BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

A family affair: brain abnormalities in siblings of patients with schizophrenia

Marcel E. Moran,[1] Hilleke Hulshoff Pol[2] and Nitin Gogtay[1]

1 Child Psychiatry Branch, National Institute of Mental Health, NIH, Bethesda Maryland, USA
2 Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Centre Utrecht, The Netherlands

Correspondence to: M. E. Moran,
National Institute of Mental Health,
Child Psychiatry Branch Building 10,
10 Center Drive,
RM 3N202,
Bethesda Maryland 20814, USA
E-mail: marcel.moran@nih.gov

Schizophrenia is a severe mental disorder that has a strong genetic basis. Converging evidence suggests that schizophrenia is a progressive neurodevelopmental disorder, with earlier onset cases resulting in more profound brain abnormalities. Siblings of patients with schizophrenia provide an invaluable resource for differentiating between trait and state markers, thus highlighting possible endophenotypes for ongoing research. However, findings from sibling studies have not been systematically put together in a coherent story across the broader age span. We review here the cortical grey matter abnormalities in siblings of patients with schizophrenia from childhood to adulthood, by reviewing sibling studies from both childhood-onset schizophrenia, and the more common adult-onset schizophrenia. When reviewed together, studies suggest that siblings of patients with schizophrenia display significant brain abnormalities that highlight both similarities and differences between the adult and childhood populations, with shared developmental risk patterns, and segregating trajectories. Based on current research it appears that the cortical grey matter abnormalities in siblings are likely to be an age-dependent endophenotype, which normalize by the typical age of onset of schizophrenia unless there has been more genetic or symptom burdening. With increased genetic burdening (e.g. discordant twins of patients) the grey matter abnormalities in (twin) siblings are progressive in adulthood. This synthesis of the literature clarifies the importance of brain plasticity in the pathophysiology of the illness, indicating that probands may lack protective factors critical for healthy development.

Keywords: schizophrenia; imaging; grey matter; endophenotype

Introduction

Schizophrenia is a debilitating mental illness that is characterized by widespread brain abnormalities. Neuroimaging studies have demonstrated that both cortical and deeper brain structures, including the white matter, in patients with schizophrenia differ significantly from healthy control subjects, and that those abnormalities change over the lifespan, with the deficits becoming more pronounced with longer illness duration (Wright *et al.*, 1999;

Pantelis *et al.*, 2005; DeLisi, 2008; Ellison-Wright *et al.*, 2008; Gogtay, 2008; Gogtay and Rapoport, 2008; Hulshoff Pol and Kahn, 2008; Fornito *et al.*, 2009; Olabi *et al.*, 2011). The most consistent anatomical abnormalities are reduction in cortical grey matter volume, particularly in prefrontal and temporal cortices, reduced volumes of medial temporal lobe structures, and increased lateral ventricular volume (Wright *et al.*, 2000; Shenton *et al.*, 2001, 2010). In the patients with typical adult-onset schizophrenia, the extent of annualized progressive brain tissue loss (-0.5%)

is twice that of healthy control subjects (-0.2%) (Hulshoff Pol and Kahn, 2008) and these deficits are more pronounced in the severe phenotype of childhood-onset cases (Rapoport *et al.*, 2005; Gogtay and Rapoport, 2008; Gogtay *et al.*, 2008).

The molecular mechanism of anatomical brain abnormalities in schizophrenia remains unclear, and an important question is whether these abnormalities are related to the illness state itself, or a more tied to genetic risk, as an endophenotype. Characterizing endophenotypes, a new focus in psychiatry and other medical disciplines (Gottesman and Gould, 2003), is a compelling venture because they may represent less complex disease antecedents that are riper for study than the illness syndrome itself. By definition, they must be associated with illness in the population, be heritable, and be primarily state independent (not more common in the disease than in high-risk relatives) (Gould and Gottesman, 2006). Brain structures present as a good endophenotype, since many are highly heritable (Peper *et al.*, 2007), and influenced by genetic variants that are beginning to emerge based on large-scale studies (Stein *et al.*, 2012). In the realm of complex neuropsychiatric disorders such as schizophrenia, endophenotypes may simplify and prioritize biological precursors for study that are highly genetic, and not directly tied to the illness itself. Non-psychotic siblings and discordant twins provide ideal populations to study this question, given that siblings and fraternal twins share on average 50% of their segregating genes with the proband, while identical twins share virtually 100% of their genes, but not the clinical phenotype (psychosis). Some criticisms have been raised about endophenotypic studies, particularly that an endophenotype may be able to satisfy all of its criteria while still being unrelated to the disease pathway (Walters and Owen, 2007), and that there may be a bi-directional relationship between the illness state and the putative endophenotype (Kendler and Neale, 2010). These potential flaws of endophenotypes must be kept in mind any time this type of research is undertaken.

Sibling studies in schizophrenia, both in adult and childhood patient populations, have attempted to address this question. A recent meta-analysis of family studies in schizophrenia showed that first-degree relatives had lower hippocampal, total grey matter, and ventricular volumes, compared with healthy volunteers (Boos *et al.*, 2007). Although these findings in schizophrenia siblings show that—at least in part—the structural brain changes in schizophrenia are familial, the extent to which these changes change over the course of development, and whether the young and adult siblings overlap in their findings or diverge is important to know. This requires a longitudinal setup to study developmental brain changes in family members of patients. Findings from these studies may tell us more about the resilience and risks that accompany developmental brain changes.

The goal of this review is to assess and summarize the structural brain imaging findings of developmental changes in siblings and twin pairs discordant for schizophrenia. It will incorporate studies on siblings of patients with childhood-onset schizophrenia, in which the siblings tend to be children and adolescents and hence provide a window into early brain development, and the more common adult-onset schizophrenia, in which the siblings are adults and thus of older average age. We seek to synthesize these results from a comprehensive neurodevelopmental perspective, of sibling brain development across a wide age range from early childhood to mid-adult age, which encompasses a large window around the typical age of onset for schizophrenia. Not only does this body of literature demonstrate the strong genetic basis of schizophrenia, but it may also lead to the identification of meaningful biological trait markers and endophenotypes for further hypothesis generation.

Siblings of patients with childhood-onset schizophrenia

Childhood-onset schizophrenia is a rare and severe form of the disorder defined by the onset of psychosis before the age of 13, which is neurobiologically continuous with the adult-onset illness (Rapoport and Gogtay, 2011). Childhood-onset schizophrenia shows profound and progressive cortical grey matter loss that spreads in a dynamic wave in a parieto-frontal and parieto-temporal direction during adolescence, finally localizing to prefrontal and temporal cortices as children become young adults (Gogtay *et al.*, 2008; Greenstein *et al.*, 2008). Independent research that highlights the positive association between cortical thickness and cognitive and overall functioning supplements these findings (Shaw *et al.*, 2006; Greenstein *et al.*, 2008), and strengthens the supposition that grey matter deficits in childhood-onset schizophrenia contribute to the illness and functional impairment. As part of ongoing investigations at the NIMH, full siblings of patients with childhood-onset schizophrenia are prospectively followed and re-scanned every 2 years.

The initial cross-sectional, volumetric analyses of structural abnormalities in healthy siblings of patients with childhood-onset schizophrenia showed that, compared with healthy control subjects, childhood-onset schizophrenia siblings had smaller total cerebellar volume and total, frontal and parietal grey matter volumes, particularly in younger ages which also suggested that sibling deficits may mirror the grey matter loss pattern that has been documented in childhood-onset schizophrenia probands (Gogtay *et al.*, 2003). This evidence provided a starting point; given that there is similarity between the probands and siblings, prospective inspection might show evidence that the neurodevelopmental trajectory itself could also be a trait marker.

These observations have since been extended in large prospectively acquired childhood-onset schizophrenia sibling samples. In the first longitudinal analyses from ages 8 to 28, healthy childhood-onset schizophrenia siblings showed an interesting pattern of cortical grey matter thickness development (Gogtay *et al.*, 2007). Non-psychotic siblings ($n = 52$, 113 scans) showed grey matter deficits in parietal, prefrontal and temporal regions compared with control subjects ($n = 52$, 108 scans) in early ages, but the deficits normalized by late adolescence (age 20), the typical age of onset of schizophrenia (Fig. 1). This intriguing finding was subsequently replicated in an independent, non-overlapping sample of non-psychotic childhood-onset schizophrenia siblings ($n = 43$, 68 scans) and healthy control subjects ($n = 86$, 136 scans) from ages 5 to 26 years, where the early prefrontal and temporal deficits again showed normalization by the age of 20 (Fig. 1) (Mattai *et al.*, 2011b). A 3D dynamic sequence of deficit
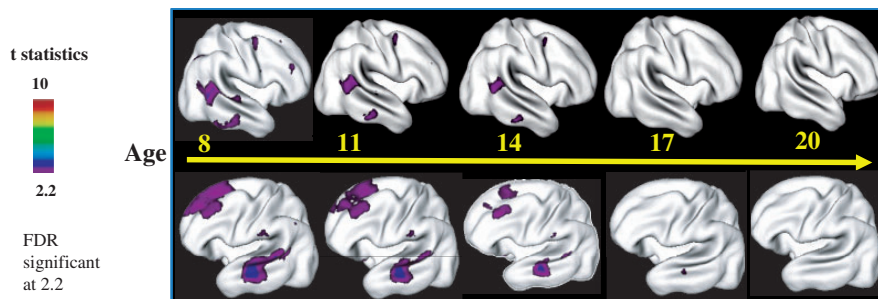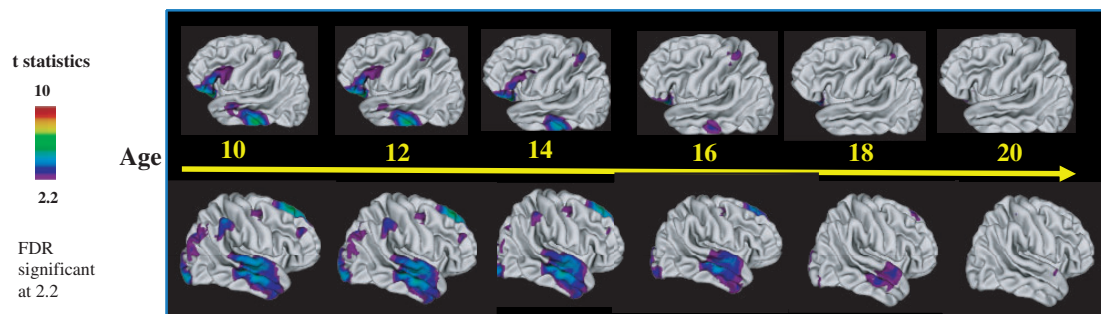
**Figure 1** Grey matter loss in healthy childhood-onset schizophrenia siblings.

normalization with age from a combined sample (childhood-onset schizophrenia: $n = 92$, 193 scans, siblings: $n = 91$, 185 scans, ages 8–24 years) is available online at https://www.dropbox.com/s/bhwksqoolv3y7q8/Sibling.mov.zip.

There are several implications that stem from this replicated result. The first is that the pattern of cortical grey matter deficit progression in healthy siblings appears to parallel that of childhood-onset schizophrenia probands except they may even begin earlier in life. The second is that there is a significant divergence from the childhood-onset schizophrenia trajectory in siblings in which their early deficits normalize, signifying protective factors in healthy siblings not present in cases with childhood-onset schizophrenia. Together these provide the basis for classifying early (prefrontal and temporal) grey matter deficits as a potential endophenotype in schizophrenia, in other words, a hypothesized antecedent and biological underpinning of this disorder that is highly genetic, and may not by itself cause disease symptoms. These results also suggest that studies on prefrontal and temporal neurocircuitry development, particularly in healthy siblings, could provide important clues in pathophysiological (or protective) mechanisms in schizophrenia.

These analyses were recently extended to the hippocampus, due to the fact that hippocampal volume loss is one of the most consistently reported findings in schizophrenia (Nelson et al., 1998). In a recent study analysing a large longitudinal sample of patients with childhood-onset schizophrenia ($n = 89$, 198 scans), non-psychotic siblings ($n = 78$, 172 scans), and matched controls

($n = 79$, 198 scans), patients with childhood-onset schizophrenia showed 6–7% loss in hippocampal volume, which appeared to be a 'fixed' deficit across ages 10 to 29 years, whereas the trajectories of hippocampal volume were not different between patients and control subjects. Childhood-onset schizophrenia siblings, however, did not differ from control subjects in either hippocampal volume or its trajectory over time (Mattai et al., 2011a). This suggested that, unlike prefrontal and temporal cortical grey matter deficits, hippocampal volume loss in childhood-onset schizophrenia is a state-marker or disease-related, perhaps secondary to some already postulated environmental associations such as early life stress (Cannon et al., 2002a). These results also suggest that the grey matter deficits in childhood-onset schizophrenia and schizophrenia generally are not only age dependent, but also regionally dependent endophenotypes, further buoyed by a recent meta-analysis of brain abnormalities in adult-onset schizophrenia that found no progressive hippocampal changes (Olabi et al., 2011).

In neuroimaging, longitudinal profiles can be more informative than cross-sectional time points (Giedd and Rapoport, 2010). The age dependent amelioration of cortical grey matter deficits in siblings offers information that would not be captured using cross-sectional data. This was also highlighted in our recent study of cerebellar development in childhood-onset schizophrenia (Greenstein et al., 2011). In a longitudinal sample of probands ($n = 94$, 208 scans), siblings ($n = 80$, 165 scans), and unrelated control subjects ($n = 110$, 269 scans), the non-psychotic siblings did not differ
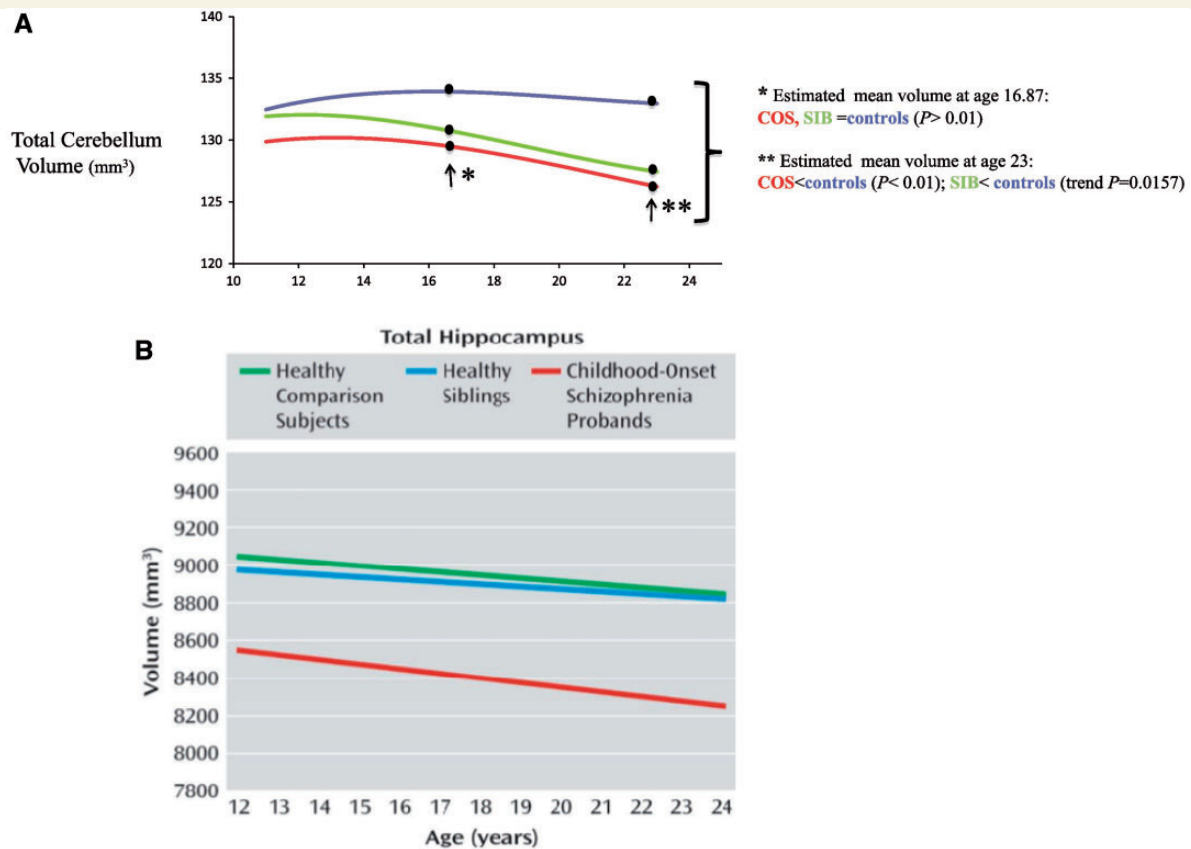
Figure 2 Volume trajectories for (**A**) cerebellum (Greenstein *et al.*, 2011) and (**B**) hippocampus (Mattai *et al.*, 2011a) among childhood-onset schizophrenia siblings and healthy controls. COS = childhood-onset schizophrenia; SIB = sibling.

significantly from control subjects in terms of total cerebellar volumes, but did so in the developmental trajectories of the total and right cerebellum, and the left inferior posterior left superior posterior and superior vermis (Greenstein *et al.*, 2011). The developmental trajectory of the siblings' cerebellar measures was not as severely abnormal as their ill brothers and sisters, but significantly more so than the control subjects. Furthermore, cross-sectional observations of early versus later age points would yield inconsistent and hence misrepresentative results. Interestingly, unlike the cortex, normalization of deficits did not occur for cerebellum in healthy siblings, again indicating a lack of synchrony, and subregional specificity of endophenotypes (Fig. 2) (Greenstein *et al.*, 2011). Alternatively, cerebellar development might be an endophenotype relegated to 'later' ages, whereas cortical grey matter deficits are endophenotypes relegated to 'early' ages and hippocampus volume loss in childhood-onset schizophrenia is a disease effect in entirety.

An implicit goal of finding endophenotypes is to locate markers or antecedents of a disease that are more upstream than the overt clinical phenotype. In terms of neurological and psychiatric diseases, this can happen by moving from structural abnormalities to the genetic variants that may cause them. One such variant is a polymorphism for an enzyme responsible for dopamine catabolism, a neurotransmitter theorized to be dysregulated in patients with schizophrenia (Howes and Kapur, 2009) and may in part mediate the deficits in cortical thickness common to this disorder. The polymorphism is a substitution of the amino acid valine for

methionine, and results in an enzyme that catabolizes dopamine at 40% greater rates, leaving far lower levels available in the CNS (Raznahan *et al.*, 2011). In one of the largest childhood-onset schizophrenia studies to date (Raznahan *et al.*, 2011), interaction between COMT genotype, structural imaging data, and age showed that among patients with childhood-onset schizophrenia and their non-psychotic siblings, homozygous Val/Val status was associated with a significantly steeper slope of cortical grey matter loss in overlapping areas (primarily the dorsolateral prefrontal cortex, along with bilateral cingulate) between childhood-onset schizophrenia probands and their healthy siblings. Given also that this was not the case for unrelated control subjects, where in fact higher doses were related to attenuated cortical thickness losses in the bilateral prefrontal cortex and temporal and superior parietal regions, these findings strongly point towards genetic polymorphism as a compelling variable, along with specific subregion and age, that influences the structural endophenotype. This effect has also been reported in young adults (aged 16–25) at high genetic risk of psychosis (McIntosh *et al.*, 2007), and those with a 22q11.2 deletion (Gothelf *et al.*, 2005). Together, this growing body of work suggests that brain abnormalities related to psychosis may develop in part because of a disruption in the pathway that links dopaminergic function to cortical maturation (Raznahan *et al.*, 2011).

To summarize the results of studies of healthy siblings of patients with childhood-onset schizophrenia, the potential
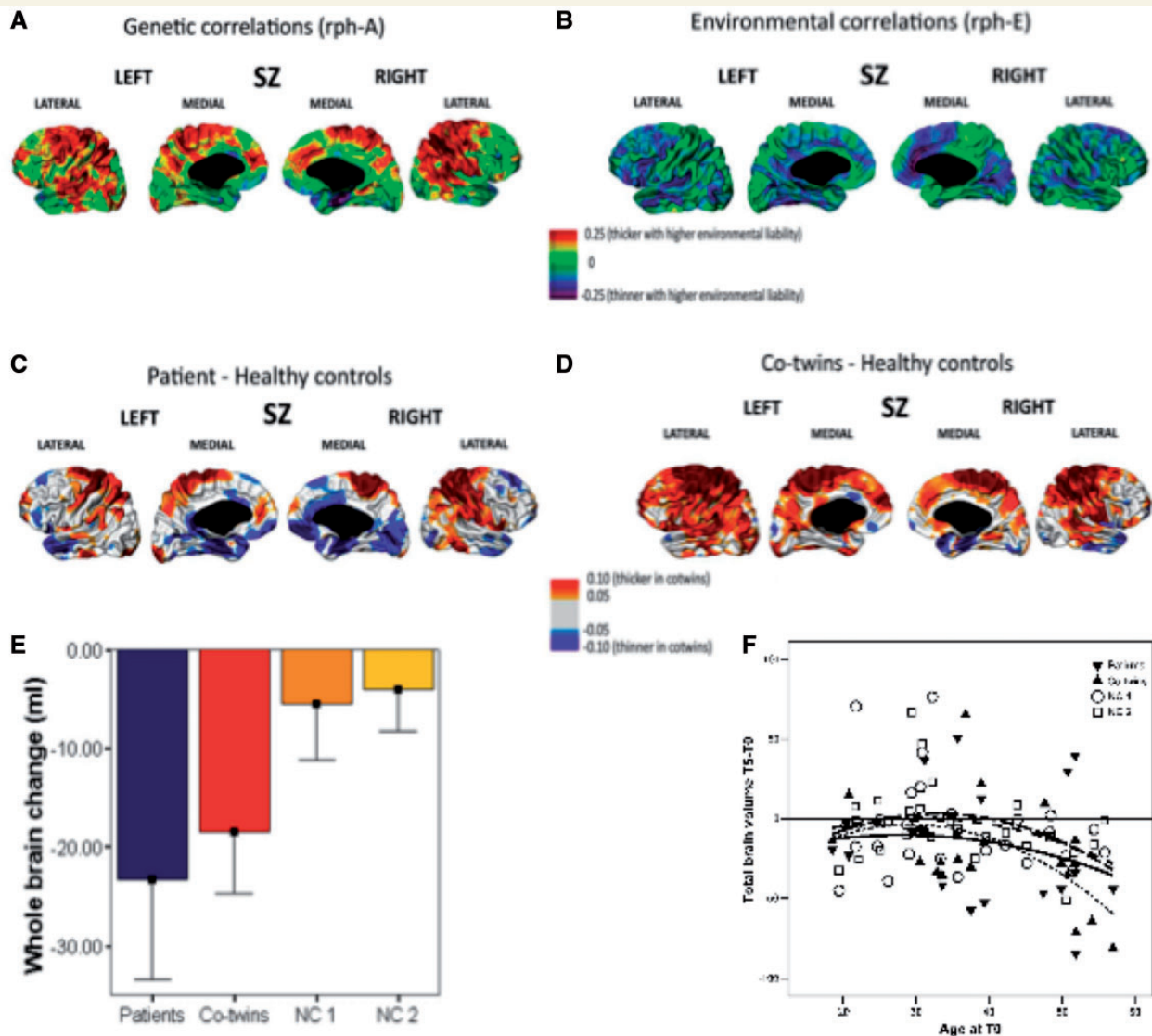
Figure 3 Structural brain changes in twins discordant for schizophrenia. Cortical thickness and genetic (**A**) and environmental (**B**) liabilities for schizophrenia (SZ) are shown based on structural equation modelling, and cortical thickness decreases (in blue) and increases (in red) in patients (**C**) and their discordant co-twins (**D**) as compared to control twins are shown based on planned comparisons (adapted from Hulshoff Pol et al., 2012). Brain volume change over time is expressed as ml change from 0 in mean (SD) (**E**) and age (**F**) plots in patients with schizophrenia, their discordant co-twins and control twins over a 5-year interval (based on data from Brans et al., 2008a).

endophenotypes that merit further scrutiny to date, are temporal and frontal cortical thickness deficits in early age, decreased cerebellar volume in later age, and the influence of individual genetic polymorphisms. The reflection that is built from the sum of these findings is also that the healthy (non-psychotic) siblings of patients with childhood-onset schizophrenia appear to have plastic nervous systems that can correct developmental abnormalities and normalize during adolescence. The specific regions identified must be pursued individually, but so too should the notion that brain plasticity in general, and the neurological basis of that ability, may be the key to treatment that can delay and even prevent the onset of psychosis for those at even the highest risk of this severely impairing disorder.

Siblings of patients with adult-onset schizophrenia

Adult-onset schizophrenia has an onset that typically occurs during late adolescence and young adulthood, is far more common (with a lifetime risk of 1% of the general population) than childhood-onset schizophrenia, and its body of research is understandably much larger (Ayuso-Mateos et al., 2006). Of note, adult-onset schizophrenia, or schizophrenia such as it is normally defined, is here contrasted with childhood-onset schizophrenia, but also includes individuals and their family members with a disease onset before the age of 18 years. In adult-onset schizophrenia, similar

attempts have been made in the adult population to differentiate state and trait markers in sibling studies, including twin studies, and these have provided important insights. Twin studies are the most informative as they offer a comparison between monozygotic twins with near identical genetic profiles, with dizygotic twins that can be considered effectively as full siblings with a 50% share of their segregating genes on average. Twin populations discordant and concordant for schizophrenia are rare and difficult to study, and practically impossible to obtain in childhood-onset schizophrenia. Concordance rate for schizophrenia in monozygotic twins, despite sharing all genes, is not 100%, but closer to 50% with an estimated heritability of 81% (Sullivan et al., 2003) and possibly lower, (Lichtenstein et al., 2009) suggesting a complex interplay between genetics and other vulnerability factors; making the study of endophenotypes even more relevant (Baare et al., 2001).

The adult-onset schizophrenia sibling brain picture has been developed over time, and one of the earliest findings was from an analysis of thalamic volume in relatives of patients with schizophrenia. This research followed studies that indicated thalamic volume in patients with adult-onset schizophrenia ($n = 16$) was reduced compared with the general population, and measured mean total thalamic volume corrected for total brain volume (Staal et al., 1998). With this metric, it was found that patient thalamic volume was the smallest, but also that sibling volume ($n = 16$) was significantly greater than probands, but lower than healthy control subjects ($n = 32$). Although small and cross-sectional, this study strengthened the idea that thalamic volume is a possible endophenotype and related to the genetic liability to develop schizophrenia.

Many adult-onset schizophrenia sibling studies followed that examined other brain regions in terms of structure and function among siblings of patients with adult-onset schizophrenia, which are summarized in Table 1.

Thus, there are a considerable number of studies in adult-onset schizophrenia siblings, although samples between studies are overlapping. The majority of studies suggest familial influences on at least part of the structural brain abnormalities in schizophrenia. This is confirmed in a meta-analysis on structural brain changes in non-psychotic siblings (including co-twins) of patients with schizophrenia finding significant smaller hippocampus and grey matter volume as well as significant larger third ventricle volume in studies published until 2005 (Boos et al., 2007). In the more than 10 studies published since, studies in twins largely confirm volume changes in schizophrenia to have a familial component. Importantly, these twin studies add that the brain volume abnormalities in schizophrenia are at least in part due to genes implicated in the disease. However, a few, considerably large studies in non-psychotic singleton adult-onset schizophrenia siblings do not show any brain abnormalities (Honea et al., 2008; Boos et al., 2012).

There could be several reasons for these inconsistencies. We cannot exclude that studies differed in their exclusion criteria for siblings regarding (schizophrenia spectrum) problems on axis I or axis II and this may explain some of these findings. However, more likely and importantly, they seem to reflect a difference in genetic loading between siblings and twins (Sullivan et al., 2003). The estimated 9% increased risk for the disease in healthy singleton siblings

from patients with schizophrenia is for the most part not reflected in brain abnormalities, whereas higher risks such as the estimated 50% increased risk in monozygotic co-twins from patients with schizophrenia can be reflected in the brain abnormalities. Alternatively, we cannot exclude that this lack of detectable differences at lower levels of relatedness, however, may not be a signal of a cut-off between genetic risk and progressive brain abnormalities, but rather that there appears to be a lower incidence of schizotypal personality disorder among siblings than twins. Studies in relatives and twins generally support familial aggregation with schizophrenia, particularly for the affective and interpersonal components (Kremen et al., 1998; Lichtenstein et al., 2009; Picchioni et al., 2010) and that in some instances older samples with decreasing chances of disease-transition, that measured with less sensitive techniques, such as voxel-based morphology (Honea et al., 2008) were employed. Indeed, studies in monozygotic and dizygotic twins concordant and discordant for adult-onset schizophrenia revealed not only that some of the brain abnormalities in schizophrenia are familial, but also that part of the brain abnormalities in schizophrenia are due to genes implicated in the disease (Baare et al., 2001; Cannon et al., 2002b; van Haren et al., 2004; Hulshoff Pol et al., 2006, 2012). Interestingly, some of the changes in brain structure, particularly loss of white matter volume and thinner cortex of parahippocampal gyri and right orbitofrontal cortex, were found not only to be heritable in adult-onset schizophrenia but also in bipolar disorder, whereas other brain changes were specific for the genetic risk for adult-onset schizophrenia but not bipolar disorder, suggesting both overlapping and segregating effects on brain structures of genetic risks for adult-onset schizophrenia and bipolar disorder (Hulshoff Pol et al., 2012).

Few longitudinal studies on adult-onset schizophrenia sibling samples have been carried out. We are not aware of any studies outside of the few cohorts followed by researchers at the University Medical Centre in Utrecht, The Netherlands. The Utrecht studies involved singleton siblings and monozygotic and dizygotic twins being re-scanned at a 5-year follow-up period. Healthy siblings of adult-onset schizophrenia did not show any evidence for progressive grey matter loss over time. However, when adult monozygotic and dizygotic twin pairs discordant for schizophrenia were studied longitudinally, evidence for progressive brain tissue loss in family members of adult-onset schizophrenia was found (Brans et al., 2008b). The progressive volume loss of total brain and particularly of frontal and temporal lobes was at least for 50% due to genes implicated in schizophrenia (Brans et al., 2008b). The genes implicated in these progressive brain tissue changes in schizophrenia may differ from those implicated in brain maturation per se, since in healthy childhood and adulthood separate gene pools are implicated in brain structure change and brain plasticity (Brans et al., 2010; van Soelen et al., 2012). Thus, increased genetic risk for schizophrenia is not only associated with brain tissue loss but also with progressive brain tissue loss in adulthood.

Synthesis and discussion

Studies from unaffected siblings of patients with both childhood and adult-onset schizophrenia demonstrate an interesting and

Table 1 Brain abnormalities in siblings of adults with schizophrenia

Study*	Participants**	Positive findings	Negative findings***
(Noga et al., 1996)	13 MZ twin pairs, discordant 9 control twin pairs		Gyral pattern Hemispheric volumes
(Seidman et al., 1997)	6 siblings 11 controls	Reduced hippocampal, right amygdala, and right putamen volumes	Total cerebral hemisphere, adjusted cerebral grey matter and white matter
(Staal et al., 1998)	16 sibling pairs, discordant 32 controls	Decreased thalamic volume	Total brain volume
(Cannon et al., 1998)	75 patients 60 siblings 56 controls	Cortical grey matter reductions	White matter volume reductions
(Seidman et al., 1999)	28 siblings 26 controls	Lower amygdala-hippocampus volume Lower thalamus volume	Total brain volume, grey matter volume, lateral ventricles, cerebellum
(Sharma et al., 1999)	29 patients 55 siblings 39 controls		Total brain volume, prefrontal, premotor, sensorimotor, occipitoparietal volume
(Staal et al., 2000)	16 sibling pairs, discordant 32 controls	Third ventricle enlargement	Intracranial, cerebellum, amygdala, hippocampus, parahippocampal gyrus, and CSF volume
(Baare et al., 2001)	15 MZ twin pairs, discordant 14 DZ twin pairs, discordant 15 MZ control twin pairs 15 DZ control twin pairs	Lower total brain volume Lower hippocampal volume	
(Narr et al., 2002)	10 MZ twin pairs, discordant 10 DZ twin pairs, discordant 10 MZ control twin pairs 10 DZ control twin pairs	Lower left hippocampal volume in MZ not DZ co-twins, supporting genetic influences	
(Cannon et al., 2002b)	20 patients 20 siblings 40 controls	Polar PFC grey matter volume	DLPFC grey matter volume
(Van Erp et al., 2002)	60 patients 58 non-psychotic siblings 53 controls	Lower hippocampal volume	
(Tepest et al., 2003)	25 patients 13 unaffected siblings 10 controls	Lower hippocampus volume, inward deformity of the head of the hippocampus	
(Hulshoff Pol et al., 2004)	11 MZ twin pairs, discordant 11 DZ twin pairs, discordant 11 MZ control twin pairs 11 DZ control twin pairs	Lower white matter volume	Grey matter volume
(van Haren et al., 2004)	14 MZ twin pairs, concordant 10 MZ twin pairs, discordant 17 MZ control twin pairs	Lower whole brain volumes	Third ventricle, and lateral ventricles
(van Erp et al., 2004)	7 MZ twin pairs, concordant 16 MZ twin pairs, discordant 32 DZ twin pairs, discordant 28 MZ control twin pairs 26 DZ control twin pairs	Lower hippocampus volumes	
(Rijsdijk et al., 2005)	14 MZ twin pairs, concordant 10 MZ twin pairs, discordant 17 MZ control twin pairs 22 siblings pairs, discordant	Significant genetic correlation with schizophrenia for whole brain Familial effects for hippocampus and third ventricle	Lateral ventricle volume

Table 1 Continued

Study*	Participants**	Positive findings	Negative findings***
(Hulshoff Pol *et al.*, 2006)	11 MZ twin pairs, discordant 11 DZ twin pairs, discordant) 11 MZ control twin pairs 11 DZ control twin pairs	Lower white matter density, Lower grey matter density	
(Ettinger *et al.*, 2007)	19 MZ twin pairs, concordant 16 MZ twins pairs, discordant 27 MZ control twin pairs	Reduced thalamic volume	
(Brans *et al.*, 2008a)	**Longitudinal study** 9 MZ twin pairs, discordant 10 DZ twin pairs, discordant 14 MZ control twin pairs 13 DZ control twin pairs	Progressive total brain frontal lobe and temporal lobe tissue loss due to genes common to schizophrenia risk	
(Brans *et al.*, 2008b)	**Longitudinal study** 11 patients 11 siblings 33 controls		Progressive change over time in whole brain and cerebral grey matter volumes
(Honea *et al.*, 2008)	169 patients 213 siblings		Grey matter deficits in medial frontal, superior temporal, and insular cortices
(Goldman *et al.*, 2009)	115 patients 192 siblings 196 matched controls		Brain wide cortical thickness
(Harms *et al.*, 2010)	26 sibling pairs, discordant 40 control pairs	Reduced inferior frontal grey matter volume	Middle frontal grey matter volume
(Rasetti *et al.*, 2011)	78 patients 171 siblings 153 controls	Abnormal DL PFC coupling with hippocampus	
(Hulshoff Pol *et al.*, 2012)	13 MZ twin pairs, discordant 13 DZ twin pairs, discordant 44 MZ control twin pairs 39 DZ control twin pairs	Thinner parahippocampus, and orbitofrontal, and calcarine cortices. Thicker temporoparietal and superior motor cortices	
(Boos *et al.*, 2012)	155 AOS patients 186 AOS siblings 122 controls		Total brain, grey matter, white matter, lateral and third ventricle, cerebellum volumes, cortical thickness and grey matter density
(Ettinger *et al.*, 2012)	21 MZ twin pairs, concordant 18 MZ twin pairs, discordant 26 MZ control twin pairs	Lower superior frontal cortex volume	Inferior, medial and orbitofrontal cortices volumes
(van Haren *et al.*, 2012)	51 MZ twin pairs, concordant 52 MZ twin pairs, discordant 39 DZ twin pairs, discordant 116 MZ control twin pairs 98 DZ control twin pairs	Lower cerebral volume Lower cerebral white matter volume Larger third ventricle volume	Cerebral grey matter

*Studies between 1997 and 2005 are included in the meta-analysis on structural brain changes in siblings of patients with schizophrenia finding significantly smaller hippocampus and grey matter volume as well as significantly larger third ventricle volume in non-psychotic first-degree relatives of patients with schizophrenia (Boos *et al.*, 2007).

**Several studies have overlapping cohorts.

***Significant changes in volumes may be present in these areas in patients with schizophrenia in these same studies. For meta-analyses on structural brain changes in schizophrenia see Wright *et al.* (2000), Olabi *et al.* (2011) and Haijma *et al.* (2012).

AOS = adult-onset schizophrenia; DZ = dizygotic; MZ = monozygotic; DL = dorsolateral; PFC = prefrontal cortex.

divergent pattern of brain development compared to unrelated healthy controls. Based on the continuity that has been established between these two forms of the disorder (Giedd *et al.*, 1999), the opportunity exists to bridge and combine the findings from both sibling groups for a more comprehensive picture. Together, these data indicate that the sibling brain often lies in between that of the patients with schizophrenia and healthy controls, with significant, but not as severe regional volume reductions. These findings

strengthen the familial and genetic basis of schizophrenia, in which siblings provide an opportunity to highlight brain development as a structural and hence functional endophenotype. Even more important than the similarities, the differences between the childhood and adult-onset cases may indicate the temporal nature of the endophenotypes in question.

In the childhood-onset schizophrenia siblings, prefrontal and temporal grey matter deficits were detected at early ages. In co-twins of patients with adult-onset schizophrenia prefrontal and temporal grey matter deficits are found that are progressive in adulthood. This suggests that the decrease in prefrontal and temporal grey matter is familial (and associated with increased genetic risk) in schizophrenia irrespective of age. There have been documented cross-sectional and longitudinal brain changes in relatives at high risk for schizophrenia, which includes siblings as well as other close relatives (Boos et al., 2007; McIntosh et al., 2011), but singleton adult-onset schizophrenia siblings brain changes are predominantly absent and do not progress over time, although this finding is based on only a small number of longitudinal follow-up sibling samples.

The longitudinal findings from the childhood-onset sample allows for a more nuanced perspective of the adult results given that the grey matter deficits in childhood-onset schizophrenia siblings normalize by young adulthood. Together, the early grey matter deficits in childhood-onset schizophrenia siblings that normalize by late adolescence combined with the largely negative grey matter findings in adult-onset schizophrenia singleton siblings—but not in adult-onset schizophrenia co-twins—suggest that grey matter deficits are an age-dependent endophenotype that are subregionally specific and highlight the neurodevelopmental nature of schizophrenia, and the plasticity of the healthy (singleton) sibling brain. Such plastic processes may reflect genetic processes implicated in subregionally specific changes in the normal brain at different ages (Brans et al., 2010; van Soelen et al., 2012). For example, large-scale healthy participant studies indicate that later developing brain regions, such as the prefrontal cortex and temporal lobes, show increasingly prominent genetic effects with brain maturation (Lenroot et al., 2009), highlighting how age (through longitudinal work) might provide the ideal filter to detecting endophenotypes. Interestingly, age-dependent genetic influences are not uncommon in medicine, including examples in Alzheimer's disease (Shi and Gibson, 2007) and Huntington's disease (Reiner et al., 2011), and add further emphasis to the notion that brain changes take place over specific and critical periods throughout life.

This allows for a model to be developed for the sibling brain that stretches in two dimensions. The first dimension is age, and the synthesis of the different populations by age indicate that cortical grey matter deficits are more prevalent earlier in life, normalize over adolescence, and are all but absent during young adulthood provided the siblings do not have schizophrenia spectrum abnormalities or higher genetic loading as in the case of monozygotic discordant twins. The second dimension is degree of genetic loading and the degree of symptom/disease burden. Structural abnormalities become more prominent and remain evident in later ages in monozygotic twins compared with non-twins, and also among childhood-onset schizophrenia and

adult-onset schizophrenia siblings that are diagnosed with schizophrenia spectrum disorders. Additionally, studies that include other relatives beyond siblings (Olabi et al., 2011) can also add focus to the larger genetic and environmental causes of schizophrenia. Together these dimensions of analysis demonstrate strongly that structural deficits in schizophrenia are genetically influenced, and represent a dimensional construct as opposed to an 'all or nothing' model of psychosis. The unification of the childhood and adult literature also adds weight to a gene dosage effect at play in schizophrenia, especially given the work done that supports childhood-onset schizophrenia as representing a more genetic form of the disorder (Eckstrand et al., 2008).

In addition to addressing the endophenotype question, sibling studies provide the basis for future hypotheses and specific directions forward. Prefrontal and temporal deficits appear to be consistent abnormalities in schizophrenia, appearing as early age endophenotypes, at least in siblings of patients with childhood-onset schizophrenia. It is important to explore factors that cause these deficits in healthy siblings, what protects siblings from schizophrenia symptoms in both children and adults, and what is underlying the (temporary) normalization of these deficits by late adolescence. Volumetric studies may not be sensitive enough to reflect the subtler involvement differences seen in adult siblings. Other imaging techniques, such as diffusion tensor imaging, magnetic transfer ratio, functional MRI, or magnetoencephalography may provide more acute insight into developing neurocircuitries, particularly to see if these observed patterns of grey matter loss reflect connectivity network changes that have been documented in patients with schizophrenia (Ellison-Wright and Bullmore, 2009; van den Heuvel et al., 2010; Pettersson-Yeo et al., 2011; Fornito et al., 2012; Hulshoff Pol and Bullmore, 2013), and their siblings (Whitfield-Gabrieli et al., 2009; Collin et al., 2011; Repovs et al., 2011), as has been validated recently in other conditions (Seeley et al., 2009).

Indeed, impaired cerebellar functional connectivity (Collin et al., 2011) as well as hyperactivity and hyperconnectivity of the default network (Whitfield-Gabrieli et al., 2009) have been found in siblings of patients with adult-onset schizophrenia. Longitudinal studies in healthy siblings may show 'normalization' of the abnormal brain activity in siblings as they get older, or a continued deficit pattern at a milder degree compared to the probands. Thus studying functional neurodevelopment in siblings, particularly from early ages through the typical age of onset of schizophrenia, may provide unique insights into which neurocircuitries are vulnerable to genetic variants and how they normalize over time. Together, a complete functional understanding of neurodevelopment can synergize with the structural one, and indicate the crucial link, or lack thereof, between the physical changes to the brain, and its illness related activity.

The benefit that comes from comparing childhood and adult-onset forms of schizophrenia should not only be employed in terms of brain changes, but in any instance that can improve the understanding and treatment of this disorder. The human body changes throughout the lifespan, and analysis that incorporates that progression is best suited to spot time and age dependent effects. Whether this involves neural dysfunction, growth, or normalization, critical information arises from longitudinal study of

individuals at the highest risk for developing schizophrenia, to better analyse its complex causes.

Funding

References

Ayuso-Mateos JL, Gutierrez-Recacha P, Haro JM, Chisholm D. Estimating the prevalence of schizophrenia in Spain using a disease model. Schizophr Res 2006; 86: 194–201.

Baare WF, van Oel CJ, Hulshoff Pol HE, Schnack HG, Durston S, Sitskoorn MM, et al. Volumes of brain structures in twins discordant for schizophrenia. Arch Gen Psychiatry 2001; 58: 33–40.

Boos HB, Aleman A, Cahn W, Hulshoff Pol H, Kahn RS. Brain volumes in relatives of patients with schizophrenia: a meta-analysis. Arch Gen Psychiatry 2007; 64: 297–304.

Boos HB, Cahn W, van Haren NE, Derks EM, Brouwer RM, Schnack HG, et al. Focal and global brain measurements in siblings of patients with schizophrenia. Schizophr Bull 2012; 38: 814–825.

Brans RG, Kahn RS, Schnack HG, van Baal GC, Posthuma D, van Haren NE, et al. Brain plasticity and intellectual ability are influenced by shared genes. J Neurosci 2010; 30: 5519–24.

Brans RG, van Haren NE, van Baal GC, Schnack HG, Kahn RS, Hulshoff Pol HE. Heritability of changes in brain volume over time in twin pairs discordant for schizophrenia. Arch Gen Psychiatry 2008a; 65: 1259–68.

Brans RG, van Haren NE, van Baal GC, Staal WG, Schnack HG, Kahn RS, et al. Longitudinal MRI study in schizophrenia patients and their healthy siblings. Br J Psychiatry 2008b; 193: 422–3.

Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. Am J Psychiatry 2002a; 159: 1080–92.

Cannon TD, Thompson PM, van Erp TG, Toga AW, Poutanen VP, Huttunen M, et al. Cortex mapping reveals regionally specific patterns of genetic and disease-specific gray-matter deficits in twins discordant for schizophrenia. Proc Natl Acad Sci USA 2002b; 99: 3228–33.

Cannon TD, van Erp TG, Huttunen M, Lonnqvist J, Salonen O, Valanne L, et al. Regional gray matter, white matter, and cerebrospinal fluid distributions in schizophrenic patients, their siblings, and controls. Arch Gen Psychiatry 1998; 55: 1084–91.

Collin G, Hulshoff Pol HE, Haijma SV, Cahn W, Kahn RS, van den Heuvel MP. Impaired cerebellar functional connectivity in schizophrenia patients and their healthy siblings. Front Psychiatry 2011; 2: 73.

DeLisi LE. The concept of progressive brain change in schizophrenia: implications for understanding schizophrenia. Schizophr Bull 2008; 34: 312–21.

Eckstrand K, Addington AM, Stromberg T, Merriman B, Miller R, Gochman P, et al. Sex chromosome anomalies in childhood onset schizophrenia: an update. Mol Psychiatry 2008; 13: 910–1.

Ellison-Wright I, Bullmore E. Meta-analysis of diffusion tensor imaging studies in schizophrenia. Schizophr Res 2009; 108: 3–10.

Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood meta-analysis. Am J Psychiatry 2008; 165: 1015–23.

Ettinger U, Picchioni M, Landau S, Matsumoto K, van Haren NE, Marshall N, et al. Magnetic resonance imaging of the thalamus and adhesio interthalamica in twins with schizophrenia. Arch Gen Psychiatry 2007; 64: 401–9.

Ettinger U, Schmechtig A, Toulopoulou T, Borg C, Orrells C, Owens S, et al. Prefrontal and striatal volumes in monozygotic twins concordant and discordant for schizophrenia. Schizophr Bull 2012; 38: 192–203.

Fornito A, Yucel M, Patti J, Wood SJ, Pantelis C. Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. Schizophr Res 2009; 108: 104–13.

Fornito A, Zalesky A, Pantelis C, Bullmore ET. Schizophrenia, neuroimaging and connectomics. Neuroimage 2012; 62: 2296–314.

Giedd JN, Jeffries NO, Blumenthal J, Castellanos FX, Vaituzis AC, Fernandez T, et al. Childhood-onset schizophrenia: progressive brain changes during adolescence. Biol Psychiatry 1999; 46: 892–8.

Giedd JN, Rapoport JL. Structural MRI of pediatric brain development: what have we learned and where are we going? Neuron 2010; 67: 728–34.

Gogtay N. Cortical brain development in schizophrenia: insights from neuroimaging studies in childhood-onset schizophrenia. Schizophr Bull 2008; 34: 30–6.

Gogtay N, Greenstein D, Lenane M, Clasen L, Sharp W, Gochman P, et al. Cortical brain development in nonpsychotic siblings of patients with childhood-onset schizophrenia. Arch Gen Psychiatry 2007; 64: 772–80.

Gogtay N, Lu A, Leow AD, Klunder AD, Lee AD, Chavez A, et al. Three-dimensional brain growth abnormalities in childhood-onset schizophrenia visualized by using tensor-based morphometry. Proc Natl Acad Sci USA 2008; 105: 15979–84.

Gogtay N, Rapoport JL. Childhood-onset schizophrenia: insights from neuroimaging studies. J Am Acad Child Adolesc Psychiatry 2008; 47: 1120–4.

Gogtay N, Sporn A, Clasen LS, Greenstein D, Giedd JN, Lenane M, et al. Structural brain MRI abnormalities in healthy siblings of patients with childhood-onset schizophrenia. Am J Psychiatry 2003; 160: 569–71.

Goldman AL, Pezawas L, Mattay VS, Fischl B, Verchinski BA, Chen Q, et al. Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. Arch Gen Psychiatry 2009; 66: 467–77.

Gothelf D, Eliez S, Thompson T, Hinard C, Penniman L, Feinstein C, et al. COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome. Nat Neurosci 2005; 8: 1500–2.

Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003; 160: 636–45.

Gould TD, Gottesman II. Psychiatric endophenotypes and the development of valid animal models. Genes Brain Behav 2006; 5: 113–9.

Greenstein D, Lenroot R, Clausen L, Chavez A, Vaituzis AC, Tran L, et al. Cerebellar development in childhood onset schizophrenia and nonpsychotic siblings. Psychiatry Res 2011; 193: 131–7.

Greenstein DK, Wolfe S, Gochman P, Rapoport JL, Gogtay N. Remission status and cortical thickness in childhood-onset schizophrenia. J Am Acad Child Adolesc Psychiatry 2008; 47: 1133–40.

Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophr Bull 2012; Oct 5 (Epub).

Harms MP, Wang L, Campanella C, Aldridge K, Moffitt AJ, Kuelper J, et al. Structural abnormalities in gyri of the prefrontal cortex in individuals with schizophrenia and their unaffected siblings. Br J Psychiatry 2010; 196: 150–7.

Honea RA, Meyer-Lindenberg A, Hobbs KB, Pezawas L, Mattay VS, Egan MF, et al. Is gray matter volume an intermediate phenotype for schizophrenia? A voxel-based morphometry study of patients with schizophrenia and their healthy siblings. Biol Psychiatry 2008; 63: 465–74.

Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. Schizophr Bull 2009; 35: 549–62.

Hulshoff Pol H, Bullmore E. Neural networks in psychiatry. Eur Neuropsychopharmacol 2013; 23: 1–6.

Hulshoff Pol HE, Brans RG, van Haren NE, Schnack HG, Langen M, Baare WF, et al. Gray and white matter volume abnormalities in

monozygotic and same-gender dizygotic twins discordant for schizophrenia. Biol Psychiatry 2004; 55: 126–30.

Hulshoff Pol HE, Kahn RS. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. Schizophr Bull 2008; 34: 354–66.

Hulshoff Pol HE, Schnack HG, Mandl RC, Brans RG, van Haren NE, Baare WF, et al. Gray and white matter density changes in monozygotic and same-sex dizygotic twins discordant for schizophrenia using voxel-based morphometry. Neuroimage 2006; 31: 482–8.

Hulshoff Pol HE, van Baal GC, Schnack HG, Brans RG, van der Schot AC, Brouwer RM, et al. Overlapping and segregating structural brain abnormalities in twins with schizophrenia or bipolar disorder. Arch Gen Psychiatry 2012; 69: 349–59.

Kendler KS, Neale MC. Endophenotype: a conceptual analysis. Mol Psychiatry 2010; 15: 789–97.

Kremen WS, Faraone SV, Toomey R, Seidman LJ, Tsuang MT. Sex differences in self-reported schizotypal traits in relatives of schizophrenic probands. Schizophr Res 1998; 34: 27–37.

Lenroot RK, Schmitt JE, Ordaz SJ, Wallace GL, Neale MC, et al. Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence. Hum Brain Map 2009; 30: 163–74.

Lichtenstein P, Yip BH, Bjork C, Pawitan Y, Cannon TD, Sullivan PF, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 2009; 373: 234–9.

Mattai A, Hosanagar A, Weisinger B, Greenstein D, Stidd R, Clasen L, et al. Hippocampal volume development in healthy siblings of childhood-onset schizophrenia patients. Am J Psychiatry 2011a; 168: 427–35.

Mattai AA, Weisinger B, Greenstein D, Stidd R, Clasen L, Miller R, et al. Normalization of cortical gray matter deficits in nonpsychotic siblings of patients with childhood-onset schizophrenia. J Am Acad Child Adolesc Psychiatry 2011b; 50: 697–704.

McIntosh AM, Baig BJ, Hall J, Job D, Whalley HC, Lymer GK, et al. Relationship of catechol-O-methyltransferase variants to brain structure and function in a population at high risk of psychosis. Biol Psychiatry 2007; 61: 1127–34.

McIntosh AM, Owens DC, Moorhead WJ, Whalley HC, Stanfield AC, Hall J, et al. Longitudinal volume reductions in people at high genetic risk of schizophrenia as they develop psychosis. Biol Psychiatry 2011; 69: 953–8.

Narr KL, van Erp TG, Cannon TD, Woods RP, Thompson PM, Jang S, et al. A twin study of genetic contributions to hippocampal morphology in schizophrenia. Neurobiol Dis 2002; 11: 83–95.

Nelson MD, Saykin AJ, Flashman LA, Riordan HJ. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. Arch Gen Psychiatry 1998; 55: 433–40.

Noga JT, Bartley AJ, Jones DW, Torrey EF, Weinberger DR. Cortical gyral anatomy and gross brain dimensions in monozygotic twins discordant for schizophrenia. Schizophr Res 1996; 22: 27–40.

Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM. Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. Biol Psychiatry 2011; 70: 88–96.

Pantelis C, Yucel M, Wood SJ, Velakoulis D, Sun D, Berger G, et al. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr Bull 2005; 31: 672–96.

Peper JS, Brouwer RM, Boomsma DI, Kahn RS, Hulshoff Pol HE. Genetic influences on human brain structure: a review of brain imaging studies in twins. Hum Brain Mapp 2007; 28: 464–73.

Pettersson-Yeo W, Allen P, Benetti S, McGuire P, Mechelli A. Dysconnectivity in schizophrenia: where are we now? Neurosci Biobehav Rev 2011; 35: 1110–24.

Picchioni MM, Walshe M, Toulopoulou T, McDonald C, Taylor M, Waters-Metenier S, et al. Genetic modelling of childhood social development and personality in twins and siblings with schizophrenia. Psychol Med 2010; 40: 1305–16.

Rapoport JL, Addington A, Frangou S. The neurodevelopmental model of schizophrenia: what can very early onset cases tell us? Curr Psychiatry Rep 2005; 7: 81–2.

Rapoport JL, Gogtay N. Childhood onset schizophrenia: support for a progressive neurodevelopmental disorder. Int J Dev Neurosci 2011; 29: 251–8.

Rasetti R, Sambataro F, Chen Q, Callicott JH, Mattay VS, Weinberger DR. Altered cortical network dynamics: a potential intermediate phenotype for schizophrenia and association with ZNF804A. Arch Gen Psychiatry 2011; 68: 1207–17.

Raznahan A, Greenstein D, Lee Y, Long R, Clasen L, Gochman P, et al. Catechol-o-methyl transferase (COMT) val158met polymorphism and adolescent cortical development in patients with childhood-onset schizophrenia, their non-psychotic siblings, and healthy controls. Neuroimage 2011; 57: 1517–23.

Reiner A, Dragatsis I, Dietrich P. Genetics and neuropathology of Huntington's disease. Int Rev Neurobiol 2011; 98: 325–72.

Repovs G, Csernansky JG, Barch DM. Brain network connectivity in individuals with schizophrenia and their siblings. Biol Psychiatry 2011; 69: 967–73.

Rijsdijk FV, van Haren NE, Picchioni MM, McDonald C, Toulopoulou T, Hulshoff Pol HE, et al. Brain MRI abnormalities in schizophrenia: same genes or same environment? Psychol Med 2005; 35: 1399–409.

Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. Neuron 2009; 62: 42–52.

Seidman LJ, Faraone SV, Goldstein JM, Goodman JM, Kremen WS, Matsuda G, et al. Reduced subcortical brain volumes in nonpsychotic siblings of schizophrenic patients: a pilot magnetic resonance imaging study. Am J Med Genet 1997; 74: 507–14.

Seidman LJ, Faraone SV, Goldstein JM, Goodman JM, Kremen WS, Toomey R, et al. Thalamic and amygdala-hippocampal volume reductions in first-degree relatives of patients with schizophrenia: an MRI-based morphometric analysis. Biol Psychiatry 1999; 46: 941–54.

Sharma T, Lancaster E, Sigmundsson T, Lewis S, Takei N, Gurling H, et al. Lack of normal pattern of cerebral asymmetry in familial schizophrenic patients and their relatives—The Maudsley Family Study. Schizophr Res 1999; 40: 111–20.

Shaw P, Greenstein D, Lerch J, Clasen L, Lenroot R, Gogtay N, et al. Intellectual ability and cortical development in children and adolescents. Nature 2006; 440: 676–9.

Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. Schizophr Res 2001; 49: 1–52.

Shenton ME, Whitford TJ, Kubicki M. Structural neuroimaging in schizophrenia: from methods to insights to treatments. Dialogues Clin Neurosci 2010; 12: 317–32.

Shi Q, Gibson GE. Oxidative stress and transcriptional regulation in Alzheimer disease. Alzheimer Dis Assoc Disord 2007; 21: 276–91.

Staal WG, Hulshoff Pol HE, Schnack H, van der Schot AC, Kahn RS. Partial volume decrease of the thalamus in relatives of patients with schizophrenia. Am J Psychiatry 1998; 155: 1784–6.

Staal WG, Hulshoff Pol HE, Schnack HG, Hoogendoorn ML, Jellema K, Kahn RS. Structural brain abnormalities in patients with schizophrenia and their healthy siblings. Am J Psychiatry 2000; 157: 416–21.

Stein JL, Medland SE, Vasquez AA, Hibar DP, Senstad RE, Winkler AM, et al. Identification of common variants associated with human hippocampal and intracranial volumes. Nat Genet 2012; 44: 552–61.

Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry 2003; 60: 1187–92.

Tepest R, Wang L, Miller MI, Falkai P, Csernansky JG. Hippocampal deformities in the unaffected siblings of schizophrenia subjects. Biol Psychiatry 2003; 54: 1234–40.

van den Heuvel MP, Mandl RC, Stam CJ, Kahn RS, Hulshoff Pol HE. Aberrant frontal and temporal complex network structure in

schizophrenia: a graph theoretical analysis. J Neurosci 2010; 30: 15915–26.

van Erp TG, Saleh PA, Huttunen M, Lonnqvist J, Kaprio J, Salonen O, et al. Hippocampal volumes in schizophrenic twins. Arch Gen Psychiatry 2004; 61: 346–53.

Van Erp TG, Saleh PA, Rosso IM, Huttunen M, Lonnqvist J, et al. Contributions of genetic risk and fetal hypoxia to hippocampal volume in patients with schizophrenia or schizoaffective disorder, their unaffected siblings, and healthy unrelated volunteers. Am J Psychiatry 2002; 159: 1514–20.

van Haren NE, Picchioni MM, McDonald C, Marshall N, Davis N, et al. A controlled study of brain structure in monozygotic twins concordant and discordant for schizophrenia. Biol Psychiatry 2004; 56: 454–61.

van Haren NE, Rijsdijk F, Schnack HG, Picchioni MM, Toulopoulou T, Weisbrod M, et al. The genetic and environmental determinants of the association between brain abnormalities and schizophrenia: the schizophrenia twins and relatives consortium. Biol Psychiatry 2012; 71: 915–21.

van Soelen IL, Brouwer RM, van Baal GC, Schnack HG, Peper JS, Collins DL, et al. Genetic influences on thinning of the cerebral cortex during development. Neuroimage 2012; 59: 3871–80.

Walters JT, Owen MJ. Endophenotypes in psychiatric genetics. Mol Psychiatry 2007; 12: 886–90.

Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Tsuang MT, Faraone SV, McCarley RW, et al. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc Natl Acad Sci USA 2009; 106: 1279–84.

Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET. Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 2000; 157: 16–25.

Wright IC, Sharma T, Ellison ZR, McGuire PK, Friston KJ, Brammer MJ, et al. Supra-regional brain systems and the neuropathology of schizophrenia. Cereb Cortex 1999; 9: 366–78.