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The Developmental Course of Executive Functioning in Schizophrenia

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Abstract

Executive dysfunction is a core feature of schizophrenia, but our understanding of the developmental course of this neuropsychological domain in the disease remains largely unexplored. A review of the research evidence points to a number of persistent debates about the course of executive functioning and its relation to illness course. A better understanding of the neurocognitive trajectories of executive functioning in schizophrenia could help identify the risk and modifying that influence the onset, severity and course of disease, and the chance to re-direct or re-shape that course and improve outcomes. To accomplish this requires assessment of the diverse and integrated nature of those abilities, and the changes over time in those abilities requires multiple instruments and techniques in order to improve the research methods and understanding of an important area of impairment in schizophrenia.

Introduction

Executive dysfunction, and neurocognitive deficits more generally, are core features of schizophrenia, and are strongly associated with functional impairments among individuals with this illness (Andreasen, Paradiso et al. 1998; Green, Kern et al. 2004; Heinrichs 2005; Mesholam-Gately, Giuliano et al. 2009). As a consequence of its core role in the illness, research concerning the trajectory of executive function in schizophrenia has the potential to elucidate more clearly the etiology, onset and course of executive deficits and the neurodevelopmental life course of the illness, and therefore, has the potential to both enhance the understanding of the disease and guide efforts to improve treatments and interventions (Green, Kern et al. 2004; Brown, Vinogradov et al. 2009). Yet, there is insufficient research on longitudinal trajectories of executive functioning in schizophrenia, and these few studies have largely focused on global neurocognitive functioning over time, rarely examining executive functioning in depth and across the span of ability areas encompassed by those functions (Welham, Isohanni et al. 2009). The lack of longitudinal,

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population based research significantly hinders, in our view, efforts to identify risk and protective factors that influence onset, severity and course of disease.

In this review, we first briefly discuss the concept of executive functioning, its neurodevelopmental course, the complexity of testing the breadth and depth of this neuropsychological domain, and its central importance to schizophrenia. Next, we review the evidence from case-control, retrospective, and prospective cohort research on global measures of cognition and discuss its application to the course of executive functioning in schizophrenia. Then, we review the research on high risk populations, conversion into psychosis, early onset psychosis and cross-sectional adult studies, because these studies offer the best evidence to date on developmental course as well as clarifying where gaps in our understanding remain. Further, we discuss prospective, population and birth cohort studies which address executive functioning in schizophrenia. We conclude by suggesting a more concerted effort to obtain data through population based, longitudinal studies which prospectively measure the trajectories of executive functioning in schizophrenia cases, and the risk and protective factors that influence onset, severity and course of illness. These efforts may have important implications for the prevention and treatment of schizophrenia.

Executive functioning

Executive functioning reflects a complex set of behaviors and operations that involve processes which are often said to define the human experience: these include the initiation of behaviors and intentionality; abstraction of patterns and concepts and giving meaning to stimuli in relation to prior experiences; appropriately prioritizing external stimuli (separating signal from noise); appropriately assessing the emotional valence in stimuli; holding concepts in working memory and information retrieval; vigilance to tasks; complex problem recognition and resolution, including resolving conceptual conflicts and cognitive dissonance; response inhibition, including changing or switching sets; and strategy development, evaluation, monitoring and implementation, (Lichter and Cummings 2001; Miller and Cummings 2007; Frangou 2010).

Executive dysfunction is a prominent and core feature of schizophrenia. For many years, a convergence of data has pointed to significantly impaired executive functioning in cases with schizophrenia compared to controls, yet the question as to whether those differences reflect a neurodevelopmental deficit, an altered neurodevelopmental trajectory, a neurodegenerative course, or some combination of these, remains uncertain (Fucetola, Seidman et al. 2000; Reichenberg and Harvey 2007; Mesholam-Gately, Giuliano et al. 2009; Reichenberg, Caspi et al. 2010).

Developmental course of executive function

Executive function abilities develop later than other cognitive functions and over a longer period of time, making the need for longitudinal data on the neurodevelopmental trajectories in these functions especially important. Executive function abilities increase with age, well into adulthood, but not uniformly across different areas of executive functioning (Keshavan, Kennedy et al. 2004; Best, Miller et al. 2009; Kalkut, Han et al. 2009). In healthy children, changes in executive ability are observed in both the very young and at school age, with continuing improvement into late adolescence and early adulthood (Miyake, Friedman et al. 2000; Garon, Bryson et al. 2008; Best, Miller et al. 2009; Kalkut, Han et al. 2009).

Neuropsychological testing demonstrates developmental differences between ability areas which are grouped together as executive functions, indicating different developmental rates for working memory, attentional control/processing speed, task monitoring, and cognitive flexibility (including shifting, goal setting, and inhibition) (Anderson, Anderson et al. 2001;

Huizinga, Dolan et al. 2006). Similarly, working memory abilities, including both the maintenance of information and its manipulation, differentially develop (Crone, Wendelken et al. 2006; Conklin, Luciana et al. 2007). This evidence is further supported by brain imaging studies which demonstrate that maturation of the frontal lobes is not completed until about age 20 or later (Gogtay, Giedd et al. 2004; Keshavan, Kennedy et al. 2004). Thus, the developmental trajectory of executive abilities differs from other cognitive ability areas, and should, in our view, be studied across the life-span.

Overall, the evidence suggests a hierarchical pattern of executive function development where more complex abilities develop later and depend on the mastery of less complex abilities in order for the higher functions to operate; this developmental course is likely not linear (Garon, Bryson et al. 2008).

Testing of executive functions

Eisenberg and Berman (2010) observed that despite decades of evidence confirming executive functioning deficits in schizophrenia, much remains unknown about the neurodevelopmental etiology, mechanisms, and course of such deficits. The breadth and complexity of executive functioning, and its crucial role in enabling social and behavioral adaptability, makes understanding impairment in these areas essential to elucidating the ontogeny of the illness, but also makes measurement of these functions time consuming and difficult. Additionally, despite the availability of numerous tests of executive functioning (Lezak 2004; Strauss, Sherman et al. 2006), little consensus has developed as to which test instruments to use or how broad the baseline of testing should be. Further, the very complexity of the behaviors and symptom patterns that constitute executive functions renders the assessment of them complex, and assessment is also made difficult because executive abilities reflect neural networks rather than being localized to specific frontal brain regions (Eisenberg and Berman 2010). Finally, by virtue of the developmental trajectory of executive functioning, assessment protocols must vary by age-expected ability and rely on age-appropriate instruments.

Thorough testing of executive functioning requires batteries of tests which examine each of the parts of the complex processes that constitute these ability areas. One approach to this, although not specifically focused on executive functioning, was suggested by the NIMH sponsored Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus battery that was designed to include repeatable tests which captured broad information on cognition (Kern, Nuechterlein et al. 2008; Nuechterlein, Green et al. 2008). The executive functioning measures in the consensus battery included tests of working memory (letter-number and spatial span tests), vigilance (continuous performance) and reasoning-problem solving (Neuropsychological Assessment Battery mazes test). MATRICS' purpose, in part, was to have a repeatable battery which could be used to assess interventions over a short course clinical trial (Buchanan, Keefe et al. 2010; Harvey, Green et al. 2010). As a result of this short term, global cognitive functioning assessment aim, MATRICS might best be considered a baseline battery, useful for cross-study comparison, but with a breadth and depth too narrow for the assessment of trajectories or able to meaningfully capture any one set of abilities completely.

Another approach has been the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS), which has sought to identify test instruments which successfully assess executive neural networks (Barch, Braver et al. 2009). Although still in development, CNTRICS has proposed the use of executive function tests which assess neural network processes underlying rule identification and set-switching abilities and go/no-go tests (recommended instruments: the Cambridge Neuropsychological Test Automated Battery ID/ED, the switching Stroop test, and a stop-signal task). Similar to

MATRICES, CNTRICS has a translational frame-work, meaning that a great deal of intervention data may be gained from it, but it is not necessarily geared towards understanding the course and consequences of executive deficits in schizophrenia.

Given the developmental trajectory of executive functioning, testing which seeks to reveal deficits in schizophrenia should account for those changes over time. However, few executive functioning tests normed for use in childhood are also normed for use in adulthood, making repeated measure testing more difficult. Hence, test instruments which are age-appropriate and ability specific need to be given over the developmental course. In addition, executive functioning batteries need to assess the range of ability areas within this neuropsychological construct, including working memory, attentional control/processing speed, task monitoring, and cognitive flexibility.

Global cognition across developmental life-course studies

Global measures of cognition

Given the limitations noted above, few studies have been conducted on the developmental course of executive function in schizophrenia. However, the broad nature of cognitive deficits in schizophrenia, reflecting impairments in myriad domains, has led to a great deal of focus on global measures of functioning, typically IQ prior to, and over the course, of schizophrenia (Nestor, Kubicki et al. 2010; Reichenberg, Caspi et al. 2010). This provides us with a conceptual basis from which to extract lessons learned on the methodological issues and challenges needed to implement developmental trajectory research on executive deficits in schizophrenia.

In a meta-analysis, schizophrenia cases and controls differed significantly in IQ whether assessed in early onset or adult onset cases, in cross-sectional studies of adults as well as studies which follow cases after onset of illness. The magnitude of the group mean differences are between 1 and 1.5 standard deviations (Frangou 2010). In addition, a significant amount of research has focused on IQ trajectory and also on IQ assessment obtained premorbidly. Moreover, like executive functioning, IQ is age dependent, and IQ predicts scores on some executive measures, such as cognitive flexibility, but not others, such as set shifting (Kalkut, Han et al. 2009). Unlike executive functioning, however, IQ differences have not been directly associated with the level of functional impairment observed in schizophrenia and low IQ is associated with many types of mental illness (Koenen, Moffitt et al. 2009). Global measures of cognitive functioning, then, may provide information relevant to executive function even while being non-specific (Urfer-Parnas, Lykke Mortensen et al. 2010).

Premorbid IQ and schizophrenia—Woodberry et al (2008), in a meta-analytic review of premorbid IQ in subjects who later developed schizophrenia, found the mean effect size to be moderate (Cohen's $d = .54$), and generally consistent across studies (Woodberry, Giuliano et al. 2008). This finding has two important consequences: first, it provides important information about IQ deficits for those who develop psychosis because it indicates significant differences antedate the onset of disease; and second, as discussed below, it indicates a methodological caution for studies which rely on premorbid estimation of IQ for those with disease.

IQ studies have two key methodological limitations. First, too few of the available studies had longitudinal IQ measures to conduct change over time analyses (meaning, analysis of the interaction between changes in scores and time period of testing) (Woodberry, Giuliano et al. 2008). Second, at least some of the studies which hypothesize a relationship between lower IQ and impaired outcomes in those with schizophrenia have used estimated pre-

morbid functioning to establish baselines which are compared to post-onset assessments (Leeson, Barnes et al. 2009). The estimation of premorbid IQ is quite common in neuropsychology for acquired injuries but quite controversial for developmental diseases (Romero, Lageman et al. 2009). Methods for such estimation, in the absence of premorbid testing, typically use post-morbid reading or language scores, IQ or demographic-based estimates for expected performance (Strauss, Sherman et al. 2006).

Some prospective studies on IQ have used early childhood testing and repeated testing, either across the life-span or in adulthood, to address the limitations discussed above. In a review of premorbid cognitive functioning in birth cohort studies, MacCabe (2008) concluded that almost all of the studies found generalized deficits for those who developed schizophrenia compared to controls, although the observed deficits were not consistent across studies in terms of which cognitive functions were impaired (MacCabe 2008).

Recently reported findings based on longitudinal cognitive ability data from a birth cohort indicated both a deficit in childhood IQ between cases and matched controls and a wider difference in adulthood, with cases performing worse in adulthood than in childhood (Kremen, Vinogradov et al. 2010). This research, resulting from the Developmental Insult and Brain Anomalies in Schizophrenia (DIBS) study, based on subjects drawn from pregnancies in northern California in the 1950's and 1960's, examined receptive vocabulary, as measured by the Peabody Picture Vocabulary Test (PPVT), in childhood and adulthood. Cases had significantly lower PPVT scores at both time points (in childhood and adulthood), but more significantly, the cases had a decline in PPVT score, whereas the controls had an average increase in score (N = 10 cases, 15 controls). The group by time interaction was apparent only across the repeated, longitudinal assessment (Kremen, Vinogradov et al. 2010).

In a prospective cohort study (N = 46 cases, 33 unaffected siblings, 5,127 controls), based on a birth cohort in Philadelphia, Cannon et al (2000) found that at ages 4 and 7, those who later developed schizophrenia scored lower on IQ measures than non-psychiatric controls (Cannon, Bearden et al. 2000). Similarly, Reichenberg et al (2010) recently reported on IQ findings for the Dunedin birth cohort tested at ages 7, 9, 11 and 13 years old with the WISC-R. Schizophrenia was assessed up to age 32 (Reichenberg, Caspi et al. 2010). Using the subtests of the WISC-R, they reported that at each of the four testing periods, scores on each subtest increased as expected for both cases and controls as subjects aged (N = 35 cases, 556 controls). While the authors observed no cognitive deterioration, they did find lower IQ in childhood and adolescence for those who later developed schizophrenia (on the information, similarities, vocabulary and picture completion subtests) and lower slope values (on block design, arithmetic and digit symbol). The differences between slope values (that is the slope generated by repeated measures over time, plotting test score by age) demonstrate that across the four testing periods, the relationship in functioning is not linear but varies by ability area at each time point. For instance, the slope for repeated testing on the information subtest of the WISC showed evidence supporting the lag hypothesis, while the slope for the picture completion subtest supported the deficit hypothesis. In sum, this study found support for both neurocognitive deficits (ability begins and remains different over time) and neurocognitive lags (ability is equal in the beginning but diverges over time) in those who go on to develop schizophrenia, depending on the subtest of the WISC-R. This study provides a benchmark for why trajectory evidence is essential by demonstrating, on repeated measures of IQ, changes and variation across time and functional area between cases and controls in a population based cohort.

Perhaps the most significant findings from the IQ studies lie in the longitudinal data which indicate healthy subjects continue to improve in areas traditionally thought to be stable,

while case subjects decline slightly. These global measures, indicate the critical need for control comparisons and the assessment of changes over time. Nevertheless, because global measures of cognition capture a broad swath of abilities, they do not provide a depth of knowledge about any particular area, such as executive functioning.

High risk, first episode and early onset of psychosis studies

High risk and first episode studies

In the absence of birth cohort or early life trajectory studies on executive functioning in schizophrenia, high risk and first episode studies offer important insights into executive functioning across smaller time windows and in more narrowly specified populations. Populations at high risk for conversion to schizophrenia and cases in their first episode represent samples with a shortened time horizon in which to assess neurocognitive changes that occur during these critical stages of schizophrenia (Cannon, Cadenhead et al. 2008). Research with these populations has provided important insights into the trajectory of cognitive functioning, especially concerning the question of whether conversion to psychosis is marked by cognitive decline.

High risk studies have revealed some short-term longitudinal changes in neurocognitive functioning (Wood, Pantelis et al. 2008) and some longer term changes have been observed in first episode cases (Stirling, White et al. 2003). Wood et al (2008), in a summary of studies examining functioning in those at heightened risk as they converted to psychosis, reported a progressive decline in visuospatial and executive functions in performance on neuropsychological testing and neuroimaging for those who converted compared to those who did not (Wood, Pantelis et al. 2008). Stirling et al (2003) followed a group of first episode cases identified from a catchment area between 10 and 12 years and reported declines in global neurocognition but not on the Wisconsin Card Sort (where the test and re-test scores were not significantly different) (Stirling, White et al. 2003).

First episode subjects—Evidence from first episode cross-sectional studies have also consistently reported deficits in executive functioning in people with schizophrenia (Keefe, Perkins et al. 2006; Mesholam-Gately, Giuliano et al. 2009; Zanelli, Reichenberg et al. 2010). Recently, a meta-analysis of first episode schizophrenia studies indicated that although varying in magnitude, most areas of cognitive functioning showed significantly reduced ability for cases compared to controls at first episode (Mesholam-Gately, Giuliano et al. 2009). The areas of impaired functioning in first episode studies included: executive functioning and working memory, as well as general cognitive ability, verbal memory (immediate and delayed), attention and processing speed, language, visuospatial function, motor ability, social cognition. The global measure of executive functioning used only the Wisconsin Card Sorting Test for comparability reasons, however, other analyses of executive functioning also revealed significant differences. These included components of the Stroop Color-Word Interference test, which measures attention and cognitive flexibility; Trails A and B, which have a processing speed component, but which also capture executive abilities; ; Controlled Oral Word Association (COWA), Category Fluency and Letter Fluency Tests, which measure primarily verbal and language ability but are also sensitive to executive impairments; and the Rey-Osterrieth Complex Figure Test, which measures memory and visuomotor ability, but also planning and strategy (Lezak 2004; Strauss, Sherman et al. 2006). Trails A and B have a processing speed component, but Trails B has been found to capture executive ability in cognitive switching as well as cognitive suppression when Trails B is given after Trails A (Arbuthnott and Frank 2000). Although a number of approaches have been used to isolate the executive elements from the processing speed components of the instrument (e.g., A minus B or A divided by B score), we prefer

regressing the B score on the A score (Kremen, Vinogradov et al. 2010). All of these additional executive measures also showed moderate to large effect sizes.

Compared to healthy controls and those with other psychotic illnesses, people with schizophrenia at first episode appear to perform more poorly on executive testing as demonstrated by a recent population based case control study of first episode patients that used a broad neuropsychological battery (Zanelli, Reichenberg et al. 2010). Although each of the psychosis groups did worse compared to controls, those diagnosed with schizophrenia performed substantially worse on executive functioning, processing speed and working memory (N = 187 cases, 177 controls). This study points out how important the broad, multi-dimensional testing batteries of executive functioning are by revealing uneven differences across domains. Studies which focus narrowly on only a few ability areas may significantly under- or over-estimate strengths and weaknesses within subjects.

High risk subjects—High risk patients who become psychotic are consistently reported to have impairments in prefrontal functioning compared to those who do not develop psychosis; however, specific ability areas are variously reported to remain stable, improve or decline at the point of onset (Hawkins, Keefe et al. 2008; Wood, Pantelis et al. 2008; Frangou 2010). For instance, a recent study which compared treatment seeking at-risk and first episode subjects, and matched controls, on a number of cognitive functions at baseline and six months later, reported worsening course for those who converted. On executive function testing (using the WCST and the Stroop), they found fairly stable within group performance on these repeated measures and significant between group differences across time periods, accounting for practice effects. The subjects who converted from at-risk to first episode of psychosis during the study period performed worse at baseline than those who did not convert on these measures (N = 48 at-risk, 20 first episode, 20 controls). This suggests a worsening course in the transition from prodrome to disease (Jahshan, Heaton et al. 2010). The differing findings from these studies leave open for further investigation whether the observed deficits result from changes caused by the disease itself (deterioration), from co-occurring syndromes, or are part of the developmental course of the disease (lag).

Early onset psychosis—As with first episode studies, early onset psychosis studies offer insights about trajectories because the case subjects are identified early and typically remain in treatment over a long period of time. Longitudinal assessment of early onset schizophrenia provides clear evidence for impaired executive functioning compared to controls, but contradictory evidence as to the course of those deficits. Oie et al (2008), reported deterioration at follow-up ten to thirteen years after first assessment compared to controls who remained stable (N = 19 cases, 30 controls) (Oie and Hugdahl 2008).

Over shorter time horizons, others have reported impaired, but stable functioning, in early onset schizophrenia (Cervellione, Burdick et al. 2007; Frangou, Hadjulis et al. 2008). Examining early onset adolescents with schizophrenia compared to healthy controls over a 13 month period (N = 26 cases, 26 controls), Cervellione et al (2007) reported no significant group by time differences on any measures including the WCST, Trails A and B, COWA and a Continuous Performance measure, all of which capture some aspects of executive functioning (Cervellione, Burdick et al. 2007). Similarly, over a four year follow-up period, using the Tower of London test, Frangou et al (2008) also reported no group by time changes for the early onset group compared to healthy controls (N = 20 cases, 20 controls) (Frangou, Hadjulis et al. 2008). These data suggest that impaired executive functioning in early onset schizophrenia is observed early and remains consistent over short follow-up periods, a finding which differs from Oie et al (2008)'s results. Further research is needed to determine why these different results have been observed.

As mentioned above, the research on global measures of cognition offer insights that can be applied to executive functioning, and that is true as well in evidence from IQ studies of early onset schizophrenia. These IQ studies show a discrepancy of findings concerning the course of functioning. Some have reported on the stability of IQ over time in early onset youth (N = 70 cases) (Gochman, Greenstein et al. 2005). However, Jepsen et al (2010), in a small, 5 year repeated measure study of early onset youth, reported that while case IQ's remained stable, healthy control IQ's increased during the five year study period (N = 10 early onset schizophrenia, 8 early onset psychosis, 35 controls) (Jepsen, Fagerlund et al. 2010). Similar findings were also reported by Kremen et al examining IQ changes in adult onset schizophrenia (Kremen, Vinogradov et al. 2010). This evidence suggests a stable course over time, but a course with significantly different trajectory than healthy controls and perhaps indicates differences between global measures and executive measures in early onset psychosis. Given this evidence from the longitudinal research on global measures, determinations concerning the trajectory for executive and global functioning in early onset schizophrenia remain uncertain.

While the efficiency offered by studying high risk and first episode patients cannot be underestimated, the current paucity of prospective, population based cohorts studied over time means that we continue to lack clear evidence concerning the developmental trajectory of executive functioning in these populations. While high risk, first episode and childhood onset psychosis studies offer important evidence for disruptions in executive functions prior to and early in the illness course, none can provide evidence about the life-span trajectory of those who develop schizophrenia. Further, generalizability from each of these populations, due largely to selection bias issues, limits the inferences which can be made.

Cross-sectional studies in adults

As with the evidence from early onset and first episode cases, cross-sectional studies in adults with schizophrenia have also provided some interesting findings suggestive of important changes across the life-span. Numerous cross-sectional neuroimaging studies have demonstrated volume and activation differences between people with schizophrenia and controls (Berman, Illowsky et al. 1988; Weinberger, Berman et al. 1992; Barch, Carter et al. 2001; Shenton, Dickey et al. 2001; Davatzikos, Shen et al. 2005; Frangou 2010). A recent review of the adult cross-sectional studies of ageing in schizophrenia and neurocognitive function found declines in executive functioning in older cases larger than those found in younger cases compared to controls. This indicates that the age of the subjects at the time of testing, as well as the stage and duration of illness, appear to meaningfully influence the results (Fucetola, Seidman et al. 2000). Using the WCST, Trails A and B, and Luria Motor tests to assess executive functioning and dividing cases and controls into three age groups (N = 87 cases, 94 controls), this study suggested selective declines in executive function that exceed normal age-related changes. In brief, it appears that older cases perform worse on executive tasks than controls, but also worse than younger cases. Nevertheless, cross-sectional studies have inherent limitations for understanding complex functional behaviors: it is difficult to infer temporality, which for executive functioning of treated cases, may result in difficulty discerning effects of illness from effects of treatments. It may also be difficult to determine within group changes, such as those observed in the differing trajectory of global cognitive functioning. Additional limitations include selection biases and attrition which are difficult to assess in cross-sectional studies (Susser and Schwartz 2006; Rothman, Greenland et al. 2008).

Interpretation of the results of cross-sectional studies in schizophrenia can often be confounded by the cognitive effects of medications as well (Bilder, Goldman et al. 2002; Keefe, Bilder et al. 2007; Moncrieff and Leo 2010). As the research on IQ suggests, changes

over time may be meaningful in comparison to the course of healthy development: where case subjects appear to have stable functioning, the performance gap, and the changes in the degree of that gap, are observable only over time and with properly chosen controls.

Research on neurodevelopmental trajectory of executive function in schizophrenia

The most persuasive evidence of a neurodevelopmental trajectory of executive functioning deficits in schizophrenia derives from carefully designed and executed population-based, prospective cohort studies which measured functioning in the cohort prior to onset of disease. Interestingly, a recent review of birth cohort studies and the antecedents of schizophrenia (Welham, Isohanni et al. 2009) found a paucity of neurodevelopmental, trajectory studies reporting on executive functioning, describing only a single population based cohort study.

Of particular note, however, Caspi et al (2003) using the Raven Progressive Matrices as their executive functioning measure, showed significant differential decline between patients and controls (N = 44 cases, 44 controls), with patients declining on functioning more quickly at first episode (Caspi, Reichenberg et al. 2003). Cases were assessed by the Israeli draft board at ages 16 or 17, and again at first episode of psychosis at an average age of 22.5, and showed little change between the time periods. However, they did find between group differences on the Raven, concluding that most of the difference in ability is observable prior to onset of schizophrenia. Still at issue, then, from these studies is the specific time of onset and course of executive dysfunction in those who develop schizophrenia.

The one population based cohort study based on the landmark Dunedin cohort, examined executive functioning at age 13 and in adulthood in those who developed schizophreniform disorder (Cannon, Moffitt et al. 2006). At age 13, those who later developed schizophreniform disorder were observed to perform significantly more poorly than controls on Trails A and B, Grooved Pegboard and Verbal fluency tests. Trails, here analyzed by regressing the score of B on A to control for processing speed, and Grooved Pegboard, a measure of fine motor function which can serve as a proxy for executive functioning, provide some limited evidence in a population based cohort of differences between cases and controls prior to onset of disease (N = 23 schizophreniform, 10 mania, 196 depression/anxiety, 470 controls).

Discussion and future directions

As reviewed by Eisenberg and Berman (2010), the work on executive functioning in schizophrenia supports the need for task specific assessment that evaluates neural networks both inward (from network to genes) and outward (from network to behavior) and such assessment requires ability specific testing across the range of executive functioning. (Eisenberg and Berman 2010). Clearly, numerous questions remain about the role of executive functioning in schizophrenia, the causes and course of the impairments, and whether risk and protective factors can be identified which would permit pre-disease prevention or intervention.

Pursuit of the understanding executive functioning in schizophrenia would be, in our view, significantly enhanced by comprehensive, population based, longitudinal cohort studies which examine specific executive capacities across the wide range of ability areas and across the developmental age span. We come to this conclusion for several reasons: first, the divergence of scores on testing between cases and controls observed at numerous points in

time cannot be said to reflect only deterioration, deficit or lag, but rather, a complex combination that changes with age and severity of illness and which is specific to ability area measured. If, contrary to the evidence, deficits in executive functioning were simply consistent at every time period measured for case subjects from early childhood throughout life, little benefit could be expected from studying trajectories. However, the evidence from repeated measure testing of IQ indicates the benefit of studying trajectories which provide a mechanism to differentiate “stable” patterns within groups from the course of functioning observable between groups across time periods. The data which have been derived from trajectory studies of executive function may have considerable potential to elucidate mechanisms of disease etiology as well as mechanisms of disease course. Careful measurement of executive function ability over time could lead to a more nuanced understanding of how and why this neurocognitive domain operates and relates to disease phenotypes.

Second, a better understanding of the neurocognitive trajectories of executive functioning in schizophrenia could help identify the risk and modifying factors that influence the onset, severity and course of disease; and a better understanding of this trajectory offers the chance to re-direct or re-shape that course and improve outcomes. For instance, some recent findings suggest that in utero exposures relate to executive dysfunction in schizophrenia. Brown et al (2009) examined executive functioning outcomes in cases and matched controls, comparing those exposed in utero to maternal infection (influenza or toxoplasma). They reported significant differences on executive functioning measures (WCST, Trails B regressed on A, Verbal and Figural Fluency tests) between cases and controls, but also for those exposed compared to those who were not. They found that exposed cases performed significantly worse on each component of the WCST, Trails B and the figural fluency test compared to unexposed cases; however, there were few differences on other tests of executive functioning (Brown, Vinogradov et al. 2009).

In our view, longitudinal assessment with diverse sets of executive functioning instruments will improve the research methodology and ultimately our understanding of an area of impairment in schizophrenia that has long been recognized but is not completely understood. Research on developmental trajectories offers the potential to elucidate not only the evolution of this neurocognitive domain but also identify risk and protective factors which co-occur with or modify the course of schizophrenia.

Research Highlights

A better understanding of the neurocognitive trajectories of executive functioning in schizophrenia could help identify the risk and modifying that influence the onset, severity and course of disease, and the chance to re-direct or re-shape that course and improve outcomes.

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