Executive Dysfunction as Risk for Depression

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LIST OF ABBREVIATIONS

ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
DASS	Depression, Anxiety, and Stress Scale
D-KEFS	Delis-Kaplan Executive Function System
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EF	Executive Function
FSIQ	Full Scale Intelligence Quotient
GAF	Global Assessment of Functioning
ICC	Intraclass Correlation
MDD	Major Depressive Disorder
OCD	Obsessive Compulsive Disorder
PTSD	Posttraumatic Stress Disorder
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
rMDD	Remitted Major Depressive Disorder
SCID-5	Structured Clinical Interview for DSM–5

SUMMARY

Major Depressive Disorder (MDD) is a common and costly illness, with only moderately efficacious treatments available. Identifying risk and potential pathways for the development of MDD can help better inform treatment and prevention efforts. One common deficit in MDD is executive dysfunction; however, few studies have examined whether deficits in executive function (EF) connote risk for MDD. The present study aimed to examine whether 1) EF is poorer among individuals with current MDD and individuals with remitted MDD, compared to depression-free controls, 2) indices of EF are positively correlated within sibling pairs, and 3) family history of MDD is associated with worse performance on EF. In a sample of 402 individuals, we assessed current and lifetime MDD, family history of MDD, and measured two components of EF: set shifting and inhibition, using four subtests from a standardized battery of EF (Delis-Kaplan Executive Function System; DKEFS). Results demonstrated that set shifting deficits were present in both the acute stage of depression as well as in remission from the disease. Set shifting abilities were also significantly associated within sibling pairs, suggesting that these abilities are familial in nature. However, family history of MDD was not associated with worse performance on set shifting or inhibition. This finding may be contributable to incomplete family psychiatric data and potential false negatives in families without a history of MDD. Additionally, inhibition deficits were not present in current MDD, potentially suggesting specificity in the EF deficits in MDD. Taken together, these results lend some support to our hypothesis that set shifting may be a potential vulnerability marker for depression.

1. INTRODUCTION

Major Depressive Disorder (MDD) is one of the most prevalent and costly forms of illnesses in the United States (Greenberg, Stiglin, Finkelstein, & Berndt, 1993; Mathers, Fat, & Boerma, 2008; Murray et al., 2013). Epidemiological data in the U.S. indicate that 15-20% of individuals will experience MDD in their adult lifetime (Kessler et al., 2003). MDD is also the second leading cause of disability and is associated with high rates of mortality in the U.S. (Greden, 2011; Satin, Linden & Phillips, 2009). Yet, despite its prevalence and considerable public health impact, existing treatments are only moderately efficacious (Bohlmeijer, Fledderus, Rokx, & Pieterse, 2011; Calear & Christensen, 2010; Kupfer, Frank, & Perel, 1989; Reynolds et al., 2012). Given the impact of MDD on disability and mortality, it is crucial to improve its treatment and intervention efforts.

One challenge in identifying treatment and intervention targets for depression is that it is often difficult to separate factors contributing to the development of depression from the downstream effects of depressive symptoms themselves. Identifying risk and potential pathways for the development of depression can better inform treatment and prevention targets. Longitudinal designs provide the most direct test of risk, as they can provide information about the temporal relationship between a disorder and their proposed vulnerability factor; however, longitudinal studies are often time-consuming and costly. In contrast, family study designs provide a viable alternative for identifying risk and may be beneficial over cross-sectional studies in parsing risk from concurrent effects and consequences or scars of depression.

One common deficit associated with depression is executive dysfunction (Austin, Mitchell, & Goodwin, 2001; Hammar & Ardal, 2009), yet the nature of the relationship between executive dysfunction and depression has not yet been fully examined, particularly whether one

connotes risk for the other. The present study aims to examine executive dysfunction as a potential vulnerability factor for the development of major depressive disorder through cross-sectional and family study methodology.

1.1 Overview of Executive Function

Executive function (EF) is a broad term often used to encompass a variety of separate higher-order cognitive control processes (Denckla, 1996; Goldstein, Naglieri, Princiotta, & Otero, 2014). Many processes have been conceptualized as a part of EF, including (but not limited to) planning, working memory, attention, inhibition, and set shifting (Goldstein et al., 2014). Planning involves goal-setting and implementing strategies to accomplish the goal (McCloskey, Perkins, & Divner, 2009). This process may involve sub-processes such as decision-making, judging, and evaluating the behaviors of self and others (Das & Heemsbergen, 1983). Working memory refers to the ability to temporarily store information and subsequently retrieve, manipulate, and use the same information (Baddley, 1992). Attention is the ability to maintain focus on certain stimuli (Dehn, 2006). Inhibition is the ability to reject an automatic response or behavior (Goldman-Rakic, Thierry, Glowinski, Goldman-Rakic, & Christen, 1994). Set shifting, the ability to flexibly switch between rules, tasks, or behaviors (Miyake et al., 2000), is also sometimes referred to as switching and is a key component of cognitive flexibility.

Given the complex and multi-dimensional nature of executive function, researchers have disagreed over the conceptualization of EF. Some researchers propose that EF is a unitary construct (Naglieri & Goldstein, 2013), whereas others posit that EF components are distinct and separate entities (Stuss & Alexander, 2007). One confirmatory factor analysis revealed that although behavioral measures of EF, such as tasks measuring switching, inhibition, and working memory, were moderately correlated with one another (range of *r*'s = .42 to .63), they reflected

separable factors (Miyake et al., 2000). Results from one lesion study also suggest three components of EF, each with distinct neural correlates: initiating and sustaining a response related to medial frontal regions, task setting related to left lateral regions, and task monitoring and updating related to right lateral regions (Stuss & Alexander, 2007). In contrast, Banich et al. (2000) proposed a series of cascading EF processes, with each process controlling the next. In this executive cascade, task-relevant information is first identified and attended to, then selection processes come online, followed by processes related to response evaluation.

Although many different definitions and models of EF exist (Goldstein et al., 2014; Jurado & Rosselli, 2007), researchers generally agree that deficits in EF are related to frontal systems dysfunction (Alvarez & Emory, 2006; Anderson, Jacobs, & Anderson, 2008; Fuster, 1993; Levin, Eisenber, & Benton, 1991; Goldstein et al., 2014; Otero & Barker, 2014; Stuss, 2006; Stuss & Benson, 1986; Tranel, Anderson, & Benton, 1994). Lesion studies in individuals with frontal lobe damage have consistently identified common deficits involved in higher-level EF abilities (Aron, Monsell, Sahakian, & Robbins, 2004; Benton, 1968; Milner, 1963; Stuss & Benson, 1986; Yochim, Baldo, Nelson, & Delis, 2007). Early behavioral observations of individuals with frontal lobe damage indicated that these patients often exhibited difficulty with goal-directed behavior, such as initiation, evaluation of their own behavior, and inhibition (Luria, 1966; Luria, 1972). More recent neuroimaging evidence further supports the association between prefrontal regions and executive function. For example, structural neuroimaging studies demonstrated that volume atrophy in prefrontal regions such as the dorsal prefrontal cortex is correlated with poorer performance on EF tasks (Keller et al., 2009; Gunning-Dixon & Raz, 2003; Salat, Kaye, & Janowsky, 2002).

1.2 How to Examine Risk for MDD?

Risk has been broadly conceptualized as a variable that increases the likelihood to developing a disease (Kraemer et al., 1997; Mrazek & Haggerty, 1994). In psychopathology research, terms such as risk, diathesis, and vulnerability have often been used interchangeably to connote etiology that contribute to psychopathology. Some researchers have argued that although risk factors are associated with increased likelihood of developing the disorder, they do not necessarily connote the mechanism of such development. Instead, only a specific subset of risk factors, *vulnerability factors*, may be informative about the causal mechanisms of the disorder (Ingram & Luxton, 2005). Zubin and Spring (1977) proposed the vulnerability model of psychopathology, originally aimed to reconcile genetic and environmental contributions to the etiology of schizophrenia. The vulnerability model states that vulnerability markers may be biological (e.g. genetic) or acquired (e.g. learned propensities or environmental influence). It also presents the possibility that vulnerabilities could be continuous in nature rather than strictly categorical. That is, vulnerabilities are proposed as trait-like factors that vary along a dimension from 'low vulnerability' to 'high vulnerability.' Based on this model, a highly vulnerable person to a certain illness with elevated levels of a vulnerability marker for that illness requires little environmental stressor to elicit illness onset. In contrast, for individuals low in vulnerability, only rare and intensely stressful situations may induce illness onset.

One way to assess risk for psychopathology is through the use of longitudinal studies to examine whether individual differences in a certain characteristic predicts future onset of psychopathology (Raulin & Lilienfeld, 2009). Given that vulnerability to a disorder necessarily occurs prior to onset of the disorder, longitudinal designs are ideal for identifying and evaluating potential vulnerability factors for psychopathology, as they allow for the measurement of

temporal precedence of a proposed vulnerability factor compared to illness onset. However, longitudinal studies are often time-consuming and costly, which limit the feasibility of this design. Additionally, longitudinal studies may suffer from selective attrition of participants, thus potentially changing the composition of the original sample and potentially reducing the generalizability of results.

In addition to longitudinal studies, another method to study risk in psychopathology is the family study method. Given that MDD is moderately heritable (Weissman et al., 2006; Joormann, Eugène & Gotlib, 2008; Hammen, 2009; Gotlib, Joormann, & Foland-Ross, 2014), vulnerability factors for MDD should also be present in healthy family members of an individual with MDD. That is, if a variable is elevated in healthy relatives of symptomatic probands, then that variable can be considered a vulnerability factor (Robins & Guze, 1970; Raulin & Lilienfeld, 2009). Additionally, vulnerability factors should also be stable over time, aggregate in families, and be present even in the absence of current depressive symptoms. Family study designs are frequently utilized in schizophrenia research. For example, abnormal saccadic eye movements have been proposed as a vulnerability factor for schizophrenia, and indeed studies have shown that healthy siblings of individuals with schizophrenia exhibit symptoms of abnormal eye movements relative to healthy individuals without a family history of schizophrenia (Takahashi et al., 2008; Ettinger et al., 2005). In contrast, family studies are used far less to identify etiological factors in depression, as the literature in this area predominantly consists of cross-sectional correlation studies between proposed vulnerability factors and individuals with current or remitted MDD. Utilizing family study designs in depression research may further help elucidate vulnerability factors for the disease process.

1.3 Executive Dysfunction in MDD

Deficits in executive function may represent one cognitive vulnerability factor for MDD. Most studies examining the relationship between executive dysfunction and depression have focused on deficits in the acute stage of the disease, when the cognitive deficits and depressive symptoms occur concurrently. Indeed, numerous studies have shown that individuals with MDD evidence broad impairments across multiple processes of executive functioning. One review of 14 studies reported that individuals in the acute phase of depression exhibited impairment in numerous executive functions during the acute phase of depression, specifically impairment in processes of inhibition, problem solving and planning, set shifting, decision making, and working memory (Hammar & Ardal, 2009). Another review reported that independent of age, depression severity and subtype, executive functioning impairments occur in task difficulty, motivation and response bias (Austin, Mitchell, & Goodwin, 2001). Beyond these qualitative reviews, meta-analyses further demonstrate support of broad deficits in executive functioning in MDD. One meta-analysis of 113 studies found that MDD is reliably associated with impaired performance on executive functions, with effect sizes ranging from 0.32 to 0.97 across different studies (Snyder, 2013). A separate meta-analysis of 15 studies including 375 individuals with MDD and 481 controls demonstrated significant executive dysfunctions in MDD compared to controls (Wagner, Doering, Helmreich, Lieb, & Tadic, 2012).

Executive dysfunction also has important predictive validity for individuals with depression - one study found that impairments in executive function predicted functional decline and mortality in elderly women, more so than deficits in global cognition (Johnson, Lui, & Yaffe, 2007), underscoring the importance of EF in the course and outcome of MDD. Consistent with these behavioral deficits, neuroimaging studies have demonstrated an association between

MDD and abnormalities in prefrontal cortical regions of the brain (see Lorenzetti, Allen, Fornito, & Yucel, 2009; Pandya, Altinay, Malone, & Anand, 2013 for recent reviews on this topic), a broad (but key) neural area that likely mediates numerous EF. In addition to abnormalities specifically localized to prefrontal cortical regions, research suggests that depression may also be characterized by disruptions in connectivity between prefrontal and limbic regions (Drevets, Price, & Furey, 2008; Mayberg, 2003; Price & Drevets, 2009; Wang, Hermens, Hickie, & Lagopoulos, 2012). Taken together, neuropsychological and neuroimaging evidence converge to demonstrate an association between MDD and executive dysfunction.

1.4 **Executive Dysfunction in Remitted MDD**

Fewer studies have examined the role of executive dysfunction in individuals with remitted depression (rMDD). Although some studies have demonstrated that neurocognitive deficits in depression may improve with treatment, other studies have found no improvements in neurocognitive performance following antidepressant treatment. For example, a meta-analysis by Wagner, Doering, Helmreich, Lieb, & Tadic (2012) found that performance on the Stroop task, a measure of inhibition, improved in individuals with MDD (n = 112) following antidepressant treatment. On the other hand, in a large longitudinal study (n = 1008), Shilyanksy et al. (2016) found no evidence of improvement on the Stroop in individuals with MDD following eight weeks of antidepressant treatment. Another longitudinal study compared deficits in EF in individuals with bipolar I, bipolar II, or MDD during both ill and remitted states (Xu et al., 2012). Results demonstrated that although all three groups presented with EF deficits during illness, only individuals with unipolar MDD showed EF deficits in clinical remission. These findings suggest that EF deficits may represent a trait-like marker (rather than state-specific phenomenon) for MDD. Additionally, a review of 11 studies comparing 500 remitted MDD and

471 healthy controls found decreased performance in domains of sustained attention, selective attention, memory, global cognitive function, and executive function in remitted MDD individuals relative to healthy controls (Hasselbach, Knorr, & Kessing, 2011). Taken together, emerging evidence has demonstrated neurocognitive deficits to be present in rMDD; however, it remains unclear whether this association suggests long-term residual effects of MDD or trait-like deficits that may have preceded illness onset.

1.5 Role of Executive Dysfunction in MDD: Precursor or Consequence?

Although executive dysfunction has been observed concurrently with depression and in individuals remitted from MDD, the direction of association between depression and executive deficits remains unclear as EF may be (a) a correlate of MDD, (b) a "scar" due to the effects of MDD, or (c) a vulnerability factor preceding the onset of MDD, connoting risk for the disorder. Few studies have directly examined the role of executive dysfunction as a precursor or vulnerability factor for depression via longitudinal study designs. In a prospective longitudinal study, Papmeyer et al. (2015) demonstrated that set shifting abilities at baseline in unaffected high-risk individuals for MDD did not appear to predict later onset of the disorder. However, given that participants were relatively young (16-25 years old) and only longitudinally followed for two years, it is possible that high-risk individuals who did not yet develop MDD during follow up may later acquire the disorder. Additionally, high-risk individuals were recruited from unaffected family members of bipolar disorder patients. Although these family members are at increased risk to develop MDD compared the general population (Smoller & Finn, 2003) and more likely to develop MDD than bipolar disorder given the higher overall prevalence of MDD (Kessler et al., 2005), it is possible that recruiting healthy family members of MDD would have increased the likelihood of detecting significant effects. Additionally, a cross-sectional high-risk

twin study demonstrated that healthy twins of affected unipolar MDD co-twins performed worse on EF measures compared to healthy controls without co-twin history of MDD (Christensen, Kyvik, & Kessing, 2006). However, these results were limited by a retrospective designation of diagnosis from existing registry information and lack of adequate control for overall IQ.

Additionally, some evidence from longitudinal studies of late-onset depression in older adults demonstrate that cerebrovascular risk factors and baseline executive function interact to predict 18-month follow-up depressive symptoms, suggesting that executive dysfunction may play a mechanistic role in the development of depressive symptoms (Mast, Yochim, MacNeill, & Lichtenberg, 2004). Additionally, another study found that deficits in attention and executive function may distinguish late-onset MDD from recurrent, early-onset MDD (Rapp et al., 2005). Relatedly, treatment research has shown that resistance to treatment in late-onset depression may be associated with impaired executive function. For example, non-responders to antidepressant (n = 21) performed worse on tasks of set shifting than treatment responders (n = 29; Baldwin, 2004). Taken together, limited research suggests that in addition to being a concurrent factor and scar of depression, executive dysfunction may play a mechanistic role in the development and maintenance of depressive symptoms. Additional research is needed to assess EF's role as risk for MDD, particularly in young adults as the majority of studies examining EF as a vulnerability factor examine EF's role in MDD in older adults. Examining the association between EF and MDD in young adults may be particularly informative for cognitive interventions and preventative efforts toward reducing MDD onset.

Although many components of EF are correlates of MDD, given the broad and heterogeneous nature of EF, it is possible that only certain processes of EF connote risk for MDD. Specifically, set shifting and inhibition may be potential vulnerability factors for MDD.

Deficits in set shifting and inhibition may lead to cognitive rigidity and inflexibility that manifest in the persistent tendency toward choosing negative interpretations and ruminative thoughts (two negative thinking styles that are prominent in individuals with depression [Beck, 1987; Kuehner & Weber, 1999; Nolen-Hoeksema, 1991]). In line with this idea, Koster, De Lissnyder, Derakshan, and De Raedt (2011) hypothesized that problems with attentional disengagement from negative information may be underlying the process of rumination. Consistent with the impaired disengagement hypothesis, meta-analytic evidence demonstrated significant negative associations between rumination and both set shifting and inhibition abilities, but not working memory (Yang, Cao, Shields, Teng, & Liu, 2017). Additionally, Yang et al. found that the affective content of EF tasks did not moderate the relationship between EF abilities and rumination, suggesting that EF deficits are not specific to negative valence information. Furthermore, Hsu et al. (2015) showed that rumination mediated the relationship between attentional control (comprised of both set shifting and inhibition) and depression symptoms, but attentional control did not mediate the relationship between rumination and depression. These findings suggest a potential mechanism for the link between specific EF deficits, particularly within set shifting and inhibition, and depression. Notably, Hsu et al. (2015) used a self-report measure of attentional control that encompassed both set shifting and inhibition abilities in their mediation analysis. Although these findings demonstrate implicate EF deficits in the development of MDD, additional research is needed to specifically examine the separate roles of set shifting and inhibition as potential vulnerability factors for MDD.

Isolating specific EF deficits (such as comparing set shifting to inhibition) in MDD may be difficult because EF processes are often measured by separate neuropsychological tests that were normed on different samples. This may be problematic as interpretation of

neuropsychological test performance varies greatly based on which normative samples were used by the test, causing the same performance to be labeled average or impaired, based on different normative data (Kalechstein, van Gorp, & Rapport, 1998). Thus, it may be informative to examine the relationship between different components of EF and MDD using tests that were normed on the same normative sample.

1.6 Concomitant Factors in MDD and EF Deficits

One factor that may further complicate the relationship between EF and MDD is the role of processing speed. Psychomotor abnormalities are one of the symptoms in the diagnostic criteria of MDD (American Psychiatric Association, 2013) and deficits in processing speed deficits (a key facet of psychomotor disturbance) are frequently associated with MDD (Austin, Mitchell, & Goodwin, 2001; Reppermund et al., 2007; Sheline et al., 2006). Given that EF is a higher order cognitive process, it often involves more basic component processes such as processing speed, making it difficult to disentangle true deficits in EF versus more basic deficits in processing speed. Indeed, many measures of EF are tasks conducted under time constraint and deficits in processing speed directly affect the measurement of EF abilities. Although it is true that some researchers account for this by calculating ratios of EF abilities and basic processing speed or use untimed tests of EF such as the Wisconsin Card Sorting Test (Heaton et al., 1993), researchers often employ heterogeneous approaches in separating effects of processing speed and EF, which may further contribute to difficulty in parsing risk and effects of MDD.

A second factor that may complicate examination of the relationship between EF and MDD is comorbid psychiatric conditions. Across numerous epidemiological and clinical cohort studies, MDD has been shown to be highly comorbid with anxiety disorders (Kessler et al., 2003; Mineka, Watson, & Clark, 1998; Rapaport, 2001; Rivas-Vasques, Saffa-Biller, Ruiz, Blais, &

Rivas-Vazquez, 2004). Given the high rates of comorbidity between depression and, for example, anxiety disorders, it is often difficult to parse the unique and shared associations between different internalizing disorders and EF abilities. That is, although prior literature has demonstrated significant relationships between EF deficits and depression (Snyder et al., 2013), it remained unclear whether these deficits were specific to MDD. In particular, of the anxiety disorders, OCD has been specifically linked with broad impairments in multiple areas of EF (Olley, Malhi, & Sachdev, 2007; Snyder, Kaiser, Warren, & Heller, 2015). Limited evidence suggests that association between EF deficits and MDD may be accounted for by comorbid anxiety. Basso et al. (2007) demonstrated that comorbid depression and anxiety was associated with greater EF deficits compared to MDD alone. However, a key limitation in this study was the use of retrospective design of designating individuals to depression groups, as the study relied on available past medical records to find the patient's diagnosis as entered by a psychiatrist, rather than determined by a structured clinical interview. This approach may have led to missing or inaccurate diagnostic information in determining psychiatric comorbidities. Baune, McAfoose, Leach, Quirk, and Mitchell (2009) examined the effect of psychiatric comorbidity on cognitive function in a sample of 96 individuals with MDD and either medical comorbidity, psychiatric comorbidity, both comorbidities, or neither comorbidities. Results suggested that psychiatric comorbidity was the strongest predictor of worse cognitive functioning. However, this study only used a cognitive screening instrument, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 2012) to measure cognitive function, and did not specifically assess for executive abilities. A third study compared cognitive control functions between individuals with MDD, comorbid MDD and anxiety, and healthy controls but did not find any significant differences in EF abilities between MDD-alone

and comorbid groups (Lyche, Jonassen, Stiles, Ulleberg, & Landro, 2010). Interesting, a further examination using more robust measures of executive abilities (Delis-Kaplan Executive Function System) in the same sample revealed that the comorbid anxiety and depression group performed significantly worse on set shifting abilities compared to healthy controls and MDD only individuals. Only the comorbid group differed on inhibition compared to controls. The two clinical groups also did not differ on inhibition or processing speed (Lyche et al., 2011). Although current findings broadly suggest that psychiatric comorbidity may influence presence of EF deficits in MDD, future research is needed to examine specific components of EF abilities and their relationships to MDD and comorbid psychopathology.

1.7 **Delis-Kaplan Executive Function System**

Given the multi-component nature of executive functioning, it is important to have a comprehensive behavioral battery to measure EF. One widely used measure of EF is the Delis-Kaplan Executive Function System (D-KEFS, Delis, Kaplan, & Kramer, 2001a). There are several advantages to utilizing D-KEFS as a measure of EF. First, D-KEFS was the first nationally standardized test measuring EF, utilizing a large representative U. S. sample (n = 1,700) of both children and adults ranging 8 to 89 years old (Delis et al., 2001a; Stephens, 2014). In comparison, other commonly used tests of EF, such as the Wisconsin Card Sorting Test (Heaton et al., 1993), are typically normed using relatively small sample sizes (Delis et al., 2001a). Second, D-KEFS assesses multiple components of EF (e.g. attention, inhibition, switching) through its nine subtests: Trail Making, Verbal Fluency, Design Fluency, Color-Word Interference, Sorting, Twenty Questions, Word Context, Tower, and Proverb. Given that these subtests were normed on the same representative sample, using D-KEFS to measure EF can

provide a more accurate comparison between performance on individual EF processes rather than using multiple individual EF tasks normed on different samples.

Additionally, each D-KEFS subtest yields multiple primary and contrast variables, allowing examiners to isolate deficits in basic cognitive processes in one subtest from problems in higher-order EF abilities on other subtests. For example, the trail making test consists of 5 conditions, 4 of which measure more basic cognitive processes that are needed to successfully complete the more complex EF task. Having 5 conditions in the same test allows for the separation of basic cognitive processes from higher-order EF abilities to more accurate pinpoint deficits (Stephens, 2014). In sum, D-KEFS is a comprehensive measure of multiple different EF components that utilizes the same normative comparison for these EF abilities in order to pinpoint specific deficits.

1.8 **Aims and Hypotheses**

The current study broadly aimed to examine the role of executive function as a potential vulnerability factor in the development of depression. Vulnerability was examined in several ways: first, cross-sectional associations between EF and MDD (in both current and remitted groups) were examined. Additionally, a family study design was utilized to assess whether EF is a vulnerability factor. Specifically, sibling pairs were recruited to examine the presence of EF as a vulnerability factor in healthy siblings of depressed probands. Family history of MDD in other first-degree family members (e.g. mother, father, other sibling) were also assessed. Given the multi-faceted nature of executive function, two components of EF, set shifting and inhibition, were examined separately in their relationship to MDD.

It was predicted that:

1) executive functioning (both set shifting and inhibition) would be poorer among individuals with current depression and individuals remitted from depression, compared to controls with no history of depression;

2) indices of set shifting and inhibition would be positively correlated within sibling pairs; and

3) family history of MDD would be associated with worse performance on set shifting and inhibition.

2. METHODS

2.1 Participants

Participants were recruited from the community and area mental health clinics based on their internalizing symptoms, and were enrolled in a larger study on familial emotional and cognitive processes (Gorka et al., 2016; Weinberg, Liu, Hajcak, & Shankman, 2015). The larger study originally included a total enrollment of 503 individuals. For the present study, 5 participants from the larger sample were excluded due to their history of simple bereavement. Additionally, 1 participant from the larger sample was excluded from the following analyses because they dropped out of the study following the clinical interview and did not complete any EF measures. The present study ultimately consisted of a sample of 402 following matching procedures described below (see Data Analysis Plan).

2.2 Inclusion/Exclusion Criteria

Complete inclusion criteria of the larger study were previously reported elsewhere (Weinberg et al., 2015; Weinberg & Shankman, 2016). "Participants were eligible for the study if they were between the ages of 18 and 30, and had a full sibling between the ages of 18 and 30 who was also interested in participating. We opted to recruit siblings rather than other relatives because this approach allowed us to have siblings and probands with comparable mean ages. We restricted the age of the probands and siblings to 18–30 because we were interested in vulnerability for internalizing psychopathology. It was therefore critical that "healthy" (or low symptom) siblings were not completely out of the peak risk period for onset of internalizing disorders (through age 45; Kessler et al., 2005). The premise of examining whether healthy or low-symptom siblings of symptomatic probands have abnormal cognitive responses is that even though siblings have not developed significant symptoms, they still may carry the vulnerability

factor (Zubin & Spring, 1977). However, if a low symptom sibling was significantly past the peak risk period (e.g., age 50) and still had not developed symptoms, they may be less likely to carry the vulnerability factor, or may even be characterized by some resilience process that counteracted their vulnerability.

Minimal symptom-based inclusion and exclusion criteria were used to ensure recruitment of a sample with a broad range of internalizing symptomatology. However, to ensure the clinical relevance of the sample, we also oversampled from individuals with severe internalizing psychopathology. Thus, the goal was to recruit a sample with normally distributed internalizing symptoms but with a mean significantly higher than the mean of the general population. To do this, prior to their involvement in the study, participants were screened via telephone using the Depression, Anxiety, and Stress Scale (DASS; Lovibond & Lovibond, 1995), a brief (21- item) measure of broad internalizing psychopathology (the measure was used to ensure that the sample had the above-mentioned distribution on internalizing symptoms).

As manic and psychotic symptoms have been shown to be separable from internalizing disorders (Watson, 2005), probands and siblings were excluded during screening if they had a personal or first-degree family history of a manic/hypomanic episode or psychotic symptoms, assessed via items from the Structured Clinical Interview for DSM–5 (SCID-5; First, Williams, Karg, & Spitzer, 2015). Participants were also excluded if they were unable to read or write English, had a history of head trauma with loss of consciousness, or were left-handed." Potential participants were not excluded based on current psychotropic medication use, or current substance use, although these variables were examined for potential inclusion as covariates (see below).

2.3 **Diagnostic Interview**

Current and lifetime diagnoses of depression were assessed via the Structured Clinical Interview for DSM-5 (SCID-5; First, Williams, Karg, & Spitzer, 2015). Participants completed the SCID-5 during session one of two lab visits. Family members (i.e. mother, father, sibling) had the option to complete their diagnostic interview in person or via telephone. Interviewers were trained to criterion on the SCID-5 by watching the *SCID 101* training videos (Biometrics Research Department, 2002); observing interviews by other interviewers previously trained to criterion, and completing two or three supervised interviews in which all diagnoses were in agreement with those made by the trained interviewers. All interviewers were supervised by a licensed clinical psychologist.

2.4 Measure of Executive Functioning

Executive functions were measured using four subtests from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001a): Trail Making, Verbal Fluency, Design Fluency, and Color-Word Interference. For individuals aged 18 through 30, internal consistency for these four subtests range from moderate to high (Spearman-Brown corrected *r*'s = .43 to .85) and test-retest reliability range from moderate to high (*r*'s = .49 to .90; Delis, Kaplan, & Kramer, 2001b). Each subtest contains several trials, separately measuring both more basic cognition (e.g. psychomotor speed, letter fluency) as well as higher-order EF processes that require these basic cognitive abilities (e.g. set shifting, inhibition). Description of specific trials and derived EF variables for each subtest is included in the following section. All subtests yield raw scores for each condition, which were then converted into scaled scores ($M = 10$, $SD = 3$) based on the respondent's age.

2.4.1 Trail Making Test.

The Trail Making Test consists of five conditions measuring psychomotor speed, attention, and visual set shifting abilities. In Condition 1: Visual Scanning,

respondents are presented with two pages of encircled numbers and asked to locate and draw a slash through all of the 3's. In Condition 2: Number Sequencing, respondents are asked to connect numbers in numerical order as quickly as possible. In Condition 3: Letter Sequencing, respondents are asked to connect letters in alphabetical order as quickly as possible. In Condition 4: Number-Letter Sequencing, respondents are asked to switch between connecting numbers and letters (e.g. 1-A-2-B...). In Condition 5: Motor Speed, respondents are asked to draw over a dotted line as quickly as possible, connecting circles along the path. Condition 4 measures switching abilities and serves as the primary EF condition, (the main EF variable of interest from this subtest for the present study). Conditions 1, 2, 3, and 5 measure visual attention and speeded responding, with conditions 2 and 3 specific to ability to process numbers and letters, respectively. Inclusion of these non-EF conditions allow for the examination of more basic processes (e.g. processing speed), which are needed for perform the more complex EF task. The raw score for each condition is completion time (recorded in seconds).

2.4.2 **Verbal Fluency Test.** The Verbal Fluency Test consists of three conditions and evaluates abilities involved in phonemic and semantic word generation, as well as verbal set shifting. In Condition 1: Letter Fluency, participants are asked to generate as many words as possible that begin with a certain letter in 60 seconds. This process is repeated three times with three different letters. In Condition 2: Category Fluency, participants are asked to generate as many words as possible in a certain semantic category in 60 seconds. This process is repeated to include two categories. In Condition 3: Category Switching, participants are asked to generate as many words as possible in two different categories, switching back and forth each time between the two categories (this is the main set shifting variable of interest from this subtest for the

present study). This task is also limited to a 60 second time limit. Raw scores for each condition consist of the total number of correct words generated.

2.4.3 **Design Fluency Test.** The Design Fluency Test measures the ability to generate as many different designs as possible in a 60 second time limit, designs are drawn by connecting dots using a specific number of straight lines. In Condition 1: Filled Dots, participants are asked to draw designs connecting dots. This condition assesses basic visuospatial ability in generating designs. In Condition 2: Empty Dots Only, participants are asked to draw designs connecting only dots in a certain category, while ignoring other dots. This condition assesses selective attention and inhibition of task-irrelevant information. In Condition 3: Switching (the main EF variable of interest from this subtest for the present study), participants are asked to draw designs by following the more complex rule of alternating between connecting two types of dots. This condition assesses visual set shifting. Raw scores for each condition are based on the number of correct designs generated.

2.4.4 **Color-Word Interference Test.** The Color-Word Interference Test is based on the stroop paradigm, which evaluates the ability to inhibit an automatic and overlearned response. The D-KEFS subtest adds another demand of set shifting between rules on an already cognitively demanding task. Specifically, in Conditions 1 and 2, participants are asked to name colors (Condition 1) or read words (Condition 2) as quickly as possible. In Condition 3, color words are printed in a different colored ink and participants are asked to inhibit reading the words and instead name the ink colors the words are printed in as quickly as possible. In Condition 4, participants are asked to switch back and forth between word reading and color naming, depending on the type of trial indicated on the page. Although Conditions 3 and 4 both measure inhibition, Condition 4 also implicates the set shifting processes with the additional

rule-switching component. This allows examiners to evaluate EF abilities under existing cognitive load as it is more difficult to engage in set shifting when cognitive demands are already in use for inhibition (Sweller, 1988). Raw scores are based on the time it takes to read words or name colors.

2.5 Procedure

Participants provided written informed consent after review of the protocol. Following informed consent, participants completed a structured clinical interview and standardized administration of the D-KEFS. Participants also completed a broader set of laboratory and neurophysiological tasks and a battery of questionnaires as part of a larger study described elsewhere (Gorka et al., 2016; Weinberg, Liu, Hajcak, & Shankman, 2015). Participants received cash as payment for participation. All procedures were approved by the University of Illinois–Chicago Institutional Review Board.

2.6 Data Analysis Plan

2.6.1 Participant Groups.

Participants were divided into four groups: current MDD, remitted MDD, psychiatric control, and healthy control. Participants with a current diagnosis of MDD were included in the current MDD group (n = 23). Participants with a history of MDD, but who did not currently meet diagnostic criteria for MDD, were included in the remitted MDD group (n = 152). The psychiatric control group was drawn from participants with a lifetime diagnosis of any non-MDD psychopathologies (i.e. panic disorder, agoraphobia, social anxiety, specific phobia, obsessive compulsive disorder, generalized anxiety disorder, posttraumstic stress disorder, substance use disorder, and alcohol use disorder) and matched on current symptom severity as measured by the symptom scale of Global Assessment of Functioning (GAF-S; Aas, 2010) compared to the current MDD group (n = 65). Participants without any lifetime diagnosis

were included as healthy controls (n = 162). See Table 1 for full demographic and clinical characteristics of each participant group.

2.6.2 **Composite Measures of EF.** All statistical analyses were conducted using SPSS (Version 24.0). Pearson's correlations revealed signification associations between set shifting conditions from all four subtests (all p's < .05, see Table 2). Further examination using mixed effects regression models corroborated the significant relationships between set shifting conditions from different subtests. Given the non-independent cases (i.e. sibling pairs) nested within families in the present study, mixed effects regression models were used in place of standard linear regression models in order to account for the shared family variance between siblings. Given the associations between the set shifting conditions, a composite score was calculated for set shifting by averaging the Z-scores of verbal switching, design switching, number-letter switching (inverse), and color-word switching (inverse). The same process was taken to calculate a composite score for inhibition, using the design inhibition and color-word inhibition (inverse) subtests. Consistent with prior literature (Miyake et al., 2000), set shifting and inhibition composite scores were moderately correlated in the current sample, r = .65, p < .001.

Additionally, a composite score was also calculated for attention/processing speed as a measure of more basic cognitive process. The composite score for basic attention/processing speed was the average of the inverse z-scores of trail making condition 5: motor speed, as well as word reading and color naming from the color-word interference test. Although trail making conditions 1 through 3 also measure processing speed, these subtests were excluded from the processing speed composite because they involved some inhibition processes. For instance, in trail making condition 2: number sequencing, participants are presented with two pages of

numbers and letters and asked to connect just the numbers. In order to successfully complete this task, participants must scan through both numbers and letters and subsequently inhibit letter items while choosing number items. This design involves more set shifting and inhibition abilities than the traditional visual scanning task (Trail Making Test, Part A; Reitan, 1955), which included only number items as stimuli, and was thus not included as a processing speed measure.

2.6.3 **Evaluation of Covariates.** Demographic and diagnostic variables were independently tested for their associations with dependent measures using mixed effects regression models. Specifically, sex, age, race, predicted FSIQ, psychiatric medication use, and non-MDD diagnoses including anxiety, trauma, and substance use were examined as potential covariates. Variables found to be associated with dependent measures were included as covariates in the appropriate models.

2.6.4 **Sample Characteristics.** Group scores on continuous demographic and clinical variables (i.e. age, predicted full scale IQ, and GAF symptom severity) were compared using one-way ANOVAs, followed by post-hoc Tukey tests. Group scores on categorical demographic (i.e. sex, race, and psychiatric medication status) and diagnostic variables were compared using chi-squared tests.

2.6.5 **The Relationship between EF and MDD.** To examine group difference in executive functioning, mixed effects regression models were conducted, separately comparing composite scores of set shifting and inhibition between different depression groups. Depression group (current MDD, remitted MDD, psychiatric control, and healthy control) was included in the models as three dummy codes using the healthy control group as the reference. In order to

compare the EF abilities between MDD groups and psychiatric controls, separate analyses were conducted using the psychiatric control group as the reference.

2.6.6 **The Relationship of EF between Siblings.** Relationships between siblings' executive functioning were tested using Pearson's correlations. Additionally, the association between siblings' EF were also tested using intraclass correlations (ICCs) with 95% confidence intervals based on mean-rating (k=2), consistency, 1-way random-effects models to account for variance due to sibling 1 and sibling 2 group assignment. As an exploratory aim, the presence of MDD in the family (yes vs. no) was tested as a potential moderator on the relationship between siblings' executive functioning. Given that EF is proposed as a risk factor for MDD, it is possible that only siblings with a family history of MDD will demonstrate a significant correlation in their EF abilities.

2.6.7 **The Role of EF as Vulnerability Factor for MDD.** Group differences in executive functioning were compared between healthy individuals (no lifetime psychopathology) with a family history of MDD and healthy individuals without a family history of MDD to examine whether executive functioning is a familial vulnerability factor for depression. For the purposes of the current study, family history of MDD was rated as either 0 = participant has no first-degree relative (i.e. sibling, mother, or father) who was assessed in the study and had a lifetime diagnosis of MDD, or 1 = participant has at least one first-degree relative with lifetime diagnosis of MDD. Number of family members per family assessed ranged from 2 (only sibling pair participated) to 6 (sibling pair and 4 additional family members participated). Family history data were available from 1 family member for 40% of participants, 2 family members for 36% of participants, and 3 or more family members for 24% of participants. The effect of family history of MDD on EF was assessed in two ways. First, an independent-samples t-test was conducted to

compare set shifting abilities among healthy individuals with a family history of depression and those without any family history of depression. Additionally, separate ANCOVAs were conducted to assess the effect of family history of MDD on set shifting and inhibition while adjusting for covariates. Set shifting and inhibition composite scores of the healthy sibling were each entered as the dependent variable in separate models.

3. RESULTS

3.1 Evaluation of Covariates

Estimates of fixed effects of potential covariates on EF variables are reported in Table 3. Predicted FSIQ and race were significantly associated with both set shifting and inhibition composite scores (all p's < .05) and were thus included as covariates in all set shifting and inhibition models. Current symptom severity (i.e. GAF-S) was also significantly associated with set shifting and inhibition abilities, but was not included as a covariate as it was instead used to match psychiatric controls with individuals with current MDD. Predicted FSIQ and race were also significantly associated with the processing speed composite and were thus included as covariates in the processing speed models.

3.2 Sample Characteristics

Full demographic and clinical characteristics of the sample are presented in Table 1. In terms of demographics, the four groups did not differ on predicted FSIQ, percentage of female participants, or percentage of white participants. Healthy controls were younger than remitted MDD individuals, but did not differ significantly from current MDD or psychiatric controls.

As expected, fewer individuals in the healthy control group were currently taking psychiatric medication, compared to psychiatric controls and individuals with current or remitted MDD. The three clinical groups did not differ on rates of current psychiatric medication use. Additionally, healthy controls presented with lower general symptomatology, compared to all other groups. Remitted MDD consisted of lower current symptom severity compared to psychiatric controls and current MDD. Individuals in the psychiatric control group were not significantly different from individuals with current MDD on current symptom severity (by design given the matching).

In terms of clinical diagnoses, the three clinical groups did not differ on rates of current and lifetime of agoraphobia, social anxiety disorder, specific phobia, obsessive-compulsive disorder, or substance use disorder. The clinical groups also did not differ on rates of lifetime panic disorder, lifetime generalized anxiety disorder, or current alcohol use disorder.

The psychiatric control group consisted of lower rates of current and lifetime PTSD, and higher rates of lifetime alcohol use disorder compared to the current MDD group. Psychiatric controls and current MDD did not differ on rates of current panic disorder or current GAD. Compared to remitted MDD, the psychiatric control group consisted of lower percentages of lifetime PTSD. Psychiatric control group also consisted of higher rates of current GAD and current panic disorder compared to remitted MDD. Psychiatric controls and remitted MDD did not differ on rates of current PTSD or lifetime AUD.

Remitted MDD group had lower rates of current PTSD, current panic disorder, current GAD, and higher rates of lifetime AUD, compared to the current MDD group. Current and remitted MDD groups did not differ on rates of lifetime PTSD.

3.3 **Executive Functioning and Depression**

Before examining whether current MDD is related to higher order EF abilities, MDD group status was first tested for associations to the more basic cognitive process of processing speed. Predicted FSIQ and race were included as covariates based on their associations with processing speed (see Table 3). Results from mixed-effects regression models demonstrated that the current MDD group did not exhibit different processing speed than healthy controls, b = -.16, SE = .171, t(359.02) = -.93, *ns*, psychiatric controls, b = -.19, SE = .19, t(357.99) = -1.02, *ns*, or remitted MDD group , b = -.14, SE = .17, t(339.90) = -.82, *ns*. Remitted MDD group did not significantly differ from healthy controls, b = -.02, SE = .09, t(373.61) = -.21, *ns,* or psychiatric

controls, b = -.05, SE = .12, t(358.70) = -.44, *ns*. Psychiatric controls also did not significantly differ from healthy controls, b = .03, SE = .11, t(361.68) = .28, *ns*. Given that basic processing speed did not significantly differ between the groups, this composite score was not included as a covariate in the following EF models.

Predicted FSIQ and race were included as covariates in the set shifting and inhibition models. Results from mixed-effects regression models demonstrated that the current MDD group exhibited worse set shifting abilities than healthy controls, b = -.34, SE = .15, t(373.74) = -2.30, p < .05. However, individuals with current MDD did not exhibit different set shifting than psychiatric controls, b = -.27, SE = .16, t(373.65) = -1.68, *ns*, or the remitted MDD group, b = -.15, SE = .15, t(363.82) = -1.05, *ns*. Psychiatric controls did not significantly differ from healthy controls on set shifting, b = -.07, SE = .10, t(373.74) = -.72, *ns*.

Current MDD did not demonstrate significantly different inhibition when compared to healthy controls, b = -.30, SE = .16, t(357.19) = -1.89, *ns*. Similarly, individuals with current MDD did not exhibit different inhibition than psychiatric controls, b = -.16, SE = .17, t(355.47) = -.91, *ns*, or individuals with remitted MDD, b = -.08, SE = .16, t(336.91) = -.49, *ns*. Psychiatric controls did not significantly differ from healthy controls on inhibition, b = -.14, SE = .10, t(359.70) = -1.37, *ns*.

Given that inhibition did not differ significantly between groups, the two measures of inhibition within the composite, design fluency inhibition and stroop inhibition, were each evaluated separately for associations with MDD. Individuals with current MDD did not perform differently from healthy controls on design fluency inhibition, b = -1.25, SE = .75, t(371.21) = -1.65, *ns*, or stroop inhibition, b = 3.40, SE = 2.34, t(359.44) = 1.46, *ns*. For design fluency inhibition, both remitted MDD and psychiatric control groups demonstrated poorer performance

compared to healthy controls (remitted MDD, b = -.85, SE = .39, t(373.11) = -2.17, p < .05; psychiatric control, b = -1.02, SE = .49, t(372.65) = -2.06, p < .05). Remitted MDD did not differ significantly from psychiatric controls, b = .17, SE = .50, t(369.76) = .34, *ns*. No group differences were found for stroop inhibition, all p's > .05.

3.4 Executive Functioning and Remitted Depression

Predicted FSIQ and race were included as covariates in all remitted MDD models. Results from mixed-effects regression models demonstrated that the remitted MDD group exhibited worse set shifting abilities than healthy controls, b = -.19, SE = .08, t(374.01) = -2.44, p < .05. However, individuals with remitted MDD did not exhibit different set shifting than psychiatric controls, b = -.12, SE = .10, t(372.85) = -1.18, *ns*. As previously described, remitted MDD also did not significantly differ from current MDD on set shifting, b = .15, SE = .15, t(363.82) = 1.05, *ns*.

Remitted MDD demonstrated significantly worse performance on inhibition when compared to healthy controls, b = -.22, SE = .08, t(373.98) = -2.70, p < .01. Remitted MDD did not significantly differ from psychiatric controls, b = -.08, SE = .11, t(354.42) = -.77, *ns,* or current MDD on inhibition, b = .08, SE = .16, t(336.91) = .49, *ns*.

3.5 Relationship of Executive Functioning between Siblings

Partial correlations adjusting for siblings' FSIQs revealed a significant positive association between siblings' set shifting abilities, r = .20, p < .05, suggesting that set shifting abilities are familial. A one-way random ICC between siblings further demonstrated a significant familial association of set shifting, ICC = .44, 95% CI = .27 - .57, p < .05. Similarly, siblings' inhibition scores were also positively correlated adjusting for siblings' FSIQs, r = .35, p < .05. A one-way random ICC also revealed significant association of inhibition between siblings, ICC =

.59, 95% CI = .46 - .68, $p < .05$.

Step-wise regression models were conducted to test whether the relationship of EF between siblings were moderated by the presence of family history of MDD. Separate models were conducted for set shifting and inhibition. For each model, sibling 2's EF was included as the dependent variable. Covariates, specifically predicted FSIQ, race, and current OCD, were entered as predictors in step 1; family history of MDD and sibling 1's EF (centered) were entered in step 2, and the interaction term between family history of MDD and sibling 1 EF was entered in step 3. The relationship between the siblings' set shifting was not moderated by family history of MDD, $\beta = .14$, $t(214) = 1.35$, *ns*. Similarly, the relationship between sibling 1 and sibling 2's inhibition was not moderated by family history of MDD, $\beta = -.11$, $t(214) = -1.88$, *ns*.[1]

3.6 Executive Functioning as Vulnerability Factor for Depression

Independent-sample t-test results revealed no significant difference in set shifting scores for healthy individuals with a family history of MDD ($M = -.002$, $SD = .73$) in comparison to those without ($M = .06$, $SD = .66$), $t(187) = .64$, *ns*. Results of the ANCOVA also indicated no significant association between family history of MDD and set shifting abilities when adjusting for predicted FSIQ, race, and current OCD as covariates, $F(1, 185) = .40$, *ns*.

Independent-sample t-test results did not reveal a significant difference in inhibition scores for healthy individuals with a family history of MDD ($M = -.03$, $SD = .77$) and those without a family history of MDD ($M = .19$, $SD = .88$), $t(187) = 1.81$, *ns*. Results of the ANCOVA indicated no significant association between family history of MDD and inhibition abilities when adjusting for predicted FSIQ, race, and current OCD as covariates, $F(1, 185) = 3.41$, *ns*.

[1] Family history of MDD also did not moderate the relationship between siblings when sibling 1 and sibling 2 assignments were reversed.

4. DISCUSSION

The aim of the present study was to investigate the role of executive function deficits as a potential vulnerability marker of MDD. Prior research consistently demonstrated significant EF deficits in current MDD; however, evidence of EF deficits in remitted MDD remained mixed. Heterogeneity in EF components and diverse methods used in measuring these constructs may further contribute to inconsistencies in the relationship between EF deficits and MDD. Given that individuals with MDD often experience cognitive rigidity and inflexibility, set shifting and inhibition deficits were specifically examined as putative vulnerability factors for MDD.

In line with our hypotheses, results demonstrated that set shifting deficits were present in both the acute stage of depression as well as in remission from the disease. These findings suggest that problems in set shifting are not simply pure state effects of MDD but may be lasting effects of depression that persist even in the absence of acute symptoms. Additionally, set shifting abilities were found to be significantly associated within sibling pairs, suggesting that these abilities are familial in nature. However, family history of MDD was not associated with worse performance on set shifting or inhibition in individuals without a history of MDD. Additionally, although set shifting abilities in individuals with MDD (both current and remitted) significantly differed from that of healthy controls, they were not significantly different from that of psychiatric controls with non-MDD psychopathologies. Despite this, it is important to note that unlike the two MDD groups, psychiatric controls did not significantly differ from healthy controls on either EF component, suggesting some specificity between EF deficits and MDD. Taken together, these results lend limited support to our hypothesis that executive function deficits, particularly in set shifting, may be a potential vulnerability marker that is specific to depression.

4.1 Set Shifting and MDD

Consistent with prior literature, set shifting abilities were positively associated within sibling pairs. For example, significant heritability in Wisconsin Card Sorting Test performance has been demonstrated in a sample of young female twins (Anokhin, Heath, & Ralano, 2003). Additionally, results are in line with report by Friedman et al. (2008), which examined the correlations of EF abilities between monozygotic and dizygotic twins through an ACE model and found that set shifting, inhibiting, and updating, were each highly heritable.

Although set shifting was found to be associated within sibling pairs, and deficits (relative to healthy controls) were present in both current and remitted MDD, family history of MDD was not associated with set shifting deficits. There are several possible explanations for the lack of association between family history of MDD and set shifting deficits in the present study. First, it is possible that set shifting deficits represent lasting consequences of MDD, rather than a vulnerability factor. According to the scar hypothesis (Lewinsohn, Steinmetz, Larson, & Franklin, 1981), longstanding residual deficits may be created by an episode of depression that persist long after an episode remits. In line with this hypothesis, it is possible that symptoms of depression may cause lasting damage to neural structures such as the prefrontal cortex, and subsequently contribute to deficits in executive functioning. However, in contrast to the scar hypothesis, meta-analytic evidence demonstrated reduced executive functioning in first-episode MDD (Lee, Hermens, Porter, & Redoblado-Hodge, 2012). Additionally, the authors found that unlikely processing speed or memory, deficits in EF were not associated with inpatient and remission status, suggesting that EF deficits in first-episode MDD are likely not state dependent and may instead represent trait markers for MDD. Results from a longitudinal study also support EF deficits as a potential trait marker for MDD. In a sample of bipolar I, bipolar II, and unipolar

MDD patients, Xu et al. (2012) found EF deficits in all three groups at baseline, but only the unipolar MDD group demonstrated EF impairment in remission. These findings further support that EF deficits may represent a state effect in bipolar disorder, but a trait-like marker in unipolar MDD.

Alternatively, it is possible that methodological limitations in the present study prevented the detection of an effect of family history of MDD on set shifting abilities. Current results were contrary to the few other family studies examining set shifting as vulnerability for MDD. For example, in a family design comparing neuropsychological performance of children of parents with current MDD and/or panic disorder versus those with healthy control parents without either disorder, Micco et al. (2009) demonstrated that parental MDD significantly predicted perseverative errors on the Wisconsin Card Sorting Test, a measure of cognitive inflexibility and set shifting deficits. These results remained even when statistically adjusting for comorbid panic disorder, age, SES, and offspring ADHD. However, parental MDD did not significantly predict offspring test performance in any other cognitive domain, including overall intelligence, processing speed, verbal memory, inhibition, or attention. Although Micco and colleagues interpreted these findings as parental MDD contributing minimally to offspring executive functioning and processing speed, these findings are in line with set shifting deficits as a specific component of EF related to family history of MDD. Similarly, Singh et al. (2018) demonstrated that set shifting abilities were impaired in both healthy youth with parental history of bipolar disorder, as well as healthy youth with parental history of MDD, compared to healthy controls with no family history of either psychopathology. In the present study, family psychiatric history was assessed through direct semi-structured clinical diagnostic interviews with first-degree family members of the sibling pairs. Although this approach ensured accurate diagnostic

information for those who were interviewed, it may have also led to potential false negatives in family MDD history as some members of the family refused to participate in the study or were unable to be contacted. Thus, incomplete family history information may have led to lack of differences observed between individuals with a family history of MDD and those without.

In addition to potential false negatives in family history of MDD, the current study also restricted the age of participants to 18-30 to maximize chances of capturing individuals at peak risk period for developing internalizing disorders. Epidemiological surveys demonstrate that risk for developing depression begins in early teenage years and increases linearly through the mid-20s (Kessler, Avenevoli, & Merikangas, 2001). In the present study, we compared healthy individuals with and without a history of MDD on measures of EF abilities. It is possible that individuals high in EF deficits (who thus carried the vulnerability factor) had already developed MDD and were excluded from the family history analyses, limiting our power to detect effects of set shifting on MDD. Given that the developmental window of MDD coincides with the age of our sample, it is possible that assessment of vulnerability factors for MDD would have been more effective in a younger sample (for example, perhaps in adolescence), prior to the peak age of developing MDD. At the same time, other problems may have been introduced if the study was conducted in a younger sample given the developmental course of EF abilities in children and adolescents. As a proposed vulnerability marker for depression, development of set shifting abilities should precede onset of depression symptoms. Indeed, simple set shifting between two rules can be observed in children as young as 3 to 4 years old (Hughes, 1998; Rennie, Bull, & Diamond, 2004). However, set shifting follows a protracted trajectory and improves significantly from preschool age through adolescence (Davidson, Amso, Anderson, & Diamond, 2006; Luna, 2009). Thus, impairments in set shifting abilities observed in children and adolescents should be

interpreted cautiously, as these deficits may resolve with further development as set-shifting abilities come more "on-line." Moreover, development of EF abilities continues through early adulthood (Blakemore & Choudhury, 2006; De Luca et al., 2003; Taylor, Barker, Heavey, & HcHale, 2013), overlapping with peak risk period for MDD. Despite this overlap, it is possible that mid- to late-adolescence may be the most appropriate age window to test for vulnerability of MDD, as set shifting abilities have largely developed, but MDD onset has not yet occurred.

4.2 **Inhibition and MDD**

Interestingly, although inhibition was also correlated within sibling pairs and significantly related to remitted MDD, it was not associated with current MDD. These results may suggest that EF deficits in MDD are more specific to set shifting, not inhibition. Although prior meta-analytic evidence demonstrated a significant association between rumination, a key cognitive component of MDD, and both set shifting and inhibition abilities (Yang et al., 2017), deficits in inhibition may not be specific to MDD. Indeed, inability to inhibit is a key feature of impulsivity, and often present in individuals with alcohol or substance use disorders (Baler & Volkow, 2006; Goldstein & Volkow, 2002; Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009; Noel et al., 2012). One review of neuropsychological performance of past, now-abstinent alcohol and drug users showed that usage of all substances except cannabis (cocaine, methamphetamines, ecstasy, opiates, and alcohol) were associated with sustained EF deficits, particularly in inhibition (van Holst & Schilt, 2011). Additionally, in a longitudinal high-risk study in children with familial history of high levels of alcohol use disorder, deficits in response inhibition significantly predicted number of illicit drugs used, as well as alcohol-related problems and drug-related problems in adolescence, independent of parental alcohol use (Nigg et al., 2006). In contrast, other EF abilities, including set shifting, did not predict onset of alcohol or

drug use. Although the relationship between inhibition and externalizing disorders has been consistently established, less is known about inhibition abilities in individuals with comorbid MDD and externalizing disorders. Sjoerds, van den Brink, Beekman, Penninx, and Veltman (2014) found that inhibition performance did not significantly differ between comorbid MDD/anxiety and alcohol use disorder patients, MDD/anxiety only patients, and healthy controls. However, alcohol problem severity was associated with inhibition impairments, whereas internalizing symptom severity was not. These findings suggest that depression and anxiety symptoms were not related to decreased inhibition. Taken together with the high rates of comorbidity between MDD and externalizing disorders (Davis, Uezato, Newell, & Frazier, 2008), it is possible that the observed inhibition deficits in remitted MDD are related to sustained deficits due to comorbid externalizing disorders.

Another possibility is that inhibition may be a weaker vulnerability marker for MDD with a smaller effect size than that for set-shifting, and the present study did not have a sufficiently powered sample in the current MDD group to detect this small effect. Additionally, it is possible that the inhibition composite utilized in the present study did not adequately capture the construct of inhibition. The two measures of inhibition included in the inhibition composite, design fluency inhibition and color-word interference inhibition, were significantly correlated, but the association was weak ($r = -.131$, $p < .05$). The weak association between the two measures of inhibition may have contributed to an unreliable composite measure. However, in parsing the inhibition composite into individual measures of inhibition, neither measure alone was significantly associated with current MDD, suggesting that inhibition deficits may not be consistently related to MDD. Instead, current findings demonstrated that in contrast to inhibition, set shifting deficits were observed in both current and remitted depression. Together these

findings may suggest that set shifting, not inhibition, is specifically implicated in EF deficits in MDD.

4.3 **Role of Psychiatric Comorbidity in Set Shifting**

Given that MDD is highly comorbid with anxiety disorders (Kessler et al., 2003; Mineka et al., 1998; Rivas-Vasques et al., 2004), researchers have proposed that EF deficits in MDD may be due to the presence of comorbid anxiety. For example, Basso et al. (2007) found that depressed individuals with comorbid anxiety performed worse on a measure of set shifting compared to healthy controls and MDD alone. In contrast, the depressed group did not differ from healthy controls on set shifting. Another study demonstrated that those with comorbid anxiety and depression group performed significantly worse than those with MDD only on set shifting, but not inhibition (Lyche et al., 2011). In the present study, we included two distinct control groups (healthy control and psychiatric control) in order to isolate the relationship between set shifting and depression, independent of potential effects due to comorbidity with other psychopathology. Specifically, the psychiatric control and current MDD groups were matched on multiple anxiety disorders, including social anxiety, specific phobia, and obsessive-compulsive disorder. Of the anxiety disorders, OCD in particular has been associated with multiple EF deficits (Olley et al., 2007; Snyder et al., 2015). By accounting for the effect of anxiety disorders, we were able to examine the specificity of group differences to MDD. Additionally, in evaluating non-MDD clinical diagnoses as potential covariates in the model for MDD and EF, no diagnosis was significantly related to set shifting or inhibition indices. Taken together, these results suggest that diagnosis of an anxiety disorder did not account for group differences observed in EF abilities, and deficits in set shifting were instead attributable to MDD.

Alternatively, it is possible that neither MDD alone nor anxiety disorders alone can account for set shifting deficits, but instead a combination of both diagnoses is necessary to detect problems in set shifting. One potential explanation for this is that comorbid depression and anxiety represents a more severe form of psychopathology than either disorder alone (Andrade, Eaton, & Chilcoat, 1994; Grunhaus, Pande, Brown, & Greden, 1994), and that severity of symptoms may contribute to higher deficits in set shifting abilities (McClintock, Husain, Greer, & Cullum, 2010; McDermott & Ebmeier, 2009). To account for this possibility, current MDD and psychiatric control groups were matched on current symptom severity using the GAF-S, thus ensuring the current MDD group did not exhibit a higher level of symptom severity despite including comorbid MDD and anxiety disorders diagnoses. Consistent with prior literature, overall symptom severity was significantly associated with set shifting abilities. When overall symptom severity was accounted for in the models, current MDD still demonstrated significantly lower set shifting abilities compared to healthy controls, whereas psychiatric controls did not. These results support the specificity of set shifting deficits in MDD, independent of symptom severity due to comorbidity. Nevertheless, the current study did not specifically test for level of set shifting in a non-comorbid, MDD-only group, and alternative explanations for the role of psychiatric comorbidity cannot be ruled out at this time (although it should be noted that a "non-comorbid, MDD-only group" may not be generalizable to MDD outside of the lab). These findings would be bolstered by future replications examining set shifting abilities as a vulnerability marker in individuals with diverse comorbid internalizing disorders, through family risk or longitudinal designs.

4.4 Processing Speed in MDD

Although previous research demonstrated slower processing speed among individuals with MDD (Reppermund et al., 2007; Sheline et al., 2006; Sobin & Sackeim, 1997), processing speed deficits were not observed in individuals with current or remitted MDD in the present study. Research on cognitive impairment in young adults with internalizing disorders suggests that in contrast to EF abilities, lower-order cognitive processes such as processing speed tend to remain intact in earlier disease processes (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari & Lonnqvist, 2008), which could have contributed to the lack of group differences in processing speed in the current sample of young adults. Additionally, heterogeneity of symptom presentations in MDD may have also contributed to lack of group differences in processing speed. Patients with MDD have been found to exhibit distinct symptom profiles and may have very few symptoms in common, despite sharing the same diagnosis (Fried & Nesse, 2015; Zimmerman, Ellison, Young, Chelminski, & Dalrymple, 2015). The diversity of phenotypes within depression may lead to inconsistent findings and hinder research on vulnerability factors (Gillihan & Parens, 2011; Hyman, 2010). Specifically, psychomotor retardation has been associated with MDD severity (Calugi et al., 2011), melancholic subtype (Schrijvers, Hulstijn, & Sabbe, 2008), and number of past depressive episodes (Gorwood, Richard-Devantory, Bayle, & Clery-Melun, 2014), suggesting that deficits may only be present in a subtest of individuals with MDD with this particularly pernicious form of MDD. Given that the overall symptom severity of the current sample is in the mild range, processing speed deficits may not have been particularly elevated in our sample.

Furthermore, heterogeneity in assessment methods of processing speed may also contribute to mixed findings. Processing speed abilities are commonly assessed by drawing tasks

such as the Trail Making Test, Part A; however, pure motor tests (e.g. actometry, finger tapping test) may assess a separate component of psychomotor deficits not captured by drawing tasks (Buyukdura, McClintock, Croarkin, 2011). Thus, the use of only drawing tasks in the present study may have contributed to lack of group differences observed in processing speed. Despite the lack of pure motor processing speed measures, current findings are in line with meta-analytic evidence demonstrating that effect sizes for psychomotor speed on MDD were smaller than that of EF measures (Snyder, 2013), suggesting that EF deficits in MDD are unlikely accounted solely by impairments in processing speed.

4.5 **Treatment Implications**

Depression is broadly associated with functional impairment (Papakostas et al., 2004); however, functional problems often remain present in remission of MDD (Angermeyer, Holzinger, Matschinger, & Stengler-Wenzke, 2002; Jaeger, Berns, Uzelac, & Davis-Conway, 2006). It is thus possible that residual problems associated with MDD, such as deficits in set shifting, may contribute to impairments in daily functioning. In line with this possibility, Bell-McGinty, Podell, Franzen, Baird, and Williams (2002) compared the associations between performance on five neuropsychological tests and participants' ability to perform instrumental activities of daily living. Results indicated that of the tests, only measures of set shifting (Trail Making Part B and Wisconsin Card Sorting Test) significantly predicted functional status, compared to measures of global cognition, phonemic fluency, and inhibition. Additionally, set shifting deficits have been found to reduce treatment response to antidepressants (Alexopoulos et al., 2005; Dunkin et al., 2000) as well as cognitive behavioral therapy (Mohlman & Gorman, 2005) in older adults. Taken together, set shifting deficits should be a specific treatment target in MDD.

Evidence suggests that Problem-Solving Therapy (PST) may be an efficacious treatment option in reducing depressive symptoms in older adults with MDD and executive dysfunction, compared to supportive therapy (Arean et al., 2010). Additionally, a cognitive training program centered around real-life strategies involved in cooking breakfast, such as deciding when to cook each item, and switching between cooking and table setting, significantly improved older adults' set shifting abilities on a letter-number sequencing task (Wang, Chang, & Su, 2011). These results suggest that individuals with executive impairments may benefit more from concrete strategies and training in common daily tasks, rather than traditional cognitive approaches.

4.6 **Strengths and Limitations**

The present study had numerous strengths. First, it employed a family design to assess set shifting as a potential vulnerability marker in depression and recruited a large, heterogeneous sample of sibling pairs and first-degree family members with diverse racial and clinical characteristics. Second, the heterogeneity of clinical diagnoses and inclusion of psychiatric comorbidities provide external validity for the clinical picture of MDD, given that few patients experience depression in isolation without comorbid symptoms (Kessler et al., 2003; Rivas-Vazquez et al., 2004). Importantly, this approach also allowed us to include a psychiatric control group to further examine set shifting deficits as a specific vulnerability marker for MDD. Finally, the current study utilized a comprehensive measure of EF to assess both set shifting and inhibition using the same method, further parsing specific EF impairments in MDD.

Although the current sample was racially diverse, we did not have sufficient power to test for differences in EF abilities across individual racial groups. Instead, individuals were coded as white and non-white for race based on self-report to ensure adequate sample sizes in each group. Racial group differences in executive functioning have primarily been demonstrated between

white and black participants (e.g. Schwartz et al., 2004; Zahodne et al., 2016), and few studies directly compare differences in EF between different minority groups. In one study, Proctor and Zhang (2008) found that European American college students scored higher overall on a composite measure of broad executive functions, compared to African American and Latino American students, who did not differ. Additionally, Razani, Burciaga, Madore, and Wong (2007) compared white Anglo-Americans to an ethnically diverse group that comprised of individuals from Hispanic, Asian, and Middle-Eastern descent on neuropsychological test performance. Results demonstrated that Anglo-Americans scored higher on multiple measures of executive functioning, including Trail Making Test Part B, a measure of set shifting; Stroop inhibition; and Auditory Consonant Trigrams, a measure of working memory. Importantly, observed racial group differences on neuropsychological testing may be accounted for by acculturation, levels of education, and English reading ability (Boone et al., 2007; Baird, Ford, & Podell, 2007; Kennepohl, Shore, Nabors, & Hanks, 2004). Furthermore, socioeconomic factors such as healthy disparities have also been demonstrated to affect racial group differences on neuropsychological performance (Bickel et al., 2014; Schwartz et al., 2004). Thus, these results suggest that it may be more important to account for individual difference factors such as acculturation, English reading ability, and health-related factors, rather categorical race. Consistent with prior research, predicted full scale IQ (as measured by ability on a word reading test) was included in all models as a covariate in the present study. Although we did not specifically measure acculturation or socioeconomic factors, all participants spoke fluent English and the majority completed some level of college, which may suggest similar socioeconomic backgrounds. Additionally, given the age range of participants in this outpatient sample, it is unlikely that health factors contributed significantly to cognition in this young sample.

Findings were also limited by incomplete family psychiatric history, as not all first-degree family members agreed to participate in a clinical interview, which may have contributed to false negative (but not false positives) in family history of MDD. As previously discussed, the present sample was restricted to young adults aged 18-30. Although this approach aimed to capture individuals at peak risk period for developing internalizing disorders, results may not generalize to geriatric or inpatient groups. Lastly, although we tested for specificity using two separate components of EF, set shifting and inhibition, we did not measure updating abilities, as measured by unstructured learning tasks such as the Wisconsin Card Sorting Test.

4.7 **Conclusion**

The present study aimed to identify specificity and causal relationships between EF deficits and depression. Results demonstrated set shifting deficits in both current and remitted MDD, relative to healthy controls. Additionally, the presence of set shifting deficits in MDD was independent of overall symptom severity or presence of anxiety disorders. Furthermore, processing speed deficits did not contribute to group differences observed in set shifting abilities. In contrast, inhibition was not reliably associated with MDD, suggesting that EF deficits in MDD may be specific to set shifting abilities alone (or at least to not all aspects of EF). Additionally, although set shifting deficits were not associated with family history of MDD, they were significantly correlated within sibling pairs, suggesting that set shifting abilities run in families. Current results suggest that future research should specifically target set shifting as a potential mechanism for the development of MDD. Specifically, longitudinal or family designs in an adolescent sample may further clarify its role as a vulnerability factor for MDD.

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Table I.

Demographic and Clinical Characteristics

	Healthy Controls (N = 162)	Psychiatric Controls (N = 65)	Remitted MDD (N = 152)	Current MDD (N = 23)	Total Sample (N = 402)
Demographics					
Age (SD)	21.71 (2.98)[a]	22.06 (2.90)[ab]	22.91 (3.35)[b]	22.65 (3.89)[ab]	22.27 (3.20)
Predicted FSIQ (SD)	104.32 (9.03)	104.03 (9.02)	106.64 (8.92)	109.50 (8.42)	105.44 (9.05)
Female (%)	103 (64)	39 (60)	106 (70)	18 (78)	266 (66)
Race					
Black (%)	18 (11)	11 (17)	27 (18)	8 (35)	64 (16)
Asian/Pacific Islander (%)	36 (22)	6 (9)	9 (6)	0 (0)	51 (13)
White (%)	69 (43)	29 (45)	75 (49)	10 (44)	183 (46)
Hispanic/Latino (%)	35 (22)	16 (25)	31 (20)	1 (4)	83 (21)
Other/Multiple Races (%)	5 (3)	3 (5)	10 (7)	4 (17)	22 (5)
General Symptomatology					
Psychiatric Medication (%)	2 (1)[a]	6 (9)[b]	29 (19)[b]	6 (26)[b]	43 (11)
GAF Symptom Severity (SD)	83.56 (8.16)[a]	58.28 (8.70)[b]	66.18 (11.25)[c]	52.52 (8.28)[b]	71.13 (14.44)
Clinical Diagnosis					
Lifetime MDD (%)	-	-	152 (100)	23 (100)	175 (44)
Current MDD (%)	-	-	-	23 (100)	23 (6)
Lifetime PTSD (%)	-	3 (5)[a]	23 (15)[b]	7 (30)[b]	33 (8)
Current PTSD (%)	-	0 (0)[a]	3 (2)[a]	3 (13)[b]	6 (1)
Lifetime Panic Disorder (%)	-	8 (12)	21 (14)	7 (30)	36 (9)
Current Panic Disorder (%)	-	5 (8)[a]	3 (2)[b]	3 (13)[a]	11 (3)
Lifetime Agoraphobia (%)	-	2 (3)	4 (3)	1 (4)	7 (2)
Current Agoraphobia (%)	-	1 (2)	3 (2)	1 (4)	5 (1)
Lifetime Social Anxiety (%)	-	16 (25)	53 (35)	11 (48)	80 (20)
Current Social Anxiety (%)	-	9 (14)	33 (22)	7 (30)	49 (12)
Lifetime Specific Phobia (%)	-	22 (34)	41 (27)	9 (39)	72 (18)
Current Specific Phobia (%)	-	19 (29)	28 (18)	8 (35)	55 (14)
Lifetime OCD (%)	-	6 (9)	16 (11)	3 (13)	25 (6)
Current OCD (%)	-	1 (2)	11 (7)	3 (13)	15 (4)
Lifetime GAD (%)	-	15 (23)	25 (16)	8 (35)	48 (12)
Current GAD (%)	-	9 (14)[a]	8 (5)[b]	5 (22)[a]	22 (5)
Lifetime SUD (%)	-	22 (34)	53 (35)	7 (30)	82 (20)
Current SUD (%)	-	10 (15)	10 (7)	4 (17)	24 (6)

Lifetime AUD (%)	-	33 (51)[a]	70 (46)[a]	3 (13)[b]	106 (26)
Current AUD (%)	-	9 (14)	12 (8)	1 (4)	22 (5)

Note. Values with different superscripts were significantly different at $p < .05$ using $\chi 2$ or Tukey tests; FSIQ = Full Scale Intelligence Quotient; IDAS = Inventory of Depression and Anxiety Symptoms; MDD = Major Depressive Disorder; PTSD = Posttraumatic Stress Disorder; OCD = Obsessive Compulsive Disorder; GAD = Generalized Anxiety Disorder; SUD = Substance Use Disorder, AUD = Alcohol Use Disorder.

Table II.

Pearson Correlations between DKEFS Set Shifting, Inhibition, and Processing Speed Measures

Set Shifting

	Verbal Switching	Design Switching	Stroop Switching	Trails Switching
Verbal Switching	--	--	--	--
Design Switching	.245**	--	--	--
Stroop Switching	-.294**	-.346**	--	--
Trails Switching	-.263**	-.372**	.445**	--

Inhibition

	Design Inhibition	Stroop Inhibition
Design Inhibition	--	--
Stroop Inhibition	-.131*	--

Processing Speed

	Stroop Color Time	Stroop Word Time	Trails Motor Time
Stroop Color Time	--	--	--
Stroop Word Time	.624**	--	--
Trails Motor Time	.294**	.241**	--

Note. ** $p < .01$, * $p < .05$

Table III.

Estimates of Fixed Effects of Covariates on Set Shifting, Inhibition, and Processing Speed

	Set Shifting	Inhibition	Processing Speed
Age	-.009	.000	.008
Predicted FSIQ	.030***	.023***	.020***
Sex (0 = female)	-.122	.038	-.076
Race (0 = non-white)	.404***	.268**	.202*
Psychiatric Medication Use	.115	.063	.026
GAF Symptom Severity	.006*	.006*	.003
Clinical Diagnosis			
Lifetime PTSD	-.190	-.141	.115
Current PTSD	-.092	-.206	.294
Lifetime Panic Disorder	.064	.037	.083
Current Panic Disorder	-.224	.167	.172
Lifetime Agoraphobia	-.349	-.377	.196
Current Agoraphobia	-.545	-.509	.200
Lifetime Social Anxiety	-.136	-.169	-.182
Current Social Anxiety	-.152	-.152	-.219
Lifetime Specific Phobia	-.055	-.080	-.046
Current Specific Phobia	-.093	-.088	-.104
Lifetime OCD	-.096	-.084	-.032
Current OCD	-.129	-.111	.059
Lifetime GAD	-.025	-.058	-.096
Current GAD	-.109	-.097	-.087
Lifetime SUD	.064	-.034	.173
Current SUD	-.055	-.136	.102
Lifetime AUD	.017	-.008	.088
Current AUD	.055	.038	.097

Note. *** $p < .001$, ** $p < .01$, * $p < .05$

APPENDIX

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Approval Notice
Continuing Review

August 29, 2017

Stewart Shankman, Ph.D.
Psychology
1007 W Harrison
Room 1018D, M/C 285
Chicago, IL 60607
Phone: (312) 355-3812 / Fax: (312) 413-4122

RE: Protocol # 2012-0646
"Family Study of Emotion and Physiology"

Dear Dr. Shankman:

Your Continuing Review was reviewed and approved by the Convened review process on August 22, 2017. You may now continue your research.

Please note the following information about your approved research protocol:

As you indicated in your response to the administrative request sent on August 24, 2017, you are not actually measuring HBA1C levels. As such, all applicable documents (i.e., research protocol, initial review application, etc.) must be revised to remove this information. You also indicated that Danelle Hee will no longer participate in the study as key research personnel. Ms. Hee has been removed as research personnel, but the recruitment document listing her as a contact must be revised to include a new contact person. Please submit an amendment to make the aforementioned changes.

Protocol Approval Period: August 22, 2017 - August 22, 2018
Approved Subject Enrollment #: 1000 Total (793 enrolled)
Additional Determinations for Research Involving Minors: These determinations have not been made for this study since it has not been approved for enrollment of minors.
Performance Sites: UIC

Sponsor: National Institute of Mental Health, NIAAA - National Institute on Alcohol Abuse and Alcoholism, NIMH
PAF#: 00028539, 00023640, Not available
Grant/Contract No: F31 AA 22273-01A1, MH098093-01, R01MH098093-03S2
Grant/Contract Title: Response to Unpredictable Threat in Alcohol Dependence and Panic Disorder, Family Study of Reward and Threat Sensitivity in Internalizing Psychopathology, Not available
Research Protocol(s):

a) Family study of emotion and physiology; Version #12, 02/09/2016

Recruitment Material(s):

a) Flyer: Family study of emotion and physiology (alcohol); Version 6, 06/19/2015
b) Flyer: Family study of emotion and physiology (panic attacks); Version 6, 06/19/2015
c) Flyer: Family study of emotion and physiology (feeling); Version 6, 06/19/2015
d) Flyer: Family study of emotion and physiology (depression); Version 6, 06/19/2015
e) Flyer: Family study of emotion and physiology (anxiety); Version 6, 06/19/2015
f) Flyer: Family study of emotion and physiology (traumatic event); Version 6, 06/19/2015
g) Flyer: Family study of emotion and physiology (social situations); Version 6, 06/19/2015
h) Telephone Screening Script for Potential Probands or Siblings; Version 8, 02/09/2016
i) Telephone Screening Script for Family Members of Participants, Version 5, 02/09/2016
j) Flyer: Family study of Emotion and Physiology, P (panic) v2-12.9.15
k) Flyer with pull tabs: Family Study of Emotion and Physiology (paid study emotions) v2 - 10.6.16
l) Flyer: Family study of Emotion and Physiology, P (anxiety) v2-12.9.15
m) Flyer: Family study of Emotion and Physiology, P (emotion) v2-12.9.15
n) Flyer: Family study of Emotion and Physiology, P (depression) v2-12.9.15
o) Flyer: Family study of Emotion and Physiology, S (controls) v3-3.2.16
p) Flyer with pull tabs: Family Study of Emotion and Physiology (dep/anx/panic) v2 - 10.6.16
q) CTA AD, "Be in a paid study with your brother or sister!" as submitted to OPRS on May 19, 2016
r) Flyer: Family study of Emotion and Physiology, P (social) v2-12.9.15
s) Flyer: Family study of Emotion and Physiology, P (alcohol) v2-12.9.15
t) Flyer: Family study of Emotion and Physiology, P (trauma) v2-12.9.15

Informed Consent(s):

a) Family Member Consent, Version 7, 02/09/2016
b) Proband/Sibling Consent; Version 12, 02/09/2016
c) Alteration of informed consent (including family members) [45 CFR 46.116(d)] and

Waiver of Documentation of informed consent [45 CFR 46.117(c)] for telephone screening.

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
08/02/2017	Continuing Review	Convened	08/22/2017	Approved

Please remember to:

→ Use your **research protocol number** (2012-0646) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements in the guidance document,
"UIC Investigator Responsibilities, Protection of Human Research Subjects"
(http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 355-1404. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Sheilah R. Graham, MPH
IRB Coordinator, IRB # 3
Office for the Protection of Research Subjects

Enclosure(s):

1. **Informed Consent Document(s):**
   a) Proband/Sibling Consent; Version 12, 02/09/2016
   b) Family Member Consent, Version 7, 02/09/2016

2. Recruiting Material(s):

a) Flyer: Family study of emotion and physiology (alcohol); Version 6, 06/19/2015
b) Flyer: Family study of emotion and physiology (panic attacks); Version 6, 06/19/2015
c) Flyer: Family study of emotion and physiology (feeling); Version 6, 06/19/2015
d) Flyer: Family study of emotion and physiology (depression); Version 6, 06/19/2015
e) Flyer: Family study of emotion and physiology (anxiety); Version 6, 06/19/2015
f) Flyer: Family study of emotion and physiology (traumatic event); Version 6, 06/19/2015
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l) Flyer: Family study of Emotion and Physiology, P (anxiety) v2-12.9.15
m) Flyer: Family study of Emotion and Physiology, P (emotion) v2-12.9.15
n) Flyer: Family study of Emotion and Physiology, P (depression) v2-12.9.15
o) Flyer: Family study of Emotion and Physiology, S (controls) v3-3.2.16
p) Flyer with pull tabs: Family Study of Emotion and Physiology (dep/anx/panic) v2 - 10.6.16
q) CTA AD, "Be in a paid study with your brother or sister!" as submitted to OPRS on May 19, 2016
r) Flyer: Family study of Emotion and Physiology, P (social) v2-12.9.15
s) Flyer: Family study of Emotion and Physiology, P (alcohol) v2-12.9.15
t) Flyer: Family study of Emotion and Physiology, P (trauma) v2-12.9.15

cc: Michael E. Ragozzino, Psychology, M/C 285
OVCR Administration, M/C 672

CURRICULUM VITA

Huiting Liu

EDUCATION

2013 – 2019	University of Illinois at Chicago, Chicago, Illinois Ph.D. in Clinical Psychology (APA accredited)
2010 – 2011	Teachers College, Columbia University, New York, New York M.A. in Psychology in Education, Personality and Psychopathology Track
2006 – 2010	Grinnell College, Grinnell, Iowa B.A. in Psychology and Policy Studies

AWARDS AND HONORS

2016	Christopher B. Keys Award for Early Outstanding Research Achievement, University of Illinois at Chicago
2015	NIMH Training Course in fMRI, selected trainee, University of Michigan
2014	Student Poster Distinguished Award, Society for a Science in Clinical Psychology
2010 – 2011	Arthur Zankel Urban Fellowship, Teachers College, Columbia University

PEER-REVIEWED JOURNAL ARTICLES

1. Correa, K. A., **Liu, H.**, & Shankman, S. A. (2019). The role of intolerance of uncertainty in current and remitted internalizing and externalizing psychopathology. *Journal of Anxiety Disorders, 62*, 68-76. http://doi.org/10.1016/j.janxdis.2019.01.001

2. **Liu, H.**, Lieberman, L., & Shankman, S. A. (2017). Ethical considerations in the use of psychophysiological methods to identify biological markers for internalizing disorders. *Journal of Ethics in Mental Health, 10,* 1-12.

3. Hayes, S. M., Hayes, J. P., Williams, V. J., **Liu, H.**, & Verfaellie, M. (2017). FMRI activity during associative encoding is correlated with cardiorespiratory fitness and source memory performance in older adults. *Cortex, 91*, 208-220. http://doi.org/10.1016/j.cortex.2017.01.002

4. **Liu, H.**, Lieberman, L., Stevens, E., Auerbach, R. P., & Shankman, S. A. (2017). Using a cultural and RDoc framework to conceptualize anxiety in Asian Americans. *Journal of Anxiety Disorders, 48*, 63-69. http://doi.org/10.1016/j.janxdis.2016.09.006

5. **Liu, H.**, Sarapas, C., & Shankman, S.A. (2016). Anticipatory reward deficits in melancholia. *Journal of Abnormal Psychology, 125*, 631-640. http://doi.org/10.1037/abn0000172

6. Lieberman, L., **Liu, H.**, Huggins, A.A., Katz, A.C., & Zvolensky, M.J., & Shankman, S.A. (2016). Comparing informant- and self-reports of personality to laboratory indices of emotional responding. *Psychophysiology, 53*, 1386-1397. http://doi.org/10.1111/psyp.12680

7. Nelson, B.D., **Liu, H.**, & Sarapas, C., Shankman, S.A. (2016). Intolerance of uncertainty mediates the relationship between panic and the startle reflex in anticipation of unpredictable threat. *Journal of Experimental Psychopathology, 7*, 172-189. http://doi.org/10.5127/jep.048115

8. Weinberg, A., **Liu, H.**, & Shankman, S.A. (2016). Blunted neural response to errors as a trait marker of melancholic depression. *Biological Psychology, 113*, 100-107. http://doi.org/10.1016/j.biopsycho.2015.11.012

9. Weinberg, A., **Liu, H.**, Hajcak, G., & Shankman, S.A. (2015). Blunted neural response to rewards as a vulnerability factor for depression: Results from a family study. *Journal of Abnormal Psychology, 124*, 878-889. http://doi.org/10.1037/abn0000081

10. Gorka, S.M., **Liu, H.**, Klein, D., Daughters, S., & Shankman, S.A. (2015). Is risk-taking propensity a familial risk factor for alcohol use problems? An examination in two separate samples. *Journal of Psychiatric Research, 68*, 54-60. http://doi.org/10.1016/j.jpsychires.2015.05.019

11. Gorka, S.M., **Liu, H.**, Sarapas, C., & Shankman, S.A. (2015). Time course of threat responding in panic disorder and depression. *International Journal of Psychophysiology, 98*, 87-94. http://doi.org/10.1016/j.ijpsycho.2015.07.005

12. Yang, L.H., Tu, M., **Liu, H.**, & Opler, M. (2011). The role of subtypes in understanding disease processes within schizophrenia: Case example of 'deficit syndrome'. *Shanghai Archives of Psychiatry, 23*, 109-111.

BOOK CHAPTERS

1. **Liu, H.**, & Shankman, S. A. (2017). Double depression. In *The SAGE Encyclopedia of Abnormal and Clinical Psychology*. Thousand Oaks, CA: SAGE Publications Inc.

MANUSCRIPTS UNDER REVIEW

1. Meissel, E. E., **Liu, H.**, Stevens, E. S., Evans, T. C., Britton, J. C., & Shankman, S. A. (under review). The reliability and validity of response-based measures of attention bias.

2. Lieberman, L., Funkhouser, C. J., Gorka, S. M., **Liu, H.**, Berenz, E. C., Phan, K. L., & Shankman, S. A. (under review). The relation between posttraumatic stress symptom severity and startle potentiation to predictable and unpredictable threat.

PEER-REVIEWED SYMPOSIA

1. Meissel, E., Stevens, E.S., **Liu, H.**, Evans, T.C., Shankman, S.A. (2017, November). The reliability and validity of novel measures of attention bias in a family study. In N. Amir (Chair), *Toward the clinical application of Cognitive Bias Modification: Addressing the psychological properties of measure.* Symposium conducted at the 51st ABCT Annual Convention, San Diego, CA.

2. Shankman, S. A., Sarapas, C., Gorka, S. M., Campbell, M. L., Katz, A. C., **Liu, H.**, Lieberman, L., DeLizza, A. A., Hodges, A. M., & Huggins, A. A. (2014, September). Family study of reward and threat sensitivity in internalizing psychopathology. In S. Morris (Chair), *The NIMH Research Domain Criteria initiative: Overview and exemplars*. Symposium conducted at the 28th annual meeting of the Society for Research in Psychopathology, Chicago, IL.

PEER-REVIEWED PRESENTATIONS

1. **Liu, H.**, Miller, M., Turner, A., Pagulayan, K., Twamley, E. W., … & Williams, R. (2019, February). *Compensatory strategy use in Veterans with mild traumatic brain injury: Secondary results from a Compensatory Cognitive Training clinical trial*. Poster session presented at the 21st annual Rehabilitation Psychology conference, Orlando, FL.

2. **Liu, H.**, Langenecker, S., Pliskin, N., Lamar, M., Nusslock, R., & Shankman, S. A. (2019, February). *Executive dysfunction as risk for depression*. Poster session presented at the 47th annual meeting of the International Neuropsychological Society, New York, NY.

3. **Liu, H.**, Hee, D., Weinberg, A., & Shankman, S. A. (2017, November). *Effects of childhood emotional neglect on subsequent error processing and psychopathology*. Poster session to be presented at the 33rd annual meeting of the International Society for Traumatic Stress Studies, Chicago, IL.

4. Correa, K., Lieberman, L., **Liu, H.**, & Shankman, S. A. (2017, April). *Does intolerance of uncertainty run in families?* Poster session presented at the 20th annual meeting of the Anxiety and Depression Association of America, San Francisco, CA.

5. Hayes, S. M., Hayes, J. P., Williams, V. J., **Liu, H.**, & Verfaellie, M. (2017, February). *fMRI activity during associative encoding is correlated with cardiorespiratory fitness and source memory performance among older adults.* Paper presented at the 45th annual meeting of the International Neuropsychological Society, New Orleans, LA.

6. **Liu, H.**, Sarapas, C., Lieberman, L., Stevens, E. S., & Shankman, S. A. (2017, February). *Relationships between emotion regulation and executive functions*. Poster session presented at the 45th annual meeting of the International Neuropsychological Society, New Orleans, LA.

7. **Liu, H.**, Funkhouser, C. J., Sarapas, C., & Shankman, S. A. (2016, September). *Reliability of two measures of attention to emotional stimuli.* Poster session presented at the 30th Annual Meeting of the Society for Research in Psychopathology, Baltimore, MD.

8. Meissel, E. E. E., Funkhouser, C. J., **Liu, H.**, & Shankman, S. A. (2016, September). *Investigating the reliability of different measures from the dot-probe task and using personal and family history of social anxiety disorder as validators*. Poster session presented at the 30th Annual Meeting of the Society for Research in Psychopathology, Baltimore, MD.

9. Sarapas, C., **Liu, H.**, Lieberman, L., Stevens, E. S., & Shankman, S. A. (2016, February). *Relationships between attention and anxiety in low- and high-stress contexts*. Poster session presented at 44th annual meeting of the International Neuropsychological Society, Boston, MA.

10. **Liu, H.**, Sarapas, C., Langenecker, S. A., & Shankman, S. A. (2015, September). *Anticipatory reward deficits in melancholia.* Poster session presented at the 55th annual meeting for the Society for Psychophysiological Research, Seattle, WA.

11. Katz, A. C., **Liu, H.**, Stevens, E., Shankman, S. A. (2015, September). *Coherence of reward-related prefrontal asymmetry between siblings.* Poster session presented at the 29th annual Meeting of the Society for Research in Psychopathology, New Orleans, LA.

12. Lieberman, L., **Liu, H.**, Huggins, A.A., Gorka, S.M., Sarapas, C., Shankman, S.A. (2015, May). *Informant-reports but not self-reports of personality predict psychophysiological indices of positive and negative emotional responding*. Poster session presented at the 27th annual Meeting for the Association for Psychological Science, New York, New York.

13. **Liu, H.**, Sarapas, C., & Shankman, S. A. (2015, March). *Reward processing as a familial risk marker for internalizing psychopathology*. Poster session presented at the first annual meeting of the International Convention of Psychological Science (under the auspices of Association for Psychological Science), Amsterdam, The Netherlands.

14. **Liu, H.**, Katz, A. C. Nelson, B. D., Sarapas, C., Gorka, S. M., Campbell, M. L. & Shankman, S. A. (2014, September). *The effect of melancholia and atypical depression on EEG asymmetry during reward processing.* Poster session presented at the 28th annual meeting of the Society for Research in Psychopathology, Chicago, IL.

15. Sarapas, C., **Liu, H.**, Huggins, A. A., DeLizza, A. A., Hogdes, A. M., & Shankman, S. A. (2014, September). *Biased attention to threat and familial risk for anxiety disorders*. Poster session presented at the 28th annual meeting of the Society for Research in Psychopathology, Chicago, IL.

16. **Liu, H.**, Gorka, S. M., Sarapas, C., & Shankman, S. A. (2014, May). *Time course of threat responding in panic disorder.* Poster session presented at the 26th annual Association for Psychological Science convention, San Francisco, CA.

17. Nguyen, K., Tu, M., **Liu, H.**, Li, V. (2012, August). *Effects of acculturation on explanatory models for schizophrenia among Chinese immigrants*. Poster session presented at the 120th annual American Psychological Association convention, Orlando, FL.

18. **Liu, H.**, Tu, M., Nguyen, K. (2012, May). *Westernization and its effects on Chinese immigrant caregivers of schizophrenics*. Poster session presented at the 24th annual Association for Psychological Science convention, Chicago, IL.

19. Tu, M., **Liu, H.**, Nguyen, K. (2012, February). *Impact of immigration and westernization on explanatory models of schizophrenia among Chinese immigrant families*. Poster session presented at the 29th annual Winter Roundtable Conference, New York, NY.

20. **Liu, H.**, Frantz, R., Pauker, R., & Hsu, Y. (2011, August). *Indigenous labeling as explanation for schizophrenic symptoms: How Chinese immigrant relatives cope with severe mental illness and its implications*. Poster session presented at the 119th annual American Psychological Association convention, Washington, DC.

EDITORIAL EXPERIENCE

Ad Hoc Reviewer *Journal of Abnormal Psychology (with Dr. Shankman)*
Psychological Science (with Dr. Shankman)
APA Annual Convention, Division 35

CLINICAL EXPERIENCE

2018 – 2019	VA Puget Sound Health Care System, Seattle Division, Seattle, WA Doctoral Internship in Clinical Psychology (APA accredited)
2017 – 2018	Edward Hines, Jr. VA Hospital, Hines, IL Neuropsychology Extern
2014 – 2018	Office of Applied Psychological Services, UIC, Chicago, IL Practicum Therapist
2016 – 2017	Illinois Neuropsychiatric Institute, Chicago, IL Neuropsychology Extern
2016 – 2017	Neuropsychological Services, PC, Chicago, IL Psychometrist
2016 – 2017	Rush University Medical Center, Chicago, IL

Psychodiagnostic Assessor, Traumatic Stress and Resilience Study

2015 – 2017 Office of Applied Psychological Services, UIC, Chicago, IL
Practicum Assessor

TEACHING EXPERIENCE

2013 – 2018 Department of Psychology, UIC, Chicago, IL
Teaching Assistant
Abnormal Psychology
Psychology of Interviewing
Developmental Psychology
Community Psychology
Community Psychology Laboratory
Introduction to Psychology

2009 – 2010 Department of Psychology, Grinnell College, Grinnell, IA
Teaching Assistant
Introduction to Psychology with Lab

2009 – 2010 Department of Psychology, Grinnell College, Grinnell, IA
Department Tutor

PROFESSIONAL EXPERIENCE

2018 – Present VA Puget Sound Health Care System, Seattle Division
Diversity Committee (Secretary)
Intern Selection Committee

2016 – 2018 Association of Neuropsychology Students in Training (ANST)
UIC Chapter co-founder and chapter representative

2012 – 2013 VA Boston Healthcare System, National Center for PTSD
Head psychology technician