Section 1 Neuropsychological processes

Why examine neuropsychological processes in mental illness?

In the first section of this volume we have included a series of chapters that examine the neuropsychological mechanisms that underlie a range of basic psychological processes with relevance to understanding mental illness. There are a number of reasons for beginning the volume in this way. First, many neuropsychological processes are more amenable to objective measurement than the core symptoms of mental disorder (which often rely on self report for their "gold-standard" measurement through diagnostic interviews – see Jackson and McGorry, Chapter 12, this volume). As such, neuropsychological evaluation of basic psychological functions may ultimately be used to aid diagnosis, especially in cases where self report is impaired.

Furthermore, although still far from complete, the brain bases for many neuropsychological functions have been established to some degree. In contrast, our understanding of the neural correlates of psychiatric symptoms is much more hazy. Studying neuropsychological processes may help our understanding of which brain regions are involved, and when they first show dysfunction. Consistent with this is the observation that although genetic risk factors for mental illness are well established (McGuffin *et al.*, 2002), many scientists conjecture that the relationship between genetic vulnerability and disease phenotypes will be clarified if intermediate phenotypes or endophenotypes are also included in models (Beauchaine *et al.*, 2008; Meyer-Lindberg & Weinberger, 2006). Because these intermediate markers fall along the causal chain between the distal genotype and disease they are likely to be more strongly associated with both the disease phenotype and the genotype than these latter variables will be with each other (Gottesman & Gould, 2003). As such, the examination of intermediate phenotypes and endophenotypes can be critical in both identifying the specific alleles associated with risk for psychopathology, and also in developing a mechanistic understanding of the particular neurobiological and behavioral expressions of the genotype that are proximally involved in the transition for risk to disorder. The neuropsychological processes examined here constitute an important set of such potential intermediate phenotypes (Abbott, 2008).

Furthermore, although the diagnostic system treats disorders as categorical entities, most disorders do not satisfy strict taxometric criteria for classes (Haslam, 2003). In other words, in many cases we are imposing a categorical distinction where none exists in nature. Associated with this issue are the facts that comorbidity between diagnoses is common (Jacobi *et al.*, 2004; Kessler *et al.*, 2005), and that similar symptoms are often observed across different disorders (Krueger, 1999). Examining basic neuropsychological process in mental disorder may therefore help to clarify the nature of the distinction between disordered and non-disordered states in a more principled way, and also may help to explain the patterns of comorbidity between diagnostic entities.

Finally, many analyses of the definition of mental disorder have emphasized that understanding the nature of disordered psychological and neuropsychological function is critical to the distinction between disordered and non-disordered states. For example Wakefield's "Harmful Dysfunction" analysis of mental disorder (Wakefield, 1999) proposes that mental disorder must have two properties. "Harmful" refers to the fact that the features of the disorder cause significant harm to a person under present cultural circumstances. This first criterion is therefore partially defined by the current social and

cultural context. However, in order to qualify as a true mental disorder the condition must also result from the inability of some internal mental mechanism to perform its "natural function." In this context "natural function" is defined as the ability of that mechanism to perform the task for which the mechanism was "designed" by evolution. In other words, one strong implication of this analysis is that one must begin with an understanding of the natural (or evolutionarily designated) neuropsychological *functions* of the brain, before neuropsychological *dysfunction* (and therefore mental disorder itself), can be defined.

With these considerations in mind, we felt that it was appropriate to begin the volume by surveying the neuropsychology of a range of basic process that are implicated in mental disorder. The section begins with a chapter by Silveri and Yurgelun-Todd on the role of developmental processes. They conclude that neuropsychological evaluation of children and adolescents can reveal important changes in cognitive function that may relate to later onset of psychopathology, and note the important role that risk status and age must have in interpreting such evaluations. They note the importance of differentiating between the normal trajectory of cognitive development, delayed achievement of developmental milestones and cognitive deficits associated with risk for psychiatric illness.

This chapter is followed by contributions addressing sensory and perceptual processes (by Klimkeit and Bradshaw). They note that while anomalies of perceptual processes are good models that partly explain higher-level neuropsychiatric dysfunction, the link between perception and action will ultimately be critical to our understanding of the neuropsychological basis of psychiatric disorder. Accordingly, motor executive processes are reviewed by Rinehart, Chua and Bradshaw. The potential etiological relevance of neuromotor dysfunction has long been noted in a number of psychiatric disorders, especially autism and schizophrenia. However, developments in our understanding of the connectivity between the prefrontal cortex, basal ganglia and cerebellum has resulted in renewed interest in the application of neuromotor assessment in psychiatry. Rinehart and colleagues particularly note advances in our understanding of higher-order awareness and control of "action," mirror neurons, the concept of affordances, utilization behavior and extreme neurological motor conditions such as the anarchic hand, and explore what these findings may have to offer our understanding of mental illness.

Whittle, Yücel and Allen provide an overview of neurobiological models of emotion, with an emphasis on the specific neuropsychological systems involved in the perception of emotional stimuli, the experience of emotion, and its regulation. Herrington, Koven, Heller, Miller and Nitschke then examine the links between emotion, personality and psychopathology, with a specific emphasis on the role of asymmetry of brain function in these processes. They note the benefit of integrating multiple theoretical perspectives from personality psychology with theories regarding the frontal lateralization of emotion. They conclude that determining which psychological construct best explains lateralization in the frontal lobes may depend on which area of the frontal cortex is being examined. They suggest that hemodynamic imaging will be an invaluable tool for addressing these questions, and explore the appropriate data analytic techniques.

The role of language is explored by Kuperberg, Ditman, Kreher and Goldberg, and they show how paradigms at various levels of language including words, sentences, and discourse, can be used to study neuropsychiatric disorders. They provide a broad theoretical framework to help understand the relationships between these levels of dysfunction and to help guide future theoretically motivated studies of language, particularly in schizophrenia. Seal and Weiss examine associative memory and note several challenges exist for associative memory research in mental illness. One is to make more extensive use of memory research in the neuropsychology of non-psychotic disorder such as depression and obsessive-compulsive disorder. Increasing the sensitivity and specificity of associative memory tasks to both cognitive processes and brain regions is also an important challenge. They also note that exploring the molecular and genetic mechanisms that underlie memory dysfunction in mental illness is a critical priority for future research.

Attentional control and selection is addressed by Ravizza, Mangun and Carter. They note that the ability to control attention involves the interaction of specific cortical and subcortical neural networks influencing multiple stages of information processing. They conclude that to elucidate the neural

mechanisms of attention, and its abnormalities in mental illness, it is essential to investigate and characterize attentional processes at a variety of levels of information processing. Likewise, Testa and Pantelis note that although the evidence of a fractionated executive system in mental illness is strong, the use of different executive tests to assess unique cognitive functions is an important challenge for future research in the area.

Clark and Robbins then explore the neuropsychology of decision-making, particularly implicating prefrontal cortical pathology in the decision-making deficits observed in mental illness. Once again, they note that developing assessment methods that isolate the various subcomponents of these neuropsychological functions is a significant challenge, albeit one upon which significant progress is being made. Finally, Russell and Green examine the neuropsychology of social cognition. Given the prominence of social dysfunction in those suffering from mental illness, understanding the neural networks subserving social cognition may prove to be particularly important for identifying the neuropathology of major psychiatric disorders, and is likely to be pertinent to the formulation of effective treatments for social cognitive disturbances in these individuals. They also address the critical question of domain specificity with respect to social cognitive processes and conclude that while neuropsychological studies suggest that social cognition cannot be fully accounted for by domain-general processes (such as attention, memory or executive function), this does not warrant an overarching conclusion that social cognition is completely independent of domain-specific processes.

In sum, this collection of chapters provides the reader with a series of up-to-date reviews of the neuropsychology of basic psychological functions as they pertain to mental illness. Critically, they also clearly lay out the future research agenda that must be addressed in order for examination of these processes to continue to advance our understanding of mental illness.

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Chapter 1

Developmental neuropsychology: normative trajectories and risk for psychiatric illness

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Introduction

Examination of neuropsychological functioning, both in healthy populations and in individuals with brain injury, has provided important information with regard to lateralization of cognitive function, sex differences in neuropsychological performance, functional differences associated with disconnection syndromes, and cognitive capacity at various developmental stages. Studies of neuropsychological performance conducted at different maturational levels have helped identify abnormalities associated with childhood disorders, including chromosomal and genetic disorders, structural abnormalities, prematurity and low birth weight, infections, toxic damage, nutritional disorders, anoxic disorders, traumatic brain injury, focal neurological disorders, convulsive disorders, hemispherectomy and other effects of surgical manipulations (Spreen *et al.*, 1995b). The utility of neuropsychological assessment in children and adolescents with neuropathologic conditions is not only to provide information regarding their progress in achieving normative developmental milestones but also to provide a framework for the identification of brain dysfunction and for the development of remediation strategies.

Significant development of the central and peripheral nervous systems occurs throughout early life, with major alterations being observed from infancy to adolescence (for review, see Huttenlocher, 1994). These rapidly evolving systems include the sensory systems (auditory, visual, chemical senses, somesthetic), motor systems (pyramidal and extrapyramidal) and integrative higher-order systems (association areas, reticular formation and brainstem chemical pathways, language areas) (Spreen *et al.*, 1995a). Both structural and functional changes in these systems permit the rapid improvements in cognitive abilities observed from infancy through late adolescence.

To date a large body of research has focused not only on structural brain development, but also on the maturation of individual neuropsychological domains and the process by which these domains become integrated during development (Webb *et al.*, 2001). It is known that both genetic and experiential factors play a role in how brain networks develop (Nelson, 2000; Williamson *et al.*, 2003). Furthermore, brain maturation and cognitive function have been shown to be sensitive to the timing of both toxic exposure and environmental experience (see Knudsen, 2004; Thompson & O'Quinn, 1979). This dynamic process of brain maturation therefore raises special challenges for the neuropsychological evaluation of children and adolescents.

Neuropsychological domains

Neuropsychological assessment is aimed at measuring cognitive-intellectual ability. Cognition is the process of knowing or thinking, and in childhood age-related changes in cognition occur, including quantitative increments in cognitive ability. Early researchers considered cognitive processing capacity as a unitary measure, however this approach proved limited, since deficits may be found in a specific cognitive area while performance in other cognitive functional areas remains essentially intact (Lezak, 1995). This led clinicians and researchers to focus on the assessment of separate functional domains. In general, these domains include attention, memory, executive function, language, visuospatial function, and processing speed, which are described in greater detail below.

The Neuropsychology of Mental Illness, ed. Stephen J. Wood, Nicholas B. Allen and Christos Pantelis. Published by Cambridge University Press.

Attention

Attention encompasses a number of functions, including four different commonly reported components: divided attention, the ability to perform two tasks simultaneously; sustained attention, the ability to maintain attention over an extended time; selective attention, the ability to filter out irrelevant information to focus on the task attention; and attentional switching, the ability to switch between attention sets. Attentional capacity can vary significantly depending on mood state and level of arousal, as well as maturational level. The neural substrate for attention is thought to lie within a complex set of networks including the frontal cortex, the posterior parietal cortex and the reticular formation (Stuss & Benson, 1984).

Memory

Memory is an active process that records information from the past so that it may be used in the present. It involves a number of processes including encoding, storage and retrieval. Memory deficits are most often due to retrieval and encoding problems rather than limitations in storage capacity. Anatomical regions implicated in memory involve multiple bilateral brain regions, with the hippocampus and the frontal lobes being particularly important. Working memory involves short-term maintenance, sorting and manipulation of new and retrieved information; and is often considered a component of the attentional domain. Brain regions important for working memory include the prefrontal cortex and the inferior parietal lobule (Goethals *et al.*, 2002), as well as the visual association area, the inferior temporal cortices and portions of the cerebellum (Berman *et al.*, 1995).

Visuospatial function

Visuospatial function encompasses the ability to visualize objects in space. Tasks that measure visuospatial function include tests of mental rotation and spatial localization, both of which require intact parietal lobes, particularly in the right hemisphere (Benton, 1985; Heilman & Van Den Abell, 1980). The visual features of an object are processed via a pathway from the occipital to the temporal cortex, called the ventral stream, and the spatial locations are processed via a pathway from the occipital to the parietal cortex, called the dorsal stream (Ungerleider & Mishkin, 1982). Studies have shown that cerebral blood flow increases are significantly higher in the right parietal lobe during rotational tests, and that subjects with lesions in their right parietal lobe perform worse on mental rotation tasks than both normal controls and subjects with lesions in their left parietal lobe (Ditunno & Mann, 1990; Papanicolaou *et al.*, 1987).

Language

Language processes can be divided into three categories, including expressive speech, object naming and language comprehension. Studies involving the electrical stimulation of the brain have implicated three main cortical areas of interest regarding language processes: the anterior language area (Broca's area), the posterior language area (Wernicke's area), and the supplementary language area (the supplementary motor area) (Penfield & Jasper, 1954; Penfield & Perot, 1963; Penfield & Roberts, 1959). Broca's area in the inferior frontal gyrus is largely responsible for language processing and speech production, and Wernicke's area in the superior temporal gyrus is important for speech comprehension (Lezak, 1995). These processes are lateralized to the left hemisphere in most individuals. The posterior-inferior temporal gyrus has been identified as the "naming center" of the brain, and is important for object naming (Penfield & Roberts, 1959).

Speed of processing

Speed of processing typically measures the required time to complete a specific cognitive task (Reitan & Wolfson, 1985; Smith, 1991). Multiple brain regions are involved in this function, although white matter integrity is thought to be particularly important, since the size of axons and the thickness of myelin are predictors of speed of processing (Gao *et al.*, 1999). Changes in white matter that are associated with a reduction in processing speed may also affect performance in other cognitive domains, such as attention and working memory.

Executive function

Executive functions include a broad range of processes involved in implementing goal-oriented behavior. These processes include inhibitory function, mental flexibility and planning. These behaviors are dependent on multiple cortical networks including prefrontal areas and posterior association areas, particularly the dorsolateral prefrontal cortex. Spontaneous flexibility in particular is reliant on the frontal cortex, whereas reactive flexibility

requires intact cortical-striatal interconnections (Eslinger & Grattan, 1993).

Age-related increases in cognitive capacity are thought to reflect brain maturational changes. During childhood and adolescence these neurobiological changes are paralleled by greater functional capacity, as well as more efficient synchronization of function between individual cognitive domains. Neuropsychological measures can provide estimates of overall intellectual ability and can assist in the identification of deficits within functional domains. It is this approach that has provided the greatest insights into the neuropsychological changes associated with psychiatric disorders.

Considerations in the assessment of children

It is important that appropriately designed neuropsychological tests are used to evaluate children. Often, adult tests are modified for use with younger populations; however, these may not provide an accurate functional assessment, because children and adolescents may not have fully developed the skills required. Further, tests designed to assess specific adult abilities may not accurately reflect the same cognitive features in children. Age-appropriate tests are clearly required to accurately assess the cognitive skills of children and adolescents, in order to consider the varying abilities associated with different developmental stages.

There are additional challenges involved in pediatric neuropsychological assessments, including the need to be aware of and account for several factors that can affect the test performance of children in different age groups. These include attentional capacity, including distractibility, as well as the level of social skill of the child. Issues related to mood, including stress and anxiety, are also important considerations when interpreting performance data, given the fear associated with separation from a parental figure, new locations and/or testing situations.

Developmental neuropsychology milestones

Cognition during infancy is largely observed as information processing. These maturing processes include the development of attention, learning and inhibitory function. Bornstein *et al.* (2006) conducted a large-scale study to measure information processing, as indexed by habituation to novel stimuli, in children examined at 4, 6, 18, 24 and 49 months of age. Habituation efficiency observed at 4 months was shown to predict performance observed on the Denver Developmental Screening Test (6 months), the Mental Development Scale (18 months), the British English MacArthur Communicative Developmental Inventory (24 months) and the Wechsler Preschool and Primary Scale of Intelligence Revised (49 months). The authors concluded that subtle differences during the development of a cascade of age-appropriate achievements could influence later academic success.

Significant improvements in cognitive processing speed and intellectual functioning have been shown to continue into childhood and adolescence, with the most dramatic improvements occurring in the development of executive functions including abstract thought, organization, decision-making and planning, and response inhibition (Anderson, 2001; Klenberg *et al.*, 2001; Rosso *et al.*, 2004; Williams *et al.*, 1999). Recent neuroimaging studies have provided evidence for changes in brain structure and function being commensurate with improvements in cognitive abilities. For instance, rapid brain reorganization has been shown to include changes in white and gray matter, each of which undergo distinct developmental patterns, with white matter increasing (reflecting myelination) and gray matter decreasing (reflecting synaptic pruning). There is a growing body of evidence demonstrating significant relationships between brain structure and function with cognitive processing speed and performance (Casey *et al.*, 1997; Reiss *et al.*, 1996; Sowell *et al.*, 2001; Yurgelun-Todd *et al.*, 2002). Age-related improvements in higher-order cognitive domains, including executive functions, are thought to be related not only to a marked re-organization of the frontal lobe (Giedd *et al.*, 1999; Pfefferbaum *et al.*, 1994; Sowell *et al.*, 1999, 2001), but also to improved functional white matter connectivity within and between brain regions during adolescence (Giedd *et al.*, 1999; Pfefferbaum *et al.*, 1994).

In summary, rapid improvements in cognitive function are observed from infancy through adolescence, as well as into adulthood. Neuropsychological assessment of a variety of cognitive domains show distinct developmental patterns, with the development of information processing occurring very early in life and more complex, higher-order cognitive

abilities, such as abstraction capacity and planning, that come online during adolescence and into adulthood. Thus, examination of normative developmental patterns of cognitive function, as well as delays or impairments in cognition, provide an informative framework for understanding and identifying individual profiles of cognitive performance deficits later in life. In addition, alterations in cognitive abilities observed in the first decades of life may reflect risk factors for the later onset of psychiatric illness.

Neuropsychological deficits: risk for psychiatric illness

As indicated earlier, studying neuropsychological performance in children serves as a valuable strategy for identifying potential risk factors associated with the development of psychiatric illness. Over the past 50 years, a number of studies have been conducted to examine neuropsychological performance in children, with the goal of identifying areas of cognitive function that might be associated with onset of psychiatric illness. In general, three types of research studies have been reported: (1) genetic high risk for psychiatric illness in children of one or both parents with a psychiatric disorder; (2) large-scale longitudinal examination of population birth cohorts; (3) short-term longitudinal examination of male conscripts; and (4) follow-back studies of pre-illness levels of cognitive functioning in adults inflicted with a psychiatric illness. Results from genetic high risk and population birth cohort and conscript studies will be briefly examined and discussed to highlight the approaches used in earlier investigations.

The majority of the genetic high-risk studies conducted during the last 50 years examined children of parents with schizophrenia (for review, see Niemi *et al.*, 2003). Sixteen high-risk studies were conducted between 1952 and 1994, requiring that at least one parent (predominantly the mother) meet criteria for schizophrenia (Niemi *et al.*, 2003). There have been a significant number of additional investigations conducted since 1994, which have examined children and adolescents who are the offspring of schizophrenic parents (e.g. see Byrne *et al.*, 1999; Cornblatt *et al.*, 1999; Cornblatt & Keilp, 1994; Davalos *et al.*, 2004; Goldstein *et al.*, 2000; Sorensen *et al.*, 2006), although only one recent high-risk study examined cognitive performance in offspring of bipolar parents (McDonough-Ryan *et al.*, 2002). The comparison groups in these studies varied, but included cohorts of children of psychiatrically healthy parents, children of parents with depressive disorder, children of parents with a physical illness, and less frequently, children of parents with manic-depression illness, or bipolar disorder.

Several large-scale cohort studies also have been conducted. These studies have typically followed thousands of participants from childhood into adulthood. Individuals are examined on clinical and cognitive measures at specified intervals, with the objective of identifying variables that may predict later onset of psychosis. As with the high-risk studies, the majority of the cohort studies have been conducted to examine adult onset of schizophrenia (for review see Jones & Tarrant, 2000). These studies include, but are not limited to, the British 1946 birth cohort (Jones *et al.*, 1994; Jones & Done, 1997), the British 1958 National Child Development Study (Done *et al.*, 1994; Jones & Done, 1997), the North Finland 1966 birth cohort (Isohanni *et al.*, 1997; Rantakallio, 1988), the 1949–1950 Swedish Conscript Study (David *et al.*, 1997; Malmberg *et al.*, 1998) and the Israeli Conscript Study (Davidson *et al.*, 1999). While these studies have focused on identifying risk factors associated with schizophrenia, additional data have been reported for risk for affective and bipolar disorders (Done *et al.*, 1994; Isohanni *et al.*, 1997; Jones *et al.*, 1994; Rantakallio, 1988; van Os *et al.*, 1997).

It has been suggested that the paucity of developmental investigations focusing on risk factors for bipolar illness is due to difficulty with diagnostic classification and limited numbers of patients with first-onset bipolar disorder within samples ideal for cohort studies. Thus, most cohort studies utilize a general affective disorder category. Furthermore, it is possible that cognitive risk factors for some forms of bipolar illness, which may have an earlier age of onset than schizophrenia, are difficult to detect against a background of rapidly changing cognitive abilities observed during the first two decades of life. The results of genetic high risk and population cohort studies are discussed below, as they relate to the manifestation of schizophrenia, bipolar disorder and depression. Although not a topic reviewed in this chapter, a number of investigations have also found abnormalities in social and emotional functioning during childhood and adolescence to be associated with heightened risk for the development of schizophrenia (e.g. Done *et al.*,

1994) and affective disorders (Dworkin *et al.*, 1991, 1994; Gotlib *et al.*, 2005).

Schizophrenia

Risk for schizophrenia has been studied extensively in children of parents with schizophrenia, with such studies examining a wide range of clinical, experimental and cognitive measures.

Genetic high-risk studies have documented abnormalities in intelligence quotient (IQ), attention, executive functioning and verbal memory in high-risk children relative to psychiatrically healthy children or children at risk for affective disorder, although study findings have been inconsistent. For instance, a number of studies have documented lower intelligence quotient (IQ) in high-risk children relative to healthy comparison children (Byrne *et al.*, 1999; Goldstein *et al.*, 2000; Goodman, 1987; Neale *et al.*, 1984; Rieder *et al.*, 1977), while other studies have failed to find such differences (Klein & Salzman, 1984; Lifshitz *et al.*, 1985; Mednick & Schulsinger, 1968; Sameroff *et al.*, 1984; Sohlberg, 1985; Worland & Hesselbrock, 1980; Worland *et al.*, 1982, 1984). Impairments in attention observed in high-risk children relative to comparison children have been observed on some (Cornblatt *et al.*, 1999; Cornblatt & Keilp, 1994; Erlenmeyer-Kimling & Cornblatt, 1992; Erlenmeyer-Kimling *et al.*, 2000; Mirsky, 1988; Nuechterlein, 1984; Schreiber *et al.*, 1992; Weintraub, 1987) but not all neuropsychological measures of attention (Driscoll, 1984). Furthermore, there is evidence that high-risk children demonstrate abnormalities in other functional domains including working memory (Davalos *et al.*, 2004), executive functioning (Byrne *et al.*, 1999), math and spelling (Ayalon & Merom, 1985; Mirsky, 1988), verbal skills (Davalos *et al.*, 2004; Weintraub, 1987), verbal memory (Erlenmeyer-Kimling *et al.*, 2000) and perceptual motor speed (Mirsky, 1988; Sorensen *et al.*, 2006).

Cohort and conscript studies examining risk for the development of schizophrenia have likewise reported evidence for attenuated levels of IQ during development, which was associated with later development of schizophrenia (Cannon *et al.*, 2002; David *et al.*, 1997; Done *et al.*, 1994; Jones *et al.*, 1994; Jones & Done, 1997; Malmberg *et al.*, 1998). Deficits in verbal and non-verbal abilities, as well as mathematical skills and organizational abilities have also been reported in cohorts of children examined prior to their later manifestation of schizophrenia (Cannon *et al.*, 2002; Davidson *et al.*, 1999; Jones *et al.*, 1994; Jones & Done, 1997).

Cohort studies, given their longitudinal nature, are particularly well suited to characterize developmental neuropsychology milestones and the role of such development on the risk for future psychopathology. For instance, subjects in the British 1946 birth cohort were examined prospectively at 11 time points prior to age 16 (Wadsworth, 1987). Thirty cases of schizophrenia were diagnosed from this birth cohort, with these subjects demonstrating later attainment of developmental milestones during the course of the study (Jones *et al.*, 1994; Jones & Done, 1997). Subjects from the British 1958 National Child Development Study were examined at birth, 7, 11, 16 and 23 years. Twenty-nine subjects from this cohort were later diagnosed with schizophrenia. Manifestation of schizophrenia was associated with pre-schizophrenic reductions in verbal and performance IQ, delayed advancement in mathematics and reading, and lower levels of general knowledge (Done *et al.*, 1994; Jones & Done, 1997). Children and adolescents were examined from ages 7–12 and again in mid-adulthood in the New York High-Risk Project. Verbal memory deficits, gross motor abnormalities and deficits in attention observed early in life predicted 83%, 75% and 58%, respectively, of adult cases of schizophrenia from this sample (Erlenmeyer-Kimling *et al.*, 2000).

Conscript studies may provide more limited information with regard to cognitive risk for psychiatric illness, as individuals who are conscripts are typically males aged 18 or older that are involuntarily enrolled in military service (i.e. "drafted"). Data from conscript studies have likewise found significant relationships between low IQ and manifestation of schizophrenia (David *et al.*, 1997; Davidson *et al.*, 1999; Malmberg *et al.*, 1998). Although these studies similarly offer a longitudinal perspective, changes observed during a younger course of cognitive development may be more informative. For instance, in the 1949–1950 Swedish Conscript Study, males were examined at age 18 and again up to 13 years after the initial assessment (David *et al.*, 1997; Malmberg *et al.*, 1998). In the Israeli Conscript Study, males were first examined at age 16 or 17 and then re-examined between 4 and 10 years after initial assessment (Davidson *et al.*, 1999). Cohort studies, given the younger age period and more repetitive assessments, may therefore be more sensitive in characterizing

developmental abnormalities associated with risk for psychiatric illness. Nevertheless, findings from conscript studies suggest that estimates of less efficient intellectual functioning were associated with a broad category of psychotic disorders. It is important to note, however, that high-risk studies typically have documented more marked abnormalities across a greater number of cognitive domains (as opposed to IQ alone) than cohort and conscript studies, underscoring the influential roles of both genetics and environmental factors on manifestation of psychiatric illness.

In summary, high-risk, cohort and conscript studies of children have indicated that attenuated maturational increases in IQ as well as deficits in several cognitive domains may be associated with later development of the disorder. Diminished psychomotor function, delayed achievement of developmental milestones, and attention deficits are all cognitive domain abnormalities that have been associated with increased risk of developing schizophrenia.

Bipolar and depressive illness

The majority of studies of individuals at risk for bipolar disorder have been conducted during adulthood rather than during childhood or adolescence (Ferrier *et al.*, 2004; Gourovitch *et al.*, 1999; Keri *et al.*, 2001; Zalla *et al.*, 2004). Cognitive changes have not been consistently reported in adult high-risk populations (Kremen *et al.*, 1998), as several adult studies have documented cognitive deficits in psychiatrically healthy relatives of people with schizophrenia but not in relatives of bipolar patients (Clark *et al.*, 2005; Gilvarry *et al.*, 2000; MacQueen *et al.*, 2004; Schubert & McNeil, 2005). However, a number of studies examining neuropsychological functions in adult unaffected relatives of bipolar patients have reported poorer performances (Gourovitch *et al.*, 1999; Sobczak *et al.*, 2003; Zalla *et al.*, 2004). These investigators suggest that deficits in verbal memory, attention and psychomotor function may be associated with risk for bipolar disorder. There is a paucity, however, of child and adolescent genetic high-risk (Decina *et al.*, 1983; Kestenbaum, 1979; McDonough-Ryan *et al.*, 2002; Worland & Hesselbrock, 1980) or cohort studies (Isohanni *et al.*, 1997; Rantakallio, 1969), and there are no conscript studies that are aimed at examining developmental cognitive deficits associated with bipolar illness.

There is evidence for a relative impairment on measures of performance ability (PIQ) versus verbal abilities (VIQ) in high-risk children compared with psychiatrically healthy controls (Decina *et al.*, 1983; Kestenbaum, 1979; McDonough-Ryan *et al.*, 2002). However, not all high-risk studies have found this deficit; Worland & Hesselbrock (1980) reported that VIQ, PIQ and general IQ did not differ between the offspring of manic depressives and non-psychiatric control children. Interestingly, of the 6 offspring of parents with manic depression and the 17 offspring of parents with unipolar depression, the offspring of manic-depressive parents demonstrated lower VIQ than offspring of parents with unipolar depression. There was also evidence from a high-risk sample of delayed achievement of cognitive milestones in individuals from the North Finland 1966 birth cohort, however, no distinction was found between subjects who developed either schizophrenia or bipolar illness (Isohanni *et al.*, 1997; Rantakallio, 1988). There have also been no significant differences in overall IQ found between children of bipolar parents and children of non-psychiatric parents (Grigoroiu-Serbanescu *et al.*, 1989; Todd *et al.*, 1994).

Surprisingly, there also are limited high-risk investigations that specifically focus on the role of neuropsychological deficits associated with major depressive disorder. Often, children of parents with depression are included as comparison subjects in studies examining children of parents with schizophrenia and bipolar disorder. To this end, the majority of studies that have included children with high-risk for depression have failed to find consistent cognitive impairments relative to healthy controls and offspring of parents with other psychopathologies. For instance, two studies failed to find differences in IQ between groups of children at risk for depression as compared with children of psychiatrically healthy parents (Pellegrini *et al.*, 1986; Weissman *et al.*, 1987). Furthermore, in the 1946 National Survey of Health and Development cohort study, although subtle decrements in educational test scores were associated with onset of affective disorder during adulthood, more pervasive cognitive abnormalities were only observed when the onset of affective disorder occurred during childhood (van Os *et al.*, 1997). Similarly, only small differences on educational tests were found in prodromal children, whereas more marked deficits were observed in pre-schizophrenic children from the 1958 National Child Development Study (Done *et al.*, 1994; Jones & Done, 1997).

In summary, there are relatively few developmental cognitive data that suggest risk for acquiring bipolar disorder. Reduced performance IQ compared with verbal IQ has been associated with increased risk for bipolar disorder, as well as delayed achievement of developmental milestones in children prior to the appearance of both schizophrenia and bipolar disorder. Evidence for cognitive impairments associated with risk for development of major depressive disorder tends to be more subtle, and appears limited to small differences on educational tests, as compared with the more pronounced deficits observed for verbal memory, attention, estimated intellectual capacity (IQ) and other complex cognitive deficits observed in children at risk for schizophrenia and bipolar illness.

Conclusion

Neuropsychological evaluation of children and adolescents can reveal important changes in cognitive function that may relate to later onset of psychopathology. There are several limitations that should be considered when identifying these deficits as potential risk factors for the later manifestation of psychiatric illness. First, data collected from children at high risk should be interpreted cautiously, as there can be increased incidence of prodromal symptoms and presence of other psychopathological traits that could contribute to the observed neuropsychological profile. In addition, children at high risk for psychosis may be exposed to a greater number of environmental stressors as a result of being reared in a household with one or two parents with a diagnosable psychiatric condition. Importantly, the age of assessment must be considered when examining the neuropsychological functioning of children, given that multiple and rapid changes in cognitive abilities are occurring during childhood and adolescence.

Cognitive impairments observed in both high-risk and cohort studies do not consistently predict psychiatric illness, as a large number of subjects who have measurable deficits during development (even in the high-risk group) do not go on to develop schizophrenia or other psychiatric illnesses. It is important to consider then, the presence of adaptive or compensatory strategies that may help overcome cognitive vulnerabilities associated with risk for psychiatric illness. In younger children, it may be particularly difficult to identify neuropsychological deficits when cognitive tasks are complex or effortful. For instance, test performance on measures of executive function and attentional capacity would be expected to differ between children and older adolescents, given the significant maturation of the frontal cortex during this age period. Therefore it is essential to differentiate between the normal trajectory of cognitive development, delayed achievement of developmental milestones and cognitive deficits associated with risk for psychiatric illness. In summary, the study of cognitive processes provides empirical research findings that complement diagnostic evaluation. Previous investigations have identified deficits in a number of functional domains including attention, verbal memory and estimated level of intellectual functioning that may predict the onset of psychiatric illness. Future studies should characterize the normative trajectory of neuropsychological function and the neurobiological correlates associated with compensatory mechanisms that would in turn improve early diagnosis and treatment approaches.

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