Symptomatic psychosis risk and physiological fluctuation in functional MRI data

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Abstract

Background: Physiological brain pulsations have been shown to play a key role in maintaining interstitial homeostasis in the glymphatic brain clearance mechanism. We investigated whether psychotic symptomatology is related to physiological variation of the human brain using fMRI.

Methods: The participants (N=277) were from the Northern Finland Birth Cohort 1986. Psychotic symptoms were evaluated with the Positive Symptoms Scale of the Structured Interview for Prodromal Syndromes (SIPS). We used coefficient of variation of BOLD signal (CV_{BOLD}) as a proxy for physiological brain pulsatility. The CV_{BOLD}-analyses were controlled for motion, age, sex, and educational level. The results were also compared with fMRI and voxel-based morphometry (VBM) meta-analyses of schizophrenia patients (data from the Brainmap database).

Results: At the global level, participants with psychotic-like symptoms had higher CV_{BOLD} in cerebrospinal fluid (CSF) and white matter (WM), when compared to participants with no psychotic symptoms. Voxel-wise analyses revealed that CV_{BOLD} was increased especially in periventricular white matter, basal ganglia, cerebellum and parts of the cortical structures. Those brain regions, which included alterations of physiological fluctuation in symptomatic psychosis risk, overlapped less than 6% with the regions that were found to be affected in the meta-analyses of previous fMRI and VBM studies in schizophrenia patients. Motion did not vary as a function of SIPS.

Conclusions: Psychotic-like symptoms were associated with elevated CV_{BOLD} in a variety of brain regions. The CV_{BOLD} findings may produce new information about cerebral physiological fluctuations that have been out of reach in previous fMRI and VBM studies.

1 Introduction

Traditionally, functional magnetic resonance imaging (fMRI) studies aim to investigate neuronal-activation-induced changes both spontaneous and task-related in the blood-oxygenation-level-dependent (BOLD) signal (Biswal et al., 2005, Ogawa et al., 1990). Neuronal activation is coupled to a hemodynamic response where T2*-weighted BOLD signal intensity increases after a hemodynamic delay of 3-5 seconds.

In addition to neuronal activity, there is also a set of other factors affecting the BOLD signal and physiological fluctuation in the brain. Such factors include cerebral blood volume and flow, oxygen and carbon dioxide extraction, and overall cardiorespiratory status (Cheng et al., 2015; Krüger et al., 2001; Murphy et al., 2009). Recent studies suggest that physiological fluctuation may be affected also by cerebrospinal fluid flow, due to the discovery of the glymphatic brain clearance mechanism (e.g. Mestre et al., 2018). That is, Nedergaard's group recently showed how the cardiovascular pulsations convey waste materials in the perivascular space in mice (Mestre et al., 2018). Along with this, there is evidence that also the human brain is pulsating markedly with cardiorespiratory frequencies and that these pulsations are altered in the areas controlling the respiration during breath hold challenges (Kiviniemi et al., 2016; Raitamaa et al., 2018). Furthermore, cardiac and respiratory cycles are noted to induce changes in the cerebrospinal fluid flow into the conduits and ventricles (Birn et al., 2012; Dreha-Kulaczewski et al., 2015; Kiviniemi et al., 2016). Taken together, physiological fluctuation appears to derive from a variety of cardiorespiratory activities and cerebrospinal fluid flow.

In most of the previous fMRI research, physiological fluctuation has been traditionally regarded as nuisance variation covering neuronal-activation related signal changes (Wise et al., 2004). Along with this, also fMRI studies in the field of psychotic disorders have made rigorous attempts to remove physiological signal sources from the fMRI data. Removing physiological fluctuation from the BOLD signal, however, may potentially exclude also valuable information

about brain physiology. Previously, it has been demonstrated that physiological fluctuation contributes to a significant part, even 10%, of the BOLD-signal variation (Birn et al., 2012; Dagli et al., 1999). Moreover, physiological fluctuations in the brain are not limited to the grey matter but are also found in the white matter and cerebrospinal fluid (Birn et al., 2006, 2012; Weissenbacher et al., 2009). Consequently, fMRI studies exploring differences in physiological fluctuation between various populations might provide novel insights into brain functioning. That is, it could provide the possibilities (i) to gain insights into the physiological activities in the brain (instead of merely neuronal activities), and (ii) to investigate neurophysiological functioning not only in grey matter but also in the white matter and cerebrospinal fluid.

Previous evidence suggests that changes in the physiological fluctuation of the brain tissues may potentially represent a biomarker for specific neurological or psychiatric disorders. For example, patients with Alzheimer's disease and small vessels disease have increased physiological fluctuation in the white matter (Makedonov et al., 2013, 2016). Further, patients with epilepsy or acute ischemic stroke are found to have reduced physiological brain fluctuation (Kananen et al., 2018; Khalil et al., 2017; Wang et al., 2008). Regarding psychosis, however, evidence is largely lacking. Until now, there exists only one study suggesting that schizophrenia might be related to increased physiological noise in the white matter in the cerebellum and parietal lobes (Cheng et al., 2015). However, no study has investigated whether the changes in physiological brain fluctuation might be detected among individuals at symptomatic risk for developing psychosis, i.e. at early stages of psychosis.

This study investigated whether psychosis risk is linked with BOLD signal fluctuations in the brain. We used data from the Oulu Brain and Mind study. All the participants were scanned with resting-state functional magnetic resonance imaging (r-fMRI). We used coefficient of variation (CV_{BOLD}) as a proxy of physiological brain pulsations (Makedonov et al., 2013, 2016; Kananen et al., 2018; Khalil et al., 2017; Tuovinen et al., 2017). To identify those brain regions that have been robustly identified as schizophrenia related, we conducted meta-analyses of

fMRI and voxel-based morphometry (VBM) studies in patients with schizophrenia (data from the Brainmap database). We hypothesized that the association between CV_{BOLD} and SIPS would overlap with these meta-analytical maps.

2 Material and methods

2.1 Participants

The participants were selected from the Oulu Brain and Mind Study, which is a part of the Northern Finland Birth Cohort 1986 (NFBC 1986) study (Järvelin et al., 1997). The NFBC 1986 consists of 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 included altogether 9432 participants.

The Oulu Brain and Mind Study was conducted in 2007−2010 for a subsample of the NFBC 1986. The aim of the Oulu Brain and Mind study was to investigate the developmental pathogenesis of psychosis among young people at 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. Research-staff were not aware of the participants' invitation criteria. A more detailed description of the Oulu Brain and Mind Study and the NFBC 1986 are available elsewhere (Jukuri et al., 2013; 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. 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 the present study, we 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 psychiatric medication (*N*=17); inadequate or missing brain scan data (*N*=12); or missing data about educational level (*N*=1). The final sample consisted of 277 participants.

2.2 Measures

2.2.1 Psychotic symptomatology

Psychotic symptomatology was evaluated with the Structured Interview for Prodromal Syndromes (SIPS, version 3.0) (McGlashan et al., 2001). The SIPS measures three separate prodromal syndromes: brief intermittent psychotic syndrome, attenuated positive prodromal syndrome, and genetic risk and deterioration syndrome. The reliability and validity of the SIPS have been confirmed previously (Miller et al., 2003). In the present study, each participants' psychotic symptomatology was defined as the highest score of the SIPS positive symptoms within the past month. The score of the SIPS positive symptoms ranged from 0 (absence of psychotic symptoms) to 6 (psychosis). This score was further recoded into 4 categories as follows: (1) the score of 0 (no psychotic symptoms); (2) the scores of 1–2 (mild psychotic symptoms); (3) the scores of 3–5 (prodromal symptoms of psychosis); (4) the score of 6 (psychotic symptoms).

2.2.2 Participants' background characteristics

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

Educational level was assessed with a self-report questionnaire. Educational level was classified into 2 categories (1=comprehensive school or less; 2=matriculation).

Smoking status was evaluated by asking participants whether they had ever smoked cigarettes regularly (1=no; 2=yes). Regarding *alcohol use*, participants were asked to rate the statement of "I drink too much alcohol or get drunk". Participants rating "very true or often true"

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were defined to have risky alcohol use. Based on the observations of the field investigators, none of the participants were under the influence of alcohol at the time of the study measurements.

Current Axis-I disorders were evaluated with Structured Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1997). *The presence of neurological disorders and times of having been unconscious* were evaluated in the interview of neurological symptoms.

Level of functioning was measured with the Global Assessment of Functioning Scale (GAF) (Spitzer et al., 1996) in the SIPS interview. The validity and reliability of the GAF are demonstrated to be adequate (Sonesson et al., 2010; Startup et al., 2002).

Full-scale intelligence quotient (FSIQ) was evaluated with the Vocabulary and Matrix Reasoning Scales of the WAIS-III (Wechsler Adult Intelligence Scale III, Finnish Edition) (Wechsler et al., 1997). The psychometric properties of the WAIS-III are shown to be excellent (Ryan et al., 1999). As has been done previously (Jukuri et al., 2013), we used the sum of the two scales as indicator for full-scale intelligence quotient.

2.3 Brain-imaging methods

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 $\times$ 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. Brain imaging methods were identical to those described in detail previously (Jukuri et al., 2013).

2.4 Data preprocessing

Neuroimaging data were analysed with FSL (http://www.fmrib.ox.ac.uk/fsl, FSL 5.0.8) (Jenkinson et al., 2001, 2002, Smith, 2002; Woolrich et al., 2001, 2004; Worsley et al., 2001) and AFNI (Cox, 1996). We conducted following steps in the pre-processing including brain extraction (AFNI's 3dSkullStrip), motion correction (MCFLIRT), linear co-registration (FLIRT), nonlinear normalization (FNIRT) to the 2 mm MNI-152 template, 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. 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-timeseries divided by the mean of preprocessed BOLD-timeseries in each voxel. This method has been used by (Kananen et al., 2018; Jahanian et al., 2014) and is similar to the method used by (Makedonov et al., 2013, 2016). We analyzed the association between SIPS and CV_{BOLD} in the brain 1) g*lobally* by exploring the relationship between SIPS and the average CV_{BOLD} in WM, GM and CSF and 2) *locally* by exploring the relationship between SIPS and CV_{BOLD} in a voxel-wise manner. We conducted the voxel-wise analysis using FSL's randomise tool (5000 permutations, applying demeaning and threshold free cluster enhancement (TFCE) (Smith & Nichols, 2009)). Sex, age, education, absolute and relative displacement were used as covariates in the above analyses.

2.5 Statistical analyses

The association of psychotic symptoms with CV_{BOLD} in the brain was investigated using multivariable regression analyses (STATA MP, version 15.1). We predicted CV_{BOLD} in the brain by the SIPS score of positive symptoms. Separate models were conducted for CV_{BOLD} in CSF, WM,

and GM. The analyses were controlled for age, sex, educational level, and absolute and relative displacement.

2.6 Comparison to meta-analytical maps of fMRI and VBM studies in schizophrenia patients

To compare our CV_{BOLD} results with previous schizophrenia imaging studies, we conducted meta-analyses of the fMRI and VBM studies in patients with schizophrenia using Brainmap database (search with Sleuth was conducted in August 2018). The aim was to explore the overlap of our findings with previously discovered results. We identified 50 fMRI studies and 27 VBM studies. We used both contrasts (i.e., schizophrenia>controls and schizophrenia<controls) in the meta-analysis of fMRI studies. This was due to the heterogeneity of the stimuli in these studies, and due to the fact that some of these studies used group x stimuli interaction. We analyzed only schizophrenia < controls contrast in VBM studies as one of the most robust discoveries in schizophrenia has been lower in grey matter volume when compared to controls (Haijma et al., 2012). GingerALE (Eickhoff et al., 2009; Turkeltaub et al., 2002) with 1000 repetitions was used for the meta-analysis. The p-values for each meta-analysis were thresholded at a cluster level corrected threshold of p<0.05 (cluster-forming threshold at voxel-level p<0.001).

3 Results

Descriptive statistics of the study variables are shown in Table 1. There were altogether 142 participants with no psychotic symptoms (the SIPS score=0), 109 participants with mild psychotic symptoms (the SIPS score=1-2), 23 participants with prodromal symptoms of psychosis (the SIPS score=3-5), and 3 participants with psychosis (the SIPS score=6). Due to the low number of psychotic participants, the groups of psychosis and prodromal symptoms of psychosis were combined into one group (the SIPS score=3-6).

[Table 1]

Table 2 shows the results of regression analyses, when predicting CV_{BOLD} in the brain by the SIPS scores. Participants in the study group with prodromal symptoms of psychosis or psychosis (the SIPS score=3-6) had higher CV_{BOLD} in CSF and WM, when compared to participants with no psychotic symptoms (SIPS=0). We did not obtain any consistent association between psychotic-like symptoms and the CV_{BOLD} in GM. These findings are illustrated in Figures 1a-c. All these findings were adjusted for age, sex, educational level, and absolute and relative parameters of displacement. The peak coordinates of the clusters that showed increased CV_{BOLD} in association with high SIPS scores are shown in Supplementary Table 1. We also rerun the analyses so that the participants with psychosis (N=3) were excluded from the sample. The associations of the SIPS scores with CV_{BOLD} in CSF and WM remained significant (for further details, see Supplementary Table 2).

Additionally, we investigated whether the SIPS score correlated with motion parameters. The SIPS score did not correlate with the parameters of absolute motion (r=-0.023) or relative motion (r=0.003). The plots about this non-significant correlation are available in Supplementary Figure 1. This indicated that the association between SIPS and CV_{BOLD} is not accounted by differences in head motion during brain imaging between participants with different SIPS scores.

[Table 2]

[Figure 1]

As additional analyses, we reran the multivariate regression analyses using the continuous variable of the current SIPS positive symptoms (ranging between 0-6). All the findings were replicated. Specifically, high score of SIPS positive symptoms was linked with higher CV_{BOLD} in CSF

(beta=0.142, p=0.001) and higher CV_{BOLD} in WM (beta=0.116, p=0.012), but not CV_{BOLD} in GM (beta=0.062, p=0.138).

Voxel-wise analyses revealed that CV_{BOLD} varied as a function of SIPS in different parts of WM and GM around the lateral ventricles in the current study. Specifically, SIPS correlated with CV_{BOLD} in a bilateral way in the deep grey matter structures and white matter around the central CSF spaces. In the basal ganglia right side changes were dominant, while in the cranial white matter areas the left side showed more changes.

In brain stem, there were two clusters in pons. In particular, the periaqueductal grey matter was involved, and there was a continuous stream of voxel along the left brain peduncle. The right side of the thalamic nuclei were nearly totally covered with significant CV_{BOLD} change, only the centerline half of the area 7 in FSL Thalamic parcellation was unaffected. On left side, the changes were spatially smaller (also areas 1, 2, and 4 were spared). Bilaterally the posterior halves of the putamina and whole caudate nuclei were involved in CV_{BOLD} change. Additionally, the right sides of both amygdala and the hippocampi had CV_{BOLD} change. Interestingly, on the left, the whole length of the hippocampi was affected, while in the right only the frontal third was affected.

In the cerebral cortical structures, the changes extended to primary sensorimotor cortices bilaterally and in middle and frontal insula. Lateral parts of the paracingulate cortex were involved, but the changes were absent from the midline cingulate and other areas of the default mode network. Additionally, CV_{BOLD} was affected in the right superior temporal gyrus. In the white matter, the mostly involved regions were the centrum semiovale areas around the CSF ventricles. Interestingly, the frontal parts of the white matter were involved, while the trigonal areas and posterior parts showed minimal involvement. In the cerebellum, the affected areas were 3,4, 7, 8 and 19 in MNI FSL, the largest cluster being posterior and above 4th ventricle. Unthresholded p-value and T-stat maps are available in Supplementary Material.

Furthermore, we conducted meta-analyses of the previous fMRI and VBM studies among patients with schizophrenia to investigate the overlap between our findings and the

previously discovered results. As shown in Figure 4, these results overlapped only modestly with the meta-analyses of fMRI and VBM studies in patients with schizophrenia. The average map of the CV_{BOLD} is provided in the Supplementary Figure 2.

[Figure 2]

4 Discussion

For the first time, this study investigated the relationship of symptomatic psychosis risk with physiological fluctuation (as measured with CV_{BOLD}) in the brain. At the global level, participants in the study group with prodromal symptoms of psychosis or psychosis (the SIPS score=3-6) had higher CV_{BOLD} in cerebrospinal fluid (CSF) and white matter (WM) but not in grey matter, when compared to participants with no psychotic symptoms (the SIPS score=0). Voxel-wise analyses revealed that CV_{BOLD} was increased especially in periventricular white matter, basal ganglia, cerebellum and parts of the cortical structures. These findings were not explained by head motion. Additionally, we conducted meta-analyses of the previous fMRI and VBM studies among patients with schizophrenia to investigate the overlap between our findings and the previously discovered results. Those brain regions, which included alterations of physiological fluctuation in symptomatic psychosis risk, overlapped less than 6% with the regions that were found to be affected in schizophrenia patients in the meta-analyses of previous fMRI and VBM studies. Hence, this implicates that our novel analyzing method of fMRI data (using variation of BOLD-signal) might reveal new viewpoints to the neurofunctional alterations related to psychotic-like symptomatology.

The small amount of overlap between our results and the meta-analyses of fMRI and VBM data is expected, as CV_{BOLD} reflects a signal source that likely has not been measured in most previous fMRI and VBM studies. This signal is usually removed (e.g. via temporal filtering) and is not present in the T1-weighted data. Furthermore, most previous fMRI studies have limited their

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analyses to signals from grey matter, whereas the method of CV_{BOLD} enabled us to investigate physiological fluctuation also in white matter and cerebrospinal fluid in fMRI data. The CV_{BOLD} findings, thus, produce new information that has been out of reach of previous fMRI and VBM studies.

Previously, patients with epilepsy, Alzheimer's disease, and acute ischemic stroke are found to have alterations in the physiological noise of the brain (Makedonov et al., 2013, 2016; Kananen et al. 2018; Khalil et al., 2017; Wang et al., 2008). Moreover, schizophrenia is found to be related to increased physiological noise in the white matter (Cheng et al., 2015). This study was the first to demonstrate that prodromal syndromes are associated with increased CV_{BOLD} in white matter, especially around the third ventricle and lateral ventricles. Previously, this would have been considered to be a factor to be recognized and removed while focusing on changes in neuro-hemodynamic responses or fluctuations. However, as indicated by latest intra-vital microscopy results, hypertension-induced abnormal pulsations like reduce brain waste removal and therefore abnormal pulsations themselves can be a more direct measure of the underlaying pathology (Mestre et al., 2018; Kiviniemi et al., 2016). The current results add proof to the idea that physiological processes maintaining brain interstitial homeostasis may be altered also in psychosis. Further, recent evidence suggests that the glymphatic paravascular cerebrospinal fluid brain clearance may be altered in normal pressure hydrocephalus (Eide & Sorteberg, 2016; Ringstad et al., 2017) that is linked to schizophrenia (Vanhala et al., 2018).

Our finding about the link between psychotic-like symptoms and increased CV_{BOLD} in CSF is in accord with previous findings. For example, there is evidence that patients with schizophrenia have enlarged ventricles (Shenton et al., 2001; Steen et al., 2006) and, conversely, patients with hydrocephalus commonly have psychotic symptoms (Roberts et al., 1983). Moreover, psychotic patients are found to have abnormal neurochemical composition of cerebrospinal fluid, for example, altered concentrations of some cytokines (Nikkilä et al., 2001; Schwieler et al., 2015), bioactive lipids (Koethe et al., 2009), proteins and peptides in cerebrospinal fluid (Huang et al.,

2006; Thompson et al., 2003). The abnormal composition of cerebrospinal fluid, in turn, is known to affect the secretion and flow of cerebrospinal fluid (Sakka et al., 2011). Taken together, among individuals with psychotic-like symptoms, increased CV_{BOLD} in cerebrospinal fluid may partly derive from altered amount and neurochemical composition of cerebrospinal fluid.

At the global (whole-brain) level, psychotic-like symptoms were not associated with CV_{BOLD} in grey matter. This may be related to the findings that the most marked cardiovascular pulsations occur in the CSF areas near the major vessels (Kiviniemi et al., 2016, Raitamaa et al., 2018). Importantly, however, our voxel-wise analyses showed that psychotic-like symptoms correlated with increased CV_{BOLD} in the deep grey matter structures around the central CSF spaces (i.e. basal ganglia, amygdala, thalamic nuclei, hippocampus, cerebellum). Previous studies in schizophrenia patients have shown that positive symptoms correlate with increased activity level in striatum (Sorg et al., 2012). Further, schizophrenia-related cognitive disturbances are linked to altered activity level in cerebellum (Lungu et al., 2012). Importantly, our findings provided evidence that psychotic-like symptoms are related to increased *fluctuation* of the BOLD-signal in the same brain regions. Hence, our findings tentatively arise the interesting question whether some of the previously found associations between psychotic symptoms and fMRI activity might partly reflect increased *variation* of the BOLD-signal.

Increased CV_{BOLD} in the brain may also reflect psychosis-related changes in cardiovascular and respiratory activities. Specifically, psychotic disorders have been related to reduced baroreflex sensitivity and heart rate variability (Bär et al., 2007a; Valkonen-Korhonen et al., 2003), reduced vagal activity (Mujica-Parodi et al., 2005), increased QT variability (Bär et al., 2007b), peripheral endothelial dysfunction and reduced reactivity of microcirculation (McGorry et al., 2007). Respiratory waves and cardiac pulsation, in turn, are found to affect the flow of cerebrospinal fluid in the ventricles and surrounding tissues (Dagli et al., 1999; Sakka et al., 2011). Consequently, psychosis has been related to alterations in cardiophysiological activities that may affect the quality of physiological fluctuation in the brain.

This study had some methodological limitations. Firstly, the group of participants with psychosis-level symptoms consisted of only three individuals. Hence, our findings cannot be directly generalized to patients with psychotic disorders. However, the link between schizophrenia and increased physiological noise in the brain has been demonstrated previously (Cheng et al., 2015). Hence, the primary aim of this study was to investigate individuals at symptomatic risk for developing psychosis, in line with the recent continuum-based viewpoint on early stages of psychosis (McGorry et al., 2007; Van Os et al., 2009). Additionally, our aim was to introduce a novel method for analyzing fMRI data in order to obtain previously uninvestigated sources of signal fluctuation. Future studies are needed to replicate our findings in larger samples.

Our sample was comparatively heterogeneous, including participants with familial risk for psychosis, attention-deficit hyperactivity disorder, or current Axis-I disorder. Previously, the high comorbidity of psychotic symptoms with a wide variety of other symptoms has been widely demonstrated (Fusar-Poli et al., 2012; Gaitatzis et al., 2004; Karatekin et al., 2010; Keshavan et al., 2003; Lee et al., 2012; Schuckit et al., 2006). Hence, individuals with psychotic symptomatology are known to represent a highly heterogeneous population. Consequently, our heterogeneous sample may enhance the generalizability of the findings to various populations.

In this study, brain scanning was conducted using the General Electric Signa 1.5 T fMRI system, which can be nowadays considered relatively slow TR (sampling time 1.8 s) and large voxel size (see Jukuri et al., 2013). It is relatively rarely used in schizophrenia research. On the other hand, it likely enabled us to obtain a relatively large amount of physiological fluctuation in the BOLD signal. Hence, our brain imaging data likely provided exceptional possibilities for investigating CV_{BOLD} in the brain.

This study had also several substantial strengths. Firstly, this was the first study to investigate whether symptomatic psychosis risk might be linked with CV_{BOLD} in the brain. Hence, we used a novel method for investigating the signal fluctuation in fMRI data. Secondly, we conducted meta-analyses of the previous fMRI and VBM studies among patients with

schizophrenia to investigate the overlap between our findings and the previously discovered results. This provided valuable information about how the novel method of CV_{BOLD} might enable identifying such alterations in white matter and cerebrospinal fluid that have not been identified with the traditional analytical methods in fMRI data. Thirdly, we used whole-brain indicators of CV_{BOLD} in grey matter, white matter, and cerebrospinal fluid, instead of creating a priori hypotheses and analyzing selectively regions of interest that might more likely result in type I error. Fourthly, the NFBC 1986 birth cohort provided a sample of roughly same-age participants in their young adulthood, i.e. the age phase with highest risk for psychosis (Beiser et al., 1993). Finally, symptomatic psychosis risk was evaluated with a widely used structural interview (SIPS) that is demonstrated to be a reliable measure of prodromal syndromes (Miller et al., 2003).

In conclusion, at the global level, psychotic-like symptoms were linked to higher CV_{BOLD} in cerebrospinal fluid (CSF) and white matter (WM). Voxel-wise analyses showed that in individuals with psychotic-like symptoms, CV_{BOLD} was increased especially in periventricular white matter, basal ganglia, cerebellum and parts of the cortical structures. The overlap between these results and the meta-analyses of previous fMRI and VBM data was small, suggesting that CV_{BOLD} might reflect such a signal source that has not been investigated in previous fMRI and VBM studies. Future studies with larger study samples should investigate whether our results can be generalized to other populations.

Contributors

A.S. drafted the manuscript and conducted statistical analyses. J.L. conducted data preprocessing, assisted with statistical analyses, and contributed to interpretation of the results and writing of the manuscript. V.K. assisted with statistical analyses and contributed to interpretation of the results and writing of the manuscript. J.H., T.T., M.H. and J.V. contributed to the interpretation of the results and collaborated with writing the manuscript. J.V. contributed to the data collection. All authors contributed to and have approved the final manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

References

Beiser, M., Erickson, D., Fleming, J.A., Iacono, W.G., 1993. Establishing the onset of psychotic illness. American Journal of Psychiatry 150, 1349–1354.

Birn, R.M., Diamond, J.B., Smith, M.A., Bandettini, P.A., 2006. Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. Neuroimage 31, 1536–1548. doi:10.1016/j.neuroimage.2006.02.048

Birn, R.M., 2012. The role of physiological noise in resting-state functional connectivity. Neuroimage 62, 864–870. doi:10.1016/j.neuroimage.2012.01.016

Biswal, B., Zerrin Yetkin, F., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magnetic Resonance in Medicine 34, 537–541. doi:10.1002/mrm.1910340409

Bär, K.J., Boettger, M.K., Berger, S., et al., 2007a. Decreased baroreflex sensitivity in acute schizophrenia. Journal of Applied Physiology 102, 1051–1056. doi:10.1152/japplphysiol.00811.2006

Bär, K.J., Koschke, M., Boettger, M.K., et al., 2007b. Acute psychosis leads to increased QT variability in patients suffering from schizophrenia. Schizophrenia Research 95, 115–123. doi:10.1016/j.schres.2007.05.034

Cheng, H., Newman, S.D., Kent, J.S., et al., 2015. White matter abnormalities of microstructure and physiological noise in schizophrenia. Brain Imaging and Behavior 9, 868–877. doi:10.1007/s11682-014-9349-1

Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Computers and Biomedical Research 29, 162–173.

Dagli, M.S., Ingeholm, J.E., Haxby, J.V., 1999. Localization of cardiac-induced signal change in fMRI. Neuroimage 9, 407–415. doi:10.1006/nimg.1998.0424

Dreha-Kulaczewski, S., Joseph, A.A., Merboldt, K.D., Ludwig, H.C., Gärtner, J., Frahm, J., 2015. Inspiration is the major regulator of human CSF flow. Journal of Neuroscience 35, 2485–2491. doi:https://doi.org/10.1523/JNEUROSCI.3246-14.2015

Eickhoff, S.B., Laird, A.R., Grefkes, C., Wang, L.E., Zilles, K., Fox, P.T., 2009. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects

approach based on empirical estimates of spatial uncertainty. Human Brain Mapping 30, 2907–2926. doi:10.1002/hbm.20718

Eide, P.K., Sorteberg, W., 2016. Outcome of surgery for idiopathic normal pressure hydrocephalus: role of preoperative static and pulsatile intracranial pressure. World Neurosurgery 86, 186–193. doi:10.1016/j.wneu.2015.09.067

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B., 1997. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. SCID-I/P. doi:10.1093/schbul/sbs136

Fusar-Poli, P., Nelson, B., Valmaggia, L., Yung, A.R., McGuire, P.K., 2012. Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. Schizophrenia Bulletin 40, 120–131. doi:10.1093/schbul/sbs136

Gaitatzis, A., Trimble, M.R., Sander, J.W., 2004. The psychiatric comorbidity of epilepsy. Acta Neurologica Scandinavica 110, 207–220.

Haijma, S.V., Van Haren, N., Cahn, W., Koolschijn, P.C.M., Hulshoff Pol, H.E., Kahn, R.S., 2012. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophrenia Bulletin 39, 1129–1138. doi:10.1093/schbul/sbs118

Huang, J.T.J., Leweke, F.M., Oxley, D., et al., 2006. Disease biomarkers in cerebrospinal fluid of patients with first-onset psychosis. PLoS Medicine 3, e428. doi:10.1371/journal.pmed.0030428

Israel, A.K., Seeck, A., Boettger, M.K., et al., 2011. Peripheral endothelial dysfunction in patients suffering from acute schizophrenia: a potential marker for cardiovascular morbidity. Schizophrenia Research 128, 44–50. doi:10.1016/j.schres.2011.02.007

Jahanian, H., Ni, W.W., Christen, T., Moseley, M.E., Tamura, M.K., Zaharchuk, G., 2014. Spontaneous BOLD signal fluctuations in young healthy subjects and elderly patients with chronic kidney disease. PloS One 9, e92539. doi:10.1371/journal.pone.0092539

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17, 825–841.

Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. Medical Image Analysis 5, 143−156.

Jukuri, T., Kiviniemi, V., Nikkinen, J., et al., 2013. Default mode network in young people with familial risk for psychosis - the Oulu Brain and Mind study. Schizophrenia Research 143, 239−245. doi:10.1016/j.schres.2012.11.020

Järvelin, M.R., Elliott, P., Kleinschmidt, I., et al., 1997. Ecological and individual predictors of birthweight in a northern Finland birth cohort 1986. Paediatric and Perinatal Epidemiology 11, 298−312.

Kananen, J., Tuovinen, T., Ansakorpi, H., et al., 2018. Altered physiological brain variation in drug-resistant epilepsy. Brain and Behavior 8, e01090. doi:10.1002/brb3.1090

Karatekin, C., White, T., Bingham, C., 2010. Shared and nonshared symptoms in youth-onset psychosis and ADHD. Journal of Attention Disorders 14,121−131. doi: 10.1177/1087054709347434

Keshavan, M.S., Sujata, M., Mehra, A., Montrose, D.M., Sweeney, J.A., 2003. Psychosis proneness and ADHD in young relatives of schizophrenia patients. Schizophrenia Research 59, 85−92.

Khalil, A.A., Ostwaldt, A.C., Nierhaus, T., et al., 2017. Relationship between changes in the temporal dynamics of the blood-oxygen-level-dependent signal and hypoperfusion in acute ischemic stroke. Stroke 48, 925−931. doi:10.1161/STROKEAHA.116.015566/-/DC1.

Kiviniemi, V., Wang, X., Korhonen, V., et al., 2016. Ultra-fast magnetic resonance encephalography of physiological brain activity–Glymphatic pulsation mechanisms. Journal of Cerebral Blood Flow & Metabolism 36, 1033−1045. doi:10.1177/0271678X15622047

Koethe, D., Giuffrida, A., Schreiber, D., et al., 2009. Anandamide elevation in cerebrospinal fluid in initial prodromal states of psychosis. The British Journal of Psychiatry 194, 371−372. doi:10.1192/bjp.bp.108.053843

Krüger, G., Glover, G.H., 2001. Physiological noise in oxygenation-sensitive magnetic resonance imaging. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine 46, 631−637.

Lee, A.H., Weintraub, D., 2012. Psychosis in Parkinson's disease without dementia: Common and comorbid with other non-motor symptoms. Movement Disorders 27, 858−863. doi:10.1002/mds.25003

Lungu, O., Barakat, M., Laventure, S., Debas, K., Proulx, S., Luck, D., & Stip, E. (2012). The incidence and nature of cerebellar findings in schizophrenia: a quantitative review of fMRI literature. Schizophrenia Bulletin 39, 797−806. https://doi.org/10.1093/schbul/sbr193

Makedonov, I., Black, S.E., MacIntosh, B.J., 2013. BOLD fMRI in the white matter as a marker of aging and small vessel disease. PloS One 8, e67652. doi:10.1371/journal.pone.0067652

Makedonov, I., Chen, J.J., Masellis, M., MacIntosh, B.J., 2016. Alzheimer's Disease Neuroimaging Initiative. Physiological fluctuations in white matter are increased in Alzheimer's disease and correlate with neuroimaging and cognitive biomarkers. Neurobiology of Aging 37, 12−18. doi:10.1016/j.neurobiolaging.2015.09.010

McGlashan, T.H., Miller, T.J., Woods, S.W., Hoffman, R.E., Davidson, L., 2001. Instrument for the assessment of prodromal symptoms and states. In Early Intervention in Psychotic Disorders (pp. 135−149). Springer, Dordrecht.

McGorry, P.D., Killackey, E., Yung, A.R., 2007. Early intervention in psychotic disorders: detection and treatment of the first episode and the critical early stages. Medical Journal of Australia 187, S8.

Mestre, H., Tithof, J., Du, T., Song, W., Peng, W., Sweeney, A.M., ..., Kelley, D.H., 2018. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. Nature Communications 9, 4878.

Miller, T.J., McGlashan, T.H., Rosen, J.L., et al., 2003. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophrenia Bulletin 29, 703–715.

Minzenberg, M.J., Laird, A.R., Thelen, S., Carter, C.S., Glahn, D.C., 2009. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Archives of General Psychiatry 66, 811–822.

Mujica-Parodi, L.R., Yeragani, V., Malaspina, D., 2005. Nonlinear complexity and spectral analyses of heart rate variability in medicated and unmedicated patients with schizophrenia. Neuropsychobiology 51, 10–15. doi:10.1159/000082850

Murphy, K., Birn, R.M., Handwerker, D.A., Jones, T.B., Bandettini, P.A., 2009. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced. Neuroimage 44, 893–905. doi:10.1016/j.neuroimage.2008.09.036

Nikkilä, H.V., Müller, K., Ahokas, A., Rimón, R., Andersson, L.C., 2001. Increased frequency of activated lymphocytes in the cerebrospinal fluid of patients with acute schizophrenia. Schizophrenia Research 49, 99–105.

Ogawa, S., Lee, T.M., Kay, A.R., Tank, D.W., 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proceedings of the National Academy of Sciences 87, 9868–9872. doi:10.1073/pnas.87.24.9868

Raitamaa, L., Korhonen, V., Huotari, N., et al., 2018. Breath hold effect on cardiovascular brain pulsations–A multimodal magnetic resonance encephalography study. Journal of Cerebral Blood Flow & Metabolism, 0271678X18798441. doi:10.1177/0271678X18798441

Ringstad, G., Vatnehol, S.A.S., Eide, P.K., 2017. Glymphatic MRI in idiopathic normal pressure hydrocephalus. Brain 140, 2691–2705. doi:10.1093/brain/awx191

Roberts, J.K., Trimble, M.R., Robertson, M., 1983. Schizophrenic psychosis associated with aqueduct stenosis in adults. Journal of Neurology, Neurosurgery & Psychiatry 46, 892–898.

Ryan, J.J., Ward, L.C., 1999. Validity, reliability, and standard errors of measurement for two seven-subtest short forms of the Wechsler Adult Intelligence Scale-III. Psychological Assessment 11, 207−211.

Sakka, L., Coll, G., Chazal, J., 2011. Anatomy and physiology of cerebrospinal fluid. European Annals of Otorhinolaryngology, Head and Neck Diseases 128, 309−316. doi:10.1016/j.anorl.2011.03.002

Schuckit, M.A., 2006. Comorbidity between substance use disorders and psychiatric conditions. Addiction 101, 76−88. doi:10.1111/j.1360-0443.2006.01592.x

Schwieler, L., Larsson, M.K., Skogh, E., et al., 2015. Increased levels of IL-6 in the cerebrospinal fluid of patients with chronic schizophrenia—significance for activation of the kynurenine pathway. Journal of Psychiatry & Neuroscience 40, 126.

Shenton, M.E., Dickey, C.C., Frumin, M., McCarley, R.W., 2001. A review of MRI findings in schizophrenia. Schizophrenia Research 49, 1−52. doi:10.1016/S0920-9964(01)00163-3

Smith, S.M., 2002. Fast robust automated brain extraction. Human Brain Mapping 17, 143−155.

Smith, S.M., Nichols, T.E., 2009. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 44, 83−98. doi:10.1016/j.neuroimage.2008.03.061

Sonesson, O., Tjus, T., Arvidsson, H., 2010. Reliability of a functioning scale (GAF) among psychiatric ward staff. Nordic Psychology 62, 53−64. https://doi.org/10.1027/1901-2276/a000005

Sorg, C., Manoliu, A., Neufang, S., Myers, N., Peters, H., Schwerthöffer, D., ... & Förstl, H. (2012). Increased intrinsic brain activity in the striatum reflects symptom dimensions in schizophrenia. Schizophrenia Bulletin 39, 387−395. https://doi.org/10.1093/schbul/sbr184

Spitzer, R.L., Gibbon, M., Williams, J.B.W., Endicott, J., 1996. Global assessment of functioning (GAF) scale. Outcome Assessment in Clinical Practice, 76−78.

Startup, M., Jackson, M.C., Bendix, S., 2002. The concurrent validity of the Global Assessment of Functioning (GAF). British Journal of Clinical Psychology 41, 417–422.

Steen, R.G., Mull, C., Mcclure, R., Hamer, R.M., Lieberman, J.A., 2006. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. The British Journal of Psychiatry 188, 510–518. doi:10.1192/bjp.188.6.510

Thermenos, H.W., Juelich, R.J., DiChiara, S.R., Mesholam-Gately, R.I., Woodberry, K.A., Wojcik, J., ..., Petryshen, T.L., 2016. Hyperactivity of caudate, parahippocampal, and prefrontal regions during working memory in never-medicated persons at clinical high-risk for psychosis. Schizophrenia Research 173, 1–12.

Thompson, P.M., Kelley, M., Yao, J., Tsai, G., van Kammen, D.P., 2003. Elevated cerebrospinal fluid SNAP-25 in schizophrenia. Biological Psychiatry 53, 1132–1137.

Tuovinen, T., Rytty, R., Moilanen, V., et al., 2017. The effect of gray matter ICA and coefficient of variation mapping of BOLD data on the detection of functional connectivity changes in Alzheimer's disease and bvFTD. Frontiers in Human Neuroscience 10, 680. doi:10.3389/fnhum.2016.00680

Turkeltaub, P.E., Eden, G.F., Jones, K.M., Zeffiro, T.A., 2002. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. Neuroimage 16, 765–780.

Valkonen-Korhonen, M., Tarvainen, M.P., Ranta-Aho, P., et al., 2003. Heart rate variability in acute psychosis. Psychophysiology 40, 716–726.

Vanhala, V., Junkkari, A., Korhonen, V.E., et al., 2018. Prevalence of Schizophrenia in Idiopathic Normal Pressure Hydrocephalus. Neurosurgery, nyy147. doi:10.1093/neuros/nyy147

Van Os, J., Linscott, R.J., Myin-Germeys, I., Delespaul, P., Krabbendam, L., 2009. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. Psychological Medicine 39, 179–195. doi:10.1017/S0033291708003814

Veijola, J., Mäki, P., Jääskeläinen, E., et al., 2013. Young people at risk for psychosis: case finding and sample characteristics of the Oulu Brain and Mind Study. Early Intervention in Psychiatry 7, 146−154. doi:10.1111/j.1751-7893.2012.00360.x

Wang, H.H., Menezes, N.M., Zhu, M.W., et al., 2008. Physiological noise in MR images: an indicator of the tissue response to ischemia. Journal of Magnetic Resonance Imaging 27, 866−871. doi:10.1002/jmri.21007

Wechsler, D., Coalson, D.L., Raiford, S.E., 1997. WAIS-III: Wechsler Adult Intelligence Scale. San Antonio, TX: Psychological Corporation.

Weissenbacher, A., Kasess, C., Gerstl, F., Lanzenberger, R., Moser, E., Windischberger, C., 2009. Correlations and anticorrelations in resting-state functional connectivity MRI: a quantitative comparison of preprocessing strategies. Neuroimage 47, 1408−1416.

Wise, R.G., Ide, K., Poulin, M.J., Tracey, I., 2004. Resting fluctuations in arterial carbon dioxide induce significant low frequency variations in BOLD signal. Neuroimage 21, 1652−1664. doi:10.1016/j.neuroimage.2003.11.025

Woolrich, M.W., Behrens, T.E., Beckmann, C.F., Jenkinson, M., Smith, S.M., 2004. Multilevel linear modelling for FMRI group analysis using Bayesian inference. Neuroimage 21, 1732−1747. doi:10.1016/j.neuroimage.2003.12.023

Woolrich, M.W., Ripley, B.D., Brady, M., Smith, S.M., 2001. Temporal autocorrelation in univariate linear modeling of FMRI data. Neuroimage 14, 1370−1386. doi:10.1006/nimg.2001.0931

Worsley, K.J., 2001. Statistical analysis of activation images. Functional MRI: An Introduction to Methods 14, 251−70.

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

	Mean	SD	Range	Frequency (%)
Age	22.89	0.77	20.95−24.64	
Sex (female)				148 (53.4)
SIPS positive symptoms	0.90	1.25	0−6	
No psychotic symptoms				142 (51.3)
Mild psychotic symptoms				109 (39.4)
Prodromal symptoms of psychosis				23 (8.3)
Psychosis				3 (1.1)
Educational level				
Comprehensive school or less				119 (43.0)
Matriculation level				158 (57.0)
Smoker				132 (47.7)
Risky alcohol use				13 (4.9)
Current Axis-I disorder				51 (18.4)
Neurological disorder				18 (6.5)
Previous times of unconsciousness (>30 min)				3 (1.1)
Level of functioning	80.12	11.61	21−96	
Full-scale intelligence quotient	96.93	25.12	25−160	

Table 2. *Results of linear regression analyses, when predicting CV$_{BOLD}$ in cerebrospinal fluid (CSF), white brain matter, and grey brain matter by*
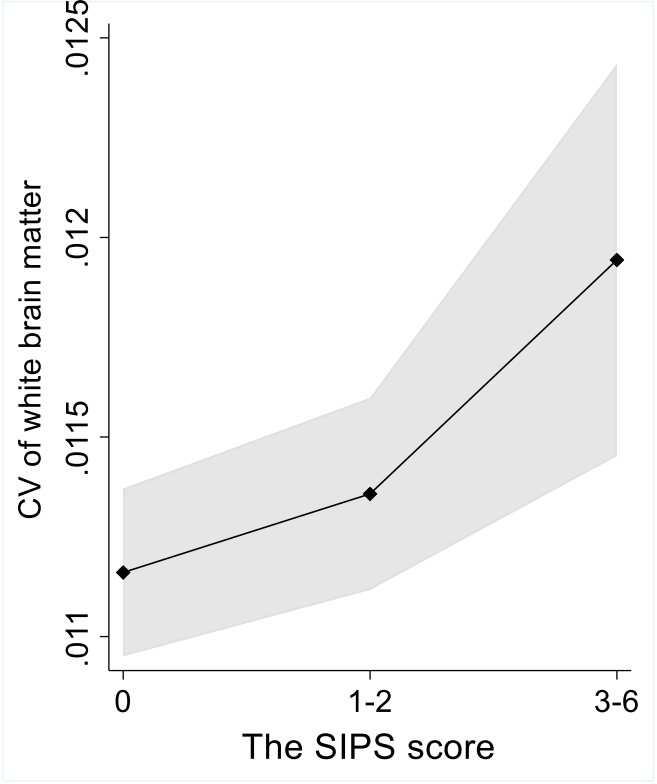
SIPS positive symptoms.

	Model 1: CV$_{BOLD}$ in CSF			Model 2: CV$_{BOLD}$ in white matter			Model 3: CV$_{BOLD}$ in grey matter		
	Beta	B	*p*	Beta	B	*p*	Beta	B	*p*
Age	-0.199	-0.001	<0.001	-0.136	0.000	0.003	-0.096	0.000	0.023
Sex[1]	-0.342	-0.002	<0.001	-0.350	-0.001	<0.001	-0.237	-0.001	<0.001
Educational level	0.045	0.000	0.315	-0.033	0.000	0.469	0.017	0.000	0.684
Absolute displacement	-0.178	-0.002	<0.001	-0.226	-0.001	<0.001	-0.180	-0.001	<0.001
Relative displacement	0.587	0.077	<0.001	0.555	0.038	<0.001	0.707	0.067	<0.001
SIPS positive symptoms									
No psychotic symptoms[2]	-	-	-	-	-	-	-	-	-
Mild psychotic symptoms	0.052	0.000	0.253	0.057	0.000	0.228	0.027	0.000	0.538
Prodromal symptoms of psychosis or psychotic symptoms	0.146	0.002	0.001	0.136	0.001	0.004	0.085	0.001	0.051

[1] Male as the reference group. [2] The reference group. *N*=276
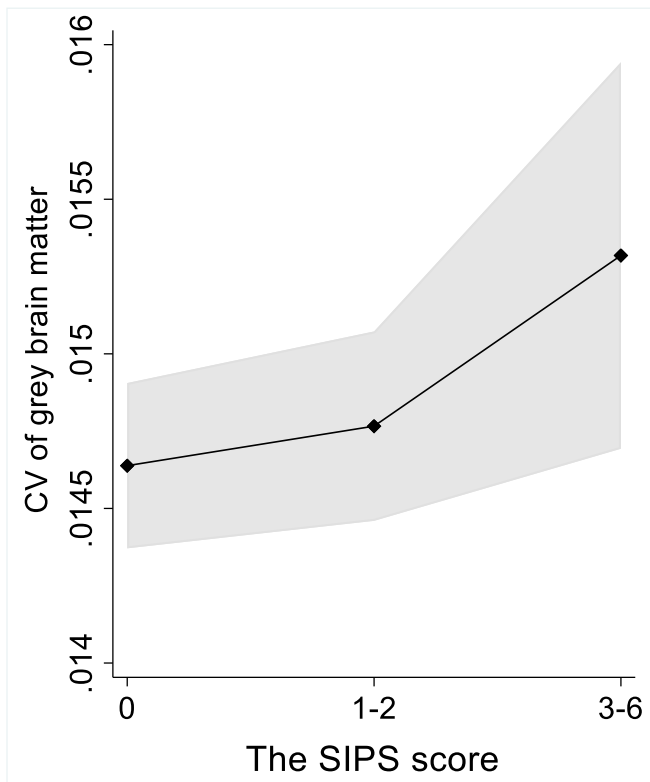
(a)
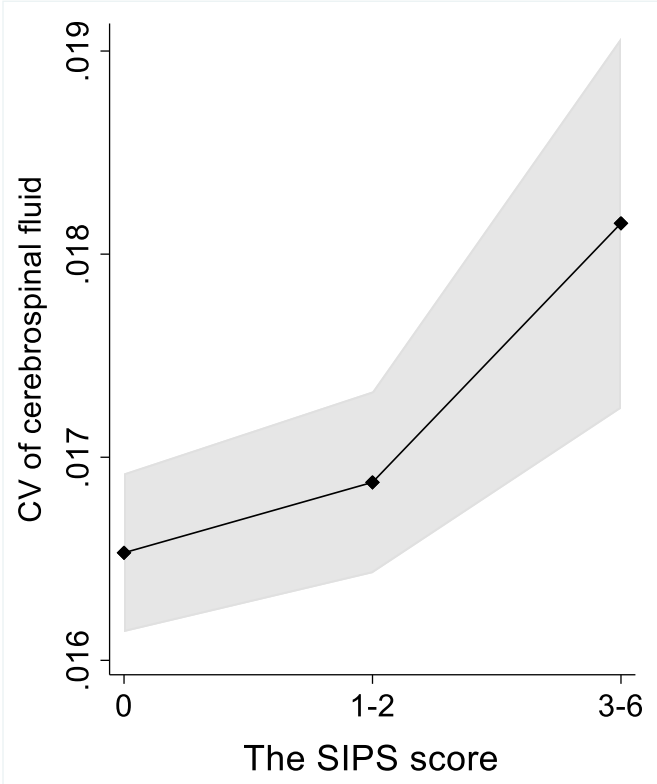
(b)

(c)

Figures 1a–c. *Predicted marginal means with 95% confidence intervals of CV in cerebrospinal fluid (a), white brain matter (b), and grey brain matter (c) for participants with different levels of SIPS positive symptoms. Adjusted for age, sex, educational level, and absolute and relative displacement.*
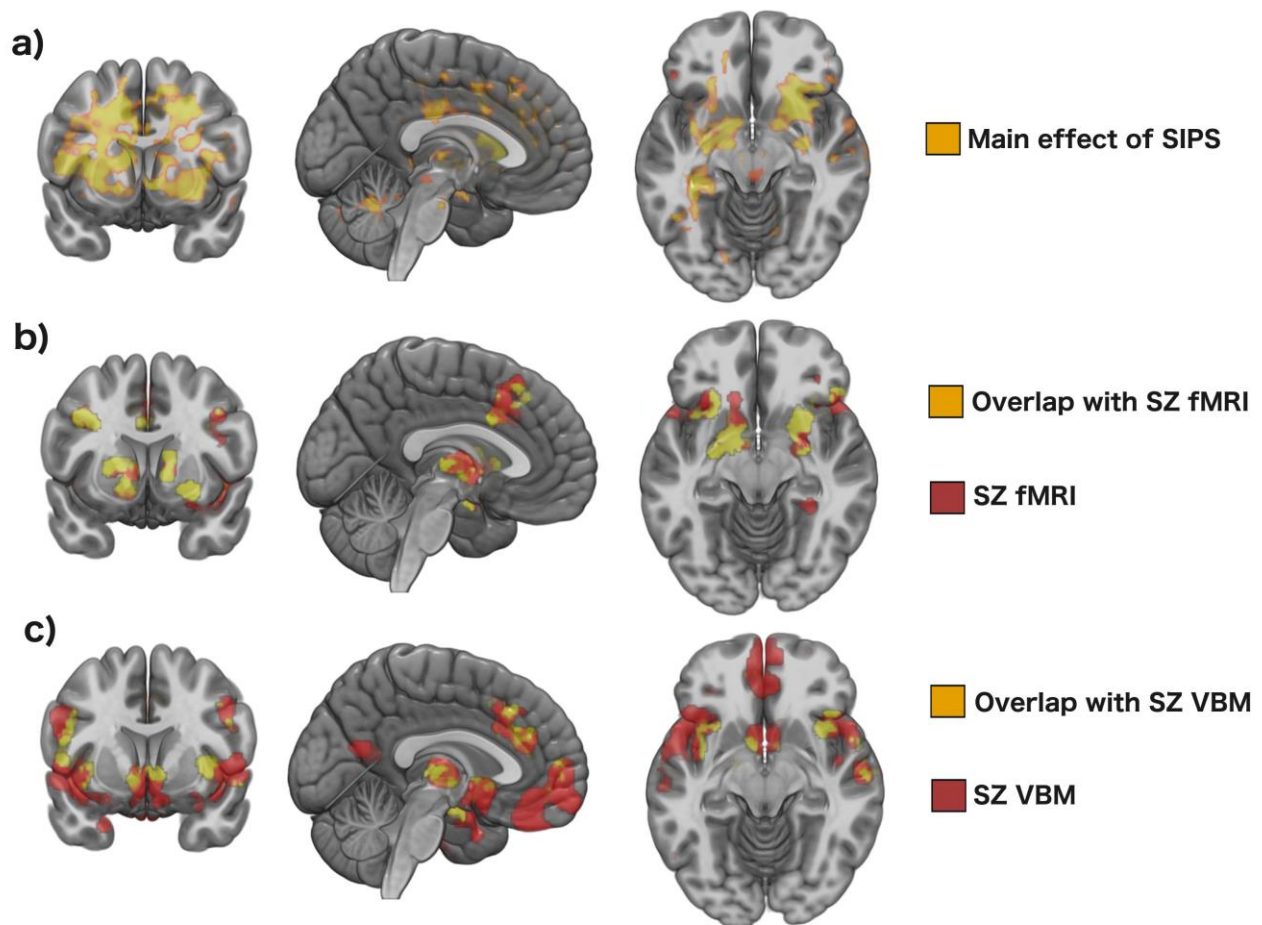
Figure 2. *(a) The brain regions with altered CV_{BOLD} among participants with psychotic-like symptoms (as measured with the SIPS) in the current study. (b) The brain regions with altered activity among schizophrenia patients in the meta-analysis of previous fMRI studies. (c) The brain regions with structural changes among schizophrenia patients in the meta-analysis of previous VBM studies.*

Supplementary Table 1. *The peak coordinates of the brain regions that showed increased CV_{BOLD} in association with high SIPS scores. Note: Thresholded at p<0.05 (corrected), cluster size > 50 voxels.*

X	Y	Z	Voxels	P-value (corrected)	T-stat	Anatomical location
-44	24	10	44215	<0.001	6.09	Inferior Frontal Gyrus (Left)
24	-60	52	441	0.028	4.72	Superior Parietal Lobule (Right)

Note: Thresholded at $p<0.05$ (corrected), cluster size > 50 voxels.

Supplementary Table 2. *Results of linear regression analyses, when predicting CV$_{BOLD}$ in cerebrospinal fluid (CSF), white brain matter, and grey brain matter by SIPS positive symptoms. Participants with psychosis (N=3) were excluded.*

	Model 1: CV$_{BOLD}$ in CSF			Model 2: CV$_{BOLD}$ in white matter			Model 3: CV$_{BOLD}$ in grey matter		
	Beta	B	*p*	Beta	B	*p*	Beta	B	*p*
Age	-0.225	-0.001	<0.001	-0.148	0.000	0.001	-0.097	0.000	0.021
Sex[1]	-0.328	-0.002	<0.001	-0.342	-0.001	<0.001	-0.235	-0.001	<0.001
Educational level	0.020	0.000	0.486	-0.046	0.000	0.322	0.014	0.000	0.740
Absolute displacement	-0.184	-0.002	<0.001	-0.232	-0.001	<0.001	-0.180	-0.001	<0.001
Relative displacement	0.607	0.077	<0.001	0.564	0.038	<0.001	0.707	0.067	<0.001
SIPS positive symptoms									
No psychotic symptoms[2]	-	-	-	-	-		-	-	-
Mild psychotic symptoms	0.050	0.000	0.260	0.056	0.000	0.235	0.026	0.000	0.543
Prodromal symptoms of psychosis	0.103	0.001	0.022	0.104	0.001	0.029	0.078	0.001	0.074

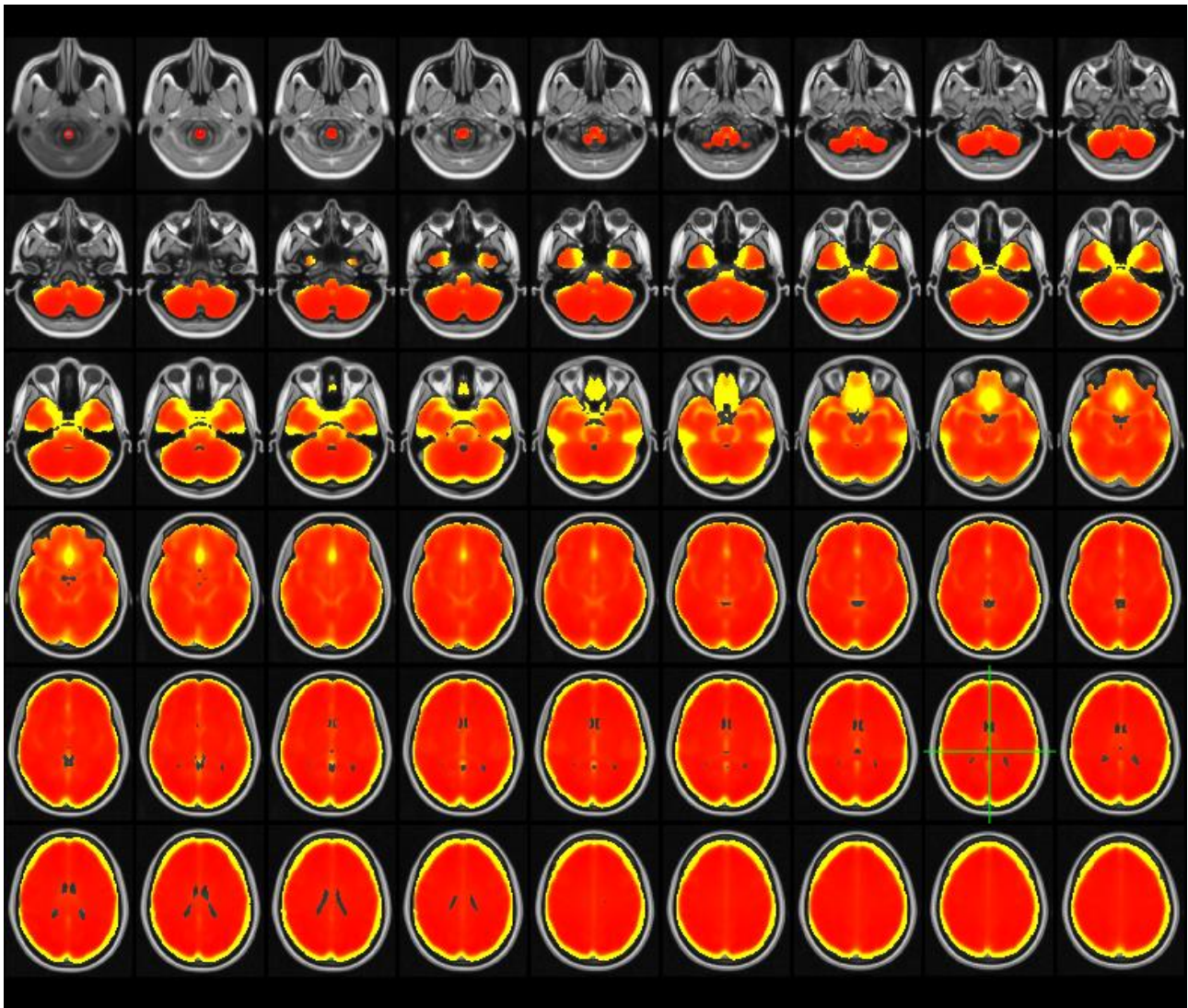[1] Male as the reference group. [2] The reference group. *N*=273
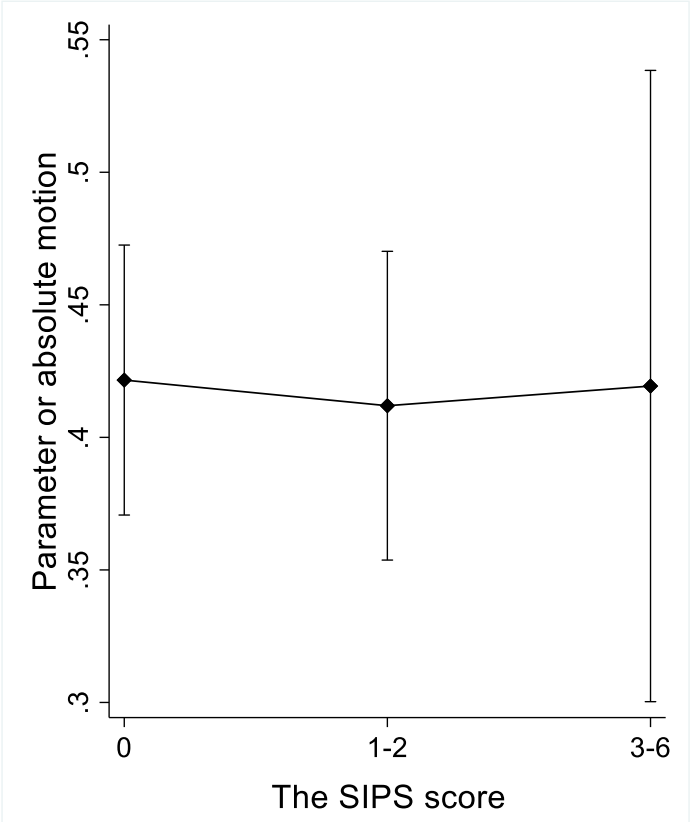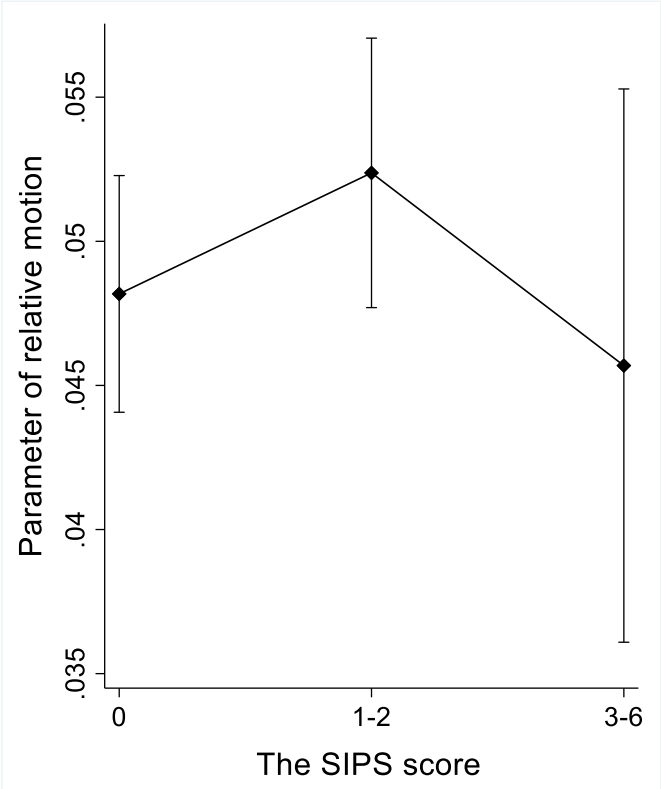
Supplementary Figure 1. *The level of absolute (a) and relative (b) motion among individuals with different SIPS scores. Adjusted for age, gender, and educational level. N=277*

Supplementary Figure 2. *The average map of the CV$_{BOLD}$ (N=277).*