Published in final edited form as:

Psychol Med. 2018 January ; 48(1): 82–94. doi:10.1017/S0033291717001283.

Left medial orbitofrontal cortical thinning is associated with negative symptom severity in schizophrenia: a meta-analysis by the ENIGMA-Schizophrenia consortium

A full list of authors and affiliations appears at the end of the article.

Abstract

Our understanding of the complex relationship between schizophrenia symptomatology and etiological factors can be improved by studying brain-based correlates of schizophrenia. Previous research has shown that impairments in executive functioning, which have been associated with prefrontal brain areas (particularly in the medial orbitofrontal cortex (MOFC)), give rise to negative symptoms. Here we tested the hypothesis that MOFC thickness is associated with negative symptom severity. This study included 1 985 individuals with schizophrenia from seventeen research groups around the world contributing to the ENIGMA Schizophrenia Working Group. MOFC thickness values were obtained from T1-weighted structural brain scans using FreeSurfer. A meta-analysis was conducted over effect sizes from a model predicting mean left or right MOFC thickness by negative symptom score (harmonized SANS or PANSS scores).

Secondary models were run to investigate the effects of antipsychotic medication, duration of illness, overall illness severity, and handedness. Meta-analytical results showed that left MOFC thickness was significantly associated with negative symptom severity ($\beta_{\text{std}} = -0.075$; $p = 0.019$) after accounting for age, gender and site. This effect remained significant ($p = 0.036$) in a model including overall illness severity. Covarying for duration of illness, antipsychotic medication or handedness weakened the association of negative symptoms with left MOFC thickness. Using an unusually large cohort and a meta-analytical approach, our findings point towards a link between prefrontal thinning and negative symptom severity in schizophrenia. This finding provides further

Corresponding author: Stefan Ehrlich, M.D; Translational Developmental Neuroscience Section, Department of Child and Adolescent Psychiatry, Faculty of Medicine, Technische Universität Dresden, Fetscherstr. 74, 01307 Dresden, Germany, Phone: +49 (0)351 458-2244, Fax: +49 (0)351 458-5754, stefan.ehrlich@tu-dresden.de.

¹⁵Collaborators

Members of the Karolinska Schizophrenia Project consortium (KaSP): Farde L., Karolinska Institutet, Department of Clinical Neuroscience, Centre for Psychiatry Research, Stockholm, Sweden; Flyckt L., Karolinska Institutet, Department of Clinical Neuroscience, Centre for Psychiatry Research, Stockholm, Sweden; Engberg G., Karolinska Institutet, Department of Physiology and Pharmacology, Stockholm, Sweden; Erhardt S., Karolinska Institutet, Department of Physiology and Pharmacology, Stockholm, Sweden; Fatouros-Bergman H., Karolinska Institutet, Department of Clinical Neuroscience, Centre for Psychiatry Research, Stockholm, Sweden; Cervenka S., Karolinska Institutet, Department of Clinical Neuroscience, Centre for Psychiatry Research, Stockholm, Sweden; Schwieler L., Karolinska Institutet, Department of Physiology and Pharmacology, Stockholm, Sweden; Piehl F., Karolinska Institutet, Department of Clinical Neuroscience, Neuroimmunology Unit, Stockholm, Sweden; Agartz I., NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, University of Oslo, and Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway, and Department of Clinical Neuroscience, Karolinska Institutet, Centre for Psychiatry Research; Ikonen P., Karolinska Institutet, Department of Clinical Neuroscience, Centre for Psychiatry Research, Stockholm, Sweden; Collste K., Karolinska Institutet, Department of Clinical Neuroscience, Centre for Psychiatry Research, Stockholm, Sweden; Orhan F., Karolinska Institutet, Department of Physiology and Pharmacology, Stockholm, Sweden; Malmqvist A., Karolinska Institutet, Department of Physiology and Pharmacology, Stockholm, Sweden; Hedberg M., Karolinska Institutet, Department of Physiology and Pharmacology, Stockholm, Sweden.

Conflict of Interest

The authors of this manuscript have no conflicts of interest to disclose.

insight into the relationship between structural brain abnormalities and negative symptoms in schizophrenia.

Keywords

schizophrenia; negative symptoms; medial orbitofrontal cortex; cortical thickness; ENIGMA

INTRODUCTION

Although advances have been made in our understanding of the pathophysiology of schizophrenia, the heterogeneity of the disorder impedes the effectiveness of biological and clinical research. The large number of cognitive and clinical symptoms within the syndrome and their considerable variability across patients likely reflects the impact of various etiological factors.¹ Such variability makes it harder to achieve a comprehensive understanding underlying brain pathology. Large sample investigations of pathology associated with dimensions of behavior that can be measured quantitatively may advance our understanding of brain behavior relationships within as well as across diagnostic categories. Investigating distinct symptoms of the disorder as a continuous variable may reveal more specific and possibly causal neurobiological mechanisms in schizophrenia.

Negative symptoms are characterized by flat or blunted affect, inability to experience pleasure (anhedonia), poverty of speech, lack of motivation and interest (avolition/apathy) and lack of desire to form relationships.² Patients with predominantly negative symptoms have poor pre-morbid adjustment during childhood or early adolescence and a low employment rate during adulthood, achieve low educational attainment and exhibit considerable cognitive impairment.^{3–5}

Studies have shown widespread cortical thickness reductions across the brain in patients with schizophrenia compared to healthy controls with frontal and temporal regions being generally more affected than others areas.^{6–8} In line with prior work, Ehrlich et al.⁹ recently reported marked reductions of cortical thickness in patients with schizophrenia, which were also related to cognitive functioning. However, little is known about the link between cortical thickness and schizophrenia symptom severity.

The medial orbitofrontal cortex (MOFC), the most ventral division of prefrontal cortex, plays a major role in the processing of positive emotional or rewarding stimuli,^{10,11} which is impaired in schizophrenia.^{12,13} This region is crucial for representing subjective value.¹⁴ MOFC lesions in humans relate to deficits in reward-based learning, which can result in apathy and lack of affect.^{15–18} Functional and structural imaging studies in healthy populations report associations between MOFC activity (and thickness) and characteristics that are comparable to the negative symptoms observed in schizophrenia.^{19,20}

Several studies have assessed the brain-based correlates of negative symptoms in schizophrenia. Plailly et al.²¹ reported lower physiological activations (as measured by fMRI) in several brain regions – including the MOFC – during hedonic judgments of positive and negative stimuli (related to anhedonia) in individuals with schizophrenia

compared with healthy controls. Simon et al.²² showed that neural responses in the ventral striatum during a reward anticipation paradigm were negatively associated with apathy – a core negative symptom; no associations between ventral striatal responses and positive symptoms were observed. Importantly, they found lower connectivity between the ventral striatum and the MOFC in individuals with schizophrenia compared with controls. With respect to structural imaging, Venkatasubramanian et al.²³ found that lower left MOFC thickness was associated with higher negative symptom severity. Similar findings have been reported by Nenadic et al.,²⁴ providing further evidence for the involvement of medial prefrontal regions in negative symptoms; though some negative findings also exist.^{25,26}

Reasons for these inconsistencies may be two-fold. First, most studies conducted to date have had rather moderate sample sizes, investigating on average about a hundred patients. Second, moderating effects of confounders such as antipsychotic medication, illness severity, or duration of illness that may influence the association between thickness and negative symptoms have not been investigated extensively. Analyses of larger samples will increase power allowing to understand prior inconsistencies in findings as well as to study potential moderator effects.

Here we set out to investigate the structural correlates of negative symptoms in a large meta-analysis including almost 2 000 individuals with schizophrenia. Based on previous structural imaging findings, we hypothesised that lower MOFC thickness is associated with negative symptom severity in schizophrenia.

MATERIALS AND METHODS

Study samples

The current study includes a total of 1 985 individuals with schizophrenia from seventeen research groups around the world as part of the ENIGMA Schizophrenia Working Group. Schizophrenia diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM, editions III-R or IV) or the International Classification of Diseases (ICD, edition 10) criteria using either the Structured Clinical Interview for DSM Disorders (SCID), the Comprehensive Assessment of Symptoms and History (CASH), the Present State Examination (PSE), and/or a review of case files/medical records by trained clinicians. All individuals had negative symptom ratings and structural imaging data available. Mean sample size at each research site was 117 patients (range: 23–244). See Supplementary Information (SI) Table 1 for more details.

Each study sample was collected with participants' written informed consent approved by local Institutional Review Boards. No individual subject imaging or clinical data were shared among the ENIGMA institutions.

Negative symptom measures and score conversion

Negative symptom severity was assessed using the Scale for the Assessment of Negative Symptoms (SANS)²⁷ and the Positive and Negative Syndrome Scale (PANSS)²⁸. Negative symptom scores were calculated as follows:

1. Total SANS (Composite) score = sum of SANS items 1–7, 9–12, 14–16, 18–21, and 23–24;
2. Global SANS (Summary) score = sum of SANS items 8, 13, 17, 22, and 25 (which include affective flattening, alogia, avolition, anhedonia, and attention global rating scores, respectively); or
3. PANSS Negative = sum of PANSS items 8–14.

To harmonize scores, we decided to convert all negative scores (i.e. PANSS Negative and Total SANS Composite scores) to Global SANS (Summary) scores following recommendations by Andreasen²⁷ and using the algorithms published in van Erp et al.²⁹. For additional details see SI Section 1.1.

Image acquisition and processing

Based on the previous literature^{23,24} we followed a region-of-interest (ROI) approach, focusing on the medial orbitofrontal cortex (MOFC; SI Figure 1). Left and right MOFC thickness values – based on the Desikan-Killiany atlas³⁰ – were obtained using FreeSurfer (<http://surfer.nmr.mgh.harvard.edu>) from high-resolution T1-weighted structural brain scans. Details on study type (single site or multisite), scanner vendor/strength/sequence, acquisition parameters and FreeSurfer versions used are provided in SI Table 1. For quality control, histograms of MOFC thickness values were generated and outliers were visually inspected by overlaying their parcellation on the subjects' anatomical images. Only parcellations judged to be accurate upon visual inspection were subjected to statistical analyses (see SI Figure 2 for left and right MOFC thickness descriptives by sample).

Statistical analyses

Within each sample, an association of negative symptoms with left and right MOFC thickness was analyzed using univariate linear regression analysis (R's linear model function *lm*) predicting mean MOFC thickness by global SANS score. The main analysis included age and gender as covariates. In cases of multi-site studies (FBIRN, MCIC, UMCU and Osaka) binary dummy covariates were included in the model to account for n–1 sites. For samples where information was available, secondary models were run separately with each of the following covariates: 1) current antipsychotic medication (atypical/typical/both/none), 2) duration of illness, 3) illness severity (measured using PANSS Total score), and 4) handedness (right/left/ambidextrous). Analyses of individual subject data were performed by the site that contributed the sample, using code created within the ENIGMA collaboration.

Meta-analyses

From each sample, standardized regression coefficients were extracted from the main and secondary models as a measure of effect size for the left and right MOFC using the *lm.beta* function in the *lm.beta* R package.³¹ A meta-analysis was conducted over these effect sizes using the *rma* function in the R package *metafor*.³² We meta-analyzed the estimates across sites by weighting Fisher's r-to-z transformed effect size values by sample size in a random-effects model using the default REML estimator. The same procedure was used to investigate the effects of age, gender, illness severity and duration of illness on MOFC

thickness. For analyses, in which both left and right MOFC were analyzed, the significance threshold was corrected for two tests ($p=0.05/2=0.025$).

Due to between-site differences in study characteristics such as antipsychotic medication, handedness and single vs multisite status (SI Table 1), we used moderator analyses to investigate between-sample differences.

RESULTS

Demographics

Mean age (weighted by sample-size) across patient samples was 34 years (range: 28–43). Patients were on average 68% male (range: 55–76%). The weighted mean duration of illness across the patient groups was 10 years (range: 1–20). For samples where current antipsychotic type and dose information was available, the weighted percentage of patients on first-generation (typical), second-generation antipsychotics (atypical), both typical and atypical or no antipsychotic medication was 11%, 71%, 9% and 9%. Ninety percent of patients were right-handed (range: 68–95), while only 8% (range: 2–14) were left-handed and 2% (range: 0–25) were ambidextrous (Table 1 and SI Table 1).

Meta-analysis

The weighted mean global SANS scores across the samples was 7.91 (range: 2.86–12.90). Weighted mean MOFC thickness was 2.46 mm (range: 2.26–2.71) in the left hemisphere and 2.42 mm (range: 2.17–2.61) in the right hemisphere. Meta-analytical results showed that global SANS scores were negatively associated with left MOFC thickness ($\beta_{\text{std}}=-0.075$; $p_{\text{SANS}}=0.019$; Figure 1) after accounting for age, gender and number of sites (if applicable). Funnel plot inspection gave no indication of bias (Egger's $p=0.193$; SI Figure 3). However, effect sizes were found to be heterogeneous ($Q(16)=26.399$; $p=0.049$; $I^2=42.38\%$). We found only a trend effect (but in the same direction) of global SANS on right MOFC thickness ($\beta_{\text{std}}=-0.064$; $p_{\text{SANS}}=0.055$). For detailed results, see SI Section 2.1, sections a and b).

Effects of covariates and moderator analyses

We carried on investigating both within-sample and moderating between-sample effects of age, gender, illness severity and duration of illness as well as antipsychotic medication, handedness and multisite status based on samples, in which this information was available (SI Table 1).

While a meta-analysis of within-sample effects indicated that left MOFC thickness decreased with age ($\beta_{\text{std}}=-0.237$; $p<0.0001$) and was lower in women ($\beta_{\text{std}}=-0.090$; $p<0.0001$), the main association of global SANS and left MOFC thickness remained significant ($\beta_{\text{std}}=-0.075$; $p_{\text{SANS}}=0.019$, see main model above and SI 2.1, sections a, c and d).

Overall illness severity did not associate with left MOFC thickness ($p=0.555$) after accounting for age, gender and site (if applicable), while the global SANS effect in the same model remained significant ($\beta_{\text{std}}=-0.113$; $p_{\text{SANS}}=0.036$; see also SI 2.1 sections e and f).

Duration of illness correlated negatively with left MOFC thickness (Fisher's $z=-0.145$; $p<0.001$), but not with global SANS score ($p=0.190$). While duration of illness also correlated strongly with age (Fisher's $z=0.834$; $p<0.001$), it did not associate with left MOFC thickness above and beyond age in the lower regression models ($p=0.199$). However, additionally accounting for duration of illness within each sample also reduced the main effect of SANS on left MOFC thickness ($p_{SANS}=0.068$; see SI 2.1 sections g and h). Similar diminishing effects were observed when investigating the influence of antipsychotic medication and handedness within each sample, which themselves did not moderate the global SANS – left MOFC thickness relationship between samples ($p_{med}=0.447$; $p_{hand}=0.580$; see SI 2.1 section i and j). Investigating the effects of antipsychotic medication further, we found that mean left MOFC thickness estimates ($p=0.007$), but not mean global SANS estimates ($p=0.454$) differed by antipsychotic medication type (i.e. percentages of patients in each medication group in each sample, SI 2.1 sections k and l). Specifically, compared to unmedicated patients, left MOFC reductions were larger at sites with a larger percentage of patients treated with atypical ($\beta_{std}=-0.006$; $p=0.002$) or typical AP ($\beta_{std}=-0.007$; $p=0.003$). Proportion of patients treated with both antipsychotic medication types was not associated with MOFC thickness ($p=0.444$; SI 2.1 section k). The reductions observed in patients treated with atypical (but not typical) antipsychotic medication remained significant in analyses that included gender, age, or duration of illness as covariates (SI 2.1 section m and n).

DISCUSSION

Summary

In this study, we investigated the relationship between MOFC thinning and negative symptom severity in schizophrenia. We found that negative symptoms related inversely to cortical thickness in this brain region, with effects appearing greater in the left hemisphere compared to the right. This finding was independent of general illness severity, age and gender, but somewhat lessened when covarying for the influence of antipsychotic medication and duration of illness. Our investigation has a number of strengths. First, using a meta-analytical approach, we were able to increase our sample size by a magnitude of 10 compared to previous studies. Second, the large sample allowed for the investigation of potentially influencing, but small effects of age, gender, illness severity, duration of illness, antipsychotic medication, and handedness. Third, our sample included diverse patient groups from ten different countries that spans a broad age range allowing for a generalization of our findings.

Cortical thickness in the left medial orbitofrontal cortex and negative symptoms

Our results are in agreement with two previously published studies. Specifically, the association between MOFC thickness and negative symptoms in the study by Venkatasubramanian et al.²³ was also negative and only present in the left hemisphere. Comparing patient groups with distinct symptom profiles, the study by Nenadic et al.²⁴ also reported prefrontal reductions (including the MOFC) in patients characterized by predominantly negative symptoms compared to subgroups with predominantly paranoid and disorganised symptoms. However, there have also been reports, which failed to identify an

association between MOFC thickness and negative symptoms.^{25,33–35} There are several potential explanations for these discrepant findings. First, all previous studies were based on rather small samples (between 40 and 130 patients) and hence potentially underpowered to detect the weak, but robust association, we were able to identify in our study based on almost 2 000 patients. Furthermore, previous samples differed substantially in important characteristics such as illness chronicity and mean age. Of note, all studies that accepted the null hypothesis consisted of young (< 25 years), first-episode patients, while studies which reported effects, such as by Venkatasubramanian et al.²³ and Nenadic et al.²⁴, included older (>30 years), chronic patients. Similarly, mean age across our samples ranged from 28 – 43 years while mean duration of illness was 10 years, indicating that the association between negative symptoms and MOFC thickness might be more apparent when patients are older or in later stages of the disorder.

Animal and human studies suggest that neurons in the MOFC encode the subjective value of expected reward,^{36,37} providing evidence that the MOFC mediates processes associated with the learning and retrieval of (subjective) value information, which guides decision-making and goal-directed behaviour.^{38,39} Several studies suggest that negative symptoms in schizophrenia are associated with reinforcement learning abnormality.^{40,41} Gold et al.⁴² observed that patients with high-negative symptoms were less able to take expected reward values into account during decision making processes. As a result, patients fail to learn actions that lead to positive outcomes, while they outperform controls in avoiding punishing outcomes, showing that the findings were not indicative of general learning deficits, but of deficits in reward-related learning. Such findings may help to explain the high prevalence of avolition and anhedonia in schizophrenia, two core dimensions of negative symptomatology. In line with this, aberrant neural responses to reward feedback was observed in medial prefrontal areas of patients with schizophrenia,⁴³ although results from this and several other studies also emphasize the relevance of ventral striatal pathways pointing towards an involvement of a wider striatal-prefrontal network in reward feedback.^{44–46} In sum, our finding of a negative association between left MOFC thickness and negative symptoms underline the importance of this region in emotional, motivational, and executive functioning, which is commonly impaired in schizophrenia patients.⁴⁷

Potential moderators

Illness severity—We found that the effect of negative symptoms on left MOFC thickness was independent of general illness severity. That is, the MOFC might be specifically involved in emotional and motivational aspects of schizophrenia as opposed to general schizophrenia psychopathology. Two other cortical thickness studies also failed to identify a significant correlation between illness severity (as measured using PANSS total scores) and thickness in any cortical region.^{48,49} Furthermore, van Haren et al.⁵⁰ identified an association between *poor functional and symptomatic outcome* (derived using a factor analysis on Global Assessment of Functioning (GAF), the Camberwell Assessment of Need scale, and PANSS) and cortical thinning in the superior temporal gyrus, but not in frontal areas. Also in line with this is a functional imaging study by Simon et al.²², who investigated whole-brain activation during a reward anticipation paradigm. The authors observed that negative symptoms (especially signs of apathy), but not positive symptoms, were inversely

correlated with activation in the ventral striatum, which at the same time showed reduced connectivity with the MOFC in patients compared to controls, further supporting the role of the MOFC in negative symptoms in schizophrenia.

Duration of illness—Duration of illness correlated strongly and negatively with left MOFC thickness (but not with negative symptom scores), although effects were dependent on age effects on thickness. Given that negative symptoms no longer predicted thickness significantly when covarying for age and duration of illness (which was highly correlated with age and not predictive of MOFC thickness in the combined model) in the same model, may indicate that some of the variance in thickness explained by negative symptoms depends on these variables. In this respect and as explained above, it is of interest that studies of first-episode patients did not find an association between symptoms and thickness in the MOFC. Ansell et al.³³ studied very young (mean age of 22 years) psychosis patients, who had been diagnosed for the first time within the last three months. The authors found no effects of negative symptoms on thickness in prefrontal areas (although they did report that negative symptoms related to reduced thickness in parietal regions, but only in patients treated with first-generation antipsychotics). Crespo-Facorro et al.²⁶ also studied first-episode patients and reported no significant relationship between negative symptoms and lobar cortical thickness. In the light of these previous findings and considering that participants in our study were predominantly older, chronic patients, our results might be more specific to later stages of the disorder.

Antipsychotic medication—Although the relationship between negative symptoms and left MOFC thickness did not vary by antipsychotic medication group in our moderator analysis, a substantial amount of variance in left MOFC thickness was explained through antipsychotic medication effects, with patients treated with atypical antipsychotics showing the most robust reductions. While past studies predominantly reported volume and thickness deficits in frontal brain regions in patients treated with typical compared to those treated with atypical antipsychotics or unmedicated patients,^{50–52} there have also been many conflicting findings.^{53,54} Attempting to reconcile previous reports, it has been suggested that antipsychotic medication effects on brain structure might be substance-specific⁵⁵ and might also depend on illness chronicity and the duration of untreated psychosis. Some studies reported that medication effects on frontal brain structures were apparent especially during the early phase of treatment and that the effect size increased with longer durations of untreated psychosis (for a review see ref⁵⁶). Genetic predisposition and substance use could also interact with antipsychotic medication.^{57,58} With respect to our own findings we would like to stress that this is a purely correlational result, which does not in any way imply a causal relationship between antipsychotic medication intake and cortical thinning. Considering that we investigated antipsychotic medication groups, future studies are necessary to investigate this observation in more detail by studying more refined antipsychotic medication estimates.

Limitations

The results of this study have to be seen in the light of the following limitations. First, our study was strongly hypothesis-driven in that we only investigated effects in the medial

orbitofrontal cortex. Secondly, given the cross-sectional design of this study, we were unable to address directional effects. That is, we were not able to determine whether cortical thinning precedes or follows the development of negative symptoms. Third, we used a measure of global negative symptom severity, but it is possible that effects were driven by subdimension-specific characteristics.

Conclusion

We investigated the relationship between negative symptoms and cortical thickness in the medial orbitofrontal cortex in a large cross-continental cohort of schizophrenia patients, comprising almost 2 000 patients. Negative symptom severity was significantly associated with thickness in this region in the left, but not the right hemisphere. This association was irrespective of age, gender and illness severity, but possibly modulated by antipsychotic medication and duration of illness. Our findings provide further insight into symptom-related pathophysiological processes of schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Esther Walton^{1,2,3}, Derrek P Hibar⁴, Theo GM van Erp⁵, Steven G Potkin⁵, Roberto Roiz-Santiañez^{6,7}, Benedicto Crespo-Facorro^{6,7}, Paula Suarez-Pinilla^{6,7}, Neeltje EM Van Haren⁸, Sonja MC de Zwart⁸, Rene S Kahn⁸, Wiepke Cahn⁸, Nhat Trung Doan⁹, Kjetil N Jørgensen^{9,10}, Tiril P Gurholt⁹, Ingrid Agartz^{9,10,11}, Ole A Andreassen^{12,9}, Lars T Westlye¹², Ingrid Melle^{9,12}, Akiyah O Berg⁹, Lynn Morch-Johnsen^{9,10}, Ann Færden¹³, Lena Flyckt¹⁴, Helena Fatouros-Bergman¹⁴, Karolinska Schizophrenia Project Consortium (KaSP)¹⁵, Erik G Jönsson^{9,11}, Ryota Hashimoto^{16,17}, Hidenaga Yamamori¹⁷, Masaki Fukunaga¹⁸, Neda Jahanshad⁴, Pietro De Rossi^{19,20}, Fabrizio Piras²⁰, Nerisa Banaj²⁰, Gianfranco Spalletta^{20,21}, Raquel E Gur²², Ruben C Gur²², Daniel H Wolf²², Theodore D Satterthwaite²², Lauren M Beard²², Iris E Sommer⁸, Sanne Koops⁸, Oliver Gruber²³, Anja Richter²³, Bernd Krämer²³, Sinead Kelly^{4,24}, Gary Donohoe²⁵, Colm McDonald²⁵, Dara M Cannon²⁵, Aiden Corvin²⁴, Michael Gill²⁴, Annabella Di Giorgio²⁶, Alessandro Bertolino²⁷, Stephen Lawrie²⁸, Thomas Nickson²⁸, Heather C Whalley²⁸, Emma Neilson²⁸, Vince D Calhoun^{29,30}, Paul M Thompson⁴, Jessica A Turner³¹, and Stefan Ehrlich²

Affiliations

¹Department of Psychology, Georgia State University, Atlanta GA 30302

²Translational Developmental Neuroscience Section, Department of Child and Adolescent Psychiatry, Faculty of Medicine, Technische Universität Dresden, Fetscherstr. 74, 01307 Dresden, Germany ³Department of Psychology, Institute of Psychology, Psychiatry and Neuroscience, King's College London, London, SE5 8AF, United Kingdom ⁴Imaging Genetics Center, Keck School of Medicine, University of Southern California, Marina del Rey, CA, United States ⁵Department of

Psychiatry and Human Behavior, University of California, Irvine, California
⁶Department of Psychiatry, University Hospital Marqués de Valdecilla, School of Medicine, University of Cantabria–IDIVAL, Avda. Valdecilla s/n, 39008, Santander, Spain
⁷Cibersam (Centro Investigación Biomédica en Red Salud Mental), Avda. Valdecilla s/n, 39008, Santander, Spain
⁸Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands
⁹NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, University of Oslo, P.O. Box 4956 Nydalen, 0424 Oslo, Norway
¹⁰Department of Psychiatric Research, Diakonhjemmet Hospital, P.O. Box 85 Vinderen, 0319 Oslo, Norway
¹¹Department of Clinical Neuroscience, Karolinska Institutet, 171 77 Stockholm, Sweden
¹²NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital, P.O. Box 4956 Nydalen, 0424, Oslo, Norway
¹³Division of Mental Health and Addiction, Oslo University Hospital, P.O. Box 4956 Nydalen, 0424, Oslo, Norway
¹⁴Karolinska Institutet, Department of Clinical Neuroscience, Centre for Psychiatry Research, Norra Stationsgatan 69, 113 64 Stockholm, Sweden
¹⁶Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University D3, 2-2, Yamadaoka, Suita, Osaka, 565-0871, Japan
¹⁷Department of Psychiatry, Osaka University Graduate School of Medicine D3, 2-2, Yamadaoka, Suita, Osaka, 565-0871, Japan
¹⁸Division of Cerebral Integration, National Institute for Physiological Sciences, 38 Nishigonaka Myodaiji, Okazaki, Aichi, 444-8585, Japan
¹⁹NESMOS Department (Neurosciences, Mental Health and Sensory Functions), School of Medicine and Psychology, Sapienza University, Rome, Italy
²⁰Department of Clinical and Behavioural Neurology, IRCCS Santa Lucia Foundation, 00179, Rome, Italy
²¹Beth K. and Stuart C. Yudofsky Division of Neuropsychiatry Menninger Department of Psychiatry and Behavioral Sciences Baylor College of Medicine Houston, TX, USA
²²Brain Behavior Laboratory, University of Pennsylvania, Philadelphia PA USA 19104
²³Center for Translational Research in Systems Neuroscience and Psychiatry, Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Von-Siebold-Str. 5, 37075 Göttingen, Germany
²⁴Trinity College, Dublin, Ireland
²⁵Neuroimaging and Cognitive Genomics Centre, NCBES Galway Neuroscience Centre, National University of Ireland Galway, Galway, Ireland
²⁶Section of Psychiatry and Psychology, IRCCS Casa Sollievo della Sofferenza, S.G. Rotondo (FG), 71013 Italy
²⁷Psychiatric Neuroscience Group, University of Bari 'Aldo Moro', Bari, 70124 Italy
²⁸Division of Psychiatry, University of Edinburgh, Royal Edinburgh Hospital, Morningside, Edinburgh, EH10 5HF
²⁹The Mind Research Network, Albuquerque, NM 87106, United States
³⁰Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, NM 87131, United States
³¹Department of Psychology and Neuroscience Institute, Georgia State University, Atlanta GA 30302

Acknowledgments

ENIGMA was supported in part by a Consortium grant (U54 EB020403 to PMT) from the NIH Institutes contributing to the Big Data to Knowledge (BD2K) Initiative, including the NIBIB and NCI. The authors would also like to express their gratitude for the personal support from the Deutsche Forschungsgemeinschaft (Research Fellowship to EW). For additional support, see SI section 3.

References

1. Jablensky A. Subtyping schizophrenia: implications for genetic research. *Mol Psychiatry*. 2006; 11:815–836. [PubMed: 16801952]
2. Andreasen NC, Olsen S. Negative v positive schizophrenia. Definition and validation. *Arch Gen Psychiatry*. 1982; 39:789–794. [PubMed: 7165478]
3. Jeppesen P, Petersen L, Thorup A, Abel M-B, Øhlenschläger J, Christensen TØ, et al. The association between pre-morbid adjustment, duration of untreated psychosis and outcome in first-episode psychosis. *Psychological Medicine*. 2008; 38:1157–1166. [PubMed: 18447961]
4. Rosenheck R, Leslie D, Keefe R, McEvoy J, Swartz M, Perkins D, et al. Barriers to Employment for People With Schizophrenia. *AJP*. 2006; 163:411–417.
5. Milev P, Ho B-C, Arndt S, Andreasen NC. Predictive Values of Neurocognition and Negative Symptoms on Functional Outcome in Schizophrenia: A Longitudinal First-Episode Study With 7-Year Follow-Up. *AJP*. 2005; 162:495–506.
6. Goldman AL. Widespread Reductions of Cortical Thickness in Schizophrenia and Spectrum Disorders and Evidence of Heritability. *Arch Gen Psychiatry*. 2009; 66:467. [PubMed: 19414706]
7. Nesvåg R, Lawyer G, Varnäs K, Fjell AM, Walhovd KB, Frigessi A, et al. Regional thinning of the cerebral cortex in schizophrenia: effects of diagnosis, age and antipsychotic medication. *Schizophr Res*. 2008; 98:16–28. [PubMed: 17933495]
8. Schultz CC, Koch K, Wagner G, Roebel M, Schachtzabel C, Gaser C, et al. Reduced cortical thickness in first episode schizophrenia. *Schizophrenia Research*. 2010; 116:204–209. [PubMed: 19926451]
9. Ehrlich S, Brauns S, Yendiki A, Ho B-C, Calhoun V, Schulz SC, et al. Associations of cortical thickness and cognition in patients with schizophrenia and healthy controls. *Schizophr Bull*. 2012; 38:1050–1062. [PubMed: 21436318]
10. Bechara A, Damasio H, Damasio AR. Emotion, Decision Making and the Orbitofrontal Cortex. *Cereb Cortex*. 2000; 10:295–307. [PubMed: 10731224]
11. Goodkind MS, Sollberger M, Gyurak A, Rosen HJ, Rankin K, Miller B, et al. Tracking Emotional Valence: The Role of the Orbitofrontal Cortex. *Hum Brain Mapp*. 2012; 33:753–762. [PubMed: 21425397]
12. Cohen AS, Minor KS. Emotional Experience in Patients With Schizophrenia Revisited: Meta-analysis of Laboratory Studies. *Schizophr Bull*. 2010; 36:143–150. [PubMed: 18562345]
13. Kalkstein S, Hurford I, Gur RC. Neurocognition in schizophrenia. *Curr Top Behav Neurosci*. 2010; 4:373–390. [PubMed: 21312407]
14. Grabenhorst F, Rolls ET. Value, pleasure and choice in the ventral prefrontal cortex. *Trends in Cognitive Sciences*. 2011; 15:56–67. [PubMed: 21216655]
15. Fellows LK, Farah MJ. Different Underlying Impairments in Decision-making Following Ventromedial and Dorsolateral Frontal Lobe Damage in Humans. *Cereb Cortex*. 2005; 15:58–63. [PubMed: 15217900]
16. Fisher T, Shamay-Tsoory SG, Eran A, Aharon-Peretz J. Characterization of recovery and neuropsychological consequences of orbitofrontal lesion: A case study. *Neurocase*. 2011; 17:285–293. [PubMed: 21667397]
17. Hornak J, Bramham J, Rolls ET, Morris RG, O'Doherty J, Bullock PR, et al. Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain*. 2003; 126:1691–1712. [PubMed: 12805109]
18. Kühn S, Gallinat J. The neural correlates of subjective pleasantness. *NeuroImage*. 2012; 61:289–294. [PubMed: 22406357]

19. Ducharme S, Albaugh MD, Hudziak JJ, Botteron KN, Nguyen T-V, Truong C, et al. Anxious/Depressed Symptoms are Linked to Right Ventromedial Prefrontal Cortical Thickness Maturation in Healthy Children and Young Adults. *Cereb Cortex*. 2014; 24:2941–2950. [PubMed: 23749874]
20. Harvey P-O, Pruessner J, Czechowska Y, Lepage M. Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. *Mol Psychiatry*. 2007; 12:767–775.
21. Plailly J, d' Amato T, Saoud M, Royet J-P. Left temporo-limbic and orbital dysfunction in schizophrenia during odor familiarity and hedonicity judgments. *NeuroImage*. 2006; 29:302–313. [PubMed: 16099179]
22. Simon JJ, Cordeiro SA, Weber M-A, Friederich H-C, Wolf RC, Weisbrod M, et al. Reward System Dysfunction as a Neural Substrate of Symptom Expression Across the General Population and Patients With Schizophrenia. *Schizophr Bull*. 2015:sbv067.
23. Venkatasubramanian G, Jayakumar PN, Gangadhar BN, Keshavan MS. Automated MRI parcellation study of regional volume and thickness of prefrontal cortex (PFC) in antipsychotic-naïve schizophrenia. *Acta Psychiatrica Scandinavica*. 2008; 117:420–431. [PubMed: 18479318]
24. Nenadic I, Yotter RA, Sauer H, Gaser C. Patterns of cortical thinning in different subgroups of schizophrenia. *Br J Psychiatry*. 2015; 206:479–483. [PubMed: 25657354]
25. Xiao Y, Lui S, Deng W, Yao L, Zhang W, Li S, et al. Altered Cortical Thickness Related to Clinical Severity But Not the Untreated Disease Duration in Schizophrenia. *Schizophr Bull*. 2013:sbt177.
26. Crespo-Facorro B, Roiz-Santiáñez R, Pérez-Iglesias R, Rodríguez-Sánchez JM, Mata I, Tordesillas-Gutiérrez D, et al. Global and regional cortical thinning in first-episode psychosis patients: relationships with clinical and cognitive features. *Psychol Med*. 2011; 41:1449–1460. [PubMed: 20942995]
27. Andreasen. Scale for the assessment of negative symptoms. Iowa City: University of Iowa; 1983.
28. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987; 13:261–276. [PubMed: 3616518]
29. Van Erp TGM, Preda A, Nguyen D, Faziola L, Turner J, Bustillo J, et al. Converting positive and negative symptom scores between PANSS and SAPS/SANS. *Schizophr Res*. 2014; 152:289–294. [PubMed: 24332632]
30. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006; 31:968–980. [PubMed: 16530430]
31. Behrendt, S. lm.beta: Add Standardized Regression Coefficients to lm-Objects. 2014. <http://CRAN.R-project.org/package=lm.beta>
32. Viechtbauer, W. [accessed 17 Dec 2015] Conducting Meta-Analyses in R with the metafor Package. *Journal of Statistical Software*. <http://www.jstatsoft.org/article/view/v036i03>
33. Ansell BRE, Dwyer DB, Wood SJ, Bora E, Brewer WJ, Proffitt TM, et al. Divergent effects of first-generation and second-generation antipsychotics on cortical thickness in first-episode psychosis. *Psychol Med*. 2015; 45:515–527. [PubMed: 25077698]
34. Bodnar M, Hovington CL, Buchy L, Malla AK, Joober R, Lepage M. Cortical Thinning in Temporo-Parietal Junction (TPJ) in Non-Affective First-Episode of Psychosis Patients with Persistent Negative Symptoms. *PLoS ONE*. 2014; 9:e101372. [PubMed: 24979583]
35. McKechnie AG, Moorhead TWJ, Stanfield AC, Whalley HC, Johnstone EC, Lawrie SM, et al. Negative symptoms and longitudinal grey matter tissue loss in adolescents at risk of psychosis: preliminary findings from a 6-year follow-up study. *The British Journal of Psychiatry*. 2015 bjp.bp.114.154526.
36. Furuyashiki T, Gallagher M. Neural encoding in the orbitofrontal cortex related to goal-directed behavior. *Ann N Y Acad Sci*. 2007; 1121:193–215. [PubMed: 17872389]
37. Roesch MR, Olson CR. Neuronal activity related to anticipated reward in frontal cortex: does it represent value or reflect motivation? *Ann N Y Acad Sci*. 2007; 1121:431–446. [PubMed: 17846160]
38. Bechara A, Tranel D, Damasio H. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain*. 2000; 123:2189–2202. [PubMed: 11050020]

39. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*. 1994; 50:7–15. [PubMed: 8039375]
40. Strauss GP, Frank MJ, Waltz JA, Kasanova Z, Herbener ES, Gold JM. Deficits in positive reinforcement learning and uncertainty-driven exploration are associated with distinct aspects of negative symptoms in schizophrenia. *Biol Psychiatry*. 2011; 69:424–431. [PubMed: 21168124]
41. Waltz JA, Frank MJ, Robinson BM, Gold JM. Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal-cortical dysfunction. *Biol Psychiatry*. 2007; 62:756–764. [PubMed: 17300757]
42. Gold JM, Waltz JA, Matveeva TM, et al. Negative symptoms and the failure to represent the expected reward value of actions: Behavioral and computational modeling evidence. *Arch Gen Psychiatry*. 2012; 69:129–138. [PubMed: 22310503]
43. Schlagenhauf F, Sterzer P, Schmack K, Ballmaier M, Rapp M, Wrase J, et al. Reward Feedback Alterations in Unmedicated Schizophrenia Patients: Relevance for Delusions. *Biological Psychiatry*. 2009; 65:1032–1039. [PubMed: 19195646]
44. Mørch-Johnsen L, Nesvåg R, Faerden A, Haukvik UK, Jørgensen KN, Lange EH, et al. Brain structure abnormalities in first-episode psychosis patients with persistent apathy. *Schizophr Res*. 2015; 164:59–64. [PubMed: 25818626]
45. Radua J, Schmidt A, Borgwardt S, Heinz A, Schlagenhauf F, McGuire P, et al. Ventral Striatal Activation During Reward Processing in Psychosis: A Neurofunctional Meta-Analysis. *JAMA Psychiatry*. 2015; 72:1243–1251. [PubMed: 26558708]
46. Schlagenhauf F, Huys QJM, Deserno L, Rapp MA, Beck A, Heinze H-J, et al. Striatal dysfunction during reversal learning in unmedicated schizophrenia patients. *Neuroimage*. 2014; 89:171–180. [PubMed: 24291614]
47. Barch DM, Dowd EC. Goal Representations and Motivational Drive in Schizophrenia: The Role of Prefrontal–Striatal Interactions. *Schizophr Bull*. 2010; 36:919–934. [PubMed: 20566491]
48. Oertel-Knöchel V, Knöchel C, Rotarska-Jagiela A, Reinke B, Prvulovic D, Haenschel C, et al. Association between Psychotic Symptoms and Cortical Thickness Reduction across the Schizophrenia Spectrum. *Cereb Cortex*. 2013; 23:61–70. [PubMed: 22291030]
49. Rimol LM, Hartberg CB, Nesvåg R, Fennema-Notestine C, Hagler DJ Jr, Pung CJ, et al. Cortical Thickness and Subcortical Volumes in Schizophrenia and Bipolar Disorder. *Biological Psychiatry*. 2010; 68:41–50. [PubMed: 20609836]
50. van Haren NM, Schnack HG, Cahn W, et al. Changes in cortical thickness during the course of illness in schizophrenia. *Arch Gen Psychiatry*. 2011; 68:871–880. [PubMed: 21893656]
51. Vita A, De Peri L, Deste G, Barlati S, Sacchetti E. The Effect of Antipsychotic Treatment on Cortical Gray Matter Changes in Schizophrenia: Does the Class Matter? A Meta-analysis and Meta-regression of Longitudinal Magnetic Resonance Imaging Studies. *Biol Psychiatry*. 2015; 78:403–412. [PubMed: 25802081]
52. Lesh TA, Tanase C, Geib BR, Niendam TA, Yoon JH, Minzenberg MJ, et al. A multimodal analysis of antipsychotic effects on brain structure and function in first-episode schizophrenia. *JAMA Psychiatry*. 2015; 72:226–234. [PubMed: 25588194]
53. Cahn W, Hulshoff Pol HE, Lems EBTE, van Haren NEM, Schnack HG, van der Linden JA, et al. Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. *Arch Gen Psychiatry*. 2002; 59:1002–1010. [PubMed: 12418933]
54. Ho B, Andreasen N, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: A longitudinal study of first-episode schizophrenia. *Arch Gen Psychiatry*. 2011; 68:128–137. [PubMed: 21300943]
55. Xiao L, Xu H, Zhang Y, Wei Z, He J, Jiang W, et al. Quetiapine facilitates oligodendrocyte development and prevents mice from myelin breakdown and behavioral changes. *Mol Psychiatry*. 2008; 13:697–708. [PubMed: 17684494]
56. Aderhold DV, Weinmann S, Hägele C, Heinz A. Frontale Hirnvolumenminderung durch Antipsychotika? *Nervenarzt*. 2014; 86:302–323.
57. Hartz SM, Ho B-C, Andreasen NC, Librant A, Rudd D, Epping EA, et al. G72 influences longitudinal change in frontal lobe volume in schizophrenia. *Am J Med Genet B Neuropsychiatr Genet*. 2010; 153B:640–647. [PubMed: 19760675]

58. Tregellas JR, Shatti S, Tanabe JL, Martin LF, Gibson L, Wylie K, et al. Gray matter volume differences and the effects of smoking on gray matter in schizophrenia. *Schizophr Res.* 2007; 97:242–249. [PubMed: 17890058]

Figure 1.

Forest plot of association between global SANS and cortical thickness in the left medial orbitofrontal cortex across all 17 study sites, controlling for age, gender and number of sites (if applicable; of note the global SANS-left MOFC thickness relationship did not differ between single vs multisite samples ($p=0.422$; see SI 2.1 section o)). Fisher's transformed standardized regression coefficients are denoted by black boxes. Black lines indicate 95% confidence intervals. The combined estimate for all sites is represented by a black diamond with the outer edges of the diamond indicating the confidence interval limits.

Table 1

Demographics. Mean are weighted by study sample size.

	estimate	range	data available for N number of studies
% males	68	55–76	17
Mean age in years	34	28–43	17
Mean SANS Global	7.91	2.86–12.90	17
Mean duration of illness in years	10	1–20	13
Mean illness severity (PANSS Total)	70.43	49.81–90.22	9
Antipsychotic medication			13
%Atypical	71	39–91	
%Typical	11	0–45	
%Both A & T	9	0–24	
%None	9	0–53	
Handedness			14
%Right	90	68–95	
%Left	8	2–14	
%Ambidextrous	2	0–25	
Cortical thickness			17
Mean left medial orbitofrontal	2.46	2.26–2.71	
Mean right medial orbitofrontal	2.42	2.17–2.61	