



## Consensus paper of the WFSBP Task Force on Biological Markers: Criteria for biomarkers and endophenotypes of schizophrenia part II: Cognition, neuroimaging and genetics

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WFSBP CONSENSUS PAPER

## Consensus paper of the WFSBP Task Force on Biological Markers: Criteria for biomarkers and endophenotypes of schizophrenia part II: Cognition, neuroimaging and genetics

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### ABSTRACT

**Objectives:** Schizophrenia is a group of severe psychiatric disorders with high heritability but only low odds ratios of risk genes. Despite progress in the identification of pathophysiological processes, valid biomarkers of the disease are still lacking.

**Methods:** This comprehensive review summarises recent efforts to identify genetic underpinnings, clinical and cognitive endophenotypes and symptom dimensions of schizophrenia and presents findings from neuroimaging studies with structural, functional and spectroscopy magnetic resonance imaging and positron emission tomography. The potential of findings to be biomarkers of schizophrenia is discussed.

**Results:** Recent findings have not resulted in clear biomarkers for schizophrenia. However, we identified several biomarkers that are potential candidates for future research. Among them, copy number variations and links between genetic polymorphisms derived from genome-wide analysis studies, clinical or cognitive phenotypes, multimodal neuroimaging findings including positron emission tomography and magnetic resonance imaging, and the application of multivariate pattern analyses are promising.

**Conclusions:** Future studies should address the effects of treatment and stage of the disease more precisely and apply combinations of biomarker candidates. Although biomarkers for schizophrenia await validation, knowledge on candidate genomic and neuroimaging biomarkers is growing rapidly and research on this topic has the potential to identify psychiatric endophenotypes and in the future increase insight on individual treatment response in schizophrenia.

### ARTICLE HISTORY

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## Introduction

The phenotype of schizophrenia is still based solely on clinical criteria, with continued changes proposed in each revision of the International Statistical Classification of Diseases and Related Health Problems (now in its 10th revision; WHO 2010) and the Diagnostic and Statistical Manual of Mental Disorders (now in its 5th revision; APA 2013). Symptoms vary considerably during the course of the disorder because

of the heterogeneous composition of psychopathological symptoms, which include hallucinations, delusions, disturbances of self, thought disorders, psychomotor abnormalities, so-called “positive”, “negative” and affective symptoms and the widespread presence of cognitive deficits (Falkai 2011). Outcome also varies considerably: one episode and remission are seen in 10% of patients, several episodes and remission in 30%, several episodes with stable residuum in

10% and a chronic course with increasing residual symptoms in 40% (Watt et al. 1983; Marengo 1994; Lambert et al. 2010). Schizophrenia is considered to be either a syndrome or a group of different disorders, the “group of schizophrenias”, as described by E. Bleuler himself (Beckmann 1999). Despite tremendous efforts during the last decade (Stöber et al. 2009), valid biomarkers for improved early diagnosis and prediction of outcome and treatment response are lacking or still being evaluated. The most promising progress has been made in the field of cognition and endophenotypes (Derntl and Habel 2011; Kalia and Costa 2015), neuroimaging (Atluri et al. 2013) and genetics (Vawter et al. 2011); this progress will probably lead to improved diagnosis and development of innovative and personalised treatment strategies (Ozomaro et al. 2013).

### Heritability of schizophrenia

Family, twin and adoption studies (Cardno and Gottesman 2000; Sullivan et al. 2003; Wray and Gottesman 2012) and estimates from genome-wide association (GWA) studies (Gusev et al. 2014) demonstrate evidence for a strong genetic component in the aetiology of schizophrenia. The risk of developing the disease increases with the genetic relatedness to an individual with the disorder. Third-degree relatives have a risk of approximately 2% for developing schizophrenia, in comparison with the 0.5–1% risk in the general population. The risk increases to approximately 9% in first-degree relatives and to a concordance rate of up to 80% in monozygotic twins (Franzek and Beckmann 1998; Sullivan et al. 2003; Lichtenstein et al. 2006; Lichtenstein et al. 2009). The genetic liability is estimated to be 64–81% (Cardno and Gottesman 2000) and the heterogeneous phenotypic characteristics indicate a non-Mendelian and complex mode of inheritance (Thibaut 2006; Lee et al. 2012a; Kendler 2015). Common alleles with a high frequency in the general population together with rare variants may contribute to the risk of the disease.

### Endophenotypes

Attempts have been made to deconstruct the complexity of the genetic underpinnings of schizophrenia by using more elementary measurable phenotypes associated with the disease (called intermediate phenotypes or endophenotypes; Ferrarelli 2013). To meet endophenotype criteria, candidate markers must have the following characteristics: (1) heritable; (2) relatively

state-independent and stable over time; (3) associated with the illness (at least in part because of shared genetic influences); and (4) found in both affected and unaffected family members at a higher rate than in the general population (Gottesman and Gould 2003; Glahn et al. 2014). In the context of low correlation between phenotype and genotype in schizophrenia, these quantitative measurements could provide intermediate links between genetic variations and clinical phenotypes. Some neuropsychological endophenotypes have been widely studied in schizophrenia (Swerdlow et al. 2015; Thibaut et al. 2015) and seem promising for both diagnosis (Louchart-de la Chapelle et al. 2005; Thibaut et al. 2015) and measurement of functional outcome or response to treatment (Arfken et al. 2009; Light et al. 2012). Among neurophysiological endophenotypes, the largest effect sizes (with Cohen’s  $d$  effect size  $>1.5$ ) were reported in schizophrenia patients for neuromotor deviation, auditory-evoked P50 paradigms, functional magnetic resonance imaging (fMRI) activation during the 2-back task, the Continuous Performance Test (CPT) and oculomotor-delayed response (Allen et al. 2009). Smaller effect sizes (Cohen’s  $d > 1$ ) were reported by Light et al. (2012) for immediate verbal recall (California Verbal Learning Test-II, CVLT-II; List A), working memory (Letter Number Span, LNS; Wisconsin perseverative responses), mismatch negativity (MMN) and P300a amplitudes (associated with the automatic “Orienting Reflex”). Medium- to large-effect-size deficits have been reported in schizophrenia patients for the CPT, prepulse inhibition (PPI) of the acoustic startle reflex, the amplitude of MMN and P300 event-related potentials (Swerdlow et al. 2015). Deficits have also been described in first-degree relatives for LNS, CVLT, P50 suppression, N100 event-related potential amplitude, smooth pursuit eye movements (SPEM) and antisaccade performance (Louchart-de la Chapelle et al. 2005; Swerdlow et al. 2015). Some deficits, such as those observed with the PPI and P50 paradigms, may be sensitive to second-generation antipsychotic effects, so treatment with these antipsychotics needs to be controlled in analyses (Yee et al. 1998; Light et al. 2000).

In general, these measurements differ significantly between groups, are robust, reliable and state independent (except for P300 amplitude) and can be used as neurophysiological endophenotypes for genetic studies (Light et al. 2012; Swerdlow et al. 2015; Thibaut et al. 2015).

### Cognition

Neuropsychological deficits in schizophrenia have remained robust over time, despite changes in

assessment instruments and diagnostic criteria, and have been replicated in different regions of the world, regardless of linguistic and cultural differences (Schaefer et al. 2013). Schizophrenia is associated with impairments across a wide range of cognitive domains and in information processing. Factor analysis studies concluded that seven distinct cognitive factors were replicable across studies and represent fundamental dimensions of cognitive deficit in schizophrenia (Nuechterlein et al. 2004): *Processing speed, Attention/vigilance, Working memory, Verbal learning and memory, Visual learning and memory, Reasoning and problem solving* and *Verbal comprehension*; the first six factors were recommended for inclusion in the MATRICS Consensus Cognitive Battery (MCCB), the final version of which consists of 10 neuropsychological tests. In 2004, a seventh cognitive domain has been included in the NIMH-MATRICES: social cognition, because of its potential implication in functional outcome in schizophrenia (Nuechterlein et al. 2004). Indeed, data suggest that social cognition is a relatively unitary dimension that may serve as a mediator between neurocognitive deficits and functional outcome in schizophrenia.

However, there is still considerable uncertainty as to which is the best test to perform (Dickinson et al. 2007; Reichenberg and Harvey 2007; Bakkour et al. 2014); competing testing arrays include the NIMH-MATRICES Consensus Cognitive Battery (Green et al. 2004) and the CogState Schizophrenia Battery (Pietrzak et al. 2009). The domains' better correlations with social skills observed by Lees et al. (2015), suggest that the MCCB performance may have an advantage for measuring cognition in relation to functional outcome (Lees et al. 2015).

Deficits in the CPT in schizophrenia were reliably detected across five Northern American sites (2,251 participants), are relatively independent of current symptom severity and are related to functional capacity (Nuechterlein et al. 2015).

The influence of gender effects on cognitive performance, especially verbal performance, is still under debate (Canuso and Pandina 2007). The correlation between cognitive impairment and symptom severity in schizophrenia is only modest (Dominguez Mde et al. 2009; Ventura et al. 2010), and neurocognitive functioning does not appear to impact medication adherence (Sendt et al. 2015). Verbal memory and social cognitive deficits appear, however, to be the more robust markers of worse clinical outcome in schizophrenia (Lepage et al. 2014). The domain of social cognition was found to have a stronger association with community functioning and mediated an indirect relationship between neurocognition and functional

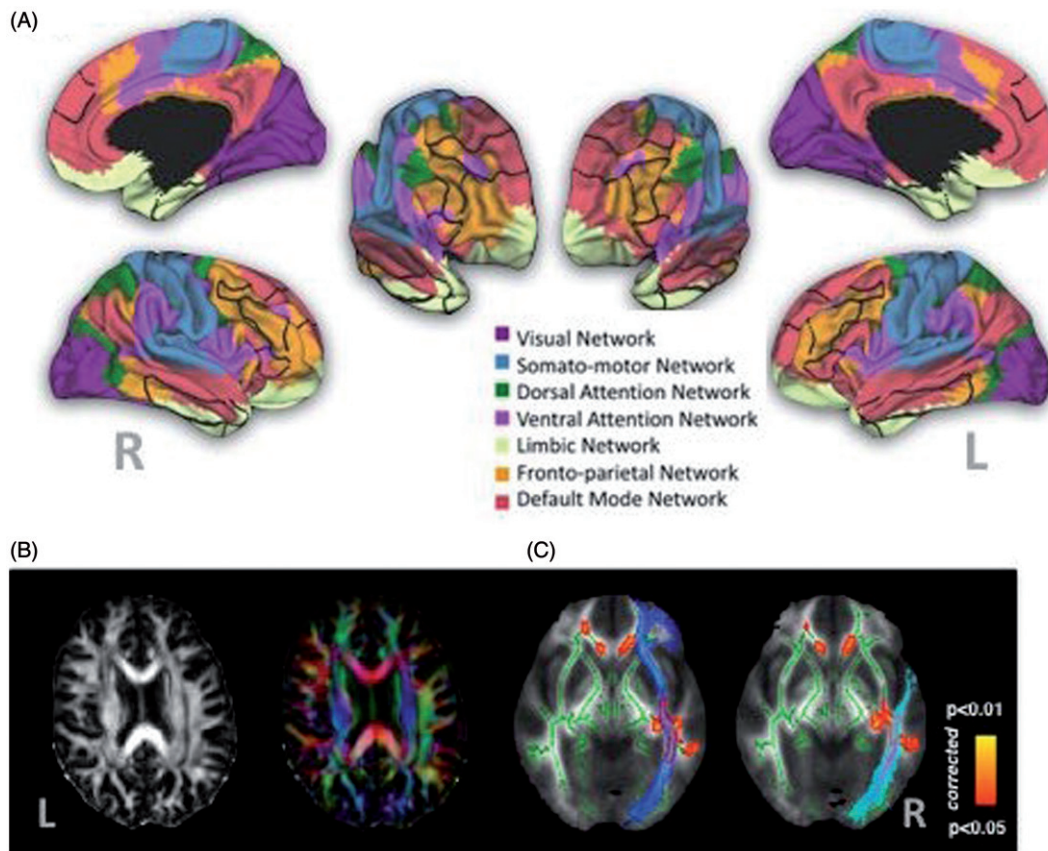
outcome (Fett et al. 2011; Schmidt et al. 2011). Cognitive function in schizophrenia patients appears to not necessarily follow a pattern of age-related decline, but deterioration accompanies and is related to: (1) onset of early symptoms and the first psychotic episode and then (2) follows natural aging at approximately age 65 years (Harvey 2014). The high-risk state of psychosis is associated with overall impairment in neurocognitive functioning and social cognition. Transition to psychosis appears to be particularly associated with deficits in verbal fluency and memory functioning (Fusar-Poli et al. 2012). Although impairment in verbal comprehension, scholastic achievement and verbal working memory are found among children at risk for schizophrenia (Dickson et al. 2014), predictive cognitive markers that discriminate acutely ill, stabilised or recovered patients from healthy individuals are still lacking (Saoud et al. 2000; Addington and Barbato 2012).

Cognitive impairment has been reported in bipolar disorders, particularly in patients with a history of psychotic symptoms (Tsitsipa and Fountoulakis 2015). Whether a generalised deficit exists across a spectrum of psychotic disorders is less clear. In addition, in the context of a broad cognitive impairment it remains difficult to identify deficits in specific cognitive processes with distinct neurochemical or regional brain substrates and linkages to particular risk-associated genetic factors (Reilly and Sweeney 2014).

## Neuroimaging

If schizophrenia has a biological basis, patients should show some characteristic structural and functional features that underlie the pathological process, and these features should be traceable by neuroimaging techniques. Indeed, a large proportion of schizophrenia patients have more or less pronounced abnormalities in various brain regions, including thinning of the frontal and temporal cortex (Haijma et al. 2013). However, it remains unclear whether these abnormalities are specific for schizophrenia and to what degree the findings of the vast majority of neuroimaging studies are clinically relevant (Sommer and Kahn 2015).

The so-called "hypofrontality" hypothesis (Weinberger & Berman 1988), which is in accordance with the dopamine (DA) hypothesis of evidence of decreased functional connectivity and impaired white matter integrity in frontal, temporal, thalamic and striatal regions in schizophrenia patients. The correspondence, i.e., the interregional coupling in neural activity associated with well-myelinated white matter pathways shown in controls was absent in schizophrenia



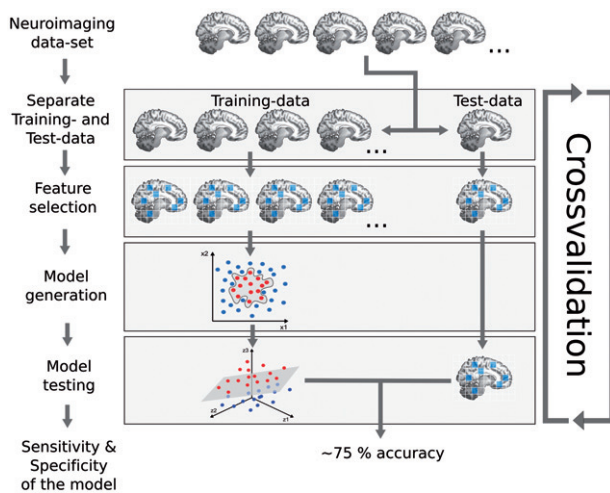
**Figure 1.** Multimodal imaging methods in schizophrenia. (A) Cortical resting-state functional MRI connectivity networks based on 1,000 healthy subjects (Yeo et al. 2011). The seven networks with similar patterns of connectivity found by Yeo et al. were used and projected on the Conte69 standard MRI template. The black lines show cortical brain regions that are frequently structurally and/or functionally impaired in schizophrenia. The left hemisphere is more often affected. Visualisation was done using workbench (<http://www.humanconnectome.org/software/connectome-workbench.html>). (B) Diffusion tensor fractional anisotropy (FA) shown as grey-scale diffusion metrics (left) as colour-coded principal direction of diffusion. Left-Right, red; anterior-posterior, green; inferior-superior, blue. Data from one sample schizophrenic patient of an ongoing study (64 diffusion directions,  $2 \times 2 \times 2$  mm spatial resolution). (C) At group-level the FA metrics of every single subject are projected on a white matter “skeleton” and differences between schizophrenic patients and healthy subjects can be displayed (used software: FSL: <http://www.fmrib.ox.ac.uk/fsl>, own data of a study with  $n = 22$  schizophrenic patients and age- and gender-matched subjects; red-yellow, significant clusters of decreased FA values in schizophrenic patients compared with healthy controls; dark-blue, left inferior fronto-occipital fasciculus; light-blue, left inferior longitudinal fasciculus). (This figure can be found in full colour in the online version of the article.)

patients. Such relations between function and structure in parietal, occipital and temporal cortices were not affected (Cocchi et al. 2014). The most characteristic change found in structural neuroimaging of schizophrenia patients is a reduction of grey matter volume, which tends to be more pronounced on the left side of the brain, especially in frontotemporal and limbic regions (Mueller et al. 2012; Fujiwara et al. 2015).

White matter changes and altered brain connectivity are considered to be related to the risk of developing schizophrenia (Sommer and Kahn 2015). Voxel-based morphometry (VBM) revealed a reduction in white matter in the frontal cortex and internal capsule bilaterally in schizophrenia patients compared to controls (Di et al. 2009), and diffusion tensor imaging (DTI) showed a reduction in fractional anisotropy values,

mainly in frontal and temporal deep white matter in the left hemisphere (Ellison-Wright and Bullmore 2009).

A multimodal approach to the structural and functional changes in schizophrenia may be optimal: a combination of fMRI, VBM and DTI revealed overlapping abnormalities (Mueller et al. 2012). Functional and structural connectivity changes have been found in schizophrenia patients compared with healthy controls (Figure 1). Resting-state functional connectivity density was decreased in schizophrenia patients in the bilateral sensorimotor cortices and the right occipital cortex (Zhuo et al. 2014). Altered structural integrity of white matter has been found in schizophrenia patients in various brain regions (frontal and temporal regions, cingulum bundles, uncinate fasciculus, internal capsules and corpus callosum), suggesting impairment of



**Figure 2.** Schematic illustration of the generation of neuroimaging-based multivariate classification models by using a cross-validation approach. Initially the data-set is separated into test and training data. In order to reduce the dimensionality of the data and to restrict the analysis to the most informative variables, a feature selection procedure might be implemented. In the model generation step a multivariate classification model is fitted to the training data. The models are then applied to the test data to estimate the classification performance of the model. In a cross-validation procedure all previous steps are repeated multiple times with different permutations of training- and test data to achieve a reliable estimate of the models' accuracy

multiple brain circuits in schizophrenia (Wheeler and Voineskos 2014).

Initial findings indicate that associations may exist between the observed structural changes and some characteristic clinical features of schizophrenia. Deficits in social cognition in schizophrenia, e.g., reduced recognition of facial emotions, were associated with structural abnormalities in various brain regions (Matsukawa and Murai 2013; Fujiwara et al. 2015). Motor abnormalities have been found in schizophrenia patients and are supported by neuroimaging studies of the cerebellum which revealed certain topographic changes in both schizophrenia patients and patients in at-risk states (Bernard and Mittal 2014). Also, parkinsonism has been associated with hyperechogenicity of the substantia nigra, both in chronic untreated schizophrenia patients and their relatives (Kamis et al. 2015).

A recent meta-analysis indicated that multivariate pattern analysis (MVPA) (Figure 2) allows schizophrenia patients to be differentiated from healthy controls with 80% accuracy on the basis structural neuroimaging data (Kambeitz et al. 2015). Another potential application of MVPA is in the field of differential diagnostics. In fact, because of the substantial symptomatic heterogeneity within and overlap across different psychiatric diagnoses, differential diagnostics might represent the

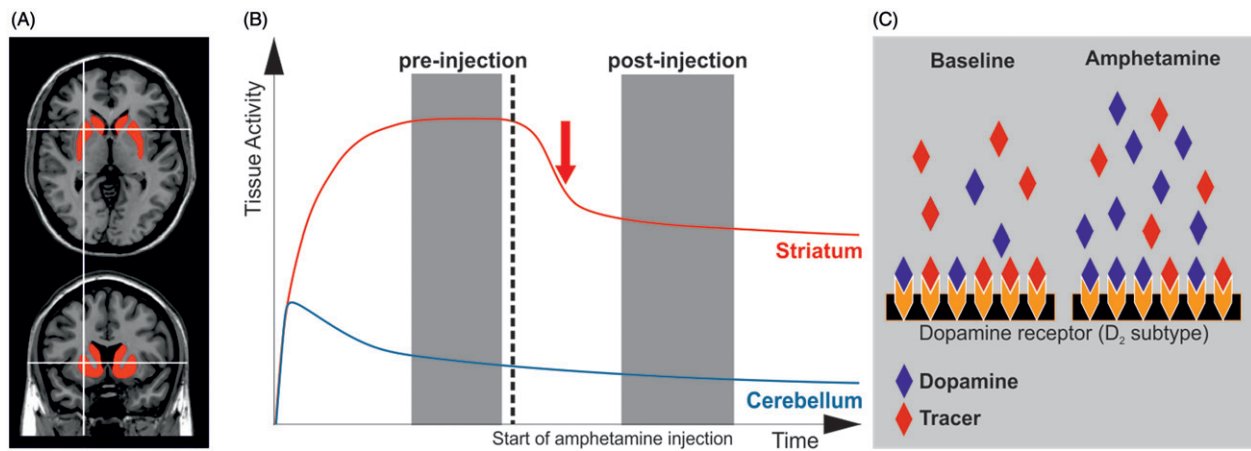
greatest clinical challenge in everyday care. Thus MRI-based differential diagnosis may develop into one of the most promising applications of MVPA. To date, several studies have investigated the reliability of MVPA techniques in separating different psychiatric populations at the single-patient level with fMRI and structural MRI (sMRI) data. Classification accuracies of 67 and 80% have been reported for the differentiation between depressive and bipolar patients on the basis of MVPA of fMRI data (Mourao-Miranda et al. 2012; Grotegerd et al. 2014). One study reported only relatively low accuracies for MVPA of sMRI data (Serpa et al. 2014), but a more recent study demonstrated 79% classification accuracy for the differentiation between patients with unipolar and bipolar depression (Redlich et al. 2014), and another study showed 88% accuracy for the differentiation between bipolar patients and patients with schizophrenia (Schnack et al. 2014). One DTI study reported accuracies of 72–88% when MVPA was used to differentiate healthy women from female schizophrenia patients (Ota et al. 2012). Another recently published study used near-infrared spectroscopy to differentiate between depressed, bipolar and schizophrenia patients (Takizawa et al. 2014) and measured classification accuracies of 75% for depressed and 86% for bipolar and schizophrenia patients. Moreover, MVPA of imaging data has been applied to differentiate between different types of dementia, e.g., to separate Alzheimer's dementia from frontotemporal dementia (Davatzikos et al. 2008). Although findings point to a promising potential application of MVPA of imaging data in the field of psychiatry, a multitude of methodological factors as well as characteristics of the investigated patient samples could likely moderate the success of MVPA-based models in classifying patients; consequently, future studies should address these factors in order to evaluate the potential of MVPA to inform everyday diagnostic workflows.

Functional imaging can identify abnormal brain function in schizophrenia patients. For instance, altered activation of the prefrontal cortex (PFC) and especially the dorsolateral prefrontal cortex (DLFPC) during working memory tasks is the most frequently documented finding in schizophrenia patients. When schizophrenia patients are compared with healthy controls, some parts of the PFC show a reduced blood oxygen level-dependent fMRI contrast and others show an increased one (Minzenberg et al. 2009). Altered activation of the PFC during working memory tasks and tasks that require "cognitive control" can be found in healthy first-degree relatives of schizophrenia patients (MacDonald et al. 2009). Recently, a growing number

of studies have documented another functional impairment in schizophrenia patients: deactivation of the default mode network when switching to a cognitive task. This applies in particular to the medial frontal cortex, which is one of the main constituents of this network (Buckner et al. 2008). Studies in resting-state functional connectivity seem to underpin these findings (Greicius 2008). Functional connectivity is defined as the temporal dependency of neuronal activation patterns of anatomically separated brain regions. However, examination of the default mode network in relatives of schizophrenia patients has so far been limited and findings have differed (Whitfield-Gabrieli et al. 2009; Sepede et al. 2010; Liddle et al. 2013). Future work in the field needs to continue to integrate brain imaging information across structural and functional modalities. In the future, these techniques could contribute to the understanding of altered brain plasticity and may lead to a better understanding of pathophysiological aspects of schizophrenia.

Research with positron emission tomography (PET) has validated the link between dopaminergic abnormalities, schizophrenia, schizophrenia symptoms and the risk for disease (Kasper et al. 2002). Furthermore, because PET allows changes to be elucidated at a molecular level it facilitates investigations into which cellular and functional components of a neurotransmitter system are affected. The most consistent PET evidence in schizophrenia has been found in the dopaminergic system. First, schizophrenia has been repeatedly associated with an increase in striatal [<sup>18</sup>F]DOPA and [<sup>11</sup>C]DOPA uptake, which reflects an increase in presynaptic dopaminergic synthesis (Fusar-Poli and Meyer-Lindenberg 2013b). Elevated dopaminergic synthesis has been demonstrated in cohorts of patients who had been, at least in part, previously or currently medicated (Lindstrom et al. 1999; Meyer-Lindenberg et al. 2002; McGowan et al. 2004; Kumakura et al. 2007; Howes et al. 2009), and neuroleptic-naïve patients (Hietala et al. 1995; Hietala et al. 1999), and has been shown to correlate with specific psychotic symptoms (McGowan et al. 2004). Persons at risk for developing schizophrenia also exhibit increased [<sup>18</sup>F]DOPA uptake, which may correlate with the severity of prodromal symptoms (Howes et al. 2009). It has been demonstrated that evaluation of striatal [<sup>18</sup>F]DOPA uptake allows for classification of schizophrenia patients and controls with approximately 60–90% sensitivity and specificity, depending on the quantification method used (Bose et al. 2008). In addition, dopamine transporter (DAT) distribution also reflects presynaptic dopaminergic function and can be interpreted as an index of dopaminergic cell density.

DAT ligand-binding results are, however, more inconsistent: Studies show evidence of increased [<sup>11</sup>C]PE2I thalamic (Arakawa et al. 2009) and reduced [<sup>18</sup>F]CFT striatal binding (Laakso et al. 2001). Symmetry of caudate DAT binding has been suggested to differ between schizophrenia patients and healthy controls (Laakso et al. 2000). Nevertheless, a meta-analysis of 13 PET studies on DAT density that included 202 patients regardless of prior or current antipsychotic medication made a strong case for a lack of change in DAT distribution in schizophrenia (Fusar-Poli and Meyer-Lindenberg 2013a). Furthermore, although extensively investigated, PET studies on DA receptor levels – in particular the D2 receptor – are similarly inconsistent (Suhara et al. 2002; Talvik et al. 2003; Yasuno et al. 2004; Buchsbaum et al. 2006; Talvik et al. 2006; Kessler et al. 2009; Kegeles et al. 2010; Suridjan et al. 2013). This inconsistency results in part from interaction between endogenous DA and the applied radioligand, and also from various factors that modulate DA levels. However, imaging of D2 and D3 receptors with radioligands such as [<sup>11</sup>C]raclopride (Farde et al. 1986; Verhoeff et al. 2002), [<sup>18</sup>F]fallypride (Mukherjee et al. 2002; Cropley et al. 2008) and [<sup>11</sup>C]PHNO (Willeit et al. 2006; Caravaggio et al. 2014) also allows for indirect assessment of DA levels in response to dynamic conditions (Figure 3). Basal DA levels, which can be assessed by DA depletion and a resulting increase in receptor availability, are significantly higher in schizophrenia patients: receptor availability increases by about 15% in patients versus 10% in controls (Kegeles et al. 2010). Schizophrenia has also been repeatedly and consistently associated with increased dopaminergic reactivity both to amphetamine (Breier et al. 1997) and psychosocial stress (Mizrahi et al. 2012). For example, amphetamine application in schizophrenia patients results in a significantly higher reduction in [<sup>11</sup>C]raclopride binding (which represents DA release) in patients (>20%) than in controls (about 15%). These results were not affected by previous antipsychotic treatment (Breier et al. 1997). Single-photon emission-computed tomography (SPECT) studies have shown a tracer reduction that is twice as high in patients than in controls (Laruelle et al. 1996). This increased reactivity to amphetamine challenge in schizophrenia patients has been replicated several times in PET and SPECT studies and might be one of the most promising molecular neuroimaging markers in schizophrenia. Such modulation of dopaminergic function is likely to reflect a neurobiological correlate of risk for schizophrenic symptoms. Perhaps most compellingly, prodromal and clinically high-risk groups also show changes in these dopaminergic PET parameters (Hirvonen et al. 2005;



**Figure 3.** Schematic representation of amphetamine challenge study design in humans. Challenge studies using PET allow for the indirect assessment of changes to synaptic dopamine (DA) levels after application of amphetamine (Breier et al. 1997; Ginovart 2005). (A) The striatum (red) is the region of interest for the assessment of changes to DA levels in amphetamine challenge studies. The striatum exhibits a high density of D2 receptors (Willeit et al. 2006), which can be imaged using [<sup>11</sup>C]raclopride (Farde et al. 1986), [<sup>18</sup>F]fallypride (Mukherjee et al. 2002) or [<sup>11</sup>C]PHNO (Willeit et al. 2006). (B) After a baseline period (pre-injection) to allow for establishment of radioligand–DA equilibrium, amphetamine is injected (denoted with dotted line) and levels of specifically bound radioligand (post-injection) decrease in the striatum (red line) due to displacement by DA, while they remain constant in the cerebellum (blue line), the reference region (Breier et al. 1997). (C) Changes to DA levels are assessed indirectly. Prior to amphetamine injection (left), DA and radioligand binding of the D2-receptor are at equilibrium. After amphetamine injection (right), DA levels increase and DA displaces the radioligand from the D2-receptor, resulting in a lower signal of specifically bound radioligand (Ginovart 2005). (This figure can be found in full colour in the online version of the article.)

Lee et al. 2008; Howes et al. 2009; Brunelin et al. 2010). However, as of yet, studies in at-risk patients lack sufficient power for assessment of the clinical applicability of these findings.

PET studies on changes to the serotonergic system are far less extensive and less conclusive. 5-HT<sub>2A</sub> represents an important target because of its role in the pharmacodynamics of atypical neuroleptics. Changes to 5-HT<sub>2A</sub> receptor distribution have been shown in a range of reports, although with widely inconclusive results (Erritzoe et al. 2008; Hurlmann et al. 2008; Rasmussen et al. 2010). In addition, changes to the 5-HT<sub>1A</sub> receptor have been demonstrated with PET in some studies (Tauscher et al. 2002), but not in others (Frankle et al. 2006). The inconsistency in serotonergic PET findings in schizophrenia may be due in part to the heterogeneity of the schizophrenia patient groups investigated in these studies and high variability within the serotonergic system, in contrast to more consistent findings in dopaminergic function in this patient group.

In summary, changes to DA synthesis and basal and challenge-related endogenous DA levels represent the most consistent and therefore convincing PET evidence in schizophrenia, especially the strongly increased DA levels after amphetamine challenge. Although data on changes to the dopaminergic system in prodromal and at-risk states show great potential for clinical relevance, sensitivity and specificity need to be investigated in

larger patient groups. Currently, PET studies have yet to reveal consistent data on changes to the serotonergic system.

A number of magnetic resonance spectroscopy (MRS) studies have demonstrated alterations in the concentrations of glutamate, glutamine (a precursor of glutamate) and Glx (a combination of both amino acids) in antipsychotic-naïve, antipsychotic-free or medicated schizophrenia patients (Poels et al. 2014a, 2014b; Salavati et al. 2015). These studies revealed elevated Glx levels in the medial prefrontal cortex (mPFC), parietal, occipital, anterior cingulate, thalamus and basal ganglia regions; elevated levels of glutamine in the mPFC, thalamus and anterior cingulate cortex; elevated levels of glutamate in the basal ganglia; decreased levels of glutamate in the thalamus; and no differences or unclear findings regarding glutamatergic metabolites in the DLFPC and temporal and cerebellum regions (Salavati et al. 2015). Some studies (de la Fuente-Sandoval et al. 2011; Kegeles et al. 2012; de la Fuente-Sandoval et al. 2015) showed elevated levels of glutamate (or Glx) in the prodromal state and in unmedicated schizophrenia patients. A recent MRS study showed an increase of glutamate in the frontal and anterior cingulate cortex of antipsychotic-naïve patients with first-episode psychosis, and found a positive correlation between glutamate and membrane lipids (phosphomonoesters and phosphodiester) in the patients (Smesny et al. 2015). Furthermore, another



recent MRS study showed an increase of glutamate in the associative striatum of antipsychotic-naïve patients with first-episode psychosis and found positive correlations between glutamate and myo-inositol (or choline) in the antipsychotic-naïve patients with first-episode psychosis (Plitman et al. 2015). Given the role of myo-inositol and choline in the glial cells, dysregulation of glial function is likely to result in the disruption of glutamatergic neurotransmission, which may play a role in the psychosis in the first-episode patients. Overall, glutamate levels are somewhat elevated in early-phase, drug-free patients and decrease after treatment (Poels et al. 2014a, 2014b). In 2005, we reported an elevated ratio of glutamine to glutamate in cerebrospinal fluid (CSF) samples of first-episode and drug-naïve patients with schizophrenia (Hashimoto et al. 2005a), suggesting an abnormality of the glutamine–glutamate cycle in neuron–glia communication in schizophrenia. A recent ultra-high resolution 7T <sup>1</sup>H-MRS study showed a lower ratio of  $\gamma$ -aminobutyric acid (GABA) to creatine in the prefrontal cortex in schizophrenia patients compared with healthy controls, although levels of glutamate were not altered (Marsman et al. 2014). The inhibitory amino acid GABA is also synthesised from glutamate via glutamic acid decarboxylase (Hashimoto 2014a). Taken together, alterations in the glutamine–glutamate–GABA cycle play a role in the pathophysiology of schizophrenia (Hashimoto 2014a, 2014b).

Glutathione (GSH; L-glutamyl-L-cysteinyl-glycine), the most abundant thiol in mammalian cells that is present at concentrations of up to 12 mM, is a nucleophilic scavenger and an enzyme-catalysed antioxidant. Glutathione potentiates the *N*-methyl-D-aspartate (NMDA) receptor response to glutamate by acting at the redox modulatory site(s) (Hashimoto 2014b). Do et al. (2000) reported that the CSF levels of GSH in drug-free schizophrenia patients were significantly (27%) lower than in controls. A <sup>1</sup>H-MRS study demonstrated that the levels of GSH in the mPFC of schizophrenia patients were 52% lower than in controls (Do et al. 2000). Subsequently, Matsuzawa et al (2008) found a negative correlation between GSH levels in the prefrontal cortex and the severity of negative symptoms in schizophrenia patients, although no differences in GSH levels were detected between the two groups (Matsuzawa et al. 2008). Currently, the MRS findings concerning GSH in the brain are inconsistent. The differences in sequences and spectral editing techniques and clinical factors (e.g., medication status, phase of illness) may contribute to the discrepancies in GSH concentration (Poels et al. 2014a). Interestingly, the antioxidant *N*-acetyl-L-cysteine, a precursor of GSH,

has been reported to be effective in the treatment of schizophrenia (Berk et al. 2008). In summary, it is likely that oxidative stress associated with reduced GSH levels in the brain plays a crucial role in the pathophysiology of schizophrenia (Hashimoto 2014b).

## Neurogenetics

In this section, we will present the most important genetic findings in neuropsychiatric diseases. Most of the GWA studies provide only small odds ratios and therefore are not suitable as biomarkers in a single individual. Nevertheless, copy number variation (CNV) studies provide very high odds ratios, assuming that these deletions or duplications will be accepted as biomarkers in the near future.

## GWA studies

GWA studies represent a major development in human genetics. Technological progress currently allows up to 1,000,000 single nucleotide polymorphisms (SNPs) to be genotyped in one run. The first GWA study on schizophrenia was performed with 178 cases and 144 controls and showed an association of CSF2RA (colony-stimulating factor, receptor 2 $\alpha$ ); the second study found no genome-wide significance (Lencz et al. 2007; Sullivan et al. 2008). Both studies seemed underpowered to provide conclusive results. The first GWA study to deal with this problem performed an initial GWA on 479 cases and 2,937 controls; in a subsequent international survey in up to 6,829 cases and 9,897 controls the research group then examined loci that had surpassed  $P < 10^{-5}$  (O'Donovan et al. 2008). Among 12 of these loci, three had strong independent support and the overall pattern of replication was unlikely to occur by chance. The association was strengthened for the top gene, ZNF804A, when bipolar disorder was included in the affected phenotype, a finding that challenged the traditional diagnostic boundaries and simultaneously reduced the specificity of ZNF804A as a biological marker for schizophrenia (O'Donovan et al. 2008). Within the SGENE + consortium, a further GWA analysed 2,663 schizophrenia cases and 13,498 controls from eight European locations (Stefansson et al. 2009). The study combined findings from the top 1,500 markers with results for these same markers (or surrogates for them) from both the International Schizophrenia Consortium (ISC; 2,602 cases/2,885 controls) and the European-American portion of the Molecular Genetics of Schizophrenia (2,687 cases/2,656 controls) studies. The top markers were followed-up in 5,013 cases and 15,559 controls from four sets of

additional samples from Europe, leading to the identification of three novel candidate schizophrenia loci: neurogranin, transcription factor 4 (TCF4) and the human leukocyte antigen (HLA) region (Stefansson et al. 2009). The HLA associations were also found in the large GWA by the ISC (International Schizophrenia Consortium et al. 2009), which studied 3,322 Europeans with schizophrenia and 3,587 controls, as well as by Shi et al. (2009).

Because sample size plays a crucial role in GWA studies, the Schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC) combines as many schizophrenia cases and controls as possible. In 2011, the PGC published results on 51,695 individuals of European ancestry. The combined analysis yielded non-replication in most of the earlier candidate regions but found genome-wide significant associations with schizophrenia for seven loci, five of which were new (1p21.3 [MIR137], 2q32.3 [PCGEM1], 8p23.2 [CSMD1], 8q21.3 [MMP16] and 10q24.32-q24.33 [CNNM2, NT5C2]) and only two of which had been implicated previously (6p21.32-p22.1 [TRIM26] and 18q21.2 [CCDC68, TCF4]). The strongest new finding was for rs1625579 within an intron of a putative primary transcript for MIR137 (microRNA 137), a known regulator of neuronal development. Four other schizophrenia loci that achieved genome-wide significance predicted targets of MIR137, suggesting MIR137-mediated dysregulation as a previously unknown aetiological mechanism in schizophrenia. In a joint analysis with a bipolar disorder sample (16,374 affected individuals and 14,044 controls), three loci reached genome-wide significance (Lee et al. 2012b): CACNA1C (rs4765905), ANK3 (rs10994359) and the ITIH3-ITIH4 region (rs2239547).

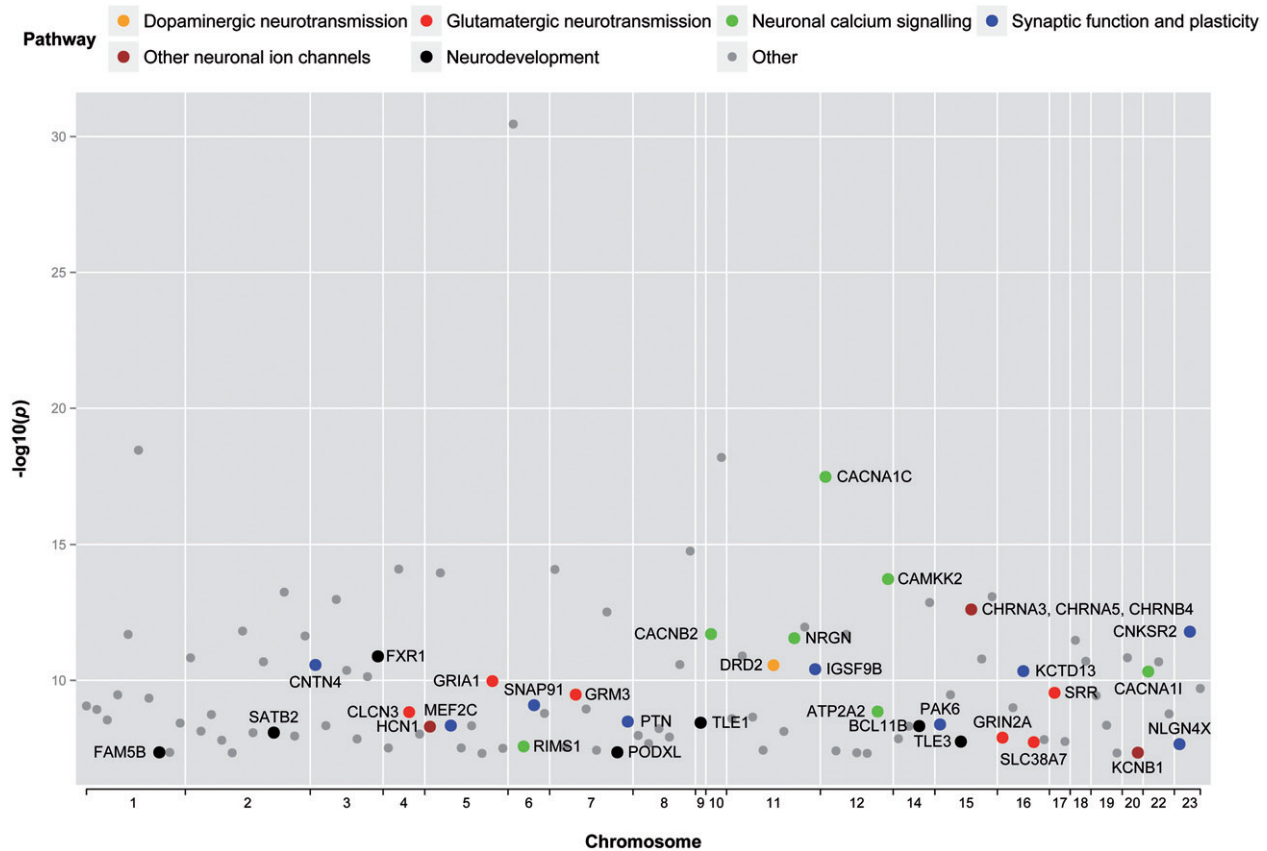
Another large GWA study, with 5,001 cases and 6,243 controls, was followed by a meta-analysis with previous schizophrenia GWA study data (8,832 cases and 12,067 controls) and finally by replication of SNPs in 168 genomic regions in independent samples (7,413 cases, 19,762 controls and 581 parent-offspring trios). Twenty-two loci were identified that were associated with genome-wide significance; five had been reported previously as having genome-wide significance for schizophrenia alone (MHC, WBP1L/C10orf26, DPYD-MIR137, SDCCAG8 and MMP16) and three had been reported to be associated with a combined phenotype including schizophrenia and bipolar disorder (CACNA1C, CACNB2 and ITIH3-ITIH4). Thirteen loci were new (MAD1L1, TSNARE1, SNX19, two loci near GRIA1, QPCT, SLC06A1, ZEB2, FONG, one locus near TCF4, C2orf82, AKT3, C12orf65, one locus near ZSWIM6) and one was previously implicated in bipolar disorder (NCAN). Examination of candidate genes at these loci

suggested the involvement of neuronal calcium signalling. Furthermore, the highest significance was seen for the MHC region, with best  $P$  values =  $1.5 \times 10^{-17}$  (Ripke et al. 2013).

It should be mentioned that most of these results have only small odds ratios and these loci are currently a long way from being biomarkers in a single individual. Nevertheless, these results provide in-depth knowledge on the pathophysiology of the disease and will pave the way for further research.

The latest and largest GWA on schizophrenia was published in 2014, again by the Schizophrenia PGC (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). In a multistage GWA study of up to 36,989 cases and 113,075 controls, 128 independent associations spanning 108 conservatively defined loci were identified; 83 of which had not been previously reported. The best  $P$  values were detected for the MHC region ( $P = 3.48 \times 10^{-31}$ ). Associations were enriched among genes expressed in the brain. Interestingly, a number of former candidate genes such as DRD2 and several genes involved in glutamatergic neurotransmission (GRM3, GRIN2A, SRR, GRIA1) reached genome-wide significance (Figure 4). This finding highlighted the relevance of molecules with known and potential therapeutic significance for schizophrenia and was consistent with the leading pathophysiological hypotheses (Cross-Disorder Group of the Psychiatric Genomics et al. 2013).

Notable associations relevant to the glutamate hypothesis of schizophrenia include the four genes *GRM3* (metabotropic glutamate receptor 3), *GRIN2A* (NMDA receptor subunit GluN2A), *GRIA1* (GluA1 subunit of AMPA receptor) and *SRR* (serine racemase) (Table 1) (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014) (Figure 4). NMDA receptor binding was increased in the putamen of schizophrenia patients compared to controls (Kornhuber et al. 1989), possibly to compensate for low tissue levels of glutamate and NMDA (Errico et al. 2013). Protein levels of mGluR3, but not mGluR2, were decreased in the DLPFC of schizophrenia compared to controls (Ghose et al. 2009). Expression of GluN1, GluN2A and GluN2B was downregulated in the DLPFC of schizophrenia patients compared to controls and correlated to lower levels of D-aspartate and NMDA in schizophrenia patients (Errico et al. 2013), confirming the NMDA receptor hypofunction hypothesis in schizophrenia. In short-term habituation, *Gria1* knock-out mice showed sensitisation and selective impairment, both of which are relevant to schizophrenia (Barkus et al. 2014). *SRR* is an enzyme that generates D-serine, an endogenous obligatory co-agonist of NMDA receptors, from L-serine (Hashimoto



**Figure 4.** P values of 108 L,D-independent genome-wide significant loci identified in the largest GWA study in schizophrenia conducted by the Psychiatric Genomics Consortium. P values of associated regions correspond to the smallest P value of all markers in that region. Highlighted are regions and selected associated genes in relevant pathways. It must be stressed that “association only implies the existence of one or more risk variant at the associated locus rather than that a specific gene is responsible for the association” (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014).

**Table I.** Glutamate-related genes identified in the most recent and largest GWA study by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014).

Gene	Chromosomal localisation	Biological function	Alteration in schizophrenia
<i>GRM3</i>	7q21.1-q21.2	Encodes the metabotropic glutamate receptor 3 (mGluR3). mGluR3 is predominantly localised in glia cells. <i>N</i> -acetylaspartylglutamate (NAAG) is an endogenous agonist at mGluR3.	Reduction in mGluR3 protein in the DLFCP in schizophrenia, with no changes in mGluR2 protein (Ghose et al. 2009).
<i>GRIN2A</i>	16p13.2	Encodes the NMDA receptor subunit GluN2A, a key modulator of synaptic plasticity. NMDA receptor antagonists such as phencyclidine and ketamine cause schizophrenia-like psychotic symptoms (e.g., positive and negative symptoms and cognitive impairment) in humans.	NMDA receptor binding was increased in the putamen of patients with schizophrenia (Kornhuber et al. 1989). Tissue levels of GluN1, Glu2A and GluN2B in the prefrontal cortex with schizophrenia were lower than those of controls (Errico et al. 2013). Furthermore, tissue levels of D-aspartate and NMDA in the prefrontal cortex of schizophrenia were also lower than those of controls (Errico et al. 2013).
<i>GRIA1</i>	5q31.1	Encodes the GluA1 subunit of AMPA receptor that mediates fast synaptic transmission.	<i>Gria1</i> knock-out (KO) mice showed selective impairments in short-term habituation and also sensitisation (Barkus et al. 2014). These deficits are relevant to patients with schizophrenia.
<i>SRR</i>	17p13	Encodes serine racemase (SRR), which synthesises D-serine from L-serine in the neuron. D-serine is an endogenous obligatory co-agonist of the NMDA receptor and binds to the glycine modulatory site of the GluN1 subunit in the NMDA receptor.	Decreased levels of D-serine in blood and CSF from schizophrenia patients (Hashimoto et al. 2003; 2005a; Bendikov et al. 2007). D-serine is effective in the treatment of patients with schizophrenia (Tsai and Lin, 2010).

et al. 2013; Hashimoto 2014b). Previously, reduced levels of D-serine and a reduced ratio of D-serine to total serine were reported in both the blood and CSF of schizophrenia patients (Hashimoto et al. 2003; Hashimoto et al. 2005b; Bendikov et al. 2007). In addition, D-serine was shown to be effective in the treatment of several symptoms of schizophrenia (Tsai and Lin 2010). Therefore, decreased D-serine levels may contribute to the NMDA receptor hypofunction in schizophrenia, and D-serine treatment may be more effective in patients with decreased D-serine levels. However, it has to be noted that beside well-known dopaminergic and serotonergic neurotransmitters, antipsychotic treatment may also influence the glutamatergic system (Zink et al. 2014).

In summary, from GWA studies it seems that the association between the HLA region and schizophrenia is the most robust and replicated result from GWA studies. Other polymorphisms suggest a glutamatergic dysfunction in schizophrenia and also in some pathways involved in neurodevelopment, but until now they do not constitute risk factors, even at the population level. In addition to common variants, rare structural variants have been associated with schizophrenia risk.

### **Identification of rare risk variants before GWA studies**

The fact that a Mendelian mode of inheritance could not be identified for schizophrenia indicated that either no or only a very few rare mutations such as the 22q11.2 microdeletion or the balanced chromosomal translocation that disrupts the *DISC1* gene (1;11)(q42.1;q14.3) play a significant aetiological role in schizophrenia. The situation changed with the detection in GWA studies of microdeletions and microduplications, which may significantly increase the risk of schizophrenia in a given person (Stefansson et al. 2008).

The disruption of genes by balanced translocations detectable at the microscopic level has played an important part in the discovery of many common Mendelian disorder genes. The Disrupted-in-Schizophrenia-1 (*DISC1*) gene is an example of such a disruption. *DISC1* was identified via a balanced translocation at 1:11 (q42; q14.3) and linked to both schizophrenia and depressive disorders in a Scottish family (St Clair et al. 1990). It is a highly pleiotropic gene with effects on cellular proliferation, migration, dendritogenesis, synaptogenesis and intracellular signalling and appears to be important for both the developing and adult brain (Porteous et al. 2014; Randall et al. 2014).

A microdeletion at 22q11.2 is responsible for velocardiofacial syndrome (VCFS), also known as DiGeorge syndrome. In 1992, besides the characteristic dysmorphic and congenital symptoms, Shprintzen et al. (1992) first described the high risk of schizophrenia-like psychotic symptoms in people with this syndrome (in about 30% of patients). The hope that this deletion could serve as a model for schizophrenia resulted in a series of animal models and cell culture studies. However, it is still unclear which of the genes in this deletion region are responsible for the predisposition of people with VCFS to neurocognitive deficits and psychosis. Catechol-O-methyltransferase (COMT) and ProDH genes may be involved in mental retardation and psychosis (Raux et al. 2007). For instance, the deletion region contains genes involved in brain function and neurodevelopment, including COMT, ProDH, TBX1, GNB1L and more (Jacquet et al. 2002; Squarcione et al. 2013; Schneider et al. 2014).

### **CNVs through GWA studies**

With the completion of the Human Genome Project, the rapid development of new whole-genome scanning technologies has started to fill the resolution gap between traditional cytogenetic analysis (>2 Mb) and mutation analysis by DNA sequencing (<1 kb). As a result, a large number of previously undetected variations in the human genome have been revealed. One of the most intriguing types of variation, whose extent was previously unappreciated, are CNVs, the loss or gain (not only deletion or duplication as the author believes) of genomic DNA with a size larger than 1 kb (Grayton et al. 2012).

A first family-based study suggested that de novo CNVs are significantly more common in sporadic cases than in controls or familial cases of schizophrenia, accounting for approximately 10% of the sporadic cases (Xu et al. 2008), whereas an independent case-control study found novel deletions and duplications of genes in 5% of controls versus 15% of cases and 20% of young-onset childhood-onset cases (Walsh et al. 2008). Both studies were statistically underpowered to prove the involvement of any specific CNV.

The SGENE + consortium studied a population-based sample by analysing 9,878 transmissions from parents to offspring (Stefansson et al. 2008). Sixty-six de novo CNVs were identified and tested for association in a sample of 1,433 schizophrenia cases and 33,250 controls; among these, three deletions (1q21.1: 0.23 and 0.02%, odds ratio [OR] = 14.83; 15q11.2: OR = 2.73; and 15q13.3: 0.17 and 0.02%, OR = 11.54; schizophrenia patients vs. controls, respectively) showed nominal

association in the first sample and were followed-up in a second sample of 3,285 cases and 7,951 controls. In a genome-wide survey of rare CNVs in 3,391 patients with schizophrenia and 3,181 controls (International Schizophrenia Consortium 2008), the total number of CNVs >100 kb in length and observed in less than 1% of the sample was increased 1.15-fold in patients with schizophrenia in comparison with controls. Associations for 15q13.3, 1q21.1 and 15q11.2 have been replicated by different studies, including meta-analyses (Kirov et al. 2009a; Levinson et al. 2011; Rees et al. 2014b).

Deletions within the neurexin 1 gene (NRXN1; 2p16.3), previously associated with autism, have also been reported in two families with schizophrenia (Kirov et al. 2008; Walsh et al. 2008). The SGENE + consortium examined NRXN1 for CNVs in 2,977 schizophrenia patients and 33,746 controls. CNVs that disrupt exons were significantly enriched in cases (0.24 vs. 0.015% in controls) with OR = 8.97 showing that NRXN1 deletions confer risk of schizophrenia (Rujescu et al. 2009). A meta-analysis of 8,789 schizophrenia patients and 42,054 controls showed a frequency of 0.19% of deletions (>100 kb) in patients and 0.04% in controls (OR = 4.78, 95% CI 2.44–9.37). Odds ratios were even higher for deletions (>100 kb) that disrupt exons (OR = 7.44, 95% CI 3.22–17.18) (Kirov et al. 2009b).

Further CNVs have been associated with schizophrenia, such as the 3q29 microdeletion (Mulle et al. 2010; Levinson et al. 2011), which showed the highest OR in a meta-analysis (OR = 57.65, 95% CI 7.58–438.44) (Rees et al. 2014b). CNVs at 16p11.2 (Guha et al. 2013), 17p12 (Kirov et al. 2009a) and 17q12 (Moreno-De-Luca et al. 2010) were confirmed in a recent meta-analysis (Rees et al. 2014b).

Further studies added new deletions at DLG2 (discs large gene2, a member of the family of membrane-associated guanylate kinases), which is a component of the postsynaptic density, and at EHMT1, a histone methyl transferase known to directly regulate DLG family members (Kirov et al. 2012).

Besides deletions, several studies have provided evidence for an increased frequency of duplications and genomic gains in schizophrenia at the following locations: 1q21.1 (Levinson et al. 2011), 7q11.23 (genomic region of Williams-Beuren syndrome; Kirov et al. 2012; Mulle et al. 2014) and 7q36.3, which involves the neuropeptide receptor gene VIPR2 (Levinson et al. 2011; Vacic et al. 2011). Although the locus at 7q36.3 initially was not found to be significant, it showed a significant association in the meta-analysis (Rees et al. 2014b).

Duplications associated with schizophrenia are seen also at other locations. These duplications include 15q11-q13 (Ingason et al. 2011a) and 16p13.11 (Ingason et al. 2011b; Rees et al. 2014b), both of which were confirmed in a meta-analysis by Rees et al. (2014b). A duplication identified at 16p11.2 (McCarthy et al. 2009; Levinson et al. 2011; Steinberg et al. 2014) showed the strongest association in a different meta-analysis (Rees et al. 2014a).

It is notable that a number of CNVs identified as enriched in psychosis have also been identified as enriched in other neurodevelopmental and neurological disorders, including mental retardation, autism and seizures (Grayton et al. 2012; Grozeva et al. 2012). 16p11 and 3q29 deletions have also been reported in people with bipolar disorder (Lee et al. 2012b).

In summary, associations for 15q13.3 and 1q21.1 microdeletions have been replicated by different studies and have been reported in schizophrenia patients without mental retardation. Both microdeletions may significantly increase the risk for schizophrenia (about 15 times) in a given person. These rare and de novo mutations may be transmitted but their mode of inheritance remains poorly understood. In addition, the same CNVs may be associated with different phenotypic expressions (e.g., bipolar disorder, schizophrenia, autism, mental retardation and cranial size, even in the same families). They may also interact with other rare or common variants or with epigenetics, which may contribute to different phenotypic expressions.

### **Next-generation sequencing**

Next-generation sequencing, a result of technological progress, is a recent breakthrough in genetics. Also, high-throughput sequencing has become available for both exome and whole-genome sequencing. These techniques can be applied in case-control studies or the detection of de novo mutations by sequencing both unaffected parents and the affected child (triads) or families with high loading of schizophrenia subtypes (Stöber et al. 2009). However, sequencing may generate some data with false-positive variants and therefore studies should be replicated in large samples. Some studies on sequencing cases and their unaffected parents have shown promising results, but these have not been replicated (Girard et al. 2011; Xu et al. 2011, 2012; Gulsuner et al. 2013; McCarthy et al. 2014). The largest sequencing project in schizophrenia was performed on 623 triads and found evidence for de novo mutations over-represented among glutamatergic postsynaptic proteins comprising activity-regulated cytoskeleton-associated protein and

N-methyl-D-aspartate receptor (NMDAR) complexes (Fromer et al. 2014); this finding is supported by the largest exome-sequencing study so far performed with 2,536 schizophrenia cases and 2,543 controls (Purcell et al. 2014). There is hope that all these new technologies will help to dissect the heritability of schizophrenia and provide further insight into the pathophysiology of this disease.

### ***Associations between endophenotypes and susceptibility genes***

In contrast to GWA and CNV studies on the phenotype schizophrenia, the findings on endophenotypes are less convincing, although several endophenotypes have been linked to genes that are potentially consistent with the pathophysiological models for schizophrenia. Deficits in sensory-motor gating in schizophrenia patients have been linked to septohippocampal cholinergic activity (involving the alpha 7 subunit of nicotinic receptors). Promoter variants (in the alpha 7 gene) or variants located in the alpha 7-like gene were associated with P50 inhibition deficits but not with schizophrenia (Leonard and Freedman 2006; Raux et al. 2007; Cabranes et al. 2013; Liu et al. 2013). In addition, polymorphic sites at the TCF4 and the DAT 1 and 2 genes (DRD1, DRD2) may interact with smoking in the modulation of sensory gating (Knott et al. 2010; Millar et al. 2011; Quednow et al. 2012).

The COMT gene (22q11) may also be considered as a candidate gene for disturbances in sensory gating, PPI or SPEM in schizophrenia because of its physiological effects on prefrontal functions, including degradation of DA. The PPI index revealed an association between pulse latency and the Val158Met COMT polymorphism (Liu et al. 2013). Considering the evidence accumulated over time, there is little support for any association between COMT Val158Met and P50 gating deficits (Lu et al. 2007; Olincy et al. 2010; Shaikh et al. 2011; Liu et al. 2013) or SPEM disturbances (Haraldsson et al. 2009; Park et al. 2009; Rybakowski et al. 2002). The antisaccade latency may be influenced by the COMT gene (Haraldsson et al. 2010b), but in men with schizotypal disorder no association is evident between the antisaccade paradigm measures and the COMT polymorphism (Stefanis et al. 2004). In contrast, other genes located in the 22q11 region, such as the zinc finger DHH domain-containing protein 8 (ZDHC8) or the Ran-binding protein (RANBP) RANBP1-ht2, might have some influence on SPEM function in schizophrenia patients, as was shown in a Korean population (Shin et al. 2010; Cheong et al. 2011).

A lack of association was reported between NRG1 and SPEM disturbances or P50 deficits in schizophrenia (Haraldsson et al. 2010a; Schmechtig et al. 2010; Shaikh et al. 2011; Kim et al. 2012) or the receptor tyrosine-protein kinase erbB-4 (ERBB4) gene (Bae et al. 2012). In contrast, NRG1 rs3924999 may affect spatial accuracy on the antisaccade task (Schmechtig et al. 2010).

Several genes have been associated with the auditory oddball P300 measures. COMT has been associated with amplitude (Gallinat et al. 2003; Golimbet et al. 2006) and NRG1 with latency (Kang et al. 2012) and a significant association was reported between the P300 amplitude elicited by novel sounds (P3b component) and ZNF804A (Del Re et al. 2014).

### ***Modifier genes***

Genetic factors that influence symptom dimensions without necessarily conferring risk for the disease have been reported as modifier genes. Edwards et al. (2015) reported associations between common genes and negative or positive symptoms of schizophrenia; notably, NKAIN2 and NRG1 were associated with negative and positive symptoms, respectively. However, no single marker has met the genome-wide significance threshold.

Some authors have reported associations between the total number of base pairs affected by copy number deletions or duplications genome wide and treatment resistance, clinical characteristics or cognitive abilities of schizophrenia patients, although the odds ratios are close to 1 (Yeo et al. 2013; Martin et al. 2014; Martin and Mowry 2015).

### ***Summary***

Genetic studies should also consider the potential for interactions between multiple loci at the same or different genes (epistasis). The genes identified so far from traditional mapping, CNV analysis and other strategies point to several biological pathways, such as the integrity of the synapse, the wnt/GSK3 $\beta$  signalling pathway (DISC1, TCF4, etc.), GRIK4 or NPAS3 (which are involved in neurogenesis in the brain), glutamatergic signalling (NRG1, DTNBP1, ProDH, D-amino acid oxidase activator, etc.), the dopaminergic system (COMT, DRD3, CHRNA7 indirectly), and the major histocompatibility complex. These findings are consistent with current developmental and biological hypotheses about schizophrenia. At the individual level, these susceptibility genes may not be helpful to predict the risk for schizophrenia (for more on this topic, see also the

guidelines of the International Society for Psychiatric Genetics [www.ispg.org](http://www.ispg.org)). Common variants (nucleotide variations) increase the risk for schizophrenia slightly ( $OR \leq 1.2$ ), in contrast to some rare variants that may increase the risk significantly (e.g.,  $OR = 15$  for some microdeletions that are found in less than 5% of schizophrenia patients).

Endophenotypes are helpful to disentangle the complexity of the genetic underpinnings of schizophrenia by using measurable, heritable and simpler phenotypes associated with the disease. Also, additional risk genes can be identified in the heterogeneous populations of schizophrenia patients through strategies aimed at refining the phenotype that are not constrained by the current dichotomous view of functional psychoses. Schizophrenia, bipolar disorder and probably autism overlap substantially, at least in terms of polygenic risk. Some endophenotypes might also be useful as potential diagnostic marker tools (see Thibaut et al. 2015).

Neuroimaging studies that use newer methodologies such as functional or structural connectivity, or methods that assess reactions to pharmacological stimuli such as dopamine PET challenge studies, may be suitable to discover biomarkers of the disorder. However, schizophrenia is a heterogeneous and complex disorder and single biomarkers are missing because they do not capture the heterogeneity and complexity of this brain disorder (Atluri et al. 2013). Combinational biomarkers may involve genomic imaging, and new computer-based methods such as multivariate pattern analysis have been developed to identify complex biomarkers that allow for individualised differential diagnosis, as indexed by MRI-based, clinical and neurocognitive measures. Most importantly, this approach allows multivariate statistical models to be used to predict treatment response at the level of the individual participant and allows for the integration of different neuroimaging modalities (sMRI, resting-state MRI, fMRI) to build and compare both uni- and multimodal predictive models. Although biomarkers for schizophrenia await validation, the knowledge on candidate genomic and neuroimaging biomarkers is growing rapidly and research on this topic has the potential to identify psychiatric endophenotypes and increase knowledge on individual treatment response.

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## Statement of interest

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## References

- Addington J, Barbato M. 2012. The role of cognitive functioning in the outcome of those at clinical high risk for developing psychosis. *Epidemiol Psychiatr Sci.* 21:335–342.
- Allen AJ, Griss ME, Folley BS, Hawkins KA, Pearlson GD. 2009. Endophenotypes in schizophrenia: a selective review. *Schizophr Res.* 109:24–37.
- APA. 2013. Diagnostic and statistical manual of mental disorders. Arlington (VA): American Psychiatric Association.
- Arakawa R, Ichimiya T, Ito H, Takano A, Okumura M, Takahashi H, Takano H, Yasuno F, Kato M, Okubo Y, et al. 2009. Increase in thalamic binding of [(11)C]PE2I in patients with schizophrenia: a positron emission

- tomography study of dopamine transporter. *J Psychiat Res.* 43:1219–1223.
- Arfken CL, Carney S, Boutros NN. 2009. Translating biological parameters into clinically useful diagnostic tests. *Curr Psychiatry Rep.* 11:320–323.
- Atluri G, Padmanabhan K, Fang G, Steinbach M, Petrella JR, Lim K, Macdonald A, 3rd, Samatova NF, Doraiswamy PM, Kumar V. 2013. Complex biomarker discovery in neuroimaging data: finding a needle in a haystack. *Neuroimage Clin.* 3:123–131.
- Bae JS, Pasaje CF, Park BL, Cheong HS, Kim JH, Kim JY, Shin JG, Park CS, Kim BJ, Lee CS, et al. 2012. Genetic association analysis of ERBB4 polymorphisms with the risk of schizophrenia and SPEM abnormality in a Korean population. *Brain Res.* 1466:146–151.
- Bakkour N, Samp J, Akhras K, El Hammi E, Soussi I, Zahra F, Duru G, Kooli A, Toumi M. 2014. Systematic review of appropriate cognitive assessment instruments used in clinical trials of schizophrenia, major depressive disorder and bipolar disorder. *Psychiatry Res.* 216:291–302.
- Barkus C, Sanderson DJ, Rawlins JN, Walton ME, Harrison PJ, Bannerman DM. 2014. What causes aberrant salience in schizophrenia? A role for impaired short-term habituation and the GRIA1 (GluA1) AMPA receptor subunit. *Mol Psychiatry.* 19:1060–1070.
- Beckmann H. 1999. Editor's comment. In: Leonhard K, editor. *Classification of endogenous psychoses and their differentiated etiology.* 2nd, revised and enlarged ed. Wien, New York: Springer.
- Bendikov I, Nadri C, Amar S, Panizzutti R, De Miranda J, Wolosker H, Agam G. 2007. A CSF and postmortem brain study of D-serine metabolic parameters in schizophrenia. *Schizophr Res.* 90:41–51.
- Berk M, Copolov D, Dean O, Lu K, Jeavons S, Schapkaizt I, Anderson-Hunt M, Judd F, Katz F, Katz P, et al. 2008. N-acetyl cysteine as a glutathione precursor for schizophrenia—a double-blind, randomized, placebo-controlled trial. *Biol Psychiatry.* 64:361–368.
- Bernard JA, Mittal VA. 2014. Cerebellar-motor dysfunction in schizophrenia and psychosis-risk: the importance of regional cerebellar analysis approaches. *Front Psychiatry.* 5:160. doi:10.3389/fpsy.2014.00160.
- Bose SK, Turkheimer FE, Howes OD, Mehta MA, Cunliffe R, Stokes PR, Grasby PM. 2008. Classification of schizophrenic patients and healthy controls using [18F] fluorodopa PET imaging. *Schizophr Res.* 106:148–155.
- Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, Weinberger DR, Weisenfeld N, Malhotra AK, Eckelman WC, et al. 1997. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. *Proc Natl Acad Sci USA.* 94:2569–2574.
- Brunelin J, d'Amato T, Van Os J, Costes N, Suaud Chagny MF, Saoud M. 2010. Increased left striatal dopamine transmission in unaffected siblings of schizophrenia patients in response to acute metabolic stress. *Psychiatry Res.* 181:130–135.
- Buchsbaum MS, Christian BT, Lehrer DS, Narayanan TK, Shi B, Mantil J, Kemether E, Oakes TR, Mukherjee J. 2006. D2/D3 dopamine receptor binding with [F-18]fallypride in thalamus and cortex of patients with schizophrenia. *Schizophr Res.* 85:232–244.
- Buckner RL, Andrews-Hanna JR, Schacter DL. 2008. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci.* 1124:1–38.
- Cabrane JA, Ancin I, Santos JL, Sanchez-Morla E, Garcia-Jimenez MA, Lopez-Ibor JJ, Barabash A. 2013. No effect of polymorphisms in the non-duplicated region of the CHRNA7 gene on sensory gating P50 ratios in patients with schizophrenia and bipolar disorder. *Psychiatry Res.* 205:276–278.
- Canuso CM, Pandina G. 2007. Gender and schizophrenia. *Psychopharmacol Bull.* 40:178–190.
- Caravaggio F, Nakajima S, Borlido C, Remington G, Gerretsen P, Wilson A, Houle S, Menon M, Mamo D, Graff-Guerrero A. 2014. Estimating endogenous dopamine levels at D2 and D3 receptors in humans using the agonist radiotracer [(11)C]-(+)-PHNO. *Neuropsychopharmacol.* 39:2769–2776.
- Cardno AG, Gottesman II. 2000. Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. *Am J Med Genet.* 97:12–17.
- Cheong HS, Park BL, Kim EM, Park CS, Sohn JW, Kim BJ, Kim JW, Kim KH, Shin TM, Choi IG, et al. 2011. Association of RANBP1 haplotype with smooth pursuit eye movement abnormality. *Am J Med Genet B Neuropsychiatr Genet.* 156B:67–71.
- Cocchi L, Harding IH, Lord A, Pantelis C, Yucel M, Zalesky A. 2014. Disruption of structure-function coupling in the schizophrenia connectome. *Neuroimage Clin.* 4:779–787.
- Cropley VL, Innis RB, Nathan PJ, Brown AK, Sangare JL, Lerner A, Ryu YH, Sprague KE, Pike VW, Fujita M. 2008. Small effect of dopamine release and no effect of dopamine depletion on [18F]fallypride binding in healthy humans. *Synapse.* 62:399–408.
- Cross-Disorder Group of the Psychiatric Genomics C, Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, Mowry BJ, Thapar A, Goddard ME, et al. 2013. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet.* 45:984–994.
- Davatzikos C, Resnick SM, Wu X, Parnpi P, Clark CM. 2008. Individual patient diagnosis of AD and FTD via high-dimensional pattern classification of MRI. *Neuroimage.* 41:1220–1227.
- de la Fuente-Sandoval C, Leon-Ortiz P, Favila R, Stephano S, Mamo D, Ramirez-Bermudez J, Graff-Guerrero A. 2011. Higher levels of glutamate in the associative-striatum of subjects with prodromal symptoms of schizophrenia and patients with first-episode psychosis. *Neuropsychopharmacology.* 36:1781–1791.
- de la Fuente-Sandoval C, Reyes-Madriral F, Mao X, Leon-Ortiz P, Rodriguez-Mayoral O, Solis-Vivanco R, Favila R, Graff-Guerrero A, Shungu DC. 2015. Cortico-Striatal GABAergic and glutamatergic dysregulations in subjects at ultra-high risk for psychosis investigated with proton magnetic resonance spectroscopy. *Int J Neuropsychopharmacol.* 19(3):pyv105. doi:10.1093/ijnp/pyv105.
- Del Re EC, Bergen SE, Meshulam-Gately RI, Niznikiewicz MA, Goldstein JM, Woo TU, Shenton ME, Seidman LJ, McCarley RW, Petryshen TL. 2014. Analysis of schizophrenia-related genes and electrophysiological measures reveals ZNF804A association with amplitude of P300b elicited by novel sounds. *Transl Psychiatry.* 4:e346.



- Derntl B, Habel U. 2011. Deficits in social cognition: a marker for psychiatric disorders? *Eur Arch Psychiatry Clin Neurosci*. 261:S145–S149.
- Di X, Chan RC, Gong QY. 2009. White matter reduction in patients with schizophrenia as revealed by voxel-based morphometry: an activation likelihood estimation meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 33:1390–1394.
- Dickinson D, Ramsey ME, Gold JM. 2007. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Arch Gen Psychiatry*. 64:532–542.
- Dickson H, Cullen AE, Reichenberg A, Hodgins S, Campbell DD, Morris RG, Laurens KR. 2014. Cognitive impairment among children at-risk for schizophrenia. *J Psychiatr Res*. 50:92–99.
- Do KQ, Trabesinger AH, Kirsten-Kruger M, Lauer CJ, Dydak U, Hell D, Holsboer F, Boesiger P, Cuenod M. 2000. Schizophrenia: glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo. *Eur J Neurosci*. 12:3721–3728.
- Dominguez Mde G, Viechtbauer W, Simons CJ, van Os J, Krabbendam L. 2009. Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. *Psychol Bull*. 135:157–171.
- Edwards AC, Bigdeli TB, Docherty AR, Bacanu S, Lee D, de Candia TR, Moscati A, Thiselton DL, Maher BS, Wormley BK, et al. 2015. Meta-analysis of positive and negative symptoms reveals schizophrenia modifier genes. *Schizophr Bull*. 42:279–287.
- Ellison-Wright I, Bullmore E. 2009. Meta-analysis of diffusion tensor imaging studies in schizophrenia. *Schizophr Res*. 108:3–10.
- Errico F, Napolitano F, Squillace M, Vitucci D, Blasi G, de Bartolomeis A, Bertolino A, D'Aniello A, Usiello A. 2013. Decreased levels of D-aspartate and NMDA in the prefrontal cortex and striatum of patients with schizophrenia. *J Psychiatr Res*. 47:1432–1437.
- Erritzoe D, Rasmussen H, Kristiansen KT, Frokjaer VG, Haugbol S, Pinborg L, Baare W, Svarer C, Madsen J, Lublin H, et al. 2008. Cortical and subcortical 5-HT<sub>2A</sub> receptor binding in neuroleptic-naive first-episode schizophrenic patients. *Neuropsychopharmacol*. 33:2435–2441.
- Falkai P. 2011. A desperate search for biomarkers in schizophrenia. What is going wrong? *World Psychiatry*. 10:38–39.
- Farde L, Hall H, Ehrin E, Sedvall G. 1986. Quantitative analysis of D2 dopamine receptor binding in the living human brain by PET. *Science*. 231:258–261.
- Ferrarelli F. 2013. Endophenotypes and biological markers of schizophrenia: from biological signs of illness to novel treatment targets. *Curr Pharm Design*. 19:6462–6479.
- Fett AK, Viechtbauer W, Dominguez MD, Penn DL, van Os J, Krabbendam L. 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neurosci Biobehav Rev*. 35:573–588.
- Frankle WG, Lombardo I, Kegeles LS, Slifstein M, Martin JH, Huang Y, Hwang DR, Reich E, Cangani C, Gil R, et al. 2006. Serotonin 1A receptor availability in patients with schizophrenia and schizo-affective disorder: a positron emission tomography imaging study with [<sup>11</sup>C]WAY 100635. *Psychopharmacology*. 189:155–164.
- Franzek E, Beckmann H. 1998. Different genetic background of schizophrenia spectrum psychoses: a twin study. *Am J Psychiatry*. 155:76–83.
- Fromer M, Pocklington AJ, Kavanagh DH, Williams HJ, Dwyer S, Gormley P, Georgieva L, Rees E, Palta P, Ruderfer DM, et al. 2014. De novo mutations in schizophrenia implicate synaptic networks. *Nature*. 506:179–184.
- Fujiwara H, Yassin W, Murai T. 2015. Neuroimaging studies of social cognition in schizophrenia. *Psychiatry Clin Neurosci*. 69:259–267.
- Fusar-Poli P, Deste G, Smieskova R, Barlati S, Yung AR, Howes O, Stieglitz RD, Vita A, McGuire P, Borgwardt S. 2012. Cognitive functioning in prodromal psychosis: a meta-analysis. *Arch Gen Psychiatry*. 69:562–571.
- Fusar-Poli P, Meyer-Lindenberg A. 2013a. Striatal presynaptic dopamine in schizophrenia, Part I: meta-analysis of dopamine active transporter (DAT) density. *Schizophr Bull*. 39:22–32.
- Fusar-Poli P, Meyer-Lindenberg A. 2013b. Striatal presynaptic dopamine in schizophrenia, part II: meta-analysis of [(18)F/(11)C]-DOPA PET studies. *Schizophr Bull*. 39:33–42.
- Gallinat J, Bajbouj M, Sander T, Schlattmann P, Xu K, Ferro EF, Goldman D, Winterer G. 2003. Association of the G1947A COMT (Val(108/158)Met) gene polymorphism with prefrontal P300 during information processing. *Biol Psychiatry*. 54:40–48.
- Ghose S, Gleason KA, Potts BW, Lewis-Amezcuca K, Tamminga CA. 2009. Differential expression of metabotropic glutamate receptors 2 and 3 in schizophrenia: a mechanism for antipsychotic drug action? *Am J Psychiatry*. 166:812–820.
- Ginovart N. 2005. Imaging the dopamine system with in vivo [<sup>11</sup>C]raclopride displacement studies: understanding the true mechanism. *Mol Imaging Biol*. 7:45–52.
- Girard SL, Gauthier J, Noreau A, Xiong L, Zhou S, Jouan L, Dionne-Laporte A, Spiegelman D, Henrion E, Diallo O, et al. 2011. Increased exonic de novo mutation rate in individuals with schizophrenia. *Nat Genet*. 43:860–863.
- Glahn DC, Knowles EE, McKay DR, Sprooten E, Raventos H, Blangero J, Gottesman II, Almasy L. 2014. Arguments for the sake of endophenotypes: examining common misconceptions about the use of endophenotypes in psychiatric genetics. *Am J Med Genet B Neuropsychiatr Genet*. 165B:122–130.
- Golimbet V, Gritsenko I, Alifimova M, Lebedeva I, Lezheiko T, Abramova L, Kaleda V, Ebstein R. 2006. Association study of COMT gene Val158Met polymorphism with auditory P300 and performance on neurocognitive tests in patients with schizophrenia and their relatives. *World J Biol Psychiatry*. 7:238–245.
- Gottesman II, Gould TD. 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 160:636–645.
- Grayton HM, Fernandes C, Rujescu D, Collier DA. 2012. Copy number variations in neurodevelopmental disorders. *Prog Neurobiol*. 99:81–91.
- Green MF, Nuechterlein KH, Gold JM, Barch DM, Cohen J, Essock S, Fenton WS, Frese F, Goldberg TE, Heaton RK, et al. 2004. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICES conference to select cognitive domains and test criteria. *Biol Psychiatry*. 56:301–307.

- Greicius M. 2008. Resting-state functional connectivity in neuropsychiatric disorders. *Curr Opin Neurol*. 21:424–430.
- Grotegerd D, Stuhmann A, Kugel H, Schmidt S, Redlich R, Zwanzger P, Rauch AV, Heindel W, Zwitserslood P, Arolt V, et al. 2014. Amygdala excitability to subliminally presented emotional faces distinguishes unipolar and bipolar depression: an fMRI and pattern classification study. *Hum Brain Mapp*. 35:2995–3007.
- Grozeva D, Conrad DF, Barnes CP, Hurler M, Owen MJ, O'Donovan MC, Craddock N, Kirov G, WTCCC. 2012. Independent estimation of the frequency of rare CNVs in the UK population confirms their role in schizophrenia. *Schizophr Res*. 135:1–7.
- Guha S, Rees E, Darvasi A, Ivanov D, Ikeda M, Bergen SE, Magnusson PK, Cormican P, Morris D, Gill M, et al. 2013. Implication of a rare deletion at distal 16p11.2 in schizophrenia. *JAMA Psychiatry*. 70:253–260.
- Gulsuner S, Walsh T, Watts AC, Lee MK, Thornton AM, Casadei S, Rippey C, Shahin H, Consortium on the Genetics of S, Group PS, et al. 2013. Spatial and temporal mapping of de novo mutations in schizophrenia to a fetal prefrontal cortical network. *Cell*. 154:518–529.
- Gusev A, Lee SH, Trynka G, Finucane H, Vilhjalmsdottir BJ, Xu H, Zang C, Ripke S, Bulik-Sullivan B, Stahl E, et al. 2014. Partitioning heritability of regulatory and cell-type-specific variants across 11 common diseases. *Am J Hum Genet*. 95:535–552.
- Hajima SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS. 2013. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. *Schizophr Bull*. 39:1129–1137.
- Haraldsson HM, Ettinger U, Magnusdottir BB, Ingason A, Hutton SB, Sigmundsson T, Sigurdsson E, Petursson H. 2010a. Neuregulin-1 genotypes and eye movements in schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 260:77–85.
- Haraldsson HM, Ettinger U, Magnusdottir BB, Sigmundsson T, Sigurdsson E, Ingason A, Petursson H. 2009. COMT val(158)met genotype and smooth pursuit eye movements in schizophrenia. *Psychiatry Res*. 169:173–175.
- Haraldsson HM, Ettinger U, Magnusdottir BB, Sigmundsson T, Sigurdsson E, Ingason A, Petursson H. 2010b. Catechol-O-methyltransferase Val 158 Met polymorphism and antisaccade eye movements in schizophrenia. *Schizophr Bull*. 36:157–164.
- Harvey PD. 2014. What is the evidence for changes in cognition and functioning over the lifespan in patients with schizophrenia? *J Clin Psychiatry*. 75:34–38.
- Hashimoto K. 2014a. Abnormalities of the glutamine-glutamate-GABA cycle in the schizophrenia brain. *Schizophr Res*. 156:281–282.
- Hashimoto K. 2014b. Targeting of NMDA receptors in new treatments for schizophrenia. *Expert Opin Ther Targets*. 18:1049–1063.
- Hashimoto K, Engberg G, Shimizu E, Nordin C, Lindstrom LH, Iyo M. 2005a. Elevated glutamine/glutamate ratio in cerebrospinal fluid of first episode and drug naive schizophrenic patients. *BMC Psychiatry*. 5:6.
- Hashimoto K, Engberg G, Shimizu E, Nordin C, Lindstrom LH, Iyo M. 2005b. Reduced D-serine to total serine ratio in the cerebrospinal fluid of drug naive schizophrenic patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 29:767–769.
- Hashimoto K, Fukushima T, Shimizu E, Komatsu N, Watanabe H, Shinoda N, Nakazato M, Kumakiri C, Okada S, Hasegawa H, et al. 2003. Decreased serum levels of D-serine in patients with schizophrenia: evidence in support of the N-methyl-D-aspartate receptor hypofunction hypothesis of schizophrenia. *Arch Gen Psychiatry*. 60:572–576.
- Hashimoto K, Malchow B, Falkai P, Schmitt A. 2013. Glutamate modulators as potential therapeutic drugs in schizophrenia and affective disorders. *Eur Arch Psychiatry Clin Neurosci*. 263:367–377.
- Hietala J, Syvalahti E, Vilkmann H, Vuorio K, Rakkolainen V, Bergman J, Haaparanta M, Solin O, Kuoppamaki M, Eronen E, et al. 1999. Depressive symptoms and presynaptic dopamine function in neuroleptic-naive schizophrenia. *Schizophr Res*. 35:41–50.
- Hietala J, Syvalahti E, Vuorio K, Rakkolainen V, Bergman J, Haaparanta M, Solin O, Kuoppamaki M, Kirvela O, Ruotsalainen U, et al. 1995. Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. *Lancet*. 346:1130–1131.
- Hirvonen J, van Erp TG, Huttunen J, Aalto S, Nagren K, Huttunen M, Lonnqvist J, Kaprio J, Hietala J, Cannon TD. 2005. Increased caudate dopamine D2 receptor availability as a genetic marker for schizophrenia. *Arch Gen Psychiatry*. 62:371–378.
- Howes OD, Montgomery AJ, Asselin MC, Murray RM, Valli I, Tabraham P, Bramon-Bosch E, Valmaggia L, Johns L, Broome M, et al. 2009. Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Arch Gen Psychiatry*. 66:13–20.
- Hurlemann R, Matusch A, Kuhn KU, Berning J, Elmenhorst D, Winz O, Kolsch H, Zilles K, Wagner M, Maier W, et al. 2008. 5-HT2A receptor density is decreased in the at-risk mental state. *Psychopharmacology (Berl)*. 195:579–590.
- Ingason A, Kirov G, Giegling I, Hansen T, Isles AR, Jakobsen KD, Kristinsson KT, le Roux L, Gustafsson O, Craddock N, et al. 2011a. Maternally derived microduplications at 15q11-q13: implication of imprinted genes in psychotic illness. *Am J Psychiatry*. 168:408–417.
- Ingason A, Rujescu D, Cichon S, Sigurdsson E, Sigmundsson T, Pietilainen OP, Buizer-Voskamp JE, Strengman E, Francks C, Muglia P, et al. 2011b. Copy number variations of chromosome 16p13.1 region associated with schizophrenia. *Mol Psychiatry*. 16:17–25.
- International Schizophrenia Consortium. 2008. Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature*. 455:237–241.
- International Schizophrenia Consortium; Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P. International Schizophrenia Consortium. 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 460:748–752.
- Jacquet H, Raux G, Thibaut F, Hecketsweiler B, Houy E, Demilly C, Haouzir S, Allio G, Fouldrin G, Drouin V, et al. 2002. PRODH mutations and hyperprolinemia in a subset of schizophrenic patients. *Hum Mol Genet*. 11:2243–2249.
- Kalia M, Costa ESJ. 2015. Biomarkers of psychiatric diseases: current status and future prospects. *Metab Clin Exp*. 64:S11–S15.
- Kambeitz J, Kambeitz-Ilankovic L, Leucht S, Wood S, Davatzikos C, Malchow B, Falkai P, Koutsouleris N. 2015. Detecting neuroimaging biomarkers for schizophrenia: a

- meta-analysis of multivariate pattern recognition studies. *Neuropsychopharmacol.* 40:1742–1751.
- Kamis D, Stratton L, Calvo M, Padilla E, Florenzano N, Guerrero G, Molina Rangeon B, Molina J, de Erausquin GA. 2015. Sex and laterality differences in parkinsonian impairment and transcranial ultrasound in never-treated schizophrenics and their first degree relatives in an Andean population. *Schizophr Res.* 164:250–255.
- Kang C, Yang X, Xu X, Liu H, Su P, Yang J. 2012. Association study of neuregulin 1 gene polymorphisms with auditory P300 in schizophrenia. *Am J Med Genet B Neuropsychiatr Genet.* 159B:422–428.
- Kasper S, Tauscher J, Willeit M, Stamenkovic M, Neumeister A, Kufferle B, Barnas C, Stastny J, Praschak-Rieder N, Pezawas L, et al. 2002. Receptor and transporter imaging studies in schizophrenia, depression, bulimia and Tourette's disorder-implications for psychopharmacology. *World J Biol Psychiatry.* 3:133–146.
- Kegeles LS, Mao X, Stanford AD, Girgis R, Ojeil N, Xu X, Gil R, Slifstein M, Abi-Dargham A, Lisanby SH, et al. 2012. Elevated prefrontal cortex  $\gamma$ -aminobutyric acid and glutamate-glutamine levels in schizophrenia measured in vivo with proton magnetic resonance spectroscopy. *Arch Gen Psychiatry.* 69:449–459.
- Kegeles LS, Slifstein M, Xu X, Urban N, Thompson JL, Moadel T, Harkavy-Friedman JM, Gil R, Laruelle M, Abi-Dargham A. 2010. Striatal and extrastriatal dopamine D2/D3 receptors in schizophrenia evaluated with [<sup>18</sup>F]fallypride positron emission tomography. *Biol Psychiatry.* 68:634–641.
- Kendler KS. 2015. A joint history of the nature of genetic variation and the nature of schizophrenia. *Mol Psychiatry.* 20:77–83.
- Kessler RM, Woodward ND, Riccardi P, Li R, Ansari MS, Anderson S, Dawant B, Zald D, Meltzer HY. 2009. Dopamine D2 receptor levels in striatum, thalamus, substantia nigra, limbic regions, and cortex in schizophrenic subjects. *Biol Psychiatry.* 65:1024–1031.
- Kim JH, Park BL, Pasaje CF, Bae JS, Park CS, Cha B, Kim BJ, Lee M, Choi WH, Shin TM, et al. 2012. Lack of associations of neuregulin 1 variations with schizophrenia and smooth pursuit eye movement abnormality in a Korean population. *J Mol Neurosci.* 46:476–482.
- Kirov G, Grozeva D, Norton N, Ivanov D, Mantripragada KK, Holmans P, International Schizophrenia Consortium, Wellcome Trust Case Control Consortium, Craddock N, Owen MJ, et al. 2009a. Support for the involvement of large copy number variants in the pathogenesis of schizophrenia. *Hum Mol Genet.* 18:1497–1503.
- Kirov G, Gumus D, Chen W, Norton N, Georgieva L, Sari M, O'Donovan MC, Erdogan F, Owen MJ, Ropers HH, et al. 2008. Comparative genome hybridization suggests a role for NRXN1 and APBA2 in schizophrenia. *Hum Mol Genet.* 17:458–465.
- Kirov G, Pocklington AJ, Holmans P, Ivanov D, Ikeda M, Ruderfer D, Moran J, Chambert K, Toncheva D, Georgieva L, et al. 2012. De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. *Mol Psychiatry.* 17:142–153.
- Kirov G, Rujescu D, Ingason A, Collier DA, O'Donovan MC, Owen MJ. 2009b. Neurexin 1 (NRXN1) deletions in schizophrenia. *Schizophr Bull* 35(5):851–854.
- Knott V, Millar A, Fisher D, Albert P. 2010. Effects of nicotine on the amplitude and gating of the auditory P50 and its influence by dopamine D2 receptor gene polymorphism. *Neuroscience.* 166:145–156.
- Kornhuber J, Mack-Burkhardt F, Riederer P, Hebenstreit GF, Reynolds GP, Andrews HB, Beckmann H. 1989. [<sup>3</sup>H]MK-801 binding sites in postmortem brain regions of schizophrenic patients. *J Neural Transm.* 77:231–236.
- Kumakura Y, Cumming P, Vernaleken I, Buchholz HG, Siessmeier T, Heinz A, Kienast T, Bartenstein P, Grunder G. 2007. Elevated [<sup>18</sup>F]fluorodopamine turnover in brain of patients with schizophrenia: an [<sup>18</sup>F]fluorodopa/positron emission tomography study. *J Neurosci.* 27:8080–8087.
- Laakso A, Bergman J, Haaparanta M, Vilkkumäki H, Solin O, Syvalahti E, Hietala J. 2001. Decreased striatal dopamine transporter binding in vivo in chronic schizophrenia. *Schizophr Res.* 52:115–120.
- Laakso A, Vilkkumäki H, Alakare B, Haaparanta M, Bergman J, Solin O, Peurasaari J, Rakkolainen V, Syvalahti E, Hietala J. 2000. Striatal dopamine transporter binding in neuroleptic-naive patients with schizophrenia studied with positron emission tomography. *Am J Psychiatry.* 157:269–271.
- Lambert M, Karow A, Leucht S, Schimmelmann BG, Naber D. 2010. Remission in schizophrenia: validity, frequency, predictors, and patients' perspective 5 years later. *Dialogues Clin Neurosci.* 12:393–407.
- Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, McCance E, Rosenblatt W, Fingado C, Zoghbi SS, et al. 1996. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci USA.* 93:9235–9240.
- Lee KJ, Lee JS, Kim SJ, Correll CU, Wee H, Yoo SY, Jeong JM, Lee DS, Lee SI, Kwon JS. 2008. Loss of asymmetry in D2 receptors of putamen in unaffected family members at increased genetic risk for schizophrenia. *Acta Psychiatr Scand.* 118:200–208.
- Lee KW, Woon PS, Teo YY, Sim K. 2012a. Genome wide association studies (GWAS) and copy number variation (CNV) studies of the major psychoses: what have we learnt? *Neurosci Biobehav Rev.* 36:556–571.
- Lee SH, DeCandia TR, Ripke S, Yang J, Schizophrenia Psychiatric Genome-Wide Association Study Consortium, International Schizophrenia Consortium, Molecular Genetics of Schizophrenia Collaboration, Sullivan PF, Goddard ME, Keller MC, et al. 2012b. Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. *Nat Genet.* 44:247–250.
- Lees J, Applegate E, Emsley R, Lewis S, Michalopoulou P, Collier T, Lopez-Lopez C, Kapur S, Pandina GJ, Drake RJ. 2015. Calibration and cross-validation of MCCB and CogState in schizophrenia. *Psychopharmacology (Berl).* 232:3873–3882.
- Lencz T, Morgan TV, Athanasiou M, Dain B, Reed CR, Kane JM, Kucherlapati R, Malhotra AK. 2007. Converging evidence for a pseudoautosomal cytokine receptor gene locus in schizophrenia. *Mol Psychiatry.* 12:572–580.
- Leonard S, Freedman R. 2006. Genetics of chromosome 15q13-q14 in schizophrenia. *Biol Psychiatry.* 60:115–122.
- Lepage M, Bodnar M, Bowie CR. 2014. Neurocognition: clinical and functional outcomes in schizophrenia. *Can J Psychiatry.* 59:5–12.

- Levinson DF, Duan J, Oh S, Wang K, Sanders AR, Shi J, Zhang N, Mowry BJ, Olincy A, Amin F, et al. 2011. Copy number variants in schizophrenia: confirmation of five previous findings and new evidence for 3q29 microdeletions and VIPR2 duplications. *Am J Psychiatry*. 168:302–316.
- Lichtenstein P, Bjork C, Hultman CM, Scolnick E, Sklar P, Sullivan PF. 2006. Recurrence risks for schizophrenia in a Swedish national cohort. *Psychol Med*. 36:1417–1425.
- Lichtenstein P, Yip BH, Bjork C, Pawitan Y, Cannon TD, Sullivan PF, Hultman CM. 2009. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet*. 373:234–239.
- Liddle EB, Bates AT, Das D, White TP, Groom MJ, Jansen M, Jackson GM, Hollis C, Liddle PF. 2013. Inefficient cerebral recruitment as a vulnerability marker for schizophrenia. *Psychol Med*. 43:169–182.
- Light GA, Geyer MA, Clementz BA, Cadenhead KS, Braff DL. 2000. Normal P50 suppression in schizophrenia patients treated with atypical antipsychotic medications. *Am J Psychiatry*. 157:767–771.
- Light GA, Swerdlow NR, Rissling AJ, Radant A, Sugar CA, Sprock J, Pela M, Geyer MA, Braff DL. 2012. Characterization of neurophysiologic and neurocognitive biomarkers for use in genomic and clinical outcome studies of schizophrenia. *PLoS One*. 7:e39434.
- Lindstrom LH, Gefvert O, Hagberg G, Lundberg T, Bergstrom M, Hartvig P, Langstrom B. 1999. Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-11C) DOPA and PET. *Biol Psychiatry*. 46:681–688.
- Liu X, Hong X, Chan RC, Kong F, Peng Z, Wan X, Wang C, Cheng L. 2013. Association study of polymorphisms in the alpha 7 nicotinic acetylcholine receptor subunit and catechol-o-methyl transferase genes with sensory gating in first-episode schizophrenia. *Psychiatry Res*. 209:431–438.
- Louchart-de la Chapelle S, Nkam I, Houy E, Belmont A, Menard JF, Roussignol AC, Siwek O, Mezerai M, Guilleumou M, Fouldrin G, et al. 2005. A concordance study of three electrophysiological measures in schizophrenia. *Am J Psychiatry*. 162:466–474.
- Lu BY, Martin KE, Edgar JC, Smith AK, Lewis SF, Escamilla MA, Miller GA, Canive JM. 2007. Effect of catechol O-methyltransferase val(158)met polymorphism on the p50 gating endophenotype in schizophrenia. *Biol Psychiatry*. 62:822–825.
- MacDonald AW, 3rd, Thermenos HW, Barch DM, Seidman LJ. 2009. Imaging genetic liability to schizophrenia: systematic review of fMRI studies of patients' nonpsychotic relatives. *Schizophr. Bull*. 35:1142–1162.
- Marengo J. 1994. Classifying the courses of schizophrenia. *Schizophr Bull*. 20:519–536.
- Marsman A, Mandl RC, Klomp DW, Bohlken MM, Boer VO, Andreychenko A, Cahn W, Kahn RS, Luijten PR, Hulshoff Pol HE. 2014. GABA and glutamate in schizophrenia: a 7 T <sup>1</sup>H-MRS study. *Neuroimage Clin*. 6:398–407.
- Martin AK, Mowry B. 2015. Increased rare duplication burden genome-wide in patients with treatment-resistant schizophrenia. *Psychol Med*. 46:469–476.
- Martin AK, Robinson G, Reutens D, Mowry B. 2014. Cannabis abuse and age at onset in schizophrenia patients with large, rare copy number variants. *Schizophr Res*. 155:21–25.
- Matsukawa N, Murai T. 2013. [Neuroimaging studies of social cognition in schizophrenia]. *Nippon Rinsho*. 71:615–618.
- Matsuzawa D, Obata T, Shirayama Y, Nonaka H, Kanazawa Y, Yoshitome E, Takanashi J, Matsuda T, Shimizu E, Ikehira H, et al. 2008. Negative correlation between brain glutathione level and negative symptoms in schizophrenia: a 3T 1H-MRS study. *PLoS One*. 3:e1944.
- McCarthy SE, Gillis J, Kramer M, Lihm J, Yoon S, Berstein Y, Mistry M, Pavlidis P, Solomon R, Ghiban E, et al. 2014. De novo mutations in schizophrenia implicate chromatin remodeling and support a genetic overlap with autism and intellectual disability. *Mol Psychiatry*. 19:652–658.
- McCarthy SE, Makarov V, Kirov G, Addington AM, McClellan J, Yoon S, Perkins DO, Dickel DE, Kusenda M, Krastoshevsky O, et al. 2009. Microduplications of 16p11.2 are associated with schizophrenia. *Nat Genet*. 41:1223–1227.
- McGowan S, Lawrence AD, Sales T, Quedsted D, Grasby P. 2004. Presynaptic dopaminergic dysfunction in schizophrenia: a positron emission tomographic [<sup>18</sup>F]fluorodopa study. *Arch Gen Psychiatry*. 61:134–142.
- Meyer-Lindenberg A, Miletich RS, Kohn PD, Esposito G, Carson RE, Quarantelli M, Weinberger DR, Berman KF. 2002. Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. *Nat Neurosci*. 5:267–271.
- Millar A, Smith D, Choueiry J, Fisher D, Albert P, Knott V. 2011. The moderating role of the dopamine transporter 1 gene on P50 sensory gating and its modulation by nicotine. *Neuroscience*. 180:148–156.
- Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. 2009. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch Gen Psychiatry*. 66:811–822.
- Mizrahi R, Addington J, Rusjan PM, Suridjan I, Ng A, Boileau I, Pruessner JC, Remington G, Houle S, Wilson AA. 2012. Increased stress-induced dopamine release in psychosis. *Biol Psychiatry*. 71:561–567.
- Moreno-De-Luca D, Consortium S, Mulle JG, Simons Simplex Collection Genetics C., Kaminsky EB, Sanders SJ, Gene Star, Myers SM, Adam MP, Pakula AT et al. 2010. Deletion 17q12 is a recurrent copy number variant that confers high risk of autism and schizophrenia. *Am J Hum Genet*. 87:618–630.
- Mourao-Miranda J, Almeida JR, Hassel S, de Oliveira L, Versace A, Marquand AF, Sato JR, Brammer M, Phillips ML. 2012. Pattern recognition analyses of brain activation elicited by happy and neutral faces in unipolar and bipolar depression. *Bipolar Disord*. 14:451–460.
- Mueller S, Keeser D, Reiser MF, Teipel S, Meindl T. 2012. Functional and structural MR imaging in neuropsychiatric disorders, part 2: application in schizophrenia and autism. *AJNR Am J Neuroradiol*. 33:2033–2037.
- Mukherjee J, Christian BT, Dunigan KA, Shi B, Narayanan TK, Satter M, Mantil J. 2002. Brain imaging of 18F-fallypride in normal volunteers: blood analysis, distribution, test-retest studies, and preliminary assessment of sensitivity to aging effects on dopamine D-2/D-3 receptors. *Synapse*. 46:170–188.
- Mulle JG, Dodd AF, McGrath JA, Wolyniec PS, Mitchell AA, Shetty AC, Sobreira NL, Valle D, Rudd MK, Satten G, et al. 2010. Microdeletions of 3q29 confer high risk for schizophrenia. *Am J Hum Genet*. 87:229–236.

- Mulle JG, Pulver AE, McGrath JA, Wolyniec PS, Dodd AF, Cutler DJ, Sebat J, Malhotra D, Nestadt G, Conrad DF, et al. 2014. Reciprocal duplication of the Williams-Beuren syndrome deletion on chromosome 7q11.23 is associated with schizophrenia. *Biol Psychiatry*. 75:371–377.
- Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. 2004. Identification of separable cognitive factors in schizophrenia. *Schizophr Res*. 72:29–39.
- Nuechterlein KH, Green MF, Calkins ME, Greenwood TA, Gur RE, Gur RC, Lazzeroni LC, Light GA, Radant AD, Seidman LJ, et al. 2015. Attention/vigilance in schizophrenia: performance results from a large multi-site study of the Consortium on the Genetics of Schizophrenia (COGS). *Schizophr Res*. 163:38–46.
- O'Donovan MC, Craddock N, Norton N, Williams H, Peirce T, Moskvina V, Nikolov I, Hamshere M, Carroll L, Georgieva L, et al. 2008. Identification of loci associated with schizophrenia by genome-wide association and follow-up. *Nat Genet*. 40:1053–1055.
- Olinicy A, Braff DL, Adler LE, Cadenhead KS, Calkins ME, Dobie DJ, Green MF, Greenwood TA, Gur RE, Gur RC, et al. 2010. Inhibition of the P50 cerebral evoked response to repeated auditory stimuli: results from the Consortium on Genetics of Schizophrenia. *Schizophr Res*. 119:175–182.
- Ota M, Sato N, Ishikawa M, Hori H, Sasayama D, Hattori K, Teraishi T, Obu S, Nakata Y, Nemoto K, et al. 2012. Discrimination of female schizophrenia patients from healthy women using multiple structural brain measures obtained with voxel-based morphometry. *Psychiatry Clin Neurosci*. 66:611–617.
- Ozomaro U, Wahlestedt C, Nemeroff CB. 2013. Personalized medicine in psychiatry: problems and promises. *BMC Med*. 11:132.
- Park BL, Shin HD, Cheong HS, Park CS, Sohn JW, Kim BJ, Seo HK, Kim JW, Kim KH, Shin TM, et al. 2009. Association analysis of COMT polymorphisms with schizophrenia and smooth pursuit eye movement abnormality. *J Hum Genet*. 54:709–712.
- Pietrzak RH, Olver J, Norman T, Piskulic D, Maruff P, Snyder PJ. 2009. A comparison of the CogState Schizophrenia Battery and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Battery in assessing cognitive impairment in chronic schizophrenia. *J Clin Exp Neuropsychol*. 31:848–859.
- Plitman E, de la Fuente-Sandoval C, Reyes-Madriral F, Chavez S, Gomez-Cruz G, Leon-Ortiz P, Graff-Guerrero A. 2015. Elevated Myo-Inositol, Choline, and Glutamate Levels in the Associative Striatum of Antipsychotic-Naive Patients With First-Episode Psychosis: A Proton Magnetic Resonance Spectroscopy Study With Implications for Glial Dysfunction. *Schizophr Bull*. 42:415–424.
- Poels EM, Kegeles LS, Kantrowitz JT, Javitt DC, Lieberman JA, Abi-Dargham A, Girgis RR. 2014a. Glutamatergic abnormalities in schizophrenia: a review of proton MRS findings. *Schizophr Res*. 152:325–332.
- Poels EM, Kegeles LS, Kantrowitz JT, Slifstein M, Javitt DC, Lieberman JA, Abi-Dargham A, Girgis RR. 2014b. Imaging glutamate in schizophrenia: review of findings and implications for drug discovery. *Mol Psychiatry*. 19:20–29.
- Porteous DJ, Thomson PA, Millar JK, Evans KL, Henna W, Soares DC, McCarthy S, McCombie WR, Clapcote SJ, Korth C, et al. 2014. DISC1 as a genetic risk factor for schizophrenia and related major mental illness: response to Sullivan. *Mol Psychiatry*. 19:141–143.
- Purcell SM, Moran JL, Fromer M, Ruderfer D, Solovieff N, Roussos P, O'Dushlaine C, Chambert K, Bergen SE, Kahler A, et al. 2014. A polygenic burden of rare disruptive mutations in schizophrenia. *Nature*. 506:185–190.
- Quednow BB, Brinkmeyer J, Mobascher A, Nothnagel M, Musso F, Grunder G, Savary N, Petrovsky N, Frommann I, Lennertz L, et al. 2012. Schizophrenia risk polymorphisms in the TCF4 gene interact with smoking in the modulation of auditory sensory gating. *Proc Natl Acad Sci USA*. 109:6271–6276.
- Randall AD, Kurihara M, Brandon NJ, Brown JT. 2014. Disrupted in schizophrenia 1 and synaptic function in the mammalian central nervous system. *Eur J Neurosci*. 39:1068–1073.
- Rasmussen H, Erritzoe D, Andersen R, Ebdrup BH, Aggernaes B, Oranje B, Kalbitzer J, Madsen J, Pinborg LH, Baare W, et al. 2010. Decreased frontal serotonin2A receptor binding in antipsychotic-naive patients with first-episode schizophrenia. *Arch Gen Psychiatry*. 67:9–16.
- Raux G, Bumsel E, Hecketsweiler B, van Amelsvoort T, Zinkstok J, Manouvrier-Hanu S, Fantini C, Breviere GM, Di Rosa G, Pustorino G, et al. 2007. Involvement of hyperprolinemia in cognitive and psychiatric features of the 22q11 deletion syndrome. *Hum Mol Genet*. 16:83–91.
- Redlich R, Almeida JJ, Grotegerd D, Opel N, Kugel H, Heindel W, Arolt V, Phillips ML, Dannlowski U. 2014. Brain morphometric biomarkers distinguishing unipolar and bipolar depression. A voxel-based morphometry-pattern classification approach. *JAMA Psychiatry*. 71:1222–1230.
- Rees E, Walters JT, Chambert KD, O'Dushlaine C, Szatkiewicz J, Richards AL, Georgieva L, Mahoney-Davies G, Legge SE, Moran JL, et al. 2014a. CNV analysis in a large schizophrenia sample implicates deletions at 16p12.1 and SLC1A1 and duplications at 1p36.33 and CGNL1. *Hum Mol Genet*. 23:1669–1676.
- Rees E, Walters JT, Georgieva L, Isles AR, Chambert KD, Richards AL, Mahoney-Davies G, Legge SE, Moran JL, McCarroll SA, et al. 2014b. Analysis of copy number variations at 15 schizophrenia-associated loci. *Brit J Psychiatry*. 204:108–114.
- Reichenberg A, Harvey PD. 2007. Neuropsychological impairments in schizophrenia: Integration of performance-based and brain imaging findings. *Psychol Bull*. 133:833–858.
- Reilly JL, Sweeney JA. 2014. Generalized and specific neurocognitive deficits in psychotic disorders: utility for evaluating pharmacological treatment effects and as intermediate phenotypes for gene discovery. *Schizophr Bull*. 40:516–522.
- Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kahler AK, Akterin S, Bergen SE, Collins AL, Crowley JJ, Fromer M, et al. 2013. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat Genet*. 45:1150–1159.
- Rujescu D, Ingason A, Cichon S, Pietilainen OP, Barnes MR, Touloupoulou T, Picchioni M, Vassos E, Ettinger U, Bramon E, et al. 2009. Disruption of the neurexin 1 gene is associated with schizophrenia. *Hum Mol Genet*. 18:988–996.
- Rybakowski JK, Borkowska A, Czerski PM, Hauser J. 2002. Eye movement disturbances in schizophrenia and a polymorphism of catechol-O-methyltransferase gene. *Psychiatry Res*. 113:49–57.

- Salavati B, Rajji TK, Price R, Sun Y, Graff-Guerrero A, Daskalakis ZJ. 2015. Imaging-based neurochemistry in schizophrenia: a systematic review and implications for dysfunctional long-term potentiation. *Schizophr Bull.* 41:44–56.
- Saoud M, d'Amato T, Gutknecht C, Triboulet P, Bertaud JP, Marie-Cardine M, Dalery J, Rochet T. 2000. Neuropsychological deficit in siblings discordant for schizophrenia. *Schizophr Bull.* 26:893–902.
- Schaefer J, Giangrande E, Weinberger DR, Dickinson D. 2013. The global cognitive impairment in schizophrenia: consistent over decades and around the world. *Schizophr Res.* 150:42–50.
- Schizophrenia Working Group of the Psychiatric Genomics Consortium. 2014. Biological insights from 108 schizophrenia-associated genetic loci. *Nature.* 511:421–427.
- Schmechtig A, Vassos E, Kumari V, Hutton SB, Collier DA, Morris RG, Williams SC, Ettinger U. 2010. Association of Neuregulin 1 rs3924999 genotype with antisaccades and smooth pursuit eye movements. *Genes Brain Behav.* 9:621–627.
- Schmidt SJ, Mueller DR, Roder V. 2011. Social cognition as a mediator variable between neurocognition and functional outcome in schizophrenia: empirical review and new results by structural equation modeling. *Schizophr. Bull.* 37:S41–S54.
- Schnack HG, Nieuwenhuis M, van Haren NE, Abramovic L, Scheewe TW, Brouwer RM, Hulshoff Pol HE, Kahn RS. 2014. Can structural MRI aid in clinical classification? A machine learning study in two independent samples of patients with schizophrenia, bipolar disorder and healthy subjects. *Neuroimage.* 84:299–306.
- Schneider M, Debbane M, Bassett AS, Chow EW, Fung WL, van den Bree M, Owen M, Murphy KC, Niarchou M, Kates WR, et al. 2014. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am J Psychiatry.* 171:627–639.
- Sendt KV, Tracy DK, Bhattacharyya S. 2015. A systematic review of factors influencing adherence to antipsychotic medication in schizophrenia-spectrum disorders. *Psychiatry Res.* 225:14–30.
- Sepede G, Ferretti A, Perrucci MG, Gambi F, Di Donato F, Nuccetelli F, Del Gratta C, Tartaro A, Salerno RM, Ferro FM, et al. 2010. Altered brain response without behavioral attention deficits in healthy siblings of schizophrenic patients: an event-related fMRI study. *NeuroImage.* 49:1080–1090.
- Serpa MH, Ou Y, Schaufelberger MS, Doshi J, Ferreira LK, Machado-Vieira R, Menezes PR, Sczufca M, Davatzikos C, Busatto GF, et al. 2014. Neuroanatomical classification in a population-based sample of psychotic major depression and bipolar I disorder with 1 year of diagnostic stability. *Biomed Res Int.* 2014:706157.
- Shaikh M, Hall MH, Schulze K, Dutt A, Walshe M, Williams I, Constante M, Picchioni M, Touloupoulou T, Collier D, et al. 2011. Do COMT, BDNF and NRG1 polymorphisms influence P50 sensory gating in psychosis? *Psychol Med.* 41:263–276.
- Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I, Dudbridge F, Holmans PA, Whittemore AS, Mowry BJ, et al. 2009. Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature.* 460:753–757.
- Shin HD, Park BL, Bae JS, Park TJ, Chun JY, Park CS, Sohn JW, Kim BJ, Kang YH, Kim JW, et al. 2010. Association of ZDHHC8 polymorphisms with smooth pursuit eye movement abnormality. *Am J Med Genet B Neuropsychiatr Genet.* 153B:1167–1172.
- Shprintzen RJ, Goldberg R, Golding-Kushner KJ, Marion RW. 1992. Late-onset psychosis in the velo-cardio-facial syndrome. *Am J Med Genet.* 42:141–142.
- Smesny S, Gussew A, Biesel NJ, Schack S, Walther M, Rzanny R, Milleit B, Gaser C, Sobanski T, Schultz CC, et al. 2015. Glutamatergic dysfunction linked to energy and membrane lipid metabolism in frontal and anterior cingulate cortices of never treated first-episode schizophrenia patients. *Schizophr Res.* 168:322–329.
- Sommer IE, Kahn RS. 2015. The contribution of neuroimaging to understanding schizophrenia; past, present, and future. *Schizophr Bull.* 41:1–3.
- Squarcione C, Torti MC, Di Fabio F, Biondi M. 2013. 22q11 deletion syndrome: a review of the neuropsychiatric features and their neurobiological basis. *Neuropsychiatr Dis Treat.* 9:1873–1884.
- St Clair D, Blackwood D, Muir W, Carothers A, Walker M, Spowart G, Gosden C, Evans HJ. 1990. Association within a family of a balanced autosomal translocation with major mental illness. *Lancet.* 336:13–16.
- Stefanis NC, Van Os J, Avramopoulos D, Smyrnis N, Evdokimidis I, Hantoumi I, Stefanis CN. 2004. Variation in catechol-o-methyltransferase val158 met genotype associated with schizotypy but not cognition: a population study in 543 young men. *Biol Psychiatry.* 56:510–515.
- Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, Werge T, Pietilainen OP, Mors O, Mortensen PB, et al. 2009. Common variants conferring risk of schizophrenia. *Nature.* 460:744–747.
- Stefansson H, Rujescu D, Cichon S, Pietilainen OP, Ingason A, Steinberg S, Fossdal R, Sigurdsson E, Sigmundsson T, Buizer-Voskamp JE, et al. 2008. Large recurrent microdeletions associated with schizophrenia. *Nature.* 455:232–236.
- Steinberg S, de Jong S, Mattheisen M, Costas J, Demontis D, Jamain S, Pietilainen OP, Lin K, Papiol S, Huttenlocher J, et al. 2014. Common variant at 16p11.2 conferring risk of psychosis. *Mol Psychiatry.* 19:108–114.
- Stöber G, Ben-Shachar D, Cardon M, Falkai P, Fonteh AN, Gawlik M, Glenthøj BY, Grünblatt E, Jablensky A, Kim YK, et al. 2009. Schizophrenia: from the brain to peripheral markers. A consensus paper of the WFSBP task force on biological markers. *World J Biol Psychiatry.* 10:127–155.
- Suhara T, Okubo Y, Yasuno F, Sudo Y, Inoue M, Ichimiya T, Nakashima Y, Nakayama K, Tanada S, Suzuki K, et al. 2002. Decreased dopamine D2 receptor binding in the anterior cingulate cortex in schizophrenia. *Arch Gen Psychiatry.* 59:25–30.
- Sullivan PF, Kendler KS, Neale MC. 2003. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry.* 60:1187–1192.
- Sullivan PF, Lin D, Tzeng JY, van den Oord E, Perkins D, Stroup TS, Wagner M, Lee S, Wright FA, Zou F, et al. 2008. Genomewide association for schizophrenia in the CATIE study: results of stage 1. *Mol Psychiatry.* 13:570–584.

- Suridjan I, Rusjan P, Addington J, Wilson AA, Houle S, Mizrahi R. 2013. Dopamine D2 and D3 binding in people at clinical high risk for schizophrenia, antipsychotic-naïve patients and healthy controls while performing a cognitive task. *J Psychiatry Neurosci.* 38:98–106.
- Swerdlow NR, Gur RE, Braff DL. 2015. Consortium on the Genetics of Schizophrenia (COGS) assessment of endophenotypes for schizophrenia: an introduction to this Special Issue of Schizophrenia Research. *Schizophr Res.* 163:9–16.
- Takizawa R, Fukuda M, Kawasaki S, Kasai K, Mimura M, Pu S, Noda T, Niwa S, Okazaki Y, Joint Project for Psychiatric Application of Near-Infrared Spectroscopy Group. 2014. Neuroimaging-aided differential diagnosis of the depressive state. *Neuroimage.* 85:498–507.
- Talvik M, Nordstrom AL, Okubo Y, Olsson H, Borg J, Halldin C, Farde L. 2006. Dopamine D2 receptor binding in drug-naïve patients with schizophrenia examined with raclopride-C11 and positron emission tomography. *Psychiatry Res.* 148:165–173.
- Talvik M, Nordstrom AL, Olsson H, Halldin C, Farde L. 2003. Decreased thalamic D2/D3 receptor binding in drug-naïve patients with schizophrenia: a PET study with [11C]FLB 457. *Int J Neuropsychopharmacol.* 6:361–370.
- Tauscher J, Kapur S, Verhoeff NP, Hussey DF, Daskalakis ZJ, Tauscher-Wisniewski S, Wilson AA, Houle S, Kasper S, Zipursky RB. 2002. Brain serotonin 5-HT(1A) receptor binding in schizophrenia measured by positron emission tomography and [11C]WAY-100635. *Arch Gen Psychiatry.* 59:514–520.
- Thibaut F. 2006. Schizophrenia: An example of complex genetic disease. *World J Biol Psychiatry.* 7:194–197.
- Thibaut F, Boutros NN, Jarema M, Oranje B, Hasan A, Daskalakis ZJ, Wichniak A, Schmitt A, Riederer P, Falkai P, et al. 2015. Consensus paper of the WFSBP Task Force on Biological Markers: Criteria for biomarkers and endophenotypes of schizophrenia part I: Neurophysiology. *World J Biol Psychiatry.* 16:280–290.
- Tsai GE, Lin PY. 2010. Strategies to enhance N-methyl-D-aspartate receptor-mediated neurotransmission in schizophrenia, a critical review and meta-analysis. *Curr Pharm Design.* 16:522–537.
- Tsitsipa E, Fountoulakis KN. 2015. The neurocognitive functioning in bipolar disorder: a systematic review of data. *Ann Gen Psychiatry.* 14:42. doi:10.1186/s12991-015-0081-z
- Vacic V, McCarthy S, Malhotra D, Murray F, Chou HH, Peoples A, Makarov V, Yoon S, Bhandari A, Corominas R, et al. 2011. Duplications of the neuropeptide receptor gene VIPR2 confer significant risk for schizophrenia. *Nature.* 471:499–503.
- Vawter MP, Mamdani F, Macciardi F. 2011. An integrative functional genomics approach for discovering biomarkers in schizophrenia. *Brief Funct Genomics.* 10:387–399.
- Ventura J, Thames AD, Wood RC, Guzik LH, Helleman GS. 2010. Disorganization and reality distortion in schizophrenia: a meta-analysis of the relationship between positive symptoms and neurocognitive deficits. *Schizophr Res.* 121:1–14.
- Verhoeff NP, Hussey D, Lee M, Tauscher J, Papatheodorou G, Wilson AA, Houle S, Kapur S. 2002. Dopamine depletion results in increased neostriatal D(2), but not D(1), receptor binding in humans. *Mol Psychiatry.* 7:233–238.
- Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, Nord AS, Kusenda M, Malhotra D, Bhandari A, et al. 2008. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science.* 320:539–543.
- Watt DC, Katz K, Shepherd M. 1983. The natural history of schizophrenia: a 5-year prospective follow-up of a representative sample of schizophrenics by means of a standardized clinical and social assessment. *Psychol Med.* 13:663–670.
- Weinberger DR, Berman KF. 1988. Speculation on the meaning of cerebral metabolic hypofrontality in schizophrenia. *Schizophr Bull.* 14:157–168.
- Wheeler AL, Voineskos AN. 2014. A review of structural neuroimaging in schizophrenia: from connectivity to connectomics. *Front Hum Neurosci.* 8:653. doi:10.3389/fnhum.2014.00653
- Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Tsuang MT, Faraone SV, McCarley RW, Shenton ME, Green AI, Nieto-Castanon A, LaViolette P, et al. 2009. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proc Natl Acad Sci USA.* 106:1279–1284.
- WHO. 2010. International Statistical Classification of Diseases and Related Health Problems 10th Revision Geneva, Switzerland: WHO.
- Willeit M, Ginovart N, Kapur S, Houle S, Hussey D, Seeman P, Wilson AA. 2006. High-affinity states of human brain dopamine D2/3 receptors imaged by the agonist [11C](+)-PHNO. *Biol Psychiatry.* 59:389–394.
- Wray NR, Gottesman II. 2012. Using summary data from the danish national registers to estimate heritabilities for schizophrenia, bipolar disorder, and major depressive disorder. *Front Genet.* 3:118. doi:10.3389/fgene.2012.00118
- Xu B, Ionita-Laza I, Roos JL, Boone B, Woodrick S, Sun Y, Levy S, Gogos JA, Karayiorgou M. 2012. De novo gene mutations highlight patterns of genetic and neural complexity in schizophrenia. *Nat Genet.* 44:1365–1369.
- Xu B, Roos JL, Dexheimer P, Boone B, Plummer B, Levy S, Gogos JA, Karayiorgou M. 2011. Exome sequencing supports a de novo mutational paradigm for schizophrenia. *Nat Genet.* 43:864–868.
- Xu B, Roos JL, Levy S, van Rensburg EJ, Gogos JA, Karayiorgou M. 2008. Strong association of de novo copy number mutations with sporadic schizophrenia. *Nat Genet.* 40:880–885.
- Yasuno F, Suhara T, Okubo Y, Sudo Y, Inoue M, Ichimiya T, Takano A, Nakayama K, Halldin C, Farde L. 2004. Low dopamine d(2) receptor binding in subregions of the thalamus in schizophrenia. *Am J Psychiatry.* 161:1016–1022.
- Yee CM, Nuechterlein KH, Morris SE, White PM. 1998. P50 suppression in recent-onset schizophrenia: clinical correlates and risperidone effects. *J Abnorm Psychol.* 107:691–698.
- Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zollei L, Polimeni JR, et al. 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol.* 106:1125–1165.

Yeo RA, Gangestad SW, Liu J, Ehrlich S, Thoma RJ, Pommy J, Mayer AR, Schulz SC, Wassink TH, Morrow EM, et al. 2013. The impact of copy number deletions on general cognitive ability and ventricle size in patients with schizophrenia and healthy control subjects. *Biol Psychiatry*. 73:540–545.

Zhuo C, Zhu J, Qin W, Qu H, Ma X, Tian H, Xu Q, Yu C. 2014. Functional connectivity density alterations in schizophrenia. *Front Behav Neurosci*. 8:404. doi:10.3389/fnbeh.2014.00404

Zink M, Englisch S, Schmitt A. 2014. Antipsychotic treatment modulates glutamate transport and NMDA receptor expression. *Eur Arch Psychiatry Clin Neurosci*. 264:S67–S82.