Schizophrenia Research 208 (2019) 67–75

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

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

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ARTICLE INFO

Article history:
Received 24 November 2018
Received in revised form 5 March 2019
Accepted 20 April 2019
Available online 7 May 2019

Keywords:
Schizotypy
Attention
Cognition
Schizophrenia risk variants
Psychosis

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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https://doi.org/10.1016/j.schres.2019.04.018
0920-9964/

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-*

Perceptual, *Interpersonal*, and *Disorganised* dimensions delineated by previous factor analyses (Axelrod et al., 2001; Compton et al., 2009). For the questionnaire as a whole and its subscores, adequate internal consistency and criterion validity have been demonstrated (Fonseca-Pedrero et al., 2018; Klein et al., 2001). In our sample, the SPQ-B showed acceptable reliability (Cronbach's $\alpha = 0.737$, for subscore values see supplementary table S5).

2.3. Neurocognitive testing

Participants underwent standardised neurocognitive testing for sustained and selective attention with the d2 test of attention (Brickenkamp, 2002). It is a cancellation test assessing the continuous ability to focus on task-relevant characteristics while ignoring similar characters, requiring constant visual perceptual speed and accuracy. Despite its simple structure and implementation, the d2 test has been shown to be a reliable and valid measure of attention capacity, both in healthy subjects and in schizophrenia patients (Brickenkamp, 2002; Lee et al., 2017). The *concentration performance* parameter (the error-adjusted number of hits) was used in this analysis as it is resistant to deception attempts and has shown high reliability in the reference sample (Brickenkamp, 2002) and a randomly drawn subset of our own sample ($n = 100$, Cronbach's alpha $\alpha = 0.981$).

2.4. Genotyping and quality control

Genomic DNA was extracted from blood samples acquired onsite. Genotyping and further preparation of genomic data was performed blinded to phenotype data at the Institute of Human Genetics of the University Hospital Bonn, Germany and at the Max Planck Institute of Psychiatry, Munich, Germany. Genotyping was conducted using the Infinium PsychArray BeadChip (Illumina, San Diego, CA, USA), according to standard protocols. Clustering and initial QC was conducted in GenomeStudio v.2011.1 (Illumina, San Diego, USA) with the Genotyping Module v.1.9.4. Full QC was performed in PLINK v1.90b5 (x) and *R* v3.3.3, based on a larger dataset of which the present subjects constituted a subset. Individuals were removed if they met any of the following criteria: genotyping call rate <98%, gender mismatches or other X-chromosome-related issues, genetic duplicates, cryptic relatives with pi-hat ≥12.5%, genetic outlier with a distance from the mean of >4 SD in the first eight ancestry components, or a deviation of the autosomal or X-chromosomal heterozygosity from the mean > 4 SD.

2.5. Statistical analyses

Sex differences in schizotypy, age, and neurocognitive performance were analysed using Student's *t*-tests for independent samples or Mann-Whitney *U* tests where the assumption of normal distribution was violated. Distributions of allelic frequencies between sexes were compared with chi-squared (χ^2) tests. Associations of genotypes and schizotypy were analysed via linear regression models, using the IBM Statistical Package for Social Sciences (SPSS, version 22, IBM, Armonk, NY) and the PROCESS macro v3.1 for SPSS (Hayes, 2013). Multidimensional scaling (MDS) analyses to estimate population stratification in the sample were conducted in PLINK (Purcell & Chang; Chang et al., 2015), the first three MDS components were included as covariates in SNP association analyses. Leave-one-out cross-validation was used to calculate the root mean PRESS (predicted residual error sum of squares) as a model fit parameter in stepwise regressions (√mPRESS). As SPQ-B scales are correlated, *p*-values were adjusted (p_{adj}) to correct for multiple comparison according to Bonferroni-Holm (Holm, 1979), using *R* (R Core Team, 2018).

3. Results

3.1. Distribution of schizotypy, attention, and allele frequencies

Descriptive statistics for SPQ-B subscores as well as genotype frequencies for *ZNF804A* rs1344706 and *CACNA1C* rs1006737 are shown in Table 1. Neither rs1344706 (χ^2(degrees of freedom (*df*) = 2) = 0.79, $p = 0.675$) nor rs1006737 ($\chi^2(2) = 3.80$, $p = 0.150$) showed significant differences in minor allele counts between sexes. We also found no significant sex differences for age ($t(613) = -0.379$, $p = 0.704$; male mean = 32.52, SD = 11.49, female mean = 32.92, SD = 13.09) or d2 performance ($t(613) = -1.45$, $p = 0.148$). Mean d2 scores for the whole sample (mean = 191.40, SD = 42.25), as well as for males (mean = 188.24, SD = 41.75) and females (mean = 193.32, SD = 42.49), were within the average range for healthy subjects, according to standard tables (Brickenkamp, 2002). As observed in previous studies (Kremen et al., 1998; Raine, 1992), we found significant sex differences for the SPQ-B *Sum* score ($U = -2.45$, $p = 0.014$, $p_{adj} = 0.028$), the *Interpersonal* ($U = -2.43$, $p = 0.015$, $p_{adj} = 0.028$) and *Disorganised* ($U = -3.84$, $p = 1.3 \times 10^{-4}$, $p_{adj} = 3.9 \times 10^{-4}$) subscores, with higher scores in males than in females; but not for the *Cognitive-Perceptual* ($U = -0.96$, $p = 0.336$) subscore.

3.2. Associations of ZNF804A, CACNA1C and schizotypy dimensions

To explore the prediction of the three schizotypy dimensions, we performed separate stepwise multiple regression analyses, entering the two SNPs, SNP × sex interaction terms, sex, age, and MDS components as possible regressors (Table 2, Suppl. Table S1a-1c).

For the *Cognitive-Perceptual* dimension (*model 1a*, √mPRESS = 1.12, Fig. 1), we found a significant effect of age ($\beta = 0.018$, $p = 5.05 \times 10^{-7}$, $p_{adj} = 2.53 \times 10^{-6}$) and rs1344706 × sex ($\beta = 0.089$, $p = 0.015$, $p_{adj} = 0.033$), with a higher number of C alleles associated with higher *Cognitive-Perceptual* schizotypy in females ($\beta = 0.212$, $p = 0.007$), but not in males ($\beta = -0.071$, $p = 0.458$).

For the *Interpersonal* dimension (*model 1b*, √mPRESS = 1.71, Fig. 1), we also found a significant effect of age ($\beta = 0.011$, $p = 0.044$, $p_{adj} = 0.044$) and rs1006737 × sex ($\beta = -0.150$, $p = 0.011$, $p_{adj} = 0.033$), with a higher number of A alleles associated with lower *Interpersonal* schizotypy in males ($\beta = -0.399$, $p = 0.035$), but not in females ($\beta = -0.162$, $p = 0.209$).

For the *Disorganised* dimension (*model 1c*), only sex was identified as a significant regressor ($\beta = -0.390$, $p = 2.16 \times 10^{-4}$, $p_{adj} = 8.64 \times 10^{-4}$).

Table 1
Distribution of schizotypy and allele frequencies for both sexes.

	total mean (SD[a])	male mean (SD[a])	female mean (SD[a])
SPQ-B			
Sum	3.42 (2.99)	3.78 (3.07)	3.20 (2.93)
Cognitive perceptual	0.90 (1.15)	0.81 (1.03)	0.95 (1.21)
Interpersonal	1.72 (1.72)	1.92 (1.76)	1.60 (1.68)
Disorganized	0.80 (1.27)	1.04 (1.43)	0.65 (1.15)
	total no. (%)	male no. (%)	female no. (%)
ZNF804A rs1344706			
AA	217 (35.3)	85 (36.6)	132 (34.5)
AC	295 (48.9)	106 (45.7)	189 (49.3)
CC	103 (16.7)	41 (17.7)	62 (16.2)
CACNA1C rs1006737			
GG	292 (47.5)	118 (50.9)	174 (45.4)
AG	267 (43.4)	99 (42.7)	168 (43.9)
AA	56 (9.1)	15 (6.5)	41 (10.7)

[a] SD = standard deviation.

Table 2
Summary of model specifications for *models 1a*, *1b and 2*. Full documentation in suppl. Tables S1–S2.

model 1a	($F(2,614) = 16.00$, $p = 1.7 \times 10^{-7}$, $R^2 = 0.050$)			
prediction of Cognitive-Perceptual *schizotypy*			√mPRESS[b] = 1.12	
	coefficient (se[a])	*t*	*p*	p_{adj}
age	0.018 (0.004)	4.34	5.05×10^{-7}	$\mathbf{2.53 \times 10^{-6}}$
rs1344706 × sex	0.283 (0.124)	2.28	0.015	**0.033**
rs1344706 (sex = m)	−0.073 (0.094)	−0.74	0.458	
rs1344706 (sex = f)	0.212 (0.079)	2.79	0.007	
model 1b	($F(2,614) = 16.58$, $p = 0.003$, $R^2 = 0.015$)			
prediction of Interpersonal *schizotypy*			√mPRESS[b] = 1.71	
	coefficient (se[a])	*t*	*p*	p_{adj}
age	0.011 (0.006)	2.02	0.044	**0.044**
rs1006737 × sex	0.283 (0.124)	−2.57	0.011	**0.033**
rs1006737 (sex = m)	−0.399 (0.188)	−2.13	0.035	
rs1006737 (sex = f)	−0.162 (0.129)	−1.26	0.209	
model 2	($F(4,610) = 38.89$, $p = 5.13 \times 10^{-29}$, $R^2 = 0.203$)			
prediction of d2 performance			√mPRESS[b] = 37.99	
	coefficient (se[a])	*t*	*p*	p_{adj}
age	−1.342 (0.125)	−10.76	7.85×10^{-25}	$\mathbf{3.14 \times 10^{-24}}$
rs1344706	−15.551 (5.208)	−2.99	0.003	**0.006**
rs1344706 × sex	6.553 (2.944)	2.23	0.026	**0.026**
rs1344706 (sex = m)	−8.145 (3.399)	−2.40	0.017	
rs1344706 (sex = f)	−3.041 (2.881)	−1.06	0.292	
Cognitive-Perceptual schizotypy	−4.509 (1.367)	−3.30	0.001	**0.003**

In bold Bonferroni-Holm-adjusted p-values after correction.
[a] SE = standard error.
[b] √mPRESS = root mean predicted residual sum of squares.

Total schizotypy was neither associated with *ZNF804A* rs1344706 (β = −0.317, $p = 0.591$) nor *CACNA1C* rs1006737 (β = −0.227, $p = 0.120$).

3.3. Associations of ZNF804A, CACNA1C, schizotypy dimensions and attention

To explore significant predictors of d2 performance, we calculated a separate stepwise multiple regression *model 2* with the two SNPs, SNP × sex interaction terms, sex, age, the three schizotypy subscores, and MDS components as possible regressors (√mPRESS = 37.99, Table 2, Suppl. Table S2). Here, age (β = −1.342, $p = 7.82 \times 10^{-25}$, $p_{adj} = 3.14 \times 10^{-24}$), *Cognitive-Perceptual* schizotypy (β = −4.509, $p = 0.001$, $p_{adj} = 0.003$), *ZNF804A* rs1344706 (β = −15.551, $p = 0.003$, $p_{adj} = 0.006$) and rs1344706 × sex (β = 6.553, $p = 0.026$, $p_{adj} = 0.026$), with a higher number of rs1344706-C associated with lower d2 performance in males (β = −8.145, $p = 0.017$) but not in females (β = −3.041, $p = 0.292$), were detected as significant regressors.

3.4. Mediation models of ZNF804A, schizotypy and attention

To analyse the proposed mediating relationship of schizotypy and attention, we hypothesised two models, derived from the associations detected in the regression models *1a-c* and *2*. *Model 3a* (Fig. 2, Suppl. Table S3) proposes *Cognitive-Perceptual* schizotypy as a risk factor for impaired cognition, thus mediating the effect of rs1344706 on d2 performance ($F(3,611) = 48.78$, $p < 1 \times 10^{-100}$, $R^2 = 0.197$). We found a significant direct effect of the dosage of *ZNF804A* rs1344706-C ($c' = -5.038$, $t(611) = -2.31$, $p = 0.021$, $p_{adj} = 0.032$) as well as a significant indirect effect of the SNP via *Cognitive-Perceptual* schizotypy (β = −4.210, $t(611) = -2.94$, $p = 0.003$, $p_{adj} = 0.013$) on d2 performance. However, the latter was again moderated by sex: Only for females (β = −0.890) but not for males (β = 0.300), a bootstrap-based

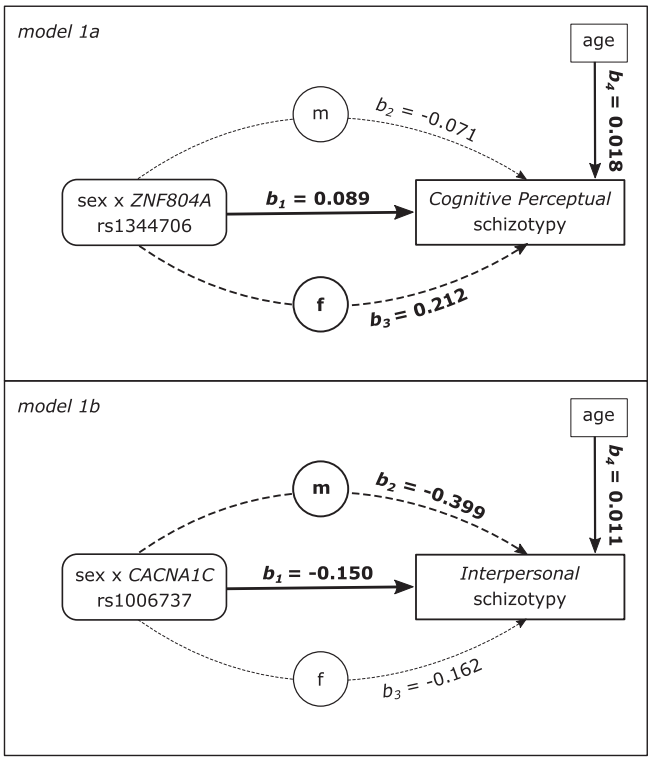

Fig. 1. Sex-moderated *models 1a* and *1b* of the effect of *ZNF804A* rs1344706-C and *CACNA1C* rs1006737-A on differential schizotypy dimensions. $b_{1\text{-}3}$ indicate unstandardised regression coefficients for each path; statistically significant paths are shown in bold.

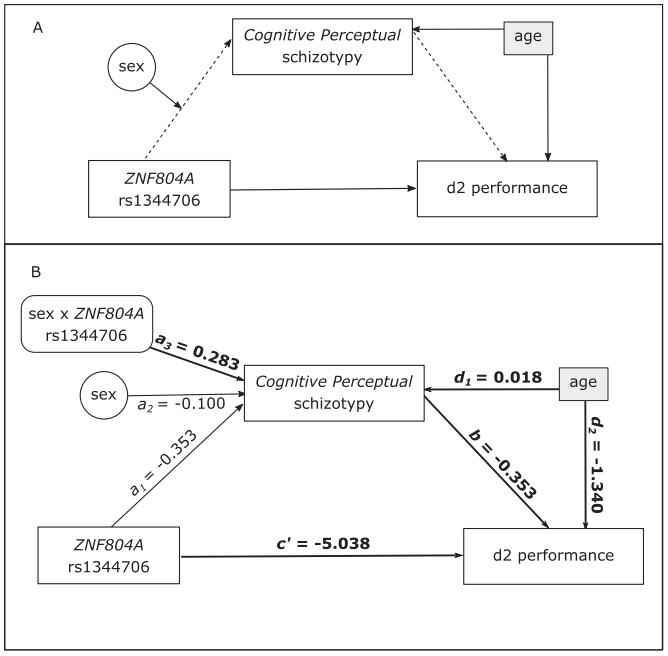

Fig. 2. Sex-moderated mediation *model 3a* of the effect of *ZNF804A* rs1344706-C on d2 performance, mediated by *Cognitive-Perceptual* schizotypy. Conceptual (A) and statistical (B) diagram. a_1–d_2 indicate unstandardised regression coefficients for each path; statistically significant paths are shown in bold.

confidence interval calculated using 10,000 bootstrap samples was consistently below zero, confirming a conditional indirect effect.

We additionally considered the opposing model, assuming cognition at an intermediate position between genes and phenotype. We tested this assumption in our data, with d2 performance mediating the sex-moderated effect of rs1344706-C on *Cognitive-Perceptual* schizotypy. This *model 3b* (Fig. 3, suppl. Table S3), although significant, explained a smaller proportion of the variance ($F(5,609) = 6.90$, $p = 2.4 \times 10^{-6}$, $R^2 = 0.071$) than *model 3a*. Post hoc *t*-tests comparing absolute z-transformed bootstrapped coefficient estimates from *models 3a* and *3b* revealed a stronger effect of rs1344706 on *Cognitive-Perceptual* schizotypy than on d2 performance (mean absolute difference (mad, *3a*) = 0.130, SD = 0.117; mad(*3b*) = 0.134, SD = 0.117) in both models ($t(9999) = -111.49$, $p < 1 \times 10^{-100}$; $t(9999) = -114.47$, $p < 1 \times 10^{-100}$, respectively).

There was no indication of a mediating effect of *Interpersonal* schizotypy on the association of CACNA1C rs1006737-A on attention or vice versa (suppl. Table S4a-b).

4. Discussion

This is the first large-scale study addressing the interplay between candidate susceptibility genes for psychotic disorders with different dimensions of schizotypy and neurocognitive performance as a putative endophenotype for psychosis in healthy subjects. Our analysis provides first support for a multivariate model of the interaction of genotype, phenotype, and cognition, linking schizotypy in the general population to a dimensional schizophrenia model. This includes two major findings: We observe, for the first time, a sex-moderated association of *ZNF804A* rs1344706 with the SPQ-B *Cognitive-Perceptual* dimension and of *CACNA1C* rs1006737 with the SPQ-B *Interpersonal* dimension. We suggest a moderated mediation model showing that in women, the effect of rs1344706 on attention is mediated by *Cognitive-Perceptual* schizotypy. Our results have implications for the role of *ZNF804A* rs1344706 and CACNA1c rs1006737 in schizotypy and cognitive function, and suggest a sex-modulated interaction between them.

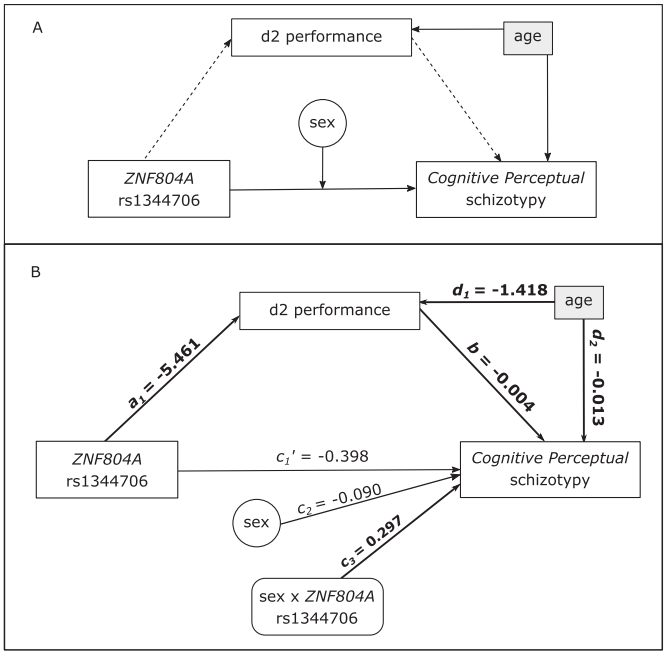

Fig. 3. Sex-moderated mediation *model 3b* of the effect of *ZNF804A* rs1344706-C on *Cognitive-Perceptual* schizotypy, mediated by d2 performance. Conceptual (A) and statistical (B) diagram. a_1–d_2 indicate unstandardised regression coefficients for each path; statistically significant paths are shown in bold.

Concurrent with previous findings (Stefanis et al., 2013; Yasuda et al., 2011), we further confirmed *ZNF804A* rs1344706 as susceptibility SNP for schizotypy. While this association has previously been reported, we provide a more detailed link to particular schizotypy dimensions, modulated by sex. Initially, Yasuda et al., reported a positive relationship between *ZNF804A* rs1344706-A and *Disorganised* schizotypal traits in healthy subjects (Yasuda et al., 2011). Concurrent with our own findings, however, Stefanis et al. reported an inverse relationship, with a higher number of rs1344706-A associated with decreased schizotypy. This effect was found for a primarily "positive" schizotypy endophenotype, including referential ideas and perceptual aberrations (Stefanis et al., 2013), in line with our results linking rs1344706 to the *Cognitive-Perceptual* dimension. Differences to Yasuda's findings might be attributed to divergent study populations and genetic backgrounds (Japanese vs. Central-European) and different A allele frequencies in those populations (38% and 61%, respectively (Clarke and Cardon, 2010; Yasuda et al., 2011)).

We now extend the simple model of a direct dependence of schizotypal features on rs1344706 allelic load by introducing sex as moderator. While previous studies on rs1344706 were either confined to all male samples (Stefanis et al., 2013) or did not test for such an interaction (Yasuda et al., 2011), a similar finding for another schizophrenia susceptibility SNP of *ZNF804A* (rs7597593, in medium linkage disequilibrium with rs1344706; $r^2 = 0.395$ calculated with LDlink for the CEU population (Machiela and Chanock, 2015)) has recently been reported, as only female C allele carriers showed elevated schizotypy levels compared to A-homozygotes (de Castro-Catala et al., 2017). Sex-dependent effects of rs7597593 are also evident in clinical measures and post-mortem brain mRNA expression levels in schizophrenia (Zhang et al., 2011). Thus, our findings can be explained with clinical and molecular mechanisms causing sex × SNP interactions for *ZNF804A* in the development of schizotypal traits.

In addition, we confirmed recent findings relating *ZNF804A* rs1344706 to neurocognitive function in general, and attention in particular (Chang et al., 2017). In healthy participants, the A allele and A/A genotype was associated with deficits in the executive control dimension of attention (Balog et al., 2011). Proposing a neural correlate of functional alterations, rs1344706-A homozygotes showed reduced thickness within the anterior cingulate cortex (Voineskos et al., 2011) and changes in functional coupling of the dorsolateral prefrontal cortex with the hippocampus (Esslinger et al., 2009; Paulus et al., 2013). Interestingly, in patients with schizophrenia, A allele load has been associated with fewer cognitive deficits (Van Den Bossche et al., 2012; Walters et al., 2010) and decreased cortical alteration (Schultz et al., 2014). It has been suggested that *ZNF804A* rs1344706 may enhance susceptibility to a certain schizophrenia subtype with less cognitive impairment (Walters et al., 2010), but also that the effects of rs1344706 might differ between healthy participants and patients (Hargreaves et al., 2012).

While Stefanis et al. linked *ZNF804A* SNPs to schizotypy, they did not detect an effect of rs1344706 on neurocognition (Stefanis et al., 2013). Differences in test batteries aside, the discrepancy between their findings and our own may be caused by marked differences in sample characteristics. Their sample comprised of young male army recruits while ours combined female and male participants within a wide range of age. Given the well-known age effects on neurocognitive measures (Lufi et al., 2015), a very selective sample with reduced variance might thus underestimate correlation or regression measures.

Despite evidence linking *ZNF804A* rs1344706 to illness susceptibility and psychosis proneness, neurocognitive functions, and variations in brain structure and function, its exact biological pathway is still unclear. *ZNF804A* is expressed widely in the human brain (Sun et al., 2015), especially within the dorsolateral prefrontal cortex and the hippocampus (Hill and Bray, 2012). Rs1344706 is non-coding but thought to have effects on *ZNF804A* expression (Hill and Bray, 2011), particularly during early prenatal brain development (Hill and Bray, 2012). *ZNF804A* has

also been associated with regulation of dopamine receptors (Girgenti et al., 2012), and alterations of dopamine concentration, and expression of dopaminergic genes have been linked to psychosis etiology (Howes and Kapur, 2009) and schizotypy (Grant et al., 2014; Mohr and Ettinger, 2014). In addition, sex-specific effects of genes involved in dopamine transmission have been discussed in schizophrenia, with oestrogens and androgens differentially modifying the development of schizophrenia symptoms through dopaminergic pathways (Godar and Bortolato, 2014). Similar mechanisms might influence the development of subclinical symptoms in schizotypy and thus explain sex-dependent effects of *ZNF804A* on schizotypal traits.

Taken together, compelling evidence suggests that effects of *ZNF804A* rs1344706 polymorphisms have a relevant impact long before potential illness manifestation. Affected brain areas and neurocognitive functions have shown to be relevant for schizophrenia as well as schizotypy. Using genetic modelling in twin samples, Toulopoulou et al. showed that a substantial part of the phenotypic overlap between schizophrenia and cognition is explained by shared genetic variability (Toulopoulou et al., 2007). The authors concluded that the next step would be to identify specific genes that influence schizophrenia together with cognitive quantities. Our results support *ZNF804A* rs1344706 as such a genetic variant relevant for schizotypy, an intermediate schizophrenia phenotype. As has been reported recently (Stotesbury et al., 2018), we particularly regard the *Cognitive-Perceptual* dimension as a risk factor for attentional difficulties.

However, Toulopoulou et al. subsequently argued that schizophrenia liability is partially expressed through cognitive deficits (Toulopoulou et al., 2015) and that cognitive functions lie upstream of schizophrenia (Toulopoulou et al., 2018). Relevant loci should then have a bigger effect on cognitive function than on schizophrenia (Toulopoulou et al., 2015). Our results, however, fail to confirm this prediction for the schizotypy phenotype. In both models tested, *ZNF804A* rs1344706 showed a larger effect on schizotypy than on cognitive function. While aware that this cannot definitively be resolved in our cross-sectional study, we believe that our results should inspire further dissection of the proposed models. Considerably, Toulopoulou's model is based on net genetic influences rather than single risk variants. It also relies on patient data and thus on the schizophrenia phenotype rather than schizotypy (Hargreaves et al., 2012) and *ZNF804A* expression seems to differ between schizophrenia patients and healthy controls (Guella and Vawter, 2014). The underlying mechanisms of schizophrenia and schizotypy are overlapping, but most likely not identical. Besides a balanced proportion of male and female participants, the application of multiple measures of both schizotypy and cognitive performance should be considered to overcome limitations of our own study.

We further showed a sex-modulated association of the psychosis susceptibility variant rs1006737 in *CACNA1C* with the *Interpersonal* schizotypy dimension. While sex-dependent effects of rs1006737 or its proxy rs10774035 have been reported for schizophrenia-spectrum disorders (Heilbronner et al., 2015) and emotional lability and resilience (Strohmaier et al., 2013), this is, to our knowledge, the first study detecting a sex-dependent effect of rs1006737 on schizotypy. In contrast to previous studies (Roussos et al., 2013, 2011), associating rs1006737-A with higher *Paranoid Ideation*, we find an inverse relationship, i.e. with lower *Interpersonal* schizotypy scores in men only. Beside the possibility of chance findings, this might be due to differences in sample characteristics, as both studies by Roussos et al. analysed young male army recruits, while our sample comprised males and females of a wide age range. Other discrepancies include the schizotypy measures and possible population differences (Greek vs. Central European) across studies (Clarke and Cardon, 2010).

As *CACNA1C* is suggested to be a susceptibility gene for a more general risk for mental illness (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), divergent effects in different studies might represent a less specific impact of the SNP. This would implicate the need for more studies with diverse samples. However, *CACNA1C* rs1006737 has repeatedly been associated with socially relevant tasks like emotion recognition and processing (Nieratschker et al., 2015; Soeiro-de-Souza et al., 2012; Tesli et al., 2013), as well as alterations in social interaction in animal models (Dedic et al., 2018; Moon et al., 2018). Thus, variations in rs1006737 seem to affect social functioning on a behavioural level, as well as brain structural and functional correlates. It might be concluded that rs1006737 primarily affects the *Interpersonal* and, as such, social dimension of schizotypy.

The results from our study provide evidence for the involvement of schizophrenia genetic susceptibility variants in psychometric schizotypy, a risk phenotype for psychosis. Our findings further provide an account of how those risk variants might modulate different dimensions of individual schizotypal traits even in healthy subjects, affecting neurocognitive performance in domains frequently impaired in schizophrenia.

Conflict of interest

None.

Contributors

TM performed the statistical analyses, TM and IN wrote the first draft of the manuscript. TFMA helped with chosing the statistical design and wrote the genetic methods part. SS, FS, KB, JM, DY, DZ, DG, KD, SM, KF, RR, NO, JR, TH and AJ participated in data acquisition, quality checking and preparation, and assisted in literature search and analyses. TFMA, AJF, SH-H, FS, SHW, MR, BM-M and MMM performed genotyping as well as further preparation and quality control of the genetic data. IN, UD, AK and TK designed the study protocol. All authors contributed to and have approved the final manuscript.

Funding

Part of this work was supported through a FlexiFunds grant (FCMH grant number 2017_2_1_5 to IN). This work was supported by German Research Foundation (DFG), grant FOR2107 (grant numbers NE 2254/1-2 to IN, KI 588/14-1 and KI 588/14-2 to TK, DA 1151/5-1 and DA 1151/5-2 to UD, KO 4291/4-1, KR 3822/5-1 and KR 3822/7-2 to AK and KO 4291/3-1) and SFB-TRR58 (projects C09 and Z02 to UD); the Interdisciplinary Center for Clinical Research (Interdisziplinäres Zentrum für Klinische Forschung, IZKF) of the medical faculty of Münster (grant number Dan3/012/17 to UD), the European Commission through ERA-NET NEURON (01EW1810 to MR), and the German Federal Ministry of Education and Research (BMBF), through the Integrated Network IntegraMent, under the auspices of the e:Med programme (grant numbers 01ZX1314A to MMN, 1ZX1314G to MR and 01ZX1614J to BMM).

Acknowledgements

We thank all participants volunteering for this study. Also, we would like to thank all student research assistants for their help.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.04.018.

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