The Role of Cognitive Deficits in Vulnerability to Depression and Anxiety:

An Individual Differences and Neuroimaging Approach

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
Psychology and Neuroscience in the Graduate School
of Duke University

2018

ABSTRACT

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Abstract

Mood and anxiety disorders are heterogenous disorders that display complex symptom presentations. While cognitive deficits have been demonstrated in meta-analyses of currently depressed individuals (Snyder, 2013), a number of questions remain as to the role of cognitive deficits in depression. Given ongoing debates about whether the FDA should approve drugs to treat cognitive deficits associated with depression (Ledford, 2016; Mullard, 2016), it is essential to gain a more complete understanding of the role of cognitive function in the disorder.

This dissertation is comprised of three studies that broadly explore the association between cognitive functioning and depressive diagnoses and symptoms. First, I look at the longitudinal relationship between cognitive function and later depression through a systematic review and meta-analysis of the extant literature, **"The Association Between Cognitive Function and Subsequent Depression: A Systematic Review and Meta-Analysis."** I find that cognitive function predicts future depressive symptoms and diagnoses, but that this effect is likely driven by depressive symptoms at the time of cognitive testing. The value of a dimensional versus categorical frameworks of psychopathology is discussed. Next, I investigate this relationship with more precision by studying the association between cognitive function and depression in two well-documented longitudinal datasets. Here, I find that comorbid diagnoses play an

important role in moderating the association between cognitive function and depression, "**Is Low Cognitive Functioning a Predictor or Consequence of Major Depressive Disorder? A Test in Two Longitudinal Birth Cohorts."** Finally, I look at neural correlates of cognitive function in relation to symptoms of mood and anxiety disorders broadly, "**Thinking and Feeling: Individual Differences in Habitual Emotion Regulation and Stress-Related Mood are Associated with Prefrontal Executive Control**." I find that dorsolateral prefrontal activity during a non-emotion-related working memory task is associated with both mood and anxiety symptoms and clinical diagnoses. Additionally, the results suggest that cognitive reappraisal is also associated with this prefrontal activity, indicating a possible mechanism through which cognitive function is related to mood and anxiety symptoms. The results of these studies are discussed in regards to implications for targeting treatments for mood and anxiety disorders.

Dedication

I dedicate this dissertation to my parents, Ellen and Larry Scult, to my brother, Corey Scult, and to my partner, Allison Pincus. Thank you for always being by my side, and for encouraging me to explore my interests, wherever they may take me.

I also dedicate this dissertation to my advisors, Ahmad Hariri and Tim Strauman. I cannot thank you enough for providing me with a balance of support, encouragement, and flexibility to forge my own unique path through graduate school. I could not imagine better mentors and role models.

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I would like to thank the Hariri and Strauman lab members and my co-authors on these publications, who provided invaluable support with data collection, analyses, figure help, and moral support over the years. Annchen Knodt played a particularly large role in teaching me fMRI and genetic analyses, and seemed to have infinite patience while doing so.

I would like to thank my community of friends throughout graduate school. My CNAP cohort: Korrina, Mai-Anh, Hanna, Jonathan and Seth, and my clinical cohort: Adrienne, Nandini, Ali, Jon, and Allison. And all my other graduate school friends, who made my time in Durham a blast.

I also have had so much support from my family: my parents, my brother and Allison, as well as from my grandfathers, and from Jonathan, Sue, Laurie and Robert.. Thank you all so much for being excited for me with every update I sent over the years.

I was also fortunate to receive funding that made this research possible. In particular, I would like to thank the National Science Foundation and the Duke Social Science Research Institute.

1. Introduction

The global public health impact of mood and anxiety disorders continues to rise while effective treatment remains lacking (Craske et al., 2017). Part of the reason for this may be the highly heterogenous nature of both the disorders and available treatments (Bandelow et al., 2015; Newby, McKinnon, Kuyken, Gilbody, & Dalgleish, 2015). While some studies have suggested the disheartening trend of decreasing treatment effectiveness over time (Johnsen & Friborg, 2015), a number of new approaches inspire hope that we may be able to improve treatment outcomes by better targeting treatments to specific characteristics of patients (e.g. Drysdale et al., 2016).

One particularly promising marker of dysfunction are cognitive deficits, which have been associated with transdiagnostic psychiatric disorder (Caspi et al., 2014). Especially relevant to the purposes of this dissertation, the diminished ability to concentrate as well as broader deficits in thinking are listed as DSM-V criteria of both major depressive disorder and generalized anxiety disorder (American Psychiatric Association, 2013). In this general introduction, I begin with an overview of cognitive functioning and related neural circuitry. I then discuss the relevance of cognitive functioning to mood and anxiety disorders. The bulk of the dissertation is spent systematically evaluating the role of cognitive function in depression and anxiety with the goal of identifying whether cognitive functioning and related neural circuitry could

act as a treatment target for enhancing the effectiveness of interventions for emotional disorders.

1.1. *Cognitive Functioning*[1]

The vast capacity of the human mind to engage in complex thought can be captured by a single factor representing general cognitive ability or "*g*" (Johnson, Bouchard, Krueger, McGue, & Gottesman, 2004; Spearman, 1904). Empirical findings have suggested the existence of this single construct of cognition through high correlations between disparate cognitive tasks (Spearman, 1904). This construct of general cognitive ability is usually determined by giving a participant a wide range of tasks and using factor analysis to determine the shared variance (Ree & Earles, 1991). Even in cases when "*g*" is not calculated, however, there are other common ways of capturing general processing by combing across cognitive tasks such as by calculating measures of executive function or intelligence.

Executive functions have been defined as "general purpose control mechanisms that modulate the operation of various cognitive subprocesses" (Miyake et al., 2000, p.50). According to an influential model of executive functioning, the three primary executive

[1] Part of this chapter is based on the following publication: Scult, M.A., Trampush, J.W., Zheng, F., Conley, E.D., Lencz, T., Malhotra, A.K., Dickinson, D., Weinberger, D.R. & Hariri, A.R. (2015). A common polymorphism in *SCN2A* predicts general cognitive ability through effects on PFC physiology. *Journal of Cognitive Neuroscience*, 27(9), 1766-1774.

functions are: updating and monitoring of information (updating), shifting between information sets (shifting), and inhibiting automatic responses (inhibition) (Miyake et al., 2000). Executive functioning is typically assessed through administration of a neuropsychological battery to tap into these domains (Delis, Kaplan, & Kramer, 2001). Similarly, the concept of intelligence has been defined as a domain-general ability that "…among other things, involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience" (Gottfredson, 1997). The common tests of intelligence produce an intelligence quotient or IQ (Deary, Penke, & Johnson, 2010). Although executive function and intelligence are often considered independently, evidence has suggested that at higher level constructs, executive function and intelligence have correlations approaching 1.0 and may best be characterized by an integrated framework based on a common neural network (Barbey et al., 2012).

The neural architecture supporting general cognitive function is thought to rely on the ability of the brain to flexibly reconfigure based on task demands (Barbey, 2018; Scult & Hariri, 2018). The prefrontal cortex, and the dorsolateral prefrontal cortex (dlPFC) in particular, may play a critical role in coordinating these network dynamics (Badre & Nee, 2018). In fact, among classic functional connectivity studies, the fronto-parietal network is virtually synonymous with central executive function, and is centered around a core hub in the dlPFC (Bressler & Menon, 2010).

Additionally relevant to this discussion, dlPFC function has been found to account for the common variance in performance across cognitive tasks (Barbey, Colom, & Grafman, 2013), in that patients with focal dlPFC lesions have lower *"g"* scores than do patients with lesions to other brain regions. Other lesion studies have come to similar conclusions, finding that dlPFC lesions lead to deficits across a wide range of functions including working memory, rule learning, planning, attention and motivation (Szczepanski & Knight, 2014). Importantly, the dlPFC appears to contribute to the shared variance across tasks rather than performance unique to particular tasks, as the correlations between dlPFC lesions and specific tasks are no longer significant once this shared variance is taken into account (Barbey et al., 2013). These findings raise the intriguing possibility that the role of the dlPFC in coordinating brain network function may extend to the shared variance of processing emotional content as well.

1.2 Cognitive Functioning in Mood and Anxiety Disorders

Parallel findings in the cognitive and affective literatures have led these fields to slowly converge over time. The influential "cognitive theory of depression" frames depression as a disorder primarily of disrupted thinking (Beck, 1963), which is now also considered a key factor in emotional disorders broadly (Ellard, Fairholme, Boisseau, Farchione, & Barlow, 2010). However, these disruptions of thinking in mood and anxiety disorders are generally described in the context of negatively-valenced content rather

than in basic deficits in information-processing (Beck, 1963). As a result of this influential early work, and later work by Abramson and colleagues (Abramson, Seligman, & Teasdale, 1978), studies on cognitive vulnerability to mood and anxiety disorders have tended to focus on negative beliefs about the self (Bohon, Stice, Burton, Fudell, & Nolen-Hoeksema, 2008; Carter & Garber, 2011) or sometimes on attention and memory biases specifically for emotional content (Mathews & MacLeod, 2005), rather than on broad deficits in the ability to process information.

This approach, however, can be overly limiting. While cognitive tests and ruminative negative beliefs may appear distinct on the surface, both require a person to process information (e.g. "someone said something mean to me" or "this shape is similar to these other shapes") in order to come to a conclusion (e.g. "I feel sad" or "the answer is option #2"). At this domain-general level of information-processing, there are important clues that could help predict how well someone will be able to process emotions, and as a result, their likelihood of developing a disorder like depression.

Neuroimaging research has supported the idea that the boundaries between cognitive and emotional functioning are superficial distinctions (Barrett, 2017), and that the dlPFC may play a critical role in processing both (Ochsner & Gross, 2005). A number of studies have found dysregulation of the dlPFC in mood and anxiety disorders (Ball, Ramsawh, Campbell-Sills, Paulus, & Stein, 2013; Hamilton et al., 2012). In particular, resting-state connectivity studies have found hypoactive frontoparietal network

connectivity, especially dlPFC connectivity with posterior parietal cortex, (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015), involved in cognitive control of attention and emotional regulation.

Furthermore, there has been evidence of hypoconnectivity between medial prefrontal cortex (mPFC) and limbic regions, reflecting weaker positive connectivity between the ventral striatum and the mPFC as well as enhanced negative connectivity between the amygdala and mPFC (Kaiser et al., 2015). The dmPFC is thought to mediate the dlPFC function on these subcortical regions (Hariri, 2015; Kaiser et al., 2015), which manifests as decreased and increased functional connectivity between the dlPFC and VS, and the dlPFC and amygdala, respectively in depression (Heller et al., 2009; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007).

1.2. *The Present Studies*

As can be seen from the aforementioned studies, cognitive functioning and related neural circuitry certainly have a role to play in mood and anxiety disorders. The nature of this relationship, however, needs further testing. In particular, there are two broad outstanding questions regarding the association between cognitive functioning and mood and anxiety disorders. The first is the temporal relationship of these deficits. The temporal relationship is important for determining whether cognitive deficits may act as a risk factor or treatment target for mood and anxiety disorders. A second

question is whether cognitive deficits show specificity for either or both of these disorders or whether cognitive functioning may serve as a transdiagnostic marker of dysfunction.

These questions are investigated through the following three studies. The first is a systematic review and meta-analysis of the extant literature on longitudinal associations between cognitive functioning and depression. The purpose of this study is to test whether cognitive deficits exist prior to the onset of depression and therefore may act as a risk factor for development of the disorder. The second study continues to investigate the temporal association by testing the role of comorbid psychiatric conditions in the development of cognitive deficits over time. The third study tests whether dlPFC function may act as a transdiagnostic marker of deficits in cognitive and emotional processing. The findings are discussed in light of the implications for targeting treatments based on prefrontal function for mood and anxiety disorders.

2. Cognitive Function and Subsequent Depression: A Systematic Review and Meta-Analysis[1]

2.1. *Background*

A growing literature has found that depression is associated with impaired cognitive functioning (Snyder, 2013). For example, broad deficits in neuropsychological functioning have been demonstrated in a number of reviews and meta-analyses on depression (Christensen, Griffiths, & Mackinnon, 1997; Rock, Roiser, Riedel, & Blackwell, 2014; Rogers et al., 2004; Snyder, 2013), and cognitive deficits have been found to correlate with symptom severity (McDermott & Ebmeier, 2009). Theoretical models have been proposed suggesting that cognitive dysfunction could either be a risk factor for later depression or that cognitive function may be impaired as a result of depression (Barnett, Salmond, Jones, & Sahakian, 2006; Stern, 2003). In support of the latter hypothesis, two recent meta-analyses concluded that the deficits in cognitive function persist after remission from depression (Bora, Harrison, Yücel, & Pantelis, 2013; Rock et al., 2014). However, evidence showing that deficits in cognitive function persist after remission from depression, which are primarily derived from cross-sectional studies, does not rule out the possibility that poor cognitive function preceded the onset of depression. The present

[1] This chapter is based on the following publication: Scult, M.A., Paulli, A.R., Mazure, E.S., Moffitt, T.E., Haririr, A.R., & Strauman, T.J. (2017). The association between cognitive function and subsequent depression: a systematic review and meta-analysis. *Psychological Medicine*, 47(1), 1-17.

review and meta-analysis sought to comprehensively summarize the state of the research on cognitive function and its association with future depressive symptoms using data from longitudinal studies.

While the clinical diagnosis of depression is relatively codified according to DSM and ICD criteria, and depression symptoms are readily measured with a number of validated instruments (Cuijpers, de Graaf, & van Dorsselaer, 2004; Lewinsohn, Solomon, Seeley, & Zeiss, 2000), a similar canonical approach to measuring cognitive function is not present. Thus, it is important to specify a working definition of cognitive function before examining its possible association with depression. Empirical work has reinforced the concept of a single construct of cognitive function through high correlations in performance among disparate cognitive tasks (Spearman, 1904). This has led to the derivation of a single factor representing general cognitive function or ability known as "*g*" (Johnson et al., 2004). The "*g*" factor is commonly determined by administering a wide range of tasks and using factor analysis to determine the shared variance across these tasks (Ree & Earles, 1991). Even in cases when "*g*" is not calculated as such, there are other customary ways of capturing this general factor by combing across cognitive tasks, e.g., by creating an index of executive functions (Miyake et al., 2000) or measuring the intelligence quotient (Gottfredson, 1997).

Although executive functions and intelligence are often considered independently, evidence has suggested that they may best be characterized by an

integrated framework based on a common neural network (Barbey et al., 2012), supporting the idea that they reflect a shared general factor of cognitive ability. In light of these findings and the observation that individuals with depression commonly exhibit deficits across a range of cognitive tasks, this review used the broadest measure of cognitive function that was available in a given study. Analyses were further restricted to prospective cohort studies with depression assessment before age 65 in order to minimize potential influences of age-related cognitive decline.

When a higher-order construct was not available, results from individual measures were used. The literature review is followed by a quantitative meta-analysis to (1) determine whether cognitive function predicts later depression, (2) evaluate whether differences in the measurement of depression (categorical vs. continuous) influence observed associations, and (3) examine whether sex or age of participants may moderate effects, and (4) whether effects are confounded by depression symptoms at baseline.

2.2. *Methods*

I followed the Meta-Analyses of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000) (Table 1) and the literature search strategies suggested by Atkinson et al. (Atkinson, Koenka, Sanchez, Moshontz, & Cooper, 2015).

Table 1: MOOSE Checklist

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	It is unknown whether cognitive deficits may act as a risk factor for depression
√	Hypothesis statement	Cognitive function predicts later depression
√	Description of study outcomes	Depression symptoms or diagnosis
√	Type of exposure or intervention used	None, time
√	Type of study designs used	I only included prospective cohort studies
√	Study population	Under age 65, with no MDD diagnosis at baseline
Reporting of search strategy should include		
√	Qualifications of searchers	A research librarian (EM) conducted the search
√	Search strategy, including time period included in the synthesis and keywords	See Table 2
√	Databases and registries searched	PubMed, EMBASE and PsycInfo
√	Search software used, name and version, including special features	A search software was not used. EndNote X7 was used to merge retrieved citations and eliminate duplicates
√	Use of hand searching	I hand-searched bibliographies of retrieved papers for additional references.
√	List of citations located and those excluded, including justifications	See Figure 1
√	Method of addressing articles published in languages other than English	An English language search was conducted, if papers were found in other languages, translated versions were used
√	Method of handling abstracts and unpublished studies	Unpublished studies were included if relevant
√	Description of any contact with authors	I contacted the authors by email if additional data was needed for the meta-analysis

Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Described in methods section
√	Rationale for the selection and coding of data	Described in methods section
√	Assessment of confounding	Subgroup analyses and meta-regression. See Figure 4.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	See Table 4
√	Assessment of heterogeneity	Heterogeneity of the studies were explored within two types of study designs using Cochrane's Q test of heterogeneity and I^2 statistic
√	Description of statistical methods in sufficient detail to be replicated	Detailed in methods section
√	Provision of appropriate tables and graphics	See figures 1-5 and tables 1-4
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2
√	Table giving descriptive information for each study included	Table 3
√	Results of sensitivity testing	Analyses controlling for baseline depression symptoms, see Figure 4
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates
Reporting of discussion should include		
√	Quantitative assessment of bias	Figure 5 and description in results section

√	Justification for exclusion	See methods section
√	Assessment of quality of included studies	Table 4
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	"…performance on cognitive tests may be a sensitive measure of motivational state that could augment self-reported symptoms. Alternatively, the co-occurrence of cognitive deficits and depression symptoms may reflect a shared etiology in dysfunction of neural circuits supporting both cognitive and emotional processes."
√	Generalization of the conclusions	"…findings suggest that prior studies of links between cognitive function and depression that did not assess baseline symptoms may have overestimated the potential protective role of higher cognitive function. "
√	Guidelines for future research	"The findings have important implications for future studies, in highlighting the need to control for subthreshold symptoms when investigating risk factors for psychological disorders."
√	Disclosure of funding source	Financial support section

2.2.1. Search Process

Systematic searches were conducted in February 2015, and updated in December 2015 in three electronic databases: PubMed, EMBASE and PsycInfo. Searches were conducted by a research librarian, EM, and overseen by MS. The search syntax was adapted for each database and designed to capture the participants, predictors, comparisons and outcomes described below, according to the PICOS framework (Moher & Liberati, 2009). The Boolean operator "OR" was used within categories and the operator "AND" was used between categories. The complete search strategy is described in Table

2. Hand searches were conducted of the reference lists of included articles.

Table 2: Search Strategy. Updated searches were run in December 2015. Additional results from each database were: PubMed: 294; Embase 326; PsycInfo: 107.

PubMed

Search	Query	Number of Results
#1	Search IQ[tiab] OR "intelligence"[MeSH:NoExp] OR "intelligence"[tiab] OR "aptitude tests"[MeSH Terms] OR "aptitude"[tiab] OR "Cognitive Ability"[tiab] OR cognitive function*[tiab] OR "Executive Function"[Mesh] OR Executive Function*[tiab] OR "neuropsychological tests"[MeSH Terms] OR neuropsychological test*[tiab] OR "Achievement"[Mesh]	165480
#2	Search MDD[tiab] OR "depressive disorder"[MeSH Terms] OR "depressive disorder"[tiab] OR "depression"[tiab] OR "depressed"[tiab] OR "depression"[MeSH Terms] OR "mood disorders"[MeSH:NoExp] OR mood disorder*[tiab]	344552
#3	Search "cohort studies"[MeSH Terms] OR "cohort"[tiab] OR longitudinal[tiab] OR prospective[tiab] OR retrospective[tiab] OR "Case-Control Studies"[Mesh] OR case-control*[tiab] OR "Follow-Up"[tiab] OR "Epidemiologic Studies"[Mesh:NoExp] OR systematic[subset] OR systematic[tw] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw]	2492651
#4	Search "risk factors"[MeSH Terms] OR risk[Mesh] OR risk[tiab] OR premorbid[tiab] OR "Prodromal Symptoms"[Mesh] OR prodromal[tiab] OR prodrome[tiab] OR "first occurrence"[tiab] OR "first episode"[tiab] OR predict[tiab] OR predictive[tiab] OR predicts[tiab] OR predicted[tiab] OR predicting[tiab] OR cause[tiab] OR causes[tiab] OR causality[tiab] OR causal[tiab] OR "statistics and numerical data"[Subheading] OR "epidemiology"[Subheading] OR "Incidence"[Mesh] OR "Prevalence"[Mesh] OR predate[tiab] OR onset[tiab] OR association[tiab] OR associated[tiab]	6322453
#5	Search "Age Factors"[Mesh] OR "Adolescent"[Mesh] OR "Middle Aged"[Mesh] OR "Adult"[Mesh:NoExp] OR "Young Adult"[Mesh] OR "Child"[Mesh] OR "Adolescent"[tiab] OR "Adolescence"[tiab] OR childhood[tiab] OR child[tiab] OR youth[tiab] OR teen[tiab] OR	6517608

Search	Query	Number of Results
	teenager*[tiab]	
#6	Search #1 AND #2 AND #3 AND #4 AND #5	2612
#7	Search english[lang]	20131774
#8	Search #6 AND #7	2524
#9	Search #8 NOT ((Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) OR (animals[mh] NOT humans[mh]))	2479

EMBASE

No.	Query	Number of Results
#1	'intelligence'/de OR 'intelligence quotient'/de OR 'intellect'/de OR 'intelligence test'/exp OR 'aptitude'/de OR 'aptitude test'/exp OR 'neuropsychological test'/exp OR 'executive function'/exp OR 'achievement'/de OR 'academic achievement'/exp OR 'achievement test'/de OR 'performance'/de OR iq:ab,ti OR intelligence:ab,ti OR aptitude:ab,ti OR 'cognitive ability':ab,ti OR 'cognitive function':ab,ti OR 'executive function':ab,ti OR 'executive functioning':ab,ti OR 'neuropsychological test':ab,ti OR 'neuropsychological tests':ab,ti	228,219
#2	'mood disorder'/de OR 'depression'/de OR 'agitated depression'/de OR 'atypical depression'/de OR 'depressive psychosis'/de OR 'dysphoria'/de OR 'dysthymia'/de OR 'endogenous depression'/de OR 'involutional depression'/de OR 'late life depression'/de OR 'major depression'/de OR 'masked depression'/de OR 'melancholia'/de OR 'mixed anxiety and depression'/de OR 'mourning syndrome'/de OR 'organic depression'/de OR 'premenstrual dysphoric disorder'/de OR 'puerperal depression'/de OR 'reactive depression'/de OR 'recurrent brief depression'/de OR 'seasonal affective disorder'/de OR 'treatment resistant depression'/de OR mdd:ab,ti OR 'depressive disorder':ab,ti OR depressed:ab,ti OR depression:ab,ti OR 'mood disorders':ab,ti OR 'mood disorder':ab,ti	525,429

#3	'cohort analysis'/de OR 'longitudinal study'/exp OR 'prospective study'/de OR 'retrospective study'/de OR 'case control study'/exp OR 'systematic review'/de OR 'meta analysis'/de OR cohort:ab,ti OR longitudinal:ab,ti OR prospective:ab,ti OR retrospective:ab,ti OR 'case control':ab,ti OR 'follow up':ab,ti OR systematic:ti OR 'meta analysis;ti' OR 'meta analyses':ti	2,426,105
#4	'epidemiology'/de OR 'epidemiological monitoring'/de OR 'risk'/de OR 'attributable risk'/de OR 'high risk population'/de OR 'intermediate risk population'/de OR 'low risk population'/de OR 'patient risk'/de OR 'high risk patient'/de OR 'intermediate risk patient'/de OR 'low risk patient'/de OR 'population risk'/de OR 'risk assessment'/de OR 'risk factor'/de OR 'risk reduction'/de OR 'incidence'/de OR 'prevalence'/de OR risk:ab,ti OR premorbid:ab,ti OR prodromal:ab,ti OR prodrome:ab,ti OR 'first occurrence':ab,ti OR 'first episode':ab,ti OR predict:ab,ti OR predictive:ab,ti OR predicts:ab,ti OR predicted:ab,ti OR predicting:ab,ti OR cause:ab,ti OR causes:ab,ti OR causality:ab,ti OR causal:ab,ti OR predate:ab,ti OR onset:ab,ti OR association:ab,ti OR associated:ab,ti	7,265,195
#5	#1 AND #2 AND #3 AND #4	3,421
#6	[article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [erratum]/lim OR [review]/lim AND [english]/lim AND ([newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim OR [young adult]/lim OR [adult]/lim OR [middle aged]/lim) AND [humans]/lim	4,627,852
#7	#5 AND #6	1832

PsycInfo

#	Query	Limiters/Expanders	Number of Results
S1	DE "Neuropsychological Assessment" OR DE "Halstead Reitan Neuropsychological Battery" OR DE "Luria Nebraska Neuropsychological Battery" OR DE "Mini Mental State Examination" OR DE "Task Switching" OR DE "Wechsler Memory Scale" OR DE "Wisconsin Card Sorting Test" OR DE "Intelligence" OR DE "Intelligence Quotient" OR DE "Intelligence	Search modes - Boolean/Phrase	247,255

	Measures" OR DE "Benton Revised Visual Retention Test" OR DE "Culture Fair Intelligence Test" OR DE "Frostig Developmental Test of Visual Perception" OR DE "Goodenough Harris Draw A Person Test" OR DE "Illinois Test of Psycholinguistic Abilities" OR DE "Kaufman Assessment Battery for Children" OR DE "Kohs Block Design Test" OR DE "Miller Analogies Test" OR DE "Peabody Picture Vocabulary Test" OR DE "Porteus Maze Test" OR DE "Raven Coloured Progressive Matrices" OR DE "Raven Progressive Matrices" OR DE "Slosson Intelligence Test" OR DE "Stanford Binet Intelligence Scale" OR DE "Wechsler Adult Intelligence Scale" OR DE "Wechsler Bellevue Intelligence Scale" OR DE "Wechsler Intelligence Scale for Children" OR DE "Wechsler Preschool Primary Scale" OR DE "Cognitive Assessment" OR DE "Ability" OR DE "Cognitive Ability" OR DE "Mathematical Ability" OR DE "Reading Ability" OR DE "Spatial Ability" OR DE "Verbal Ability" OR DE "Learning Ability" OR DE "Executive Function" OR DE "Cognitive Control" OR DE "Set Shifting" OR DE "Task Switching" OR DE "Aptitude Measures" OR DE "Armed Services Vocational Aptitude Battery" OR DE "College Entrance Examination Board Scholastic Aptitude Test" OR DE "Differential Aptitude Tests" OR DE "General Aptitude Test Battery" OR DE "Graduate Record Examination" OR DE "Achievement" OR DE "Academic Achievement" OR DE "Occupational		

	Success" OR DE "Achievement Measures" OR DE "Iowa Tests of Basic Skills" OR DE "Stanford Achievement Test" OR DE "Wide Range Achievement Test" OR DE "Woodcock Johnson Psychoeducational Battery" OR TI (intelligence OR IQ OR aptitude OR "cognitive ability" OR "cognitive function*" OR "executive function*" OR "neuropsychological test*") OR AB (intelligence OR IQ OR aptitude OR "cognitive ability" OR "cognitive function*" OR "executive function*" OR "neuropsychological test*")		
S2	DE "Depression (Emotion)" OR DE "Major Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Postpartum Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR DE "Affective Disorders" OR TI (MDD OR "depressive disorder*" OR depression OR depressed OR "mood disorder*") OR AB (MDD OR "depressive disorder*" OR depression OR depressed OR "mood disorder*")	Search modes - Boolean/Phrase	220,555
S3	DE "Cohort Analysis" OR DE "Longitudinal Studies" OR DE "Prospective Studies" OR DE "Followup Studies" OR DE "Retrospective Studies" OR DE "Meta Analysis" OR DE "Causal Analysis" OR DE "Attribution" OR TI (cohort OR longitudinal OR prospective OR retrospective OR "case-control*" OR "follow-up" OR systematic OR "meta-analysis" OR "meta-analyses") OR AB (cohort OR longitudinal OR prospective	Search modes - Boolean/Phrase	274,168

	OR retrospective OR "case-control*" OR "follow-up")		
S4	DE "Risk Assessment" OR DE "At Risk Populations" OR DE "Risk Perception" OR DE "Risk Factors" OR DE "Predisposition" AND DE "Premorbidity" OR DE "Susceptibility (Disorders)" OR DE "Prodrome" OR DE "Epidemiology" OR TI (risk OR premorbid OR prodromal OR prodrome OR "first occurrence" OR "first episode" OR predict OR predictive OR predicts OR predicted OR predicting OR cause OR causes OR causality OR causal OR Incidence OR Prevalence OR predate OR onset OR association OR associated) OR AB (risk OR premorbid OR prodromal OR prodrome OR "first occurrence" OR "first episode" OR predict OR predictive OR predicts OR predicted OR predicting OR cause OR causes OR causality OR causal OR Incidence OR Prevalence OR predate OR onset OR association OR associated)	Search modes - Boolean/Phrase	1,037,431
S5	S1 AND S2 AND S3 AND S4	Search modes - Boolean/Phrase	1,488
S6	S1 AND S2 AND S3 AND S4	Limiters - English; Age Groups: Childhood (birth-12 yrs), Neonatal (birth-1 mo), Infancy (2-23 mo), Preschool Age (2-5 yrs), School Age (6-12 yrs), Adolescence (13-17 yrs), Adulthood (18 yrs & older), Young Adulthood (18-29 yrs), Thirties (30-39 yrs), Middle Age (40-64 yrs); Population Group: Human; Document Type:	1,238

		Dissertation, Erratum/Correction, Journal Article, Review-Any Search modes - Boolean/Phrase	

2.2.1.1. Eligibility Criteria

The review included English language empirical studies investigating the longitudinal association of cognitive function (IQ, neuropsychological tests, executive functions) with unipolar depression diagnosis or symptoms. Detailed inclusion/exclusion criteria were as follows:

Participant Characteristics

Eligible studies included children, adolescents and adults under the age of 65. This age range was specified because of the possible impact of cognitive decline in older populations. Articles examining a highly specific population (e.g., with a particular medical diagnosis) were excluded so as to not limit the generalizability of results. Studies that required MDD diagnosis, hospitalization or admission to a treatment center as part of the inclusion criteria at baseline were also excluded from the review so as to permit conclusions about depression onset. This was to ensure that a majority of study participants did not have depression at baseline. However, cohort studies were included even if they did not measure depression at baseline, assuming that these samples would

have depression prevalence rates that were comparable to population norms. Subgroup analyses were subsequently performed on the studies that specifically excluded for any history of depression. If there were several papers about one cohort, the paper with larger sample size or better study quality was included.

Predictor Type

Eligible studies included a measure of cognitive, executive or neuropsychological function. This review included a range of cognitive predictors, given that previous studies have found broad deficits in cognitive function in depression (Christensen et al., 1997; Rock et al., 2014; Rogers et al., 2004; Snyder, 2013). When more than one cognitive predictor was reported as an outcome in a study, the broadest measure of cognitive functioning was used. If no measure captured broad cognitive functioning, the measure that was most closely aligned with constructs on a standard IQ test (working memory, processing speed, verbal comprehension, or perceptual reasoning) was used in the meta-analysis.

Studies were excluded from the primary analysis if cognitive function was assessed via educational achievement, given that these measures can be more easily influenced by learning disabilities than by general cognitive functioning (Siegel, 1999). Self-report descriptive measures of cognitive functioning were also excluded in favor of more objective measures. Lastly, since this study sought to investigate general

information processing abilities rather than cognitive attributional style, studies with cognitive attribution measures as the sole cognitive measure were excluded.

Comparisons

Search terms used to indicate the possible association between cognitive function and depression included: *risk*, *premorbid*, *prodromal*, *onset*, *predict* and *association* (for a full list, see search terms in Table 2). When data were reported from multiple time-points, the analysis accounting for the longest time between assessments was used.

Outcomes

Eligible studies reported depression diagnosis or symptoms determined by investigator or self-report. Presence of comorbidity was permitted given that depression has been found to be highly comorbid with other disorders (Kessler et al., 2003; Melartin et al., 2002). Articles not adequately specifying how depression was assessed or articles that did not uniquely measure depression (ie. only had an index of "mental disorders" or the category of "mood disorders" lumped together (Gale, Batty, Tynelius, Deary, & Rasmussen, 2010)), were excluded if no unique measure of depression could be obtained from study authors. This is because, although comorbidity was permitted, these could have represented instances of pure anxiety disorders with few or no depressive symptoms

or instances of bipolar disorder.

Study Design

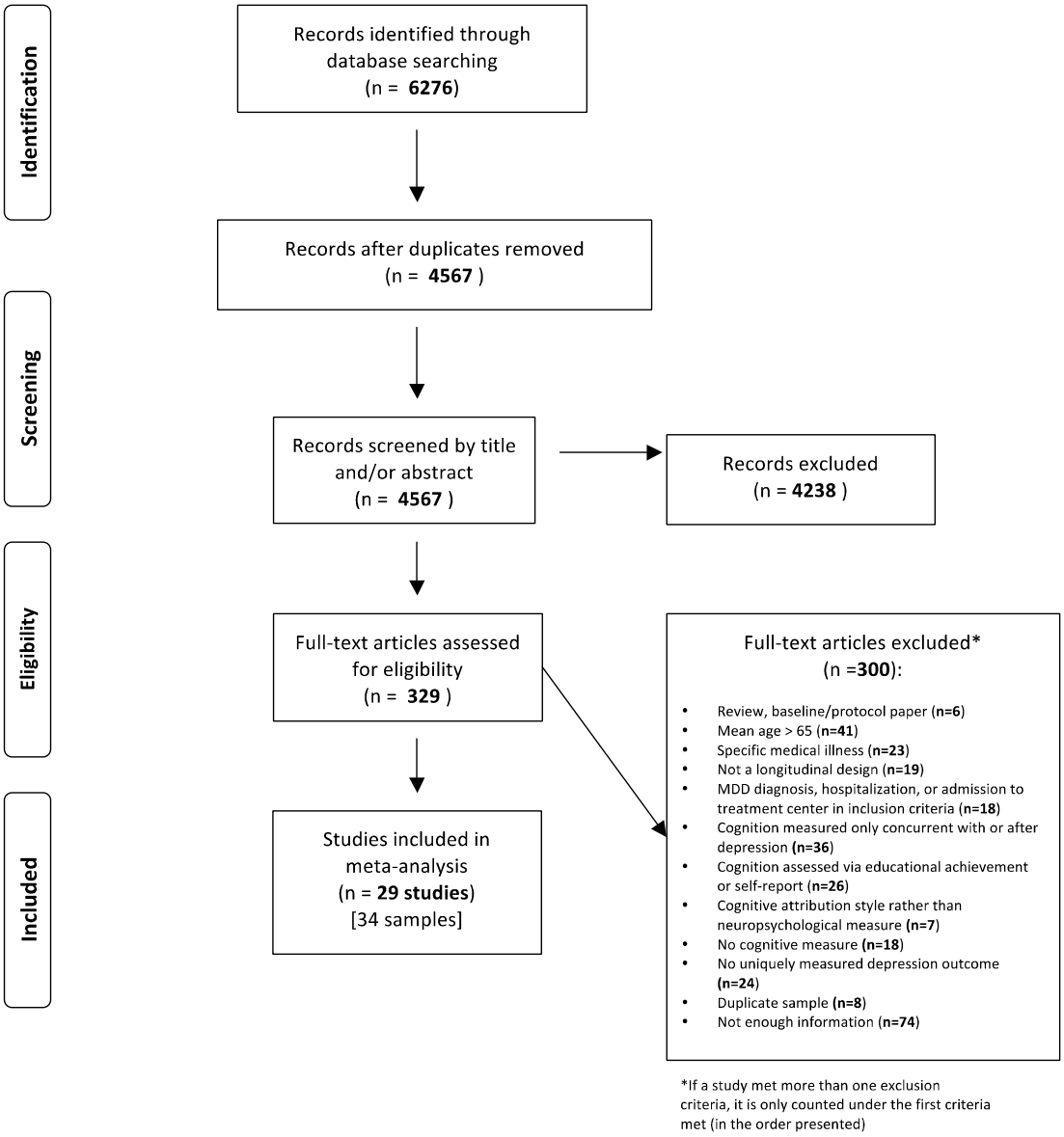
Eligible study search terms included: *cohort studies*, *longitudinal*, *epidemiological*, *prospective*, *retrospective*, *follow-up* or *case-control* studies. Studies not following a longitudinal design were excluded during full-text review. Additionally, studies where cognitive function was assessed only concurrently with or after depression were excluded, given that the purpose of the review was to investigate whether cognitive function predicted later depression.

Studies were included regardless of whether they were reported in peer-review journals in order to account for potentially biased reporting of results. Review articles were included in the search terms to find additional relevant references, but were not included in the meta-analysis. Baseline and protocol studies without follow-up data were excluded.

2.2.2. Study Selection

A flow diagram of the process of study selection shows the overall procedures (Figure 1). Records identified from the search processes were combined in EndNote software version X7 and duplicates were removed. Titles and abstracts were reviewed independently by two reviewers (MS & AP) according to the eligibility criteria described

above, and marked as either potentially eligible or not eligible. If either author marked an article as potentially eligible, it was included in the full-text review for closer examination by MS and AP, who used an electronic form to indicate if an article should be included or excluded in the final selection. When an article was excluded, the reason for exclusion was selected from a hierarchical list of exclusion criteria presented in Figure 1. Both MS and AP were initially blinded to the other's decisions. After both MS and AP completed their reviews, discrepancies about whether a study should be included or excluded were resolved via discussion and consensus amongst MS, AP, TM, AH, and TS.



Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Figure 1: Flow diagram of the search process.

2.2.3. Data Extraction

Study information was extracted independently by MS and AP using an electronic form created for this study. Information was collected and coded based on report characteristics, participant characteristics, study setting, predictors, outcome measures and quality assessment (Cooper, 2010). Any discrepancies (approximately 3% of data points) were resolved via consensus.

For studies with categorical depression diagnoses, effect sizes were generally presented as odds ratios. For these studies, the odds ratio plus the upper and lower bound of the confidence interval were recorded. Two of the studies (Gale et al., 2008; Zammit et al., 2004) reported odds ratios greater than one to indicate that lower IQ was associated with greater risk of depression. The other studies reported odds ratios in the reverse, leading to odds ratios less than one for the same direction of the effect. Therefore the odds ratios from the first two studies were recalculated by dividing (1/odds ratio). Another study (Mccord & Ensminger, 1997) reported results from chi-squared tests. Additional studies reported mean premorbid IQ scores rather than odds ratios, in which case the means, sample sizes and/or p-values and number of tails of the t-test were utilized to calculate the effect size.

For studies in which depression was measured as a continuous variable, effect sizes were presented as correlation coefficients. The direction of the effect (positive or negative) and the sample size were also extracted to be used in the meta-analysis. Two

studies reported only beta weights (Rawal & Rice, 2012; Simons et al., 2009) and I was not able to obtain zero-order correlations from the authors. Given that previous reports have suggested that beta weights can be used as an estimate of correlation coefficients in meta-analysis (Peterson & Brown, 2005), the beta weights were used instead, and analyses were run both including and excluding these data points.

When insufficient information was presented in the article, authors were contacted requesting further detail. An additional 6 studies were included at this point. One study (Hatch et al., 2007) included effect sizes for the female half of the cohort, but did not provide statistics for the males, but did indicate a null effect. Only women from this study were included in the meta-analyses, but imputing a score of 0 for the males yielded similar overall results.

Follow-up analyses directly compared studies that reported zero-order correlations between IQ at Time 1, Depression at Time 1 and Depression at Time 2. It was possible to calculate the partial correlation coefficient using the following formula:

$$r_{y1.2} = \frac{r_{y1} - r_{y2} r_{12}}{\sqrt{(1 - r^2_{y2})(1 - r^2_{12})}}$$

The adjusted and unadjusted results from these studies were entered into separate subgroup meta-analyses. Subsequently the adjusted effect size was subtracted from the unadjusted effect size to evaluate whether the difference was statistically significant in a third sensitivity meta-analysis.

2.2.4. Statistical Methods

Data were analyzed using Comprehensive Meta-Analysis software (Version 3.0, Biostat Inc, Englewood, NJ, USA). A random-effects model was used for expected heterogeneity across studies. A random-effects model also allows for broader generalization of results to the population at large. Heterogeneity of effects was calculated using the Q statistic, where a significant p-value indicates that true effect varies across studies. The I^2 statistic was used to calculate the ratio of the true heterogeneity to total variation, acting as an index of signal-to-noise ratio. When I^2 is large, it is has been recommended to consider subgroup analysis or meta-regression to account for the variance (Borenstein, Hedges, Higgins, & Rothstein, 2011).

Subgroup analyses were conducted using a mixed-effects analysis in which a random effects model was used to combine studies within each subgroup, and a fixed effect model was used to combine subgroups and yield the overall effect (the study-to-study variance is not assumed to be the same for all subgroups). Subgroup analyses were conducted comparing type of outcome (continuous vs. categorical), broad vs. specific cognitive measures, and outcomes that were adjusted vs. unadjusted for baseline depression symptoms.

Meta-regression was performed using the following variables on unadjusted analyses: age at baseline, age at follow-up, time between assessments, IQ, percent white,

year of cognitive assessment, year of follow-up assessment, percent female, and study quality score.

2.2.5. Study Quality and Publication Bias

Study quality was evaluated independently by MS and AP using a checklist adapted from Luppino & Wit (Luppino et al., 2010). The checklist contained 12 items and studies were rated with a "+" if it met criteria for that item, a "-" if it did not meet criteria for an item, and a "?" if unclear. "+" were coded as a score of 1 and -/? were coded as a score of 0. Total scores and percentages were calculated. Articles with total scores of 0-3 were considered to be of low quality, scores of 4-7 were considered a medium quality, and scores of 8-12 were considered to be of high quality. Any discrepancies (approximately 3% of data points) were resolved via consensus.

Publication bias was assessed using a funnel plot, which presents study size on the vertical axis (as standard error, in this case) as a function of effect size on the x-axis. When no publication bias exists, the studies should be distributed symmetrically about the combined effect size (Borenstein et al., 2011). If evidence of publication bias was observed, Duval and Tweedie's Trim and Fill Method was used (Duval & Tweedie, 2000), which recalculates effects based on imputing data from studies that are likely to be missing. Lastly, the Fail-Safe N was calculated (Cooper, 1979), which indicates the number of missing studies that would need to exist to nullify the observed effect.

2.3. *Results*

A flow diagram of the search process is shown in Figure 1. The search identified 2,773 records through PubMed, 2,158 through EMBASE and 1,345 through PsycInfo, for a total of 6,276 records. Duplicate records (1,709) were removed in EndNote, resulting in 4,567 unique records. After title and abstracts were reviewed, 329 records were identified as potentially eligible for the meta-analysis. These 329 records were reviewed in full and 300 articles were excluded hierarchically if they were: a review, baseline or protocol paper (n=6), if the sample had a mean age over 65 at the depression assessment (n=41), if the sample had a specific medical illness (n=23), if the study was not a longitudinal design (n=19), if MDD diagnosis, hospitalization or admission to treatment center was part of the inclusion criteria of the study (n=18), if cognitive function was assessed only concurrently with or after depression (n=36), if cognitive function was assessed by educational achievement or self-report (n=26), if cognitive function was assessed by attribution style rather than neuropsychological measure (n=7), if there was no measure of cognitive function (n=18) or no uniquely measured depression outcome (n=24). Furthermore, if articles reported on the same sample as another article with higher quality or more information, the duplicate articles were excluded (n=8). Lastly, a number of studies appeared to measure both cognitive function and depression, but did not report enough information to be included in the meta-analysis and did not respond to requests for additional information (n=74, approximately 59 unique samples). In total,

29 publication were included in the meta-analysis, comprising 34 samples (one study included two separate birth cohorts and another four reported data separately for men and women).

2.3.1. Study Characteristics

The characteristics of included samples are detailed in Table 3. Sample sizes ranged from 43 to 50,053 with a median of 339.5. The most common types of samples were school samples, (9/34), community samples (8/34), and birth cohorts (7/34). The samples were majority white, with two samples having exclusively black participants. Additionally, 8 samples were men only, 6 samples were women only, and the rest reported combined effect sizes. Mean age of participants at baseline ranged from 3.5 to 59 years with a median of 12 years. Most samples did not report whether comorbid diagnoses were present (23/34).

Of the 74 papers excluded for having insufficient information (representing 60 unique samples), the median number of subjects was not statistically different between those studies and the studies included in the meta-analysis (n= 288 and n= 339.5, respectively; p=0.19), nor did the average age of study participants at baseline statistically differ (median across studies = 11 vs. 12, respectively; p=0.57). The types of cognitive measures used were also similar across the excluded and included studies, with the most common measure being IQ (28/60 and 20/29), followed by Verbal Comprehension (8/60 and 5/29).

Table 3: Characteristics of Included Studies. Sample size is the number of subjects included in reported analyses of interest. NR = not reported. ~ indicates only a range was reported. *This column notes covariates included in the meta-analysis. I focused on controlling for depressive symptoms at T1, but some studies reported effect sizes that also included controlling for other variables-- when the zero-order correlations were unavailable, these estimates were used.

Study	Name of Cohort	Type of Cohort	Sample Size	Comorbidity	How Depression Assessed	Mean IQ at Baseline	Name of Cognitive Measure	Type of Cognitive Measure	Name of Depression Outcome	Type of Depression Outcome	Covariates included in Meta-Analysis*	Percent Female	Race/Ethnicity	Continent	Mean Age at Baseline	Time Between Assessments (years)	Year of Initial Assessment
Baer et al. 2013	Concordia Longitudinal Retirement Project	Retirees	333	NR	Study Assessment	NR	Montreal Cognitive Assessment	Verbal Comprehension, Perceptual Reasoning, Working Memory	Center for Epidemiological Studies Depression Scale (CES-D)	Continuous	Depression symptoms at Time 1	NR (both male and female)	NR	North America	59.06	4	~2005
Beaujean et al. 2013	National Longitudinal Study of Adolescent Health	Community Sample	14,322	NR	Study Assessment	100.61	Add Health Picture Vocabulary Test (AHPVT) -- an abridged version of the PPVT-R	Verbal Comprehension	Created for this study	Continuous	Depression symptoms at Time 1	50	76.31% White; 16.74% Black; 4.22% Asian; 2.5% American Indian; 11.83% Hispanic; 0.05% Mixed Race	North America	15.98	7	1994
Belsky et al. 2012	Environmental Risk Longitudinal Twin Study (E-Risk)	Birth Cohort	2,123	Conduct disorder, anxiety, psychosis, borderline personality disorder	Study Assessment	100	Wechsler Preschool and Primary Scale of Intelligence (WPPSI)	General Intelligence, Verbal Comprehension, Perceptual Reasoning	Children's Depression Inventory (CDI)	Continuous	None	51	~90% White	Europe	5	7	1999
Betts et al. 2016	Mater University Study of Pregnancy (MUSP)	Pre-Birth Cohort	1,934	Psychosis, Mania	Study Assessment	NR	Peabody Picture Vocabulary Test-Revised (PPVT-R)	Verbal Comprehension	Composite International Diagnostic Interview (CIDI-Auto)	Continuous (latent factor)	None	NR	NR	Australia	5	16	1989
Canals et al. 2002 (females)	NR	Community Sample	99	NR	Study Assessment	NR	Academic aptitude test (AAT)	General Intelligence, Verbal Comprehension, Perceptual Reasoning	Schedules for Clinical Assessment in Neuropsychiatry	Categorical	None	100	NR	Europe	~11	6	NR
Canals et al. 2002 (males)	NR	Community Sample	100	NR	Study Assessment	NR	Academic aptitude test (AAT)	General Intelligence, Verbal Comprehension, Perceptual Reasoning	Schedules for Clinical Assessment in Neuropsychiatry	Categorical	None	0	NR	Europe	~12	6	NR
Connolly et al. 2014	Temple University Adolescent Cognition and Emotion (ACE) Project	Community Sample	200	NR	Study Assessment	NR	Digit Span from Wechsler Intelligence Scale for Children (WISC)	Working Memory	Children's Depression Inventory (CDI)	Continuous	Depression symptoms at Time 1	56.5	45.2% White; 51.3 % Black	North America	12.41	1	NR
Der et al. 2009	US National Longitudinal Survey of Youth 1979	Community Sample	7,458	Noted a range of health conditions	Study Assessment	NR	Armed Services Vocational Aptitude Battery (ASVAB)/Armed Forces Qualification Test (AFQT)	General Intelligence, Verbal Comprehension	Center for Epidemiological Studies Depression Scale (CES-D)	Continuous	Depression symptoms at Time 1	52	31% Black; 19% Hispanic	North America	17.9	~22	1979
Dubow et al. 2008 (females)	Columbia County Longitudinal Study (CCLS)	School Children Grade 3	215	NR	Study Assessment	~104	California Short-Form Test of Mental Maturity	General Intellignce	Minnesota Multiphasic Personality Inventory (MMPI) Scale 2	Continuous	None	100	90% White; 3% Black; <1%Asian, <1% Hispanic	North America	8	11	1960
Dubow et al. 2008 (males)	Columbia County Longitudinal Study (CCLS)	School Children Grade 3	211	NR	Study Assessment	~104	California Short-Form Test of Mental Maturity	General Intelligence	Minnesota Multiphasic Personality Inventory (MMPI) Scale 2	Continuous	None	0	90% White; 3% Black; <1%Asian, <1% Hispanic	North America	8	11	1960
Evans et al. 2015	NR	School Children Grades 5-9	192	Some with ADHD	Study Assessment	111	Wechsler Abbreviated Scale of Intellignece (WASI)	General Intelligence, Verbal Comprehension, Perceptual Reasoning, Working Memory, Set-Shifting	Children's Depression Inventory (CDI)	Continuous	Depression symptoms at Time 1	52.1	71.4% White; 18.2% Black; 2.6% Asian; 3.6% Hispanic; 4.2% Mixed Race	North America	12.36	0.3	~2000s

Franz et al. 2011	Vietnam Era Twin Study of Aging	Military Cohort	1,231	NR	Study Assessment	NR	Armed Forces Qualification Test (AFQT Form 7A)	General Intelligence, Perceptual Reasoning, Working Memory, Processing Speed, Set-Shifting, Inhibition	Center for Epidemiological Studies Depression Scale (CES-D)	Continuous	None	0	86% White	North America	20	35	~1970
Gale et al. 2008	Vietnam Experience Study (VES)	Military Cohort	3,258	Mix	Study Assessment	100	General technical section of the Army Classification Battery	General Intelligence, Verbal Comprehension, Arithmetic reasoning	Diagnostic Interview Schedule (DIS)	Categorical	Socioeconomic Status, Ethnicity, Place of service	0	80.8% White; 12.7 % Black	North America	20.4	~17	~1964
Gale et al. 2009 (1958 Cohort)	1958 National Child Development Survey	Birth Cohort	6,369	NR	Study Assessment	102.8	General ability test, devised by the National Foundation for Educational Research in England and Wales	General Intelligence	Rutter's Malaise Inventory	Continuous	None	NR (both male and female)	NR	Europe	11	22	1969
Gale et al. 2009 (1970 Cohort)	1970 British Cohort Study	Birth Cohort	6,074	NR	Study Assessment	101.8	British ability Scale	General Intelligence	Rutter's Malaise Inventory	Continuous	None	NR (both male and female)	NR	Europe	10	20	1980
Gjerde et al. 1995 (females)	NR	Recruited from a nursery school	51	NR	Study Assessment	118.7	Wechsler Adult Intelligence Scale (WAIS)	General Intelligence	General Behavior Inventory (GBI) Depression scale	Continuous	None	100	~66% White; ~25% Black; ~0.05% Asian	North America	18	5	1983
Gjerde et al. 1995 (males)	NR	Recruited from a nursery school	45	NR	Study Assessment	111.12	Wechsler Adult Intelligence Scale (WAIS)	General Intelligence	General Behavior Inventory (GBI) Depression scale	Continuous	None	0	~66% White; ~25% Black; ~0.05% Asian	North America	18	5	1983
Hatch et al. 2007	1946 British Cohort Study	Birth Cohort	957	NR	Study Assessment	NR	National Foundation for Educational Research Test	General Intelligence, Verbal Comprehension, Perceptual Reasoning	General Health Questionnaire (GHQ-28)- severe depression subscale	Continuous	None	51	NR	Europe	8	45	1954
Hipwell et al. 2011	Pittsburgh Girls Study (PGS)	Community Sample	195	NR	Study Assessment	99.54	Wechsler Intelligence Scale for Children (WISC) III-R	Verbal Comprehension	Schedule for Affective Disorders for School-Age Children- Present and Lifetime Version (K-SADS-PL)	Continuous	Depression symptoms at Time 1	100	70% Black or multiracial	North America	11.54	1	1998
Horowitz et al. 2003	NR	Elementary school cohort	196	NR	Study Assessment	104.61	Wechsler Intelligence Scale for Children (WISC) -R	General Intelligence, Verbal Comprehension, Perceptual Reasoning	Schedule for Affective Disorders for School-Age Children-Epidemiological Version (K-SADS-E)	Categorical	Depression symptoms at Time 1	54.2	89% White, 14.7% Black, 3.3% Other	North America	11.86	6	~1980
Koenen et al. 2009	Dunedin Cohort	Birth Cohort	730	None	Study Assessment	NR	Wechsler Intelligence Scale for Children (WISC)	General Intelligence, Verbal Comprehension, Perceptual Reasoning, Working Memory, Processing Speed	Diagnostic Interview Assessment (for DSM-IV)	Categorical	Sex, Socioeconomic Status, Physical Health, childhood maltreatment	48	"Primarily White"	New Zealand	9	23	1981
McCord & Ensminger 1997 (females)	Woodlawn Cohort	Elementary school cohort	346	Some with alcoholism	Study Assessment	NR, (13% of sample had scores over 110)	Unspecified IQ	General Intelligence	Composite International Interview Schedule (according to DSM-III-R)	Categorical	None	100	100% Black	North America	~6	27	1966
McCord & Ensminger 1997 (males)	Woodlawn Cohort	Elementary school cohort	313	Some with alcoholism	Study Assessment	NR, (11% of sample had scores over 110)	Unspecified IQ	General Intelligence	Composite International Interview Schedule (according to DSM-III-R)	Categorical	None	0	100% Black	North America	~6	27	1966
Meyer et al. 2004	NR	Risk Sample	86	NR	Study Assessment	~118	WISC	General Intelligence, Verbal Comprehension, Perceptual Reasoning	SCID	Categorical	None	63	90% White, 9% Black, 1% Hispanic	North America	11	13	1989
Papmeyer et al. 2015	Scottish Bipolar Family Study	Risk Sample	111	NR	Study Assessment	Controls: 108 Patients: 107	National Adult Reading Test (NART)	Verbal Comprehension	Structured Clinical Interview for DSM Disorders (SCID) symptoms	Categorical	None	52	NR	Europe	21	2	NR
Pine et al. 1997	NR	Community Sample	644	NR	Study Assessment	100.7	Unspecified "IQ"	General Intelligence	Based on Diagnostic Interview Schedule for Children	Continuous	Depression symptoms at Time 1	52	91% White	North America	13.8	9	1983

Quinn & Joormann 2015	NR	Undergraduate Students	43	NR	Study Assessment	NR	n-back	Working Memory	Beck Depression Inventory II (BDI-II)	Continuous	Depression symptoms at Time 1	63	58% White, 30% Hispanic or Latino, 19% Asian, 2% African American, 2% American Indian, 2% Native Hawaiian, 2% Indian	North America	19	0.14	NR
Rawal & Rice 2012	Early Prediction of Adolescent Depression study	Risk Sample	230	None	Study Assessment	97.46	Wechsler Intelligence Scale for Children (WISC)	General Intelligence, Verbal Comprehension, Perceptual Reasoning, Working Memory, Processing Speed	Child and Adolescent Psychiatric Assessment (CAPA)	Both	Depression symptoms at Time 1, Age, Overgenerality to negative cues	59.6	NR	Europe	13.71	1	NR
Sharp et al. 2008	The Child Behaviour Study	Community Sample	439	NR	Study Assessment	105	Wechsler Intelligence Scale for Children (WISC)	General Intelligence, Verbal Comprehension, Perceptual Reasoning	The Mood and Feelings Questionnaire	Continuous	Depression symptoms at Time 1	52	97% White; 0.5% Black; 2.5% Asian	Europe	9.4	1	NR
Simons et al. 2009	East Flanders Prospective Twin Survey	Twin Registry	444	NR	Study Assessment	NR	Principal component from Stroop, Concept Shifting Test, and Letter Digit Substitution Test	Processing Speed, Set-Shifting, Inhibition	Structured Clinical Interview for DSM Disorders (SCID) symptoms	Continuous	Depression symptoms at Time 1	100	NR	Europe	28	2	NR
Slykerman et al. 2015	Auckland Birthweight Collaborative Study	Birth Cohort/ Risk Sample	609	NR	Study Assessment	NR	Stanford-Binet Intelligence Scale, 4th Ed	General Intelligence, Fluid Reasoning, Knowledge, Qunatitative Reasoning, Visual-Spatial Processing, Working Memory	Center for Epidemiological Studies Depression Scale (CES-D)	Categorical (cut-point)	None	49	NR	New Zealand	3.5	7.5	~2000
Sørensen et al. 2012	Danish Draft-Board Study	Military Cohort	21,914	NR	Psychiatric Registry	Controls: 100 Patients: 96-98	Børge Priens Prøve (BPP)	General Intelligence, Verbal Comprehension, Perceptual Reasoning	Danish International Classification of diseases (ICD) 8 & 10	Categorical	None	0	NR	Europe	19.5	~36	1968-1989
Vinberg et al. 2013	NR	High-Risk Twins	224	Bipolar disorder, anxiety, substance abuse, other	Study Assessment/ Psychiatric Registry	NR	Cambridge Cognitive Assessment (CAMCOG)	General Neuropsychological Function, Orientation, Lanugage, Memory, Attention, Abstract Thinking, Visual Perception	Beck Depression Inventory (BDI)	Continuous	Depression symptoms at Time 1	65	NR	Europe	43.9	7	2003
Zammit et al. 2004	Swedish Conscripts (1969-1970)	Military Cohort	50,053	None	Hospital Linkage	NR	Unspecified "IQ"	General Intelligence, Verbal Comprehension, Perceptual Reasoning, General Knowledge, Mechanical Knowledge	International Classification of diseases (ICD) hospital psychiatric admissions	Categorical	Diagnosis at baseline, disturbed behavior, drug use, raised in a city	0	NR	Europe	~19	27	1969

2.3.2. Meta-Analysis

The overall analysis yielded a significant association between cognitive function and subsequent depression outcomes (r=-0.088; 95% CI: -0.121, -0.054; p<0.001; Figure 2). Results were similar when excluding the two studies that used beta-weights (r=-0.071; 95% CI: -0.100, -0.042; p<0.001) or when using episodic memory in place of processing speed in a study reporting both outcomes (r=-0.085; 95% CI: -0.118, -0.051; p<0.001).

Heterogeneity across samples was significant (Q=801.54, p<0.001), suggesting substantial variation across the individual samples. The ratio of the true heterogeneity to total variation was large (I^2=95.88%). I^2 is on a relative scale and values close to 100 indicate that most of the observed variance is real rather than spurious and suggests that subgroup analyses or meta-regression may help to explain this variability (Borenstein et al., 2011).

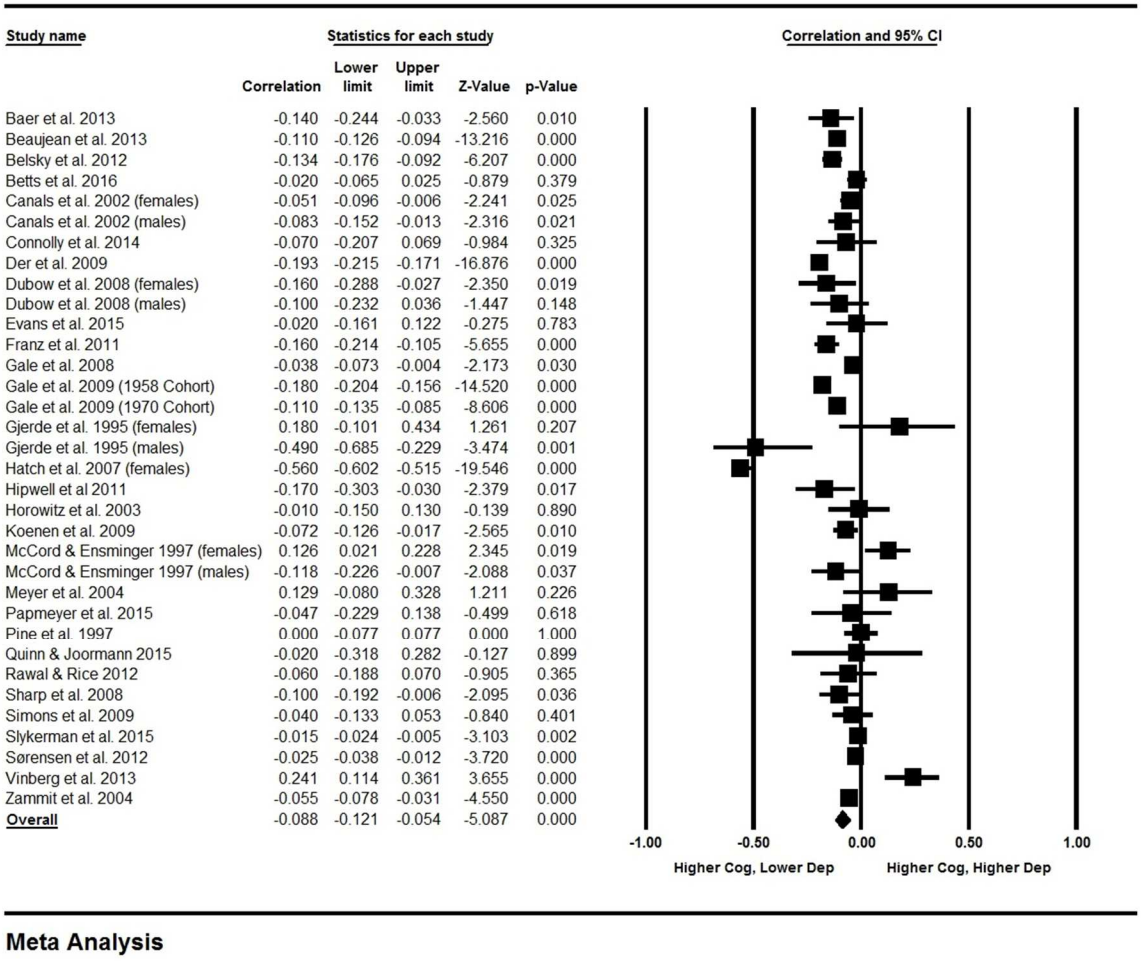


Figure 2: Meta-Analysis of the Association Between Cognitive Function and Subsequent Depression. A forest plot for all studies that investigated associations between cognition and later depression. Results are reported as correlation coefficients denoted by squares, and 95% confidence intervals indicated by lines (effect sizes are converted to correlation coefficients if reported as odds ratios). Meta-analysis results are displayed as the diamond. The overall analysis found a significant effect of cognition on depression (r=-0.088; 95% CI: -0.121, -0.054; p<0.001).

Follow-up analyses were conducted in the sample of studies reporting educational attainment and self-report outcomes (Figure 3). In order to sufficiently study the association between educational achievement it would be important to complete a

separate meta-analysis using different search terms to properly capture studies with this data. However, to preliminarily test whether an association might exist, I have reviewed the studies that were originally excluded due to them assessing cognitive function via "educational achievement or self-report." Of those, 8 samples provided sufficient data to preliminarily test this hypothesis. It was found that across these samples, educational achievement and self-reported cognitive function did predict subsequent depression (r=-0.229; 95% CI: -0.303, -0.152; p<0.001). Although I again caution that this is not based on a systematic review of available studies, it suggests that educational variables may also predict depressive symptoms (with the additional caveat that future analyses will also need to be careful to control for baseline depressive symptoms, as in the case of the primary analyses).

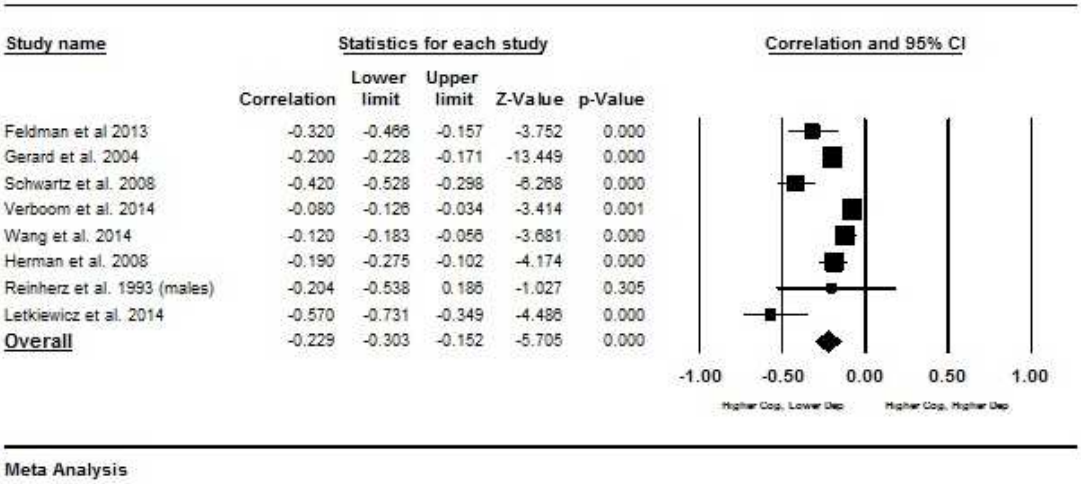


Figure 3: Association between Educational Attainment and Self-Reported Cognitive Function with Subsequent Depression. Educational achievement and self-reported cognitive function did predict subsequent depression (r=-0.229; 95% CI: -0.303, -

0.152; p<0.001), with the caveat that future analyses will also need to be careful to control for baseline depressive symptoms, as in the case of the primary analyses.

2.3.3. Subgroup Analyses and Meta-Regression

A significant difference was found between categorical and continuous effect sizes (p<0.001). The studies assessing continuous outcomes were found to have a larger effect (r=-0.121; 95% CI: -0.168, -0.073; p<0.001; n=22) than studies assessing categorical outcomes (r=-0.035; 95% CI: -0.054, -0.017; p<0.001; n=12). No differences were observed between studies utilizing broad vs. specific cognitive measures (p=0.57).

Outcomes were also compared adjusting for baseline depression symptoms at the time of cognitive assessment. Nine studies provided enough detail to calculate the partial correlation coefficients adjusting for baseline depression symptoms. Using the partial correlation coefficients led to a null result (r=-0.032; 95% CI: -0.078, 0.014; p=0.169; n=9; Figure 4). The null result does not seem to be due to a lack of power because using the unadjusted correlation coefficients for the same nine studies still led to a significant result (r=-0.120; 95% CI: -0.169, -0.070; p<0.001; n=9; Figure 4). As a follow-up, the difference in effect sizes between the adjusted and unadjusted values for these 9 studies were tested (r=0.082; 95% CI: 0.069, 0.095; p<0.001; n=9), suggesting that the effects are significantly different when directly comparing the values that do and do not control for baseline depression symptoms.

Expanding the subgroup analyses to include studies that controlled for baseline depression plus other covariates (Rawal & Rice, 2012; Simons et al., 2009; Zammit et al., 2004), and studies that explicitly excluded for a history of depression diagnosis (Gale et al., 2008; Papmeyer et al., 2015; Vinberg, Miskowiak, & Kessing, 2013), did not change the null result (r=-0.027; 95% CI: -0.058, 0.005; p=0.097; n=15).

None of the meta-regression analyses were significant, indicating that the between-study variance was not attributable to age at baseline, IQ, percent of sample that was female, or percent of the sample that was white.

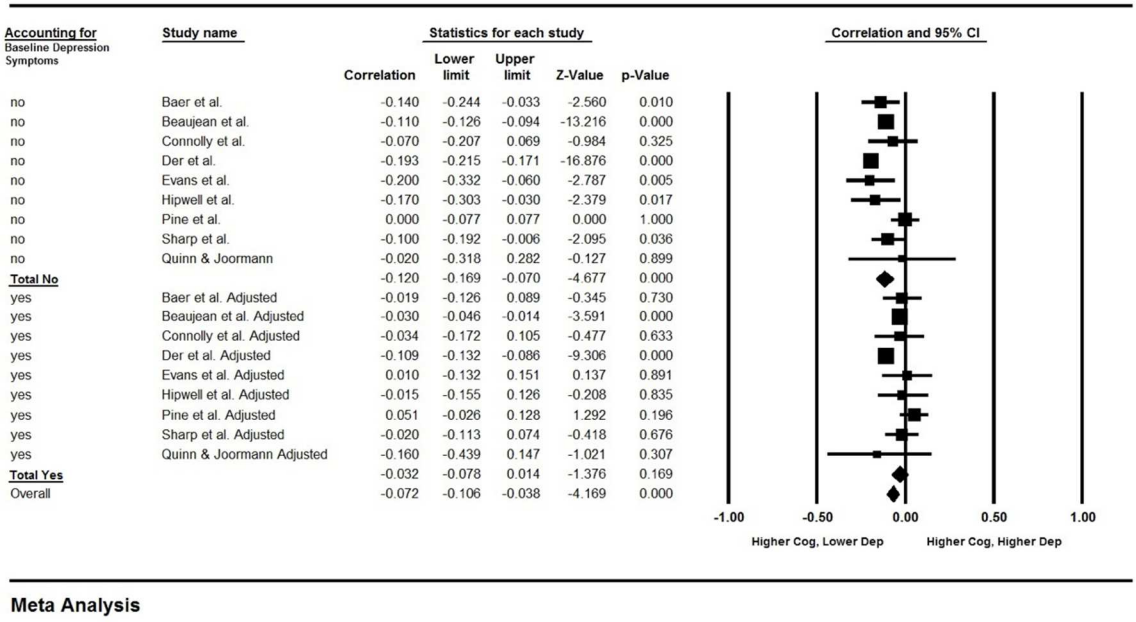


Figure 4: Meta-analysis Comparing Values Adjusted for Baseline Depression Symptoms vs. Unadjusted. A Forest plot for analysis comparing results from a subset of the same set of studies reported in Figure 2 when using unadjusted values compared to using values that are adjusted for baseline depression. Effects are significant for unadjusted values (r=-0.120; 95% CI: -0.169, -0.070; p<0.001), but not for adjusted values

(r=-0.032; 95% CI: -0.078, 0.014; p=0.169). Results are reported as correlation coefficients denoted by squares, and 95% confidence intervals indicated by lines. Meta-analysis results are displayed as diamonds.

2.3.4. Study Quality and Publication Bias

Multiple samples within a study were combined for the purposes of quality assessment, given that studies within the same publication were found to employ the same methodology. Of the 29 publications reviewed, 12 were rated as high quality and 17 were rated as medium quality. Details are provided in Table 4. Comparable results to the overall findings were obtained when just using high quality studies (r=-0.085; 95% CI: -0.141, -0.029; p=0.003).

Table 4: Quality Assessment. Adapted from Luppino et al., 2010. Scoring: "+" = 1,"-" = 0, "?" = 0. Interpretation of total score: 0-3= low study quality, 4-7 = medium study quality, 8-12 = high study quality. Ratings apply for statistics utilized in meta-analysis only-- some studies have additional variables in SEM models, which were not amenable to meta-analysis.

Study	Sampling procedure of the cohort described	Inclusion and exclusion criteria described	Study excludes for baseline depression diagnosis	Sample characteristics described	Follow-up of at least a year	Loss to follow-up <20%	Information about completers vs. non-completers	Study controls for baseline depressive symptoms	Study controls for other potential cofounders	Study uses a broad measure of cognitive function	Study uses a validated depression measure	Study assesses depression severity	Total	Study Quality
Baer et al. 2013	+	+	-	-	+	+	+	+	-	+	+	+	9	High
Beaujean et al. 2013	-	-	?	+	+	?	-	+	-	-	-	+	4	Medium
Belsky et al. 2012	+	+	-	+	+	+	-	-	-	+	+	+	8	High
Betts et al. 2016	+	-	-	-	+	-	+	-	+	-	-	+	5	Medium
Canals et al. 2002	+	+	-	-	+	-	+	-	-	-	+	-	5	Medium
Connolly et al. 2014	+	+	-	+	+	?	-	+	-	-	+	+	7	Medium
Der et al. 2009	+	+	-	+	+	-	+	-	+	+	+	+	9	High
Dubow et al. 2008	+	+	-	+	+	-	+	-	-	+	+	+	8	High
Evans et al. 2015	+	+	-	+	-	?	-	+	+	+	+	+	8	High
Franz et al. 2011	+	+	-	+	+	+	?	-	-	+	+	+	8	High
Gale et al. 2008	+	+	+	+	+	+	+	-	+	+	+	-	10	High
Gale et al.2009	+	-	?	-	+	-	+	-	+	+	+	-	6	Medium
Gjerde et al. 1995	+	-	-	+	+	?	?	-	-	+	+	+	6	Medium
Hatch et al. 2007	+	+	-	-	+	-	+	-	+	+	-	+	7	Medium
Hipwell et al. 2011	+	+	-	+	+	+	+	+	-	-	+	+	9	High
Horowitz et al. 2003	+	+	-	+	+	+	+	+	-	+	+	-	9	High
Koenen et al. 2009	+	-	-	-	+	+	-	-	+	+	+	+	7	Medium
McCord & Ensminger 1997	+	-	-	-	+	-	+	-	-	?	+	-	4	Medium
Meyer et al. 2004	+	+	-	+	+	-	+	-	-	+	+	-	7	Medium
Papmeyer et al. 2015	+	+	+	-	+	-	+	-	-	+	+	+	8	High
Pine et al. 1997	+	-	-	+	+	+	+	-	-	?	+	+	7	Medium
Quinn & Joormann 2015	-	-	-	+	-	+	+	+	+	-	+	+	7	Medium
Rawal & Rice 2012	+	+	-	-	+	+	-	+	+	+	+	+	9	High
Sharp et al. 2008	+	?	-	+	+	-	+	-	-	+	+	+	7	Medium
Simons et al. 2009	+	-	-	-	+	-	+	+	?	+	+	+	7	Medium
Slykerman et al. 2015	+	+	-	-	+	-	+	-	+	+	+	-	7	Medium
Sørensen et al. 2012	+	+	?	-	?	?	-	-	-	+	+	-	4	Medium
Vinberg et al. 2013	+	+	+	-	+	+	-	+	-	+	+	+	9	High
Zammit et al. 2004	+	+	-	-	+	?	?	?	+	+	+	-	6	Medium
Total meeting criteria	27	19	3	15	26	11	18	10	11	21	26	20	7.14	
Percent of samples meeting criteria	93%	66%	10%	52%	90%	38%	62%	34%	38%	72%	90%	69%	**Overall:**	**Medium**

Inspection of the funnel plot (Figure 5) found no evidence of publication bias to support the hypothesis. In fact, imputation of negative correlations suggested that additional studies favoring the hypothesis may be missing. While the calculated effect size is -0.088 (95% CI: -0.121, -0.054), using Duval and Tweedie's Trim and Fill Method, the imputed effect size estimate is larger at -0.137 (95% CI: -0.176, -0.099; imputed studies n=11). Lastly, the Fail-Safe N procedure found that 3,583 null studies would need to be located for the combined 2-tailed p-value to exceed 0.05. This suggests that significant results are not likely to be confounded by publication bias and may even underestimate true effect sizes.

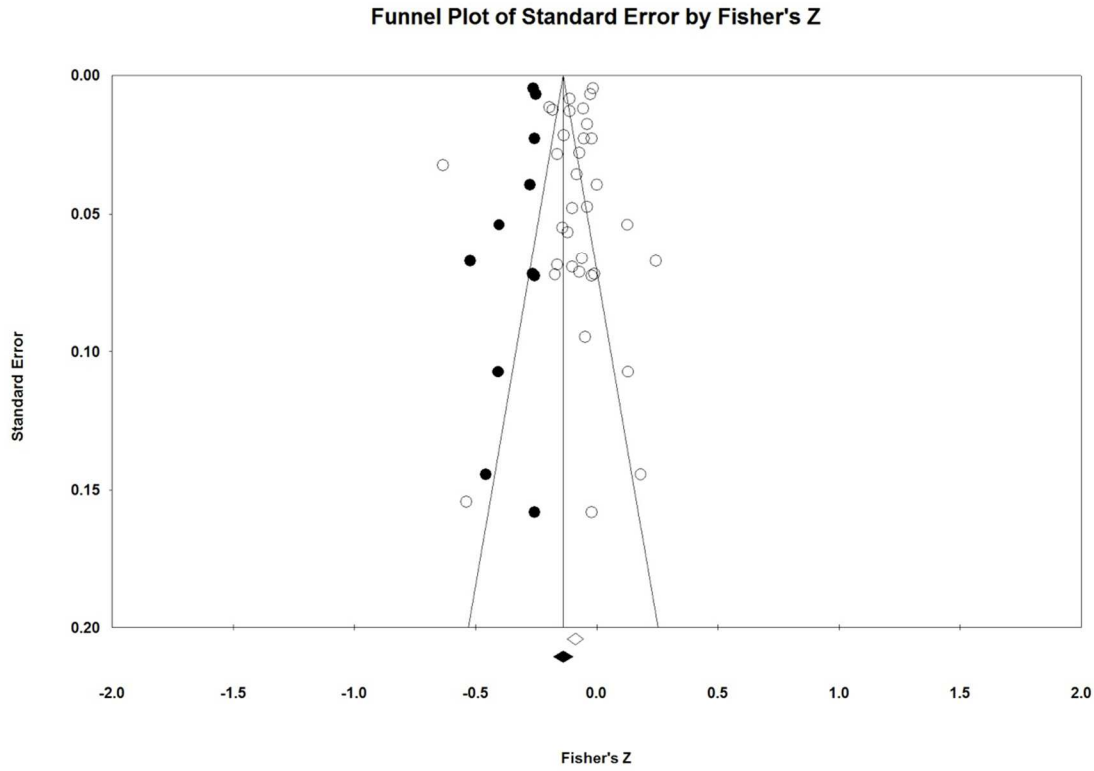


Figure 5: Trim and Fill Funnel Plots for All Samples. Fisher's Z, a measure of effect size, is plotted on the x-axis and the standard error is plotted on the y-axis. Larger studies appear toward the top of the graph and smaller studies towards the bottom. In the absence of publication bias, the studies are symmetrically distributed around the mean. Actual studies are shown in open circles and imputed studies would be shown in black circles. No additional studies would be expected in the opposite direction (to the right) of the observed effect, but an additional 11 studies are imputed to the left of the mean effect size. While the calculated effect size is -0.088 (95% CI: -0.121, -0.054), using Duval and Tweedie's Trim and Fill Method, the imputed effect size estimate is larger at -0.137 (95% CI: -0.176, -0.099; imputed studies n=11).

2.4. *Discussion*

The present systematic review and meta-analysis of 29 longitudinal publications, including 121,749 participants, revealed that after accounting for baseline depression

symptoms, variability in cognitive function did not predict subsequent depression. Consistent with prior reports, there was a significant contemporaneous association between higher depression symptoms and lower cognitive function. These patterns have implications for understanding the association between cognitive function and depression and may be important for advancing etiologic and treatment research.

First, the findings reinforce models positing that cognitive function tracks with depression severity (McDermott & Ebmeier, 2009). One possible explanation for this contemporaneous association is that depression symptoms interfere with the capacity to complete cognitive assessments, possibly through the general lack of motivation that is one hallmark of the disorder. While this explanation represents an experimental confound for studies focused on assessment of cognitive function, it likewise represents an opportunity for studies to focus more comprehensively on the assessment of both depression and mood disorder symptoms, since performance on cognitive tests may be a sensitive measure of motivational state that could augment self-reported symptoms. Alternatively, the co-occurrence of cognitive deficits and depression symptoms may reflect shared genetic etiology (Hagenaars et al., 2016) and dysfunction of neural circuits supporting both cognitive and emotional processes (Scult et al. in press). In particular, dysfunction of prefrontal and striatal circuits have been associated with both depression and cognitive function (Aarts, van Holstein, & Cools, 2011; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005).

Second, the findings suggest that prior studies of links between cognitive function and depression that did not assess baseline symptoms may have overestimated the potential protective role of higher cognitive function. While the importance of accounting for subclinical symptoms is not novel, the implementation of such accounting is often neglected in psychiatric epidemiology, given the current categorical, threshold-based diagnostic system. In this meta-analysis, larger effects were observed for continuous as compared to categorical outcomes, which aligns with growing emphasis on dimensional measures of psychopathology (Cuthbert & Kozak, 2013).

Third, the associations between cognitive function and either current or later depression were not moderated by data quality or participant age, sex, and race. However, there are a number of additional potential moderators that could not be addressed in the current review and meta-analysis. For example, the number and type of comorbid conditions with depression were often not reported in the included studies, but could represent an important moderator of the observed effects. Modeling the effects of comorbid illness is an important avenue for future research.

One limitation of the current literature is that only a handful of studies reviewed explicitly excluded for depression diagnosis at baseline (Gale et al., 2008; Papmeyer et al., 2015; Vinberg et al., 2013); however, consistent with the finding that controlling for baseline depression symptoms led to a null association between cognition and subsequent depression, there was no effect observed when including these studies in the subgroup

analyses, further suggesting that the association between cognitive function and depression is likely contemporaneous. It will be important to follow-up these analyses with individual studies that include rigorous assessment of baseline depression symptoms and other potentially confounding factors to further clarify this relationship.

An open question that remains for future research is whether deficits in cognitive function are likely to predict the development of more severe or recurrent depression later in life. Only one of the included studies (Koenen et al., 2009), specifically investigated recurrent depression and found that lower IQ was associated with greater persistence of disorder.

A final consideration is that while the present review and meta-analysis focused on general cognitive function mainly assessed via IQ, there may be specific subtypes of cognitive function that are more predictive of later depression. For example, a lack of cognitive flexibility may more closely match with the ruminative style characteristic of depression, and therefore tasks specifically measuring this component of cognitive function might have some predictive utility. While the present review did not find differences between broad and specific measures of cognitive function, there were not enough studies identified to allow for precise consideration of differences between individual cognitive domains.

A limitation of the meta-analysis is that while the present study followed standard guidelines (Atkinson et al., 2015; Stroup et al., 2000), decisions about study selection, data

extraction, and quality assessment, include a number of decision points that necessarily involve a level of subjectivity. Reliability was ascertained by using independent raters, however, different inclusion/exclusion criteria or a different approach to the evaluation of those criteria, could result in a different set of studies being included. Ultimately, the quality of the meta-analysis is dependent upon the underlying studies that are analyzed. Furthermore, although studies with insufficient information to be included in the meta-analysis were not found to differ based on basic study data from those studies included in the meta-analysis, nonetheless it is unknown how if at all data from these studies could change the overall results.

Acknowledging these limitations, the present review and meta-analysis found that while an association is evident between cognitive function and later depression, general cognitive function does not appear to be a risk factor for depression, but rather is more likely related to performance decrements associated with concurrent depressive symptoms. The results suggest that low cognitive function is therefore probably not a causal factor of depression and that clinical practice may benefit more from a focus on how decreased cognitive function in the depressed state is likely to influence treatment outcomes (Gyurak et al., 2015). These findings have important implications for better understanding depression and for the design of future studies in highlighting the need to control for subthreshold depression symptoms when investigating risk factors for mental illness as well as when assessing cognitive function more generally.

3. Is Low Cognitive Functioning a Predictor or Consequence of Major Depressive Disorder? A Test in Two Longitudinal Birth Cohorts[1]

3.1. *Background*

Major depressive disorder (MDD) is the most common of all psychiatric disorders and a leading cause of disability worldwide (Whiteford et al., 2013). Although lifetime prevalence rates generated by cross-sectional epidemiologic surveys suggest that roughly a third of a population will develop MDD at some point during the life course (Kessler et al., 2005), corresponding figures drawn from longitudinal studies suggest that the true lifetime prevalence of the disorder may be substantially higher (Farmer, Kosty, Seeley, Olino, & Lewinsohn, 2013; Moffitt et al., 2010; Schaefer et al., 2016). This high prevalence is concerning, as MDD has been shown to predict lower life expectancy, increased susceptibility and risk of mortality from physical disease, and higher risk of suicide (Cassano & Fava, 2002). MDD also negatively affects multiple measures of occupational and interpersonal functioning (Adler et al., 2006; Hirschfeld et al., 2000).

Interestingly, many of these functional impairments associated with MDD have been shown to persist even after patients' depressed mood has remitted (Kennedy, Foy, Sherazi, McDonough, & McKeon, 2007), suggesting that non-affective factors may play a

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[1] This Chapter is based on the following publication: Schaefer, J.D.*, Scult, M.A.*, Caspi, A., Arseneault, L., Belsky, D.W., Hariri, A.R., Harrington, M., Houts, R. Ramrakha, S., Poulton, R., & Moffitt, T.E., (2017). Is low cognitive functioning a predictor or a consequence of major depressive disorder? A test in two longitudinal birth cohorts. *Development and Psychopathology,* 1-15.

critical role in determining functional outcomes. One such well-established predictor of overall functioning is cognitive functioning. Although deficits in the ability to think or concentrate have been listed among the diagnostic criteria for MDD since the term "major depressive disorder" was first introduced in the mid-1970s (Philipp, Maier, & Delmo), substantial interest in the treatment of cognitive impairment in the context of MDD has emerged more recently. For example, the National Academies of Sciences have hosted several workshops focused on understanding and treating cognitive dysfunction in depression in recent years (Bain & Stroud, 2015), and the Food & Drug Administration (FDA) has considered proposals to approve drugs that specifically target cognitive deficits associated with depression (Ledford, 2016; Mullard, 2016). These initiatives have been motivated by a number of cross-sectional reviews and meta-analyses on MDD, which report (1) that depressed individuals score lower than healthy controls across a wide variety of cognitive tasks (Christensen et al., 1997; Rock et al., 2014; Rogers et al., 2004; Snyder, 2013), even at first episode (Lee, Hermens, Porter, & Redoblado-Hodge, 2012), and (2) that these deficits can be observed even in individuals whose depression has remitted (Bora et al., 2013; Rock et al., 2014). Greater cognitive deficits in the context of MDD, in turn, are associated with increased symptom severity (McDermott & Ebmeier, 2009), higher rates of relapse and recurrence (Majer et al., 2004), and impaired functioning after discharge from psychiatric hospitalization (Jaeger, Berns, Uzelac, & Davis-Conway, 2006). Consequently, there is now considerable interest in the identification of novel

therapeutic agents capable of bringing about "cognitive remission" in depressed patients (Bortolato et al., 2016; Ledford, 2016), in addition to the remission of affective symptoms.

Before recommending that cognitive impairment in MDD should become a target of treatment, however, it is important to understand the origin and developmental course of these deficits. To date, two theoretical models have been proposed to explain the relationship between persistent cognitive impairments and MDD. The first, called the "cognitive reserve hypothesis," suggests that individuals with high intelligence are simply less likely to develop depression, either due to superior neural integrity or an increased ability to cope with or avoid stressful situations (Barnett et al., 2006; Koenen et al., 2009; Salmond, Menon, Chatfield, Pickard, & Sahakian, 2006; Scult et al., 2017b). Thus, cognitive "deficits" seen in cross-sectional studies that compare the cognitive performance of depressed or remitted individuals to healthy volunteers would be an indicator of "trait-like" differences that present early in development, well before MDD onset. This model draws support from a number of longitudinal studies documenting that low intelligence at time 1 is a robust predictor of subsequent depression at time 2, summarized in my recent meta-analysis (Scult et al., 2016). Here it is worth noting, however, that the majority of the studies demonstrating a predictive association between intelligence and MDD appear to be driven by depressive symptoms already present at the time of baseline cognitive assessment.

A second explanatory model, termed the "scarring hypothesis," suggests that the cognitive deficits observed in depressed patients result from enduring changes in physiology and neurochemistry that begin around the time of MDD onset and impair cognitive functioning from that point forward (Lewinsohn, Steinmetz, Larson, & Franklin, 1981). In this model, cognitive impairment in the context of MDD falls somewhere between "trait" and "state" factors. Although cognitive deficits are not proposed to precede the onset of depressive symptoms, they are hypothesized to persist well *after* the resolution of affective symptoms, potentially leaving MDD patients with a lifelong (albeit mild) impairment.

Although both of these models have been supported by previous research, the existing body of literature on persistent cognitive deficits in MDD is characterized by at least four important limitations. First, many of the studies that report associations between MDD and cognitive functioning have used small, clinical samples. Because depressed individuals receiving psychiatric care may differ from those who are not in several significant ways, the generalizability of these findings to the larger population of depressed individuals is unclear. This possibility is underscored by a recent study using population-representative data from the National Comorbidity Survey Adolescent Supplement (NCS-A), which reported that adolescents with past-year depression or dysthymia scored *higher* (rather than lower) on a measure of fluid intelligence compared to peers with no distress disorders (Keyes, Platt, Kaufman, & McLaughlin, 2017).

Second, the majority of studies that report associations between IQ and MDD have assessed MDD at only a single time point. Multiple psychiatric assessments are desirable in this context because longitudinal studies that have calculated the lifetime prevalence of MDD using both single and repeated assessments have generally found that repeated assessments generate 2.5 to 3 times higher prevalence estimates (Moffitt et al., 2010; Takayanagi et al., 2014). Thus, studies that use cognitive functioning to predict MDD at a single point in time are more likely to miscategorize individuals who have experienced or will experience depression as "healthy controls," potentially biasing estimates of effect size.

Third, it is also desirable to analyze data drawn from studies with multiple cognitive assessments, particularly when evaluating participants for evidence of cognitive "scarring". Despite this, the majority of studies that examine associations between cognitive performance and remitted depression are cross-sectional in nature, making it difficult to determine whether or not observed deficits represent a true decline from baseline ability following a depressive episode.

Fourth, relatively few studies of the link between IQ and MDD have taken rigorous steps to account for the presence or absence of comorbid diagnoses in diagnostic groups (see Scult et al., 2017), and those that *have* assessed participants for comorbidity have tended to use a single assessment wave (Scult et al., 2016; Snyder, 2013). These designs limit interpretation of previous findings, as prior work has shown that many

psychiatric disorders apart from MDD are predicted prospectively by low IQ (Batty, Mortensen, & Osler, 2005; Gale et al., 2008, 2010), associated with contemporaneous impairments in cognitive test performance (Airaksinen, Larsson, & Forsell, 2005; Horner & Hamner, 2002; Muller & Roberts, 2005; Schaefer, Giangrande, Weinberger, & Dickinson, 2013), and associated with cognitive "scarring" that lingers after symptomatic remission (Mann-Wrobel, Carreno, & Dickinson, 2011; Meier et al., 2012, 2014; Stavro, Pelletier, & Potvin, 2013). This raises the possibility that observed deficits thought to be associated with MDD are, in fact, driven by either unobserved comorbidities or some shared, transdiagnostic process.

To address these limitations, I present tests of both the cognitive reserve and scarring hypotheses using data drawn from two population-representative, longitudinal studies. The first sample, the Dunedin Study, follows a population-representative cohort from birth to midlife, with IQ tests administered at ages 7, 9, 11, and 38 years, and neuropsychological testing conducted at ages 13 and 38. At age 38, Dunedin Study members were also administered a set of self- and informant-report questionnaires asking questions about perceived cognitive functioning. In addition, Dunedin Study members completed psychiatric interviews assessing them for a variety of common psychiatric disorders every few years starting at age 11.

Over its course, the Dunedin Study also assessed Study members for a number of clinical indicators relevant to MDD, including disorder age of onset,

persistence/recurrence of depressive episodes, self-rated impairment due to MDD, number of MDD diagnostic criteria endorsed, whether the Study member received clinical attention for their MDD, and psychiatric comorbidity. These variables were used to test whether evidence of cognitive reserve or scarring is especially pronounced among Study members with particularly early-onset, severe, comorbid, or otherwise extreme cases of MDD.

The second sample, the Environmental Risk (E-Risk) Longitudinal Twin Study, follows a cohort of twins born in the U.K. from birth to age 18 years, with IQ tests administered at age 12 and a single psychiatric assessment using DSM criteria administered at age 18 years. The E-Risk Study's twin design allows for examination of whether the lower-IQ member of each twin pair is at relatively elevated risk of receiving a depression diagnosis at age 18. Because this design controls for shared environmental and (in monozygotic twin pairs) genetic factors that might normally account for an association between IQ and MDD, a positive finding would indicate that lower IQ predicts risk of MDD independent of these factors, providing support for a causal relationship.

3.2. *Methods*

Because the article makes use of data drawn from two different longitudinal studies, the methods section is divided into two parts. Part I describes the assessment of

IQ, neuropsychological assessment, and mental disorder in the Dunedin Study, whereas Part II describes how these same constructs were assessed in the E-Risk Study.

3.2.1. The Dunedin Study

3.2.1.1. Sample

The Dunedin Multidisciplinary Health and Development Study is a 4-decade, longitudinal investigation of health and behavior in a population-representative birth cohort. Study members (N = 1,037; 91% of eligible births; 52% male) were all individuals born between April 1972 and March 1973 in Dunedin, New Zealand who were eligible for the longitudinal study based on residence in the province at age 3, and who participated in the first follow-up assessment at age 3. The cohort represents the full range of socioeconomic status on New Zealand's South Island. In adulthood, the cohort matches the New Zealand National Health and Nutrition Survey on health indicators (e.g., BMI, smoking, GP visits) (Poulton, Moffitt, & Silva, 2015). The cohort is primarily white; fewer than 7% self-identify as having partial non-Caucasian ancestry. Assessments were carried out at birth and at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and, most recently, 38 years, when 95% of the 1,007 Study Members still alive took part. At each assessment wave, each Study member is brought to the Dunedin research unit for a full day of interviews and examinations. The Otago Ethics Committee approved each phase of the Study and informed consent was obtained from all Study members.

Measures of Intelligence (IQ)

Childhood intelligence. Results are reported from the Wechsler Intelligence Scale for Children—Revised (WISC-R;(Wechsler, 1974), using participants' total scores averaged over the three assessment points at ages 7, 9, and 11 to represent intelligence in childhood.

Adult intelligence. Results are reported from the Wechsler Adult Intelligence Scale, 4th Edition (WAIS-IV; (Wechsler, 2008), administered at age 38.

Measures of neuropsychological functioning

All testing occurred in the morning in two 50-min counterbalanced sessions. Dunedin Study members completed a small number of neuropsychological measures at age 13, and then a larger battery at age 38.

Neuropsychological functioning at age 13 years. Executive functioning was assessed using *Trails-B*, a test of scanning and tracking, divided attention, and mental flexibility, which involves drawing lines to connect consecutively numbered and lettered circles, alternating between numbers and letters. Scores represent the time, in seconds, to complete the test. Lower scores are better (Army Individual Test Battery, 1944). Test-retest reliability=0.73-0.89. Memory was assessed with the *Rey Auditory Verbal Learning Test.* The Total Recall score of the test is a measure of verbal learning and memory that involves a

five-trial presentation of a 15-word list and a one- time presentation of an interference list. Four trials of the 15-word list were administered due to time constraints. The Total Recall indexes the total number of words (0–60) recalled over four trials (the sum of words recalled across trials 1–4). Higher scores are better (Lezak, 2004); Test-retest reliability=0.86. The Delayed Recall version of the Rey indexes the total number of words from the original list (0–15) recalled after a 25–30 minute delay. Higher scores are better (Lezak, 2004). Test-retest reliability=0.80.

Neuropsychological functioning at age 38 years. The CANTAB Rapid Visual Information Processing: A‘ (A-prime), is a signal-detection measure that taps sustained attention, often called attentional vigilance. The participant scans for a 3-digit target sequence in a digit stream that is ongoing for 7 minutes, and responds whenever a target sequence is spotted. At the most difficult level, the participant scans simultaneously for two target sequences. Higher scores are better (Sahakian & Owen, 1992); Test-retest reliability=0.76.

CANTAB Rapid Visual Information Processing: Total False Alarms records impulsive jumping to respond too soon before the correct target digit sequence is complete. Because relatively few participants made numerous false alarms, this measure is categorical, coded 0=none, 1=1 false alarm, 2=2 or more false alarms. Lower scores are better (Sahakian & Owen, 1992); Test-retest reliability not available.

WAIS Working Memory Index was derived from the Arithmetic and Digit-span subtests. The Arithmetic subtest of WAIS requires working memory processes to be applied to orally presented verbal information. It involves numerical knowledge, short-term memory, attention, and concentration. Arithmetic problems are presented in story format. Performance requires holding information in short-term memory, accessing long-term memory to retrieve numerical rules of mathematical operation, and using the rules to manipulate the stored data. Items are arranged according to the level of difficulty and have time limits. The Digit-span subtest of WAIS is a test of memory span, attention/concentration, and ability to mentally manipulate information. The test requires listening to a sequence of digits read aloud and repeating them in forward, backward, and ascending order. Digit sequences range in length from 2 to 9 digits and are presented in order of difficulty. Higher scores on the WAIS Working Memory Index are better (Wechsler, 2008); Test-retest Reliability=0.90

Wechsler Memory Scale-III: Months of the Year Backwards Test is a test of attention and tracking. It requires reciting the months of the year in backwards order, starting with December. Responses were scored according to the instructions in the WMS-III manual. Scores ranged from 1 (poor performance) to 5 (good performance) and reflect both accuracy and speed. Higher scores are better (Wechsler, 1997); Test-retest Reliability=0.80

Trails-B is a test of scanning and tracking, divided attention, and mental flexibility, which involves drawing lines to connect consecutively numbered and lettered circles,

alternating between numbers and letters. Scores represent the time, in seconds, to complete the test. Lower scores are better (Army Individual Test Battery, 1944). Test-retest reliability=0.73-0.89.

CANTAB Paired Associates Learning: First Trial Memory Score is a test of visual memory and new learning. Boxes are displayed on the screen and are opened in a random order. One or more of them will contain a pattern. The patterns are then displayed in the middle of the screen, one at a time, and the subject must touch the box where the pattern was originally located. If the subject makes an error, the patterns are re-presented to remind the subject of their locations. The difficulty level increases through the test. The number of patterns increases across eight stages (i.e., two 1-pattern stages, two 2-pattern stages, two 3-pattern stages, one 6-pattern stage, one 8-pattern stage), which challenges even very able subjects. For each stage, up to 10 trials are presented until all the patterns are located correctly. For the First Trial Memory Score, the number of patterns correctly located after the first trial of each stage is summed across the stages completed (range 0–26, with 26 meaning that all the patterns were correctly located for all stages the first time). Higher scores are better (Sahakian & Owen, 1992); Test-retest reliability=0.87.

CANTAB Paired Associates Learning: Total Errors is based on the same protocol as above but considers the total number of errors (with an adjustment for each stage not attempted due to previous failure). Lower scores are better (Sahakian & Owen, 1992); Test-retest reliability=0.64.

Wechsler Memory Scale-III: Verbal Paired Associates Total Recall is a test of verbal learning and memory. Eight pairs of unrelated words (e.g., hat-sofa) are read aloud and followed by a recall task (one of the words from each word pair is given, and the associated word must be recalled). Four trials of the eight word-pairs are presented. Presentation of the word-pairs is randomized across trials. The total recall score represents the total number of words (0–32) recalled across four trials. Higher scores are better (Wechsler, 1997); Test-retest reliability=0.75.

Wechsler Memory Scale-III: Verbal Paired Associates Delayed Recall is based on the same protocol as above but represents the total number of words (0–8) recalled after a 25–35 minute delay. Higher scores are better (Wechsler, 1997); Test-retest reliability=0.73.

Rey Auditory Verbal Learning Test: Total Recall is a test of verbal learning and memory that involves a five-trial presentation of a 15-word list and a one-time presentation of an interference list. Four trials of the 15-word list were administered due to time constraints. The Total Recall indexes the total number of words (0–60) recalled over four trials (the sum of words recalled across trials 1–4). Higher scores are better (Lezak, 2004); Test-retest reliability=0.86.

Rey Auditory Verbal Learning Test: Delayed Recall indexes the total number of words from the original list (0–15) recalled after a 25–30 minute delay. Higher scores are better (Lezak, 2004). Test-retest reliability=0.80.

Self-reported cognitive functioning

At age 38, Study members were queried about problems related to memory and attention. Study members reported how often in the past year (never, sometimes, or often) they experienced problems with keeping track of appointments, remembering why they went to a store, and repeating the same story to someone, among other items. Scores on each of the 17 questions were summed to create an overall measure of cognitive difficulties (M = 9.1; SD = 5.3; range = 0-31; internal consistency reliability = 0.83). Study members were also asked to rate the extent to which their cognitive difficulties interfered with their lives on a scale from 1 (some impairment) to 5 (severe impairment). Both self-reported cognitive difficulties (r = -0.15) and the extent of impairment (r = -0.16) were negatively correlated with adult full-scale IQ (both p's < 0.0001).

Informant-reported cognitive problems

Informant reports of Study members' cognitive function were obtained at age 38. Study members nominated people who "knew them well." These informants were mailed questionnaires and asked to complete a checklist, including whether the Study member had problems with his or her attention and memory over the past year. The informant-reported attention problems scale consisted of four items: "Is easily distracted, gets side-tracked easily," "Can't concentrate, mind wanders," "Tunes out instead of focusing," and

"Has difficulty organizing tasks that have many steps" (internal consistency reliability = 0.79). The informant-reported memory problems scale consisted of three items: "Has problems with memory," "Misplaces wallet, keys, eyeglasses, paperwork," and "Forgets to do errands, return calls, pay bills" (internal consistency reliability = 0.64). Both informant-reported attention problems ($r = -0.26$) and informant-reported memory problems ($r = -0.14$) were negatively correlated with adult full-scale IQ (both p's < 0.0001).

Assessment of Mental Disorders

Mental disorders were ascertained in the Dunedin Study longitudinally using a periodic sampling strategy: Every 2 to 6 years, Study members were interviewed about past-year symptoms in a private in-person interview at the research unit by trained interviewers with tertiary qualifications and clinical experience in a mental health-related field such as family medicine, clinical psychology, or psychiatric social work (i.e. not lay interviewers). Interviewers used the Diagnostic Interview Schedule for Children (DIS-C) at the younger ages (11-15 years) and the Diagnostic Interview Schedule at the older ages (18-38 years). At each assessment, interviewers were kept blind to Study members' previous data, including mental health status. At ages 11, 13, and 15, diagnoses were made according to the then-current DSM-III and grouped for this article into a single wave reflecting the presence or absence of specific juvenile mental disorders. At ages 18 and 21, diagnoses were made according to the DSM-III-R (American Psychiatric Association,

1987), and at ages 26, 32, and 38 diagnoses were made according to the DSM-IV (American Psychiatric Association, 1994). This method led to 6 waves in total representing ages 11-15, 18, 21, 26, 32, and 38. In addition to symptom criteria, diagnosis required impairment ratings for that disorder ≥ 2 on a scale from 1 (some impairment) to 5 (severe impairment). Each disorder was diagnosed regardless of the presence of other disorders. Variable construction details, reliability and validity, and evidence of life impairment for diagnoses have been reported previously (Feehan, McGee, Raja, & Williams, 1994; Kim-Cohen et al., 2003; Moffitt et al., 2010; Moffitt et al., 2007; Newman et al., 1996).

3.2.2. The Environmental Risk (E-Risk) Cohort

3.2.2.1. Sample

Participants were members of the Environmental Risk (E-Risk) Longitudinal Twin Study, a birth cohort of 2,232 British children. The sample was drawn from a larger birth register of twins born in England and Wales from 1994-1995 (Trouton, Spinath, & Plomin, 2002). Full details on the sample have been previously reported (Moffitt, 2002). Briefly, the E-Risk sample was constructed in 1999–2000, when 1,116 families (93% of those eligible) with same-sex 5-year-old twins participated in home-visit assessments. This sample comprised 56% monozygotic (MZ) and 44% dizygotic (DZ) twin pairs. Within zygosity, 48% of MZ twins were male, and 50% of DZ twins were male. Families were recruited to represent the UK population of families with newborns in the 1990s, on the

basis of residential location throughout England and Wales and mother's age. Teenaged mothers with twins were over-selected to replace high-risk families who were selectively lost to the register through nonresponse. Older mothers having twins via assisted reproduction were under-selected to avoid an excess of well-educated older mothers. The study sample represents the full range of socioeconomic conditions in Great Britain, as reflected in the families' distribution on a neighborhood-level socioeconomic index (ACORN [A Classification of Residential Neighborhoods], developed by CACI Inc. for commercial use) (Odgers, Caspi, Bates, Sampson, & Moffitt, 2012): 25.6% of E-Risk families live in "wealthy achiever" neighborhoods compared to 25.3% nationwide; 5.3% vs. 11.6% live in "urban prosperity" neighborhoods; 29.6% vs. 26.9% live in "comfortably off" neighborhoods; 13.4% vs. 13.9% live in "moderate means" neighborhoods; and 26.1% vs. 20.7% live in "hard-pressed" neighborhoods. E-Risk underrepresents "urban prosperity" neighborhoods because such households are likely to be childless.

Follow-up home visits were conducted when the children were aged 7 (98% participation), 10 (96% participation), 12 (96% participation), and, most recently in 2012–2014, 18 years (93% participation). There were 2,066 children who participated in the E-Risk assessments at age 18, and the proportions of MZ (56%) and male same-sex (47%) twins were almost identical to those found in the original sample at age 5. The average age of the twins at the time of the assessment was 18.4 years (SD = 0.36); all interviews were conducted after the 18th birthday. Home visits at ages 5, 7, 10, and 12 years included

assessments with participants as well as their mother (or primary caretaker); the home visit at age 18 included interviews only with the participants. Each twin participant was assessed by a different interviewer.

The Joint South London, Maudsley, and the Institute of Psychiatry Research Ethics Committee approved each phase of the study. Parents gave informed consent and twins gave assent between 5 and 12 years and then informed consent at age 18.

Measure of Intelligence (IQ)

A short version of the Wechsler Intelligence Scale for Children-Revised (WISC-R) was administered when Study members were age 12 years. Using two subtests (Matrix Reasoning and Information), Study members' IQs were prorated and standardized to M = 100 (SD = 15), according to the method recommended by (Sattler, 2008).

Assessment of Depression

Unlike the Dunedin cohort, which underwent repeated diagnostic assessments from age 11 to 38, the E-Risk Study members participated in only one diagnostic interview at age 18, during which they were assessed for past-year DSM-IV symptoms of MDD using the Diagnostic Interview Schedule (DIS) (Robins, Cottler, Bucholz, & Compton, 1995). As in the Dunedin Study, E-Risk Study members meeting symptom criteria for

MDD also needed to report impairment ratings ≥ 2 on a scale from 1 (some impairment) to 5 (severe impairment) to receive a diagnosis.

3.3. *Results*

Results are presented in three parts. Part I presents tests of the cognitive reserve hypothesis, in which lower IQ in childhood is hypothesized to predict an increased risk of subsequent MDD. Part II presents tests of the scarring hypothesis, in which IQ deficits are hypothesized to persist in individuals with a history of MDD, even after remission of their affective symptoms. Finally, Part III extends both of these analyses to neuropsychological measures assessing memory and executive functioning, two domains that have been repeatedly linked to MDD in previous work (Bora et al., 2013; Hsu & Davison, 2017; Rock et al., 2014).

3.3.1. The Cognitive Reserve Hypothesis

3.3.1.1. Does lower IQ in childhood predict increased risk of developing Major Depressive Disorder?

To address this question, I started with 957 (92.3%) of the original 1,037 Dunedin Study members, including only those individuals who (a) had participated in at least half of the six mental health assessment waves from ages 11 to 38 and (b) had available childhood IQ data. Because schizophrenia is often accompanied by depression, and is associated with pronounced pre-morbid and post-onset cognitive deficits as well as

thought disorder symptoms (Kendler, Ohlsson, Sundquist, & Sundquist, 2014; Meier et al., 2014; Reichenberg et al., 2010; Schaefer et al., 2013), I further refined the analytic sample by excluding all Study members who received a diagnosis of schizophrenia by age 38 (N = 37). This step ensured that any observed associations between MDD and IQ were not driven by these individuals.

Of the remaining 920 Study members, 812 (88.3%) contributed 6 waves of mental health data, 67 (7.3%) contributed 5 waves of mental health data, 26 (2.8%) contributed 4 waves of mental health data, and 15 (1.6%) contributed 3 waves of mental health data. From ages 11 to 38, 431 (46.9%) of these Study members received a diagnosis of major depressive disorder (MDD) at one or more assessment waves. These Study members constituted the "ever-depressed" group. The remainder of the cohort (*N* = 489, 53.2%) did not meet criteria for a diagnosis of MDD between the ages of 11 and 38. These Study members constituted the "never-depressed" group. Together, these groups composed the full analytic sample (Figure 6A).

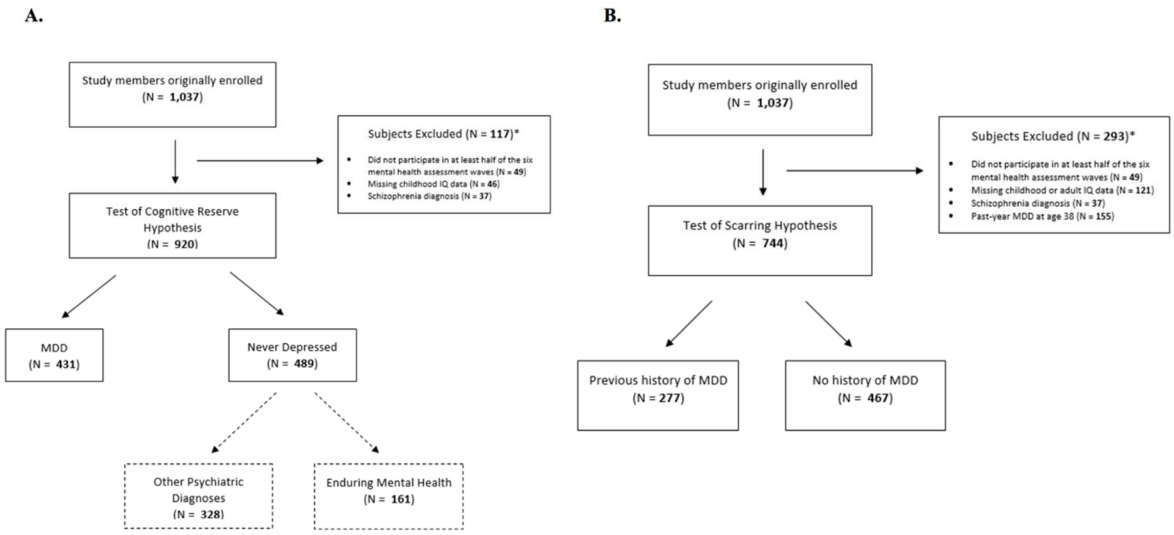

Figure 6: Dunedin Study member flow diagrams for tests of the (A) cognitive reserve hypothesis and (B) cognitive scarring hypothesis.

As an initial test of the cognitive reserve hypothesis, I conducted a follow-forward analysis using a modified Poisson regression model with robust standard errors to estimate relative risk for the binary outcome of lifetime MDD (Zou, 2004). Methodologists have suggested that risk ratios are less inflated than odds ratios in situations where the outcome is common, which is the case for MDD in the present sample (Cummings, 2009). The risk ratios presented can be understood as the ratio change in average risk of MDD for every one point increase in IQ. Using this approach, it was found that risk of membership in the ever-depressed (N = 431; mean childhood IQ = 100.0, SD = 14.4) versus never-depressed group (N = 489; mean childhood IQ = 101.4, SD = 13.8) did not differ as a function of childhood IQ, controlling for sex (IRR = 0.997; 95% CI = 0.992, 1.002; p = 0.247).

Previous studies have suggested that low childhood IQ is associated with an

increased risk of developing not only depression, but also a number of other psychiatric conditions, including anxiety and substance use disorders (Fergusson, Horwood, & Ridder, 2005; Gale et al., 2008; Koenen et al., 2009; Rajput, Hassiotis, Richards, Hatch, & Stewart, 2011). Thus, it is possible that the ability to detect a predictive relationship between childhood IQ and lifetime depression is limited by the presence of other psychiatric disorders in the "never-depressed" group. Fortunately, one advantage afforded by the Dunedin Study's repeated mental health assessments is that they allowed for the identification of the small group of individuals who have never met criteria for *any* of the mental disorders assessed by the Study (hereafter referred to as the "enduring-mental-health" group; (Schaefer et al., 2016), and to use these Study members as a new comparison group (N = 161 who had childhood IQ data; mean childhood IQ = 102.3, SD = 14.0) (Figure 6A). Additional follow-forward analysis were therefore conducted to test whether childhood IQ was a significant predictor of membership in the ever-depressed versus enduring-mental-health groups, controlling for sex. Consistent with previous results, it was found that childhood IQ still did not appear to distinguish between the two groups (IRR = 0.997; 95% CI = 0.994, 1.001; p = 0.136).

To provide a point of comparison, it was also tested whether childhood IQ was a significant predictor of membership in the small group of Study members with schizophrenia (N = 37; mean childhood IQ = 94.0, SD = 17.6) versus the majority of the cohort who were never diagnosed with schizophrenia (N = 920; mean childhood IQ =

100.7, SD = 14.1), controlling for sex. Here, low childhood IQ *was* associated with higher risk of receiving a schizophrenia diagnosis (IRR = 0.968; 95% CI = 0.944, 0.992; p = 0.010).

3.3.1.2. Does lower IQ in childhood exert an effect on an individual's later risk of developing Major Depressive Disorder independent of family-wide and genetic risk?

An even more powerful approach to testing the cognitive reserve hypothesis is to compare two children growing up in the same family. If the cognitive reserve hypothesis is correct, the sibling with higher IQ should be at lower risk of developing MDD. This hypothesis was tested in E-Risk Longitudinal Twin Study using the following mixed-effects model:

$$\text{logit}(\pi_{ij}) = \beta_0 + \beta_w(X_{ij} - \bar{X}_i) + \beta_B\bar{X}_i$$

In this specification, IQ effects are parsed into *between-twin pair effects* and *within-twin pair effects* using a logistic regression model, where *i* is used to index twin pairs and *j* represents individual twins within pairs, so π_{ij} and X_{ij} represent, respectively, the probability of receiving a depression diagnosis and childhood IQ values for the j^{th} twin of the i^{th} pair, whereas $\bar{X}_i$ represents the mean childhood IQ of both twins within the i^{th} pair. The between-twin pair regression coefficient (β_B) estimates whether pairs of twins with higher average age-12 IQ are at lower risk of being diagnosed with MDD at age 18. In contrast, the within-twin pair regression coefficient (β_w) estimates whether the twin with higher IQ than his or her co-twin is less likely to be diagnosed with MDD than his or her co-twin.

This model was first estimated using data from all available twin pairs (MZ and DZ) in E-Risk. A significant between-twin-pair effect would reflect family-wide factors common to both twins that influence IQ and MDD and may underlie their association. A significant within-twin-pair effect, on the other hand, would indicate that possessing low IQ in childhood predicts MDD independent of any factors that are shared between siblings growing up in the same family (Carlin, Gurrin, Sterne, Morley, & Dwyer, 2005). The model was then estimated using only the MZ twin pairs in the E-Risk Study. Because MZ twins are genetically identical, a significant within-twin pair effect would rule out the possibility that the association between IQ and MDD arises solely due to a shared genetic susceptibility that elevates risk of both phenotypes.

The parameters estimated from each of these models are reported in **Table 5**. Of the original 2,232 Study members, 2,003 (89.7%) were included, excluding twins if they belonged to a twin pair in which (a) 1 or more twins lacked IQ data at age 12, or (b) both twins lacked mental health assessment data at age 18. Of these 2,003 Study members, 404 (20.2%) received a diagnosis of MDD. Both the full-cohort and MZ-twin-only models indicated that neither between-twin-pair nor within-twin-pair differences in IQ tested at age 12 appear to predict risk of MDD at age 18, consistent with results from the follow-forward analysis conducted in the Dunedin Cohort. These findings did not support the assumption that lower IQ is causally related to increased risk of subsequent depression.

Table 5: Testing the "cognitive reserve" hypothesis. Between- and within-twin pair effects of childhood IQ on risk of depression at age 18 in the E-Risk Cohort. Notes: β_B represents the between-pair effects of mean childhood IQ (assessed at age 12) on risk of depression at age 18. β_w represents the effect of within-pair differences in childhood IQ, controlling for the effects of shared family environment and (in MZ twins) genetics. Sex was included in each model as a covariate.

Effects	All Twins (*N* = 2,003)		MZ Twins (*N* = 1,124)	
	RR (95% CI)	p	RR (95% CI)	P
β_B	1.00 (0.99-1.00)	0.279	1.00 (0.99-1.01)	0.685
β_w	1.00 (0.99-1.01)	0.720	0.99 (0.97-1.01)	0.344

3.3.1.3. Could lower IQ in childhood predict particularly early-onset or severe MDD?

Although childhood IQ did not predict risk of future MDD in either cohort, it is still possible that a predictive relationship might exist between IQ in childhood and specific types of MDD, especially given previous research indicating a link between lower cognitive functioning and higher rates of relapse/recurrence, increased symptom severity, and impaired global functioning among depressed individuals (Jaeger et al., 2006; Majer et al., 2004; McDermott & Ebmeier, 2009). Thus, I next tested the hypotheses that childhood IQ would predict measures of MDD age-of-onset, persistence, self-rated impairment, number of diagnostic criteria endorsed, clinical attention, or psychiatric comorbidity in the Dunedin Cohort.

Age of onset

I tested whether childhood IQ predicted an earlier age of depression onset by

conducting a Cox proportional hazards regression using data from the full analytic sample (N = 920), controlling for sex. The assessment wave during which each Study member in the ever-depressed group received his or her first diagnosis of MDD was used as the age of depression onset (M = 23.3, SD = 7.0, range = 15-38). It was found that childhood IQ did not significantly predict depression age of onset (HR = 1.00; 95% CI = 0.99, 1.00; p = 0.381), indicating that Study members with low IQ did not appear to develop depression any earlier than Study members with higher IQ.

Persistent course

The depression recurrence/persistence for each Study member in the ever-depressed group (N = 431) was calculated as the *proportion* of waves during which that Study member met diagnostic criteria for MDD ($M_{proportion}$ = 0.30, SD = 0.16, range = 0.17-1.00). A linear regression was used to predict the proportion of waves each Study member had received an MDD diagnosis as a function of childhood IQ, controlling for sex. No significant association was found between childhood IQ and this measure (*b* = -0.001; 95% CI: -0.002, 0.000; *t*(428) = -1.31; p = 0.19), indicating that Dunedin Study members with low IQ who were diagnosed with MDD did not appear to spend significantly more Study waves suffering from depression than their higher-IQ peers with MDD.

Self-rated impairment

Dunedin Study members were asked to rate the functional impairment caused by their depressive symptoms on a scale from 1 (some impairment) to 5 (severe impairment) at each assessment wave between the ages of 18 and 38. Self-rated impairment in this cohort was recorded as the maximum impairment rating given between the ages of 18 and 38 (M = 4.05, SD = 0.88, range = 2-5) by each Study member who met diagnostic criteria for MDD at least once during this same period (N = 412). The analysis of impairment was limited to this age range because self-ratings of impairment were not collected in earlier assessments.

A linear regression model was used to predict self-rated impairment as a function of childhood IQ, controlling for sex, and it was found that childhood IQ was a significant predictor of self-rated impairment (b = -0.01; 95% CI: -0.01, 0.00; $t(409)$ = -2.05; p = 0.041), suggesting that individuals with lower IQs who develop MDD tend to rate their depression as more impairing than their higher-IQ peers with MDD. Such an effect is likely to be of little practical significance, however, as each 1-point increase in IQ is associated with a predicted decrease of only 1/100th of a point on a 5-point self-rated impairment scale.

Symptom count

Symptom count was calculated as the number of MDD criteria endorsed by Study members between the ages of 18 and 38 (M = 15.03, SD = 7.78, range = 4-41) by each Study member who met diagnostic criteria for MDD at least once during this same period (N = 413). Analysis of symptom criteria was limited to this age range because symptom count data from earlier waves were not available.

A linear regression was used to predict symptom count between the ages of 18 and 38 as a function of childhood IQ, controlling for sex, and found no significant association between childhood IQ and this measure (b = -0.02; 95% CI: -0.07, 0.03; $t(410)$ = -0.86; p = 0.392), suggesting that Study members with lower IQs tended to endorse a similar number of MDD symptoms relative to Study members with higher IQs.

Clinical attention

Dunedin Study members reported if they had contacted a professional (i.e. a general practitioner, psychologist, or psychiatrist) for a mental health problem or received psychiatric medication between the ages of 20 and 38. Of the 350 Study members diagnosed with MDD during this same period in the full analytic sample (with present treatment contact data), 249 (71.1%) endorsed some form of treatment contact. A Poisson regression model with robust standard errors was conducted to calculate risk ratios for

the binary outcome of treatment contact as a function of childhood IQ, controlling for sex. No significant association was found between childhood IQ and this measure (IRR = 1.002; 95% CI: 0.997, 1.006; p = 0.464), suggesting that individuals with lower IQs who develop MDD were no more likely to receive treatment than their higher-IQ peers with MDD.

Comorbidity

In the Dunedin Study, comorbidity is operationalized as the number of diagnostic families (including depressive disorders, anxiety disorders, substance use disorders, attention-deficit/hyperactivity disorder, and conduct disorder) represented in a Study member's complete history of psychiatric diagnoses accumulated between the ages of 11 and 38 years (M = 1.70, SD = 1.21, range 0-5 in the full analytic sample; M = 2.54, SD = 0.97, range 1-5 in the ever-depressed group). Schizophrenia was not included in the count of psychiatric comorbidities because Study members who developed schizophrenia were excluded from the analytic sample.

The association between childhood IQ and lifetime psychiatric comorbidity was tested using a Poisson regression model that predicted the count of diagnostic families represented in each Study member's diagnostic history between the ages of 11 and 38 as a function of childhood IQ, controlling for sex, and found an association between childhood IQ and comorbidity in both the full analytic sample (N = 920; IRR = 0.993; 95% CI: 0.989, 0.996; p <0.001), and among ever-depressed Study members (N = 431; IRR =

0.995; 95% CI: 0.991, 0.999; p = 0.025).

Figure 7A charts mean IQ as a function of psychiatric comorbidity in the context of MDD. Here IQ scores are plotted for Dunedin Study members who have never had depression, Study members who have had depression only, and Study members who have had depression alongside 1 or more additional psychiatric conditions. Figure 7A shows that early IQ deficits were pronounced only among depressed Study members with multiple psychiatric comorbidities. Interestingly, Dunedin Study members with "pure" depression—that is, those who were diagnosed *only* with depression between the ages of 11 and 38 years—appeared to have slightly higher IQs in childhood than Study members who were never diagnosed with depression. This observation was confirmed through follow-forward analysis using Poisson regression, which indicated that Dunedin Study members with higher IQs were more likely to experience pure depression than no depression at all, controlling for sex (N = 543; IRR = 1.019; 95% CI = 1.001, 1.037; p = 0.040).

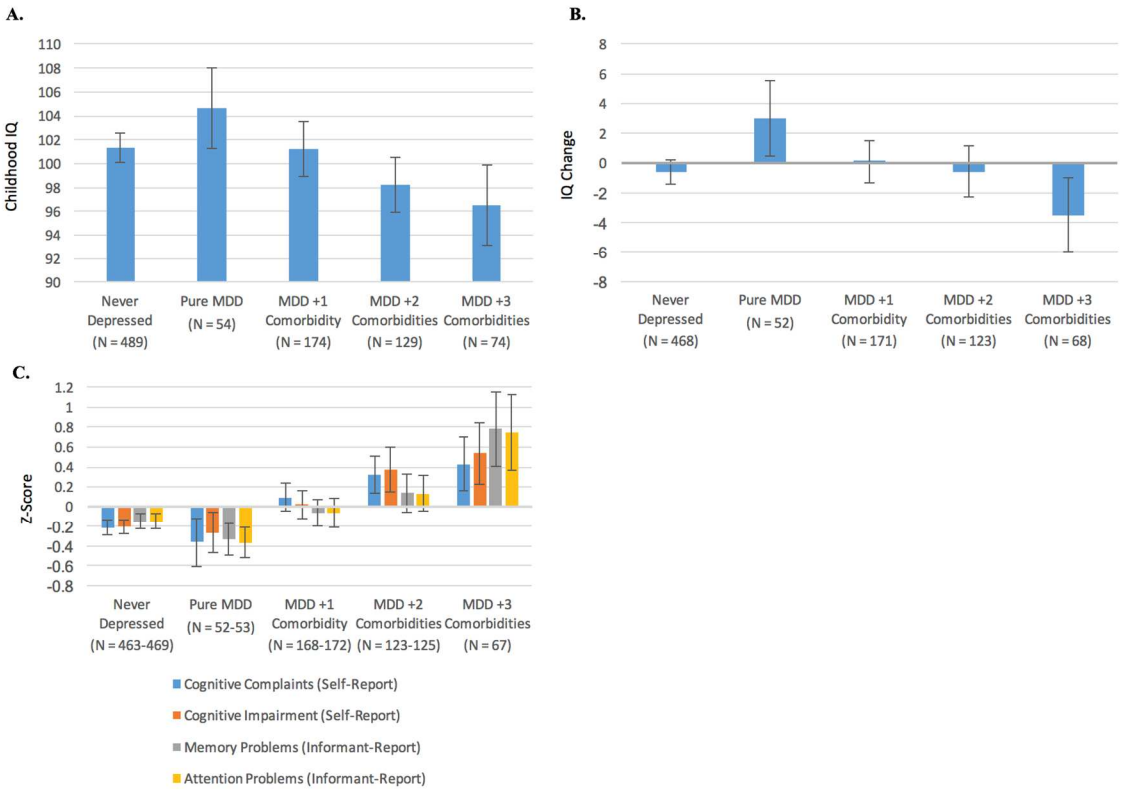

Figure 7: Mean (A) childhood IQ, (B) change in IQ from childhood to adulthood, and (C) subjective adult cognitive problems by lifetime psychiatric comorbidity in the Dunedin Cohort.

Finally, a modified Poisson regression with robust standard errors was used to test whether low childhood IQ predicted the emergence of certain types of lifetime psychiatric comorbidities, but not others. It was found that children who went on to develop MDD (N = 420) with lower childhood IQs were also at increased risk of developing anxiety disorders (IRR = 0.993; 95% CI = 0.989, 0.996; $p < 0.001$), attention-deficit/hyperactivity disorder (IRR = 0.949; 95% CI = 0.929, 0.969; $p < 0.001$), and conduct disorder (IRR = 0.983; 95% CI = 0.971, 0.996; $p = 0.008$), but not substance use disorders (IRR = 0.999; 95% CI =

0.993, 1.006; p = 0.861).

3.3.2. The Scarring Hypothesis

3.3.2.1. Are individuals with a history of MDD more likely to show evidence of or report lingering cognitive impairment as adults?

Data from the Dunedin Study was next used to test for enduring cognitive deficits in previously-depressed Study members whose MDD had remitted by age 38, the time of adult cognitive assessment. Evidence of intellectual decline among these remitted individuals could be interpreted as evidence of a lingering depression-induced "scar" on cognitive functioning (Lewinsohn et al., 1981). For these analyses, I used data from 744 Study members who were assessed for mental disorder at age 38 but who did not meet criteria for a diagnosis of past-year MDD at age 38. This decision allowed for the separation of lingering cognitive "scarring" effects of a diagnostic history of MDD from the contemporaneous effects of a current episode of MDD. Similar to previous analyses, these individuals were also required to have (a) participated in at least half of the six mental health assessment waves from ages 11 to 38, (b) available childhood and adult IQ data, and (c) never received a diagnosis of schizophrenia. These individuals were divided into two groups: those with a previous history of MDD (N = 277; mean adult IQ = 101.2, SD = 14.4), and those with no previous history of MDD (N = 467; mean adult IQ = 101.0, SD = 14.4) (Figure 6B).

I conducted a series of one-way ANOVAs testing whether Study members with a previous history of MDD differed from Study members without such a history on age-38

IQ, self-reported cognitive functioning, or informant-reported cognitive functioning, controlling for sex. As shown in **Table 6**, it was found that Study members with a history of depression scored lower on *subjective* measures of cognitive functioning (i.e., self- and informant-report), but not on any of *objective* measures of cognitive functioning (i.e. WISC-R and WAIS-IV IQ, IQ change from childhood to adulthood). Taken together, these results suggest that Study members with a history of depression were more likely to report that their cognitive functioning was impaired despite little to no measurable change (on average) in objective cognitive functioning as assessed by IQ tests.

Table 6: Testing the "scarring hypothesis." Cognitive functioning in Study members who were not diagnosed with past-year MDD at age 38, by lifetime diagnostic history. Notes: This table includes only those Study members who (a) were not diagnosed with past-year MDD at age 38 and (b) had present data for adult IQ. The "no history of MDD" group represents Study members who had never met criteria for MDD. The "past history of MDD" group represents Study members who had met diagnostic criteria for MDD during a previous wave but no longer met criteria at age 38. Scores on objective measures are reported as IQ points (mean = 100, SD = 15). Scores on subjective measures were standardized in the full cohort to a mean of 0 and a standard deviation of 1. Means were compared across diagnostic groups through a series of one-way ANOVAs, controlling for sex.

Measure (Age at Assessment)	No History of MDD		Past History of MDD			
	N	Mean (95% CI)	*N*	Mean (95% CI)	*F*	p
Objective Measures						
WISC IQ (Age 7-11)	467	101.6 (100.4, 102.8)	277	101.3 (99.8, 102.9)	0.02	0.897
WAIS IQ (Age 38)	467	101.0 (99.7, 102.3)	277	101.2 (99.5, 102.9)	0.23	0.631
IQ Change	467	-0.62 (-1.44, 0.20)	277	-0.14 (-1.27, 0.99)	0.31	0.577
Subjective Measures						
Self-Reported						
Cognitive Complaints (Age 38)	467	-0.21 (-0.29, -0.13)	277	0.11 (-0.01, 0.22)	13.99	<0.001
Impairment (Age 38)	467	-0.20 (-0.27, -0.13)	277	0.04 (-0.07, 0.16)	13.33	<0.001
Informant-Reported						
Memory Problems (Age 38)	460	-0.15 (-0.22, -0.07)	275	-0.02 (-0.13, 0.10)	7.08	0.008
Attention Problems (Age 38)	460	-0.15 (-0.23, -0.07)	275	-0.04 (-0.15, 0.07)	6.04	0.014

3.3.2.2. Is there evidence of cognitive scarring following an episode of particularly severe or early-onset MDD?

One criticism of the analyses summarized in **Table 6** is that, in comparing only those individuals who were *not* depressed at age 38, it potentially ignores many of the most severe, chronic cases of MDD who continued to meet diagnostic criteria at the age-38 assessment wave. Consequently, I next tested whether any of six clinical indicators (i.e., MDD age-of-onset, persistence/recurrence, self-rated impairment, number of diagnostic criteria endorsed, clinical attention, and comorbidity) predicted change in IQ from childhood (ages 7-11) to adulthood (age 38). If cognitive scarring is more common following severe or early-onset cases of MDD, higher scores on these indicators should predict a more severe decline in IQ following a depressive episode.

As shown in **Table 7**, only psychiatric comorbidity was found to predict a steeper decline in IQ from childhood to adulthood. This finding suggests that the cognitive scarring reported following a depressive episode may be more attributable to disorders commonly comorbid with MDD rather than the experience of a depressive episode per se. **Figure 7B** charts mean change in IQ between childhood (ages 7-11) and adult (age 38) assessments as a function of psychiatric comorbidity in the context of MDD, whereas **Figure 7C** does the same with four subjective measures of cognitive functioning. Consistent with **Figure 7A**, **Figures 7B** and **7C** show that evidence of IQ decline and high subjective impairment was apparent only for depressed Study members with multiple psychiatric comorbidities.

Table 7: Testing the "scarring hypothesis," part 2. Cognitive functioning in Study members who were not diagnosed with past-year MDD at age 38, by lifetime diagnostic history. Notes: This table includes only those Study members who (a) were not diagnosed with past-year MDD at age 38 and (b) had present data for adult IQ. The "no history of MDD" group represents Study members who had never met criteria for MDD. The "past history of MDD" group represents Study members who had met diagnostic criteria for MDD during a previous wave but no longer met criteria at age 38. Scores on objective measures are reported as IQ points (mean = 100, SD = 15). Scores on subjective measures were standardized in the full cohort to a mean of 0 and a standard deviation of 1. Means were compared across diagnostic groups through a series of one-way ANOVAs, controlling for sex.

Clinical Indicators	Change in IQ					
	b (SE)	b (SE)	b (SE)	b (SE)	b (SE)	b (SE)
Age of onset	-0.06 (-1.01, 0.88)					
Persistence/Recurrence		0.11 (-1.02, 1.24)				
Self-rated impairment			-0.33 (-1.29, 0.63)			
# of Symptom Criteria				-0.29 (-1.40, 0.82)		
Clinical Attention					0.26 (-0.89, 1.41)	
Psychiatric Comorbidity						-2.41*** (-3.68, -1.15)

3.3.2.3. Beyond IQ

A second potential criticism of the analyses presented in this paper is that IQ is too crude or too global of a measure to detect the subtle changes in cognitive functioning associated with MDD. This may be particularly true for tests of the scarring hypothesis, as previous work has suggested that scarring is most noticeable in the domains of executive functioning (e.g., working memory, attention regulation, inhibitory control, and cognitive flexibility/switching) and long-term memory (Bora et al., 2013; Rock et al., 2014).

To address this concern, I selected from the datasets the measures most closely associated with these cognitive domains.

Poisson regression with robust standard errors was used to test whether childhood scores on neuropsychological measures were significant predictors of future MDD in the Dunedin Study, controlling for sex (a further test of the "cognitive reserve hypothesis"). Because Study members completed neuropsychological testing at age 13, I removed individuals who received a diagnosis of MDD during the first, juvenile assessment wave (ages 11 to 15) from the full analytic sample (shown in **Figure 6A**) in order to ensure that scores predicted future, rather than concurrent, MDD. As shown in **Table 8**, the association between MDD status and performance on Trails B was approaching significance (IRR = 1.00; 95% CI: 1.00, 1.01; p = 0.053), but otherwise there was little evidence to suggest that any of these measures significantly predicted future MDD risk.

I next conducted a series of one-way ANOVAs testing whether Study members with a previous history of MDD differed from Study members without such a history on neuropsychological measures of executive functioning and memory administered at age 38, controlling for sex (a further test for cognitive scarring). As shown in **Table 9**, Study members with a history of MDD scored significantly lower than Study members without such a history on a measure involving the delayed recall of multiple word pairs (WMS-IV Verbal Paired Associates) ($F(1, 738) = 4.40$, $p = 0.036$). However, this difference did not survive correction for multiple comparisons and no other significant between-group

differences were observed. Viewed as a whole, the results provide little support for the notion that lower performance on measures of executive functioning or memory are predictors or enduring consequences of MDD.

Table 8: Testing the "cognitive reserve hypothesis," part 2. Neuropsychological test performance of Study members who did and did not receive a diagnosis of MDD by age 38. Notes: This table includes Study members from the full analytic sample (see Figure 6A) who completed neuropsychological testing at age 13. To ensure that cognitive functioning at age 13 was being used to predict *future* MDD, Study members who received a diagnosis of MDD prior to age 18 were excluded from this analysis. The "Never Depressed" group represents Study members who did not ever meet criteria for MDD between the ages of 18 and 38. The "Ever Depressed" group represents Study members who did meet diagnostic criteria for MDD during this same period. Relative risk (IRR) of MDD was calculated using a modified Poisson regression model with robust standard errors (Zou, 2004).

Measures (All Administered at Age 13)	Never Depressed		Ever Depressed		Poisson Regression Results	
	N	Mean (95% CI)	*N*	Mean (95% CI)	IRR (95% CI)	p
Executive Functioning						
Trails B (time in seconds)	368	35.5 (33.6, 37.3)	286	37.5 (35.5, 39.4)	1.00 (1.00, 1.01)	0.053
Memory						
Rey Auditory Verbal Learning Test -- Total words recalled	375	40.6 (39.9, 41.3)	290	41.3 (40.5, 42.1)	0.99 (0.96, 1.02)	0.551
Rey Auditory Verbal Learning Test -- Delayed recall	374	9.9 (9.7, 10.2)	289	10.0 (9.7, 10.4)	1.00 (0.99, 1.01)	0.733

Table 9: Testing the "scarring hypothesis," part 3. Neuropsychological test performance of Study members who were not diagnosed with past-year MDD at age 38, by lifetime diagnostic history. Notes: This table includes only those Study members who (a) completed neuropsychological testing at age 38, (b) were not diagnosed with past-year MDD at age 38 and (c) had present data for adult IQ. The "no history of MDD" group represents Study members who had never met criteria for MDD. The "past history of MDD" group represents Study members who had met diagnostic criteria for MDD during a previous wave but no longer met criteria at age 38. Means were compared across diagnostic groups through a series of one-way ANOVAs, controlling for sex. Significant group differences ($p < 0.05$) are shown in bold.

Measures (All Administered at Age 38)	No History of MDD		Past History of MDD			
	N	Mean (95% CI)	*N*	Mean (95% CI)	*F*	p
Executive Functioning						
Rapid Visual Processing -- A prime	458	0.91 (0.91, 0.92)	271	0.91 (0.91, 0.92)	0.01	0.916
Rapid Visual Processing -- False alarms	460	0.25 (0.20, 0.30)	271	0.23 (0.18, 0.30)	0.11	0.743
WAIS-IV Working Memory Index	467	104.4 (103.0, 105.7)	277	103.5 (101.6, 105.4)	0.03	0.867
WMS-III Months of the Year Backwards	467	3.12 (3.00, 3.25)	276	3.12 (2.96, 3.28)	1.93	0.165
Trails B (time in seconds)	466	63.4 (61.6, 65.2)	277	63.9 (61.5, 66.3)	0.81	0.367
Memory						
CANTAB Paired Associates -- First Trial	460	20.3 (20.0, 20.6)	273	20.2 (19.8, 20.7)	0.21	0.649
CANTAB Paired Associates -- Total Errors	461	11.0 (9.8, 12.1)	273	12.3 (9.8, 14.8)	1.83	0.176
Verbal Paired Associates -- Total N correct	467	15.6 (14.9, 16.4)	276	17.1 (16.1, 18.1)	3.07	0.080
Verbal Paired Associates -- Delayed recall total	**465**	**5.1 (4.8, 5.3)**	**276**	**5.6 (5.3, 5.9)**	**4.40**	**0.036**
Rey Auditory Verbal Learning Test -- Total words recalled	467	37.1 (36.4, 37.8)	275	38.7 (37.8, 39.6)	1.32	0.252
Rey Auditory Verbal Learning Test -- Delayed recall	467	9.0 (8.7, 9.3)	276	9.4 (9.1, 9.8)	0.11	0.745

1.4. Discussion

Contrary to prior research, the present study found little evidence to suggest that low cognitive functioning is either a predictor or an enduring consequence of a major depressive episode. It was repeatedly found that associations between cognitive functioning and MDD were evident only in the context of comorbid psychiatric diagnoses. The finding was true for both objective measures of cognitive functioning (i.e., WISC-R and WAIS-IV IQ, IQ change) and for self- and informant-reported indices of cognitive impairment. This pattern of findings suggests that, to the extent that evidence of cognitive reserve or cognitive scarring in MDD exists, it seems to be largely attributable to psychiatric comorbidities rather than to depressive symptoms per se.

The first hypothesis tested in the present study—the cognitive reserve hypothesis—suggested that individuals with lower cognitive functioning in childhood would be at increased risk of developing MDD later in life. However, childhood IQ did not predict risk of future MDD between the ages of 11 and 38 in the Dunedin Study, even when comparing individuals who developed MDD to those who experienced no diagnosable psychopathology of any sort. Similarly, Study members' performance on specific measures of memory and executive functioning at age 13 also did not predict future risk of MDD. In addition, there was no evidence that childhood IQ predicted MDD risk independent of family-wide and genetic risk when comparing E-Risk Study twins discordant for IQ. Together, these findings indicate that low IQ in childhood does

not meaningfully increase risk of a depressive episode between early adolescence and midlife in these two cohorts from different eras and countries.

The second hypothesis tested in this paper—the scarring hypothesis—suggests that the experience of MDD is associated with cognitive impairments that persist even after affective symptoms have remitted. Surprisingly, in remitted Study members there was little to no difference in mean childhood IQ, adult IQ, IQ change, or adult neuropsychological test scores between those with and without a past history of MDD, suggesting that the scarring effects of a depressive episode are not readily detected by these objective measures. However, it was also found that those with an MDD history (and their informants) reported significantly greater subjective cognitive impairment than those without such a history.

The finding of greater subjective cognitive impairment in the context of no measurable *objective* deficit suggests at least two possible explanations. First, it is possible that any "lingering" cognitive impairments attributable to a history of MDD are largely subjective in nature. If this were true, the greater self-rated impairment reported by individuals with a history of MDD could reflect either (a) a tendency towards negative self-evaluation commonly seen in individuals vulnerable to depressive episodes, or (b) a form of the "good ol' days bias," in which individuals tend to view themselves as having been healthier (e.g., more cognitively advantaged) prior to a negative event (e.g., a depressive episode) (Iverson, Lange, Brooks, & Rennison, 2010).

The greater informant-rated impairment, in turn, could be caused by Study members communicating these beliefs to their informants.

A second possibility, however, is that the cognitive deficits that either predispose individuals to depression or follow a depressive episode are contextual in nature. In other words, because formal cognitive testing is designed to measure patients' optimal cognitive functioning under ideal conditions in the clinic, IQ and other neuropsychological tests may fail to capture genuine impairments that occur only under real-world conditions of high arousal, distraction, or affective distress in vulnerable individuals (i.e., those with a history of depression). The results of the present study do not, therefore, necessarily indicate that reports of cognitive impairment following a depressive episode are solely a product of patients' cognitive distortions.

Results presented here differ from those of ancillary analyses featured in previous papers that also used data from the Dunedin Study, which reported weak but statistically significant associations between IQ and MDD (Koenen et al., 2009; Meier et al., 2014). These papers, however, like others in the literature, did not control for comorbidity when estimating the association between IQ and MDD. Moreover, the fact that results can differ even in the same sample speaks to the fact that correlations between IQ and MDD are ephemeral and depend heavily on a study's analytical design and comparison groups.

To some, the proportion of Dunedin Study members diagnosed with MDD may seem unusually high, raising concerns about the representativeness of the sample. However, it has been shown elsewhere that (a) the past-year prevalence rates of mental disorders in the Dunedin cohort are similar to prevalence rates in nationwide surveys of the United States and of New Zealand (Moffitt et al., 2010) and (b) that lifetime prevalence estimates of Axis-I mental disorders in the Dunedin Study are comparable to estimates calculated in other cohorts with repeated psychiatric assessments (Schaefer et al., 2016). These observations indicate that the high lifetime prevalence rate of MDD reported here is due primarily to the advantage of prospective assessment method rather than to an overabundance of mental disorder in New Zealand, or in this cohort.

Despite the methodological advantages provided by these two cohorts, several limitations must be acknowledged. First, although the study features results from two independent samples, the E-Risk Study did not contain enough psychiatric assessment waves to replicate the analyses conducted using the Dunedin Cohort. Thus, it will be important to test the extent to which the findings generalize across different populations in future studies—particularly those findings that relate to lifetime history of disorder.

Second, Study members were assessed for past-year (rather than *current*) depressive symptoms. Moreover, Dunedin Study members tend to schedule data collection when they feel well, reducing the likelihood of acute depressive symptoms on the day of cognitive testing. This design feature meant that it was not possible to control

for baseline depressive symptoms at the time of cognitive assessment in the follow-forward analyses. However, given that no association was observed between childhood cognitive functioning and later MDD, it is unlikely that this would alter the conclusions. In addition, it was not possible to examine the extent to which MDD was associated with short-term, contemporaneous decreases in cognitive functioning—an important question for future research.

Third, assessment of mental disorder in the Dunedin cohort is both left- and right-hand censored, which means the relationship between IQ and episodes of MDD that occurred prior to age 11 cannot be assessed, or future cases that may onset after the most recent assessment at age 38. This limitation means that it is not possible to comment on the extent to which either childhood-onset or late-onset depression are associated with childhood IQ, or the extent to which such episodes might "scar" future cognitive functioning.

In spite of these limitations, the results have implications for the study and treatment of depression. In particular, they suggest that the persistent cognitive deficits commonly associated with MDD may not be attributable to depression per se, but rather to other psychiatric conditions that frequently co-occur with MDD (Kessler et al., 2003; Melartin et al., 2002). Previous studies comparing the premorbid IQs of individuals who developed MDD to those who did not have found individuals with MDD had premorbid IQs approximately 3 points lower than healthy controls (Sørensen, Sæbye,

Urfer-Parnas, Mortensen, & Parnas, 2012), which is comparable to the effect of comorbidity reported in the present study. These findings also shed light on some of the questions highlighted in recent workshops hosted by the National Academies of Sciences (Bain & Stroud, 2015), and suggest that researchers interested in treating the cognitive deficits associated with depression should perhaps widen their focus to consider alterations in fear-learning, attention, and executive functioning common to multiple disorders.

The results further suggest that investigators seeking to demonstrate the existence of cognitive impairment in the context of a particular disorder should carefully assess participants for current and past psychiatric comorbidities. This step allows investigators to distinguish between impairments that are attributable to the disorder of interest versus other, comorbid conditions or some shared, transdiagnostic process.

The findings also have implications for the prevention and treatment of MDD. The finding that low childhood IQ does not appear to predict the development of MDD suggests that low IQ should not be considered a risk factor for MDD. Similarly, the finding that even the most severely disordered individuals (diagnosed with MDD and 3+ comorbidities) scored only about 5 points lower, on average, than those with no history of depression, indicates that the ability to predict the course of any one person's MDD based on premorbid intelligence is limited at best. Nevertheless, because subjective ratings of Study members' cognitive impairment tended to increase with each

additional psychiatric comorbidity, it may be helpful to screen individuals who report ongoing cognitive impairment following a depressive episode for past and current anxiety, substance-use, attention-deficit, or psychotic disorders. In addition, such patients may benefit from cognitive therapy that examines the function and impact of beliefs of cognitive impairment, as well as therapies aimed at regulating affect and managing psychiatric symptoms, which may continue to impact cognitive functioning in certain contexts (e.g., when multi-tasking or under conditions of high emotional arousal).

In summary, I find that cognitive deficits are neither an antecedent nor enduring consequence of MDD, absent psychiatric comorbidities. Thus, future research that seeks to assess and treat cognitive scarring in the context of psychiatric illness would be wise to investigate psychopathology broadly rather than MDD specifically. In addition, rather than focusing on cognitive impairment as a risk factor for MDD or a lingering consequence of the disorder, the results suggest that treatment and prevention efforts should focus on evaluating—and perhaps treating—cognitive deficits that co-occur with depressive symptoms. The hope is that the findings will inform studies aiming to develop treatments for these impairments, as well as spur additional research dedicated to better understanding the complex interplay between affective symptoms and cognitive functioning in the individuals who suffer from this disorder.

4. Thinking and Feeling: Individual Differences in Habitual Emotion Regulation and Stress-Related Mood are Associated with Prefrontal Executive Control[1]

4.1. *Background*

The ability to adaptively regulate emotional experiences in everyday life is related to a range of outcomes including mental health, relationship quality, academic achievement, and job performance (Nadia Garnefski & Kraaij, 2006; Graziano, Reavis, Keane, & Calkins, 2007; Gross & John, 2003; Newman, Joseph, & MacCann, 2010). One of the primary strategies for regulating emotional experiences is cognitive reappraisal, which involves changing one's interpretation of negative emotions or experiences in an attempt to be more neutral or objective (Goldin, McRae, Ramel, & Gross, 2008; Ochsner, Bunge, Gross, & Gabrieli, 2002). As such, cognitive reappraisal is hypothesized to represent an important specific skill that can be developed through Cognitive Behavioral Therapy (CBT), an umbrella term describing psychotherapies for improving dysfunctional mood and affect by teaching individuals to identify, evaluate, and respond to maladaptive thoughts and beliefs through guided questioning and behavioral experiments (Beck, 2011). Although cognitive reappraisal of emotion has been hypothesized to relate to neural processes supporting 'cold' (i.e. not emotion-related)

[1] This Chapter is based on the following publication: Scult, M.A., Knodt, A.R., Swartz, J.R., Brigidi, B.D., & Hariri, A.R. (2017). Thinking and feeling: individual differences in habitual emotion regulation and stress-related mood are associated with prefrontal executive control. *Clinical Psychological Science,* 5(1), 150-157.

executive control (Ochsner & Gross, 2005), there has only been indirect evidence in support of this hypothesis. Identifying 'cold' executive control processes that support the use of cognitive reappraisal will not only deepen our understanding of fundamental mechanisms supporting adaptive emotional functioning but also inform the search for novel approaches to therapy that could target these executive functions and potentially increase the effectiveness of teaching cognitive reappraisal to individuals with mood and anxiety disorders.

Executive control is typically divided into three inter-related subprocesses: (1) updating and monitoring of information in working memory, (2) shifting between information sets, and (3) selecting goal-relevant responses (Miyake et al., 2000). The neural processes supporting executive control have been established as relating to functioning of the dorsolateral prefrontal cortex (dlPFC; Barbey, Colom, & Grafman, 2013; Wager & Smith, 2003). Functional neuroimaging studies of healthy individuals have generally associated higher activity of the dlPFC with better executive control (Braver et al., 1997; D'Esposito et al., 1995).

Functioning of the dlPFC has also been found to be important in controlling emotions, which can be thought of as a state-like skill or as a trait-like disposition (Lee, Heller, van Reekum, Nelson, & Davidson, 2012). Both state- and trait-like emotion regulation have been associated with increased dlPFC activation (Drabant, McRae, Manuck, Hariri, & Gross, 2009; Goldin et al., 2008; Heller et al., 2013; Ochsner et al., 2002),

and the specific use of cognitive reappraisal has been found to decrease feelings of distress and reduce symptoms of anxiety and depression (Gross & John, 2003; Hofmann, Heering, Sawyer, & Asnaani, 2009).

Dysfunction of the dlPFC has also been linked with depression (e.g. Heller et al., 2009). For example, dlPFC lesions specifically have been associated with increased depressive symptoms (Koenigs et al., 2008), and stimulation of the dlPFC through TMS has led to decreased depressive symptoms in patients with Major Depressive Disorder (MDD) and anxiety in Generalized Anxiety Disorder (GAD) (Bystritsky et al., 2008; O'Reardon et al., 2007). Furthermore, abnormal prefrontal activation has been demonstrated in individuals with MDD (Erk et al., 2010; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007) and individuals at risk for MDD (Joormann, Cooney, Henry, & Gotlib, 2012), specifically during the process of emotion regulation. Similarly consistent patterns have been identified for anxiety disorders, with individuals showing an increase in dlPFC activation pre- to post-CBT treatment during the process of emotion regulation (Goldin et al., 2013).

Though implicit in the associations noted above (Ochsner & Gross, 2005), no direct links have been established between dlPFC function during 'cold' executive control with dysfunctional mood and anxiety, and the use of cognitive reappraisal. Establishing such direct links, can help illuminate shared biological foundations of these behavioral processes. Here I used functional magnetic resonance imaging to measure dlPFC activity

during working memory computation, and evaluated the extent to which variability in this activity was associated with (1) trait-like or habitual regulation of negative emotion using cognitive reappraisal, (2) self-reported mood and anxiety symptoms in the context of stress, and (3) clinical diagnosis of a mood or anxiety disorder. Based on the existing literature, I hypothesized that increased dlPFC activity supporting computation would be associated with increased habitual use of cognitive reappraisal as an emotion regulation strategy, and decreased self-reported symptoms of mood and anxiety as well as clinical disorder. Given the critical role of stressful life events in precipitating increases in symptoms of depression and anxiety (Faravelli, 1985; Kendler, Karkowski, & Prescott, 1999), as well as the necessity to regulate negative emotions (Garnefski, Kraaij, & Spinhoven, 2001), I explicitly tested the moderating role of recent stress on symptoms.

4.2. *Methods*

4.2.1. Participants

Data were available from 186 university students who successfully completed the ongoing Duke Neurogenetics Study (DNS) between September 3rd, 2014 and January 27th, 2016. Informed consent was obtained for all participants in accordance with the Duke University School of Medicine Institutional Review Board. Exclusion criteria included: (1) medical diagnoses of cancer, stroke, head injury with loss of consciousness, untreated migraine headaches, diabetes requiring insulin treatment, chronic kidney or

liver disease, or lifetime history of psychotic disorder; (2) use of psychotropic, glucocorticoid, or hypolipidemic medication; and (3) conditions affecting cerebral blood flow and metabolism (e.g. hypertension). The DNS seeks to establish broad variability in multiple behavioral phenotypes related to psychopathology, so other than psychotic disorders, participants were not excluded based on diagnosis of past or current DSM-IV Axis I or select Axis II (borderline and anstisocial personality) disorder. However, no participants were taking psychotropic medication at the time of or at least 10 days prior to study participation.

4.2.2. Self-Report Questionnaires

The Emotion Regulation Questionnaire (ERQ) is a 10-item self-report questionnaire designed to assess individual differences in two emotion regulation strategies: cognitive reappraisal and expressive suppression (Gross & John, 2003). Instructions ask subjects to report on how they control both their emotional experience and their emotional expression. Items are rated on a 7-point-Likert scale from "strongly disagree" to "strongly agree." The cognitive reappraisal subscale, which prior work links to executive control and dlPFC function, was used in the analyses.

The Mood and Anxiety Symptom Questionnaire – Short Form (MASQ-SF;) is a 62-item self-report questionnaire designed to assess symptoms during the past week. across four subscales: general distress depression, anhedonic depression, general distress

anxiety, and anxious arousal (Watson et al., 1995). Items are rated on a 5-point-Likert scale from "not at all" to "extremely." One item from the anhedonic depression subscale that asked about suicidality was removed from the questionnaire in order to comply with IRB protocol. Items were summed to create a total score for mood and anxiety symptoms.

The Life Events Scale for Students (LESS; Clements & Turpin, 1996) is a 46-item self-report questionnaire that assesses the number of life events that occurred in the past 12 months. Participants rate the impact that the life event had on them on a 1 to 4 scale (4 = severe impact). The impact score for each event reported was summed to yield a LESS total impact score; higher values indicate both greater number and severity of life events.

4.2.3. Clinical Interview

All participants were assessed for common mental disorders using the electronic version of the M.I.N.I International Neuropsychiatric Interview (Sheehan et al., 1998), administered by trained staff under the supervision of a licensed clinical psychologist (BDB). The interview follows DSM-IV (American Psychiatric Association, 1994) and ICD-10 (World Health Organization, 2004) diagnostic criteria.

4.2.4. Working Memory fMRI Paradigm

Activity of the dlPFC was measured during BOLD fMRI using an event-related working memory paradigm (Tan et al., 2007). This task was chosen because it specifically

allows for explicit modeling of component subprocesses of working memory (Fig. 8). In particular, it was hypothesized that higher order aspects of executive control, including the manipulation of information in working memory (Miyake et al., 2000), would support the complex process of cognitive reappraisal by allowing for the manipulation of information in constructing new appraisals (Silvers et al., 2014). Previous studies have found that this updating component is related to emotion regulation success (Pe, Raes, & Kuppens, 2013).

The paradigm included 10 trials for each of 6 different conditions, including 3 control conditions, consisting only of a 3s response phase, and 3 working memory (WM) conditions, consisting of a 0.5s encoding phase followed by a 4s maintenance interval and a 3s response phase (Fig. 8). Control and WM conditions were interleaved with jittered rest intervals lasting 4s to 8.5s for a total scan length of 11m 48s. Responses were recorded via an MR-compatible button box using the index (left button) and middle (right button) fingers of the dominant hand.

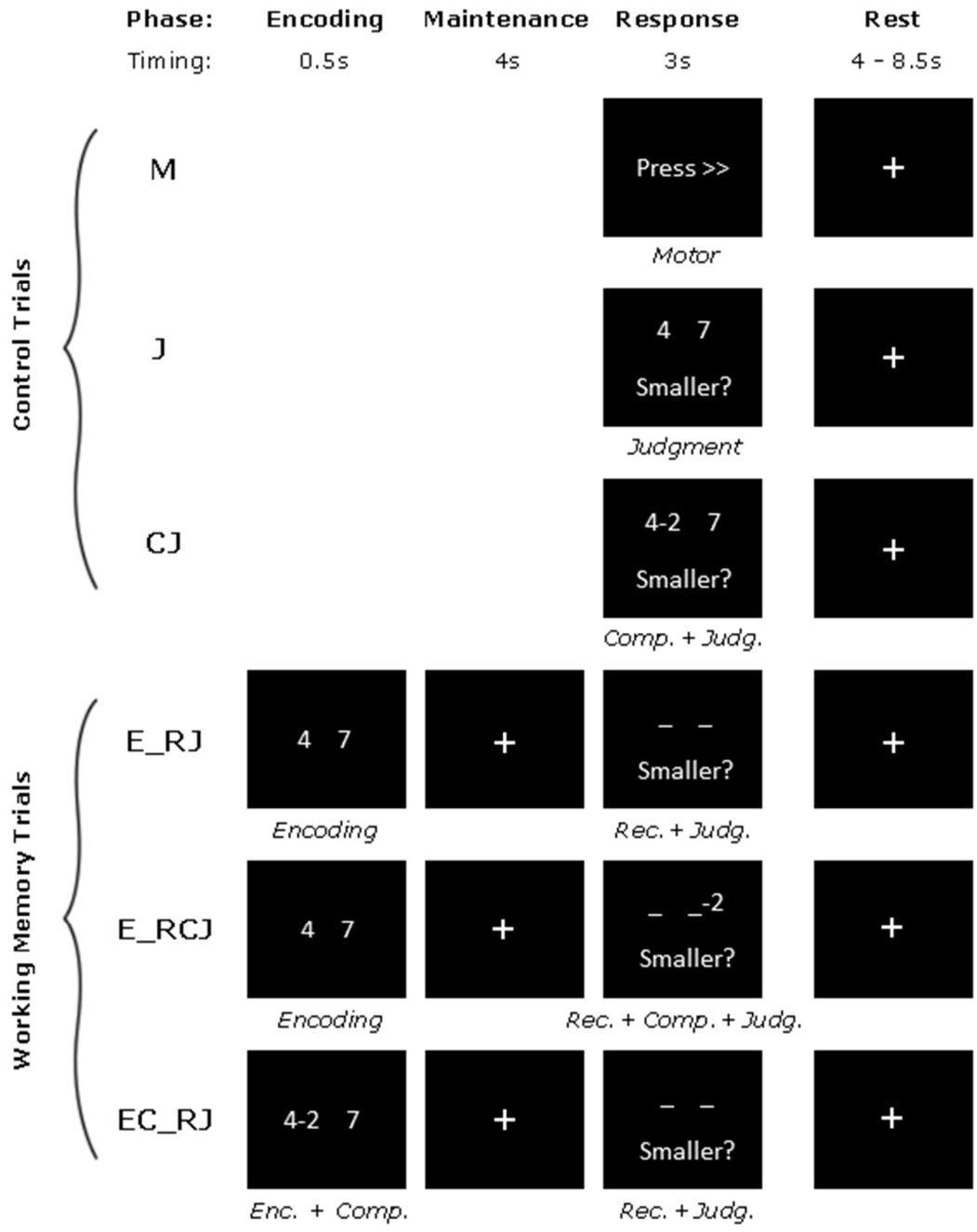

Figure 8: Working Memory Task. In order to isolate the computational component of working memory, the contrast of E_RCJ>EC_RJ was used in the analyses. This comparison isolates updating/manipulation component of working memory by focusing on computation on information that has been maintained over a delay.

During the control conditions, participants performed 1) a simple motor task (M) in which they pressed either the left or the right button according to a prompt, 2) a numerical size judgment task (J) in which they chose the number on the left or right based on an instruction to choose either the larger or the smaller number, and 3) a numerical computation and size judgment task (CJ) in which they performed a numerical subtraction of 2 or 3 from either the left or right number, and made a numerical size judgment as instructed.

In the first WM condition, participants viewed two numbers during the brief encoding phase, then recalled the numbers and performed a numerical size judgment as instructed (E_RJ). In the second WM condition, the participants additionally performed subtraction of 2 or 3 from one of the remembered numbers as indicated before making the numerical size judgment during recall (E_RCJ). In the final WM condition, participants performed subtraction of 2 or 3 from one of the two numbers during the brief encoding phase, then recalled the resulting two numbers and performed a numerical size judgment as instructed during the response phase after the maintenance interval (EC_RJ). In each WM condition trial, all the numbers were single digits from 0 to 9; the two numbers on which the numerical size judgment was ultimately performed (after numerical computation if applicable) were equally balanced across 0 to 9, and equally likely to differ by either 1 or 3 units. Numerical computation was equally likely on the left or right number, with correct responses equally balanced on the left or right, and equally likely to

be the larger or smaller number for each WM trial type. The trials were performed in an order that was optimized using a sequencing program (Wager & Nichols, 2003).

Here, I focus on this computational function of the dlPFC by isolating activity during the contrast of trials wherein participants subtract 2 or 3 from a remembered number and then making a numerical size judgment against a second number during recall ("E_RCJ," Fig. 8) versus trials wherein participants subtract 2 or 3 from one of two numbers during a brief encoding phase *before* recalling the resulting two numbers and performing a numerical size judgment ("EC_RJ," Fig. 8), in order to isolate the manipulation of information component of working memory.

4.2.5. BOLD fMRI

The general linear model of SPM8 (http://www.fil.ion.ucl.ac.uk/spm) was used to conduct analyses of BOLD fMRI data acquired using a standard protocol. Each participant was scanned using one of two identical research-dedicated GE MR750 3T scanner equipped with an eight-channel head coil for parallel imaging at high bandwidth. A semiautomated high-order shimming program was used to ensure global field homogeneity. A series of 34 interleaved axial functional slices aligned with the anterior commissure–posterior commissure plane were acquired for full-brain coverage using an inverse-spiral pulse sequence to reduce susceptibility artifact. To allow for spatial registration of each participant's data to a standard coordinate system, structural

images were acquired in 34 axial slices co-planar with the functional scans. For additional details on data acquisition parameters see (Ahs, Davis, Gorka, & Hariri, 2014).

Preprocessing was conducted using SPM8 (www.fil.ion.ucl.ac.uk/spm). Images for each participant were slice-time corrected, realigned to the first volume in the time series to correct for head motion, spatially normalized into a standard stereotactic space (Montreal Neurological Institute template) using a 12-parameter affine model (final resolution of functional images = 2mm isotropic voxels) and smoothed to minimize noise and residual differences in gyral anatomy with a Gaussian filter set at 6mm full-width at half-maximum. Next, the Artifact Detection Tool was used to generate regressors accounting for the possible confounding effects of volumes with large motion deflections (http://www.nitrc.org/projects/artifact_detect). Specifically, individual whole-brain BOLD fMRI volumes varying significantly from mean-volume signal intensity variation (i.e., within volume mean signal of greater or less than 4 standard deviations of mean signal of all volumes in time series) or individual volumes where scan-to-scan movement exceeded 2mm translation or 2º rotation in any direction were assigned a lower weight in analyses. Of the 216 participants with available fMRI data, 13 participants had >5% outlier volumes and were excluded from further analyses. Data for another 14 participants were excluded from further analyses for poor task performance reflected as less than 75% overall accuracy or below 50% accuracy on any trial type. Data for an additional 3

participants were lost due to scanner malfunction. Thus, the primary analyses were conducted in 186 participants.

Following preprocessing, events were modeled for correctly performed trials for the response phase for each of the 6 trial types, and the maintenance and encoding (with and without computation modeled separately) phases for WM trials. Incorrect responses were also modeled as regressors of no interest. A linear contrast employing the canonical hemodynamic response function was used to estimate main effects for each participant for the comparison of E_RCJ > EC_RJ in order to isolate the manipulation of information in working memory above and beyond basic computation and maintenance of information across a delay. Individual contrast images for E_RCJ > EC_RJ were then used in second-level random effects models accounting for scan-to-scan and participant-to-participant variability to determine mean condition-specific regional responses using one-sample t-tests with a voxel-level statistical threshold of $p<0.05$, family wise error (FWE) corrected for multiple comparisons across the whole brain. Regions of interest for the dlPFC were created using the WFU Pickatlas with the conjunction of bilateral BA9 and BA46. Mean parameter estimates from the primary activation cluster (Fig. 9A; -42, 2, 30, k=274) within these anatomical regions of interest surviving FWE correction were extracted to test hypotheses using IBM SPSS Statistics 23 (Chicago, IL, USA).

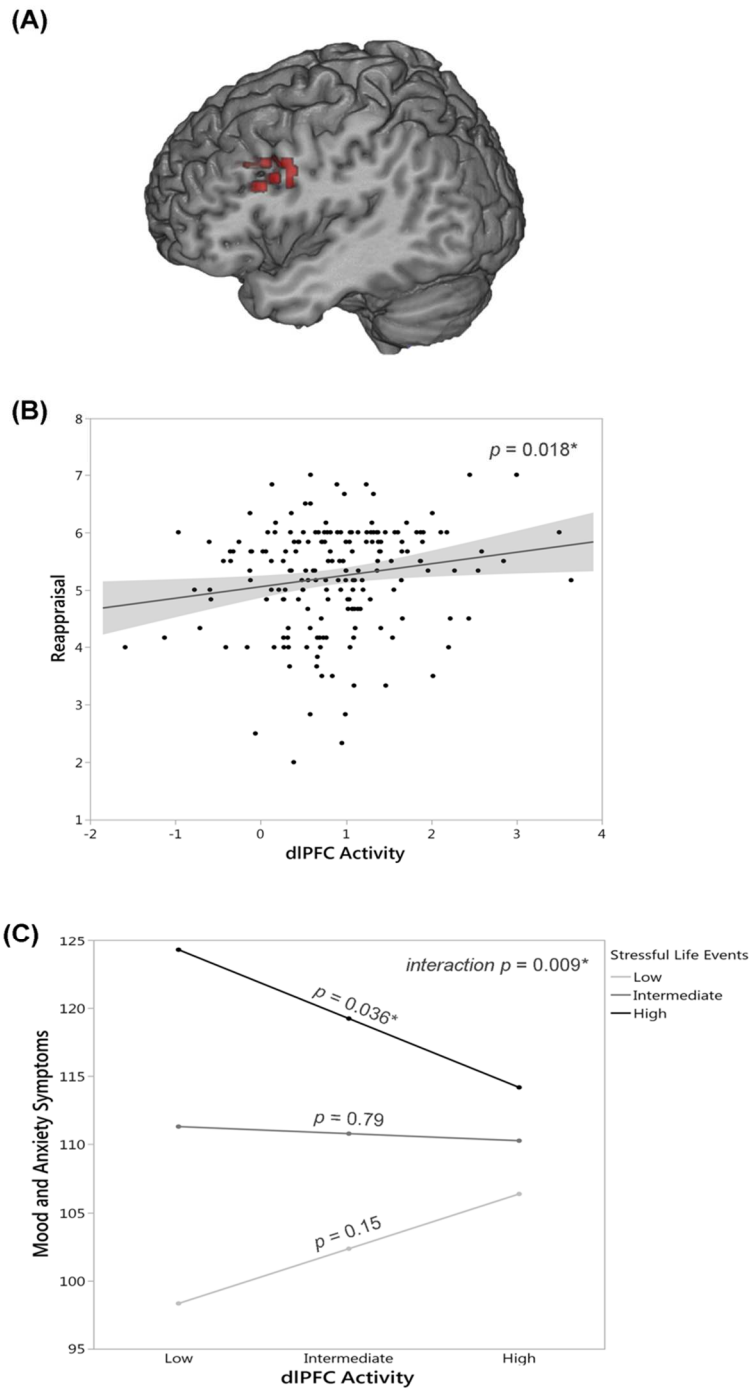

Figure 9: 'Cold' working memory-related dlPFC activation is related to habitual reappraisal as well as mood and anxiety symptoms in the context of stress. A) Peak dlPFC cluster extracted for subsequent analyses. B) Increased dlPFC activation during

computation of information in working memory is associated with greater levels of self-reported cognitive reappraisal during everyday life as measured by the ERQ (p=0.018). C) At high levels of stress, increased dlPFC activity is associated with fewer mood and anxiety symptoms (p=0.036).

4.2.6. Hypothesis Testing

Extracted values from the dlPFC cluster, associated with computation during working memory, were entered into a general linear model with ERQ Cognitive Reappraisal scores as the dependent variable. Additionally a moderation model using PROCESS for SPSS (Hayes, 2012), was used to test whether the dlPFC activity in interaction with self-reported stressful life events, was associated with MASQ total scores as well as with diagnosis of a mood or anxiety disorder. Lastly, a moderation model tested whether ERQ Cognitive Reappraisal in interaction with stressful life events, was associated with MASQ total scores as well as with clinical diagnosis. Sex was included as a covariate in all analyses.

4.3. *Results*

The final sample of 186 participants (118 women; 63.4%) had a mean age of 19.81 (± 1.28) years and self-reported as being European American (110; 59.1%), African American (15; 8.1%), Asian (42; 22.6%), Multi-racial (14; 7.5%), Other (5, 2.7%), and Hispanic/Latino (18; 9.7%). With regards to socioeconomic status, participants were asked to rank on a 0-10 scale where they were in comparison to others in the United States in

terms of money, education, respected jobs, etc. The sample mean was 6.97 (1.65). Clinical interview identified 43 participants (23.1%) as having a DSM-IV diagnosis. Additional details regarding demographics of the cohort as a function of DSM-IV diagnoses including comorbidity are provided in Table 10.

Table 10: Diagnoses in the DNS cohort.

	N (%)
One Diagnosis	24 (12.9)
More Than One Diagnosis	19 (10.2)
Major Depressive Disorder	21 (11.3)
Bipolar Disorder	4 (2.2)
Panic Disorder	11 (5.9)
Agoraphobia	8 (4.3)
Generalized Anxiety Disorder	4 (2.2)
Social Anxiety Disorder	2(1.1)
Obsessive Compulsive Disorder	3 (1.6)
Alcohol Abuse or Dependence	13 (7.0)
Other Substance Abuse or Dependence	7 (3.8)
Eating Disorder	2 (1.1)
Missing	1 (0.5)

4.3.1. Working Memory Task Performance and Behavioral Measures

Mean accuracy across all conditions was 95% (±5%), range 71-100%, and mean accuracy on the E_RCJ condition specifically was 89% (±11%), range 50-100%. The mean score for the ERQ Reappraisal subscale was 5.23 (±0.92), range 2-7. The mean score on the

MASQ-SF was 110 (±27), range of 65-213. The mean score on the LESS was 10.37 (±8.30), range of 0-48.

4.3.2. Working Memory fMRI

The contrast E_RCJ > EC_RJ used to isolate the manipulation of information in working memory, resulted in large clusters of activity across the frontal and parietal cortices as well as the temporal cortices (Fig. 10). Mean parameter estimates were extracted specifically from a 274-voxel cluster within the dlPFC region of interest.

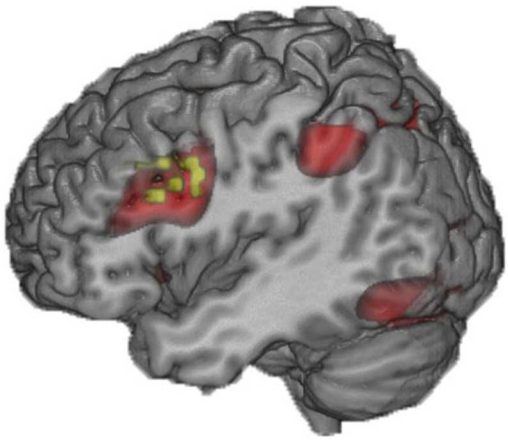

Figure 10: Whole-brain pattern of working memory-related activity. Main effects for the contrast of E_RCJ>EC_RJ (see Figure 8 for details) across frontal, parietal, and temporal cortices (red) at $p<0.05$, FWE-corrected for multiple comparisons. The dlPFC region of interest is highlighted in yellow.

4.3.3. Associations between dlPFC Activity, Symptoms, and Cognitive Reappraisal

A significant positive association was found between dlPFC activity and ERQ Reappraisal (Fig. 9B; b=0.18, p=0.018, R^2 change=3.0%). The effects were specific to Reappraisal as dlPFC activity was not associated with ERQ Suppression (p=0.50). The magnitude of dlPFC activity interacted with stress to predict symptoms of mood and anxiety (p=0.009, R^2-change=3.4%). In particular, for individuals with high levels of stressful life events, higher dlPFC activity was associated with fewer symptoms of anxiety and depression (Fig. 9C). The effects did not change significantly after controlling for presence or absence of DSM-IV diagnosis or after controlling for task accuracy. A similar pattern was observed when predicting mood or anxiety diagnoses (p=0.050, R^2-change =2.0%).

Lastly, ERQ Cognitive Reappraisal interacted with stress to predict symptoms of mood and anxiety (p=0.043, R^2-change =1.9%). In particular, for individuals with intermediate or high levels of stressful life events, greater reappraisal was associated with fewer symptoms of anxiety and depression (Fig. 11). After controlling for presence or absence of DSM-IV diagnosis, this interaction was reduced to a trend effect (p=0.06). A similar pattern was observed when predicting mood or anxiety diagnoses (p=0.003, R^2-change =4.4%).

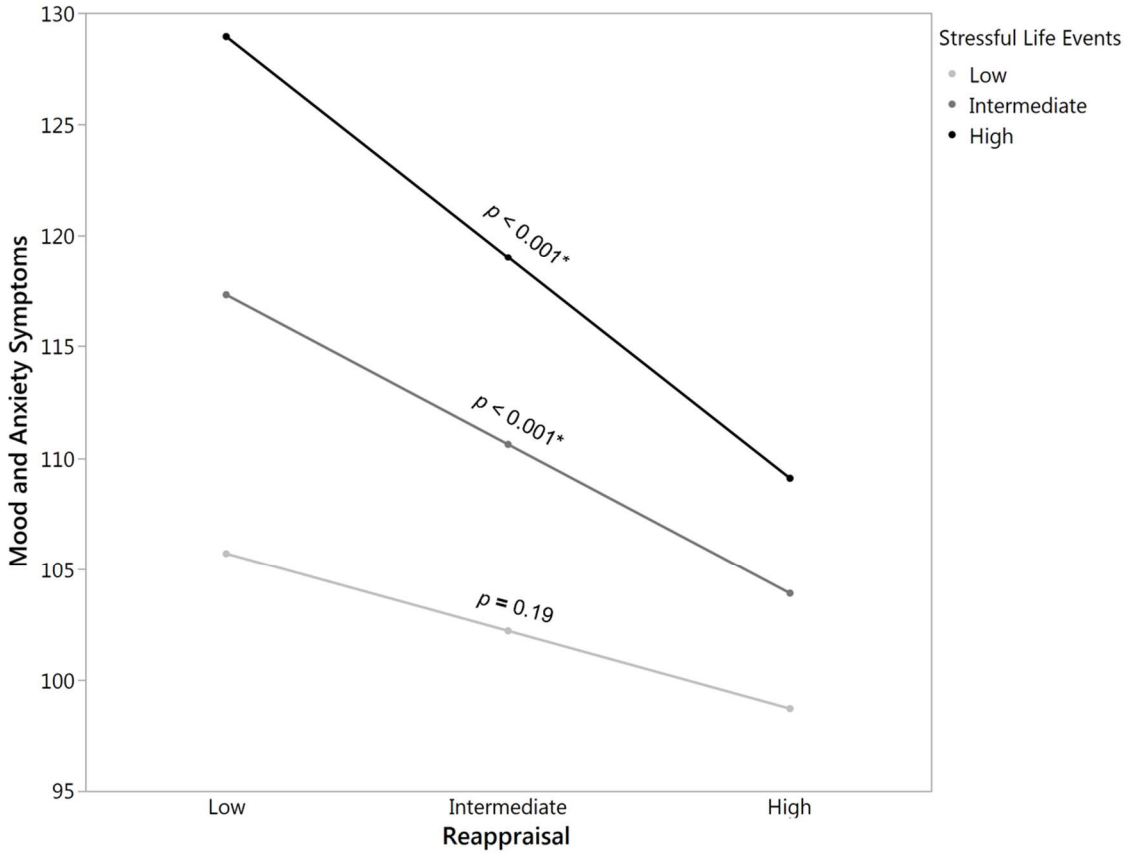

Figure 11: Habitual use of reappraisal is associated with decreased symptoms of anxiety and depression in the context of stress. At intermediate and high levels of stress, increased use of habitual reappraisal is associated with fewer mood and anxiety symptoms ($p<0.001$).

4.4. *Discussion*

Here I provide initial evidence that dlPFC function supporting general executive control is associated with the everyday use of cognitive reappraisal as a strategy for regulating emotions. Furthermore, I find that the use of cognitive reappraisal is associated with fewer mood and anxiety symptoms in the context of greater life stress as

well as clinical diagnosis of a mood or anxiety disorder. Although the cross-sectional nature of the data makes formal tests of mediation unfeasible, the findings are consistent with prior behavioral work finding that coping strategies, including cognitive reappraisal, mediate the relationship between executive control and mood (Campbell et al., 2009; Evans, Kouros, Samanez-Larkin, & Garber, 2016). Thus, the current findings fill a gap in understanding the cognitive control of emotion. Specifically, the results suggest that cognitive and emotional processing may not just utilize the same brain regions, but instead rely on shared information processing itself. The analyses lend support for the theory that coping with emotional distress relies on the ability to construct expectations, select among alternative explanations, and make judgments about emotional stimuli through 'cold' executive control processes (Ochsner & Gross, 2005).

Recently, cognitive training programs that impact working memory ability and other neuropsychological function have begun to show reliable and generalizable therapeutic effects in depression (e.g. Anguera et al., 2013). In light of this work, the current results suggest the intriguing hypothesis that such domain general strategies could be implemented as an adjunct to cognitive behavioral therapy techniques as a means of enhancing efficacy. Given that working memory and other executive control functions have been shown to be impaired in depression (Snyder, 2013), the enhancement of general working memory might facilitate cognitive reappraisal, leading

to improved outcomes. Additionally, methods of directly strengthening dlPFC function may buttress executive control and associated emotion regulation leading to decreased anxiety and depression. In support of this strategy, functional neuroimaging studies have demonstrated that individuals are able to upregulate dlPFC activity supporting working memory using real-time neurofeedback leading to improved performance (Zhang, Yao, Zhang, Long, & Zhao, 2013). Similarly, transcranial magnetic stimulation (TMS) of the dlPFC is associated not only with improved working memory performance (Fregni et al., 2005) but also decreased symptoms of anxiety and depression (Bystritsky et al., 2008; O'Reardon et al., 2007), although the effects of dlPFC-targeted TMS on executive control and mood symptoms have not been considered jointly in a single experiment. Given that changes in working memory performance would be an immediately observable outcome when using TMS, one possibility is that working memory performance could act as an intermediate index of the effectiveness of stimulation parameters in treating mood and anxiety disorders.

A limitation of the present study is the cross-sectional nature of the data. Therefore, while I hypothesize that habitual use of cognitive reappraisal may mediate the association between dlPFC function and stress-related mood, it is also possible that dlPFC function may act as the mediator. Future longitudinal studies will be better positioned to explore these alternate models. Another limitation of the present sample is that it was comprised of relatively high-functioning undergraduate students. While a

range of clinical psychopathology was observed in the present sample, the prevalence rates were slightly below population norms (Moffitt et al., 2010). Thus, it will be important to extend these findings to samples with higher base rates of psychopathology or at higher risk for disorder. A further limitation is the conceptualization of recent life stress, which was developed specifically for students (e.g., failing a course), and thus may not capture stressors more common in the general population (e.g., unemployment). While the measure of stress used in this study is easily administered via self-report and accounts for both the number and subjective severity of these stressful life events, it may be subject to retrospective bias or confounded by current symptoms (i.e., more depressed individuals may be more likely to rate past life events more severely). These limitations can be addressed in future work using different measures of common life stressors not unique to students as well as through longitudinal studies capable of establishing temporal order of events.

These limitation notwithstanding, the results show that dlPFC function supporting general executive control is related to the habitual use of cognitive reappraisal to regulate negative emotions and the experience of stress-related mood and anxiety dysfunction. As such, the results encourage further consideration of the importance of domain general executive control processes in emotion regulation and in the experience of mood and anxiety dysfunction particularly in the context of stressful

life events, motivating ongoing efforts to better understand top-down prefrontal executive control as a target for clinical intervention.

5. Conclusions[1]

In this dissertation, I have systematically tested the relationships between cognitive functioning and mood and anxiety disorders, with the purpose of assessing whether cognitive functioning and related neural circuitry may feasibly act as a marker for targeting treatment. **Study 1**, showed via meta-analysis of the extant literature that deficits in cognitive functioning do not precede the onset of depression and therefore cannot act as a risk factor for the disorder. **Study 2**, utilized two longitudinal datasets to demonstrate that cognitive deficits occur primarily in the context of comorbid depression and therefore may be better conceptualized as a transdiagnostic risk factor. **Study 3** showed that dlPFC function during a mathematical working memory task is related to both mood and anxiety symptoms in the context of stressful life events and is further associated with cognitive reappraisal in everyday life. This observation is consistent with the proposed critical importance of the dlPFC in shaping the adaptive, contextually-appropriate responses through top-down regulation (Heller, 2016; Ochsner & Gross, 2005). In total, these findings paint a picture of cognitive deficits that primarily exist in the context of contemporaneous and comorbid mood and anxiety symptoms, and that are likely attributable to general detriments in dlPFC information-processing.

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[1] Part of this chapter is based on the following publication: Scult, M.A., Knodt, A.R., Radtke, S.R., Brigidi, B.D., & Hariri, A.R. (2017). Prefrontal executive control rescues risk for anxiety associated with high threat and low reward brain function. *Cerebral Cortex*, 1-7.

There are a number of implications of this line of research. The first is that preventative treatments targeting cognitive dysfunction, while potentially helpful in their own right, are not likely to help protect against the onset of depression. While there very well may exist cognitive deficits in the context of a major depressive episode, the totality of these studies suggests that cognitive deficits are likely better attributed to psychiatric disorders other than depression and/or can be seen as a transdiagnostic marker of general dysfunction. This is a noteworthy finding because cognitive functioning in depression has been gaining interest as both a drug development target (Ledford, 2016; Mullard, 2016), and TMS treatment target in depression (Ilieva et al., 2018).

Given the results of this dissertation and the work of others, it is probable that individuals who are most likely to benefit from TMS to the dlPFC for depression treatment, are individuals with comorbid symptomatology. It may therefore be worthwhile to study differential treatment outcomes based on symptom profiles of individuals undergoing TMS treatment and prioritizing those individuals with comorbid symptom presentations. To build on this further, it may be the case that brain regions other than the dlPFC could be more effective treatment targets for individuals with "pure" unipolar depression symptom presentations. Lastly, this line of research suggests that further study of TMS treatment for anxiety disorders is warranted.

Additional follow-up research that I have conducted further points to the utility of focusing on prefrontal cognitive control in anxiety. In a recent study, I found that for individuals with low-to-average dlPFC activity, relatively higher amygdala activity and lower ventral striatum activity was associated with greater increases in somatic anxiety over the following six months (Scult, Knodt, Radtke, Brigidi, & Hariri, 2017). This finding fits into a body of research showing that anxious individuals have altered prefrontal activity during attentional control (Bishop, 2009), working memory (Balderston et al., 2017), and inhibitory control (Basten, Stelzel, & Fiebach, 2011). Moreover, preliminary evidence shows that targeting prefrontal executive control using either behavioral or stimulation protocols is associated with decreased anxiety (Balderston, Quispe-Escudero, et al., 2016; Diefenbach et al., 2016) possibly through improvements in emotion regulation (Diefenbach, Assaf, Goethe, Gueorguieva, & Tolin, 2016) or decreased attentional bias to threat related cues (Heeren et al., 2017). The current findings provide initial evidence that intrinsic prefrontal executive control function may further represent a prognostic biomarker of risk for both current and future anxiety.

This ongoing line of research helps to identify a brain marker of anxiety and more broadly highlights that a translational neuroscience approach is a promising means of identifying potential biomarkers of risk (Hariri & Holmes, 2015). In this vein, recent work has shown that relatively higher activity of the amygdala, predicts risk for

stress-related negative mood and anxiety up to four years later (Swartz, Knodt, Radtke, & Hariri, 2015), as well as the development of posttraumatic stress disorder (McLaughlin et al., 2014; Stevens et al., 2016). Likewise, relatively lower activity of the ventral striatum, predicts lower positive affect in interaction with stressful life events (Nikolova, Bogdan, Brigidi, & Hariri, 2012), as well as future depression up to a year later (Telzer, Fuligni, Lieberman, & Galvan, 2014). Moreover, the combination of relatively high threat-related amygdala and low reward-related ventral striatum activity has been found to predict alcohol abuse and alcohol use disorder as a coping mechanism in response to stress (Corral-Frías et al., 2015; Nikolova, Knodt, Radtke, & Hariri, 2016).

In sum, this dissertation finds that prefrontal cognitive function as operationalized in the present studies does not appear to be a marker of risk for the development of depression, but is a promising biomarker of risk for anxiety, especially when also considering threat-related amygdala and reward-related ventral striatum function. Future work will seek to assess whether matching these risk markers with related treatment approaches can both rescue abnormal neural circuit function and enhance treatment effectiveness, ultimately answering the question of which therapies will work for whom.

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Biography

Matthew Scult grew up in Wayland, MA. He graduated from Brown University with a Bachelor of Science in Neuroscience, and then worked for two years at the Benson-Henry Institute for Mind Body Medicine at Massachusetts General Hospital. In 2012, he entered the Cognitive Neuroscience Admitting Program at Duke University. He affiliated with the Psychology & Neuroscience program, Clinical Track and spent a year at UC Berkeley and a year at Weill Cornell Medicine while completing his Ph.D.

First-Author Publications from Ph.D. Program

1. **Scult, M.A.** & Hariri, A.R. (2018). A Brief Introduction to the NeuroGenetics of Cognition-Emotion Interactions. *Current Opinion in Behavioral Sciences*, 19, 50-54.
2. **Scult, M.A.,** Knodt, A.R., Radtke, S.R., Brigidi, B.D., & Hariri, A.R. (2017). Prefrontal Executive Control Rescues Risk for Anxiety Associated with High Threat and Low Reward Brain Function. *Cerebral Cortex*, 1-7.
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