Global brain asymmetry is increased in schizophrenia and related to avolition

(Accepted for publication in Acta Psychiatrica Scandinavica)

Pre-print version

Running title: Global brain asymmetry in schizophrenia

Christian Núñez*[1], Nataly Paipa[1], Carl Senior[2], Marta Coromina[1], Sara Siddi[1,3,4,5], Susana Ochoa[1,5], Gildas Brébion[1,5], Christian Stephan-Otto[1,5]

[1] Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, Spain

[2] School of Life & Health Sciences, Aston University, Birmingham, UK

[3] Facultat de Medicina, Universitat de Barcelona, Barcelona, Spain

[4] Section of Clinical Psychology, Department of Education, Psychology, and Philosophy, University of Cagliari, Italy

[5] Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Madrid, Spain

Corresponding author:

*Christian Núñez (mail: c.nunez@pssjd.org; phone: 93 640 63 50)

Address: C/Doctor Antoni Pujadas, 42, 08830 Sant Boi de Llobregat, Barcelona, Spain

Abstract

Objective

Schizophrenia may be the result of a failure of the normal lateralization process of the brain. However, whole-brain asymmetry has not been assessed up to date. Here we propose a novel measure of global brain asymmetry based on the Dice coefficient in order to quantify similarity between brain hemispheres.

Method

Global gray and white matter asymmetry was calculated from high-resolution T1 structural images acquired from 24 patients with schizophrenia and 26 healthy controls, age- and sex-matched. Some of the analyses were replicated in a much larger sample (n = 759) obtained from open-access online databases.

Results

Patients with schizophrenia had more global gray matter asymmetry than controls. Additionally, increased gray matter asymmetry was associated with avolition, whereas the inverse relationship was found for anxiety. These analyses were replicated in a larger sample and confirmed previous results.

Conclusion

Our findings suggest that global gray matter asymmetry is related to the concept of developmental stability and is a useful indicator of perturbations during neurodevelopment.

Keywords: Schizophrenia; Neuroimaging; Neurodevelopment

Significant outcomes

- Global gray matter is more asymmetric in patients with schizophrenia than in controls. This finding was replicated in large and independent samples.

- Avolition and anxiety are associated with global gray matter asymmetry in patients.

- Global gray matter asymmetry may be an indicator of early developmental perturbations.

Limitations

- Information on verbal IQ and education level could not be analyzed in Study II.

- Scores of anxiety symptoms were not available for participants of Study II.

- The potential effects of the psychiatric medication could not be analyzed.

Introduction

The concept of developmental stability (DS) refers to the capacity of an organism to buffer its development against genetic or environmental perturbations. The most common measure to estimate DS is fluctuating asymmetry (FA), which assumes that the development of the two sides of a symmetric organism is influenced by the same genes. Therefore, any difference between the two sides is assumed to be a consequence of a genetic or environmental perturbation, thus reflecting the DS efficiency of the organism [1]. FA aims to quantify the left-right asymmetry degree, and accounts for the slight random variations present in the organism [2], rather than for systematic asymmetry variations. However, this measure has been commonly employed in the body, e.g. by measuring the length of the fingers of both hands [3], but it has not been used to quantify the degree of asymmetry between brain hemispheres. Rather, research on brain asymmetries has focused mainly on the systematic structural asymmetries that exist between left and right hemispheres [2]. Some brain functions, such as language and spatial attention, have been shown to be lateralized. Moreover, lateralization of functions seems to be associated with structural changes [4, 5]. Hemispheric dominance derived from these brain asymmetries may have some evolutionary advantages, such as greater processing speed, as a consequence of not having to rely on communication between the two hemispheres, and the avoidance of duplicated functions and redundant neural circuits [2].

Brain asymmetries have received a good deal of attention in schizophrenia. Crow et al. [6] considered schizophrenia to be the result of a failure in the normal brain lateralization process. A review by Oertel-Knöchel and Linden [7] showed that, in fact, a reduced degree of cerebral asymmetry in localized regions is often associated with schizophrenia, e.g., patients seem to have reduced structural asymmetry in the temporal lobe, and the normal cerebral torque is reduced or absent. A meta-analysis concluded that the process of cortical gray matter volume loss in patients with schizophrenia was more active in the left than in the right hemisphere, which could explain the abnormal asymmetries seen in these patients [8]. Reduced white matter asymmetry in localized regions has also been found in schizophrenia, which has been attributed to neurodevelopmental abnormalities [9]. Furthermore, a meta-analysis of dichotic listening studies concluded that reduced language lateralization was

particularly marked in those patients with schizophrenia suffering from auditory hallucinations [10]. Additionally, the degree of reduced lateralization of the temporal lobe seems to be positively correlated with severity of hallucinations and other positive symptoms [7, 11]. Differences in the left-right sulcal asymmetry between patients with and without visual hallucinations have also been found [12]. Studies examining potential associations between cerebral asymmetry and negative or affective symptoms are scarce, although these symptoms have been shown to have important clinical [13] and cognitive [14, 15] effects in schizophrenia. Even though results are inconclusive, it seems that both negative symptoms and depression are associated with loss of asymmetry [16, 17].

To our knowledge, all of the studies published to date regarding cerebral asymmetry and schizophrenia have focused on the characterization of specific brain regions known to present abnormal degrees of symmetry. A global measure of asymmetry between the left and right hemispheres, which could provide additional information about neurodevelopment and which might be related to the concept of developmental stability, has yet to be tested. In order to compare global gray and white matter asymmetry between patients with schizophrenia and healthy controls, we developed a novel approach of global asymmetry that accumulates all the local asymmetries found in the brain and which may account for the random variations of it, rather than for the systematic variations. This measure is based on the Dice coefficient [18] and has not been used previously in this kind of study.

Aims of the study

Here we present two studies in which we employ this new measure. In Study I, we compare global gray and white matter asymmetry, with the measure based on the Dice coefficient, between patients with schizophrenia and healthy controls. In addition, we will also evaluate whether hallucinations, delusions, negative symptoms, and/or affective symptoms are associated with global brain asymmetry in patients with schizophrenia. Given the lack of literature assessing brain asymmetries with a global approach, these analyses are exploratory. In Study II, we will try to replicate results from Study I, employing the same methodology as in Study I with a larger sample of patients with schizophrenia and healthy controls obtained from several open-access databases.

STUDY I

1. Methods

1.1. Participants

A total of 50 participants, 24 patients with schizophrenia and 26 age- and sex-matched healthy control participants, were included in Study I, which is part of a broader reality-monitoring study. This study was approved by the Ethics Committee of Fundació Sant Joan de Déu. Patients were recruited from the Parc Sanitari Sant Joan de Déu network of mental health services in Barcelona, Spain. Inclusion criteria for patients were age between 18 and 60 years, native fluency in Spanish, and the ability to provide informed consent. Exclusion criteria for patients were having an organic mental disorder, dementia, intellectual disability, head injury, alcohol or other drug abuse in the past 6 months, current severe physical disease, and the standard exclusion criteria for participation in neuroimaging procedures, i.e., claustrophobia and metallic implants. Healthy control participants were recruited from the general population by advertisements in the public access areas of the hospital campus. Inclusion criteria for healthy control participants were age between 18 and 60 years and native fluency in Spanish. Exclusion criteria for healthy control participants were having a neurological or mental disease, intellectual disability, head injury, alcohol or other drug abuse in the past 6 months, current severe physical disease, and the standard exclusion criteria for participating in neuroimaging procedures. Comparison was made of sociodemographic and clinical data between patients with schizophrenia and healthy control participants from Study I by means of a T-test for independent samples. Differences in sex distribution were analyzed with a chi-square test. This information is presented in the Supplementary Table 1. As expected, there were no significant differences in age or sex distribution. However, healthy controls were significantly better educated and scored higher in verbal IQ than patients. Verbal IQ was assessed with the Test de Acentuación de Palabras (TAP) [19] vocabulary test, a Spanish equivalent of the National Adult Reading Test (NART).

1.2. Clinical evaluation

Positive, negative, and affective symptoms (depression and anxiety) were assessed in patients by means of the following scales:

- Positive symptoms: the Spanish version of the Scale for the Assessment of Positive Symptoms (SAPS) was used. Scores on the hallucinations and delusions subscales were used for the analyses.

- Negative symptoms: the Spanish version of the Scale for the Assessment of Negative Symptoms (SANS) was used. Since attention disorders are considered as different from negative symptomatology, the attention items were discarded. The items of the other four categories (flat affect, alogia, avolition, and anhedonia) were added together to constitute SANS-4, the negative symptoms score considered in the analyses.

- Affective symptoms: depression scores were obtained by means of the Calgary Depression Scale, whereas anxiety scores were obtained by means of the Hamilton Anxiety Rating Scale.

Clinical evaluation was conducted after the completion of the neuroimaging procedure by an experienced clinical psychologist trained in the administration of all these scales.

1.3. Data acquisition

MRI data were acquired using a General Electric 1.5 Tesla Signa HDe scanner at Parc Sanitari Sant Joan de Déu. For each participant, a high-resolution T1-weighted FSPGR structural image with the axial plane parallel to the AC-PC axis was acquired using the following parameters: 2 mm slice thickness, TR = 12.24 ms, TE = 3.84 ms, FOV = 24 cm, acquisition matrix = 512 × 512, flip angle = 20°, voxel size = 0.47 × 0.47 × 2.00 mm^3. The protocol included the acquisition of other experimental images not used in the present study.

1.4. Data processing

Neuroimaging data were analyzed with SPM8 (Wellcome Department of Imaging Neuroscience, London; www.fil.ion.ucl.ac.uk/spm) running under MATLAB (Release 2009a, The MathWorks, Inc., Natick, Massachusetts), following an adaptation of a recently published protocol to analyze gray matter asymmetries [20].First of all, gray matter and white matter were segmented for all the participants. These gray and white matter segments were then flipped, i.e., a new image was created with the left

and right hemispheres reversed. This process allowed the creation of a symmetric DARTEL anatomical template from the original and flipped gray and white matter segments of all the participants. Finally, the original and flipped gray and white matter segments for each participant were registered to the newly created symmetric DARTEL template in order to align the brains of all the participants in a common space. Aiming to prevent volume changes as a consequence of the registration process, the gray and white matter segments were modulated, as suggested by Kurth et al. [20]

1.5. Data analysis

Once the modulated gray and white matter segments were warped into the symmetric DARTEL template, the Dice coefficient of the modulated original and flipped images (i.e., between left and right hemispheres) was calculated for each participant. The Dice coefficient was originally used in ecology to quantify the degree of association between different species [18], and it has also been employed in MRI studies to validate the quality of image segmentation [21]. The Dice coefficient was obtained according to the following formula:

$$\frac{2|i1 \cap i2|}{|i1_{int}| + |i2_{int}|},$$

in which, in our case, *i1* and *i2* are the images containing the original and flipped gray or white matter segments, respectively, and $i1_{int}$ and $i2_{int}$ are the total intensity values for each image. The intersection for each voxel was considered as the minimum intensity value between the two images. This was later multiplied by 2 and divided by the sum of the total intensities of the two images. The 'nii_dice.m' MATLAB script (https://github.com/neurolabusc) was used to automatically calculate the Dice coefficient. The resulting Dice score was used as a measure of global brain asymmetry. The Dice coefficient score ranges from 0 to 1, with higher values indicating a lower degree of asymmetry. A graphical representation of the Dice coefficient is depicted in Figure 1. In addition, the total volume of each hemisphere was computed for each participant. The left/right hemisphere volume ratio was then obtained by dividing the volume of the left hemisphere over the volume of the right hemisphere.

1.6. Statistical analysis

First, in order to be certain that the potential significant results from asymmetry analyses were not due to uneven volume loss between hemispheres [8], the left/right hemisphere volume ratio was compared between patients with schizophrenia and healthy control participants by means of an ANCOVA, with diagnostic group (patients or controls) as the between-subject factor, and verbal IQ score and education level as covariates. Second, a comparison of global gray and white matter asymmetry between patients with schizophrenia and healthy controls was made by means of an ANCOVA conducted for the Dice scores, with diagnostic group as the between-subject factor, and verbal IQ score and education level as covariates. After that, aiming to determine which clinical variables were associated with global gray or white matter asymmetry, a backward elimination regression analysis was performed on the gray and white matter Dice scores of the patients. The following clinical variables were tested and included as predictors in the analysis: hallucinations, delusions, SANS-4, depression, and anxiety. Furthermore, the following sociodemographic variables were also included as predictors in the analysis to account for potential confounding factors: age, sex, education, verbal IQ, and years of duration of the illness. Afterwards, the schizophrenia sample was divided in accordance with the variables that were significantly associated with the gray or white matter Dice score in the backward elimination analysis previously performed. These subsamples of patients with or without the symptom of interest were also compared to the healthy control participants with further ANCOVA conducted for the Dice scores, with diagnostic group as the between-subject factor. Verbal IQ score and/or education level were included as covariates when they were significantly different between the corresponding subsample of patients and the healthy controls, since they could have an impact on gray and white matter [22]. Clinical variables were normalized by square root normalization when required.

2. Results

2.1. Group comparison in cerebral asymmetry

Left/right hemisphere gray matter volume ratio was not different between patients with schizophrenia and healthy control participants ($p = .418$). The ANCOVA controlling for verbal IQ and education level showed that patients with schizophrenia had more asymmetric global gray matter than the healthy

controls [$F(1, 46) = 4.361$, $p = .042$, $\eta^2 = .069$] (Table 1 and Figure 2). No differences were seen when analyzing global white matter asymmetry ($p = .874$).

2.2. Cerebral asymmetry and clinical symptoms in schizophrenia

Backward elimination regression analyses were carried out in order to assess which clinical variables were associated with gray or white matter global asymmetry. Only anxiety ($\beta = .618$, $p = .020$) was found to be significantly positively correlated with the gray matter Dice score, while SANS-4 ($\beta = -.655$, $p = .015$) was significantly negatively correlated with the gray matter Dice score. No associations between global gray matter asymmetry and hallucinations, delusions, depression or the sociodemographic variables were found either. In addition, none of the clinical and sociodemographic variables analyzed were associated with the white matter Dice score. Given the significant association found between SANS-4 and gray matter global asymmetry, another backward elimination regression analysis on the gray matter Dice scores was carried out to determine which of the negative symptoms were responsible for this association. In this case, each of the four negative symptoms, as well as anxiety, were included as predictors. This analysis yielded a model ($F(2, 21) = 6.65$, $p = .006$; $R^2 = 0.39$) in which avolition was significantly negatively associated with the gray matter Dice score ($\beta = -.735$, $p = .002$) while the previous positive association between anxiety and the gray matter Dice score was maintained ($\beta = .619$, $p = .008$). No significant associations arose for the rest of the negative symptoms. Further analyses separating by patients presenting those symptoms or not were carried out. Patients were separated into low anxiety (n = 12) or high anxiety (n = 12) according to the median score (M = 5.5, IQR = 8.5) of all the patients in the Hamilton Anxiety Rating Scale. In the case of avolition, patients were considered not to have avolition if they scored 0 points in the avolition item (n = 17); otherwise they were considered to have avolition (n = 7). The analyses conducted on anxiety revealed that patients with low scores of anxiety were more asymmetric than the healthy controls, with a trend towards significance ($p = .059$, $\eta^2 = .087$), whereas there were no differences in symmetry between patients with high scores of anxiety and controls ($p = .171$, $\eta^2 = .051$). Conversely, analyses separating by patients with or without avolition showed that patients with avolition were significantly more asymmetric than the healthy controls ($p = .001$, $\eta^2 = .296$), whereas patients without avolition did not differ from healthy controls in global asymmetry ($p = .226$, $\eta^2 = .026$). These results are displayed in Table 1 and depicted in Figure 2.

STUDY II

1. Methods

1.1. Participants

A total of 759 participants, 355 patients with schizophrenia and 404 healthy controls, were included in Study II. Data from these participants were obtained from four open-access databases available for download from schizconnect.org and openfmri.org. Specifically, the data used were obtained from the 'NU Schizophrenia Data and Software Tool (NUSDAST)', the 'Mind Clinical Imaging Consortium (MCIC)' [23], and the 'Center of Biomedical Research Excellence (COBRE)' [24] databases available at schizconnect.org, as well as from the database with accession number 'ds000115' [25] at openfmri.org. High-resolution T1 images were also available from these databases. The age range of the group of patients with schizophrenia went from 16 to 65, whereas in the group of healthy control participants went from 12 to 67. Age and sex distribution were compared between patients with schizophrenia and healthy control participants by means of a T-test for independent samples and a chi-square test, respectively. These analyses showed that patients with schizophrenia were significantly older (patients = 34.68 ± 12.46 years old; controls = 31.48 ± 13.08 years old, $p < .001$) and included a significantly larger proportion of males (patients = 73% of males; controls = 59% of males, $p < .001$). Neither verbal IQ nor education could be compared between patients and controls as their assessment was different between studies and it was not possible to establish an equivalence of the scores.

1.2. Clinical variables

Of the two variables that were significantly associated with gray matter asymmetry in Study I, avolition and anxiety, only avolition scores were available for all the participants. Avolition was assessed by means of either the item 17 ('Global rating of avolition-apathy') of the Scale for the Assessment of Negative Symptoms (SANS) or the item G13 ('Disturbance of volition') of the Positive and Negative Syndrome Scale (PANSS). Participants were divided into three groups according to their avolition scores. Hence, those participants scoring 0 (absent) or 1 (questionable/minimal) were considered as part of the group of 'No avolition' (n = 142); those scoring 2 (mild) or 3 (moderate) were considered as part of the 'low avolition' group (n = 156); and finally, those participants scoring from 4 (marked/moderate severe)

to 5 (severe) or 6 (extreme, only in the PANSS) were considered as part of the 'high avolition' group (n = 57).

1.3. Data processing and analysis

All the neuroimaging data were processed and analyzed, independently for each database, exactly as described in sections 1.4 and 1.5 of Study I.

1.4. Statistical analysis

First, in order to ascertain that the potential significant results from asymmetry analyses were not due to uneven volume loss between hemispheres, the left/right hemisphere volume ratio was compared between patients with schizophrenia and healthy control participants by means of an ANCOVA, with diagnostic group (patients or controls) as the between-subject factor, and age, sex, and database number as covariates. Second, a comparison of global gray and white matter asymmetry between patients with schizophrenia and healthy controls was performed by means of an ANCOVA conducted for the Dice scores, with diagnostic group as the between-subject factor, and age, sex, and database number as covariates. After that, another ANCOVA was performed among the patients with schizophrenia, with avolition (three categories, see above) as the between-subject factor and the gray and white matter Dice scores as the dependent variable. Age and database number were included as covariates. Sex was not included as covariate since its distribution was not different among the three avolition categories. Overall, age and sex were included as covariates, when they differed between groups, because they could have an impact on brain asymmetry [26]. Database number was always included as a covariate to control for potential differences due to the scanner used to acquire structural images.

2. Results

2.1. Group comparison in cerebral asymmetry

Left/right hemisphere gray matter volume ratio was not different between patients with schizophrenia and healthy control participants ($p = .336$). The ANCOVA controlling for age, sex, and database number

confirmed results seen in Study I, i.e., patients with schizophrenia had more asymmetric global gray matter than the healthy controls [$F(1, 754) = 13.790$, $p < .001$, $\eta^2 = .012$] (Figure 3). This difference was not seen when analyzing global white matter asymmetry ($p = .584$). Interestingly, age ($p < .001$, $\eta^2 = .235$) and sex ($p < .001$, $\eta^2 = .063$) were also importantly associated with global gray matter asymmetry. A graphical representation of the asymmetry differences between patients with schizophrenia and healthy control participants is depicted in Figure 4.

2.2. Cerebral asymmetry and avolition in schizophrenia

Patients were separated into three categories according to their score in avolition. An ANCOVA controlling for age and number of study showed an association between avolition and global gray matter asymmetry [$F(2, 350) = 4.001$, $p = .019$, $\eta^2 = .016$. A post-hoc analysis revealed that the 'high avolition' group had significantly more global gray matter asymmetry than the 'no avolition' group ($p = .018$) and the 'low avolition' group ($p = .050$). On the other hand, no differences were seen between the 'low avolition' and the 'no avolition' groups (Figure 3). All the avolition groups, however, had significantly more global gray matter asymmetry than the group of healthy controls ('no avolition', $p = .004$; 'low avolition', $p = .003$; 'high avolition', $p < .001$). As was expected from the results of Study I, there was no association between avolition and global white matter asymmetry.

Discussion

This is the first study to compare global brain asymmetry, by means of the Dice coefficient, of patients with schizophrenia and healthy control participants, and also the first to look for potential associations between global brain asymmetry and clinical symptomatology in patients with schizophrenia. Our main findings show that patients with schizophrenia have more globally asymmetric gray matter than healthy control participants. With respect to clinical symptoms in patients with schizophrenia, anxiety and avolition were associated with global gray matter asymmetry, while other symptoms, including hallucinations, were not.

Global gray matter was found to be more asymmetric in patients with schizophrenia than in healthy controls, whereas no differences were seen for global white matter asymmetry. This is in contrast to studies assessing specific local brain asymmetries, with most of them reporting that patients with schizophrenia had reduced structural asymmetry in certain brain regions when compared with the general population (for a review, see Oertel-Knöchel and Linden [7]). However, we have to consider global cerebral asymmetry and regional cerebral asymmetry as different things. Indeed, while lateralization of some brain functions may provide an evolutionary advantage [2] and the lack of lateralization could be an indicator of an abnormal development of the brain, this assumption should not be generalized when considering the brain as a whole. In this sense, there are a number of reasons to consider that, aside from the normal lateralization process, the brain is expected to develop symmetrically. One of these is that most brain structures are found symmetrically in the two hemispheres. In addition, since the brain is largely devoted to communicating, through motor and sensory systems, with the body, which is almost perfectly symmetric in the left-right plane, it is reasonable to think that preserving this symmetry in the brain would have an intrinsic evolutionary advantage. Hence, a high degree of global cerebral asymmetry may also be an indicator of abnormal brain development. This supposition could be linked with the concept of developmental stability. Indeed, Euler et al. [27] found that patients with schizophrenia had lower DS than healthy controls, i.e., had presumably more perturbations during development. The degree of DS was assessed by means of a measure of body FA, and their results provide additional evidence for the link between schizophrenia and developmental perturbations. Therefore, quantifying global gray matter asymmetry, by means of the Dice coefficient, could be a good measure of FA and a reflection of early neurodevelopmental problems. Compared with body FA measures, quantifying global gray matter asymmetry has the advantage of being a more direct and objective measure of neurodevelopment, and one that is less exposed to physical disturbances, making it potentially more reliable. In addition, this finding cannot be explained by a larger loss of volume in the left hemisphere as compared with the right hemisphere, as suggested in the meta-analysis of Vita et al. [8], since the left/right hemisphere volume ratio was not different between patients with schizophrenia and healthy control participants.

A graphical representation of gray matter asymmetry differences between patients with schizophrenia and healthy control participants allowed us to verify that the distribution of these differences was broad and present all over the brain, thus confirming the relevance of considering global brain asymmetry. As expected, larger regions of the brain were more symmetric in healthy control participants than in patients with schizophrenia, although the latter showed some regions in which they were more symmetric. Particularly, it is important to emphasize that the prefrontal region, the thalamus, and the insula were markedly more symmetric in healthy control participants than in patients with schizophrenia. These regions have been deemed as being important in the psychopathology of schizophrenia [28-30]. Conversely, the caudate nucleus was more symmetric in patients with schizophrenia than in healthy control participants. In this sense, abnormalities related to schizophrenia in the functional lateralization of the caudate nucleus have been already reported [31].

We also explored the potential associations between global gray or white matter asymmetry and clinical symptoms. No such association arose for delusions, depression, or, most importantly, hallucinations. Although some previous studies found a relationship between asymmetry or lateralization and hallucinations [10-12], this relationship was not found for global gray or white matter asymmetry in the present study. On the other hand, we found global gray matter asymmetry to be negatively associated with anxiety and positively associated with negative symptomatology. Further analyses showed that the specific negative symptom responsible for this association was avolition, which some authors have proposed as the core of the negative symptoms [32]. There were no significant global gray matter asymmetry differences between patients with schizophrenia scoring high on anxiety and healthy control participants, whereas patients scoring low on anxiety had more asymmetric global gray matter than controls at a trend level of significance. Conversely, patients with schizophrenia presenting avolition had significantly more asymmetric global gray matter than healthy controls, whereas patients without avolition were as symmetric as controls. Although in Study II we did not have anxiety data, we tried to replicate the association between avolition and global gray matter asymmetry. The large sample used in this study permitted us to split the sample of patients into three categories according to their avolition score. The analyses showed that patients with the highest level of avolition had significantly more asymmetric global gray matter than those without symptoms of avolition or with low avolition

symptoms. Taken together, these results suggest a strong relationship between avolition and gray matter asymmetry. In addition, results also suggest that anxiety and avolition are opposite in terms of gray matter asymmetry, although this has yet to be replicated in larger samples. Attending to the characterization of both clinical symptoms, this may not be surprising. While anxiety implies anticipatory changes in response to an uncertain potential future threat [33], avolition is defined as a lack of motivation and a decrease in goal-directed behaviors [32]. That is, anxiety can be seen as an extreme worry for the future, whereas avolition indicates a lack of interest in the future, thus representing the opposite ends of a continuum. Moreover, avolition has been associated with reduced prefrontal activation [34] and bilateral frontal volume reduction [35], while anxiety has been associated with prefrontal hyperactivation [36]. Our results in global gray matter asymmetry may be a reflection of the underlying brain activation. In this case, patients with anxiety symptoms may have an abnormal increase in the gray matter symmetry of the prefrontal cortex, which would presumably represent an excess of prefrontal functioning. This hypothetical gray matter symmetry increase in the prefrontal cortex would also explain why patients with anxiety symptoms show similar gray matter Dice coefficients as healthy control participants. Consistent with our findings, other studies have found anxiety and depression, which might be related to avolition, to have opposite effects on brain activation during an object perception task [14]. Overall, these results suggest that anxiety and avolition may be partly explained by differences in global gray matter asymmetry, and they underline the importance of considering not only the negative but also the affective symptoms in the pathology of schizophrenia [37, 38].

There are some important open questions that future studies may address. First of all, it would be interesting to replicate these analyses in samples of first-episode schizophrenia patients or patients in high risk of psychosis. Such studies would clarify whether asymmetry differences between patients and controls are present before the illness onset, therefore strengthening the neurodevelopmental hypothesis, or whether these differences appear later and are due to the illness itself. Secondly, age and sex had important effects in all the analyses performed on gray matter asymmetry in Study II. Although the effects of age and sex on brain asymmetry have been previously assessed [26], a deeper analysis of these variables with the measure based on the Dice coefficient presented here might be of interest for future studies. Moreover, it has to be taken into account that brain development can stretch on until

the twenties and that the changes in gray and white matter are not linear [39], overall representing a major challenge that may be faced by studying brain asymmetry in different age groups.

Finally, there were some limitations that should be mentioned. First, information regarding verbal IQ and education level could not be analyzed in Study II. Moreover, scores of anxiety symptoms were not available for the participants of Study II, making it impossible to replicate results on anxiety from Study I and leaving an unresolved question that future studies may also address. Lastly, since no information was available regarding psychiatric medication of the participants, its potential effects on gray and white matter could not be evaluated.

In conclusion, we have used the Dice coefficient as a measure of global cerebral asymmetry for the first time. We showed that patients with schizophrenia have more globally asymmetric gray matter than controls. Findings from the present study suggest that global gray matter asymmetry could be a useful measure of fluctuating asymmetry and a tool to easily detect possible neurodevelopmental abnormalities.

Acknowledgments

This work was supported by a Miguel Servet contract (CP09/00292) and grant PI10/02479 from the Instituto de Salud Carlos III – Subdirección General de Evaluación y Fomento de la Investigación Sanitaria – co-funded by the European Regional Development Fund (ERDF), both to GB; grant PRRMAB-A2011-19251 from the Sardinia Region to SS, and contract PTA2011-4983-I from the Ministerio de Ciencia e Innovación, Spain to CS-O.

We thank both openfmri.org and schizconnect.org projects for hosting the data and for making them publicly available. Data collection and sharing for the schizconnect.org project was funded by NIMH cooperative agreement 1U01 MH097435. Part of these data were downloaded from the COllaborative Informatics and Neuroimaging Suite Data Exchange tool (COINS; http://coins.mrn.org/dx) and this data collection was performed at the Mind Research Network, and funded by a Center of Biomedical Research Excellence (COBRE) grant 5P20RR021938/P20GM103472 from the NIH to Dr. Vince Calhoun.

Other parts of these data were obtained from the NU Schizophrenia Data and Software Tool (NUSDAST) database (http://central.xnat.org/REST/projects/NUDataSharing); data collection and sharing for this project was funded by NIMH grant 1R01 MH084803. The last part of the data from schizconnect.org used in this work was collected and shared by [University of Iowa, University of Minnesota, University of New Mexico, Massachusetts General Hospital] the Mind Research Network supported by the Department of Energy under Award Number DE-FG02-08ER64581.

Declaration of interest

None of the authors have potential conflicts of interest.

References

1 . CLARKE GM. The genetic basis of developmental stability. IV. Individual and population asymmetry parameters. Heredity 1998;**80**:553-561.

2. CORBALLIS MC. The evolution and genetics of cerebral asymmetry. Philos Trans R Soc Lond B Biol Sci 2009;**364**:867-879.

3. SENIOR C, MARTIN R, THOMAS G, TOPAKAS A, WEST M, YEATS RM. Developmental stability and leadership effectiveness. Leadership Quart 2012;**23**:281-291.

4. VERNOOIJ MW, SMITS M, WIELOPOLSKI PA, HOUSTON GC, KRESTIN GP, VAN DER LUGT A. Fiber density asymmetry of the arcuate fasciculus in relation to functional hemispheric language lateralization in both right- and left-handed healthy subjects: a combined fMRI and DTI study. Neuroimage 2007;**35**:1064-1076.

5. BIDUŁA SP, KRÓLICZAK G. Structural asymmetry of the insula is linked to the lateralization of gesture and language. Eur J Neurosci 2015;**41**:1438-1447.

6. CROW TJ, BALL J, BLOOM SR et al. Schizophrenia as an anomaly of development of cerebral asymmetry. A postmortem study and a proposal concerning the genetic basis of the disease. Arch Gen Psychiatry 1989;**46**:1145-1150.

7. OERTEL-KNÖCHEL V, LINDEN DE. Cerebral asymmetry in schizophrenia. Neuroscientist 2011;17:456-467.

8. VITA A, DE PERI L, DESTE G, SACCHETTI E. Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. Transl Psychiatry

2012;2:e190.

9. PARK HJ, WESTIN CF, KUBICKI M et al. White matter hemisphere asymmetries in healthy subjects and in schizophrenia: a diffusion tensor MRI study. Neuroimage 2004;**23**:213-223.

10. OCKLENBURG S, WESTERHAUSEN R, HIRNSTEIN M, HUGDAHL K. Auditory hallucinations and reduced language lateralization in schizophrenia: a meta-analysis of dichotic listening studies. J Int Neuropsychol Soc 2013;**19**:410-418.

11. OERTEL V, KNÖCHEL C, ROTARSKA-JAGIELA A et al. Reduced laterality as a trait marker of schizophrenia--evidence from structural and functional neuroimaging. J Neurosci 2010;**30**:2289-2299.

12. CACHIA A, AMAD A, BRUNELIN J et al. Deviations in cortex sulcation associated with visual hallucinations in schizophrenia. Mol Psychiatry 2015;**20**:1101-1107.

13. PATEL R, JAYATILLEKE N, BROADBENT M et al. Negative symptoms in schizophrenia: a study in a large clinical sample of patients using a novel automated method. BMJ Open 2015;**5**:e007619.

14. STEPHAN-OTTO C, SIDDI S, CUEVAS ESTEBAN J et al. Neural activity during object perception in schizophrenia patients is associated with illness duration and affective symptoms. Schizophr Res 2016;**175**:27-34.

15. BRÉBION G, STEPHAN-OTTO C, HUERTA-RAMOS E et al. Visual encoding impairment in patients with schizophrenia: contribution of reduced working memory span, decreased processing speed, and affective symptoms. Neuropsychology 2015;**29**:17-24.

16. CROW TJ. Brain changes and negative symptoms in schizophrenia. Psychopathology 1995;**28**:18-21.

17. BRUDER GE, STEWART JW, HELLERSTEIN D, ALVARENGA JE, ALSCHULER D, MCGRATH PJ. Abnormal functional brain asymmetry in depression: evidence of biologic commonality between major depression and dysthymia. Psychiatry Res 2012;**196**:250-254.

18. DICE LR. Measures of the Amount of Ecologic Association Between Species. Ecology 1945;**26**:297-302.

19. GOMAR JJ, ORTIZ-GIL J, MCKENNA PJ et al. Validation of the Word Accentuation Test (TAP) as a means of estimating premorbid IQ in Spanish speakers. Schizophr Res 2011;**128**:175-176.

20. KURTH F, GASER C, LUDERS E. A 12-step user guide for analyzing voxel-wise gray matter asymmetries in statistical parametric mapping (SPM). Nat Protoc 2015;**10**:293-304.

21. ZOU KH, WARFIELD SK, BHARATHA A et al. Statistical validation of image segmentation quality based on a spatial overlap index. Acad Radiol 2004;**11**:178-189.

22. NARR KL, WOODS RP, THOMPSON PM et al. Relationships between IQ and regional cortical gray matter thickness in healthy adults. Cereb Cortex 2007;**17**:2163-2171.

23. GOLLUB RL, SHOEMAKER JM, KING MD et al. The MCIC collection: a shared repository of multi-modal, multi-site brain image data from a clinical investigation of schizophrenia. Neuroinformatics 2013;**11**:367-388.

24. ÇETIN MS, CHRISTENSEN F, ABBOTT CC et al. Thalamus and posterior temporal lobe show greater inter-network connectivity at rest and across sensory paradigms in schizophrenia. Neuroimage 2014;**97**:117-126.

25. REPOVS G, CSERNANSKY JG, BARCH DM. Brain network connectivity in individuals with schizophrenia and their siblings. Biol Psychiatry 2011;**69**:967-973.

26. KOVALEV VA, KRUGGEL F, VON CRAMON DY. Gender and age effects in structural brain asymmetry as measured by MRI texture analysis. Neuroimage 2003;**19**:895-905.

27. EULER M, THOMA RJ, GANGESTAD SW, CAÑIVE JM, YEO RA. The impact of developmental instability on Voxel-Based Morphometry analyses of neuroanatomical abnormalities in schizophrenia. Schizophr Res 2009;**115**:1-7.

28. OWENS SF, PICCHIONI MM, ETTINGER U et al. Prefrontal deviations in function but not volume are putative endophenotypes for schizophrenia. Brain 2012;**135**:2231-2244.

29. CSERNANSKY JG, SCHINDLER MK, SPLINTER NR, et al. Abnormalities of thalamic volume and shape in schizophrenia. Am J Psychiatry 2004;**161**:896-902.

30. WYLIE KP, TREGELLAS JR. The role of the insula in schizophrenia. Schizophr Res 2010;**123**:93-104.

31. MUELLER S, WANG D, PAN R, HOLT DJ, LIU H. Abnormalities in hemispheric specialization of caudate nucleus connectivity in schizophrenia. JAMA Psychiatry 2015;**72**:552-560.

32. FOUSSIAS G, REMINGTON G. Negative symptoms in schizophrenia: avolition and Occam's razor. Schizophr Bull 2010;**36**:359-369.

33. GRUPE DW, NITSCHKE JB. Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. Nat Rev Neurosci 2013;**14**:488-501.

34. CHUNG YS, BARCH DM. Frontal-striatum dysfunction during reward processing: Relationships to amotivation in schizophrenia. J Abnorm Psychol 2016;**125**:453-469.

35. ROTH RM, FLASHMAN LA, SAYKIN AJ, MCALLISTER TW, VIDAVER R. Apathy in schizophrenia:

reduced frontal lobe volume and neuropsychological deficits. Am J Psychiatry 2004;**161**:157-159.

36. MONK CS, NELSON EE, MCCLURE EB et al. Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. Am J Psychiatry 2006;**163**:1091-1097.

37. LYSAKER PH, SALYERS MP. Anxiety symptoms in schizophrenia spectrum disorders: associations with social function, positive and negative symptoms, hope and trauma history. Acta Psychiatr Scand 2007;**116**:290-298.

38. HARTLEY S, BARROWCLOUGH C, HADDOCK G. Anxiety and depression in psychosis: a systematic review of associations with positive psychotic symptoms. Acta Psychiatr Scand 2013;**128**:327-346.

39. TOGA AW, THOMPSON PM, SOWELL ER. Mapping brain maturation. Trends Neurosci 2006;**29**:148-159.

Table 1. Global gray matter comparison between patients and controls from Study I.

ANCOVA analyses of the Dice coefficient scores between patients with schizophrenia and healthy controls from Study I. Higher Dice scores indicate a lower degree of asymmetry. Verbal IQ and/or education level were included as covariates when they were significantly different between the corresponding subsample of patients and the healthy controls. Observed mean (SD) values are reported.

	Patients with schizophrenia		Healthy control participants (n=26)		ANCOVA			
	Mean	SD	Mean	SD	F test	df	p	η_p^2
GENERAL								
All patients (n=24)	0.8196	0.010	0.8263	0.008	4.36	1, 46	**.042**	.07
ANXIETY								
Patients with anxiety (n=12)	0.8221	0.011	0.8263	0.008	1.95	1, 36	.171	.05
Patients without anxiety (n=12)	0.8172	0.01	0.8263	0.008	3.81	1, 35	**.059**	.09
AVOLITION								
Patients with avolition (n=7)	0.8143	0.008	0.8263	0.008	13.03	1, 31	**.001**	.30
Patients without avolition (n=17)	0.8218	0.011	0.8263	0.008	1.52	1, 39	.226	.03

Figure 1. A comparison is shown of A) a patient with one of the lowest Dice scores (i.e., one of the most asymmetric participants, with a Dice score of 0.7902), and B) a healthy control with one of the highest Dice scores (i.e., one of the most symmetric participants, with a Dice score of 0.8435). Multiple axial slices, as well as a 3D view of the brain, are depicted. Both participants are 23 year-old females that were selected from the same database. Therefore, differences are not due to age, sex, or study. Only those regions with a Dice score greater than 0.5 are showed. It can be visually noted that the participant with the highest Dice score (B) has a larger proportion of her brain colored than the participant with the lowest Dice score (A). See section 1.5 of Study I for further details.

Figure 2. Comparison of the Dice coefficient scores for global gray matter, from Study I, between healthy control participants ('HC', n = 26) and all the patients with schizophrenia ('SCH', n = 24) (left side of the chart), patients with avolition ('SCH / Avol +', n = 7) and without avolition ('SCH / Avol -', n = 17) (middle), and patients without anxiety ('SCH / Anx -', n = 12) and with anxiety ('SCH / Anx +', n = 12) (right). Differences in global gray matter asymmetry between healthy control participants and all the patients were significant (p = .042), as were differences between patients with avolition and healthy control participants (p = .001). The difference between the patients without anxiety and healthy control participants showed a trend towards significance (p = .059). On the other hand, patients without avolition and patients with anxiety did not have more asymmetric global gray matter than healthy control participants. The crosses represent all the individual observations, for each category, of the Dice scores for global gray matter asymmetry. The circles represent the estimated mean of the Dice scores for global gray matter asymmetry after covarying for verbal IQ and education, when necessary (see section 1.6 of Study I for more information). Error bars represent the standard error of the mean. See Table 1 and sections 2.1 and 2.2 of Study I in the text for further details.

Figure 3. Comparison of the Dice coefficient scores of global gray matter, from Study II, between healthy control participants ('HC', n = 404) and all the patients with schizophrenia ('SCH', n = 355) (left side of the chart), as well as between patients without avolition ('SCH / No avol', n = 142), patients with low avolition ('SCH / Low avol', n = 156), and patients with high avolition ('SCH / High avol', n = 57) (right). Differences in global gray matter asymmetry between healthy control participants and all the patients were significant ($p < .001$). Patients with high avolition had significantly more asymmetric global gray matter than patients without avolition ($p = .018$) and patients with low avolition ($p = .050$). All the avolition groups had significantly more global gray matter asymmetry than the group of healthy controls. The circles represent the estimated means of the Dice score for global gray matter asymmetry after covarying for age, sex, and database number, when necessary (see section 1.4 of Study II for more information). Error bars represent the standard error of the mean. See sections 2.1 and 2.2 of Study II in the text for further details.

Figure 4. Graphical representation of asymmetry differences between patients with schizophrenia and healthy control participants. A) multiple axial slices are depicted showing regions where patients with schizophrenia were more symmetric than healthy control participants (top) and where controls were more symmetric than patients (bottom). These differences were also depicted in B) a 3D view, and C) a coronal section, in which the brain on the left side shows where patients were more symmetric than controls, and the brain on the right side shows where controls were more symmetric than patients. Composite group images for both patients with schizophrenia and healthy control participants were created from the individual Dice score images. These composite images were subtracted to each other to generate the images depicting inter-group asymmetry differences. All participants from Study I and Study II were included. For illustration purposes, we show only those regions with asymmetry differences larger than 25% of the maximum difference.

Figure 1.

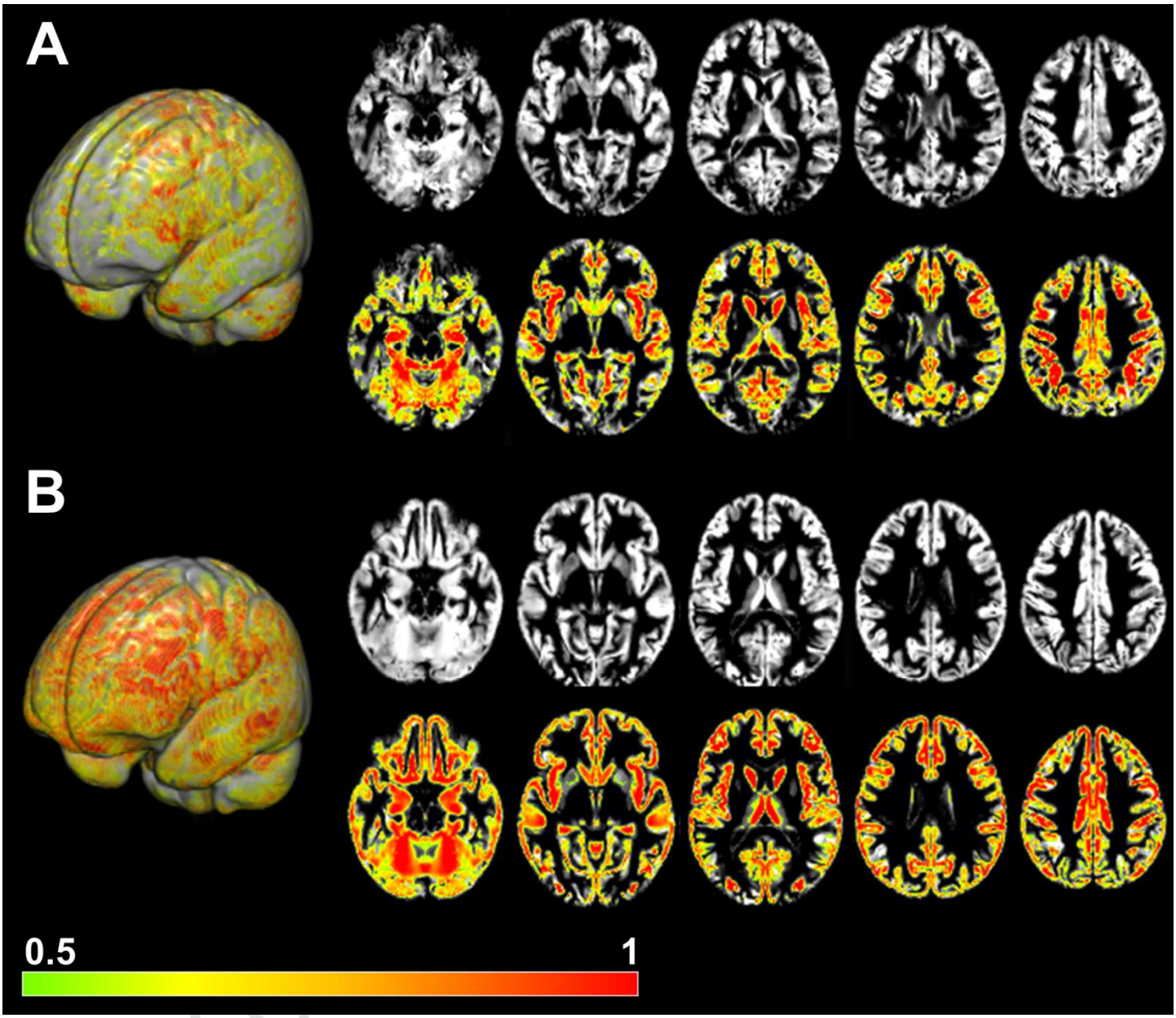

Figure 2.

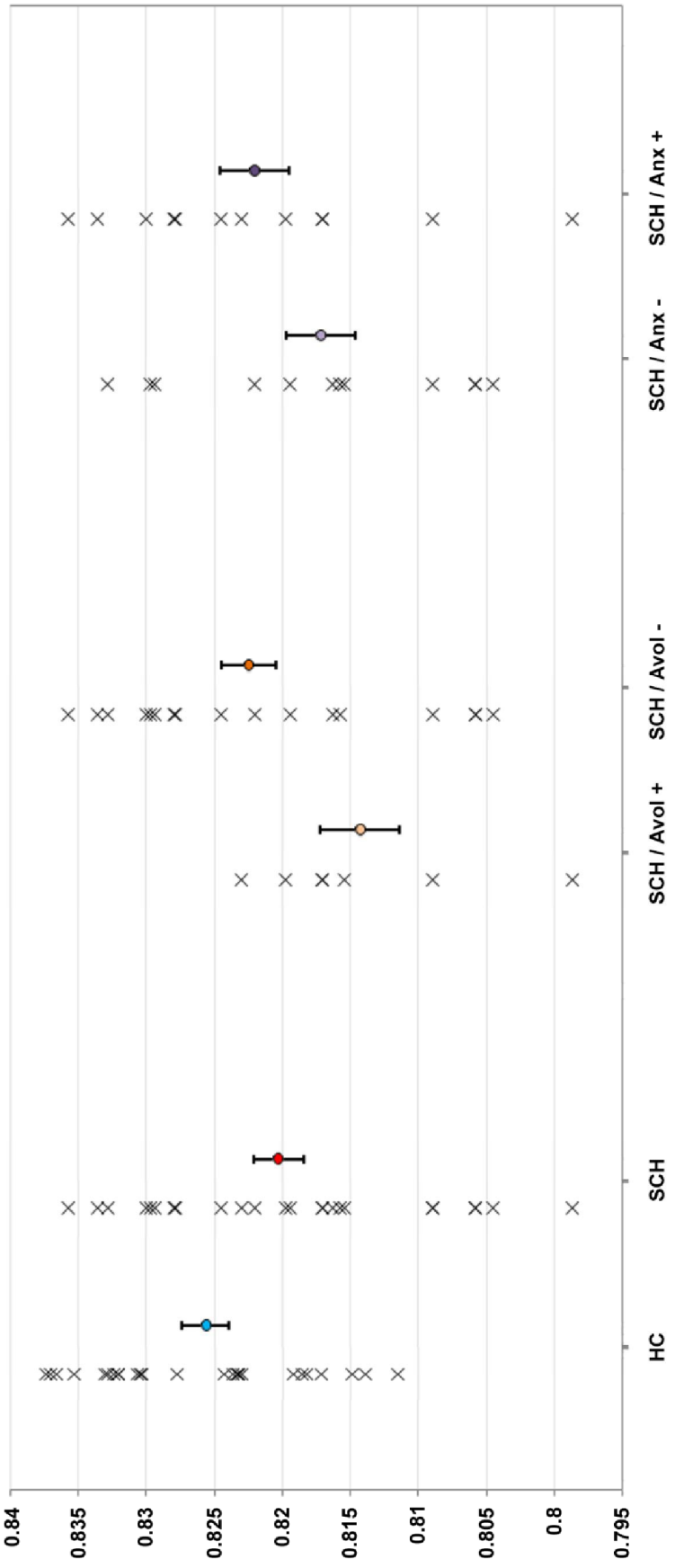
0.84
0.835
0.83
0.825
0.82
0.815
0.81
0.805
0.8
0.795
HC
SCH
SCH / Avol +
SCH / Avol -
SCH / Anx -
SCH / Anx +

Figure 3.

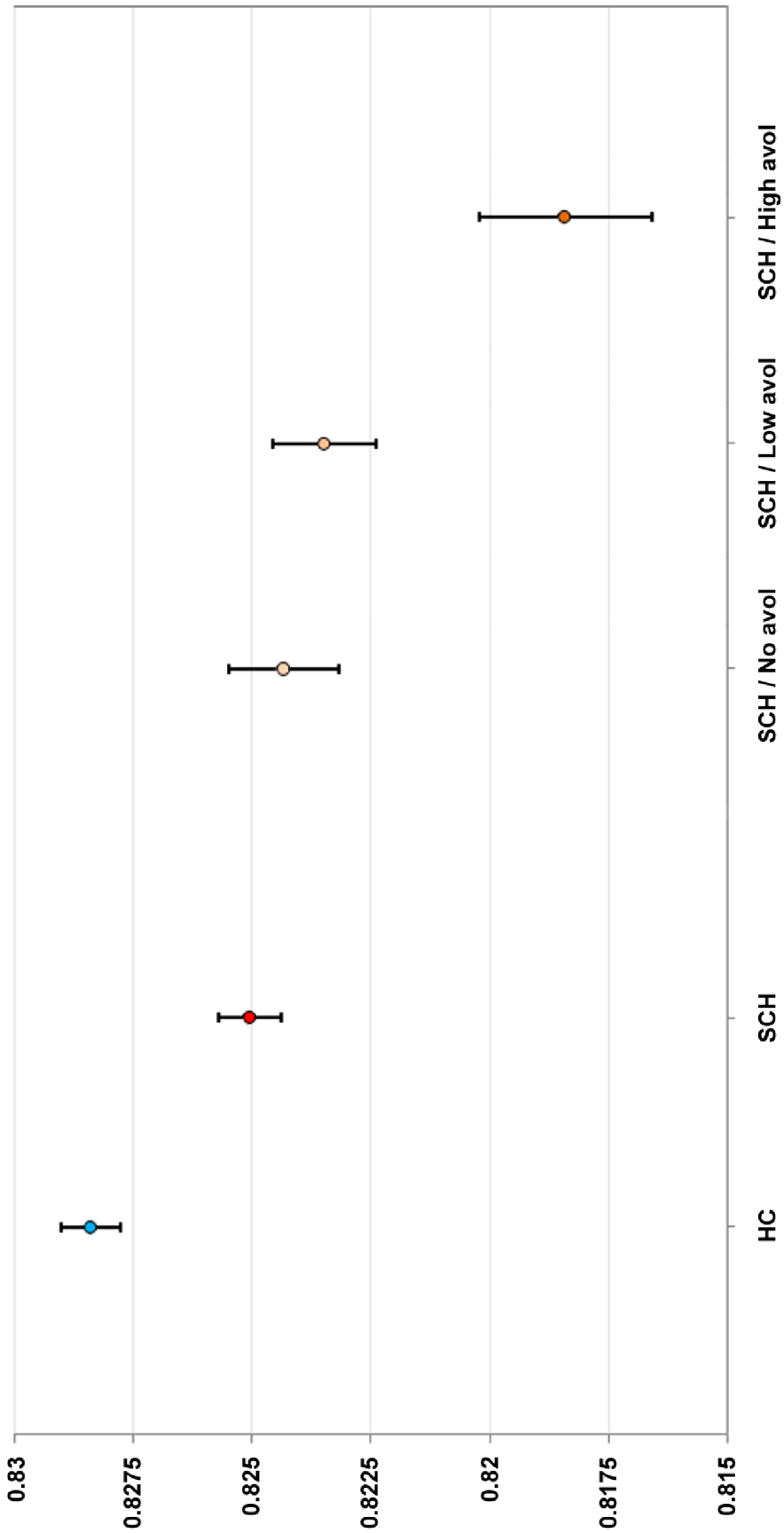
0.83
0.8275
0.825
0.8225
0.82
0.8175
0.815
HC
SCH
SCH / No avol
SCH / Low avol
SCH / High avol

Figure 4.