Mapping alterations in the local synchrony of the cerebral cortex in schizophrenia

Jesus Pujol (✉ 21404jpn@comb.cat)  
Hospital Del Mar

Nuria Pujol  
Hospital del Mar

Anna Mané  
Hospital del Mar

Gerard Martínez-Vilavella  
MRI Research Unit, Hospital del Mar

Joan Deus

Víctor Pérez-Sola  
Hospital del Mar

Laura Blanco-Hinojo

Article

Keywords:

Posted Date: December 8th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2353061/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License

Additional Declarations: There is NO Competing Interest.
Mapping alterations in the local synchrony of the cerebral cortex in schizophrenia

Jesus Pujol\textsuperscript{1,2*}, Nuria Pujol\textsuperscript{2,3}, Anna Mané\textsuperscript{2,3}, Gerard Martínez-Vilavella\textsuperscript{1}, Joan Deus\textsuperscript{1,4}, Víctor Pérez-Sola\textsuperscript{2,3,5}, Laura Blanco-Hinojo\textsuperscript{1,2,6}

\textsuperscript{1}MRI Research Unit, Department of Radiology, Hospital del Mar, Barcelona, Spain.  
\textsuperscript{2}CIBER de Salud Mental, Instituto de Salud Carlos III, Barcelona, Spain.  
\textsuperscript{3}Institute of Neuropsychiatry and Addictions, Hospital del Mar-IMIM, Barcelona, Spain.  
\textsuperscript{4}Department of Clinical and Health Psychology, Autonomous University of Barcelona, Barcelona, Spain  
\textsuperscript{5}Pompeu i Fabra University, Barcelona, Spain  
\textsuperscript{6}Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain.

\textbf{Corresponding author:} Dr. Jesus Pujol. MRI Department, Hospital del Mar, Passeig Marítim 25-29, 08003, Barcelona, Spain. Email: 21404jpn@comb.cat Telephone: +34932212180 Fax: +34932212181
Abstract

Observations from different fields of research coincide in indicating that a defective gamma-aminobutyric acid (GABA) interneuron system could be among the primary factors accounting for the varied clinical expression of schizophrenia. GABA interneuron deficiency is locally expressed in the form of neural activity desynchronization. We mapped the functional anatomy of local synchrony in the cerebral cortex in schizophrenia using a novel functional connectivity MRI approach. Patients with schizophrenia showed weaker local functional connectivity (i.e., lower MRI signal synchrony) in a set of cerebral cortex areas largely coinciding with the synchronization effect of the GABA agonist alprazolam and the cortical areas showing higher density of parvalbumin and somatostatin GABA interneurons in humans. Our results provide detail of the functional anatomy of synchrony changes in the cerebral cortex in schizophrenia and suggest which elements of the interneuron system are affected. The information could ultimately be relevant in the search for specific treatments.
Background

Substantial research has been conducted to better understand the origin of schizophrenia in the hope of identifying one or few primary factors accounting for most of its varied clinical expression. Succeeding in this effort is important insofar as the identification of selective alterations may well reveal new targets for the development of more specific treatments.

In addition to the advances in dopamine and glutamate neurotransmission research in schizophrenia (Uno and Coyle, 2019; Howes and Shatalina, 2022), converging evidence has indicated that the gamma-aminobutyric acid (GABA) interneuron system may be defective at multiple levels of the neuroaxis. Neurophysiological studies have demonstrated GABA system-related deficiencies in the modulation of brainstem reflexes (Swerdlow et al., 2006; San-Martin et al., 2020), auditory stimuli filtering (Kim et al., 2020), inhibitory control of corticospinal pathway and prefrontal evoked responses (Kim et al., 2020; Li et al., 2021) and cortical synchronization (Uhlhaas and Singer, 2015; Ferrarelli and Phillips, 2021).

Early postmortem research suggested a defect in GABA interneurons expressing parvalbumin, which would predominantly implicate the prefrontal cortex (Blum and Mann, 2002). Other studies indicate that the alterations may extend beyond the frontal lobe (Hashimoto et al., 2008; Gonzalez-Burgos et al., 2010; Thompson et al., 2009) and additionally affect somatostatin interneurons (Van Derveer et al., 2021). Nevertheless, the information regarding the anatomical distribution of the cortical GABA-system defect is incomplete.

In the cerebral cortex, GABA interneuron deficiency is expressed in the form of local neural activity desynchronization (Uhlhaas and Singer, 2015; Ferrarelli and Phillips, 2021; Gonzalez-Burgos et al., 2010) and changes in cortical synchrony may be captured using functional connectivity MRI measures (Niessing et al., 2005; Chen et al., 2017). Abundant neuroimaging research has demonstrated alterations in functional connectivity of multiple types at multiple
levels in schizophrenia (reviewed in Fornito et al., 2012; Sabaroedin et al., 2022; Li et al.,
2019), and some studies indeed revealed a local neural uncoupling compatible with inhibitory
interneuron deficiency (e.g., Ouyang et al., 2017; Duan et al., 2019; Dong et al., 2021).
However, the anatomy of cerebral cortex changes in local MRI signal synchrony in
schizophrenia has not been detailed and the potential relationship with the interneuron system
has not been analyzed.

We mapped the functional anatomy of local, short-range synchrony in schizophrenia using a
combination of (Iso-Distance Average Correlation- IDAC) functional connectivity measures
that comprehensively inform on the local functional structure of the cerebral cortex (Macià et
al., 2018; Pujol et al., 2019; Pujol et al., 2021). It is important to note that variations in local
functional connectivity can express activity variations in both principal (pyramidal) neurons and
inhibitory interneurons (Buzsáki and Watson, 2012; Mathalon and Sohal, 2015), and thus a
context is needed to properly interpret the direction of change.

We have previously characterized the effect of a typical GABA agonist (alprazolam) on local
functional connectivity using our mapping approach (Blanco-Hinojo et al., 2021). The
inhibitory agent alprazolam increased local functional connectivity in the cerebral cortex with a
notably system-specific pattern. Significant changes were found in prefrontal, motor,
somatosensory, auditory, visual and orbitofrontal areas. A local synchronization effect has also
been demonstrated for other GABA agonists (Kiviniemi et al., 2005; Licata et al., 2013; Pflanz
et al., 2015; Bosch et al., 2018).

We hypothesized that our IDAC measures would be able to detail the repercussions of the
GABA system defect on the cerebral cortex of patients with schizophrenia in the form of
weaker local functional connectivity. We anticipated that the changes in functional MRI signal
synchrony would involve, and most likely not be limited to, the prefrontal cortex and cortical
areas processing sensory information.
Methods

Study populations

Publicly available neuroimaging data from patients with schizophrenia and healthy subjects were obtained from two open-source datasets: (1) the Center for Biomedical Research Excellence (COBRE) (Çetin et al., 2014), available at the SchizConnect database (http://schizconnect.org); and (2) the UCLA Consortium for Neuropsychiatric Phenomics LA5c Study (Poldrack et al., 2016), available at the OpenNeuro web platform (https://openneuro.org) under the accession number ds000030.

In both studies, the clinical diagnosis of schizophrenia was established following the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision (DSM-IV-TR; American Psychiatric Association, 2000), and was based on the Structured Clinical Interview for DSM-IV Axis-I Disorders (First et al., 1998). Subjects were excluded if they had a history of neurological disorders including head trauma with loss of consciousness, mental retardation, history of substance abuse or dependence (except for nicotine) within the past year, or contraindications to scanning (e.g., claustrophobia, metallic implants). Additional exclusion criteria for healthy volunteers included a current or past psychiatric disorder (except for one lifetime major depressive episode). All subjects had a negative toxicology screen for drugs of abuse at the start of the study. Stable medications were permitted for the patients.

Each study was approved by the corresponding local ethics committees or institutional review board (Çetin et al., 2016; Poldrack et al., 2014). All participants provided written informed consent according to the corresponding institutional guidelines.

A total of 124 patients with both functional and structural MRI were available in the repositories. Eighty-six patients (71 males and 15 females) were included in the present study based on a functional MRI exam of optimal quality (see quality control in Supplementary
Material). From the control subject repository pool (213 cases), 137 optimal-quality functional MRI exams were included in the analysis. The control sample contained all the available control males with optimal exams (n= 111) and a group of 26 females randomly selected to make patients and controls comparable as to sex distribution. The characteristics of the study sample are reported in Table 1.

Assessment of symptom severity

Symptom severity in patients was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) in the COBRE study and the Scale for the Assessment of Negative/Positive Symptoms (SANS, Andreasen, 1983; SAPS, Andreasen, 1984) in the UCLA study. To harmonize symptom variables, SANS and SAPS total scores were converted to PANSS negative and positive subscale scores, respectively, following procedures by van Erp et al. (2014).

MRI acquisition

All functional MRI images were collected on 3-Tesla Siemens Trio scanners (Siemens, Erlangen, Germany) using a conventional single-shot, gradient-echo echoplanar imaging (EPI) sequence. Acquisition parameters in the COBRE study were set as repetition time, 2000 msec; echo time, 29 msec; pulse angle, 75º; 24-cm field of view; 64 x 64-pixel matrix; and slice thickness of 3.5 mm (slice gap, 1.05 mm). Thirty-three sequential sections, parallel to the anterior-posterior commissure line, were acquired to generate 150 whole-brain volumes (total duration of 5 min), excluding 2 initial additional dummy volumes. The parameters in the UCLA study were set as repetition time, 2000 msec; echo time, 30 msec; pulse angle, 90º; 19.2-cm field of view; 64 x 64-pixel matrix; and slice thickness of 4 mm. Thirty-four sections were acquired to generate 152 whole-brain volumes (total duration of 5 min 4 sec). Participants were asked to remain relaxed and keep their eyes open throughout. 3D anatomical images were also obtained in each case based on a high-resolution T1-weighted three-dimensional magnetization-
prepared rapid gradient-echo (MPRAGE) sequence, which served to assist functional connectivity image processing.

**Iso-Distant Average Correlation (IDAC) maps**

Imaging data were processed using MATLAB version 2016a (The MathWorks Inc, Natick, Mass) and Statistical Parametric Mapping software (SPM12; The Wellcome Department of Imaging Neuroscience, London). Image processing steps adopted to generate the cerebral cortex IDAC maps have been previously reported (Macià et al., 2018) and a detailed description is provided in Supplementary Material. Below is a summary.

Functional MRI images were slice-time corrected, realigned, co-registered to their corresponding anatomical image, re-sliced to 3x3x3 mm resolution and smoothed by convolving the image with a 4x4x4 mm full width at half maximum (FWHM) Gaussian kernel. Motion-affected image volumes were discarded using conventional scrubbing procedures (Power et al., 2014).

IDAC measures were then estimated in native space. The computation was conducted in a gray matter mask split into left and right hemispheres. Whole-cortex IDAC maps were generated by estimating the average temporal correlation of each voxel with all its neighboring voxels placed at increasingly separated Euclidean iso-distant intervals (definition and mathematical formulation is provided in the Supplementary Material). Three IDAC maps were obtained at distance intervals 5-10 mm, 15-20 mm and 25-30 mm. The analyses were adjusted by including 6 rigid body realignment parameters, their first-order derivatives, average white matter, CSF and global brain signal as regressors. All functional MRI time series were band-passed with a Discrete Cosine Transform (DCT) filter letting through frequencies in the 0.01-0.1 Hz interval.

Finally, the resulting IDAC maps in native space were normalized to the Montreal Neurological Institute (MNI) space with a back-transformation process. That is, individual 3D anatomical
images had previously been segmented and registered to the MNI space and the inverse
deformation fields provided by SPM in this step were applied to the IDAC maps.

Multi-distance IDAC color maps were obtained from the overlay of the three IDAC maps using
an RGB color codification (see Figure 1). RGB color channels enabled the display of three
values simultaneously. RED corresponding to the results from 5-10 mm IDAC map analyses,
GREEN from 15-20 mm and BLUE from 25-30 mm. The overlapping of these primary colors
produces a full range of secondary colors. Composite RGB maps were generated from one-
sample t-maps obtained for each distance in both study groups and from the between-group
comparison t-maps.

**Statistical analysis**

IDAC connectivity maps were included in SPM group-wise random-effects analyses adopting a
2x3 mixed design ANOVA (ANCOVA) model (i.e., group [patients, controls] by distance [5-10
mm, 15-20 mm and 25-30 mm]). A motion summary measure (mean inter-frame motion (Power
et al., 2014)) for each participant was included as a covariate in all analyses. We specifically
tested for group effects to map cortical areas with altered connectivity (primary study question)
and for group-by-distance interactions to determine whether the alterations concerned the spatial
structure (i.e., differential implication of distinct local distances). In all analyses, results were
considered significant when clusters formed at a threshold of $p< 0.005$ survived whole-brain
family-wise error (FWE) correction ($p< 0.05$), calculated using SPM.

**Results**

One-sample maps of cerebral cortex functional connectivity were generated for the three local
distances and the outputs are presented together using RGB display. Figure 1 and
Supplementary Figure 1 illustrate the extent to which the human cerebral mantle is functionally
heterogeneous in these measures. Distinct anatomo-functional areas show a different functional
structure determined by variations in the relative strength of connectivity at locally short, locally
middle and locally long distances. Cortical area differentiation is evident in both control subjects and patients with schizophrenia. However, as can be appreciated upon visual inspection, the maps are not identical.

Two-sample analyses confirmed that both groups were significantly different in local functional connectivity. Supplementary Table 1 reports the results from ANOVA showing group differences across the three distances. All the identified group differences were in the direction of patients showing weaker local functional connectivity (i.e., lower functional MRI signal synchrony) (Figure 2). Highly significant changes were bilaterally observed in each sensory cortex, primary motor cortex, insula extending to the frontal operculum and orbitofrontal cortex, anterior cingulate cortex, dorsal prefrontal cortex and hippocampus. Remarkably, the primary somatosensory cortex was affected in almost its entire extension. The alteration in the auditory cortex was maximal in the primary auditory area. By contrast, the visual cortex showed widespread changes, but virtually excluded the occipital pole.

Figure 3 shows group differences at a higher threshold (voxel t > 4) to emphasize the areas with the largest effect. Note the conspicuous cortical area coincidence with the synchronization effect of the GABA agonist alprazolam observed using identical local functional connectivity measures in an early study by our group (Blanco-Hinojo et al., 2021). That is, patients with schizophrenia at rest showed weaker local synchrony in cortical areas typically synchronized by the GABA agonist alprazolam.

The anatomical resemblance between the study results and the cortical GABA system was also notable with the combined distribution of parvalbumin and somatostatin GABA interneurons in humans (summarized in Anderson et al., 2020, from the Allen Human Brain Atlas [https://human.brain-map.org/]). The human expression of parvalbumin GABA interneurons is maximal in the motor cortex, somatosensory cortex, auditory cortex, visual areas and dorsal
prefrontal cortex (Figure 4). On the other hand, the expression of somatostatin GABA interneurons is maximal in the anterior insula-orbitofrontal cortex and anterior cingulate cortex. Therefore, the areas most affected in patients with schizophrenia characteristically show a high density of parvalbumin or somatostatin GABA interneurons.

Although the weakening in local functional connectivity affected the three measured distances (Supplementary Figure 2), a tendency to a greater effect in long distances was observed in some association cortices and, in short distances, in the sensorimotor cortex and visual areas. However, formally tested group-by-distance interaction was significant only for a restricted area in the sensorimotor cortex (Supplementary Table 1 and Supplementary Figure 3).

Finally, a regression analysis was conducted in the patient group to establish whether symptom severity was associated with the identified functional connectivity alterations (Supplementary Table 2 and Figure 5). Negative symptoms were associated with weaker functional connectivity in the anterior cingulate cortex and visual areas in the short- and middle-distance maps. Positive symptom scores did not show a net negative correlation, but instead they were associated with the combination of weaker functional connectivity in short-distance maps and stronger connectivity in the long-distance map in the motor cortex and prefrontal cortex. A marginal, but relevant, finding emerged in the analysis of individual distances implicating the association of positive symptoms with stronger connectivity at long distances in the Broca area region and its homologue in the right hemisphere.

**Discussion**

We used functional connectivity MRI measures to capture potential alterations in cerebral cortex local synchrony in patients with schizophrenia. Robust changes were identified in several brain areas in the form of weaker functional connectivity compatible with GABA system dysfunction. Importantly, details concerning the anatomical distribution of such changes may
provide useful information as to the nature of the inhibitory system defect by further indicating which interneuron types may be predominantly affected.

Patients with schizophrenia showed weaker functional MRI signal synchrony involving distinct cortical domains ranging from the prefrontal cortex to the limbic system. The alterations were evident in the frontal association cortex, each sensory cortex modality and motor cortex, the paralimbic system at the anterior insula and anterior cingulate cortex, and the hippocampus. As for the sensory cortex, the changes were more obvious in somatosensory, visual and auditory areas. However, regions including the gustatory (insula-frontal operculum) and olfactory (orbitofrontal) cortices were also implicated.

Two data sets served to establish the resemblance between the cortical distribution of our findings and the cortical GABA system. Firstly, we used data from a previous study by our group testing the effect of alprazolam on cerebral cortex local functional connectivity in healthy volunteers (Blanco-Hinojo et al., 2021). Alprazolam is a GABA agonist with inhibitory action and obvious effects on functional MRI signal synchronization. It is an interesting example of how functional connectivity MRI measures may relate neural inhibition to “paradoxical” increases in functional connectivity. We observed a notable similarity between the synchronization effect of alprazolam and the distribution of the defect in cortical area synchrony in schizophrenia (Figure 3).

The complex GABA system includes a variety of inhibitory interneuron types with different morphology, anatomical distribution and gene expression (Tremblay et al., 2016; Benes and Berretta, 2001). One of the most abundant types of interneurons expresses parvalbumin. A high density of parvalbumin interneurons in humans is found in a few subcortical structures (e.g., thalamus, trigeminal nuclei and cerebellum) and in prefrontal, somatosensory, visual, auditory and motor areas of the cortical mantle (Hawrylycz et al., 2012; Anderson et al., 2020). The
cortical sites we found with altered functional MRI signal synchrony in patients with schizophrenia precisely include the set of cortical areas with high parvalbumin density in humans. The parvalbumin interneuron defects identified in selected areas in post-mortem studies in patients with schizophrenia are also consistent with the anatomy of our findings (Blum and Mann, 2002; Hashimoto et al., 2008; Gonzalez-Burgos et al., 2010).

Also, importantly, a few studies indicate that the alterations may not be limited to the parvalbumin-type interneurons (Hashimoto et al., 2008; Van Derveer et al., 2021). In our analysis, functional connectivity changes in schizophrenia additionally implicated the areas showing a high density of somatostatin interneurons. We therefore provide novel evidence with a more complete picture of the repercussions of the GABA system dysfunction on the cerebral cortex.

Cortical maps of parvalbumin and somatostatin GABA interneurons in humans are minimally overlapped. Instead, areas showing high parvalbumin interneuron density show low somatostatin interneuron density, and vice versa (Anderson et al., 2020). Therefore, the influence of both cell lines on brain function needs to be different and complementary. In general, parvalbumin interneurons are most abundant in the neocortex and somatostatin interneurons in paralimbic areas. This is consistent with the fact that the clinical expression of schizophrenia includes symptoms related to both the cognitive and affective domains.

The hippocampus may be an exception to the minimal interneuron type anatomical overlapping as it shows a relatively high abundance of parvalbumin and somatostatin interneurons (Anderson et al., 2020; Heckers and Konradi, 2015). Consistently, we found altered local functional connectivity in the hippocampus in patients with schizophrenia and post-mortem studies have demonstrated a lower expression of both interneuron types (Wegrzyń et al., 2022; Heckers and Konradi, 2015).
It is worth noting that the auditory and visual cortices were not affected in the same way in our study. That is, whereas early auditory areas at the Heschl's gyri were uniformly altered, functional connectivity changes were not evident in the occipital pole. This part of the visual cortex serves central, high acuity vision. In contrast, eccentric areas in the occipital lobe are more involved in holistic and peripheral vision (Wandell et al., 2007; Musel et al., 2013; Levy et al., 2001). Relevantly, one of the most characteristic perceptive dysfunctions in patients with schizophrenia is instability in the rapid extraction of global information from a visual stimulus, which relies more on global and peripheral vision than on central vision (Adámek et al., 2022; Musel et al., 2013; Javitt, 2009; Butler et al., 2001). Also, we wonder whether a higher prevalence of auditory as opposed to visual hallucinations in patients with schizophrenia (Clark et al., 2017) might be related to a different nature of local synchrony alterations in auditory and visual cortices.

The normal differentiation of short-range, local functional connectivity is highly active during adolescence (Ouyang et al., 2017) and is sexually dimorphic in some cortical areas showing a synchrony defect in schizophrenia in the present study (i.e., sensorimotor cortex, visual cortex and prefrontal cortex). Specifically, boys physiologically appear to require a lower maturational reduction in local functional connectivity in such areas during the transition from childhood to adulthood (Pujol et al., 2021). Therefore, it is possible that the risk of developing schizophrenia in this critical period and the higher incidence in males (Howes and Shatalina, 2022), could to some extent be related to the effect of environmental stressors on cortical inhibitory interneurons, presumably via promoting excessive synaptic pruning (Howes and Shatalina, 2022; Ouyang et al., 2017; Paus et al., 2008).

In our correlation analysis, weaker functional MRI signal synchrony was coherently associated with the severity of schizophrenia symptoms in a part of the altered cortical areas. In the visual cortex and anterior cingulate cortex, higher negative symptom scores predicted weaker functional connectivity. And higher positive symptoms predicted a combination of weaker
functional connectivity at short distances and stronger functional connectivity at long distance in the motor cortex and prefrontal cortex. These are relevant results emphasizing the functional significance of the observed alterations in the cerebral cortex in patients with schizophrenia.

We also observed a positive correlation between symptom severity and functional connectivity measures. Positive symptoms of schizophrenia predicted higher synchrony, particularly in the Broca area region and its homologue in the right hemisphere. Importantly, significant correlations were observed only for long distances. This marginal, but relevant, association may be more directly interpreted as related to the activity of principal (pyramidal) neurons, rather than inhibitory interneurons. Positive symptoms of schizophrenia (e.g., the experience of hallucinations) are associated with cortical hyperactivity (Diederen et al., 2012; Barber et al., 2021) and increased functional connectivity (Čurčić-Blake et al., 2017). Thus, for such an association, stronger functional connectivity could better express the increase in the number of co-activated principal neurons. Our finding may be of interest in the debate on the participation of language-related areas in the generation of auditory hallucinations (Barber et al., 2021; Čurčić-Blake et al., 2017).

An important limitation of our study concerns to the medication status of patients. All patients were taking one or more drugs. Antipsychotics and benzodiazepines have a demonstrated effect on neural inhibition (Swerdlow et al., 2016; Blanco-Hinojo et al., 2021). Therefore, our functional connectivity measures may be sensitive to the effect of schizophrenia treatments. However, medication in our study may more likely have attenuated differences in functional connectivity between patients and controls rather than causing them. Indeed, antipsychotic agents, particularly atypical antipsychotics, reduce differences between patients and controls in terms of the neurophysiological measures of neuronal inhibition deficit (Swerdlow et al., 2006; Swerdlow et al., 2016), and can restore the expression of parvalbumin in experimentally altered
GABA interneurons (e.g., Benes and Berretta, 2001; Todorović et al., 2019; Rossetti et al., 2018).

In conclusion, we used an imaging approach to map the local functional structure of the cerebral cortex in patients with schizophrenia and identified alterations in functional MRI signal synchrony compatible with a GABA system defect. Robust changes were observed in prefrontal lobe areas and sensory cortices showing high density of parvalbumin-expressing interneurons in humans. Functional connectivity alterations also implicated paralimbic areas showing a high density of somatostatin-expressing interneurons. Our results thus provide novel details regarding the functional anatomy of the local synchrony defect at the cerebral cortex and suggest which elements of the inhibitory interneuron system are affected. This information could ultimately be relevant in the search for specific treatments with the aim of improving the symptoms of schizophrenia without affecting global brain function.
References


Andreasen NC. (1983). The scale for the assessment of negative symptoms (SANS). Iowa City, IA: University of Iowa.


Blum BP, Mann JJ. The GABAergic system in schizophrenia. Int J Neuropsychopharmacol. 2002 Jun;5(2):159-79.


Heckers S, Konradi C. GABAergic mechanisms of hippocampal hyperactivity in schizophrenia. Schizophr Res. 2015 Sep;167(1-3):4-11.


Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76.


Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage. 2014 Jan 1;84:320-41.


Figures

Figure 1. Composite one-sample Iso-Distant Average Correlation (IDAC) brain maps. The images show the result of superimposing the three IDAC maps using an RGB (red, green and blue) color display. Note that such multi-distance maps are able to discriminate between various cortical areas. Ctls, control subjects. Sz, schizophrenia.
Figure 2. Differences between patients with schizophrenia and control subjects in IDAC measures across the three distance maps. The images show ANOVA results in the direction of patients showing weaker local functional connectivity. Orthogonal displays (bottom images) are shown to detail the implication of the anterior cingulate cortex (A), the hippocampus (B) and the relative preservation of the occipital pole (C and D).
Figure 3. Alterations in the local synchrony of the cerebral cortex in schizophrenia and the cortical synchronization action of GABA inhibition. Top, the identified group differences at a higher threshold (voxel $t > 4$) to emphasize the areas with the largest effect. Bottom, cortical synchronization by the GABA agonist alprazolam observed using identical functional connectivity measures. Adapted, with permission, from Blanco-Hinojo et al. (2021).
Figure 4. Alterations in the local synchrony of the cerebral cortex in schizophrenia and the distribution of parvalbumin and somatostatin GABA interneurons in humans (adapted, with permission, from Anderson et al., 2020). Differences between patients with schizophrenia and control subjects in IDAC measures (top) are presented as in Figure 1.
Figure 5. Illustration of the correlation analysis results. Negative symptoms were associated with weaker functional connectivity in the short-distance maps (top images). Positive symptoms were associated with the combination of weaker functional connectivity in short-distance maps and stronger connectivity in the long-distance map (middle images). In addition, positive symptoms were associated with stronger connectivity at long distances (bottom images).
Table 1. Demographic and clinical characteristics of the samples

<table>
<thead>
<tr>
<th></th>
<th>86 Patients (COBRE=45 and UCLA=41)</th>
<th>137 Controls (COBRE=60 and UCLA=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>35.4 ± 11.6</td>
<td>35.4 ± 10.5</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>71/15</td>
<td>111/26</td>
</tr>
<tr>
<td>Handedness, R/L/Amb.</td>
<td>80/5/1</td>
<td>131/3/3</td>
</tr>
<tr>
<td>Age at symptoms onset, yrs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20.4 ± 7.9</td>
<td></td>
</tr>
<tr>
<td><strong>Symptom severity</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS positive</td>
<td>15.7 ± 5.0</td>
<td></td>
</tr>
<tr>
<td>PANSS negative</td>
<td>15.3 ± 4.9</td>
<td></td>
</tr>
<tr>
<td><strong>Medication, n&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics typical</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Antipsychotics atypical</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Ant. typical and atypical</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation. Patients and controls did not significantly differ as to mean age and the distribution of sex and handedness. PANSS, Positive and Negative Syndrome Scale. <sup>a</sup>Data available for 45 out of 86 patients. <sup>b</sup>From PANSS (n=37) or converted from SAPS/SANS to PANSS (n=41) using the method of van Erp et al. (2014). <sup>c</sup>Data available for 80 out of 86 patients.
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterialSzNNS.pdf