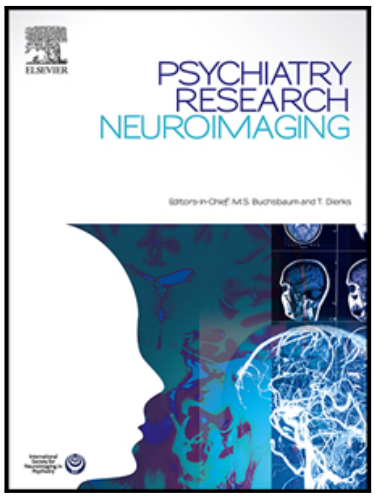

The relationship of genetic susceptibilities for psychosis with physiological fluctuation in functional MRI data

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Highlights

- We measured physiological fluctuation with the variance of BOLD-signal in fMRI data.
- We assessed participants' familial risk for psychosis (FR).
- We also calculated a polygenic risk score for schizophrenia (PRS).
- FR or PRS was not related to changes in the physiological fluctuation in the brain.

The relationship of genetic susceptibilities for psychosis with physiological fluctuation in functional MRI data

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Abstract

Previously, schizophrenia is found to be related to the variability of the functional magnetic resonance imaging (fMRI) signal in the white matter. However, evidence about the relationship between genetic vulnerabilities and physiological fluctuation in the brain is lacking. We investigated whether familial risk for psychosis (FR) and polygenic risk score for schizophrenia (PRS) are linked with physiological fluctuation in fMRI data. We used data from the Oulu Brain and Mind study (n=140–149, aged 20–24 years) that is a substudy of the Northern Finland Birth Cohort 1986. The participants underwent a resting-state fMRI scan. Coefficient of variation (CV) of blood oxygen level dependent (BOLD) signal (CV_{BOLD}) was used as a proxy of physiological fluctuation in the brain. Familial risk was defined to be present if at least one parent had been diagnosed with psychosis previously. PRS was computed based on the results of the prior GWAS by the Schizophrenia Working Group. FR or PRS were not associated with CV_{BOLD} in cerebrospinal fluid, white matter, or grey matter. The findings did not provide evidence for the previous suggestions that genetic vulnerabilities for schizophrenia become apparent in alterations of the variation of the BOLD signal in the brain.

Keywords

Psychosis; Schizophrenia; Polygenic risk score; Familial risk; fMRI; Physiological fluctuation

1 Introduction

The strongest known risk factor predicting onset of schizophrenia and other psychotic disorders is familial risk (Mäki et al. 2005). Roughly 10% of individuals with a first-degree relative with schizophrenia develop the disorder (Gottesman et al. 2010). The heritability estimate of schizophrenia is approximately 80–90% (Rijsdijk et al., 2011; Sullivan et al., 2003). Recently, polygenic risk score for schizophrenia (PRS) has been introduced as a new method to estimate genetic risk for developing schizophrenia or other psychotic disorder (Vassos et al. 2016). Previously, it has been highlighted that the association of schizophrenia-related genes with symptom onset may be mediated via genetically determined alterations in the cerebral physiological processes (Birnbaum & Weinberger, 2013). That is, schizophrenia-related genes may predispose to neurodevelopmental impairments in the formation of brain networks that, in turn, increase the risk for the onset of psychotic symptoms. (Birnbaum & Weinberger, 2013).

A variety of studies have established that there exist structural and functional brain abnormalities in individuals with familial risk for schizophrenia. Meta-analyses of fMRI studies have shown that familial risk for psychosis is linked to altered neuronal activity particularly in the right temporal and frontal lobes, left thalamus and left cerebellum, and striatum (Cooper et al., 2014; Fusar-Poli et al., 2007). Additionally, there is evidence that polygenic risk score for schizophrenia is related to neural inefficiency in the left dorsolateral prefrontal cortex (Walton et al., 2013). In our previous study, we found that high PRS (vs. low PRS) relates to lower inter-regional correlations of BOLD fMRI signal and grey-matter volume within the face-processing network (Lieslehto et al., 2018).

Usually, functional magnetic resonance imaging (fMRI) studies aim to examine neuronal-activation-induced changes in the blood-oxygenation-level-dependent (BOLD) signal (Biswal et al., 1996). Importantly, however, the BOLD signal is affected also by a variety of other

activities than those of neuronal origin, for example, cerebral blood volume and flow and oxygen and carbon dioxide extraction (Cheng et al., 2015; Krüger & Glover, 2001; Murphy et al., 2009; Wise et al., 2004). This physiological fluctuation in BOLD signal, however, is traditionally regarded as noise variation and is excluded from the fMRI data (e.g. Birn et al., 2012). However, physiological fluctuation provides an important viewpoint to essential neurophysiological processes in the brain. Specifically, cardiac and respiratory cycles induce pulsations in the brain tissues (Kiviniemi et al., 2016; Raitamaa et al., 2018). Moreover, cardiorespiratory frequencies influence the flow of cerebrospinal fluid into the ventricles and conduits (e.g. foramina, subarachnoid space, interstitial space) (Birn et al., 2012; Dreha-Kulaczewski et al., 2015; Kiviniemi et al., 2016). Consequently, it is possible to explore physiological fluctuation in the white matter and cerebrospinal fluid, besides of grey matter (Birn et al., 2006, 2012; Birnbaum & Weinberger, 2013).

Excluding physiological fluctuation from the fMRI data may be a particularly severe limitation in the context of schizophrenia research. It is possible that genetic vulnerabilities for schizophrenia become apparent in specific alterations of the signal-to-noise ratio of the BOLD signal (Harrison & Weinberger, 2005) that refers to the amount of physiological fluctuation in the brain. Previously, it has been suggested that physiological fluctuation in the white matter is linked with schizophrenia (Cheng et al., 2015) and prodromal symptoms of psychosis (Saarinen et al., submitted). Still, however, no study has investigated whether genetic risk for schizophrenia might be linked with physiological fluctuation in fMRI data.

The aim of the present study was to investigate whether familial risk for psychosis and polygenic risk score for schizophrenia might be linked with physiological fluctuation in the brain. We used data from the Oulu Brain and Mind study (participants were aged 20–24 years) that is a substudy of the Northern Finland Birth Cohort 1986. The participants were scanned with resting-state functional magnetic resonance imaging (r-fMRI). Coefficient of variation (CV) of BOLD-signal (CV_{BOLD}) was used as an indicator of physiological fluctuation in the brain.

2 Methods

2.1 Participants

We used data from the Oulu Brain and Mind Study that is a substudy of the Northern Finland Birth Cohort 1986 (NFBC 1986) study. The NFBC 1986 includes individuals with an expected date of birth between July 1985 and June 1986 in the two northernmost provinces of Finland. The original sample of the NFBC 1986 consisted of 9432 participants. The data collection began prospectively before the birth of the participants and has continued since then. For further information of the NFBC 1986, see Järvelin et al. (1997).

The Oulu Brain and Mind Study, a field study with brain-imaging, was conducted in 2007−2010 for a subsample of the NFBC 1986. The primary aim of the Oulu Brain and Mind study was to examine the early neurophysiological alterations in the brain functioning among young individuals with high risk for psychosis. The sample (total *n*=329) consisted of 5 groups: (i) participants with familial risk for psychosis, (ii) participants with symptomatic risk for psychosis, (iii) participants with previous psychosis, (iv) participants with attention-deficit/hyperactivity disorder, and (v) healthy controls. When selecting the participants for the Oulu Brain and Mind study, data from health care registers and previous follow-ups of the NFBC 1986 were used. More information about the Oulu Brain and Mind Study is available elsewhere (Veijola et al., 2013).

The design of the NFBC 1986 study and the Oulu Brain and Mind Study were approved by the Ethics Committee of the Northern Ostrobothnia Hospital District in Finland. Moreover, the studies were carried out in accordance with the Declaration of Helsinki. All the participants provided written informed consent after the nature of the procedures was fully explained.

In this study, we first excluded all the participants with a positive urine drug test for opiates, benzodiazepines, and cannabis (*n*=22); participants with current use of benzodiazepines, neuroleptics, or other non-specified psychiatric medication (*n*=17); inadequate or missing brain scan data (*n*=12); or missing data about educational level (*n*=1). This resulted in a sample of 277 participants. Thereafter, we included in the analyses all the participants with full data on study variables (familial risk for schizophrenia or PRS; control variables, i.e. age, sex, educational level, and absolute and relative displacement). Consequently, the final sample consisted of 140-149 participants in the analyses.

2.2 Measures

2.2.1 Familial risk for psychosis

Participants with familial risk for psychosis were selected from the sample of the NFBC 1986 study. Specifically, participants of the NFBC 1986 who had at least one parent with a non-organic psychosis or cluster A personality disorder (paranoid, schizotypal, and schizoid) were invited to this study as participants with familial risk for psychosis. The diagnoses of non-organic psychoses and cluster A personality disorders were assessed using the Finnish Hospital Discharge Register (FHDR) between 1972-2005. Cluster A personality disorders were included because of the genetic closeness to schizophrenic psychosis (Tienari et al., 2003).

The FHDR covers all the Finnish mental and general hospitals, beds in local health centres, and private hospitals. During that time ICD-8, ICD-9 and ICD-10 were used, and respective ICD codes either from principal or subsidiary diagnoses were collected. The ICD diagnoses used for psychotic disorders in ICD-8 and ICD-9 were codes 295–299, 3010, 3012 and in ICD-10: codes F20–33 (except non-psychotic mood disorders), F600 and F601. In the NFBC 1986 sample, altogether 272 participants with familial risk were detected. Of them, 1 participant died, 5

participants were living abroad, and 4 participants could not be reached. Consequently, a total of 262 individuals with familial risk were sent an invitation letter.

2.2.1 Polygenic risk score for schizophrenia (PRS)

Detailed information on the collection of the genetic samples and quality control of the genome-wide data are provided in a previous study (Lieslehto et al., 2018). Briefly, the results of the genome wide association studies (GWAS) by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) were used for the calculation of PRS for schizophrenia in the NFBC 1986 sample. We calculated the score on single-nucleotide polymorphisms (SNPs) reaching genome-wide significance (p=5×10^{-8}). A total of 112 SNPs were found in the imputed NFBC 1986 GWAS dataset. The PRS was calculated as a weighted sum of the schizophrenia-related SNPs. That is, before summing together, each risky SNP was multiplied by the effect size of its association with schizophrenia (logarithm of the odds ratio of the SNP when predicting schizophrenia). This method has been used also previously (Kendler, 2016). PRS was adjusted for four principal components to account for population stratification since the presence of a systematic difference in allele frequencies between subpopulations of a population may lead to both type I and II errors (Price et al., 2010).

2.2.3 Participants' background characteristics

Background information was collected about participants' age, sex, educational level, full-scale intelligence quotient, smoking status, alcohol use, current Axis-I disorders, psychotic-like symptoms, presence of neurological disorders, times of having been unconscious, and level of functioning.

Educational level was assessed with a self-report questionnaire. Educational level was classified 1 (comprehensive school or less) or 2 (matriculation). *Full-scale intelligence quotient*

(FSIQ) was assessed using the Vocabulary and Matrix Reasoning Scales of the Wechsler Adult Intelligence Scale III (WAIS-III, Finnish Edition) (Wechsler et al., 1997). The validity and reliability of the WAIS-III are demonstrated to be excellent (e.g. Ryan & Ward, 1999). As in previous research (e.g. Jukuri et al., 2013), full-scale intelligence quotient was defined as the mean of the two scales.

Smoking status was assessed by asking participants whether they had smoked cigarettes regularly during their life (1=no; 2=yes). With regard to *alcohol use*, participants rated the statement of "I drink too much alcohol or get drunk" with a 3-point scale (0=not true; 1=somewhat or sometimes true; 2=very true or often true). Participants rating "very true or often true" were defined to have risky alcohol use.

Current Axis-I disorders were assessed with Structured Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 2002). *The presence of neurological disorders and times of having been unconscious* were evaluated in the interview of neurological symptoms.

Psychotic-like symptoms were assessed with the Structured Interview for Prodromal Syndromes (SIPS, version 3.0) (Miller et al., 2003). The SIPS measures three separate prodromal syndromes: brief intermittent psychotic syndrome, attenuated positive prodromal syndrome, and genetic risk and deterioration syndrome. Each participants' psychotic symptomatology was defined as the highest score of the SIPS positive symptoms within the past month, ranging from 0 (absence of psychotic symptoms) to 6 (psychosis). This score was further recoded into 4 categories: (i) the score of 0 (no psychotic symptoms); (ii) the scores of 1–2 (mild symptoms); (iii) the scores of 3–5 (prodromal symptoms of psychosis); (iv) the score of 6 (psychotic symptoms).

Level of functioning was evaluated with the Global Assessment of Functioning Scale (GAF) (Spitzer et al., 1996). The psychometric properties of the GAF are shown to be adequate (Sonesson et al., 2010; Startup et al., 2002). The values of the GAF range from 0 to 100, with a

higher score of the GAF referring to a higher level of social, occupational, and psychological level of functioning.

2.3 Brain-imaging methods and data pre-processing

Resting-state BOLD (Blood Oxygen Level Dependent-signal) data were collected on a General Electric Signa 1.5 T whole body system with an eight channel receive coil, using an EPI (Echo Planar Imaging) GRE (Gradient Echo) sequence TR (Repetition Time) 1800 ms, TE (Echo Time) 40 ms, 280 time points, 28 oblique axial slices, slice thickness 4 mm, inter-slice space 0.4 mm, covering the whole brain, FOV (Field of View) 25.6 cm × 25.6 cm, with 64 × 64 matrix, parallel imaging factor 2, and a flip angle of 90°. T1-weighted scans were imaged using a 3D FSPGR (Fast Spoiled Gradient echo) BRAVO (Brain Volume imaging) sequence (TR 12.1 ms, TE 5.2 ms, slice thickness 1.0 mm, FOV 24.0 cm, matrix 256 × 256, and flip angle 20°), and NEX (Number of Excitations) 1 in order to obtain anatomical images for co-registration of the fMRI data to standard space coordinates. For further information, see Jukuri et al. (2013).

Neuroimaging data were analysed with FSL (http://www.fmrib.ox.ac.uk/fsl, FSL 5.0.8) [31-36] and AFNI [37]. We performed the following steps in preprocessing: brain extraction with AFNI's 3dSkullstrip (Cox, 1996; Smith, 2002), motion correction with MCFLIRT [Jenkinson et al., 2002], spatial smoothing with a Gaussian kernel of FWHM 5.0 mm, co-registration with FLIRT, non-linear normalization of structural data to 2mm MNI-152 template using FNIRT (Jenkinson & Smith, 2001; Jenkinson et al., 2002), and detrending with AFNI's 3dDetrend due to the potential scanner-related effect on standard deviation. Relative and absolute root-mean-square (RMS) head displacement (millimeter) was determined from FSL's MCFLIRT and used as covariates in the model. Average absolute displacement refers to the mean of head motion in fMRI time-series in relation to a reference time point (i.e. the first volume in time-series). Average relative displacement, in turn, represents the mean head motion in fMRI time-series in relation to

the subsequent time point. FSL's FAST was used for the segmentation of T1-weighted structural images into white matter (WM), grey matter (GM) and cerebrospinal fluid (CSF).

For each study participant, CV_{BOLD} map was calculated as a ratio between standard deviation of preprocessed BOLD-time series divided by the mean of preprocessed BOLD-time series in each voxel. This method has been used by (Kananen et al., 2018; Jahanian et al., 2017; Tuovinen et al., 2017, 2018) and is similar to the method used by (Makedonov et al., 2013, 2016). A close concept for CV_{BOLD} is signal-to-noise ratio that is calculated as $1/CV_{BOLD}$ and has been used previously (e.g. Harrison & Weinberger, 2005). Next, we extracted the average CV_{BOLD} in WM, GM and CSF (segmented with FSL's FAST). Sex, age, education, absolute and relative displacement were used as covariates in the model.

2.4 Statistical analyses

The statistical analyses were run using STATA SE (version 15.0). The associations of familial risk for psychosis and polygenic risk score for schizophrenia with CV_{BOLD} in the brain were investigated using linear regression analyses. Familial risk for psychosis and polygenic risk score for schizophrenia were added separately to the model. Further, separate models were estimated for CV_{BOLD} in CSF, WM, and GM. As additional analyses, all the analyses were rerun in a subsample consisting of the participants who had no psychotic-like symptomatology (i.e. the current SIPS score was less than 3). All the analyses were adjusted for age, sex, educational level, absolute and relative displacement. We assessed the level of multicollinearity using the value of VIF (variance inflation factor). VIF values less than 10 are stated to indicate low level of multicollinearity (see Alin, 2010). In our analyses, the VIF (variance-inflating factor) scores of different predictors ranged between 1.01-1.20, indicating that there was not significant multicollinearity.

3 Results

Descriptive statistics of the study variables are shown in Table 1. In the sample, there were 72 participants (34.3%) with familial risk for psychosis.

[Table 1 about here]

Table 2 shows the results of the regression analyses, when predicting CV_{BOLD} in CSF, WM, and GM by familial risk for psychosis. Familial risk for psychosis was not related to CV_{BOLD} in CSF, WM, or GM. Table 3 presents the results of the regression analyses, when predicting CV_{BOLD} in CSF, WM, and GM by polygenic risk score for schizophrenia. Polygenic risk score for schizophrenia was not associated with CV_{BOLD} in CSF, WM, or GM. All the findings were adjusted for age, gender, educational level, and absolute and relative displacement.

As additional analyses, the regression analyses were rerun among participants without psychotic-like symptoms (the current SIPS < 3, *n*=132 for familial risk analyses, *n*=133 for PRS analyses). All the associations remained non-significant. The results of the additional analyses are described with more detail in Supplementary Tables 1–2.

Finally, we investigated the associations of familial risk for psychosis and polygenic risk score for schizophrenia with parameters of motion in the fMRI data. Familial risk for psychosis was not linked with absolute (beta=-0.093, *p*=0.283) or relative parameters of motion (beta=0.100, *p*=0.246). Moreover, polygenic risk score was not linked with absolute (beta=-0.064, *p*=0.439) or relative parameters of motion (beta=-0.074, *p*=0.375). For further information, see Supplementary Tables 3–4.

[Table 2 about here]

[Table 3 about here]

4 Discussion

To the best of our knowledge, this study was the first to investigate whether familial risk for psychosis and polygenic risk score for schizophrenia might be related to physiological fluctuation (variation of the BOLD signal) in the brain. The results showed that neither familial risk for psychosis nor polygenic risk score was associated with lower CV_{BOLD} in cerebrospinal fluid, white matter, or grey matter. All the findings were controlled for age, sex, educational level, and absolute and relative displacement. Finally, all the results remained non-significant when including only those participants with no psychotic-like symptoms (the current SIPS score < 3). Taken together, familial or genetic risk for psychosis appeared not to be related to physiological fluctuation (variation of the BOLD signal) in the brain.

Previous studies have shown that physiological fluctuation is related to Alzheimer's disease (Makedonov et al., 2016), acute ischemia (Khalil et al., 2017), epilepsy (Kananen et al., 2018), schizophrenia (Cheng et al., 2015), and prodromal syndromes of psychosis (Saarinen et al., submitted). This study was the first to investigate whether physiological fluctuation in the fMRI data is linked with genetic factors. Previously, it has been postulated that genetic vulnerabilities for schizophrenia become apparent in specific alterations of the signal-to-noise ratio (Harrison & Weinberger, 2005) that refers to the variance of BOLD signal in the brain. However, the present study did not provide evidence for this postulation. It seems that the changes in the physiological fluctuation of the brain are evident only after the onset of neuropsychiatric diseases.

The null results about the link between psychosis-related genes and physiological fluctuation in the brain may have several explanations. Firstly, there is previous evidence for the heritability of heart rate variability (Kupper et al., 2004; Snieder et al., 2007), ambulatory

cardiorespiratory coupling (Kupper et al., 2005), systemic arterial stiffness (Snieder et al., 2000), and respiratory control (Gaultier, 2004). These qualities of cardiorespiratory functioning, in turn, are closely related to the amount of physiological fluctuation in the brain (e.g. Birn et al., 2012; Cheng et al., 2015; Krüger & Glover, 2001; Murphy et al., 2009; Wise et al., 2004). The current study indicates that the genes, which are related to the elements of physiological fluctuation, may not be overlapping with the schizophrenia-related genes. Secondly, it may be that schizophrenia-related genes are linked to physiological fluctuation in the brain only when co-occurring with some other genes. For example, one study reported that dopamine-related genes are related to cortical signal-to-noise ratio but only in the presence of another genetic polymorphism (in the gene for the enzyme catechol-*o*-methyltransferase) (Winterer & Weinberger, 2003).

Thirdly, it might be speculated that our null results might be accounted by a compensatory effect. That is, for example, individuals with prodromal symptoms have increased activity in certain brain regions during prodromal symptoms, but decreased activity during improvement of the symptoms (Fusar-Poli et al., 2010). Thus, individuals at risk for psychosis may need more neurophysiological effort in order to achieve the same level of brain functioning (Cooper et al., 2014). Similarly, some degree of physiological fluctuation (signal-to-noise ratio) appears to be necessary for adequate brain functioning (e.g. Birn et al., 2012; Dreha-Kulaczewski et al., 2015; Kiviniemi et al., 2016). This is because signal-to-noise ratio partly reflects the rhythm of arterial pulsations that, in turn, influences the flow of cerebrospinal fluid into perivascular spaces and induce clearance of metabolic waste (Mestre et al., 2018). Accordingly, individuals at genetic risk for psychosis might have an innate susceptibility for increased physiological fluctuation in the brain, but they might have compensated it and, in this way, captured the "normal" level of fluctuation. This might possibly explain why we did not obtain any associations between schizophrenia-related genes and alterations in the level of physiological fluctuation.

This study has some limitations that are necessary to be taken into consideration. Firstly, our samples were relatively small in the analyses (n=140−149). Previously, it has been stated that in the context of complex genetic disorders, a small sample size may result in the lack of power to obtain any associations between genetic factors and disease-related neurophysiological alterations (Harrison & Weinberger, 2005). In this study, all the associations of familial risk and polygenic risk score with CV_{BOLD} in the cerebrospinal fluid, white matter, and grey matter were statistically non-significant. However, the null results may not likely be accounted by the relatively small sample size because gender, for example, was significantly associated with CV_{BOLD} in the brain in our sample.

Secondly, our sample was relatively heterogeneous, including participants with familial risk for psychosis, earlier adolescent attention-deficit hyperactivity disorder, or current Axis-I disorder. There is previous evidence that psychotic symptoms have a high comorbidity level with other psychiatric and neurological symptoms, for example, depression, anxiety, epilepsy, ADHD, and substance use disorders (Fusar-Poli et al., 2012; Gaitatzis et al., 2004; Karatekin et al., 2010; Keshavan et al., 2003; Schuckit et al., 2006). Hence, excluding all the individuals with any other psychiatric or neurological diagnosis might result in a substantial selective bias in the sample and limit the generalizability of the findings to other populations. Another possibility might have been to control for all the other psychiatric and neurological diagnoses. This method, however, would likely have resulted in a large number of covariates and statistical problems with multicollinearity. Consequently, we ended up to control for the basic covariates in the analyses (i.e. sex, age, educational level, and absolute and relative displacement).

The current study had also a variety of strengths. Overall, this study was the first to investigate whether genetic vulnerabilities for psychosis might be linked with CV_{BOLD} in the brain. Additionally, we had two different indicators of genetic vulnerabilities: familial risk for psychosis and polygenic risk score for schizophrenia. This is line with a previous statement that when

investigating neuroimaging-based phenotypes for schizophrenia, it is necessary to obtain the findings both among individuals with a high genetic risk score and among first-degree relatives of psychotic individuals (Birnbaum & Weinberger, 2013). Secondly, we used whole-brain indicators of CV_{BOLD} in grey matter, white matter, and cerebrospinal fluid, instead of investigating selectively some brain regions of interest. Thirdly, familial risk for psychosis was assessed reliably on the basis of the Finnish Hospital Discharge Register. The PRS, in turn, was based on a total of 112 SNPs derived from genome wide association studies. Fourthly, the NFBC 1986 study provided a sample of roughly same-aged participants in their young adulthood. This is in line with previous recommendations that the neurophysiological correlates of schizophrenia should be investigated in the early adulthood in order to ensure that the findings are present prior to the onset of illness (Cooper et al., 2014).

In conclusion, this study showed that genetic vulnerabilities for schizophrenia were not related to physiological fluctuation (amount of variation of the BOLD signal) in the brain. With regard to future studies, the measures of CV_{BOLD} are close to the recently detected BOLD delay maps in acute ischemia and small vessel disease (see Khalil et al., 2017; Lv et al., 2013; Tong et al., 2017). Hence, the link of psychosis with the BOLD delay maps could be addressed in the future.

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Table 1. Means, standard deviations (SD), ranges, and frequencies of the study variables.

	Mean	SD	Range	Frequency (%)
Age	22.81	0.80	20.95; 24.64	
Sex (female)				69 (32.9)
Familial risk for psychosis				72 (34.3)
Polygenic risk score for schizophrenia	0.05	0.98	-2.10; 2.50	
SIPS positive symptoms				
No psychotic symptoms				111 (52.9)
Mild symptoms				81 (38.6)
Prodromal symptoms of psychosis				17 (8.1)
Psychosis				1 (0.5)
Educational level				
Comprehensive school or less				81 (38.6)
University / graduate-level				129 (61.4)
Smoker				91 (43.3)
Risky alcohol use				51 (24.3)
Current Axis-I disorder				37 (26.2)
Neurological disorder				33 (15.7)
Current level of functioning	80.97	10.65	21; 96	
Full-scale intelligence quotient	97.14	24.36	25; 160	

Table 2. Results of linear regression analyses, when predicting CV_{BOLD} in cerebrospinal fluid, white matter, and grey matter by familial risk for psychosis.

	CV_{BOLD} in cerebrospinal			CV_{BOLD} in white matter			CV_{BOLD} in grey matter		
	Beta	B	*p*	Beta	B	*p*	Beta	B	*p*
Age	-0.322	-0.001	<0.001	-0.229	0.000	0.002	-0.172	-0.000	0.014
Sex[1]	-0.361	-0.002	<0.001	-0.364	-0.001	<0.001	-0.271	-0.001	<0.001
Educational level	-0.013	0.000	0.853	-0.105	0.000	0.180	-0.032	0.000	0.662
Absolute displacement	-0.198	-0.002	0.006	-0.220	-0.001	0.005	-0.206	-0.001	0.005
Relative displacement	0.439	0.062	<0.001	0.321	0.023	<0.001	0.548	0.055	<0.001
Familial risk for psychosis[2]	-0.135	-0.001	0.050	-0.061	0.000	0.419	-0.096	0.000	0.177

[1] Male as the reference group. [2] Participants without familial risk for psychosis as the reference group. *n*=140

Table 3. Results of linear regression analyses, when predicting CV_{BOLD} in cerebrospinal fluid, white matter, and grey matter by polygenic risk score for schizophrenia.

	CV_{BOLD} in cerebrospinal			CV_{BOLD} in white matter			CV_{BOLD} in grey		
	Beta	B	*p*	Beta	B	*p*	Beta	B	*p*
Age	-0.279	-0.001	<0.001	-0.225	0.000	0.001	-0.143	0.000	0.016
Sex[1]	-0.337	-0.002	<0.001	-0.345	-0.001	<0.001	-0.282	-0.001	<0.001
Educational level	-0.033	0.000	0.607	-0.146	0.000	0.025	-0.038	-0.000	0.521
Absolute displacement	-0.276	-0.003	<0.001	-0.316	-0.002	<0.001	-0.287	-0.002	<0.001
Relative displacement	0.569	0.064	<0.001	0.534	0.033	<0.001	0.703	0.059	<0.001
Polygenic risk score for schizophrenia	-0.041	0.000	0.518	-0.019	0.000	0.771	-0.032	0.000	0.583

[1] Male as the reference group. [2] The reference group. *n*=148