

# Neurodevelopmental origin of cognitive impairment in schizophrenia

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Cognitive impairment is a common feature of schizophrenia; however, its origin remains controversial. Neurodevelopmental abnormalities clearly play a role in pre-morbid cognitive dysfunction in schizophrenia, yet many authors believe that schizophrenia is characterized by illness-related cognitive decline before and after onset of the psychosis that can be the result of neurodegenerative changes. The main reasons behinds such arguments include, first, the evidence showing that effect sizes of the cognitive deficits in subjects who develop adult schizophrenia gradually increase in the first two decades of life and, second, the fact that there is functional decline in many patients with schizophrenia over the years. In this Editorial, I argue that current evidence suggests that illness-related cognitive impairment is neurodevelopmental in origin and characterized by slower gain (developmental lag) but not cognitive decline continuing throughout the first two decades of life. I introduce a model suggesting that neurodevelopmental abnormality can in fact explain the course of cognitive dysfunction and variations in the trajectory of functional decline throughout the life in individuals with schizophrenia. In this model, the severity of underlying neurodevelopmental abnormality determines the age that cognitive deficits first become apparent and contributes to the cognitive reserve of the individual. Interaction of neurodevelopmental abnormality with clinical symptoms, especially negative symptoms and aging, vascular changes, psychological and iatrogenic factors contributes to the heterogeneity of the functional trajectory observed in this disorder.

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## Introduction

Schizophrenia is associated with substantial cognitive dysfunction (Gold & Harvey, 1993; Heinrichs & Zakzanis, 1998; Bora *et al.* 2010). Neurocognitive deficits are persistent characteristics of schizophrenia throughout the illness and are predictors of level of functioning (Green, 1996; Bora *et al.* 2010; Kahn & Keefe, 2013). Several studies have provided evidence indicating that cognitive and intellectual deficits are evident early in neurodevelopment, well before the onset of psychosis (Fuller *et al.* 2002; Reichenberg *et al.* 2010; Kahn & Keefe, 2013). Evidence also suggests that cognitive deficits are stable at follow-up in both chronic and early years of the illness even though performance of schizophrenia patients might improve less than healthy controls at follow-up (Szöke *et al.* 2008; Bora & Murray, 2013; Hedman *et al.* 2013). Neurodevelopmental theories argue that schizophrenia is related to genetic and non-genetic risk factors leading to abnormal development of the brain that can be associated with problems in acquiring cognitive abilities throughout development (Weinberger, 1986; Murray & Lewis, 1987), and

that neurodevelopmental abnormality can be considered as the source of most of the cognitive deficits observed in adults with schizophrenia. However, one of the challenges of the neurodevelopmental model is that both timing of the emergence and level of severity of functional deficits are variable and these deficits are not always apparent before the illness. Although some patients with schizophrenia have a clear history of pre-morbid intellectual difficulties from childhood and have low functioning throughout their life, many others experience functional decline during prodrome or early years of the illness after seemingly normal early development (Bilder *et al.* 1992; Kelley *et al.* 1992; Doody *et al.* 1998; Addington & Addington, 2005; Morgan *et al.* 2008; Foussias & Remington, 2010; Strauss *et al.* 2012). It is also evident that some chronic and older-age patients with schizophrenia have very significant functional deficits compared to their level of functioning in earlier years of the illness (Davidson *et al.* 1995; Harvey & Davidson, 2002). Some of these patients are not able to live independently and some have functional deficits comparable to dementia. These observations suggest that neurodegenerative or neuroprogressive changes lead to the onset of illness, and cognitive and functional decline in schizophrenia (Feinberg, 1982–1983; Wyatt, 1991; Keshavan *et al.* 1994; Lieberman, 1999; Perkins *et al.* 2005).

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Another key issue to address is the nature of the relationship between pre-morbid cognitive deficits and schizophrenia. It could be argued that these cognitive deficits are specific neurodevelopmental substrates and early signs of schizophrenia (Kahn & Keefe, 2013), or they might be markers of a range of developmental abnormalities that increase the risk of developing schizophrenia.

In this Editorial, I review the developmental course of cognitive impairment in schizophrenia and then explore the relationship between neurodevelopmental cognitive abnormality and functional decline later in life. The evidence regarding the course of the cognitive abilities in non-neurodevelopmental (i.e. neurodegenerative such as Huntington disorder, metachromatic leukodystrophy frontotemporal dementia) conditions that can sometimes initially mimic schizophrenia are not reviewed here.

### **Developmental course of cognitive impairment in schizophrenia**

Earlier accounts of neurodevelopmental theory regarded schizophrenia as the outcome of a developmental fixed 'lesion' occurring most commonly in the second trimester of intrauterine life (Weinberger, 1986). Cognitive deficits were considered a consequence of this 'static encephalopathy'. However, neurodevelopment is an extended process. Some aspects of normal cortical development, such as proliferation and migration, occur mostly during the prenatal life; other developmental processes (arborization and myelination) continue at least through the first two post-natal decades (Catts *et al.* 2013). In accordance with neurodevelopment, some basic cognitive functions, mostly crystallized skills, typically develop during the early years of postnatal life, and the development of complex executive functions and other fluid skills are the outcome of protracted development well into early adulthood (Levin *et al.* 1991; Anderson *et al.* 2001; Brocki & Bohlin, 2004). Cognitive dysfunction in schizophrenia can be better conceptualized as the outcome of aberrant neurodevelopment continuing throughout the first two to three decades of life.

#### ***Levels of severity of neurodevelopmental abnormality and age when cognitive deficits become apparent***

One of the key questions for the field of neuropsychology of schizophrenia has been: 'When precisely do cognitive problems begin in people with schizophrenia?' In reality, the time when cognitive deficits become apparent is variable across patients. The level of severity of underlying neurodevelopmental

impairment influences both the degree of cognitive deficits and the time range when cognitive dysfunction can be detected with traditional neuropsychological batteries. In individuals who have more severe underlying neurodevelopmental abnormality, cognitive dysfunction would be apparent from early childhood. Several research findings support the existence of such early cognitive deficits in some people with schizophrenia (Doody *et al.* 1998; Morgan *et al.* 2008; Reichenberg *et al.* 2010; Khandaker *et al.* 2011; Dickson *et al.* 2012; Schulz *et al.* 2014). Pre-morbid intelligence quotient (IQ) deficits and learning difficulties in childhood and adolescence precede adult schizophrenia. Current evidence suggests that individuals who develop adult schizophrenia exhibit an IQ deficit (approximately 0.5 standard deviation) in their childhood (Khandaker *et al.* 2011; Dickson *et al.* 2012). Childhood-onset intellectual disabilities are over-represented in schizophrenia samples compared to controls and psychosis is more prevalent in people with mental retardation than in the general population (Doody *et al.* 1998; Morgan *et al.* 2008).

However, the effect size of pre-morbid abnormalities in schizophrenia is fairly small (for  $d=0.5$ , 67% overlap with controls), suggesting that cognitive deficits are not detected early in most patients. More often, neurodevelopmental abnormalities in schizophrenia would be more moderate and cognitive dysfunction would manifest as a failure to acquire more advanced cognitive functions in the second decade following seemingly normal neurodevelopment in early childhood. These individuals would only struggle as the demands of academic and social environments get complicated in later years. It is important to note that a subgroup of schizophrenia patients have no cognitive impairment even in adulthood (MacCabe *et al.* 2012), suggesting that neurodevelopmental abnormality is much milder in other patients.

#### ***Course of neurodevelopmental cognitive deficits***

The course of development of cognitive abilities (growth curves) in the first two to three decades of life can supply important information for the neurodegenerative/neurodevelopmental debate in schizophrenia (Testa & Pantelis, 2009). If schizophrenia is a neurodevelopmental condition, problems in acquisition of cognitive abilities (developmental lag or arrest) during development are expected. By contrast, neurodegeneration would be associated with pre-morbid or post-onset loss of acquired skills at follow-up. Recent evidence provides important insights into the developmental course of these pre-morbid cognitive deficits after the first few years of the life. For example, the Dunedin study of a longitudinal cohort

of 1037 males and females clearly demonstrated that deficits in several cognitive domains, including verbal and visual acquisition and conceptualization, were already evident at age 7 years and remained stable at age 13 years (Reichenberg *et al.* 2010). However, evidence suggests that individuals who develop adult schizophrenia have slower development (developmental lag) in other cognitive abilities during puberty and adolescence. In the Dunedin study, children between the ages of 7 and 13 years exhibited developmental lag on tests indexing visuospatial problem solving, processing speed and attention. Importantly, early verbal deficits significantly predicted later developmental lag in working memory and processing speed. Findings of a recent study reporting cognitive changes between ages 13 and 28 years in the Dunedin sample suggest that a similar pattern of slower cognitive development after age 13 continues in individuals who developed schizophrenia (Meier *et al.* 2014). There is also some evidence for association between relative IQ decline (developmental lag) between ages 4 and 7 and adult-onset schizophrenia (Kremen *et al.* 1998). A recent study (MacCabe *et al.* 2013) showed that the relative decline in several cognitive domains (especially verbal ability) between ages 13 and 18 was predictive of psychotic disorder in adulthood (mean age of first hospitalization). In all of these studies, 'relative decline' was indicating a problem in acquisition of cognitive abilities (developmental lag or arrest) rather than real decline in raw scores, as in both studies tests at follow-up were age corrected or included more challenging items (Bora, 2014). These findings do not support the idea of pre-morbid cognitive decline in schizophrenia. However, other authors, based on cross-sectional comparison of cognitive studies in ultra-high risk (UHR) to psychosis, first-episode psychosis (FEP) and schizophrenia, have suggested that cognitive decline might occur later, around the time psychotic symptoms develop. Nevertheless, follow-up studies in UHR and FEP have clearly rejected this suggestion (Bora & Murray, 2013).

The evidence reviewed above suggests that cognitive deficits are evident in young children who develop adult schizophrenia; these patients gradually fall behind even further, compared to normal controls, in some cognitive abilities throughout development. A similar pattern of developmental lag in the background of early cognitive dysfunction has been reported in other conditions characterized by low brain reserve, such as Fragile X syndrome, autism and velocardiofacial syndrome. For example, in Fragile X syndrome, studies found slower gain in cognitive development in adolescence leading to a relative decline in standardized scores such as IQ; this abnormal neurodevelopment is related to aberrant frontal lobe maturation in adolescents (Hall *et al.* 2008;

Bray *et al.* 2011). It is not surprising that aberrant early neurodevelopment has a negative impact on later phases of cognitive maturation, as more advanced cognitive skills depend on the integrity of basic cognitive processes and the negative impact of many genetic abnormalities do not need to be restricted to early childhood as they do play a role in neurodevelopment throughout life.

### *Neurodevelopmental cognitive impairment and psychosis*

The findings reviewed above suggest that, with regard to the nature of the relationship between pre-morbid cognitive deficits and schizophrenia, neurodevelopmental cognitive abnormalities are not simple co-morbidities to schizophrenia in the large majority of the cases given the high prevalence of such problems in schizophrenia compared to healthy controls. Cognitive dysfunction is robustly associated with, but not necessary for, developing psychosis. The level of neurodevelopmental cognitive deficits is largely variable and a sizeable minority of schizophrenia patients have preserved cognitive abilities (MacCabe *et al.* 2012). It is also important to note that only a subset of individuals who have such neurodevelopmental abnormalities would develop psychosis. Clearly, most of these findings are non-specific and are not necessarily indicators for the development of psychotic symptoms. These cognitive deficits should be considered as manifestations of a heterogeneous group of developmental abnormalities with different, but mostly yet unknown, genetic and other neurodevelopmental etiological factors and serve as a risk factor to the development of psychosis. However, most people with such abnormalities would never develop psychotic symptoms.

This does not mean that psychosis has no common neurobiological substrate or associated specific subtle cognitive dysfunction. It is likely that different developmental syndromes increase the risk of psychosis by their converging effect on a much more limited neural network. However, only a small fraction of findings observed in patients should be related to the schizophrenic syndrome. Nevertheless, we do not know what these specific deficits are and how to detect them. It is very unlikely that traditional neuropsychological test batteries will be able to reliably detect such subtle but specific psychosis-related deficits.

### **Neurodevelopmental cognitive abnormality and functional decline later in life**

Neurodevelopmental cognitive deficits contribute to pre-morbid functioning levels and these functional difficulties become more pronounced as academic

and social demands increase during adolescence and early adulthood, overlapping with years of prodrome and the early post-onset period. However, not all functional decline should be considered as an outcome of cognitive dysfunction in schizophrenia. The frequency and intensity of episodes, residual symptoms and social defeat are among the other factors that contribute to functional decline in schizophrenia. I also argue that interaction between neurodevelopmental cognitive dysfunction and other factors, including negative symptoms, aging, antipsychotics and medical co-morbidities, are the main factors for post-onset functional decline in schizophrenia.

#### *Neurodevelopment, cognitive reserve and functional decline*

Neurodevelopmental abnormality and cognitive reserve are related, and are important concepts in understanding the functional decline observed later in life (Satz *et al.* 1993; Stern, 2002, 2012). Schizophrenia-related neurodevelopmental abnormalities have a profound negative impact on brain and cognitive reserve. Brain reserve is the brain's resilience, its ability to cope with increasing damage while still functioning adequately, and it depends on the structural integrity of the neural system (hardware) and is mostly determined by genetic and neurodevelopmental factors. Therefore, the severity of neurodevelopmental abnormality determines the loss of brain reserve in schizophrenia. Unlike brain reserve, cognitive reserve in schizophrenia is not determined only by genetic/early neurodevelopmental abnormality. Cognitive reserve is more about functional efficiency; it is the ability to optimize performance through differential recruitment of brain networks and/or alternative cognitive strategies. Genetic and early neurodevelopmental factors are still the most important, but not the only, determinant of cognitive reserve. Education, lifestyle and mental and physical activities modify the cognitive reserve through the neuroplasticity of our neural system throughout life (Fratiglioni *et al.* 2004; Roe *et al.* 2007; Nithianantharajah & Hannan, 2009). In patients with schizophrenia, brain reserve and cognitive reserve are low as a consequence abnormal neurodevelopment. However, cognitive reserve of schizophrenia patients is also modified by other factors, including family environment and socio-economical status, that can compensate for subtle neurodevelopmental abnormalities in some patients, such as those who have no apparent cognitive deficits. Some authors have suggested that cognitive reserve plays a role in differences in functional, clinical and cognitive outcomes of schizophrenia patients (Barnett *et al.* 2006; Rund, 2009; Leeson *et al.* 2011).

Neurodevelopmental abnormality (and low cognitive reserve) can influence the outcome of follow-up studies in several ways. First, lower baseline cognitive reserve would lead to less improvement in schizophrenia patients than in healthy controls, given that better baseline cognitive function is related to better practice effects (Rappoport *et al.* 1997). More importantly, neurodevelopmental abnormality is likely to be associated with temporary or permanent functional decline in response to a large number of events later in life. Dementia research clearly shows that people with high cognitive reserve are resilient to the effects of aging (Stern, 2012) and it can be expected that aging and other factors can lead to non-schizophrenia-related cognitive decline or ineffective cognitive improvement in some patients with schizophrenia later in life. Such changes can have devastating effects on independent living skills in schizophrenia patients, who already have a severe pre-morbid cognitive dysfunction. However, the effect of these changes on functioning levels of patients with subtle neurodevelopmental abnormality might be more striking, given that these patients might have normal pre-morbid functioning.

#### *Negative symptoms, cognitive reserve and functional decline before or after onset of psychosis in schizophrenia*

A recent meta-analysis found that cognitive dysfunction in schizophrenia was stable in follow-up studies of prodrome and first-episode schizophrenia samples (Bora & Murray, 2013). However, a subgroup of patients with schizophrenia has clear functional decline during a time period starting from a few years before onset of psychosis to a few years following the first episode (Kelley *et al.* 1992; Addington & Addington, 2005; Foussias & Remington, 2010; Strauss *et al.* 2012). This functional decline is associated with negative symptoms (Addington & Addington, 1993; Brill *et al.* 2009) and its time-frame overlaps with the development of negative symptoms as these symptoms are commonly observed a few years before the first psychotic experiences, in prodrome and after the first episode of psychosis (Dominguez *et al.* 2010; Foussias & Remington, 2010; Cullen *et al.* 2011). Patients with negative symptoms have significantly lower levels of pre-morbid functioning during late adolescence and greater pre-morbid deterioration between childhood and adolescence (Kelley *et al.* 1992). Deficit schizophrenia that presents with persistent negative symptoms is also characterized by significant functional impairment (Strauss *et al.* 2012).

Interaction of neurodevelopmental cognitive impairment and neuroplastic changes leading to negative symptoms in schizophrenia can influence the level of

functional decline. Although there is no obvious decline in raw scores of neuropsychological tests in longitudinal studies, negative symptoms probably impair learning and practice effects in schizophrenia. Therefore, it is expected that patients with negative symptoms would improve less in cognitive tasks at follow-up. In accordance with this view, our recent meta-analysis showed that persistence of negative symptoms was related to lack of cognitive improvement at follow-up (Bora & Murray, 2013). Importantly, negative symptoms would be expected to influence learning abilities of patients with low cognitive reserve more than others. In addition, low cognitive reserve is more common in patients with negative symptoms (Harvey *et al.* 2006; Cohen *et al.* 2007; Konstantakopoulos *et al.* 2011). The emergence of negative symptoms and their interaction with neurodevelopmental abnormality can explain a significant part of the functional decline observed before and after the first psychotic episode, even in patients who seemed to have had no previous functional deficits.

#### *Neurodevelopment and medical co-morbidities, substance use and antipsychotics*

Although pre-morbid neurodevelopmental abnormalities comprise the main factor leading to cognitive dysfunction in schizophrenia, the interaction of neurodevelopmental factors with numerous other factors also contributes to cognitive deficits in patients with established schizophrenia. Antipsychotics, including the second-generation antipsychotics (SGAs), clearly play a role in these cognitive deficits. Although antipsychotics can have both positive and negative effects (direct and/or indirect) on cognition in actively psychotic patients, their cognitive side-effects become clear once patients are stabilized. In recent studies, both dose reduction and guided discontinuation of SGAs were shown to lead to cognitive improvement in stable patients (Faber *et al.* 2012; Takeuchi *et al.* 2013). Several factors associated with cognitive dysfunction in healthy subjects, such as metabolic syndrome, chronic substance use and stress (Johnsen & Asbjørnsen, 2008; Panza *et al.* 2010; Stavro *et al.* 2013), are more common in schizophrenia and there is no doubt that they can contribute to cognitive impairment in schizophrenia. For example, some studies have shown that schizophrenia patients who have co-morbid metabolic syndrome, diabetes mellitus, hypertension, obesity, post-traumatic stress disorder (PTSD) and alcohol use disorder have more cognitive impairment than other patients without such co-morbidities (Goodman *et al.* 2007; Dickinson *et al.* 2008; Fan *et al.* 2008; Manning *et al.* 2009; Friedman *et al.* 2010; Lindenmayer *et al.* 2012; Takayanagi *et al.*

2012; Guo *et al.* 2013). However, it is important to note that negative cognitive effects of some factors, such as cannabis use, can be difficult to demonstrate in schizophrenia because these factors can decrease the threshold and age of onset for FEP in people with less severe underlying neurobiological abnormality, leading to increased frequency of patients with better pre-morbid cognitive skills (Yücel *et al.* 2012).

All of these vascular risk and substance use factors have been associated with white matter disruption in healthy controls and schizophrenia patients (Segura *et al.* 2009; Brickman *et al.* 2011; Hsu *et al.* 2012; Eloffson *et al.* 2013), and stress has been associated with hippocampal atrophy (Karl *et al.* 2006). Such abnormalities would add to schizophrenia-related cerebral atrophy and white matter disruptions (Bora *et al.* 2011) and can explain the more pronounced cognitive dysfunction observed in schizophrenia patients with these co-morbidities. These structural changes can interact with neurodevelopmental abnormalities in the deterioration of functional and cognitive deficits; according to cognitive reserve theory, it can be argued that people with neurodevelopmental abnormalities are more susceptible to effects of these factors. Low cognitive reserve would influence the level of resilience of patients with schizophrenia and would lead to more severe permanent (i.e. vascular changes) and temporary (i.e. antipsychotics) cognitive impairment and functional decline.

#### *Neurodevelopment and the aging brain in schizophrenia*

Neurodevelopmental abnormalities can also interact with the aging process. People with neurodevelopmental syndromes do not age well. Dementia is up to five times more common in people with intellectual disabilities (Cooper, 1997; Strydom *et al.* 2013). Lower childhood cognitive ability is a risk factor for dementia in old age (McGurn *et al.* 2008). People with milder neurodevelopmental abnormalities are also vulnerable to the effects of aging. In a recent study, it was shown that asymptomatic carriers of Fragile X syndrome have a higher risk for development of late-onset dementia (Tassone *et al.* 2012). Therefore, it should be expected that the interaction of aging with manifest and latent neurodevelopmental abnormalities would lead to further loss of functioning in some patients with schizophrenia.

Whether schizophrenia patients have accelerated decline by age is the subject of controversy. Some authors support accelerated age-related decline in schizophrenia but others do not (Friedman *et al.* 1999; Harvey, 2001; Rajji & Mulsant, 2008; Jeste *et al.* 2011; Irani *et al.* 2011; Shah *et al.* 2012). Importantly,

the meta-analysis of Irani *et al.* (2011) found that cognition did not change significantly at follow-up in old-aged patients with schizophrenia. However, it is important to note that, in old-aged patients, there was no cognitive improvement; in fact there was a marginal (and non-significant) change in the negative direction ( $d=-0.1$ ), rather than a positive change as found in meta-analyses of follow-up studies in younger patients. In another study including 201 older-aged schizophrenia patients, there was evidence of more rapid cognitive decline in a subgroup of patients in comparison to controls and other patients (Thompson *et al.* 2013). These patients had severe negative symptoms and were more likely to be living in a board-and-care facility. Lifetime poor functioning has also been associated with such changes (Friedman *et al.* 1999). These findings suggest that, although most people with schizophrenia and healthy subjects have a similar trajectory of age-related cognitive changes, there might be a subgroup of older-aged schizophrenia patients with low cognitive reserve and severe negative symptoms whose cognitive and functional deficits worsen more significantly.

### Conclusions

Most neurocognitive deficits in schizophrenia are neurodevelopmental in origin and are explained by continuing problems in acquisition during development (developmental lag and arrest) rather than loss of acquired skills. These cognitive deficits are reflections of various developmental abnormalities that also increase the risk of developing psychosis. Neurobiological heterogeneity of such developmental conditions is likely to be related to the severity of cognitive abnormalities and determines the first age that cognitive deficits become apparent. In individuals who have severe cognitive dysfunction apparent from early childhood, more severe neurodevelopmental abnormalities, such as problems in migration, gyrification and activity-independent, hard-wired connectivity, are more likely to be found. In most individuals with schizophrenia who have less pronounced cognitive deficits, the progressive aspects of later neurodevelopment, including activity-dependent fine-tuning of synaptic connectivity (myelination, synaptic remodeling/dendritic arborization) in high-level association cortices, are likely to be abnormal. Such abnormalities would also lead to a further developmental lag during adolescence in individuals who already have severe problems in earlier phases of neurodevelopment.

In some patients, the interaction of neurodevelopmental abnormality and low cognitive reserve with neuroplastic changes related to the development of

negative symptoms, vascular risk factors, antipsychotic use and aging leads to further loss of functioning over the years. Studies investigating the relationship between developmental trajectories of cognitive skills, its brain imaging correlates and psychosis-risk genes are important to fully understand cognitive impairment in schizophrenia.

### Declaration of Interest

None.

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