to incongruent and congruent stimuli in the visual flanker task, which has been shown to reflect inhibitory control and interference suppression, were examined between groups. It was expected that the DEP group would show smaller N2 amplitudes and increased latencies vs. the HC group.
d) The incongruent and congruent P3 ERP in the visual flanker task is thought to reflect selective attentional processes. It was expected that the incongruent and congruent P3 amplitudes would be smaller, and latencies increased, in the DEP vs. the HC group.

e) We also assessed behavioural measures during these tasks (i.e., ERP flanker and ERP novelty oddball tasks). Based on previous literature (Alderman et al., 2015; Bange & Bathien, 1998; Chiu & Deldin, 2007; Clawson et al., 2013; Dillon et al., 2015; Greimel et al., 2015; Ruchsow et al., 2008; Santopetro et al., 2020; Zhou et al., 2018), we expected that there would be no significant group differences on task performance measures of reaction time (RT) and number of correct responses (i.e., accuracy) for both the oddball and flanker task due to ceiling effects.

Secondary aims were to assess putative cognitive impairments in TAY using well-validated cognitive tasks tapping into similar cognitive domains as those assessed using the flanker and oddball ERP tasks, namely, stimulus evaluation, inhibition, and working memory. As such, we compared fully corrected t-scores (corrected for age, gender, education, and race/ethnicity) between the DEP and HC on the:

a) NIH 'Flanker Inhibitory Control and Attention' test (NIH Flanker),

b) NIH 'List Sorting Working Memory' test (NIH List Sort), and

c) NIH 'Dimensional Change Card Sort' test (NIH Card Sort).

For each of these tests, it was expected that scores on these cognition tests would be significantly lower in the DEP compared with the HC groups. These behavioural group differences were expected, in contrast to the lack of behavioural measure differences in the ERP Flanker and ERP Oddball tasks, due to the scoring algorithm used by the NIH Toolbox, which combines reaction time and hits into one composite score, perhaps making the task more sensitive, as well as correcting for demographic factors.

Exploratory aims included assessing the relation between specific Oddball and Flanker ERP measures and scores on the three NIH tasks. It was hypothesized that:

a) the NIH Flanker task scores would correlate positively with both incongruent and congruent ERP Flanker task P3 amplitudes, and negatively with P3 latencies;

b) the NIH List Sort task scores would correlate positively with ERP Oddball task P3b amplitudes and negatively with P3b latencies; and

c) the NIH Card Sort task would correlate positively with ERP Oddball task P3a/b amplitudes and with ERP Flanker task P3 and N2 amplitudes to both congruent and incongruent trials (though more so to incongruent ones), and negatively with the corresponding latencies of these ERPs.

Finally, the relations between ERP features for both tasks and a self-rated measure of depression symptoms, as assessed with the Beck Depression Inventory (BDI-II; Beck et al., 1996), were assessed. It was expected that BDI scores would correlate negatively with the amplitudes of the Flanker P3 ERPs and Oddball P3a/b ERPs; as well as positively with the Flanker P3 and Oddball P3b latencies.

3. METHODOLOGY

3.1 Participants

The participant group for this thesis was defined as unmedicated TAY (16-24yr) with diagnosed or suspected MDD or PDD as confirmed by a clinician, and are currently experiencing a depressive episode. Unmedicated TAY (16-24yr) were recruited through several methods, including posters posted on university campuses (including medical services), social media (e.g., Facebook posts), advertising websites (Reddit, Kijiji), and mental health service providers (e.g., local youth support groups and counselling offices). Interested participants first underwent an initial phone screening to determine study eligibility (**Appendix I & II)**. Screened participants were then brought in for a thorough in-person assessment. The initial phone screen was used to screen for depression, mania, anxiety disorders, psychotic symptoms, acute suicidal behaviours, drug or alcohol dependence, neurological or neuromuscular issues, learning disabilities, and familial history of mental illness. Participants were re-screened for depression, mania, anxiety disorders, psychotic symptoms, suicidality, and drug or alcohol dependence during the in-person assessment (details below). Inclusion criteria for DEP participants included having a primary history of MDD or persistent depressive disorder (PDD; established in-person, details below). Exclusion criteria for both HC and DEP participants included: using antidepressant pharmacology within the past 5 weeks, participating in another exercise trial or currently exercising more than 1hr/week (these exclusion criteria are related to the broader clinical trial); having a serious medical/neurological condition; having another psychiatric disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5; (American Psychiatric Association, 2013) criteria, with the exception of co-morbid anxiety disorders for DEP participants; exhibiting significant suicidal risk; current (within 6 months) drug or alcohol

dependence; unwilling to abstain from recreational drug use >3 weeks prior to testing; being a current, daily smoker; unwilling to abstain from caffeine for >6hr prior to testing; having a body mass index (BMI) >40 kg/m^2; potential magnetic resonance imaging (MRI)-incompatibility (MRI is a component of the study, but, is not part of this thesis); and currently pregnant or breastfeeding. Furthermore, all HC participants were required to meet with a researcher to verify that they had no history of depression, anxiety, or other psychiatric disorders, nor are currently engaging in psychiatric pharmacological treatments and/or psychotherapies.

3.2 Behavioural and EEG Measures

Upon arrival to the laboratory at The Royal's Ottawa Mental Health Centre, a consent form was signed (Research Ethics Board approval was obtained from The Royal [REB # 2018025], **Appendix III**; and uOttawa [REB # H-08-18-1065], **Appendix IV**). Subsequently, a clinical interview using the Mini International Neuropsychiatric Interview v.7.0.0 (MINI; Sheehan, 2015; Sheehan et al., 1998) was administered, as was the Hamilton Depression Rating Scale ($HAMD_{24}$; Hamilton, 1960; J. B. W. Williams, 1988), Columbia Suicide Severity Rating Scale (CSSRS; Posner et al., 2011), and Montgomery-Äsberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) by experienced research personnel. These scales were used to assess depression and suicide severity; all clinician measures are not discussed as part of the thesis (expect as part of demographics). During this session, DEP participants were randomized to either a high or moderate intensity exercise intervention condition (single-blind; personnel who conduct clinical ratings are blind to the intervention arm). However, this will not be discussed as part of this thesis. DEP participants were then scheduled for their EEG session. All baseline testing for HCs occurred during the same visit, while testing for the DEP participants was split between two visits. HCs were administered the same measures as DEP participants. After COVID-19

measures were put in place, consent forms were sent and signed digitally while clinical interviews were held via video conferencing. Personal protective equipment (PPE) was worn at all times when testing was permitted to resume in-person in June 2021; all testing was halted in March 2020 due to the closure of the laboratory as a result of the COVID-19 pandemic.

Prior to the EEG recordings, participants underwent a hearing test (Audiometer, Lafayette Instrument Inc.) to ascertain that they can hear 500, 1000, and 2000Hz at a 30dB minimum in each ear, as hearing is critical for some of the tasks pertinent to this thesis. Their CO levels were assessed (piCO$^+$ Smokalyzer®, coVita) to verify non-smoking status. They were then seated in a dimly-lit testing chamber approximately 100cm in front of a computer monitor. During EEG hook-up, participants filled out various self-report questionnaires, including the Beck Depression Inventory (BDI; **Appendix V**; Beck et al., 1996). EEG data was collected using 64 active electrodes embedded within a cap (**Appendix VII**; ActiCAP; BrainVision Solutions) in accordance with the 10-20 system of electrode placement (Klem et al., 1999). One of the 64 electrodes (Iz) was attached under the participant's right eye to measure eye movements. Electrode impedances were maintained at <10kΩ, and EEG was sampled at 500Hz using BrainVision Recorder V1.4.3 (BrainVision Solutions, Germany). Subsequently, resting-state EEG data was collected as part of the larger study (not presented herein). Then, the participants were administered the flanker and oddball tasks during which time EEG activity was recorded.

3.2.1 ERP Flanker Task

The ERP Flanker task is an adapted version of the original (Seer et al., 2017); see **Figure 7**). On average, each trial lasts 2600ms and occurs in the following order: a white fixation cross is presented (800-1200 ms) followed by pre-target flanking stimuli (100 ms), subsequently, the target appears and stays on, along with the flanking stimuli for 250ms, this is followed by a

blank screen response window (1250ms; Presentation Software, Neurobehavioral Systems, Albany, CA, USA). The participant was instructed to respond to the central target at any time after target onset and during the response window using a keyboard (left control button if the central arrow was pointing left, right control button if it was pointing right). Participants responded using their index fingers. The task was administered in three blocks with each block consisting of 50 congruent and 50 incongruent randomized trials, for a total of 150 congruent and 150 incongruent trials.

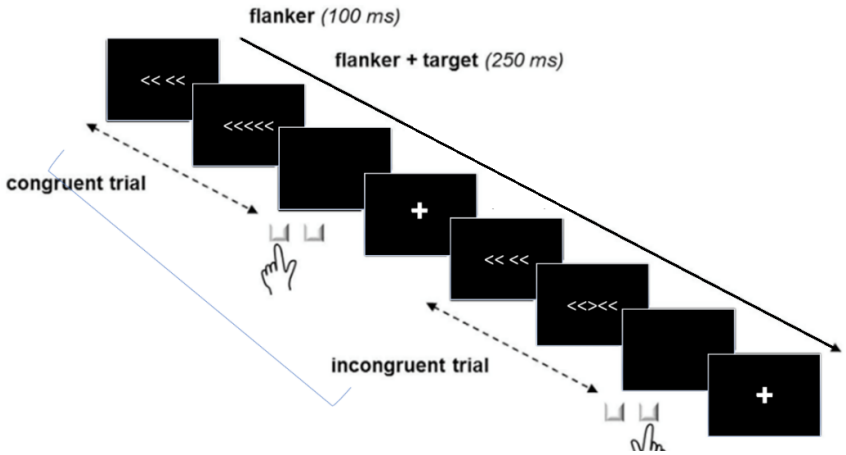

Figure 7. Diagram demonstrating congruent and incongruent trials of the flanker task. Adapted from Seer et al., 2017.

3.2.2 ERP Oddball Task

The novelty oddball (ERP Oddball, see **Figure 8**) task consisted of 800 auditory tones presented in four blocks, wherein 80% of the tones were non-target tones ("standard"; 1000Hz, 70dB) that lasted for 336ms, 10% were target tones that were of a lower frequency than the standard tones ("target"; 700Hz, 70dB) that lasted for 336ms. Finally, 10% were distractor sounds ("novel"; 65-75dB) that lasted for 169-399ms. The inter-stimulus interval lasted for 1000ms (Presentation Software, Neurobehavioral Systems, Albany, CA, USA). Participants were asked to respond only to the target tones by pressing the right control key on a keyboard. As

participants listened to the task through headphones (Sennheiser), they focused on a fixation cross presented on the computer monitor positioned approximately 100cm in front of them.

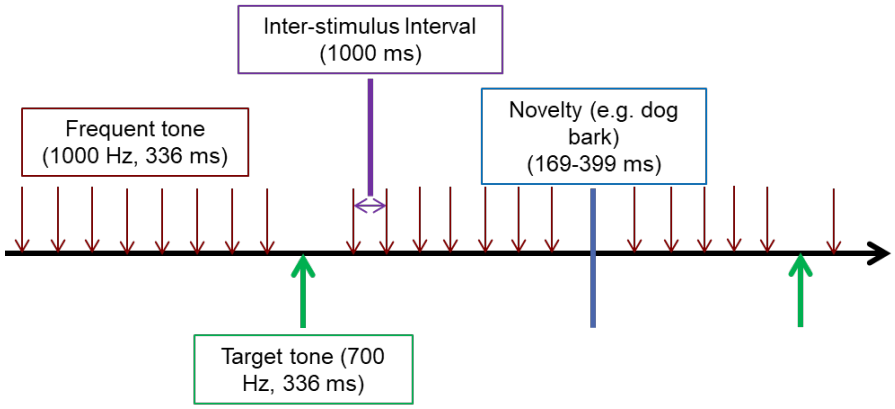

Figure 8. Diagram demonstrating the types and frequency of tones during the novelty oddball task.

3.2.3 Cognition

The results of all NIH Toolbox tasks are presented individually and also compiled together to result in a total cognitive function composite score (Gershon et al., 2013). For the purposes of this thesis, the fully corrected T-scores of the NIH Flanker, NIH List Sort, and NIH Card Sort tasks are presented. The scores of the other two tasks that comprise fluid cognition are available in the supplementary materials (**Appendix VIII**). The fully corrected T-scores are corrected for age, gender, education, and race/ethnicity (Gershon et al., 2013). Other cognitive measures using the NIH Toolbox cognitive battery were obtained (administered via iPad) as part of the broader study but are not discussed further as part of this proposal.

The NIH Flanker (National Institutes of Health, 2021; see **Figure 1**) is adapted from the Eriksen Flanker task (Eriksen & Eriksen, 1974). The task is comprised of 40 trials, not including the instructions and practice, and takes about 4 minutes to complete. Scores are computed using a two-vector scoring method, with accuracy and reaction time (RT) as the two vectors. Accuracy

is the primary vector, wherein participants who have an accuracy of <80% receive a final score that is equal to their accuracy score alone. In those with >80% accuracy, RT scores are generated using the participant's raw, incongruent median RT, which is computed only from correct trials that have a RT value no more than 3 standard deviations (SD) from their mean. This median RT is then added to the accuracy, and this value is then converted to normative scores. In this context, higher scores are indicative of better performance.

The NIH Card Sort test (National Institutes of Health, 2021; see **Figure 2**) is a simplified version of the Wisconsin Card Sorting Test (Grant & Berg, 1948). It requires participants to evaluate a picture based on two dimensions (colour and shape). Participants were primed with the dimension they must match the picture to first, and the picture in question then follows. Participants responded by clicking one of two pictures that best matches the primed dimension for that particular trial. The task is comprised of 40 trials, not including the instructions and practice, and takes about 4 minutes to complete. Scoring is based on the same two-vector scoring method as used for the NIH Flanker test; wherein a minimum accuracy of 80% is needed before the median RT vector is calculated and added to the final score. Median RT is computed in the same method as the NIH Flanker test and is converted to normative scores once added to the accuracy score. For this task, higher scores are indicative of better performance.

The NIH List Sort test (National Institutes of Health, 2021; see **Figure 3**) involved having participants listen to increasingly longer lists of animal or food items that they then recited in size order (from smallest to largest). The first trial is two items, and each trial increased by one item (up to seven items). The participant recited the lists aloud to a research assistant administering the task, who inputted either a 1 for a correct response or a 0 if an error was made on a keyboard. An incorrect response resulted in attempting the secondary trial with

the same number of items as the trial that an error was made in. The participant continued to the second portion of the task if two incorrect trials were made in a row, or they complete the 7-item trial. The second portion of this task combined both food and animals into the same list, and participants were instructed to recite the food items in size order, followed by the animals in size order. As with the first portion of the task, the participant recited the lists aloud, to which the research assistant entered a 1 or a 0 into the keyboard. An incorrect response resulted in attempting the secondary trial. The participant completed the task if two incorrect trials were made in a row, or they complete the 7-item trial. The task is scored by summing the total number of items correctly remembered and sequenced from the two lists. This score can range from 0-26 and is then converted to normed standard scores, with a higher score indicating better task performance.

3.3 ERP Processing

EEG data was processed using BrainVision Analyzer 2.2 (BrainVision Solutions, Germany). The data was first re-referenced to the averaged mastoids, and filtered (0.1-30Hz; notch = 60Hz; slope = 24dB/Oct). Ocular correction was applied using the Gratton & Coles method (Gratton et al., 1983). Data was segmented at -200ms to 800ms for the ERP Oddball (0ms was the onset of the target and novel sounds) and ERP Flanker tasks (time-locked to the onset of the congruent/incongruent targets). Baseline correction was then applied (-200ms prior to stimulus onset for ERP Oddball; -200ms to -100ms pre-stimulus for ERP Flanker as flankers [without target] were presented at -100ms). Artifact rejection was then applied, with a criterion of ±75μV being applied to data segments/epochs. Any participants with <40 epochs per the novel and target stimuli for the ERP Oddball task, or <75 epochs for congruent/incongruent stimuli in the ERP Flanker task following artifact rejection were flagged for further manual

inspection. Manual inspection included topographic interpolation of no more than five channels, independent component analyses (ICA) removing no more than five components (e.g., electrocardiogram [ECG] artifacts; residual ocular artifacts), and/or disabling no more than 3 channels in artifact rejection for further cleanup. Following manual inspection of problematic data, if the total number of epochs was still < 50% of all available epochs, the participant was removed from that task due to insufficient epochs. Manual inspection was done on data that was not blinded (i.e., one could identify who was a DEP or HC participant based on assigned codes); however, the automatic process that was done initially to clean up the data was not subject to any potential bias.

ERP peaks were defined by examining the grand averages of all participants combined who were included following artifact rejection. The ERP Flanker N2 was the most negative amplitude within a 90-210ms window post-stimulus onset at site Fz. The ERP Flanker P3 was the most positive amplitude within a 250-450ms window post-stimulus onset and was measured at sites Cz, where it was maximal (previous research has shown the Flanker P3 to be more maximal at posterior sites such as Pz, however, this was not the case for our data). The ERP Oddball task elicited P3a was the most positive amplitude within a 200-310ms window following the onset of the novel stimuli for the exploratory early P3a (eP3a), 311-410ms window for the late P3a (lP3a), and a 200-410ms window post-stimulus onset for the total P3a (tP3a); all P3a peaks were extracted at Cz where they were maximal. Finally, the ERP Oddball task elicited P3b was the most positive amplitude within a 280-580ms window post-target onset at Pz. Peak detection was applied automatically and then manually inspected (for any obvious mislabelling; N=2 per participant group per task). Amplitudes and latencies of each of the ERP peaks were exported using the mean value of five sampling points around the peak.

3.4 Power Calculations

Power analyses were done with G*Power v.3.1 (Erdfelder et al., 2009). Previous studies using the auditory oddball task to compare healthy versus depressed participants on the P3 ERP amplitude showed an average effect size of d=0.85 (Ancy et al., 1996; Bruder et al., 2009; Feldmann et al., 2018; Gangadhar et al., 1993; Kawasaki et al., 2004) and power of β=.80 (Feldmann et al., 2018). As such, based on d=0.85 and a power of β=.80, N=23 per group was required to observe a difference between HC and DEP groups on P3a and P3b oddball ERP features using a one-way analysis of variance (ANOVA). Based on a study by Ruchsow et al. (2008), who noted a difference in amplitude between depressed vs. non-depressed individuals on a hybrid No-Go/Flanker task elicited P3 ERP, an effect size of d=0.81 was reported. Thus, using this effects size (d=0.81) and a power of β=.80, N=25 per group was required to observe a difference between HC and DEP groups on P3 and N2 flanker ERP features using a one-way ANOVA. As such, we aimed to recruit an N=25/group.

3.5 Statistical Analysis

Seven cases of mild outliers (± 1.5 interquartile ranges; IQR) were identified across six measures (1-2 outliers per measure) during analyses (determined via IQR of box and whisker plots); however, no outliers were extreme outliers (± 3 IQR). Due to the small sample sizes and lack of extreme outliers (and given that no outlier was consistent for all of the outcome measures), no outliers were removed for the analyses. A Shapiro-Wilk test of normality and Levene's test for homogeneity of variances was conducted on DEP and HC oddball eP3a, lP3a, tP3a, and P3b ERP latency and amplitude. The data was not normally distributed, and variances were not equal; thus, a Mann-Whitney U test was carried out to compare the groups on the ERPs (IBM SPSS Statistics 27, Chicago, IL, USA). Similar checks for parametric analyses

assumptions were carried out for the Flanker task N2 and P3 ERP features. No parametric assumptions were violated, as such, an ANOVA test was carried out. Significance was set to $p < 0.05$ for the above analyses. Further, two paired-samples t-tests were used to examine differences between the Flanker ERP tasks' congruent and incongruent N2 and P3 ERPs within each group. This was done to ensure that expected task effects were observed; specifically, that ERPs would be larger to incongruent vs. congruent stimuli (Alderman et al., 2015; Downes et al., 2017; Kopp et al., 1996; Larson et al., 2014; Ligeza et al., 2018; Purmann et al., 2011). Further, an exploratory analysis of covariance (ANCOVA) test was carried out, with the inclusion of self-reported depression scores (BDI) as a covariate; this was only carried out for any significant group differences to assess the extent to which the data were related to by depression severity (outcomes in **Appendix IX**).

A Shapiro-Wilk test of normality and Levene's test for homogeneity of variances was conducted on DEP and HC fully-corrected t-scores of the NIH Flanker, NIH List Sort, and NIH Card Sort tasks. No parametric assumptions were violated, as such, a one-way ANOVA was used for between-group comparisons of these NIH scores.

Correlations were carried out between ERP Flanker P3/N2 and ERP Oddball P3a/P3b amplitudes and latencies, and the fully-corrected t-scores of the NIH Flanker, NIH Card Sort, and NIH List Sort tasks. Given that the assumption of normality was violated, and there appeared to be some potential outliers (defined as any below the 25th percentile or above the 75th percentile using a box and whisker plot [IBM SPSS Statistics 27, Chicago, IL, USA]), a Spearman's correlation was carried out. This correlation was carried out across the whole sample given that we found no group differences (DEP vs. HC) on any of the NIH task scores (please see **Results section 4.3.3**). The aim of these correlations was to explore the relation between neuronal

features and putative associated behavioural cognition correlates. Given that a total of 48 correlations were carried out, we chose to correct for multiple comparisons by setting a significance level of $p<.01$ (a strict Bonferroni correction was deemed too stringent given the sample size and exploratory nature of this work). Finally, we also carried out correlations within the DEP group only between clinical scores, specifically between the BDI (Beck et al., 1996) and the fully-corrected t-scores of the NIH Flanker, NIH Card Sort, and NIH List Sort tasks. Due to a violation of the assumption of normality and potential outliers as determined using a box and whisker plot, a Spearman's correlation was also carried out. The aim of these correlations was to examine relations between the severity of depressive symptoms and behavioural measures of cognitive domains of interest. A total of 16 correlations were carried out, thus multiple comparisons were corrected by setting a significance level of $p<.01$. Means, standard deviations, and effect size (eta squared) are presented unless stated otherwise for all analyses.

4. RESULTS

4.1 Participants

A total of 183 potential DEP participants expressed an interest in study participation. Of these, N=63 did not respond to further contact, and N=16 were no longer interested. Thus, N=104 potential participants were screened for eligibility. Of these, N=6 did not respond to further contact, N=2 were no longer interested, and N=67 were found to be ineligible due to antidepressant use, additional DSM-5 comorbidities, or not being sedentary (exclusionary for the broader clinical study). In total, N=30 potential participants consented and completed the clinical interview, however, N=9 were found to be ineligible during the clinical interview (e.g., very high suicidality, MDD not a primary diagnosis). N=21 participants were assigned a participant ID, however, N=2 were withdrawn from the study prior to data collection resulting in a final N=19 DEP participants. A total of N=44 potential HCs expressed an interest in study participation; of these, N=1 did not respond to further contact. Out of the N=43 screened for eligibility, N=1 lost interest and N=20 were ineligible due to past depressive or other psychiatric disorder history, or not being sedentary. In total, N=22 potential participants consented, completed the clinical interview, and were assigned a participant ID; however, N=3 HC participants dropped out prior to data collection, resulting in a final N=19 HCs. No differences in sex, age, ethnicity, or years of education existed between groups. Descriptive statistics and clinical scores are presented in **Table 3**.

Table 3. Means and standard deviations of descriptive statistics and clinical scores of healthy controls (HC) and depressed (DEP) groups.

	Healthy Controls (HC) N = 19	Depressed (DEP) N = 19	Significance (t or X^2) N = 38
Sex	7 Male; 12 Female	3 Male; 16 Female	$X^2 = 2.17$ $p = .141$

Age (M ± SD)	21.00 ± 2.21	21.21 ± 1.93	t = -.31 p = .869
Education Years (M ± SD)	14.68 ± 1.97	14.32 ± 1.42	t = .66 p = .338
$HAMD_{21}$ (M ± SD)	1.37 ± 1.50	17.33 ± 4.69 (N = 18)	t = -14.11 p < .001
BDI-II (M ± SD)	2.74 ± 2.92	32.42 ± 8.09	t = -15.04 p < .001
BAI (M ± SD)	4.37 ± 4.75	22.61 ± 12.48 (N = 18)	t = -5.94 p < .001
Ethnicity	9 Caucasian; 4 Black/African American; 4 Asian; 1 Hispanic/Latinx; 1 Other	13 Caucasian; 5 Black/African American; 1 Asian	X^2 = 4.64 p = .326

$HAMD_{21}$: Hamilton Depression Rating Scale, 21-item version; BDI-II: Beck Depression Inventory-II
BAI: Beck Anxiety Inventory

4.2 Behavioural Results

No group differences in task performance (correct "hits" and reaction time) were found for the ERP Oddball or the ERP Flanker tasks. Performance features of both tasks are presented in **Table 4**.

Table 4. Means and standard deviations of task performance of healthy controls (HC) and depressed (DEP) groups in the event-related potential (ERP) Oddball and ERP Flanker tasks.

	Healthy Controls (HC) N = 19	Depressed (DEP) N = 14	Mann-Whitney U Test
Oddball Correct Hits (#, out of 80)	78.47 ± 4.74	78.93 ± 1.33	p = .84 η^2 = 0.03
Oddball Reaction Time (ms)	481.71 ± 54.93	488.95 ± 50.55	p = .43 η^2 = .001
Flanker Congruent Hits (#, out of 150)	147.07 ± 4.85	142.60 ± 12.93	p = .22 η^2 = .053
Flanker Congruent Reaction Time (ms)	388.84 ± 51.65	369.83 ± 43.59	p = .29 η^2 = .041
Flanker Incongruent Hits (#, out of 150)	139.13 ± 11.22	130.20 ± 18.16	p = .12 η^2 = .086
Flanker Incongruent Reaction Time (ms)	474.18 ± 60.96	452.51 ± 49.36	p = .29 η^2 = .039

4.3 Event Related Potentials (ERPs)

4.3.1 Oddball ERPs

A total of N=14 DEP (N=2 participants were removed due to insufficient correct responses, N=1 removed due to EEG data recording errors, and N=2 did not participate in the EEG portion) and N=19 HC participants had useable ERP data from the ERP Oddball task; results are presented below in **Table 5**. As outlined, due to parametric test violations, a Mann-Whitney U test was used to examine group differences between the amplitudes and latencies of the early P3a (eP3a), late P3a (lP3a), total P3a (tP3a), and P3b ERPs during the ERP Oddball task. We found that eP3a latency was significantly different between groups (U = 74.00, p = .031, η^2 = 0.15; **Figure 9**), wherein the DEP group had a *faster* latency than the HC group. No other statistically significant results were found. Exploratory ANCOVA results examining depression and anxiety scores as covariates are provided in **Appendix IX**. After correcting for depression and anxiety individually, no group differences were found for the eP3a latency.

Table 5. P3a (at site Cz) and P3b (at site Pz) measures during ERP Oddball task in healthy controls and depressed groups (mean ± standard deviation).

	Healthy Controls (HC) N = 19	Depressed (DEP) N = 14	Mann-Whitney U Test
Early P3a Latency (ms)	282.00 ± 16.26	267.57 ± 5.75	p = .031* η^2 = 0.15
Early P3a Amplitude (μV)	4.43 ± 2.55	5.75 ± 5.56	p = .74 η^2 = .003
Late P3a Latency (ms)	362.11 ± 25.81	359.14 ± 27.08	p = .61 η^2 = .008
Late P3a Amplitude (μV)	4.46 ± 2.94	4.68 ± 5.07	p = .80 η^2 = .002
Total P3a Latency (ms)	320.74 ± 50.05	304.71 ± 53.56	p = .22 η^2 = .048
Total P3a Amplitude (μV)	5.38 ± 2.45	7.38 ± 4.16	p = .19 η^2 = .054
P3b Latency (ms)	448.11 ± 91.26	453.57 ± 88.89	p = .94 η^2 < .001

P3b Amplitude (μV)	7.80 ± 4.10	9.22 ± 5.59	p = .61 η^2 = .008

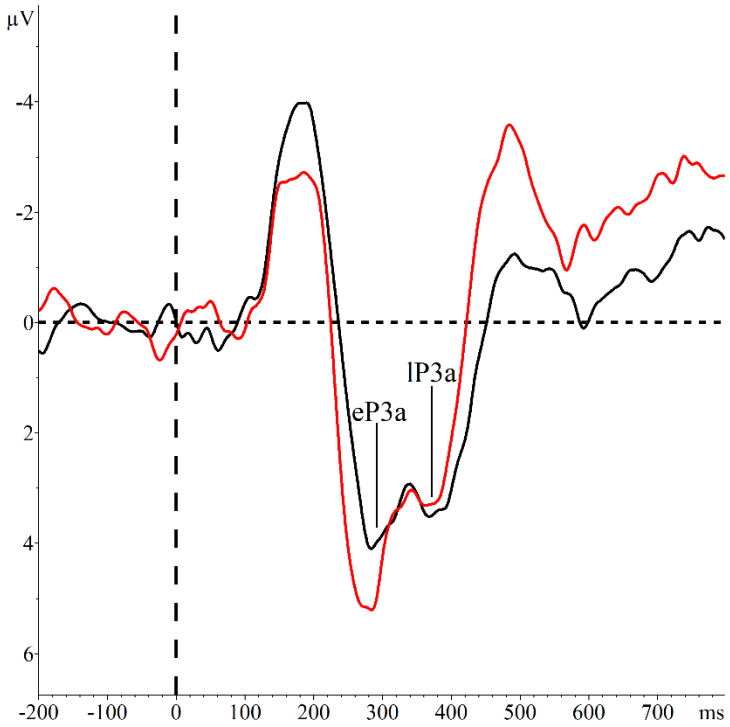

Figure 9. Oddball eP3a and lP3a event-related potentials (ERP) at site Cz for depressed group (red) and healthy control group (black).

4.3.2 Flanker ERPs

A total of N=15 DEP and N=15 HC (N=1 DEP and N=1 HC participants were removed due to insufficient correct responses, N=1 DEP and N=1 HC were removed due to EEG recording data errors, N=2 HC due were removed due to task versions errors, and N=2 DEP participants did not complete the EEG portion) participants had useable ERP Flanker data, which are presented in **Table 6**. Two paired-samples t-tests were used to examine differences between congruent and incongruent N2 and P3 ERPs within each group. In the DEP group, significant differences were found between the incongruent and congruent N2 ($t(14) = -3.65$, $p = .003$) and P3 amplitudes ($t(14) = 4.36$, $p = .001$; **Figure 10**). As expected, and consistent with the literature

(e.g. Alderman et al., 2015; Downes et al., 2017; Kopp et al., 1996; Larson et al., 2014; Ligeza et al., 2018; Purmann et al., 2011), the N2 was significantly more negative and the P3 more positive to the incongruent vs. congruent stimuli. Similarly, a significant difference was also found in P3 amplitude between incongruent vs. congruent trials in the HC group ($t(14) = 3.58$, $p = .003$; **Figure 11**), wherein the incongruent was more positive. Means and standard deviations are presented in **Tables 6** and **7.** ERP images are presented below (**Figures 10-11**).

Table 6. Means and standard deviations of the Flanker task congruent and incongruent N2 (at site Fz) and P3 (at site Cz) amplitudes and latencies of the depressed (DEP) group (N=15).

	Incongruent	Congruent	Paired Samples t-test
N2 Latency (ms)	132.13 ± 16.31	138.80 ± 18.80	$p = .11$ $d = -.45$
N2 Amplitude (μV)	-3.18 ± 2.74	-2.07 ± 3.48	$p < .01$ $d = -.94$
P3 Latency (ms)	358.93 ± 36.01	362.27 ± 58.32	$p = .80$ $d = -.07$
P3 Amplitude (μV)	12.22 ± 5.01	8.13 ± 3.86	$p = .001$ $d = 1.13$

Table 7. Means and standard deviations of the Flanker task congruent and incongruent N2 (at site Fz) and P3 (at site Cz) amplitudes and latencies of the healthy control (HC) group (N=15).

	Incongruent	Congruent	Paired Samples t-test
N2 Latency (ms)	133.07 ± 23.24	141.33 ± 29.97	$p = .26$ $d = -.30$
N2 Amplitude (μV)	-.04 ± 2.82	.08 ± 2.84	$p = .74$ $d = -.09$
P3 Latency (ms)	375.07 ± 45.37	348.80 ± 61.36	$p = .08$ $d = .49$
P3 Amplitude (μV)	9.40 ± 5.50	5.62 ± 3.90	$p < .01$ $d = .93$

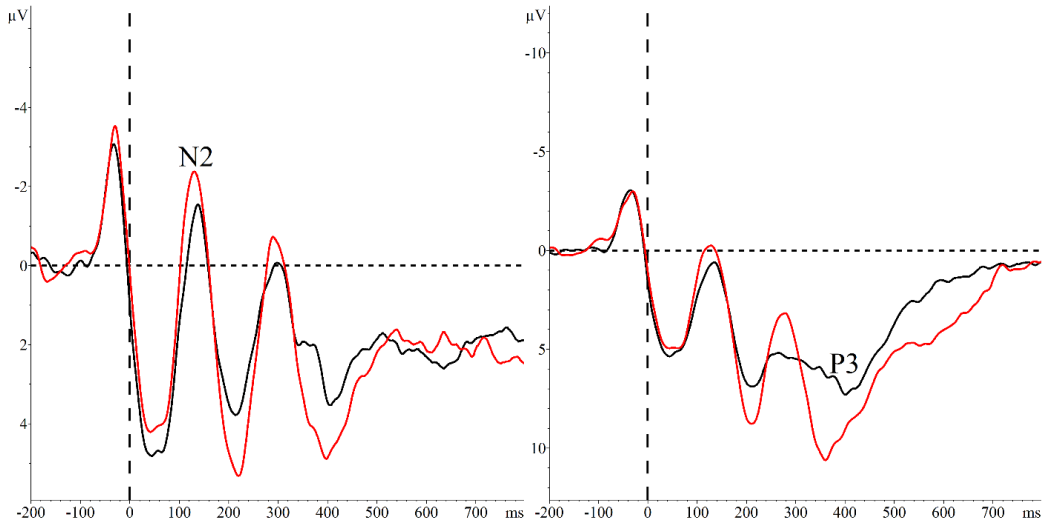

Figure 10. The N2 (left) and P3 (right) event-related potentials (ERP) to the congruent (black) and incongruent (red) conditions of the flanker task in the depressed (DEP) group.

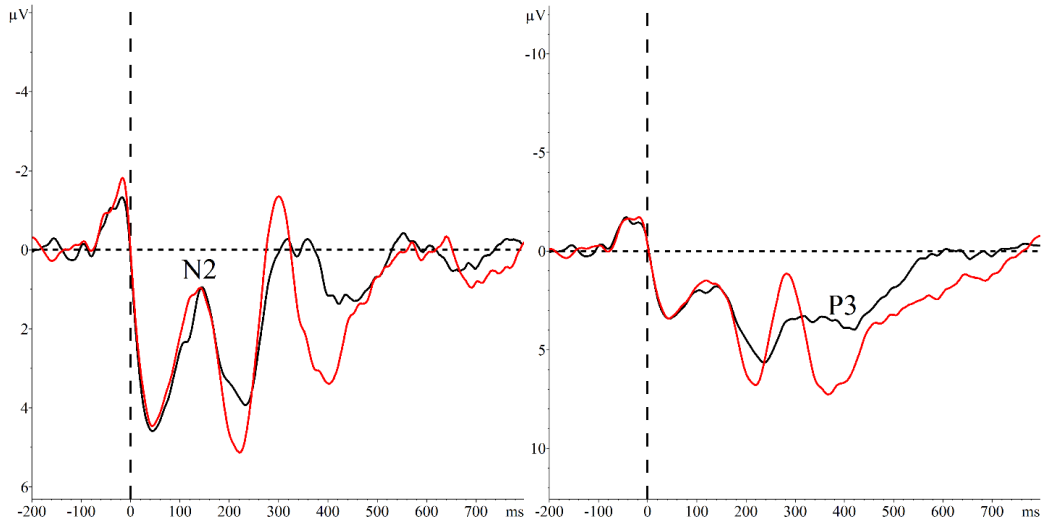

Figure 11. The N2 (left) and P3 (right) event-related potentials (ERP) to the congruent (black) and incongruent (red) conditions of the flanker task in the healthy control (HC) group.

A one-way ANOVA was used to examine group differences between amplitudes and latencies of the incongruent and congruent N2 and P3 ERPs from the ERP Flanker task; amplitudes and latencies are presented in **Table 8**. A significant difference was found between DEP and HC incongruent N2 amplitudes ($F(1, 28) = 9.54$, $p = .004$, $\eta^2 = .254$), wherein the DEP group had a *more negative* amplitude than the HC group (**Figure 12**). No other statistically

significant results were found. Exploratory ANCOVA results examining depression scores as a covariate are provided in **Appendix IX**. After correcting for depression, no group differences were found for the incongruent N2 amplitude.

Table 8. P3 (at site Cz) and N2 (at site Fz) measures during ERP Flanker task in healthy controls and depressed groups (mean ± standard deviation).

	Healthy Controls (HC) N = 15	Depressed (DEP) N = 15	ANOVA
Flanker Congruent N2 Latency (ms)	141.33 ± 29.97	138.80 ± 18.80	$p = .78$ $\eta^2 = .003$
Flanker Congruent N2 Amplitude (μV)	0.08 ± 2.84	-2.07 ± 3.48	$p = .074$ $\eta^2 = .110$
Flanker Incongruent N2 Latency (ms)	133.07 ± 23.24	132.13 ± 16.31	$p = .90$ $\eta^2 = .001$
Flanker Incongruent N2 Amplitude (μV)	-.04 ± 2.82	-3.18 ± 2.74	$p = .004$** $\eta^2 = .254$
Flanker Congruent P3 Latency (ms)	348.80 ± 61.36	362.27 ± 58.32	$p = .54$ $\eta^2 = .013$
Flanker Congruent P3 Amplitude (μV)	5.62 ± 3.90	8.13 ± 3.86	$p = .087$ $\eta^2 = .101$
Flanker Incongruent P3 Latency (ms)	375.07 ± 45.37	358.93 ± 36.01	$p = .29$ $\eta^2 = .040$
Flanker Incongruent P3 Amplitude (μV)	9.40 ± 5.50	12.22 ± 5.01	$p = .15$ $\eta^2 = .072$

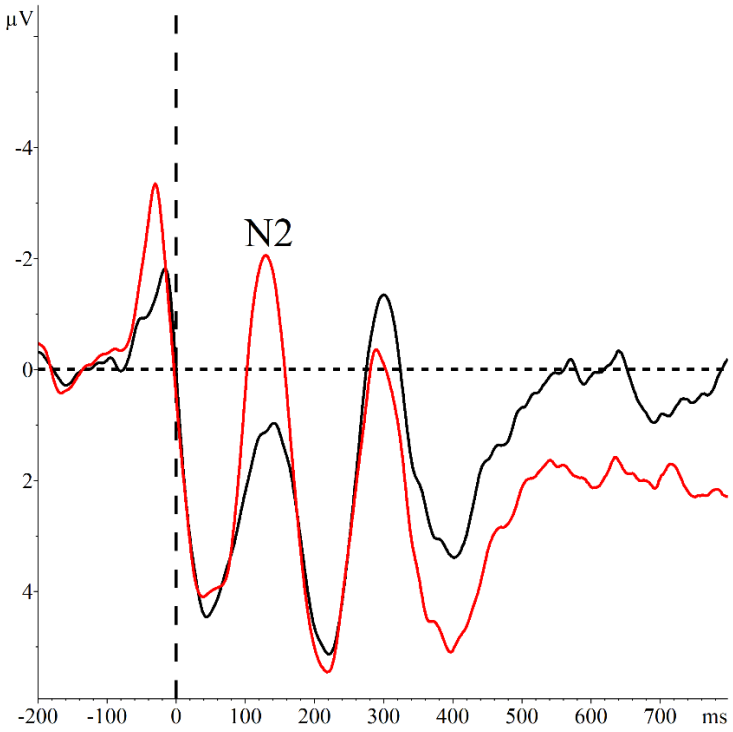

Figure 12. Flanker incongruent N2 event-related potential (ERP) at site Fz for depressed group (red) and healthy control group (black).

4.3.3 NIH Toolbox Cognition Tasks

An N=19 HC and N=18 DEP participants were included in the analysis of the NIH tasks (N=1 DEP participant was not included due to data collection delays). No parametric assumptions were violated, as such, a one-way ANOVA was used to examine group differences of fully-corrected t-scores of the NIH Flanker, NIH List Sort, and NIH Card Sort tasks. No significant differences were found (**Table 9**). Supplementary data of total NIH toolbox composite scores as well as other fluid cognition tasks not examined are presented in **Table S1 (Appendix VIII)**.

Table 9. National Institutes of Health (NIH) cognition task fully-corrected t-scores of three tasks in healthy controls and depressed groups (mean ± standard deviation).

	Healthy Controls (HC) N = 19	Depressed (DEP) N = 18	ANOVA

NIH Flanker Fully-Corrected T-Score	59.47 ± 8.49	60.94 ± 9.54	p = .62 η^2 = .007
NIH List Sort Fully-Corrected T-Score	45.53 ± 9.12	49.94 ± 10.15	p = .17 η^2 = .053
NIH Card Sort Fully-Corrected T-Score	49.58 ± 12.99	54.56 ± 10.12	p = .20 η^2 = .046

Normative scores: *M*=50, *SD*=10

4.4 Correlations

A total of N=15 DEP and N=15 HC were available for correlations with ERP Flanker features; N=4 DEP and N=4 HC were removed due to insufficient correct responses, EEG data recording errors, or because the participant did not complete the EEG portion. A total of N=14 DEP (N=5 removed for similar reasons as above) and N=19 HC participants were used for correlations with ERP Oddball features.

4.4.1 Cognition Correlations

As there were no group differences in scores on the three NIH toolbox tasks, both groups were combined for correlations. All variables were shown to be linear and homoscedastic, however, due to a violation of normality, a Spearman's correlation was used to correlate ERP Oddball and ERP Flanker ERPs to the three NIH toolbox tasks. To correct for multiple comparisons, alpha level was set to α=.01.

As hypothesized, the NIH Card Sort task performance scores were positively correlated with ERP Flanker congruent P3 amplitude (*rho*(28) = .59, p = .001; **Figure 13**) and incongruent P3 amplitude (*rho*(28) = .48, p = .009; **Figure 13**). Surprisingly, the NIH Flanker task scores were positively correlated with ERP Flanker congruent P3 latency (*rho*(28) = .53, p = .003; **Figure 14**). All correlations are presented in **Table 10**.

Table 10. Correlations between National Institutes of Health (NIH) cognition tasks and Flanker task event-related potential (ERP) measures, and Oddball task ERP measures across the whole group.

	NIH Flanker	NIH List Sort	NIH Card Sort
Flanker Congruent N2 Latency (ms)	-.016 *p* = .93 N = 29	-.250 *p* = .19 N = 29	-.22 *p* = .25 N = 29
Flanker Congruent N2 Amplitude (μV)	.112 *p* = .56 N = 29	-.222 *p* = .25 N = 29	.091 *p* = .64 N = 29
Flanker Incongruent N2 Latency (ms)	.017 *P* = .93 N = 29	-.396 *p* = .03 N = 29	.021 *p* = .92 N = 29
Flanker Incongruent N2 Amplitude (μV)	-.023 *p* = .90 N = 29	-.168 *p* = .40 N = 29	-.115 *p* = .55 N = 29
Flanker Congruent P3 Latency (ms)	.530** *p* < .01 N = 29	-.034 *p* = .86 N = 29	.297 *p* = .12 N = 29
Flanker Congruent P3 Amplitude (μV)	.330 *p* = .08 N = 29	.078 *p* = .69 N = 29	.592** *p* < .01 N = 29
Flanker Incongruent P3 Latency (ms)	.089 *p* = .65 N = 29	-.290 *p* = .13 N = 29	.087 *p* = .65 N = 29
Flanker Incongruent P3 Amplitude (μV)	.307 *p* = .11 N = 29	.234 *p* = .22 N = 29	.477** *p* = .01 N = 29
Early P3a Latency (ms)	-.293 *p* = .10 N = 32	.092 *p* = .62 N = 32	-.107 *p* = .56 N = 32
Early P3a Amplitude (μV)	.107 *p* = .56 N = 32	.134 *p* = .46 N = 32	.056 *p* = .76 N = 32
Late P3a Latency (ms)	.322 *p* = .07 N = 32	-.317 *p* = .08 N = 32	.137 *p* = .46 N = 32
Late P3a Amplitude (μV)	.258 *p* = .16 N = 32	.366 *p* = .04 N = 32	.188 *p* = .30 N = 32
Total P3a Latency (ms)	.030 *p* = .87 N = 32	.038 *p* = .84 N = 32	-.023 *p* = .90 N = 32
Total P3a Amplitude (μV)	.341 *p* = .06 N = 32	.339 *p* = .06 N = 32	.305 *p* = .09 N = 32
P3b Latency (ms)	-.339 *p* = .06 N = 32	-.263 *p* = .15 N = 32	-.270 *p* = .14 N = 32
P3b Amplitude (μV) at site Pz	.023 *p* = .90 N = 32	.033 *p* = .86 N = 32	.163 *p* = .37 N = 32

**Significant at .001 level. N2 ERPs measured at site Fz; P3/P3a ERPs measured at site Cz; P3b ERP measured at site Pz

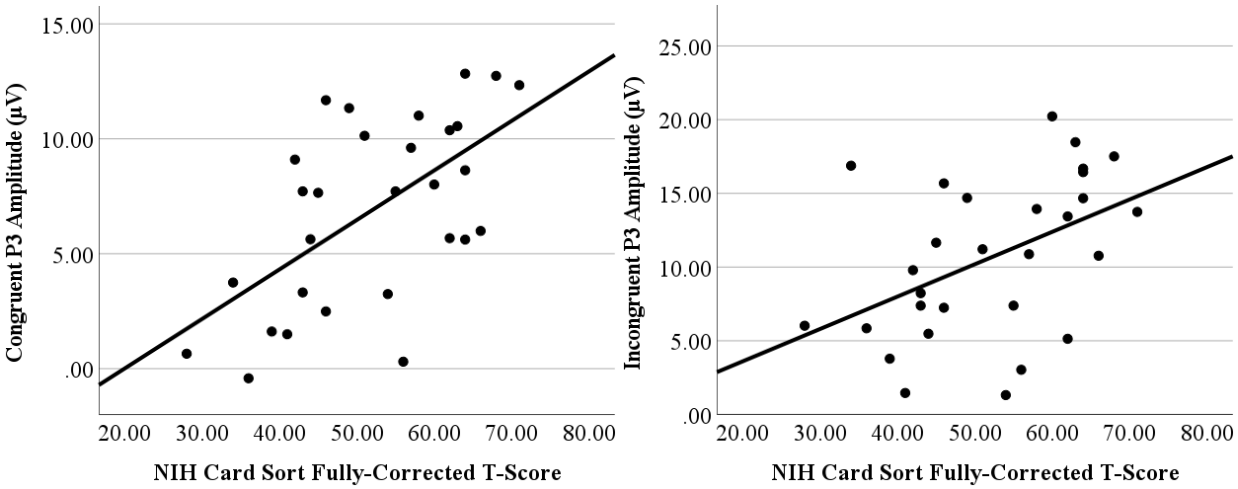

Figure 13. Scatterplots of correlations between the National Institutes of Health (NIH) Card Sort fully-corrected t-scores and P3 amplitude to the congruent condition (left, $R^2 = 0.36$) and incongruent condition (right, $R^2 = 0.22$) of the flanker task at site Cz.

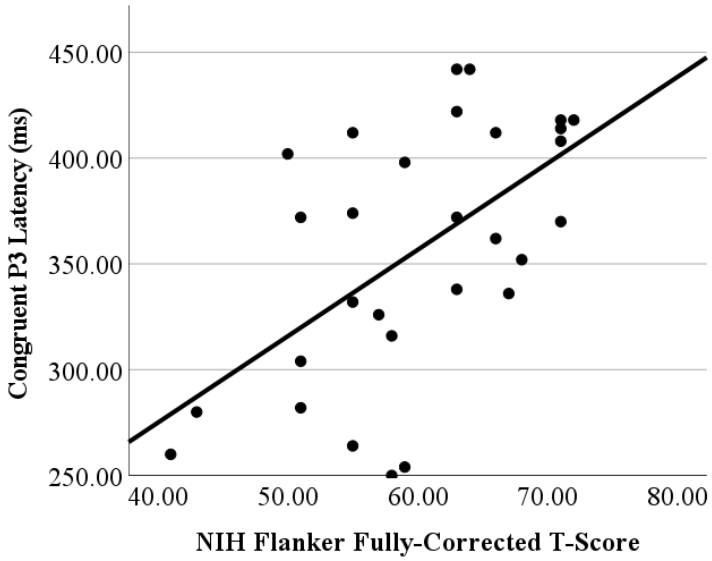

Figure 14. Scatterplot of significant correlation between National Institutes of Health (NIH) Flanker fully-corrected t-scores and P3 latency to the congruent trial of the flanker task at site Cz ($R^2 = 0.33$).

4.4.2. Clinical Correlations

Clinical correlations were conducted on the DEP group only. Due to a violation of normality and linearity, a Spearman correlation was used. To correct for multiple comparisons,

alpha level was set to α = .01. No significant correlations were found between ERPs and BDI scores (**Table 11**).

Table 11. Correlations between clinical measures of depression/anxiety and Flanker task event-related potential (ERP) measures, and Oddball task ERP measures across the depressed (DEP) group.

	BDI Scores
Flanker Congruent N2 Latency (ms) (N=15)	.12 *p* = .67
Flanker Congruent N2 Amplitude (μV) (N=15)	-.17 *p* = 55
Flanker Incongruent N2 Latency (ms) (N=15)	-.079 *p* = .80
Flanker Incongruent N2 Amplitude (μV) (N=15)	-.070 *p* = .80
Flanker Congruent P3 Latency (ms) (N=15)	.47 *p* = .08
Flanker Congruent P3 Amplitude (μV) (N=15)	.21 *p* = .46
Flanker Incongruent P3 Latency (ms) (N=15)	.14 *p* = .62
Flanker Incongruent P3 Amplitude (μV) (N=15)	-.084 *p* = .77
Early P3a Latency (ms) (N=14)	.10 *p* = .73
Early P3a Amplitude (μV) (N=14)	.19 *p* = .52
Late P3a Latency (ms) (N=14)	.32 *p* = .27
Late P3a Amplitude (μV) (N=14)	-.28 *p* = .34
Total P3a Latency (ms) (N=14)	-.25 *p* = .39
Total P3a Amplitude (μV) (N=14)	.14 *p* = .65
P3b Latency (ms) (N=14)	.25 *p* = .38
P3b Amplitude (μV) (N=14)	.20 *p* = .49

BDI-II: Beck Depression Inventory-II. N2 ERPs measured at site Fz; P3/P3a ERPs measured at site Cz; P3b ERP measured at site Pz

5. DISCUSSION

5.1 Summary

The primary aim of this study was to assess ERP-indexed neural profiles of attention, including novelty orienting, and inhibition during the auditory ERP Oddball and visual ERP Flanker tasks in depressed, unmedicated TAY vs. non-depressed TAY. The secondary aims centered on assessing cognitive impairments in TAY using three tasks that tap into similar cognitive processes as those involved in the ERP tasks. These three tasks (NIH Flanker, NIH Card Sort, and NIH List Sort) were administered using the NIH Cognition Toolbox on an iPad, a well-validated cognitive assessment battery. Exploratory aims included examining potential correlations between specific ERP Oddball (i.e., P3a/b) and ERP Flanker (i.e., N2 and P3) measures and scores on the three NIH tasks across the whole sample. Finally, correlations were explored between self-rated measures of depression, as indexed using the BDI, and ERP Oddball and ERP Flanker features within the DEP group.

In summary, for the ERP Oddball task, the DEP group showed a significantly shorter eP3a latency to novel stimuli than HCs. For the ERP Flanker task, group differences existed for the incongruent N2 amplitude wherein the DEP group had a more negative/more pronounced amplitude. No differences were found between groups for the NIH Flanker, NIH Card Sort, and NIH List Sort tasks. Correlations with the NIH tasks and the ERP tasks revealed positive correlations between the NIH Card Sort task composite score with the ERP Flanker task P3 amplitudes to both congruent and incongruent trials. Additionally, there was a positive correlation between the NIH Flanker score and P3 latency to congruent trials in the ERP Flanker

task. Finally, no correlations were found between ERP Oddball and ERP Flanker features and the BDI in the DEP group. Overall, these results suggest that the DEP group displayed faster novelty violation detection (or novelty orienting) and increased cortical resource allocation to inhibiting responses to incongruent flankers than the HC group.

5.1.1 Participants and Performance

The HC and DEP groups were, by design, well-matched on demographic features such as age, sex, and years of education. Expectedly, the DEP group displayed significantly higher scores of self- and clinician-rated depression symptoms, and higher scores of self-rated anxiety. The latter is also expected as comorbid anxiety was not exclusionary and is common in the context of depression (Axelson & Birmaher, 2001; Fava et al., 2000; Hranov, 2007). As hypothesized, there was no difference in ERP Oddball and ERP Flanker task performance (i.e., accuracy and RT) between groups, with the two groups having comparable RT and number of correct responses. This is consistent with previous studies examining the Flanker (Alderman et al., 2015; Chiu & Deldin, 2007; Clawson et al., 2013; Ruchsow et al., 2008) and Oddball (Bruder et al., 2012; Feldmann et al., 2018; Greimel et al., 2015; Zhou et al., 2019) tasks in depressed adult and TAY populations. This is likely due to the ceiling effects seen in simple cognitive tasks such as the ERP Oddball and ERP Flanker tasks resulting from the young age of the cohort, as well as mild-to-moderate levels of depression in the DEP group. While outside the scope of this thesis due to time restraints, there is the potential to examine other indices of performance that may be more sensitive to deficits, such as speed-accuracy trade-off or variabilities in reaction time, as they could provide a window into putative differences in performance in MDD.

5.2 Primary Aims

5.2.1 DEP vs HC Oddball P3a/P3b ERPs

Interestingly, for the ERP Oddball task ERPs, we noted group differences that were opposite to what was hypothesized and previously found in other studies. Specifically, the DEP group showed a significantly shorter eP3a latency than HCs, suggesting that, at least at the cortical level, the DEP group's automatic detection of environmental violations by novel sounds is faster than that of the HC group. This is, to an extent, inconsistent with findings in previous studies examining the oddball's P3 latency in depressed TAY (Feldmann et al., 2018; lv et al., 2010) and adult (Kemp et al., 2010; Nan et al., 2018; Urretavizcaya et al., 2003; Zhou et al., 2019) populations, wherein longer P3 latencies were found in depressed versus healthy groups. While other research found no difference in P3 latencies of depressed and healthy youth (Greimel et al., 2015; Houston et al., 2004), none of the examined studies found the depressed youth had shorted P3 latencies. However, it is important to note, that these above-mentioned studies examined the P3 ERP as a whole and did not examine the P3a ERP subcomponent independent of the P3b (i.e., most did not use the novel oddball task). Further, none of the studies assessed the eP3a and lP3a ERP subcomponents, thus, direct comparisons with existing literature in depressed populations are not feasible.

It is possible that some of the mixed results concerning the P3a in previous research in the context of depression may result from the fact that the P3a is rarely subdivided into subcomponents (Bruder et al., 2002, 2009, 2012; Pierson et al., 1996). As discussed earlier, the P3a ERP can be subdivided into the eP3a: thought to reflect the automatic detection of violation by novel stimuli (and *not* novelty orienting); and the lP3a: thought to reflect attentional

orientation towards non-target, novel stimuli (Escera et al., 1998, 2001). The neural generators of the P3a tend to be the prefrontal cortex, anterior cingulate cortex (ACC), and the hippocampus (Bruder et al., 2012; Jaworska & Protzner, 2013; Volpe et al., 2007) and it typically has a maximum amplitude at frontocentral scalp sites (Jaworska & Protzner, 2013). The scalp localizations of the P3a are split amongst the eP3a and lP3a; with the eP3a maximal at central sites, and the lP3a maximal at frontal sites (Escera et al., 1998). By examining these subcomponents, researchers can more precisely pinpoint the cognitive processes affected by depression. Thus, future work assessing putative cognitive dysfunction in depression should subdivide the P3a into the eP3a and lP3a in order to facilitate a better understanding of the neural processes underlying cognition, and how they are affected by depression and its associated comorbidities.

However, some research examining comorbid anxiety may better explain the results found in this work. For instance, Pierson et al. (1996) divided depressed patients into subgroups of anxious-agitated-impulsive patients and blunted affect participants during a simple forewarned reaction-time task and found that the anxious vs. blunted affect group showed *greater* P3a amplitudes to information processing paradigms. Given that our group of depressed individuals also exhibited high anxiety scores, it is feasible that anxiety may play a role in explaining our results. It is feasible that novelty orienting may be more "primed" or faster in those with higher anxiety (perhaps due to a higher vigilance state). Another group found that depressed patients with a comorbid anxiety disorder were found to have a smaller early P3 (comparable to the P3a; (Bruder et al., 2012) than healthy controls, while those with depressive disorder alone did not; further, those with anxiety disorder only showed a larger early P3 subcomponent amplitude

compared to healthy controls (Bruder et al., 2002). These results again suggest that anxiety may influence the P3a ERP features. Similar results have also been reported in post-traumatic stress disorder (PTSD), wherein veterans with PTSD showed more positive amplitudes of the early P3 ERP during a novelty oddball task than veterans without PTSD (Butt et al., 2019; Kimble et al., 2000), again suggesting a hypervigilant state to novelty. While results are mixed, overall, these studies suggest that comorbid anxiety might play a key role in the P3a ERP, and by extension potentially in the eP3a and lP3a. In this work, self-reported Beck Anxiety Inventory (BAI; Beck & Steer, 1993), were obtained; their inclusion as an exploratory covariate in the P3a latency analyses did fundamentally change the outcomes (**Appendix IX**).

5.2.2. DEP vs HC Flanker N2/P3 ERPs

For the ERP Flanker task, group differences were found for the incongruent N2 amplitude wherein the DEP group had a significantly more negative amplitude, suggesting the DEP group used more neuronal resources, perhaps indexing more inhibitory process engagement to incongruent stimuli than the HC group. This is inconsistent with previous literature in TAY and young adults wherein depressed individuals usually show blunted N2 amplitudes (Alderman et al., 2015; Bruder et al., 2012; Clawson et al., 2013). The smaller N2 amplitude in the HC group may be due to the task being too easy for healthy controls (i.e., requiring very limited neural resources), and not strongly eliciting the conflict that is believed to be reflected by the N2. This might also be due to personality differences between the HC and DEP groups: depression is often associated with neuroticism (Aldinger et al., 2014; Jeronimus et al., 2016; Klein et al., 2011), a trait that might be associated with DEP participants feeling more pressure to perform well during the task, resulting in significantly larger ERPs as a result of increased attentional

resources and inhibition of incorrect responses. It is also feasible that the HC group was less motivated than the DEP group to perform the task well since they did not get any intrinsic value from participating in the study. However, this is speculative, and future comparable work may choose to assess the moderating effect of specific personality traits on such measures.

Further, the DEP group was recruited as a part of a larger study involving a 12-week exercise intervention. This may result in a group of DEP participants that are more motivated than a typical depression cohort in seeking help to improve their depressive symptoms. In other words, motivation (along with the above-mentioned personality differences) could account for the group differences; granted, this is speculative. Second, there is generally an inverse relationship between depression symptom severity and N2 impairments; wherein more severe depression tends to be correlated with lower N2 amplitudes (reflecting perhaps poorer early-state neural responses of inhibition). Given that the DEP group was screened for acute suicidal behaviour (a symptom of more severe depression), and were required to not be on any antidepressant medication, the DEP group averaged mild-moderate levels of depression severity. Thus, our hypotheses were formed based on previous literature on more severely depressed cohorts, and might not necessarily be valid for a younger cohort with milder forms of depression. Finally, it is also feasible that the HCs were neuronally more "efficient" and thus did not need to devote as much cortical resources to processing the incongruent trials as the DEP group, resulting in a lower N2 amplitude.

These unexpected results in the ERP Oddball and ERP Flanker may be due to the sample size being smaller than the required sample size as calculated using our *a priori* power analyses (N = 23 ERP Oddball; N = 25 ERP Flanker). Further, the young age of participants may mean

that participants in the DEP group may be experiencing one of their first episodes of depression, and may not be suffering from compounded cognitive (and associated neural cognitive feature) impairments that might result from repeated depressive episodes. As such, this may not result in pronounced cognitive deficits or associated ERP modifications. As mentioned above, the hypotheses could also have been formed based on previous literature of more severely depressed cohorts, which may not translate to a less depressed, younger cohort with fewer episodes of depression. However, results of a supplementary ANCOVA revealed that group differences disappeared after controlling for depression scores (BDI), suggesting that depression does have a role in the DEP group's ERP features.

5.3 Secondary Aims

The secondary aims of this study involved examining differences between the DEP and HC group on fully-corrected t-scores of the NIH Flanker, NIH Card Sort, and NIH List Sort tasks. We found no differences between the groups on all three scores. This was not expected given previous research noting differences between depressed and non-depressed cohorts on similar cognitive tasks. For example, several studies using the Wisconsin Card Sort task (Grant & Berg, 1948) have found that depressed adults perform worse/score lower than healthy controls (Channon, 1996; Ilonen et al., 2000; Merriam et al., 1999). Comparable to the working memory features of the NIH List Sort, research has reported deficits in performance during the Sternberg working memory task (Pelosi et al., 2000), the N-back working-memory task (See Nikolin et al., 2021 for meta-analysis), and most applicably, the verbal episodic memory tasks (Fossati et al., 2004; Hammar & Årdal, 2013). Granted, most of these studies have been carried out in adults. Finally, as previously mentioned, research on the Flanker task in depressed populations has

noted mixed results, with some studies finding slower reaction times compared to healthy controls (Bange & Bathien, 1998; Dillon et al., 2015; Santopetro et al., 2020); and others finding no difference in reaction time or accuracy (Chiu & Deldin, 2007; Clawson et al., 2013; Ruchsow et al., 2008).

While well-validated and often used in adults (Weintraub et al., 2013, 2014; Zelazo et al., 2014) the NIH Flanker is based on the original flanker task by Eriksen & Eriksen (1974), which is often considered a fairly simple task in those without cognitive or neurological impairments. This may result in the fairly simple task proving to not be particularly challenging for TAY (being ages 16-24yr), creating ceiling effects similar to those observed in the behavioural outcomes of the ERP Flanker task. This is supported by the finding that both the MDD (M = 60.94 ± 9.54) and HC (M = 59.47 ± 8.49) groups scored, on average, a full deviation above the normative score of the NIH Flanker task (M = 50 ± 10). While the results of the current study do not support those found by Kavanaugh et al. (2020), this might be due to the fact that their group examined a younger cohort for whom the tasks may have been more challenging. Indeed, fluid cognitive abilities peak at around 20 years of age and steadily decline throughout adulthood (Murman, 2015); as such, the group we examined was squarely within this optimal cognitive functioning age range.

5.4 Exploratory Aims

For the correlations with the NIH tasks, results were mixed. As hypothesized, the NIH Card Sort task correlated positively with the ERP Flanker congruent and incongruent P3 amplitudes. This was expected as the NIH Card Sort task, similarly to the Flanker P3 ERP, taps into stimulus evaluation processes. Thus, as more cortical resources are devoted to the execution

of the ERP Flanker task, as reflected through increased P3 amplitudes, performance on the NIH Card Sort task also increased. This is in line with previous research, wherein better task performance (which would result in a higher score on the NIH tasks) was correlated with larger P3 amplitudes (Amin et al., 2015; Saliasi et al., 2013). Interestingly, the ERP Flanker's congruent P3 also showed a strong correlation with NIH Card Sort scores. This was unexpected, as the incongruent P3 has been shown to have higher amplitudes and thereby require more cortical resources than the congruent P3 (Alderman et al., 2015; Downes et al., 2017; Kopp et al., 1996; Larson et al., 2014; Ligeza et al., 2018; Purmann et al., 2011). However, a possible explanation is due to performance motivation: participants who score higher on the NIH Card Sort may be more motivated to perform all tasks well, and thus may have also shown increased attention and increased cortical resource allocation to even congruent trials of the ERP Flanker task.

Opposite to what was hypothesized, the NIH Flanker task composite scores (i.e., reflecting better task performance) correlated positively with P3 latency to congruent stimuli on the ERP Flanker task. In other words, better performance was associated with longer attentional processing, at least from a neuronal perspective. While RT is included as a variable in the calculation of the NIH Flanker score, the primary factor is accuracy; therefore, the correlation with congruent P3 latencies may be due to increased stimulus evaluation that results in higher response accuracy (Amin et al., 2015; Saliasi et al., 2013). No correlations were found with the NIH List Sort task performance, which was expected to correlate positively with the P3b amplitude and negatively with the P3b latency of the ERP Oddball task, due to parallel processes of working memory and stimulus evaluation in both tasks. This may be due to the ERP Oddball

task having substantially easier working memory requirements than the NIH List Sort, as the NIH List Sort has been validated against more cognitively challenging tasks such as the Wechsler Adult Intelligence Scale (WAIS-IV) Letter Number Sequence, the Paced Auditory Serial Addition Test (PASAT) and the Delis-Kaplan Executive Function System (D-KEFS); rather than an auditory oddball task (Tulsky et al., 2014).

Finally, no correlations were found between ERP measures and clinical scores of the DEP group, which again may be a result of the analysis being underpowered, unexplored personality factors, the DEP group not being comprised of a group of individuals characterized by mild-moderate depression severity, and/or the young age of participants. The younger age reflects the fact that the DEP group may not be suffering from the cognitive impairments that result from repeated depressive episodes, and the potential interaction with increased age.

5.5 Limitations

As previously mentioned, this study faced a strong limitation in sample size due to a prolonged suspension of recruitment during the COVID-19 pandemic, resulting in underpowered analyses. The *a priori* power analyses revealed that an N=23 for the ERP Oddball and N=25 for the ERP Flanker tasks were needed, however, these numbers were unattainable due to a more than yearlong interruption in recruitment. Within the sample itself, the groups were not normally distributed and were not necessarily well-representative of the broader depressed population. After all, on average, the DEP group was characterized by low-to-moderate depression severity and excluded TAY with high suicidality and those who were currently on antidepressant medications. As such, although the sample was relatively homogenous, and still suffering from MDD, it is somewhat limited in its generalizability. Further, both groups were unbalanced in the

sexes of the participants; while both groups were matched to each other, they both had substantially more female participants than males. As such, sex or gender could not be explored as meaningful variables in the context of this work. Ideally, future work would be able to tap into this. Further, salient personality features (such as neuroticism) were also not controlled for in our analyses, such as in correlations between clinical scores and ERP measures of the DEP group due to limited power. It is recommended that this should be explored in future comparable work as this may have explanatory effects on the outcomes. Finally, potential outliers in clinical and cognitive scores, as well as ERP features were not removed due to the small sample size. While nonparametric tests can partially protect against outliers, there is the possibility that outliers may have skewed the results.

5.6 Conclusions and Future Directions

One of the most novel aspects of this work was assessing the lP3a and eP3a. Given our findings of group differences in the eP3a, future studies would benefit from further examining these P3a subcomponents in depressed individuals. The examination of novelty orienting in depression is greatly understudied in all populations, not just in youth or depressed youth populations. The P3b ERP has been widely researched as a potential marker of depression prognosis (Klawohn et al., 2020; lv et al., 2010; Santopetro et al., 2020, 2021; Urretavizcaya et al., 2003; Zhou et al., 2018, 2019). The P3a may prove to be just as reliable of a biomarker as the P3b if not more so (Bruder et al., 2002, 2009, 2012; Jaworska et al., 2013; Pierson et al., 1996). Indeed, it is possible that the P3a, in conjunction with the P3b, might be the most useful markers of depression illness prognosis; this should be feasible given that they are typically obtained in the same task. This may provide great clinical benefit, as ERP research has shown relations

between ERPs feature and depression symptom severity (Bruder et al., 2012). Further, research on youth with depression should focus on pinpointing differences in the youth population versus that of the adult population, including differences in reactions to various types of treatment for depression. This would enhance our understanding of depression in TAY (and how it overlaps and contrasts with depressed adults), which, in turn, could help reduce the deficits and associated negative consequences of depression in young people. Finally, future research should examine the effects of anxiety on the P3 ERP, as it is frequently comorbid with depression (Bruder et al., 2002, 2012; Butt et al., 2019; Kimble et al., 2000; Pierson et al., 1996). Previous work suggests that comorbid anxiety and depression might have unique effects on brain features (Auerbach et al., 2021; Jaworska et al., 2016); assessing the P3a/b may shed further light on this.

In conclusion, this study failed to replicate previous reports of reduced ERP amplitudes and increased latencies of ERPs (N2, P3) on the Oddball and Flanker tasks in a depressed population. Instead, we surprisingly found more negative ERP Flanker N2 amplitudes and shortened ERP Oddball eP3a latencies in the DEP group compared to the HC group. Importantly, this study provided novel electrophysiological information about the eP3a and lP3a in youth with depression, and the potential effects of depression on related cognitive processes. Finally, this study found correlations between performance on tasks from the NIH Cognition Toolbox and ERP features derived from tasks that tap into similar cognitive processes as those in the NIH Toolbox.

ERPs give us insight into the neural underpinnings of the disorder in a cost-effective, non-invasive manner, and give temporally detailed information in a way other measures, such as fMRI, cannot (i.e., processes like the N2/P3 typically occur on a temporal scale that is <600ms,

which is far superior to the temporal resolution of fMRI). This research, in particular, is relatively novel as it examined P3 subcomponents (P3a and P3b), as well as the P3a subcomponents, namely the eP3a and lP3a, which have never before been assessed in the context of depression, to our knowledge. Assessing these ERPs can give us a more granular understanding of the cognitive disturbances associated with depression, such as alterations in working memory, inhibitory processes, and attentional orienting and evaluation processes. Additionally, this research may be beneficial in highlighting key differences between depression in adults and TAY, furthering the clinical applications of exploring potential treatments that may help (or hinder) clinical outcomes in different age groups. Given the urgent need to better understand how depression affects youth, and the limited research on the subcomponents of the P3 ERP in this population, the findings of this work are an important contribution to research in this domain.

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APPENDIX I

SCREENING SCRIPT – MDDEXY Study
PATIENT VERSION

Date of screening: _____

The following information may have been obtained before the screen (e.g. from e-mail or phone msg.)

Name: _____ Sex: M or F
Age & DOB: _____ (Must be **16-24 yr**)
Employment: _____
Highest Level of Education:_____
Height: _____ Weight: _____ **Exclude if BMI >40kg/m²** Handedness: L R BOTH
Telephone:_____
Email:_____
How did you hear about this study?:_____

The following is intended as a guide. You do not need to read it word-for-word.
Hello (INSERT INDIVIDUAL'S NAME)
My name is (FIRST NAME) and I am a(n) (POSITION) from the Clinical EEG Lab at the Royal Ottawa Hospital. I am calling about our study on the effects of exercise on symptoms of depression, which you had expressed an interest in participating in.

OR

Thank you for calling us to find out more about our research.

Do you have a moment so that I can explain the study to you?

The purpose of our study is to examine if moderate or intense exercise is an effective treatment in depressed youth, and if so, if one provides a greater benefit than the other. We'd also like to better understand the changes that occur in the brain as a result of aerobic exercise – also known as cardio exercise.

Participants will be randomized into either a moderate or high intensity exercise group in which they will be required to attend a guided cardio-based session at the hospital 3 times per week for a total of 12 consecutive weeks. Each session will last ~45 min.

We will also ask you to come in for three additional visits before beginning the exercise program so that we can perform several assessments.

During the first visit, you would meet with a clinician or researcher and carry out a psychiatric interview, self-report questionnaires, and undergo a baseline physical fitness assessment. This visit is expected to last ~3hrs.

Within 1 week of this visit, you will return 2 more times so that we can measure your brain activity and structure using two common, non-invasive methods.

The first is called EEG – it involves placing sensors on your head to measure brain electrical activity. You will be asked to complete a few computerized tasks while connected to the EEG. This will last ~1.5 hr.

On a separate day, we will also measure your brain structure and function using magnetic resonance imaging (MRI). You will be asked to complete a few computerized tasks similar to the EEG session while inside the MRI machine. This visit will last ~ 2 hr.

All of these visits will be repeated at the end of the 12 week exercise program. You will also be asked to come for another brief visit after the half-way point, at week 6, to again meet with a researcher or clinician, and repeat a few questionnaires.

All testing will be carried out at the Royal Ottawa Hospital on Carling Avenue. Your data will be kept private and confidential, and you have the right to withdraw from the study without penalty at any time. Lastly, you will be paid up to a maximum total of $210 CDN for your time and effort according to the number of experimental sessions attended.

Are you still interested in participating in this study and continuing with the screen?
[IF NO]: Thank you very much for your time.

[IF YES – still interested]:
Are you currently participating in any other studies involving exercise?
[IF YES]: Thank you for your time.

[If NO]: Is this a good time to do the phone screen – it may take ~15-30 minutes?
[IF NO]: Set up a time to call back:

Date: _____ Time: _____

[IF YES]: "Before having you come into the lab, we need to ask you some questions to determine if you are eligible for the study. It is possible that some of these questions may make you feel uncomfortable or distressed. If this happens, let me know, and we can stop this screen, or take a break. You also have the right to refuse to answer any questions. Any information collected during this call will be kept confidential, and will be destroyed if you do not qualify for the study or choose not to participate. If you qualify, this information will be kept in a safe place.Do I have your consent to proceed?"
YES NO

[IF NO]: Thank you very much for your time.
[IF YES]: Can you confirm your age for me? _____ **(16-24 years of age for inclusion)**

Before we begin, do you consent to allowing us to keep your contact information on file for the purpose of contacting you for potential future studies you may qualify for? This does not mean you are consenting to participating in these studies.
YES NO

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1. GENERAL MEDICAL

"I am going to start by asking you a series of questions about your medical history and physical health."

First I wanted to ask you, do you have a family doctor?
YES NO
[IF YES]: Who? _____

Do you consent that we communicate your involvement in this study to your doctor, for the purposes of safety monitoring?
YES NO
[IF YES]: Contact information?_____

Have you been diagnosed with or are you currently being treated for any major medical problems?

YES NO
[IF YES]: Which ones? _____

Do you have a history of any neurological or neuromuscular problems? (e.g. stroke, epilepsy, brain cysts, migraines, MS).
YES NO
[IF YES]: Which ones? _____

Have you ever had a concussion?
YES NO
[IF YES]: Did you lose consciousness? How long? ***Exclude if >5 min**_____

Have you ever been diagnosed with a development problem? (e.g. autism)
YES NO
[IF YES]: Which ones? _____

Have you ever been diagnosed with or struggled with major learning disabilities? (e.g. severe reading problems, dyslexia)
YES NO
[IF YES]: Which ones? _____

Do you currently use any nicotine products, including cigarettes/cigars, e-cigarettes/vaporizers, chewing tobacco, gum, etc.?
YES NO
[IF YES]: Which ones? How often? _____ (Cannot be a **current** daily smoker: ≥1 full cigarette/week)

[FEMALE PARTICIPANTS]
Are you currently pregnant and/or breastfeeding? Y / N
[IF YES]: EXCLUDE

Are you currently using any of oral contraceptive or intrauterine device? Y / N
[IF YES]: Which kind / brand? _____
Participant may be excluded if they have a metal IUD; ask the brand name and verify whether MRI compatible.

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2. PHYSICAL ACTIVITY

Do you have any physical limitations that might impair your ability to engage in exercise using equipment such as treadmills, stationary bikes, elliptical machines, etc?
[IF YES]: Describe: _____

How many times per week, on average, do you engage in moderate or vigorous physical activity? This would include any activity which causes a big increase in your breathing or heart rate?
Frequency: _____ time(s)/week
Duration: _____

***Participant must be relatively inactive (1x / week, max 1hr is ideal). Use discretion, and verify if unsure.**

"Since participation in this study will require doing cardio exercise 3X/week, I'd like to gather a few more details just to make sure there are no health risks to your involvement":

Physical Activity Readiness Questionnaire (PAR-Q+)

1. Has your doctor ever said that you have a heart condition or high blood pressure? Y N
2. Do you feel pain in your chest at rest, during your daily activities of living, OR when you do physical activity? Y N
3. Do you lose balance because of dizziness OR have you lost consciousness in the last 12 months? Y N
4. Have you ever been diagnosed with a chronic medical condition (other than heart disease or high BP)? Y N

If Y, list condition(s): _____

5. Are you currently taking prescribed medication for a chronic medical condition? Y N

If Y, list condition/med(s): _____

6. Do you currently have (or have you had within the last 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Y N

If Y, list condition(s): _____

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

If participant answers NO to all of the above, they are cleared for physical activity.

If participant answers YES to questions, they must complete PARmed-X+ with study physician for final determination.

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3. FURTHER MEDICAL – STUDY COMPATIBILITY - NEUROIMAGING

Do you have any issues with back pain?
YES NO
[IF YES]: Would this impede you from sitting up straight or lying still for prolonged periods of time? _____

Have you ever had an EEG or previously participated in an EEG study?
YES NO
[IF YES]: What for/when? _____

Have you ever had an MRI or participated in an MRI study?
YES NO
[IF YES]: What for/when? _____

Are you uncomfortable in enclosed spaces?
YES NO
[IF YES]: Details/would MRI be problematic? _____

Do you have any metal in your body? (e.g. pacemakers, surgical/aneurysm clips, prosthetic valves, metal plates/screws, pins, cochlear implants, braces, etc.?)
YES NO
[IF YES]: What for/when? _____

Have you ever worked with metal (ie. filing, grinding, welding) or had any metal fragments in the eye?
YES NO
[IF YES]: Details: _____

Do you wear eyeglasses/contacts?
YES NO

[IF YES]: Inquire about whether they can wear their contact lenses to testing
[IF NO]: Inquire about glasses prescription (we have MR-compatible glasses: Left eye:_____ Right eye_____

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4. MENTAL HEALTH SECTION

Questions adapted from the Structured Clinical Interview for DSM-5 (SCID).

***Exclude patients with if any disorders other than MDD (co-morbid anxiety disorders are OK).**

"I am now going to ask you some questions about your mental health".

The following two questions can be asked as a rapid determinant of exclusion - ie. prior treatment for schizophrenia, undergoing substance abuse treatment, etc. Use discretion and complete the subsequent questions if unsure.

- Have you ever sought treatment or been treated for emotional or psychiatric problems? NO YES

If YES: What for? Treatment?_____ _____

- Have you ever sought treatment or been treated for drug or alcohol abuse? NO YES

If YES, details: _____

- Have you ever been hospitalized or visited the emergency room for emotional or psychiatric problems? NO YES

If YES: What for? Length? Location?_____

MOOD EPISODES

Depressive

- Has there been a period of time when you were feeling depressed or down most of the day nearly, every day?
  NO YES: _____
- …what about losing interest or pleasure in things you usually enjoy?
  NO YES: _____

(Skip the following if NO)
If YES: How long did this period last? _____
If YES: When was the most recent time you felt this way? _____ **Must be currently experiencing MDD**
_____
If YES: Just before this began were you: Physically ill? Drinking alcohol or using street drugs? Did this begin soon after someone close to you died?
NO YES: _____

DEPRESSION – STUDY SPECIFIC

Have you ever been diagnosed with major depressive disorder (MDD)/depression YES NO
[IF YES]: When? _____

Have you ever taken medication for depression? YES NO
[IF YES]: Are you currently taking these medications? _____ YES NO
[IF YES]: **Exclude**

[IF NO]: When did you stop? _____

***Participant must be medication-free for >5 weeks prior to Baseline EEG/fMRI sessions. If participant has only recently stopped meds, inform them of this criterion & ask to follow-up in an appropriate amount of time (be flexible/if unsure ask).**

Are you currently or have you ever received any form of psychotherapy?
YES NO
[IF YES]: What kind? For how long / frequency etc?
_____

PERVASIVE DEPRESSIVE DISORDER

- Have you felt sad, low, or depressed most of the time (more often than not/more than 50% of the time) for the last two years?
  NO YES: _____
- Was this period interrupted by you feeling ok for 2 months or more (i.e. feeling OK more often than not/more than 50% of the time)?
  NO YES: _____

At this point administer the BDI over phone. Exclude if score is <10.

IN THE <u>PAST TWO WEEKS:</u>	
1. How frequent would you rate your sadness?	**2. How would you rate your pessimism?**
0 = I do not feel sad	0 = I am not discouraged about my future
1 = I feel sad much of the time	1 = I feel more discouraged about my future than I used to be
2 = I am sad all the time	2 = I do not expect things to work out for me
3 = I am so sad that I can't stand it	3 = I feel my future is hopeless and will only get worse
3. How would you rate past failures?	**4. How would you rate recent loss of pleasure?**
0 = I do not feel like a failure	0 = I get as much pleasure as I ever did from the things I enjoy
1 = I have failed more than I should have	1 = I don't enjoy things as much as I used to
2 = As I look back, I see a lot of failures	2 = I get very little pleasure from the things I used to enjoy
3 = I feel I am a total failure as a person	3 = I can't get any pleasure from the things I used to enjoy
5. How would you rate any guilty feelings that you have?	**6. How you would rate feelings of punishment?**
0 = I don't feel particularly guilty	0 = I don't feel like I am being punished
1 = I feel guilty over many things I have done or should have done	1 = I feel I may be punished
2 = I feel quite guilty most of the time	2 = I expect to be punished
3 = I feel guilty all of the time	3 = I feel I am being punished
7. How would you rate your feelings of self-dislike?	**8. How critical do you find you are of yourself?**
0 = I feel the same about myself as ever	0 = I don't criticize or blame myself more than usual
1 = I have lost confidence in myself	1 = I am more critical of myself than I used to be
2 = I am disappointed in myself	2 = I criticize myself for all of my faults
3 = I dislike myself	3 = I blame myself for everything bad that happens
9. How would you rate suicidal thoughts or wishes?	**10. How would you rate recent crying?**
0= I don't any have any thoughts of killing myself	0 =I don't cry any more than I used to
1 = I have thoughts of killing myself, but I would not carry them out	1 = I cry more than I used to
2 = I would like to kill myself	2 = I cry over every little thing
3 = I would kill myself if I had the chance	3 = I feel like crying, but I can't

11. How would you rate your agitation? 0 = I am no more restless or wound up than usual 1 = I feel more restless or wound up than usual 2 = I am so restless or agitated that it's hard to stay still 3 = I am so restless/agitated that I have to keep moving/doing something **13. How would you rate loss of interest?** 0 = I have not lost interest in other people or activities 1 = I am less interested in other people or things than before 2 = I have lost most of my interest in other people or things 3 = It's hard to get interested in anything **15. How would rate your indecisiveness?** 0 = I make decisions about as well as ever 1 = I find it more difficult to make decisions than usual 2 = I have much greater difficulty in making decisions than I used to 3 = I have trouble making any decisions **17. How would you rate your feelings of worthlessness?** 0 = I do not feel I am worthless 1 = I don't consider myself as worthwhile and useful as I used to 2 = I feel more worthless as compared to other people 3 = I feel utterly worthless **19. How would you rate loss of energy?** 0= I have as much energy as ever 1 = I have less energy than I used to have 2 = I don't have enough energy to do very much 3 = I don't have enough energy to do anything **21. How would you rate recent changes in your sleeping pattern?** 0= I have not experienced any change in my sleeping pattern 1a = I sleep somewhat more than usual 1b = I sleep somewhat less than usual 2a = I sleep a lot more than usual 2b = I sleep a lot less than usual 3a = I sleep most of the day 3b = I wake up 1-2 hours early and can't get back to sleep **SUM (total of all scores)**_____	**12. How would you rate your irritability?** 0 = I am no more irritable than usual 1 = I am more irritable than usual 2 = I am much more irritable than usual 3 = I am irritable all the time **14. How would you rate recent changes in appetite?** 0 = I have not experienced any change in my appetite 1a = My appetite is somewhat less than usual 1b = My appetite is somewhat greater than usual 2a = My appetite is much less than before 2b = My appetite is much greater than usual 3a = I have no appetite at all 3b = I crave food all the time **16. How would you rate your concentration?** 0 = I can concentrate as well as ever 1 = I can't concentrate as well as usual 2 = It's hard to keep my mind on anything for very long 3 = I find I can't concentrate on anything **18. How tired or fatigued are you?** 0 = I am no more tired or fatigued than usual 1 = I get more tired or fatigue more easily than usual 2 = I am too tired/fatigued to do a lot of the things I used to do 3 = I am too tired /fatigued to do most of the things I used to do **20. How you rate loss of interest in sex?** 0 =I have not noticed any recent change in my interest in sex 1 = I am less interested in sex than I used to be 2 = I am much less interested in sex now 3 = I have lost interest in sex completely

Mania

Was there a period in your life when, for at least a continuous one week period:

-You were so happy/excited/energized that other people thought you were not your normal self and/or this was abnormal for you?

YES NO **[IF YES]** Details?_____

-You were extremely irritable or angry for most of the time (for at least a week)? Did you fight or argue with people outside of your family? YES NO **[IF YES]** Details?_____

[IF YES TO ABOVE] During this time:

Did you feel you had special talents or abilities? **[IF YES]** What kinds talents/abilities_____	Yes	No
Became impulsive in a way that was highly unusual for you (e.g. spent a lot of money, had sexual indiscretions)?	Yes	No
Needed significantly less sleep but did not feel tired?	Yes	No
[IF YES TO ANY OF ABOVE] Are you currently experiencing any of these feelings?	Yes	No

[IF YES] to any of above: INELIGIBLE (*please use discretion – ask about context*)

ANXIETY DISORDERS

Panic

- Have you ever had a panic attack, when you suddenly felt frightened or suddenly developed a lot of physical symptoms?

NO YES: _____

(Skip the following if NO)

If YES: Have these attacks ever come on completely out of the blue – in situations where you don't expect to be nervous or uncomfortable? NO YES: _____

If YES: Just before you began having panic attacks, were you taking any drugs, caffeine, diet pills, or any other medications? Physically ill? NO YES: _____

Suicidal & Self-Injurious Behaviour

- Have you ever committed a potentially self-injurious act with at least some wish to die as a result of the act?

NO YES: _____

If YES: Could you provide me with some details?_____

_____

- Have you ever physically hurt or mutilated your body with the purpose of intentionally hurting yourself (with *no* wish to die as a result of the act)?

NO YES:

_____

If YES: Could you provide me with some details?_____

_____

NOTE: If participant seems at **imminent** threat of committing suicide direct to emergency room and/or Crisis Line (613.722.6914)

If not at imminent threat but reasonable risk detected, suggest Crisis Line as well, and send resources document.

Agoraphobia

- Were you ever afraid of going out of the house alone, being in crowds, standing in a line or traveling on buses or trains?

NO YES: _____

(Skip the following if NO)

If YES: What were you afraid would happen? _____

Does participant mention anxiety about being in places/situations in which escape may be difficult or embarrassing or in which help may not be available in the event of panic-like symptoms?

NO YES: _____

If YES: Just before you began having these fears, were you taking any drugs, caffeine, diet pills, or any other medications? Physically ill? NO YES: _____

Social Phobia

- Is there anything that you have been afraid to do/felt uncomfortable doing in front of other people eg. speaking, eating or writing?

NO YES: _____

(Skip the following if NO)

If YES to "Public Speaking": Do you think that you are much more uncomfortable than most people who are in a similar situation?

NO YES: _____

IF YES: What were you afraid would happen? _____

Does participant mention that exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic-attack?

NO YES: _____

If YES: Just before you began having these fears, were you taking any drugs, caffeine, diet pills, or any other medications? Physically ill? NO YES: _____

GAD

- In the last six months, have you been particularly nervous or anxious?

NO YES: _____

(Skip the following if NO)

IF YES: What do you worry about? _____

- During the past six months, would you say that you are worrying more often than not?
  NO YES: _____
- When you are worrying, do you find it difficult to stop?
  NO YES: _____
- When you're feeling anxious or nervous, do you feel:

___Restless ___Frequently tired ___Trouble concentrating/Mind goes blank ___Irritable ___Tense muscles ___Sleep disturbance

(3 of the above must be present)

NOTE: Occasional use of anti-anxiety medication is NOT exclusionary.

PSYCHOTIC SYMPTOMS

Delusions

- Has it ever seemed like people were talking about you or taking special notice of you?

NO YES: _____

(Skip the following if NO)

If YES: Were you convinced they were talking about you or did you think it might have been your imagination?

NO YES: _____

- What about receiving special messages from the TV, radio, or newspaper, or from the way things were arranged around you?

NO YES: _____

- What about anyone going out of their way to give you a hard time, or trying to hurt you?

NO YES: _____

- Did you ever feel that you were especially important in some way, or that you had special powers to do things that other people couldn't do?

NO YES: _____

- Did you ever feel that someone or something outside yourself was controlling your thoughts or actions against you will?

NO YES: _____

Auditory Hallucinations

- Did you ever hear things that other people couldn't hear, such as noises, or the voices of people whispering or talking? (were you awake at the time?)

NO YES: _____

(Skip the following if NO)

If YES: What did you hear? How often did you hear it?_____

If VOICES: Did they comment on what you were doing or thinking_____

How many voices did you hear? Were they talking to each other? _____

Visual Hallucinations

- Did you ever have visions or see things that other people couldn't see? (were you awake at the time?)

NO YES: _____

ALCOHOL & DRUG USE

Alcohol use

- Has there been any time in your life when you had five or more drinks (beer, wine, or liquor) on one occasion?
  NO YES: _____

- What are your drinking habits like? (How much do you drink?)_____
- Average per week or month?_____ When did you start drinking?_____
- Once you started drinking, was it the same as your current use?_____
- When in your life were you drinking the most? (How long did that period last?)

Record time of heaviest use and describe pattern:_____

***During that time**…*

- How often were you drinking? _____
- What were you drinking? How much? _____
- Did your drinking cause problems for you? _____
- Did anyone object to your drinking?_____

*If CURRENT alcohol dependence seems likely, then participant **CANNOT** participate in this study. Given the age of participants use discretion regarding alcohol dependence vs typical adolescent/youth adult behavior, ie. Parties, social gatherings, etc.*

DRUG & MEDICINE USE

***Any past or current substance abuse is an exclusion criteria. Cannabis use may be okay, as long as they abstain 3 weeks prior to testing - use discretion.**

- Have you ever become dependent on a prescribed medication or taken a lot more of it than you were supposed to? NO YES
- Have you **ever** used street drugs? NO YES

(Skip the following section if NO)

If YES: Have you ever used any of the following:

Circle the name of each drug ever used (or write in name if other)	Period of heaviest use (age or date, duration) & **describe pattern of use (THE MORE DETAILS THE BETTER)**	Level of use
Sedatives - hypnotics – anxiolytics: Quaalude, Seconal, Valium, Xanax, Librium, barbiturates, Miltown, Ativan, Dalmane, Halcion, Restoril, or other : _____	_____ _____ _____	1 2 3
Cannabis: marijuana, hashish , THC, or other: _____	_____ _____ _____	1 2 3
Stimulants: amphetamine, "speed", crystal meth, dexadrine, Ritalin, "ice", or other: _____	_____ _____ _____	1 2 3

Opioids: heroin, morphine, opium, Methadone, Darvon, codein, Percodan, Demerol, Dilaudid, unspecified or other: _____		1 2 3
Cocaine: intranasal, IV, freebase, crack, "speedball", unspecified or other: _____		1 2 3
Hallucinogens/PCP: LSD, mescaline, peyote, psilocybin, STP, mushrooms, PCP ("angel dust"), Ecstasy, MDMA, or other: _____		1 2 3
Other: steroids, "glue", paint, inhalants, nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers"), nonprescription sleep or diet pills, unknown, or other: _____		1 2 3

"This study will require that you to abstain from caffeine for 6 hours before your baseline & week 12 assessments (those sessions that involve an EEG & MRI), as well as from all street drugs, including marijuana, for at least 3 weeks prior to these assessments. Abstinence from alcohol and over-the-counter drugs (with the exception of prescribed medications) is also required from midnight the night before your visit until your session is complete." We will ask you to provide a urine sample during the screening session to confirm abstinence.

Do you think this would be a problem? YES NO_____
[IF YES]: Ask them if they would like to be contacted for future studies and thank them for their time.

*Family Interview for Genetic Studies (*FIGS): Adapted General Screening Questions

We're almost done. I'm going to ask you a couple of questions regarding your family history, specifically your immediate family – these include your parents, any siblings, and any offspring/children.. I'd like you to keep these particular individuals in mind as we go through the questions:

Was anyone in your immediate family adopted?
NO YES:_____
Does/did anyone in your family have a developmental disability?
NO YES:_____

Did/does anyone have problems with their nerves or emotions? …to the extent that they take meds e.g. lithium or see a doctor ?
NO YES:_____

Feel very low for a couple of weeks or more, or have a diagnosis of depression?
NO YES:_____

Attempt or complete suicide?
NO YES:_____

Seem over-excited (or manic) day and night, or have a diagnosis of mania?
NO YES:_____

Have visions, hear voices, or have beliefs that seem strange or unreal?
NO YES:_____

Have unusual or bizarre behavior, or have a diagnosis of schizophrenia?
NO YES:_____

"Just a few final questions before we wrap up."

As mentioned, this study will require that you come to the Royal Ottawa Hospital for ~45min-1 hr, 3X/week, for 12 consecutive weeks. We will be as flexible as possible in scheduling the sessions to suit your schedule, and we know that occasionally you cannot attend. However, good attendance is really important to this study. Do you foresee any issues with this commitment, or any scheduling conflicts that might prevent you from attending any of these sessions over the next 3 months (i.e. exams, going home, big vacations, employment, etc.)?
NO YES:_____

If participant seems PERFECT for the study (i.e., no red flags):

Based on this preliminary screen, you seem like a great candidate for the study. Do you have any questions and are you still interested in participating?

[IF YES]: Great! I would like to tentatively schedule you to come in for your first session, although I must first review your file with my supervisor.

Is there a date/time that would work for your initial visit? ***Obtain more than 1 if possible to allow for flexibility***

_____
Alright, I will email or call you to confirm an appointment date as soon as possible. [Confirm phone email]
Thank you.

If participant DOES NOT seem perfect for the study/there are some concerns:

Based on this preliminary screen, you seem like you may qualify for study participation. However, I will need to review this interview with one of the researchers to be sure. While I have you on the phone, why don't we tentatively schedule the first visit in the event that your file is approved? I will call/email you regardless to let you know the outcome.

Is there a date/time that would work for your initial visit? ***Obtain more than 1 if possible to allow for flexibility***

_____
Do you have any further questions?
NOTES:

APPENDIX II

SCREENING SCRIPT – MDDEX Study
HEALTHY CONTROL VERSION

The following information may have been obtained before the screen (e.g. from e-mail or phone msg.)

Name: _____ Sex: M or F
Age & DOB: _____ (Must be **16-24 yr**)
Employment: _____ Highest Level of Education:_____
Height: _____ Weight: _____ **Exclude if BMI >40kg/m²** Handedness: L R BOTH
Telephone:_____Email:_____

The following is intended as a guide. You do not need to read it word-for-word.
Hello (INSERT INDIVIDUAL'S NAME)
My name is (FIRST NAME) and I am a(n) (POSITION) from the Clinical EEG Lab at the Royal Ottawa Hospital. I am calling about our study on the effects of exercise on symptoms of depression, which you had expressed an interest in participating in as a healthy volunteer. Specifically, we will be comparing brain activity and clinical measures between depressed youth before they start exercise intervention with data from healthy controls.

OR

Thank you for calling us to find out more about our research.

Do you have a moment so that I can explain the study to you?

The purpose of our study is to better understand how the brains of depressed youth differ compared to non-depressed youth. Specifically, we'd like to see if there are any differences in the brain wave patterns that occur while performing a few computerized tasks measuring attention and inhibition.

If you qualify, you will be invited to come in to our laboratory for a one-time visit lasting ~3 hours.

During this visit you would be asked to complete a few self-report questionnaires, and then perform the computerized tasks while hooked up to an EEG - a common, non-invasive technique that involves placing sensors on your head to measure brain electrical activity. You will also be asked to complete a short physical assessment on a treadmill, and finally carry out a cognitive test battery on an iPad after the EEG recording.

All testing will be carried out at the Royal Ottawa Hospital on Carling Avenue. Your data will be kept private and confidential, and you have the right to withdraw from the study without penalty at any time.

****If a participant is excluded at ANY point, ask if they consent to use keeping their information on file for the purpose of contacting them for potential future studies.****

Are you still interested in participating in this study and continuing with the screen?
[IF NO]: Thank you very much for your time.

[IF YES – still interested]:
Are you currently participating in any other studies involving exercise? **Y / N** _____
[IF YES]: Thank you for your time.

[If NO]: Is this a good time to do the phone screen – it may take ~15-30 minutes?
[IF NO]: Set up a time to call back:

Date: _____ Time: _____

[IF YES]: "Before having you come into the lab, we need to ask you some questions to determine if you are eligible for the study. It is possible that some of these questions may make you feel uncomfortable or distressed. If this happens, let me know, and we can stop this screen, or take a break. You also have the right to refuse to answer any questions. Any information collected during this call will be kept confidential, and will be destroyed if you do not qualify for the study or choose not to participate. If you qualify, this information will be kept in a safe place. Is it alright if I proceed, and are you in a location where you feel comfortable discussing some private information?"

[IF NO]: Thank you very much for your time.
[IF YES]: Before we start, can you confirm for me your age? _____ **(16-24 years of age for inclusion)**

---

1. GENERAL MEDICAL

"I am going to start by asking you a series of questions about your medical history and physical health."

Have you been diagnosed with or are you currently being treated for any major medical problems?
YES NO
[IF YES]: Which ones? _____

Do you have a history of any neurological or neuromuscular problems? (e.g. stroke, epilepsy, brain cysts, migraines, MS).
YES NO
[IF YES]: Which ones? _____

Have you ever had a concussion?
YES NO
[IF YES]: Did you lose consciousness? How long? ***Exclude if loss of consciousness lasted >5 minutes**
_____

Have you ever been diagnosed with a development problem? (e.g. autism)
YES NO
[IF YES]: Which ones? _____

Have you ever been diagnosed with or struggled with major learning disabilities? (e.g. severe reading problems, dyslexia)
YES NO
[IF YES]: Which ones? _____

Do you currently use any nicotine products, including cigarettes/cigars, e-cigarettes/vaporizers, chewing tobacco, gum, etc.?
YES NO
[IF YES]: Which ones? How often? _____ (Cannot be a **current** daily smoker: ≥1 full cigarette/week)

Have you *ever* used any nicotine products? YES NO
[If YES]: When did you begin? Stop? What was your typical consumption frequency?

---

2. PHYSICAL ACTIVITY

How many times per week, on average, do you engage in moderate or vigorous physical activity? This would include any activity which causes a big increase in your breathing or heart rate?

Frequency: _____ time(s)/week
Duration: _____

***Participant must be relatively inactive (1x / week, max 1hr is ideal). Use discretion, and verify if unsure.**

---

3. MENTAL HEALTH SECTION

Questions adapted from the Structured Clinical Interview for DSM-5 (SCID).

***Exclude patients with any AXIS I/II DSM-V disorders.**

"I am now going to ask you some questions about your mental health".

The following two questions can be asked as a rapid determinant of exclusion - ie. prior treatment for schizophrenia, undergoing substance abuse treatment, etc. Use discretion and complete the subsequent questions if unsure.

- Have you ever sought treatment or been treated for emotional or psychiatric problems? NO YES

If YES: What for? Treatment? _____

- Have you ever sought treatment or been treated for drug or alcohol abuse? NO YES

If YES, details: _____

MOOD EPISODES

DEPRESSION – STUDY SPECIFIC

Have you ever been diagnosed with major depressive disorder (MDD)/depression?
YES NO
[IF YES]: How recently did you receive this diagnosis? Is it still current? _____
Exclude if diagnosis of MDD is current or relatively recent.

Have you ever taken medication for depression?
YES NO
[IF YES]: EXCLUDE

Are you currently or have you ever received any form of psychotherapy?
YES NO
[IF YES]: EXCLUDE

Depressive

- Has there been a period of time when you were feeling depressed or down most of the day nearly, every day for at least a two week period?
  NO YES: _____
- …what about losing interest or pleasure in things you usually enjoy for at least a two week period?
  NO YES: _____

(Skip the following if NO)
If YES: How long did this period last? _____
If YES: When was the most recent time you felt this way? _____
If YES: Just before this period began were you: Physically ill? Drinking alcohol or using street drugs? Did this begin soon after someone close to you died?
NO YES: _____

Mania
Was there a period in your life when, for at least a continuous <u>one week period</u>:
-You were so happy/excited/energized that other people thought you were not your normal self and/or this was highly abnormal for you?
YES NO **[IF YES]** Details?_____
-You were extremely irritable or angry for most of the time (for at least a week)? Did you fight or argue with people outside of your family? YES NO **[IF YES]** Details?_____
[IF YES TO ABOVE] During this time:

Did you feel you had special talents or abilities?	Yes	No
[IF YES] What kinds talents/abilities_____		
Became impulsive in a way that was highly unusual for you (e.g. spent a lot of money, had sexual indiscretions)?	Yes	No
Needed significantly less sleep but did not feel tired?	Yes	No
[IF YES TO ANY OF ABOVE] Are you currently experiencing any of these feelings?	Yes	No

[IF YES] to any of above: INELIGIBLE (*please use discretion – ask about context*)

<u>ANXIETY DISORDERS</u>
Panic

- Have you ever had a panic attack, when you suddenly felt frightened or suddenly developed a lot of physical symptoms?

NO YES:
Describe:

(Skip the following if NO)
If YES: Have these attacks ever come on completely out of the blue – in situations where you don't expect to be nervous or uncomfortable? NO YES: _____
If YES: Just before you began having panic attacks, were you taking any drugs, caffeine, diet pills, or any other medications? Physically ill? NO YES: _____

Agoraphobia

- Were you ever afraid of going out of the house alone, being in crowds, standing in a line or traveling on buses or trains?

NO YES: _____

(Skip the following if NO)
If YES: What were you afraid would happen? _____
Does participant mention anxiety about being in places/situations in which escape may be difficult or embarrassing or in which help may not be available in the event of panic-like symptoms?
NO YES: _____
If YES: Just before you began having these fears, were you taking any drugs, caffeine, diet pills, or any other medications? Physically ill? NO YES: _____

Social Phobia

- Is there anything that you have been afraid to do/felt uncomfortable doing in front of other people eg. speaking, eating or writing?

NO YES: _____
(Skip the following if NO)
If YES to "Public Speaking": Do you think that you are **much** more uncomfortable than most people who are in a similar situation?
NO YES: _____
IF YES: What were you afraid would happen? _____
Does participant mention that exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic-attack?
NO YES:
If YES: Just before you began having these fears, were you taking any drugs, caffeine, diet pills, or any other medications? Physically ill? NO YES: _____

GAD

- In the last six months, have you been particularly nervous or anxious?

NO YES: _____
(Skip the following if NO)
IF YES: What do you worry about? _____

- During the past six months, would you say that you are worrying more often than not?

NO YES: _____

- When you are worrying, do you find it difficult to stop?

NO YES: _____

- When you're feeling anxious or nervous, do you feel:

___Restless ___Frequently tired ___Trouble concentrating/Mind goes blank ___Irritable ___Tense muscles ___Sleep disturbance
(3 of the above must be present) **If 3 of the above are present: EXCLUDED**
NOTE: Occasional use on anti-anxiety medication is NOT exclusionary.

PSYCHOTIC SYMPTOMS

Delusions

- Has it ever seemed like people were talking about you or taking special notice of you?

NO YES: _____
(Skip the following if NO)
If YES: Were you convinced they were talking about you or did you think it might have been your imagination?
NO YES: _____

- What about receiving special messages from the TV, radio, or newspaper, or from the way things were arranged around you?

NO YES: _____

- What about anyone going out of their way to give you a hard time, or trying to hurt you?

NO YES: _____

- Did you ever feel that you were especially important in some way, or that you had special powers to do things that other people couldn't do?

NO YES: _____

- Did you ever feel that someone or something outside yourself was controlling your thoughts or actions against you will?

NO YES: _____

Auditory Hallucinations

- Did you ever hear things that other people couldn't hear, such as noises, or the voices of people whispering or talking? (were you awake at the time?)

NO YES: _____

(Skip the following if NO)

If YES: What did you hear? How often did you hear it?_____

If VOICES: Did they comment on what you were doing or thinking?

_____

How many voices did you hear? Were they talking to each other? _____

Visual Hallucinations

- Did you ever have visions or see things that other people couldn't see? (were you awake at the time?)

NO YES: _____

If YES: EXCLUDE

ALCOHOL & DRUG USE

Alcohol use

- Has there been any time in your life when you had five or more drinks (beer, wine, or liquor) on one occasion?

NO YES: _____

- What are your drinking habits like? (How much do you drink?)_____
- Average per week or month?_____ When did you start drinking?_____
- Once you started drinking, was it the same as your current use?_____
- When in your life were you drinking the most? (How long did that period last?)

Record time of heaviest use and describe pattern:_____

During that time*…*

- How often were you drinking? _____
- What were you drinking? How much? _____
- Did your drinking cause problems for you? _____
- Did anyone object to your drinking?_____

*If CURRENT alcohol dependence seems likely, then participant **CANNOT** participate in this study. Given the age of participants use discretion regarding alcohol dependence vs typical adolescent/youth adult behavior, ie. Parties, social gatherings, etc.*

Drug & Medicine Use

***Any past or current substance abuse is an exclusion criteria. Cannabis use may be okay, as long as they abstain 3 weeks prior to testing - use discretion.**

- Have you ever become dependent on a prescribed medication or taken a lot more of it than you were supposed to? NO YES
- Have you **ever** used street drugs, including cannabis? NO YES

(Skip the following section if NO)

If YES: Have you ever used any of the following:

Circle the name of each drug ever used (or write in name if other)	Period of heaviest use (age or date, duration) & **describe pattern of use (THE MORE DETAILS THE BETTER)**	Level of use
Sedatives - hypnotics – anxiolytics: Quaalude, Seconal, Valium, Xanax, Librium, barbiturates, Miltown, Ativan, Dalmane, Halcion, Restoril, or other : _____		1 2 3
Cannabis: marijuana, hashish , THC, or other: _____		1 2 3
Stimulants: amphetamine, "speed", crystal meth, dexadrine, Ritalin, "ice", or other: _____		1 2 3
Opioids: heroin, morphine, opium, Methadone, Darvon, codein, Percodan, Demerol, Dilaudid, unspecified or other: _____		1 2 3
Cocaine: intranasal, IV, freebase, crack, "speedball", unspecified or other: _____		1 2 3
Hallucinogens/PCP: LSD, mescaline, peyote, psilocybin, STP, mushrooms, PCP ("angel dust"), Extasy, MDMA, or other: _____		1 2 3
Other: steroids, "glue", paint, inhalants, nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers"), nonprescription sleep or diet pills, unknown, or other: _____		1 2 3

"This study will require that you to abstain from caffeine for 6 hours before your appointment, as well as from all street drugs, including marijuana, for at least 3 weeks. Abstinence from alcohol and over-the-counter drugs (with the exception of prescribed medications) is also required from midnight the night before your visit until your session is complete."

Do you think this would be a problem? YES NO_____

[IF YES]: Ask them if they would like to be contacted for future studies and thank them for their time.

Family Interview for Genetic Studies (FIGS): Adapted General Screening Questions

We're almost done. I'm going to ask you a couple of questions regarding your family history, specifically your immediate family – these include your parents, any siblings, and any offspring/children. I'd like you to keep these particular individuals in mind as we go through the questions:

Was anyone in your immediate family adopted?
NO YES:_____

Does/did anyone in your family have a developmental disability?
NO YES:_____

Did/does anyone have problems with their nerves or emotions? …to the extent that they take meds e.g. lithium or see a doctor ?
NO YES:_____

Feel very low for a couple of weeks or more, or have a diagnosis of depression?
NO YES:_____

Attempt or complete suicide?
NO YES: _____

Seem over-excited (or manic) day and night, or have a diagnosis of mania?
NO YES:_____

Have visions, hear voices, or have beliefs that seem strange or unreal?
NO YES:_____

Have unusual or bizarre behavior, or have a diagnosis of schizophrenia?
NO YES:_____

"That concludes the screening interview"

If participant seems PERFECT for the study (i.e., no red flags):
Based on this preliminary screen, you seem like a great candidate for the study. Do you have any questions and are you still interested in participating?
[IF YES]: Great! I would like to tentatively schedule you to come in for your session, although I must first review your file with my supervisor.

Is there a date/time that would work for your visit? ***Obtain more than 1 if possible to allow for flexibility***

Alright, I will email or call you to confirm an appointment date as soon as possible. [Confirm phone/email]

If participant DOES NOT seem perfect for the study/there are some concerns:

Based on this preliminary screen, you seem like you may qualify for study participation. However, I will need to review this interview with one of the researchers to be sure. While I have you on the phone, why don't we tentatively schedule the first visit in the event that your file is approved? I will call/email you regardless to let you know the outcome.

Is there a date/time that would work for your initial visit? ***Obtain more than 1 if possible to allow for flexibility***

Do you have any further questions?
NOTES:

APPENDIX III

The | Le Royal
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Santé mentale - Soins et recherche

1145 avenue Carling Avenue
Ottawa ON K1Z 7K4
theroyal.ca / leroyal.ca

Tel. / Tél. 613.722.6521
Toll free / Ligne sans frais 1.800.987.6424

RESEARCH ETHICS BOARD

August 7, 2018

Natalia Jaworska, PhD
Principal Investigator

Re: REB# 2018025
What are the Effects of Aerobic Exercise on the Brain, Mood and Cognitive Function in Depressed Transitional-Aged Youth?

Dear Dr. Jaworska,

This letter is to acknowledge receipt of your letter (dated July 31, 2018; received August 3, 2018) which included revised copies of the Protocol (version 2 date: July 2018), COREB Application Form (version 2 date: July, 2018) Information Sheet and Informed Consent Form (version 2 date: July, 2018), Recruitment Poster (version 2 date: July 2018) and Budget Overview & Outline (version 2 date: July 2018, in response to our letter (dated July 24, 2018) for the above-titled protocol.

The revised material and responses to our questions have been reviewed and **your protocol has now received approval for the period of one (1) year from the date of this letter [due date is August 6, 2019].**

This approval is contingent upon maintaining adherence to the normal approval process, namely,

- Reporting to the Board any adverse events of the project in progress
- Seeking prior approval from the Board of any direct use of public media to recruit research participants

Annual progress reports must be submitted to the Board for continuation of Research Ethics approval. Failure to provide annual reports by the due date specified will result in suspension of participant recruitment and ongoing operation of the study. A *termination report* is required at the conclusion of the study.

Sincerely, on behalf of the Board,

APPROVED
Aug. 7/18
Valid After
Aug 6/19
Royal Ottawa Health Care Group REB

Pierre Blier, MD PhD
Chair, Research Ethics Board

APPENDIX IV

26/09/2018

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

CERTIFICAT D'APPROBATION ÉTHIQUE | CERTIFICATE OF ETHICS APPROVAL

Numéro du dossier / Ethics File Number	H-08-18-1065
Titre du projet / Project Title	Assessing the Clinical & Neural Outcomes in Depressed Youth Randomized to One of Two Intensities of Aerobic Exercise
Type de projet / Project Type	Recherche de professeur / Professor's research project
Statut du projet / Project Status	Approuvé / Approved
Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)	26/09/2018
Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)	06/08/2019

Équipe de recherche / Research Team

Chercheur / Researcher	Affiliation	Role
Natalia JAWORSKA	Département de médecine cellulaire et moléculaire / Department of Cellular and Molecular Medicine	Chercheur Principal / Principal Investigator
Verner KNOTT	Département de psychiatrie / Department of Psychiatry	Co-chercheur / Co-investigator
Jennifer BRUNET	École des sciences de l'activité physique / School of Human Kinetics	Co-chercheur / Co-investigator
Ian MANION		Co-chercheur / Co-investigator
Jason STEFFENER	École interdisciplinaire des sciences de la santé / Interdisciplinary School of Health Sciences	Co-chercheur / Co-investigator
Gary GOLDFIELD		Co-chercheur / Co-investigator

Conditions spéciales ou commentaires / Special conditions or comments

550, rue Cumberland, pièce 154 Ottawa (Ontario) K1N 6N5 Canada
550 Cumberland Street, Room 154 Ottawa, Ontario K1N 6N5 Canada

613-562-5387 • 613-562-5338 • ethique@uOttawa.ca / ethics@uOttawa.ca
www.recherche.uottawa.ca/deontologie | www.recherche.uottawa.ca/ethics

26/09/2018

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

Le Comité d'éthique de la recherche (CÉR) de l'Université d'Ottawa, opérant conformément à l'*Énoncé de politique des Trois conseils* (2014) et toutes autres lois et tous règlements applicables, a examiné et approuvé la demande d'éthique du projet de recherche ci-nommé.

L'approbation est valide pour la durée indiquée plus haut et est sujette aux conditions énumérées dans la section intitulée "Conditions Spéciales ou Commentaires". Le formulaire « Renouvellement ou Fermeture de Projet » doit être complété quatre semaines avant la date d'échéance indiquée ci-haut afin de demander un renouvellement de cette approbation éthique ou afin de fermer le dossier.

Toutes modifications apportées au projet doivent être approuvées par le CÉR avant leur mise en place, sauf si le participant doit être retiré en raison d'un danger immédiat ou s'il s'agit d'un changement ayant trait à des éléments administratifs ou logistiques du projet. Les chercheurs doivent aviser le CÉR dans les plus brefs délais de tout changement pouvant augmenter le niveau de risque aux participants ou pouvant affecter considérablement le déroulement du projet, rapporter tout évènement imprévu ou indésirable et soumettre toute nouvelle information pouvant nuire à la conduite du projet ou à la sécurité des participants.

The University of Ottawa Research Ethics Board, which operates in accordance with the *Tri-Council Policy Statement* (2014) and other applicable laws and regulations, has examined and approved the ethics application for the above-named research project.

Ethics approval is valid for the period indicated above and is subject to the conditions listed in the section entitled "Special Conditions or Comments". The "Renewal/Project Closure" form must be completedfour weeks before the above-referenced expiry date to request a renewal of this ethics approval or closure of the file.

Any changes made to the project must be approved by the REB before being implemented, except when necessary to remove participants from immediate endangerment or when the modification(s) only pertain to administrative or logistical components of the project. Investigators must also promptly alert the REB of any changes that increase the risk to participant(s), any changes that considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project or the safety of the participant(s).

Germain ZONGO
Responsable d'éthique en recherche / Protocol Officer
Pour/For **Daniel LAGAREC** Président(e) du/ Chair of the **Comité d'éthique de la recherche en sciences sociales et humanités / Social Sciences and Humanities Research Ethics Board**

550, rue Cumberland, pièce 154
Ottawa (Ontario) K1N 6N5 Canada

550 Cumberland Street, Room 154
Ottawa, Ontario K1N 6N5 Canada

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www.recherche.uottawa.ca/deontologie | www.recherche.uottawa.ca/ethics

APPENDIX V

Roche

V 0477

Beck Depression Inventory

CRTN: _____ CRF number: _____

Page 14 patient inits: _____

Baseline

BDI-II®

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

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Subtotal Page 1

Continued on Back

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NR15645

11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

3 4 5 6 7 8 9 10 11 12 A B C D E

_____ Subtotal Page 2

_____ Subtotal Page 1

_____ Total Score

Beck Anxiety Inventory (BAI)

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not At All	Mildly but it didn't bother me much	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	☐	☐	☐	☐
Feeling hot	☐	☐	☐	☐
Wobbliness in legs	☐	☐	☐	☐
Unable to relax	☐	☐	☐	☐
Fear of worst happening	☐	☐	☐	☐
Dizzy or lightheaded	☐	☐	☐	☐
Heart pounding/racing	☐	☐	☐	☐
Unsteady	☐	☐	☐	☐
Terrified or afraid	☐	☐	☐	☐
Nervous	☐	☐	☐	☐
Feeling of choking	☐	☐	☐	☐
Hands trembling	☐	☐	☐	☐
Shaky / unsteady	☐	☐	☐	☐
Fear of losing control	☐	☐	☐	☐
Difficulty in breathing	☐	☐	☐	☐
Fear of dying	☐	☐	☐	☐
Scared	☐	☐	☐	☐
Indigestion	☐	☐	☐	☐
Faint / lightheaded	☐	☐	☐	☐
Face flushed	☐	☐	☐	☐
Hot/cold sweats	☐	☐	☐	☐

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info@easycap.de
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Green Holders: Label 1-32, Hardware Channel 1 – 32

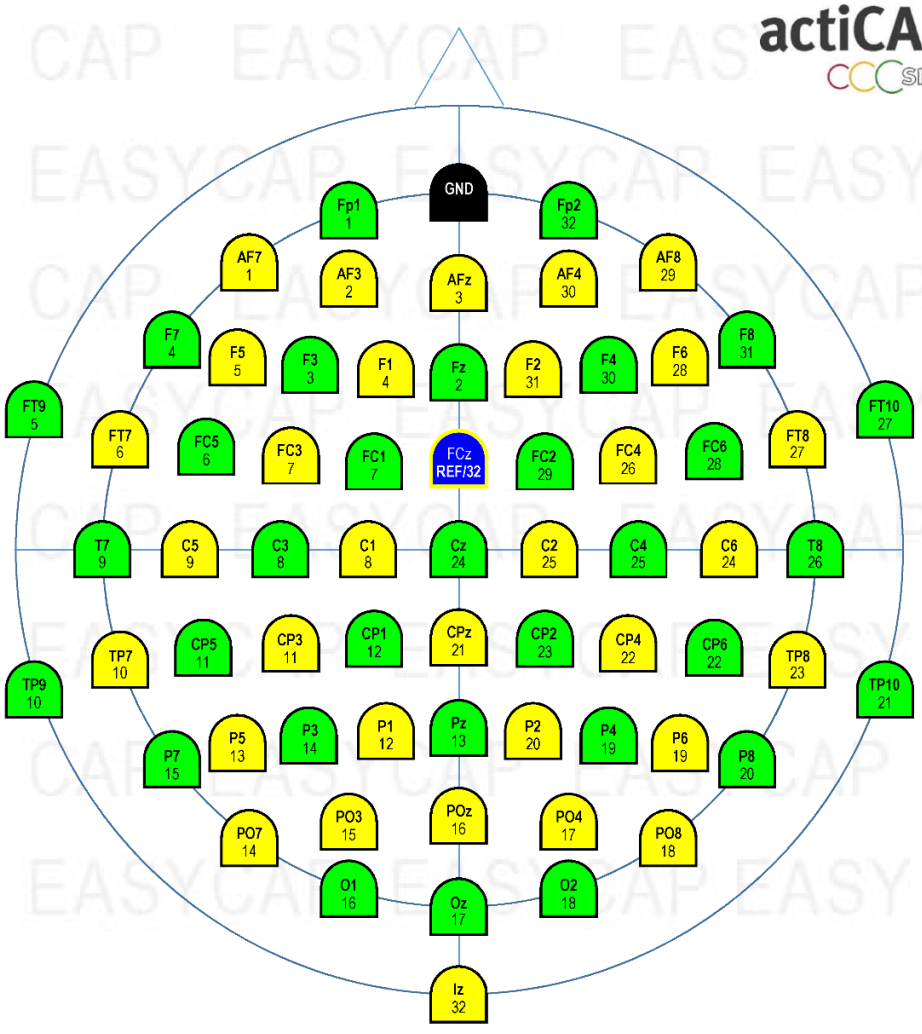
Yellow Holders: Label 1-32, Hardware Channel 33 - 64

Blue holder: For REF or Ch64 (yellow 32)

Black holder: Label & hard-wired GND

Electrode Names and Number Labels

actiCAP snap



APPENDIX VIII

Table S1. National Institutes of Health (NIH) cognition task fully-corrected t-scores in healthy controls and depressed groups (mean ± standard deviation).

	Healthy Controls N = 19	Depressed N = 18
NIH Total Cognition	53.95 ± 11.97	57.11 ± 6.89
NIH Crystallized Cognition	51.74 ± 15.94	54.72 ± 9.10
NIH Fluid Cognition	55.00 ± 10.03	57.33 ± 8.64
NIH Pattern Comparison*	60.21 ± 11.26	57.72 ± 10.79
NIH Picture Sequence *	51.42 ± 9.75	51.56 ± 7.69

*Task is a component of Fluid Cognition

APPENDIX IX

Analysis of Covariance (ANCOVA) - Oddball

An ANCOVA with BDI scores as the covariate was carried out on eP3a latency. After correcting for depression, no significant difference was found between groups ($F(1, 30) = 2.50$, $p = .12$, $\eta^2 = .08$). An additional ANCOVA with BAI score as the covariate was also run; after correcting for anxiety, there were also no group differences for the eP3a latency ($F(1, 29) = 1.78$, $p = .19$, $\eta^2 = .06$).

Analyses of Covariance (ANCOVA) - Flanker

An ANCOVA with BDI score as the covariate was carried out on N2 amplitudes to the incongruent flanker stimuli. After correcting for depression scores, no group differences were found ($F(1, 27) = 0.72$, $p = .41$, $\eta^2 = .03$).