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Associations of schizophrenia risk genes *ZNF804A* and *CACNA1C* with schizotypy and modulation of attention in healthy subjects

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ABSTRACT

Schizotypy is a multidimensional risk phenotype distributed in the general population, constituting of subclinical, psychotic-like symptoms. It is associated with psychosis proneness, and several risk genes for psychosis are associated with schizotypy in non-clinical populations. Schizotypy might also modulate cognitive abilities as it is associated with attentional deficits in healthy subjects. In this study, we tested the hypothesis that established genetic risk variants *ZNF804A* rs1344706 and *CACNA1C* rs1006737 are associated with psychometric schizotypy and that schizotypy mediates their effect on attention or vice versa. In 615 healthy subjects from the FOR2107 cohort study, we analysed the genetic risk variants *ZNF804A* rs1344706 and *CACNA1C* rs1006737, psychometric schizotypy (schizotypal personality questionnaire-brief SPQ—B), and a neuropsychological measure of sustained and selective attention (d2 test). *ZNF804A* rs1344706 C (non-risk) alleles were significantly associated with higher SPQ-B Cognitive-Perceptual subscores in women and with attention deficits in both sexes. This schizotypy dimension also mediated the effect of *ZNF804A* on attention in women, but not in men. *CACNA1C* rs1006737-A showed a significant sex-modulated negative association with Interpersonal schizotypy only in men, and no effect on attention. Our multivariate model demonstrates differential genetic contributions of two psychosis risk genes to dimensions of schizotypy and, partly, to attention. This supports a model of shared genetic influence between schizotypy and cognitive functions impaired in schizophrenia.

1. Introduction

Schizotypy is a multidimensional construct of personality traits phenomenologically resembling subclinical schizophrenia symptoms. It is considered a phenotypic marker of psychosis proneness and schizophrenia risk (Barrantes-Vidal et al., 2015) and elevated in patients

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with psychotic disorders (Brosey and Woodward, 2015). Schizotypy, having predictive value for conversion probability into schizophrenia-spectrum disorders (Chapman et al., 1994; Gooding et al., 2005; Kwapil et al., 2013), is also considered a high-risk marker in early intervention research.

The phenotype comprises aspects of deviations in cognition, emotion, speech, and perception (Ettinger et al., 2015), but is also associated with higher creativity (Fink et al., 2014; Mohr and Claridge, 2015), possibly even constituting an evolutionary advantage (Nettle and Clegg, 2006). Schizotypy is often delineated into three dimensions (Dodell-Feder et al., 2019), namely *positive/cognitive-perceptual* (magical thinking, referential ideas, unusual perceptual experiences, and paranoid ideation), *negative/interpersonal* (difficulties in social interaction and blunted affect) and *disorganised* ("odd" speech and behaviour).

While different cognitive dimensions have been linked to schizotypy (Siddi et al., 2017), relative deficits in sustained and selective attention have been robustly reported (Breeze et al., 2011; Fuggetta et al., 2015; Gooding et al., 2006; Moreno-Samaniego et al., 2017). Findings even point to a possible genetic link between attention-deficit hyperactivity disorder and schizotypy (Ettinger et al., 2006). While impaired attention has often been associated with the negative schizotypy dimension (Alvarez-Moya et al., 2007; Chen and Faraone, 2000; Smyrnis et al., 2007), recent evidence also suggests the cognitive-perceptual dimension as a risk factor for attentional difficulties (Gooding et al., 2006; Stotesbury et al., 2018). Attention deficits are also found in schizophrenia patients compared to healthy controls (Elvevåg and Goldberg, 2000; Hill et al., 2008; Lee et al., 2017; Nuechterlein et al., 2004), and in first-degree relatives of schizophrenia patients (Snitz et al., 2005), indicating genetic effects. Attention therefore represents a putative cognitive link between these risk genotypes and phenotypes.

Growing evidence also suggests a partially shared genetic basis between schizotypy and psychotic disorders. Genome-wide association studies (GWAS) have currently identified >120 common genetic variations contributing to the risk for schizophrenia (Pardiñas et al., 2018), and while at least some risk genes are shared among clinical psychosis phenotypes (Craddock et al., 2009; Sheldrick et al., 2008), it seems that polygenic risk scores for psychosis are only marginally associated with schizotypy (Hatzimanolis et al., 2018; Jones et al., 2016). However, recent studies reporting significant associations of schizophrenia risk variants with schizotypy measures support a partially mutual genetic background (Barrantes-Vidal et al., 2015).

Among the most prominent susceptibility genes for schizophrenia is *ZNF804A*, involved in neurodevelopmental processes (Lencz et al., 2010) and coding for the zinc-finger binding protein 804A (Voineskos et al., 2011). The major A allele of the single-nucleotide polymorphism (SNP) rs1344706 was initially reported to be associated with schizophrenia in a GWAS by O'Donovan et al., with an even stronger association to a broader psychosis phenotype that includes bipolar disorder (O'Donovan et al., 2008). This association has since been replicated and shown to be one of the strongest susceptibility variants for schizophrenia (Pardiñas et al., 2018; Riley et al., 2010; Williams et al., 2011). Rs1344706-A has been associated with decreased expression of *ZNF804A* in fetal brain tissue (Hill and Bray, 2012) and with neurocognitive and brain structural variations in schizophrenia patients and in healthy controls (Chang et al., 2017; Donohoe et al., 2011; Nenadic et al., 2015). Two recent studies linked *ZNF804A* rs1344706 with schizotypy (Stefanis et al., 2013; Yasuda et al., 2011), but with heterogeneous dimensional associations: While Yasuda and colleagues found carriers of the rs1344706 major A-allele to have higher disorganised schizotypal levels, Stefanis et al. reported the opposite effect, i.e., a positive association of the minor C-allele with positive schizotypy, calling for further research.

A second gene strongly associated with the psychosis spectrum is *CACNA1C*, encoding a subunit of the calcium channel $Ca_v1.2$, which is involved in the modulation of gene transcription, synaptic plasticity and cell survival in the brain (Bhat et al., 2012). *CACNA1C*'s intronic SNP rs1006737 with risk allele A has been established as a susceptibility variant for schizophrenia (Jiang et al., 2015; Ripke et al., 2013; Ruderfer et al., 2014) and bipolar disorder (Ferreira et al., 2008; Moon et al., 2018; Ruderfer et al., 2014). It has been associated with cognitive variation like decreased attentional performance and reduced corresponding neural activity in risk-allele carriers (Thimm et al., 2011), impaired working memory (Zhang et al., 2012), but also impaired facial emotion recognition (Soeiro-de-Souza et al., 2012) and increased interpersonal distress (Erk et al., 2010). In two previous studies, rs1006737-A has also been linked to elevated positive schizotypy and schizotypal personality disorder (Roussos et al., 2013, 2011). While the influence of *CACNA1C* variants on cognition and its neural correlates has been shown repeatedly (Dietsche et al., 2014; Krug et al., 2014), it is unclear whether the gene is also linked to variation in cognitive function in schizotypy.

Taken together, current research suggests an association of psychosis risk genes *ZNF804A* and *CACNA1C* with impaired cognition and schizotypy in the general population, and an association of both schizophrenia and schizotypy with cognitive deficits. It is, however, lacking models integrating those univariate associations into a joint framework. As there are sex differences in schizophrenia prevalence and symptom profiles (Abel et al., 2010) as well as schizotypy (Kremen et al., 1998; Raine, 1992), and sex-specific effects have recently been reported for both genes (de Castro-Catala et al., 2017; Strohmaier et al., 2013), a differential impact for males and females should be considered.

Therefore, the first aim of the present study was to analyse the differential effects of *ZNF804A* rs1344706 and *CACNA1C* rs1006737 on dimensional schizotypy as a phenotypic psychosis proneness marker, considering sex-dependent modulations. Secondly, we tested the opposing models of (a) the relatively stable personality trait schizotypy mediating genetic influence on attention, expecting the *Cognitive-Perceptual* dimension to particularly affect cognition as recently suggested (Stotesbury et al., 2018) and (b) attentional variation mediating genetic influence on schizotypal traits, as derived from recent studies of cognition in schizophrenia (Toulopoulou et al., 2018, 2015).

2. Material and methods

2.1. Sample

We analysed data of 615 healthy Central European subjects (age 18–65 years, mean = 32.77, standard deviation (SD) = 12.50) drawn from the FOR2107 cohort, a multi-centre study, recruiting through newspaper advertisements and mailing lists from the areas of Marburg and Muenster in Germany (Kircher et al., 2018). Ethics approval was obtained from the ethics committees of the Medical Schools of the Universities of Marburg and Muenster, respectively, in accordance with the Declaration of Helsinki. All subjects volunteered to participate in the study and provided written informed consent. Subjects of non-European origin were excluded from the analyses because of known population differences in the studied genetic polymorphisms. Exclusion criteria were current or former psychiatric disorders (assessed with SCID-I interviews (Wittchen et al., 1997) by trained raters), history of neurological or other severe medical disorders, verbal IQ <80 (Multiple Choice Word Test-B (Lehrl, 1995)), or current psychotropic medication. The resulting sample comprised 232 (37.7%) male and 383 (62.3%) female participants.

2.2. Assessment of psychometric schizotypy

Self-reported schizotypy was assessed with the German version (Klein et al., 1997) of the Schizotypal Personality Questionnaire-Brief (SPQ-B (Raine and Benishay, 1995)). Based on Raine's original SPQ (Raine, 1991), it has recently been validated across multi-national studies, including the German version (Fonseca-Pedrero et al., 2018). Beside a total schizotypy score, the SPQ-B provides measures on the *Cognitive-*