



# The concept of schizotypy – A computational anatomy perspective<sup>☆</sup>



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## ABSTRACT

Despite major progress in diagnostic accuracy and symptomatic treatment of mental disorders, there is an ongoing debate about their classification aiming to follow current advances in neurobiology. The main goal of this review is to provide a comprehensive summary of the put forward schizotypy concept that follows the needs for objective assessment of schizophrenia-like personality traits in the general population. We focus on major achievements in the field from the perspective of magnetic resonance imaging-based computational anatomy of the brain. Particular interest is devoted to overlapping brain structure findings in schizotypy and schizophrenia to promote a dimensional view on schizophrenia as extension of phenotype traits in the non-clinical general population.

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## 1. A dimensional perspective on mental disorders

In the field of clinical neuroscience there is an ongoing debate about the general principles of diagnosis and classification of psychiatric disorders. The already established International Classification of Disease (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) are built on the supposition of mental disorders, which represent qualitatively well-segregated nosological entities. However, similarities in clinical phenotype presentation and frequently observed comorbidities confirm the assumption that psychiatric disorders are not discrete entities. Accordingly, the Research Domain Criteria project (RDoC) by the U.S. National Institute of Mental Health ([www.nimh.nih.gov/research-priorities/rdoc](http://www.nimh.nih.gov/research-priorities/rdoc)) proposed a diagnostic system for psychiatric disorders following a dimensional perspective based on objective measures of the underlying neurobiological and behavioural mechanisms (Cuthbert, 2014). Naturally, the RDoC approach became subject of criticism, in particular questioning the use of animal models of psychiatric diseases or the inability to accommodate social or interpersonal factors when investigating behavioural aspects in patients (Kirmayer and Crafa, 2014).

Following RDoC's dimensionality perspective on mental disorders, the concept of schizotypy presumes a quantitative rather than qualitative characterisation of schizophrenia (Nelson et al., 2013). Furthermore, this concept can be extended to the assumption of behavioural dimension present in the general healthy population and reaching a particular threshold where behaviour is qualified as part of the

pathological clinical phenotype. In this review we provide a comprehensive summary of the recent publications on schizotypy and associated brain anatomy changes to lay the grounds for a dimensional perspective on schizophrenia and related disorders.

## 2. Schizotypy: historical perspective

Schizophrenia is not only a debilitating condition with severe repercussions for patients and their relatives, but it also presents a significant ethical and economic burden for the society (Olesen et al., 2012). The growing needs for early and accurate diagnosis motivated clinical research towards identification of “at risk” populations representing a higher risk to develop schizophrenia. First attempts in the field dating half a century ago defined “at risk” individuals among the offspring of parents with mental disorders (Pearson and Kley, 1957). Contrary to the concept of higher risk for schizophrenia based on genetic grounds in intra-familial cases, the theory of a psychosis-proneness continuum proposed that high levels of the personality trait “psychoticism” are linked to schizophrenia (Eysenck, 1992).

The term “schizotypy” was coined by Rado and Meehl (Meehl, 1962) where schizotypy is defined not as nosological entity, but much more as a form of personality organisation that results from particular biological predisposition: schizoaetia (Meehl, 1962; Rado, 1953). The psychosis continuum concept has been supported by empirical evidence describing psychotic-like experiences in the general population (Chapman et al., 1994; Chapman et al., 1995; David, 2010; Johns and van Os, 2001; Meehl, 1962; Siever et al., 1993).

Historically, the seminal work by Claridge and colleagues helped our current understanding of schizotypy by proposing a differentiation between the quasi-dimensional and the fully-dimensional models of

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schizotypy and schizophrenia (Claridge, 1994). The quasi-dimensional or psychiatric model attributed to Meehl is based on the notion of interaction between the inherited predisposition, schizotaxia (Faraone et al., 2001), and the environment. Meehl postulated that the vulnerability to psychosis is specific to a small percentage of the population and is due to a single gene called the schizo-gene, which causes hypokrisia, a synaptic aberration. Schizotaxia is seen as not sufficient to induce psychosis, but the interaction with the environment could lead to clinically full-blown schizophrenia (Lenzenweger, 2006). The quasi-dimensional model is supported mainly by taxometric studies (Haslam et al., 2012). Conversely, the fully dimensional model puts forward a description of a continuum between personality traits, genetic variation and cognitive states. The advantage of the fully dimensional model is that it provides a framework for description of the inter-individual variability and integrates most of the elements of the quasi-dimensional model (Claridge, 1994). During the last decades, the concept of schizotypy or schizophrenia continuum in the general population is considered as established with the assumption of high prevalence of transitory anomalous experiences in the general population (van Os et al., 2009).

### 3. Schizotypy: phenomenology and assessment

The increasing interest towards the schizotypy concept follows the current attempts to understand the neurobiological basis of schizophrenia merging findings from genetics, brain imaging and clinical observations (Carpenter, 2011; Kapur, 2011; Keshavan et al., 2011; Tandon et al., 2010). The schizotypy concept is organised in a three factors/dimensions model: i) cognitive–perceptual or positive schizotypy dimension, ii) interpersonal deficit or negative schizotypy dimension, and iii) disorganisation dimension, which is equivalent to the three factors model of schizophrenia (Wuthrich and Bates, 2006). This model was proved to be independent of gender, culture, religion, family adversity and psychopathology (Reynolds et al., 2000). Empirical evidence of the overlap between schizophrenia and schizotypy is provided by studies investigating genetic variability, perception and motor control, psychopharmacology and brain structure and function (Ettinger et al., 2014; Nelson et al., 2013).

Over the years many different approaches were developed to objectively assess schizotypy (Rust 1988; Raine, 2006). Several scales have been proposed in the form of clinical interview or self-report questionnaires such as the Chapman scales assessing psychotic traits and the Schizotypy Personality Scale (STA) (Lenzenweger, 2006; Mason and Claridge, 2006). Nevertheless, all different types of assessment converge on the schizotypy characterisation by the three factor model (Raine, 2006). Adjustments were made to include the impulsive nonconformity factor (Fonseca-Pedrero et al., 2011). The Oxford–Liverpool Inventory of Feelings and Experiences (O-LIFE) is based on a four factor model obtained by factor analysis in a large cohort of one thousand individuals combined with established psychosis proneness scales (Claridge et al., 1996). The O-LIFE construct is based on the fully-dimensional model to focus on personality traits rather than on clinical symptoms (Mason and Claridge, 2006).

### 4. Schizotypy and brain anatomy

Previous studies in schizophrenia, which investigated brain structure using computer tomography (CT) or magnetic resonance imaging (MRI) show ventricle enlargement and grey matter volume reductions in temporo-parietal and frontal areas in addition to changes in hippocampus, basal ganglia, amygdala and cerebellum (Olabi et al., 2011; Shenton et al., 2010; Shepherd et al., 2012).

With the emergence of sophisticated MRI-based methods for automated whole-brain anatomy assessment–computational anatomy, there were numerous attempts to investigate the link between schizotypy traits and brain structure. One of the pioneering computational anatomy studies in schizotypy demonstrated correlation between

pre-frontal grey matter reduction and high schizotypal scores (Raine et al., 2002). This was followed by demonstration of similar correlations affecting medial prefrontal cortex, orbito-frontal cortex and temporal cortex (Ettinger et al., 2012). A recent study reported correlation between higher positive schizotypy scores and larger global brain volume paralleled by grey matter volume increase in the medial posterior cingulate cortex and precuneus (Modinos et al., 2010). Volume increases were also observed by Kuhn (Kühn et al., 2012), where schizotypy scores correlate with increases in frontal lobe cortical thickness and reduced thalamus volume. Despite advances in the field, there is no published study taking into account all schizotypy dimensions together.

While most of the published results on the brain anatomy correlates of schizotypy are consistent with the pattern of brain anatomy changes in schizophrenia, the directionality of brain alterations associated with schizotypy is controversial. MRI offers a non-invasive way to investigate subtle changes of the brain anatomy, however current MRI-based studies of brain anatomy are limited to a qualitative and phenomenological description of relative changes in grey matter volume, cortical thickness and blurring of the grey–white matter boundary. Main limitation of computational brain anatomy studies is that none of the provided metrics provide further insight into the underlying neurobiological processes due to the fact that the mechanisms driving MR signal changes in brain tissue at the microstructural level remain largely unknown. Another limitation is the observational character of the studies published up to date. One of the future directions for research could focus on longitudinal assessment of the brain anatomy changes and individual schizotypy traits to infer causality with respect to brain structure and behaviour.

In the majority of published studies, white matter changes are investigated using diffusion-weighted imaging (DWI) techniques, which are sensitive to water diffusion and are thought to represent microstructural properties of brain tissue. These methods are used in the context of schizotypy research to investigate features of structural brain connectivity according to one of the earliest hypothesis in schizophrenia as dys-connectivity syndrome (White et al., 2008). Here, the presumption is of pathological connectivity between fronto-temporal brain regions underlying schizophrenia symptoms such as hallucinations and delusions (Friston, 1998; Friston and Frith, 1995). DWI findings in schizophrenia are consistent in showing a decreased connectivity between frontal and temporal lobes (Yao et al., 2013). Focusing on the schizophrenia spectrum, studies investigating white matter connectivity in schizotypal personality disorder patients show similar findings to schizophrenia studies. However, schizotypal personality disorder patients show white matter abnormalities to a lesser degree than in schizophrenia patients and more consistently in the temporal lobe (Hazlett et al., 2012).

One of the most interesting perspectives from the imaging neuroscience point of view is the link between brain development, anatomy changes and particular stages of disease progression (Peters and Karlsgodt, 2015). Schizophrenia onset in late adolescence is intrinsically related to white matter development, especially the maturation of association tracts. Accordingly, a number of descriptive developmental models were put forward. One of these models suggests normal white matter development until a certain critical period in late adolescence when with the appearance of first clinical signs there is a progressive white matter loss explained by unknown neurotoxic effects. In the second model white matter development is compromised long before adolescence, and even if the development follows a similar trajectory to that of normal brain anatomy, the impairment persists into adulthood. The third model combines the neurotoxic and neurodevelopment models in a way that early impairment in white matter maturation is followed after disease onset by neurotoxic effects further compromising the white matter microstructure. It appears that the latest model seems to be the most plausible because it confirms mounting evidence of impaired white matter tract function in high-risk individuals. These models are following theoretical concepts on heterogeneity of cortical pruning abnormalities in the development of schizophrenia (Hoffman and McGlashan, 1994).

In the first study comparing directly schizotypal personality disorder and schizophrenia patients, Lener and colleagues found that schizotypal personality disorder individuals present white matter changes in frontal and temporal tracts that are intermediate between schizophrenics and controls (Lener et al., 2015). The same study also identified a relative preservation of the cingulate white matter anatomy contradicting evidence for cingulate pathology in schizophrenia. The authors suggest that the unaffected areas may represent a correlate of compensatory phenomena in schizotypal personality disorder individuals. This hypothesis is consistent with the previously proposed model of schizophrenia spectrum pathophysiology. This model suggests that schizotypal personality disorder individuals do not develop full-blown psychosis, but milder cognitive and social impairment, because of protective or compensatory factors. Such compensatory factors are for example the ability to recruit cortico-subcortical circuits, which are less responsive to the up-regulation of the dopaminergic system as a consequence from the presumed frontal hypo-dopaminergic state (Siever and Davis, 2004).

Only a few studies have used DWI to investigate white matter changes associated with schizotypy. A first diffusion-tensor imaging study on healthy subjects found that higher psychotic scores were associated with higher fractional anisotropy in the left arcuate fasciculus and that lower psychotic scores were associated with higher fractional anisotropy in the corpus callosum, the right arcuate fasciculus and in fronto-parietal areas (Volpe et al., 2008). The second study exploring white matter integrity found fractional anisotropy reductions in fronto-temporal white matter tracts associated with increased cognitive-perceptual scores (Nelson et al., 2011). Overall these results demonstrate altered structural brain connectivity in schizotypy, however the accumulated up to date evidence is not sufficient to find a clear causal link with white matter changes observed in schizophrenia.

## 5. Conclusion

There is a growing body of evidence confirming the correlation between facets of human behaviour and brain anatomy, which can be extended to deviations of normal behaviour in mental disorders. Recent findings in the field of computational anatomy of the brain support this notion by demonstrating significant overlap between brain structure changes in clinical cases of schizophrenia and spatial patterns correlating with schizotypy traits in the general non-clinical population. Our review of the recent literature on the topic confirms the important role of imaging neuroscience to provide a rich set of brain anatomy measures, which can be used as endophenotype of schizophrenia. We show that this is an efficient strategy that allows to establishing the link between brain structure, function and resulting behaviour in the healthy and diseased brain.

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