Part I

Clinical relevance of cognitive dysfunction in major depressive disorder

Chapter 1

Does cognitive dysfunction predate the onset of incident depression?

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Introduction

Major depressive disorder (MDD) is currently associated with the highest disability among all mental, substance use, and neurological disorders; moreover, MDD is the greatest contributor to years of life lost due to ill health (World Health Organization, 2008). Major depressive disorder is one of the most common mental illnesses and is associated with the highest lifetime prevalence of all mental disorders in the United States (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). Major depressive disorder is associated with mood, behavioral, as well as cognitive symptoms. The common age of onset of MDD is between 23 and 32 years (Kessler et al., 2005). These symptoms, in combination with the early age of onset, contribute to MDD being the worldwide leading cause of disability in the workplace, resulting in a loss of US $36.6 billion annually (Kessler et al., 2006, 2012). The cognitive deficits that are associated with MDD are a significant contributor to the disabling effects that this mood disorder poses on day-to-day functioning and work performance (see Appendix Table A1.1). The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) describes MDD as a disorder with cognitive symptoms; however, little research has focused on the cognitive deficits of MDD and their effect(s) on psychosocial functioning (Kessler et al., 2006).

The cognitive symptoms seen in MDD are characterized by deficits in one or more cognitive domains, such as attention or working memory, in combination with a negative cognitive bias toward social situations and other environmental stimuli (McIntyre et al., 2013). These deficits can be categorized into hot and cold cognitive symptoms. Hot cognition describes emotionally valenced cognitive characteristics (e.g. bias toward negative stimuli, rumination, and catastrophic responses), which result in depressed patients' exaggerated reactions toward negative events (Roiser & Sahakian, 2013). Much research has focused on classifying hot cognitive deficits, proposing possible developmental origins and investigating how they result in incident depression (Abramson et al., 1999; Alloy et al., 2001, 2004; De Raedt & Koster, 2010; Ingram, 2001; Ingram & Ritter, 2000). In contrast, cold cognitive symptoms of MDD describe deficits in executive function, attention, learning, memory, and processing speed (Roiser & Sahakian, 2013). The foregoing cognitive deficits have been associated with a particularly negative effect on day-to-day functioning and a reduction in work performance; however, there is a dearth of data

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that has focused on exploring the developmental origins of cold cognitive symptoms and their etiological contribution to MDD (Roiser & Sahakian, 2013; Zakzanis, Leach, & Kaplan, 1998).

Evidence suggests that cognitive deficits observed during a major depressive episode (MDE) remain even after mood and behavioral symptoms have been resolved (Buist-Bouwman et al., 2008; Conradi, Ormel, & De Jonge, 2011; Jaeger, Berns, Uzelac, & Davis-Conway, 2006). Moreover, some research suggests that cold cognitive symptoms may precede the onset of an MDE (McIntyre et al., 2013). This chapter will review existing evidence for the role of cold cognitive deficits, including executive function and working memory, in the development of MDD. The overarching aim of the chapter is to better understand the extent to which cognitive dysfunction predates the onset of syndromal depression in those affected.

Cognitive function in healthy individuals and future depression

There is evidence that cognitive deficits observed in otherwise healthy individuals can predict the development of future depressive episodes (Airaksinen, Wahlin, Forsell, & Larsson, 2007; Berger, Small, Forsell, Winblad, & Bäckman, 1998; Simons et al., 2009; Zammit et al., 2004). In a population-based longitudinal study in Stockholm, Berger and colleagues (1998) reported that lower cognitive function could predict the development of MDD. The aim of this study was to find potential pre-clinical markers for MDD; 185 participants over the age of 75 years were tested for behavioral and mood symptoms, typically associated with MDD, as well as on measures of cognitive function. Cognitive function was assessed with the Mini Mental State Exam (MMSE) and participants were surveyed for the development of depressive symptoms three years later. Subjects who had developed MDD at the three-year follow-up were more likely to have had a lower performance score on the MMSE, specifically in the domain of delayed word recall (Berger et al., 1998). The results of another prospective longitudinal study suggest that deficits in executive function as well as low performance on attention and language tasks might predict the onset of future depression development (Vinberg, Miskowiak, & Vedel Kessing, 2013). In this study 234 healthy twins who had a co-twin with or without a history of affective disorder were followed for nine years to assess for the development of psychiatric illnesses. At the baseline session of this experiment, participants completed cognitive function tasks, including the Trail Making Test Parts A and B, the Stroop Test, and the Cambridge Cognitive Examination-Revised (CAMCOR). Participants who had a co-twin with a history of affective disorder were more likely to develop psychiatric illnesses, especially affective and anxiety disorders. Moreover, lower performance on executive function, attention, and language measures were particularly associated with the development of affective and anxiety disorders.

Simons and colleagues (2009) suggested that deficits in episodic memory show a particularly strong association with future depressive symptoms. In their study they compared neuropsychological functioning, including episodic memory and information processing, to the development of current and future depressive symptoms and found a significant association between low neuropsychological functioning and future depressive episodes, but not current episodes. In line with this research, Airaksinen and colleagues (2007) followed 20–64-year-old non-depressed participants from a Swedish population over a three-year time period to compare cognitive function with future depression. Participants (n = 708) completed measures of cognitive function (i.e. episodic memory, psychomotor speed, verbal fluency, and mental flexibility). After controlling for socioeconomic and demographic factors, as well as alcohol use and anxiety, the results of this study suggested that those who performed lower on episodic memory tests were more likely to receive a diagnosis of MDD. It was concluded that cognitive dysfunction might predispose and portend incident depression, underscoring cognitive dysfunction as a risk factor for the development of MDD.

As outlined by the foregoing studies, cognitive deficits in otherwise healthy individuals have been linked to a higher incidence of MDD. A study by Zammit and colleagues (2004) suggested that individuals who exhibited better premorbid cognitive function were less likely to develop MDD as a result of cognitive reserve, wherein better premorbid cognitive function may protect individuals from developing MDD through mechanisms that have yet to be elucidated (Zammit et al., 2004). Cognitive reserve describes individual differences in the activation of brain networks (e.g. dentate gyrus and CA3 pathways (Kempermann, 2008)), medial temporal and dorsolateral prefrontal cortices (McIntosh et al., 1999), as well as differences in cerebral blood flow (Grady et al., 1993) that can help in the efficient execution of a specific task (Stern, 2003). Originally, the concept of reserve was used to describe individual differences in performance after brain injury wherein individuals with high reserve would increase the efficiency at which they could perform different behaviors following brain damage. The foregoing observation suggests that some brain networks involved in cognition may therefore act as a protective factor against cognitive decline (Stern, 2003). For example, in Zammit and colleagues' (2004) population-based longitudinal study, participants completed an IQ test and were followed for 27 years to compare the development of MDD to baseline IQ scores. In this study, low IQ was associated with a greater risk for the development of future depressive episodes. The researchers suggested that high IQ might act as a protective factor for those at risk of developing MDD.

Childhood ADHD and future depressive episodes

Research suggests that impaired neurodevelopment in childhood increases the likelihood of early-onset affective disorders and that cognitive abilities in childhood are associated with MDD in both adults and children (Van Os, Jones, Lewis, Wasworth, & Murray, 1997). A longitudinal study conducted by Colman and colleagues studied a particular birth cohort in Britain for 40 years, investigating the role of childhood-onset disorders as being a phenomenological antecedent to adult-onset depressive and anxiety symptoms (Colman, Ploubidis, Wadsworth, Jones, & Croudace, 2007). The results of this study suggest that neurodevelopmental abnormalities were predictive of symptoms portending the development of MDD later in life, and that this association might be mediated by cognitive deficits.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood disorders and is an example of a cognitive developmental disorder characterized by deficits in executive function including, but not limited to, deficits in working memory and response inhibition (American Psychiatric Association, 2013; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Hervey, Epstein, & Curry, 2004; Isohanni et al., 1998; Pennington and Ozonoff, 1996). Individuals with ADHD are at a greater risk for developing psychiatric illnesses, including oppositional defiant disorder (ODD), obsessive-compulsive disorder (OCD), mood disorders, anxiety disorders, and substance abuse disorders (Yoshimasu et al., 2012). Since ADHD is a cognitive disorder, it serves as a candidate for investigating whether cognitive symptoms could act as an antecedent to the development of MDD. One study suggested that ADHD might act as a risk factor for the development of MDD as 16 percent of their 116 adult MDD patients were diagnosed with childhood ADHD and 75 percent of the participants continued to experience symptoms of ADHD into adulthood (Alpert et al., 1996).

Several studies have suggested that the association between childhood ADHD and adulthood MDD is more prevalent in females (Alpert et al., 1996; Biederman et al., 2008; Cannon et al., 1997; Roiser & Sahakian, 2013). In a prospective study conducted by Biederman and colleagues (2008), 140 female participants with ADHD and 122 without ADHD were assessed for cognitive, social, and educational functioning and followed for five years to assess the

development of psychiatric conditions. Cognitive function was assessed by obtaining each participant's IQ score with part of the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) and evaluating their literacy skills with the Wide Range Achievement Test-Revised. Educational functioning was assessed by counting the number of participants who repeated a grade, attended special needs classes, or received extra help with schoolwork. In this study, ADHD was associated with impaired cognitive and educational outcomes. Furthermore, ADHD was significantly associated with an increase in the development of future MDD. More specifically, the presence of ADHD was reported to exert a five-fold higher risk for future MDD development. Moreover, a diagnosis of MDD in those previously diagnosed with ADHD was associated with an earlier age at onset, longer duration, and more severe impairment than in those that were not previously diagnosed with ADHD. This study provides preliminary empirical evidence for how cognitive symptoms frequently observed in patients with ADHD might presage the development of future depressive symptoms.

In addition to studying the association between ADHD and MDD, several research studies have focused on understanding the long-term consequences that deficits in executive function during childhood might have on future psychosocial functioning (Hellgren, Gillberg, Bågenholm, & Gillberg, 1994; Knouse, Barkley, & Murphy, 2013). Executive function describes a range of neuropsychological functions that allow one to focus and shift attention, process information in working memory, as well as plan and organize responses (Pennington & Ozonoff, 1996); moreover, deficits in executive function have consistently been described in ADHD as well as in MDD (Baune, Fuhr, Air, & Hering, 2014). In one study, 146 adults with ADHD and 97 adults without ADHD were measured for executive function and the development of MDD (Knouse et al., 2013). Executive function was measured with the Deficits in Executive Function Scale (DEFS); in addition, estimated intelligence scores were obtained with the Shipley Institute of Living Scale, and depressive symptoms were measured with the Symptom Checklist 90-revised. In this study, low performance on DEFS predicted the emergence of an MDE in the participant's lifetime and deficits in executive function were associated with an increased severity of depressive symptoms. Notably, specific subsets of the DEFS assessment tool were associated with current and lifetime MDD, including deficits in self-management, self-organization, and problem-solving skills.

A similar study followed 56 children with attention, motor, and perception deficits compared with a healthy control group over ten years to examine the development of future schizophrenia, MDD, and bipolar disorder (Hellgren et al., 1994). Fifty-nine percent of children with prior attention, motor, and perception deficits exhibited a later-onset psychiatric disorder (i.e. ten years later) compared to 11 percent of the control group. Interestingly, MDD was the most common psychiatric illness in the experimental group. Similar to the previous study, the researchers suggested that inattentive behavior could increase the risk for MDD wherein social exclusion and/or deficits in goal-directed behavior could interfere with these youths' psychosocial function (Knouse et al., 2013).

Another research approach that could provide evidence for cognitive symptoms acting as an antecedent to the development of MDD is the comparison of individuals treated for ADHD during childhood with those that were not. It has been suggested that treatment for ADHD during childhood is associated with a better outcome on psychosocial functioning, which may lend support to the notion that the cognitive deficits seen in ADHD directly contribute to the development of depressive symptoms (Goksøyr & Nøttestad, 2008). In their comparative analysis, Goksøyr and Nøttestad studied 17 individuals who had received treatment for childhood ADHD and 74 individuals without previous treatment for ADHD. Investigators measured alcohol and substance use, criminality, and psychosocial

functioning. It was determined that individuals treated for ADHD had a better outcome in all of the domains measured, and demonstrated more than a two-fold increase in their score on the Global Severity Index for psychological functioning. The aforementioned results provide support for the notion that the cognitive deficits commonly observed in ADHD are a contributing factor to the development of future depressive episodes.

Cognitive antecedents to bipolar disorder

Bipolar disorder (BD), like MDD, is a mood disorder characterized by neuropsychological symptoms that include cognitive deficits manifested as impairments in memory, attention, and executive function (Martínez-Arán et al., 2004). Cognitive impairments have been suggested to be a risk factor for the development of BD (De Raedt & Koster, 2010; McGillivray & Baker, 2009). Individuals with BD are believed to have pre-existing impairments in intellectual abilities (Cannon et al., 1997; Isohanni et al., 1998) and approximately 20 percent of children and adolescents with ADHD develop BD (Biederman et al., 1996). A retrospective study with a comparative case-control design suggested that neurodevelopmental antecedents exist for the development of BD. The researchers of this study assessed 38 adolescents diagnosed with BD or psychotic depression using the Denver Development Screening Test (DDS) to screen for developmental delays during the first six years of their life (Sigurdsson, Fombonne, Sayal, & Checkley, 1999). Individuals with BD had a higher rate of developmental delays in language, social, and motor function as well as a lower IQ. In a similar study, researchers assessed premorbid intellectual, behavioral, and language abilities of a group of 16–17-year-olds who were hospitalized for schizophrenia, schizoaffective disorder, or non-psychotic BD (Reichenbert et al., 2002). In this study, impaired premorbid intellectual functioning was seen not only in schizophrenia, but also in non-psychotic BD.

The cognitive deficits that are documented for people with BD are similar to what is observed in individuals with MDD; however, convergent evidence indicates a greater overall deficit in the BD population. Taken together, the question as to *how* cognitive deficits might act to increase vulnerability to depressive symptoms remains.

Potential underlying biological mechanisms

Accumulating evidence supports the idea that cognitive deficits may act as an antecedent to the development of MDD. This section will describe possible biological mechanisms to explain how cognitive deficits could arise and how they may facilitate the development of MDD.

Various environmental and biological factors during brain development can lead to abnormalities in structures needed for normal cognitive function. For example, prenatal stress could alter the development of the hypothalamic–pituitary–adrenal (HPA) axis, which could lead to an abnormal stress response and negatively affect hippocampal development (Colman et al., 2007). Likewise, childhood trauma could lead to impairments of normal brain development, which has also been associated with reduced cognitive function (Aas et al., 2012). Physical and sexual abuse has commonly been linked to the development of future depressive symptoms (Jacobson, Fasman, & DiMascio, 1975; Poznanski, Krahenbuhl, & Zrull, 1976). Physical and sexual abuse as well as neglect have been suggested to reduce working memory and executive function, resulting in cognitive deficits, which may be a contributing factor to the development of future depression (Aas et al., 2012).

Specific structural abnormalities in the brain have been associated with the development of cognitive deficits. In MDD, deficits in executive function are believed to be the result of prefrontal cortex abnormalities (Barrera, Torres, & Muñoz, 2007; World Health Organization, 2008;

Zammit et al., 2004). Specifically, bilateral hippocampus reduction and over-activity of the anterior cingulate cortex have been linked to deficits in executive function, attention, learning, memory, and processing speed. Structural changes in the frontal lobes, amygdala, and hippocampus have also been associated with deficits in declarative memory, and impaired hippocampal function has been associated with poor episodic memory before the onset of an MDE (Campbell, Marriott, Nahmias, & MacQueen, 2004; Frodl et al., 2002; McIntyre et al., 2013; Sheline, Gado, & Price, 1998).

Continuous exposure to stress (e.g. physical abuse) can result in hypercortisolism, which is reported to decrease activity in the dorsolateral PFC (De Raedt & Koster, 2010). Increased activation of the amygdala via the anterior cingulate cortex (ACC) in response to stress, in combination with reduced attention as a result of the reduced activity in the dorsolateral PFC areas, could then increase negative affect and rumination. Impaired function of the dorsolateral PFC and its associated brain regions thereby inhibits top-down processes and abilities relevant to cold cognition (Roiser & Sahakian, 2013). These impaired top-down processes result in impaired executive function and could thereby contribute to the development of depressive symptoms. The three-component model of executive function identifies that *updating* of new information stored in working memory, attention *shifting*, and *inhibiting* of irrelevant responses are three important aspects of executive function (Friedman et al., 2008; Miyake, Friedman, Rettinger, Shah, & Hegarty, 2001). This model could be used to explain how deficits in executive function might lead to the development of depressive symptoms. Impairments in these executive function domains could lead to individuals being unable to update their working memory framework after a negative stimuli has subsided, shift their attention away from negative stimuli, or inhibit negative responses (Ingram, Steidtmann, & Bistricky, 2008). In this way, deficits in cold cognition might impact hot cognition by facilitating the development of negative self-schemas, rumination, and catastrophic responses (Roiser & Sahakian, 2013). Deficiencies in these cold cognitive symptoms may also include deficiencies in short-term memory, which have previously been reported in depressed individuals (Colby & Gotlib, 1988). Impaired memory function may not only be a symptom of depression but may contribute to the development of depressive symptoms by impairing normal day-to-day functioning, making activities less joyful and resulting in a reduction of these activities (Berger et al., 1998). Cold cognitive deficits might thereby contribute to the development of depressive symptoms through their interaction with hot cognitive deficits (Figure 1.1).

Cognitive deficits are often associated with altered brain structure and function. Moreover, impairments in cognition have been posited to contribute to the development of depressive symptoms, suggesting that cognitive deficits predate disturbances in mood (Simons et al., 2009). Taken together, cognitive deficits may represent an endophenotype, linking specific environmental stressors and brain abnormalities to the development of MDD (De Raedt & Koster, 2010).

Identifying cognitive deficits to develop new prevention strategies

If cognitive deficits indeed act as an antecedent to the development of MDD, researchers and clinicians could use this information to better our understanding of the etiological development of MDD. Currently, not many prospective longitudinal research studies have been conducted in this research area (Baune et al., 2014). Given the significant implications research

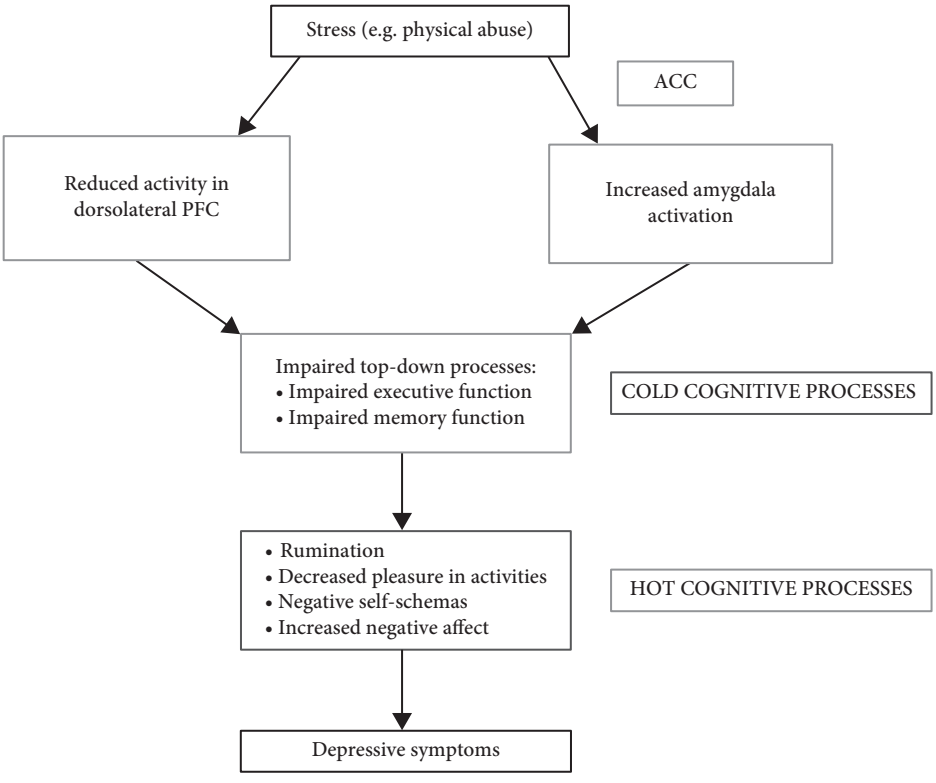

Figure 1.1 The impact of hot and cold cognitive processes on depressive symptoms.

findings in this field could have on the prevention of MDD, future research studies should focus on better understanding of the relationship between depressive symptoms and neurocognitive deficits (Baune et al., 2014).

It has previously been suggested that early detection of executive and memory impairments could be used as a screening tool to identify individuals at risk for developing BD; similar strategies might be used to identify those at risk for developing MDD (Olvet, Burdick, & Cornblatt, 2013). Current prevention methods are applied and focused on the recurrent course of MDD; however, the significant impact MDD has on those affected in terms of disability indicates that more attention should be given to preventing the onset of MDD (Barrera et al., 2007). Currently, most studies identify individuals at risk for MDD as those who have had an MDE in the past. However, the ideas presented in this chapter could lead to the development of new, tangible risk factors to improve the identification of individuals who are at risk for developing an MDE *before* it occurs. According to Vinberg and colleagues (2013), individuals at heritable risk for affective disorders, who show deficits in executive and attention function, are more likely to develop affective disorders in the future. Early psychiatric assessments that include neuropsychological function measures could help to identify those at increased risk for the development of affective disorder. Beck (2008) outlined that the treatment of MDD should include agents or strategies that target deficits in

executive function; however, it may be possible to treat deficits in executive function before the onset of an MDE. The results of research presented in this chapter suggest that early intervention among children with ADHD may lower their risk for developing MDD. Moreover, the translation of knowledge between medical specialties (e.g. psychiatry and pediatrics) should aim to improve patients' long-term health by evaluating frequently comorbid and/or antecedent conditions (e.g. childhood adversity, psychiatric disorders, and cognitive dysfunction are frequently associated with the development of MDD later in life). This awareness could be used to implement screening tools to identify those at risk for developing MDD to provide access to prevention programs (e.g. cognitive behavioral therapy) that could help to reduce the overall number of MDD cases.

Conclusion

MDD is a common and often serious mental disorder that impacts mood, behavior, and cognition, greatly inhibiting normal day-to-day functioning. There is a paucity of data that primarily aims to evaluate the impact of cognitive dysfunction in individuals affected by MDD. Evidence suggests that cognitive deficits precede the onset of MDD and may predispose individuals to developing depressive symptoms. Environmental stressors could result in structural and functional changes in certain brain regions, which could result in a reduction in top-down processes. This could lead to a reduction in cognitive abilities, including executive function and memory, which contribute to the development of depressive symptoms. The research findings reviewed in this chapter serve to propose novel research targets; namely, cognition, and its role in the development of MDD. The foregoing evidence provides the basis for evaluating cognition among individuals at increased risk of MDD (e.g. childhood adversity, ADHD, family history) to determine whether these measures could then be used to identify those at risk for developing MDD prior to their first MDE by administering early intervention programs (e.g. cognitive remediation, cognitive behavioral therapy) and/or treatments to prevent the manifestation of MDD (e.g. treatments to ameliorate established childhood disorders such as ADHD).

Appendix 1.1

Table A1.1 Summary of research findings supporting cognitive deficits acting as an antecedent to the development of depression

Category	Study set-up	Results	Reference
Cognitive deficits in healthy individuals and future MDD	• Population-based prospective study • 20–64-year-old non-depressed individuals (n = 708) • Surveyed cognitive function with episodic memory, psychomotor speed, verbal fluency, and mental flexibility measures	• Those who performed lower on episodic memory tests were more likely to develop MDD during the three-year follow-up	Airaksinen et al., 2007
	• Population-based longitudinal study • Healthy participants (n = 185) over the age of 75 years • Tested behavioral and mood symptoms of MDD • Tested cognitive function using Mini Mental State Exam (MMSE)	• Lower cognitive performance associated with increased prevalence of MDD three years later	Berger et al., 1998

Category	Study set-up	Results	Reference
	• Population-based prospective study • Healthy female twins (n = 569) • Completed neuropsychological battery to assess for episodic memory and information processing speed • Measured subclinical and clinical depressive symptoms with Symptom Checklist-90 (SCL-90) and Structured Clinical Interview for DSM-IV respectively	• Depressive symptoms assessed by Structured Clinical Interview for DSM-IV disorders associated with poor information processing speed • Depressive symptoms assessed by SCL-90 associated with poor episodic memory performance at baseline	Simons et al., 2009
	• Longitudinal prospective study • Healthy monozygotic and dizygotic twins with and without co-twin with affective disorder (n = 234) • Tested for affective symptoms with Schedules for Clinical Assessment in Neuropsychiatry and the 17-item Hamilton Depression Rating Scale (HDRS) • Measured cognitive function with the Trail Making Test Parts A and B, Stroop Test, and the Cambridge Cognitive Examination-Revised (CAMCOR) • Followed for nine years with six-month interval follow-ups to investigate development of future psychiatric illness	• Individuals with a co-twin with a history of affective disorder were more likely to develop psychiatric illness in the future (mostly affective and anxiety disorders) • Development of psychiatric illness was predicted by reduced executive function, attention, and language skills	Vinberg et al., 2013
	• Population-based longitudinal study • Male conscripts (n = 50,087), IQ scores at conscription • *International Classification of Disease, Eighth Revision or Ninth Revision* was used to receive diagnoses for schizophrenia, bipolar disorder, and severe depression 27 years after conscription	• Low IQ score associated with greater risk for severe depression and schizophrenia, but not bipolar disorder	Zammit et al., 2004
Childhood ADHD and future MDD	• Retrospective study • MDD patients (n = 116) between 18 and 65 years • Assessed for individuals meeting criteria for childhood ADHD as measured with DSM-III-R	• 16% of participants met criteria for childhood ADHD	Alpert et al., 1996
	• Prospective study • Females with ADHD (n = 140) and without ADHD (n = 122) • Followed for five years and reassessed for psychiatric, cognitive, educational, interpersonal, and family functioning • Psychiatric measures taken with Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version and Structured Clinical Interview for DSM-IV • Cognitive and psychosocial function was assessed with the DSM-IV Global Assessment of Functioning, IQ test, and Wide Range Achievement Test-Revised • Family function was assessed with the Hollingshead Scale and the Family Environment Scale	• Participants with ADHD had 2.5 times greater association with future MDD diagnosis • MDD in participants with childhood ADHD associated with earlier onset, greater impairment, longer duration, increased likelihood of psychiatric-related hospitalization, and suicidal attempts	Biederman et al., 2008

Continued

Table A1.1 Summary of research findings supporting cognitive deficits acting as an antecedent to the development of depression (*Continued*)

Category	Study set-up	Results	Reference
	• Longitudinal latent variable prospective study • n = 4,627 • Measured symptoms of MDD and anxiety disorders at ages 13, 15, 36, 43, and 53 years • Depressive and anxious symptoms measured with the Rutter B2 teacher questionnaire at ages 13 and 15, with the Psychiatric Symptom Frequency scale at ages 36, and with General Health Questionnaire at age 53 • Took measures of neurodevelopment from early hospital records and mothers' accounts of their child's achievement of various developmental milestones (e.g. sitting, crawling, walking, first words)	• Specific neurodevelopmental characteristics might predict development of depressive and anxious symptoms • Delay in standing and walking associated with greater likelihood of future depressive symptoms	Colman et al., 2007
	• Retrospective study • Individuals with previous treatment for childhood ADHD (n = 17) and individuals without previous treatment for childhood ADHD (n = 74) • Measured "Index of Burden" as indicated by alcohol and substance abuse, criminality, results of Global Severity Index of SCL-90, and "Functioning and Quality of Life" questionnaire	• Individuals who had not received treatment for ADHD during childhood had a higher "Index of Burden." • Individuals treated for ADHD during childhood showed better outcome on all measures, including a two-fold increase in their score on the Global Severity Index, indicative of better psychological functioning	Goksøyr & Nøttestad, 2008
	• Prospective longitudinal study • 6-year-old children (n = 56), children with deficits in motor control, perception, and attention • 6-year-old children (n = 45), children without motor, perception, and attention deficits • Followed participants for 16 years • Took measures on psychological and social functioning through 34-item teacher questionnaire, Personality Disorder Examination Interview, Structured Clinical Interview for DSM-III-R	• Future development of affective disorders was highly associated with childhood deficits in motor control, perception, and attention • Children with deficits in motor control, perception, and attention were also more likely to develop personality disorders	Hellgren et al., 1994
	• Retrospective study • Adults with ADHD (n = 146) and adults without ADHD (n = 97) were assessed for executive function deficits • Development of current and lifetime MDD was assessed • ADHD was assessed with structured interview according to DSM-IV • Executive function was assessed by evaluating deficits in self-management to time, problem-solving, self-discipline, self-motivation, and self-concentration • Measure of executive function was taken from Conners' Continuous Performance Test, Stroop Color Word Test, Wisconsin Card Sort Test, Five-Points Test of Design Fluency, and Digit Span Task from the Learning and Memory Battery • Symptom Checklist 90-revised was used to assess for depressive symptoms	• Adults with ADHD showed greater deficits in executive function and had a greater risk of lifetime MDD • Deficits in self-management to time, self-organization, and problem-solving were particularly related to the risk for MDD development	Knouse et al., 2013