Neuroanatomical predictors of functional outcome in individuals at ultra-high risk for psychosis

Reniers, Renate; Lin, Ashleigh; Yung, Alison R; Koutsouleris, Nikolaos; Nelson, Barnaby; Cropley, Vanessa L; Velakoulis, Dennis; McGorry, Patrick D; Pantelis, Christos; Wood, Stephen

DOI:
10.1093/schbul/sbw086

Document Version
Peer reviewed version

Citation for published version (Harvard):
Reniers, R, Lin, A, Yung, AR, Koutsouleris, N, Nelson, B, Cropley, VL, Velakoulis, D, McGorry, PD, Pantelis, C & Wood, S 2017, 'Neuroanatomical predictors of functional outcome in individuals at ultra-high risk for psychosis', *Schizophrenia bulletin*, vol. 43, no. 2, pp. 449-458. https://doi.org/10.1093/schbul/sbw086

OXFORD UNIVERSITY PRESS | Schizophrenia Bulletin

Neuroanatomical predictors of functional outcome in individuals at ultra-high risk for psychosis

Journal:	*Schizophrenia Bulletin*
Manuscript ID	SZBLTN-ART-15-0726.R2
Manuscript Type:	Regular Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Reniers, Renate; University of Birmingham, Psychology Lin, Ashleigh; Telethon Kids Institute, Yung, Alison; University of Manchester, Institute of Brain, Behaviour and Mental Health Koutsouleris, Nikolaos; Ludwig-Maximilian-University, Department of Psychiatry and Psychotherapy Nelson, Barnaby; Orygen, The National Centre of Excellence in Youth Mental Health Cropley, Vanessa; University of Melbourne, Psychiatry Velakoulis, Dennis; The University of Melbourne and Melbourne Health, Melbourne Neuropsychiatry Centre, Department of Psychiatry McGorry, Patrick; OYHRC, CYPMH Pantelis, Christos; Melbourne Neuropsychiatry Centre Wood, Stephen; University of Birmingham, School of Psychology
Keywords:	voxel-based morphometry, negative symptoms, clinical high risk, functional outcome, grey matter density

Neuroanatomical predictors of functional outcome in individuals at ultra-high risk for psychosis

Running head: Neuroanatomical predictors of functional outcome

Renate LEP Reniers[a*], Ashleigh Lin[b], Alison R Yung[c], Nikolaos Koutsouleris[d], Barnaby Nelson[e], Vanessa L Cropley[f], Dennis Velakoulis[f], Patrick D McGorry[e], Christos Pantelis[f], Stephen J Wood[af]

[a] School of Psychology, University of Birmingham, United Kingdom
[b] Telethon Kids Institute, The University of Western Australia, Australia
[c] Institute of Brain Behaviour and Mental Health, University of Manchester, United Kingdom
[d] Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University of Munich, Germany
[e] Orygen, The National Centre of Excellence in Youth Mental Health, The University of Melbourne, Australia
[f] Melbourne Neuropsychiatry Centre, The University of Melbourne and Melbourne Health, Australia

* Corresponding author
School of Psychology
University of Birmingham
Edgbaston
Birmingham B15 2TT
United Kingdom
R.L.E.P.Reniers@bham.ac.uk
T: +44 (0)121 414 4937
Fax: +44 (0)121 414 4897

Word count abstract:	234
Word count article body:	3470
Manuscript length:	3898
Number of figures:	2
Number of tables:	3
Supplemental information:	1

Abstract

Most individuals at ultra-high risk (UHR) for psychosis do not transition to frank illness. Nevertheless, many have poor clinical outcomes and impaired psychosocial functioning. This study used voxel-based morphometry to investigate if baseline grey and white matter brain densities at identification as UHR were associated with functional outcome at medium- to long-term follow-up. Participants were help-seeking UHR individuals (n=109, 54M:55F) who underwent magnetic resonance imaging at baseline; functional outcome was assessed an average of 9.2 years later. Primary analysis showed that lower baseline grey matter density, but not white matter density, in bilateral frontal and limbic areas, and left cerebellar declive were associated with poorer functional outcome (SOFAS). These findings were independent of transition to psychosis or persistence of the at-risk mental state. Similar regions were significantly associated with lower self-reported levels of social functioning and increased negative symptoms at follow-up. Exploratory analyses showed that lower baseline grey matter densities in middle and inferior frontal gyri were significantly associated with decline in GAF score over follow-up. There was no association between baseline grey matter density and IQ or positive symptoms at follow-up. The current findings provide novel evidence that those with the poorest functional outcomes have the lowest grey matter densities at identification as UHR, regardless of transition status or persistence of the at-risk mental state. Replication and validation of these findings may allow for early identification of poor functional outcome and targeted interventions.

Keywords: grey matter density; functional outcome; psychosis; ultra-high risk; voxel-based morphometry; negative symptoms; clinical high risk

Introduction

For many years, transition to frank psychotic illness has been the outcome measure of interest in research investigating people at ultra-high risk (UHR) for psychosis[1]. It is now thought that the structural brain alterations seen in schizophrenia and other psychoses (such as increases in ventricular volume and decreases in grey and white matter volume[2-4]) may arise during or even before the onset phase of psychosis[5-8]. These brain changes have a demonstrated relationship with transition to psychosis[5, 9-12] and may serve as biomarkers for onset of illness[13] and inform intervention efforts[14].

However, the majority of UHR individuals do not transition to psychosis[15] and despite this, many still show poor psychosocial functioning at follow-up[16-19]. Cornblatt et al.[20] explain this using a model consisting of two dimensions. The first dimension represents a period of vulnerability caused by early insult that impacts brain pathology. This vulnerability is manifested in psychosocial problems such as Cognitive deficits, Affective disturbances, Social Isolation, and School failure that are together referred to in abbreviated form as the CASIS model. Presence of basic symptoms[21, 22] could be associated with this dimension, which may underlie poor functioning and is necessary, but not sufficient, for the development of schizophrenia. The second dimension is characterised by an underlying vulnerability for positive psychotic symptomatology. These symptoms may develop in only a subset of individuals with CASIS vulnerability[20] who eventually develop psychosis. Measuring psychosocial outcome, particularly in the early stages of psychosis, is thus important not only for our understanding of psychotic illnesses and their causes[19, 23-25] but also for our understanding of those who are in the first dimension and show poor functioning, but never transition to frank psychotic illness. Furthermore, functional impairment may be related to the presence or development of non-psychotic disorders that are common in UHR individuals[26].

Research in UHR individuals[16, 27, 28] has shown that reduced neurocognitive performance on measures of verbal learning and memory, processing speed and attention, and verbal fluency predicts poor functional outcome. Functional outcomes also appear to be associated with a history of childhood maltreatment, regardless of transition status[29], and non-resolving attenuated psychotic symptoms[30, 31]. The limited research on associated brain functioning shows that poorer social functioning as measured by the Social Attainment Survey[32] can be predicted by increased activation in anterior cingulate and left inferior frontal gyrus during performance of a reasoning language processing task[33]. Likewise, poor functioning as indicated by low Global Assessment of Functioning (GAF[34]) scores has been predicted by increased left inferior frontal and insula activation during performance of a verbal fluency task and lower thalamic glutamate levels[35]. On the structural level, lower baseline fractional anisotropy (FA) in the hippocampus and inferior longitudinal fasciculus in UHR individuals has been shown to predict deterioration in social and role functioning at 15 month follow-up[36]. These latter studies have been limited by the small UHR samples and short follow-up period (6-24 months) for assessment of functional outcome.

The current study aimed to further investigate the structural alterations associated with poor functional outcome in a larger sample of UHR individuals followed over the medium- to long-term. We adopted a voxel-based morphometry approach to investigate whether grey and white matter brain density of individuals at UHR for psychosis could predict functional outcome 2.4 to 12.9 years later, and if this association would be related to transition status. Based on the findings described above, we predicted that lower densities in frontal and temporal regions at baseline would be associated with poorer psychosocial functioning at follow-up.

Methods

Participants

UHR individuals were recruited from the Personal Assessment and Crisis Evaluation (PACE) Clinic at Orygen Youth Health (now Orygen, The National Centre of Excellence in Youth Mental Health), in Melbourne, Australia. They were part of a cohort of UHR patients recruited to participate in research studies between 1993 and 2006. Current data are from participants with both baseline MRI and follow-up functional outcome data (n=109, 54M:55F). Inclusion criteria were based on the UHR entry criteria for PACE which are the presence of attenuated psychotic symptoms, brief limited intermittent psychotic symptoms (BLIPS), and/or trait vulnerability for psychotic illness (presence of schizotypal personality disorder or a first-degree family history of psychosis), as well as deterioration in functioning or persistent low functioning. Up to 1999, these criteria were established using the Brief Psychiatric Rating Scale (BPRS[37])/Comprehensive Assessment of Symptoms and History (CASH[38])/GAF[34] and the Comprehensive Assessment of At-Risk Mental States (CAARMS[39]). From 1999, the CAARMS replaced the BPRS/CASH as the means of establishing UHR status. Participants were aged between 15-30 years old and had no history of psychotic illness, organic cause for presentation or past neuroleptic exposure equivalent to a total continuous haloperidol dose of more than 15 mg (i.e. neuroleptics being taken day after day until the 15mg haloperidol equivalent had been reached). Exclusion from imaging studies were neurological disorder, history of significant head injury, seizures or contraindication for magnetic resonance imaging (MRI). All participants provided written informed consent and the study was approved by the local Research and Ethics Committee (Melbourne Health).

Participants were followed up using the tracking system described in Lin et al.[40] More details regarding this long-term follow-up study can be found in Nelson et al.[15] Follow-up

assessments of this sample took place between 2.4 and 12.9 (mean=9.2, SD=2.5, median=9.8) years after study entry at PACE.

Assessments

Participants underwent clinical assessment and MRI at baseline. Clinical assessment included assessment of positive symptoms using the BPRS[37], negative symptoms using the Scale for the Assessment of Negative Symptoms (SANS[41]), and GAF[34] for functioning. During the follow-up assessment, baseline measures were re-administered and the Social and Occupational Functioning Assessment Scale (SOFAS[42]) and Quality of Life Scale (QLS[43]) were used as indices of functional outcome. For participants recruited before the year 2000 (n=73, 67% of the current sample), IQ at follow-up was measured using subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R[44]) proposed by Ward[45]. These subtests are information, picture completion, block design, arithmetic, digit span, similarities and digit symbol. For participants recruited from the year 2000 onwards (n=36, 33% of the current sample), the full Wechsler Abbreviated Scale of Intelligence (WASI[46]) was used to measure IQ at follow-up. Transition to frank psychosis was established using the CAARMS[39] or the state public mental health records when CAARMS data were not available.

MRI acquisition

80% (n=87) of the T1-weighted MRI scans were obtained using a 1.5T GE Signa MR scanner: 124 slices of 1.5mm thickness, TR=1.43s, TE=3.3ms, flip angle 30º, matrix 256x256, FOV 24cm. The remaining 20% (n=22) of the T1-weighted MRI scans were obtained using a 3T GE LX Horizon Scanner: 124 slices of 2mm thickness, TR=3.6s, TE=9ms, flip angle 30º, matrix 410x410, FOV 20cm.

Data analysis

Behavioural data were analysed using IBM SPSS Statistics 21 for Windows (IBM Corp., Armonk, NY). T1-weighted MRI images were automatically processed using the optimised voxel-based morphometry (VBM8) toolbox (http://dbm.neuro.uni-jena.de/vbm/) in statistical parametric mapping software (SPM8, Friston, The Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm). For details on the preprocessing of the data see supplementary materials. Regionally specific differences in the association of baseline grey and white matter density (both lower and higher) with functional outcome were assessed using multiple regressions with gender, age, field strength of the scanner, length of the follow-up period and transition status specified as nuisance variables. Threshold-free cluster enhancement (TFCE) is a spatially sensitive statistical inference algorithm that is based on the sensitivity benefits of cluster-based inference but is not dependent on an arbitrary cluster-forming threshold[47]. This algorithm was applied to optimise activation in areas that show spatial contiguity and results were considered significant at $p<0.05$ Family-Wise Error (FWE) corrected.

SOFAS scores were used to investigate the association of baseline grey and white matter densities with psychosocial functioning at follow-up. The strength of the SOFAS is that, in contrast with the GAF, its scores are independent of the overall severity of the individual's psychological symptoms and are based on the clinician's judgment of the overall level of functioning. Whilst we argue superiority of the SOFAS over the GAF for use in this study, the GAF is commonly used and data were available for 108 participants at both baseline and follow-up for this measure (in contrast with SOFAS scores which were only available at follow-up). The association between baseline grey matter density and baseline GAF score and change in GAF score over time was therefore also investigated. Change in GAF score was calculated for each participant relative to their baseline score and constituted

of a percentage change score and an absolute change score. The SOFAS does not assess social and role functioning separately and therefore the QLS was additionally employed. The QLS is based on self-report but has the advantage that its items can be factored into social functioning, vocational functioning and engagement[48]. Data on this measure was available for 108 participants and scores on the social and vocational functioning scales were used to investigate if density associations were more specifically associated with either social- or vocational functioning.

Given that negative symptoms and general cognitive ability are strongly associated with functional outcome[23, 27], density associations with negative symptoms and IQ measured at follow-up were additionally examined, along with density associations with positive symptoms at follow-up. Available follow-up data were as follows; SANS n=107, IQ n=102, and BPRS positive n=105.

Results

Characteristics of the sample are presented in Table 1. Of the 109 participants, 38 (35%) had transitioned to psychosis by the time of follow-up. The average length of time to conversion was 622 days (SD=719 days). Of those who had not transitioned to psychosis by the time of follow-up, 27 (38%) met APS or BLIPS criteria. Further details about the sample are presented in the supplementary materials.

-Table 1-

Primary analysis

Lower than average baseline grey matter density was significantly associated with lower SOFAS scores at follow-up. This association was found in large clusters in medial

prefrontal cortex, right cingulate gyrus extending into anterior cingulate, left anterior cingulate extending into anterior frontal cortex and subcallosal gyrus, and left cerebellar declive (Table 2, Figure 1). These areas of association were lower in size when symptom severity (SANS and BPRS psychotic subscale scores at baseline) were additionally added as nuisance variables (supplementary materials Table A2). To determine whether this pattern was being driven by the individuals who had transitioned to psychosis at follow-up (note, transition status at follow-up was entered as a nuisance variable in all analyses), a secondary analysis was conducted. A comparison of the relationship of baseline grey matter with functional outcome in the identified bilateral frontal and limbic areas, and left declive, in those who had transitioned to psychosis at follow-up (n=37) with those who had not (n=69) revealed no significant differences. The same comparison for those who had not transitioned to psychosis but met APS or BLIPS criteria at follow-up (n=27) with those who had not transitioned to psychosis and did not meet APS or BLIPS criteria at follow-up (n=42) revealed no significant differences either. There was no significant association between higher baseline grey matter density and lower SOFAS scores at follow-up. There was no significant association between baseline white matter density (lower or higher) and SOFAS scores at follow-up and therefore subsequent analyses focussed on grey matter density associations only.

-Table 2, Figure 1-

Exploratory analyses

No significant association was found between baseline grey matter density (lower or higher) and baseline GAF score or percentage change in GAF score. Lower baseline grey

matter density in middle and inferior frontal gyri was, however, significantly associated with decline in GAF score over follow-up (supplementary materials Table A3, Figure A1).

Lower baseline grey matter density in left medial prefrontal cortex was significantly associated with lower social functioning scores on the QLS at follow-up (Table 2, Figure 1). There was no significant association between higher baseline grey matter density and social functioning scores on the QLS at follow-up. No significant association was observed between baseline grey matter density (lower or higher) and vocational functioning scores on the QLS at follow-up.

Significantly lower baseline grey matter density was observed in a large cluster extending from medial prefrontal cortex into cingulate gyrus and anterior cingulate, and clusters in right precentral and cingulate gyrus, left orbitofrontal cortex extending into anterior cingulate, and left anterior cingulate extending into caudate in association with higher SANS scores at follow-up (Table 3, Figure 2). Further exploratory analyses revealed that this association was not driven by a particular SANS subscale. There was no significant association between higher baseline grey matter density and SANS scores at follow-up.

No significant association was observed between baseline grey matter density and IQ at follow-up or between baseline grey matter density and positive symptoms at follow-up.

-Table 3, Figure 2-

Discussion

This study investigated the association between baseline grey and white matter density and functional outcome 2.4 to 12.9 years after identification as UHR for psychosis. Lower baseline grey matter density in large clusters in bilateral frontal and limbic regions and left cerebellar declive were associated with poorer functional outcome. These findings were

independent of transition status or persistence of the at-risk mental state at follow-up (although in this regard we were only powered to detect a large effect and replication in larger samples is required). We did not observe an association between larger baseline grey matter density and poorer functional outcome, and there was no association between baseline white matter density (lower or higher) and functional outcome. Lower baseline grey matter density in middle and inferior frontal gyri was associated with absolute decline in functioning. When social and vocational functioning were investigated separately, poorer social functioning at follow-up was associated with lower baseline grey matter density in an area of left medial prefrontal cortex that overlapped with the medial prefrontal region observed for the association with functional outcome. Even though both social and vocational functional scores on the QLS showed a strong relationship with functioning as measured by the SOFAS, vocational functioning at follow-up was not associated with baseline grey matter density. Exploration of the association between baseline grey matter density and increased negative symptoms at follow-up revealed areas of lower density in bilateral frontal and limbic regions that partially overlapped with those observed in the association with functional outcome. No association was found between baseline grey matter density and IQ or positive symptoms at follow-up.

The findings regarding QLS social functioning do advocate for a key role for social dysfunction in the poor functional outcomes in this sample. Both the anterior and medial prefrontal regions have been shown to play an important role in emotion processing[49], and in social abilities such as self-referential processing[50, 51], empathy, Theory of Mind and perspective taking[52-54]. The brain areas observed in the association of baseline grey matter density and SOFAS scores at follow-up support this suggestion as recruitment of the anterior cingulate has been associated with performance of emotional tasks with cognitive demand and emotional recall/imagery[49]. Lower baseline grey matter density of the declive was

associated with poorer functional outcome but not with increased negative symptoms at follow-up, providing additional support for the suggestion that social dysfunction may underlie poorer functional outcome in the current sample. The cerebellum has been implicated in social-cognitive functioning in that it provides domain-general executive and semantic support[55], consistent with findings of higher cerebellar activity when executive resources are demanded to support mentalizing in contexts with a high level of abstraction[55]. It needs noting that the current SOFAS findings represent an overall association between lower baseline grey matter density and poorer psychosocial outcome that includes social and role functioning. While many of the observed areas respond to social cognitive paradigms, they may also have involvement in so called 'cold cognition' paradigms in which rational reasoning takes prominence over emotions [56, 57].

The observed partial overlap in brain areas that showed lower grey matter density at baseline in association with poorer functional outcome and increased negative symptoms illustrates the strong association between negative symptoms and functional outcome on both the conceptual and neural level and is consistent with the manifestation of cognitive deficits, affective disturbances, social isolation and school failure as suggested by the first dimension of vulnerability of the CASIS model[20].

The brain areas that show lower grey matter density in association with poorer functional outcome as assessed by the SOFAS do not include the dorsolateral prefrontal cortex, suggesting that changes in baseline density of this brain area and associated cognitive impairments are not associated with poorer functioning in later years. This is consistent with our failure to observe an association between baseline grey matter density and estimated IQ at follow-up as an approximate measure of general cognitive ability. This is also in line with our earlier finding[16] which showed that specific neurocognitive domains (verbal learning and memory, processing speed and attention, and verbal fluency), but not global cognitive

impairment, predicted poor functional outcome. In contrast, the area observed in association with decline in GAF score in the period between baseline and follow-up does overlap with the dorsolateral prefrontal cortex. Lower densities observed in this association may, however, reflect worse symptomatic outcome rather than cognitive impairment (for further discussion see our recent paper on attenuated psychotic symptoms in this sample[30]) or general low functioning at follow-up.

The current findings support recent statements that treatment should not only be focussed on those who will develop above threshold psychotic symptoms but also on those with poor functional outcome[23, 25, 58]. Moreover and consistent with the current findings, treatments that specifically target social impairments, such as social cognitive remediation[59, 60], could be a way of alleviating long-term social disability and distress. Lower grey matter densities as observed in the current study are commonly found in first-episode psychosis[6, 7, 61] and chronic schizophrenia[2, 62]. Detection of these structural alterations as early as the at-risk mental state supports early intervention approaches in those with a prospective diagnosis of psychosis but also in those with a prospective diagnosis of non-psychotic disorders that are associated with poor functional outcome. Evidence is emerging that interventions involving exercise or the administration of essential fatty acids alter brain structure[63-67] and a recent meta-analysis has shown that these efforts, as well as administration of neuroleptics and cognitive behavioural therapy, may show efficacy in preventing or delaying transition[68]. Cognitive enhancement therapy in patients with schizophrenia or schizoaffective disorder has been shown to not only improve neurocognitive functioning[69], but to also have neuroprotective properties as demonstrated by preservation and even increase of grey matter density in limbic areas[70]. Early intervention using these techniques may preserve function[21]. The next step should therefore involve implementation and evaluation of the efficacy of

psychosocial interventions in individuals at UHR for psychosis to reverse the structural alterations that may lead to poorer psychosocial functioning.

A limitation of the current study is the long recruitment period spanning the years 1993-2006. During this period, changes in recruitment, treatment and operationalisation of the UHR criteria took place at the PACE clinic. As these changes did not fully account for the decline in transition rates that has been observed over the years, and other factors may have had additional impact[71], they were not controlled for in the current study. A further limitation is the time to follow-up; this varied widely from 2.4 to 12.9 years after baseline assessment and may have had an impact on functional outcome. Participants scanned at the 3T scanner were recruited later, resulting in a shorter follow-up period for this sample than data acquired on the 1.5T scanner. To control for this, length of the follow-up period and field strength of scanner were specified as nuisance variables in all analyses. However, as there are likely to be a number of sample differences over the recruitment periods[71], including over the period where data were obtained at 1.5T, this makes any direct comparison between 1.5T and 3T data far less informative. Finally, only limited information was available regarding participants' treatment at baseline and during the period between baseline and follow-up making it difficult to control for the potential impact of this factor in our analyses. Future research would do well to record these factors in more detail and control for them in subsequent analyses.

Taken together, the current findings provide novel evidence that those with the poorest functional outcomes have the lowest grey matter densities at identification as UHR, regardless of transition status or persistence of the at-risk mental state. These findings increase our understanding of psychotic illnesses and their causes and once replicated and validated may increase our ability to predict which UHR individuals are at greatest risk of having the poorest functional outcome. This may enable us to target interventions for this

group accordingly. Moreover, the current findings provide scope for application in the wider context of mental health, by increasing our understanding of those who show poor functioning but never transition to frank psychotic illness, and may suggest a shift of focus to functioning rather than distinct diagnostic categories.

Financial Disclosures

This work was supported by National Health and Medical Research Council of Australia (NHMRC) Project (grant number 209062) and Program Grants (grant numbers 350241, 566529), and by the Colonial Foundation. Dr Reniers was supported by a Medical Research Council Research Grant (grant number MR/K013599/1). Dr Lin and Dr Cropley were supported by NHMRC Early Career Fellowships (AL: fellowship number 1072593, VC: fellowship number 628880). Professor Yung was supported by a NHMRC Senior Research Fellowship (fellowship number 566593). Dr Nelson was supported by an NHMRC Clinical Career Developmental Award (award number 1027532). Professor McGorry and Professor Pantelis were supported by NHMRC Senior Principal Research Fellowships (PM: fellowship number 1060996; CP: fellowship number 628386). Professor Pantelis was furthermore supported by a NARSAD Distinguished Investigator Award (award number 18722). Professor Wood was supported by a NHMRC Clinical Career Developmental Award (award number 359223) and a NARSAD Young Investigator Award. The funding sources had no role in the study design, in the collection, analysis and interpretation of the data, in the writing of the manuscript, and in the decision to submit the manuscript for publication.

All authors declare that they have no conflicts of interest in relation to the subject of the study.

References

1. Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, McGorry PD. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophrenia research* Mar 1 2003;60(1):21-32.

2. Bora E, Fornito A, Radua J, et al. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. *Schizophrenia research* Apr 2011;127(1-3):46-57.

3. Velakoulis D, Wood SJ, Wong MT, et al. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. *Archives of general psychiatry* Feb 2006;63(2):139-149.

4. De Peri L, Crescini A, Deste G, Fusar-Poli P, Sacchetti E, Vita A. Brain structural abnormalities at the onset of schizophrenia and bipolar disorder: a meta-analysis of controlled magnetic resonance imaging studies. *Current Pharmaceutical Design* 2012;18(4):486-494.

5. Fusar-Poli P, Borgwardt S, Crescini A, Deste G, Kempton MJ, Lawrie S, Mc Guire P, Sacchetti E. Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis. *Neuroscience and Biobehavioral Reviews* Apr 2011;35(5):1175-1185.

6. Fusar-Poli P, Radua J, McGuire P, Borgwardt S. Neuroanatomical Maps of Psychosis Onset: Voxel-wise Meta-Analysis of Antipsychotic-Naive VBM Studies. *Schizophrenia Bulletin* Nov 17 2012;38(6):1297-1307.

7. Sun D, Phillips L, Velakoulis D, et al. Progressive brain structural changes mapped as psychosis develops in 'at risk' individuals. *Schizophrenia research* Mar 2009;108(1-3):85-92.

8. Pantelis C, Velakoulis D, McGorry PD, et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* Jan 25 2003;361(9354):281-288.

9. Dazzan P, Soulsby B, Mechelli A, et al. Volumetric abnormalities predating the onset of schizophrenia and affective psychoses: an MRI study in subjects at ultrahigh risk of psychosis. *Schizophrenia Bulletin* Sep 2012;38(5):1083-1091.

10. Garner B, Pariante CM, Wood SJ, et al. Pituitary volume predicts future transition to psychosis in individuals at ultra-high risk of developing psychosis. *Biological Psychiatry* Sep 1 2005;58(5):417-423.

11. Koutsouleris N, Meisenzahl EM, Davatzikos C, et al. Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. *Archives of general psychiatry* Jul 2009;66(7):700-712.

12. Walterfang M, McGuire PK, Yung AR, et al. White matter volume changes in people who develop psychosis. *British Journal of Psychiatry* Sep 2008;193(3):210-215.

13. Pantelis C, Yucel M, Bora E, Fornito A, Testa R, Brewer WJ, Velakoulis D, Wood SJ. Neurobiological markers of illness onset in psychosis and schizophrenia: The search for a moving target. *Neuropsychology Review* Sep 2009;19(3):385-398.

14. Wood SJ, Pantelis C, Velakoulis D, Yucel M, Fornito A, McGorry PD. Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. *Schizophrenia Bulletin* Mar 2008;34(2):322-329.

15. Nelson B, Yuen HP, Wood SJ, et al. Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: the PACE 400 study. *JAMA Psychiatry* Aug 2013;70(8):793-802.

16. Lin A, Wood SJ, Nelson B, et al. Neurocognitive predictors of functional outcome two to 13 years after identification as ultra-high risk for psychosis. *Schizophrenia research* Oct 2011;132(1):1-7.

17. Addington J, Cornblatt BA, Cadenhead KS, et al. At clinical high risk for psychosis: outcome for nonconverters. *The American Journal of Psychiatry* Aug 2011;168(8):800-805.

18. Salokangas RK, Nieman DH, Heinimaa M, et al. Psychosocial outcome in patients at clinical high risk of psychosis: a prospective follow-up. *Social Psychiatry and Psychiatric Epidemiology* Feb 2013;48(2):303-311.

19. Brandizzi M, Valmaggia L, Byrne M, Jones C, Iwegbu N, Badger S, McGuire P, Fusar-Poli P. Predictors of functional outcome in individuals at high clinical risk for psychosis at six years follow-up. *Journal of Psychiatric Research* Jun 2015;65:115-123.

20. Cornblatt BA, Lencz T, Smith CW, Correll CU, Auther AM, Nakayama E. The schizophrenia prodrome revisited: a neurodevelopmental perspective. *Schizophrenia Bulletin* 2003;29(4):633-651.

21. Pantelis C, Wannan C, Bartholomeusz CF, Allott K, McGorry PD. Cognitive intervention in eary psychosis - preserving abilities versus remediating deficits. *Current Opinion in Behavioral Sciences* 2015;4:63-72.

22. Schultze-Lutter F. Subjective symptoms of schizophrenia in research and the clinic: the basic symptom concept. *Schizophrenia bulletin* Jan 2009;35(1):5-8.

23. Lin A, Wood SJ, Yung AR. Measuring psychosocial outcome is good. *Curr Opin Psychiatry* Mar 2013;26(2):138-143.

24. Lin A, Nelson B, Yung AR. 'At-risk' for psychosis research: where are we heading? *Epidemiology and Psychiatric Sciences* Dec 2012;21(4):329-334.

25. Yung AR, Nelson B, Thompson A, Wood SJ. The psychosis threshold in Ultra High Risk (prodromal) research: is it valid? *Schizophrenia research* Jul 2010;120(1-3):1-6.

26. Lin A, Wood SJ, Nelson B, Beavan A, McGorry P, Yung AR. Outcomes of nontransitioned cases in a sample at ultra-high risk for psychosis. *American Journal of Psychiatry* 2014.

27. Cotter J, Drake RJ, Bucci S, Firth J, Edge D, Yung AR. What drives poor functioning in the at-risk mental state? A systematic review. *Schizophrenia research* Nov 2014;159(2-3):267-277.

28. Carrion RE, McLaughlin D, Goldberg TE, Auther AM, Olsen RH, Olvet DM, Correll CU, Cornblatt BA. Prediction of functional outcome in individuals at clinical high risk for psychosis. *JAMA Psychiatry* Nov 2013;70(11):1133-1142.

29. Yung AR, Cotter J, Wood SJ, McGorry PD, Thompson A, Nelson B, Lin A. Childhood maltreatment and transition to psychotic disorder independently predict long term functioning in young people at Ultra High Risk for psychosis. *Psychological Medicine* 2015;45(16):3453-3465.

30. Cropley VL, Lin A, Nelson B, et al. Baseline grey matter volume of non-transitioned "ultra high risk" for psychosis individuals with and without attenuated psychotic symptoms at long-term follow-up. *Schizophrenia research* May 29 2015.

31. Kambeitz-Ilankovic L, Meisenzahl EM, Cabral C, et al. Prediction of outcome in the psychosis prodrome using neuroanatomical pattern classification. *Schizophrenia research* Mar 26 2015.

32. Goldstein MJ. Further data concerning the relation between premorbid adjustment and paranoid symptomatology. *Schizophrenia Bulletin* 1978;4(2):236-243.

33. Sabb FW, van Erp TG, Hardt ME, Dapretto M, Caplan R, Cannon TD, Bearden CE. Language network dysfunction as a predictor of outcome in youth at clinical high risk for psychosis. *Schizophrenia research* Feb 2010;116(2-3):173-183.

34. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.

35. Allen P, Chaddock CA, Egerton A, et al. Functional Outcome in People at High Risk for Psychosis Predicted by Thalamic Glutamate Levels and Prefronto-Striatal Activation. *Schizophrenia Bulletin* Aug 14 2014.

36. Karlsgodt KH, Niendam TA, Bearden CE, Cannon TD. White matter integrity and prediction of social and role functioning in subjects at ultra-high risk for psychosis. *Biological Psychiatry* Sep 15 2009;66(6):562-569.

37. Faustman WO. Brief psychiatric rating scale. In: Maurish ME, ed. *The use of psychological testing for treatment planning and outcome assessment*. NJ: Lawrence Erlbaum Associates; 1994:371-401.

38. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. *Archives of general psychiatry* Aug 1992;49(8):615-623.

39. Yung AR, Yuen HP, McGorry PD, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Australian and New Zealand Journal of Psychiatry* Nov-Dec 2005;39(11-12):964-971.

40. Lin A, Yung AR, Nelson B, Brewer WJ, Riley R, Simmons M, Pantelis C, Wood SJ. Neurocognitive predictors of transition to psychosis: medium- to long-term findings from a sample at ultra-high risk for psychosis. *Psychological Medicine* Nov 2013;43(11):2349-2360.

41. Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. *British Journal of Psychiatry Supplement* Nov 1989(7):49-58.

42. Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM-IV: a review of measures of social functioning. *The American Journal of Psychiatry* Sep 1992;149(9):1148-1156.

43. Heinrichs DW, Hanlon TE, Carpenter WT, Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophrenia Bulletin* 1984;10(3):388-398.

44. Wechsler D. *Wechsler Adult Intelligence Scale-Revised*. New York: Psychological Corporation; 1981.

45. Ward LC. Prediction of verbal, performance, and full scale IQs from seven subtests of the WAIS-R. *Journal of Clinicial Psychology* Jul 1990;46(4):436-440.

46. Wechsler D. *Wechsler Abbreviated Scale of Intelligence (WASI) manual*. San Antonio, TX: Psychological Corporation; 1999.

47. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage* Jan 1 2009;44(1):83-98.

48. Shtasel DL, Gur RE, Gallacher F, Heimberg C, Cannon T, Gur RC. Phenomenology and functioning in first-episode schizophrenia. *Schizophrenia Bulletin* 1992;18(3):449-462.

49. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* Jun 2002;16(2):331-348.

50. Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America* Mar 27 2001;98(7):4259-4264.

51. Christoff K, Ream JM, Geddes LP, Gabrieli JD. Evaluating self-generated information: anterior prefrontal contributions to human cognition. *Behavioral Neuroscience* Dec 2003;117(6):1161-1168.

52. Frith U, Frith CD. Development and neurophysiology of mentalizing. *Philosophical Transactions of the Royal Society of London Series B, Biological Sciences* Mar 29 2003;358(1431):459-473.

53. Völlm BA, Taylor AN, Richardson P, Corcoran R, Stirling J, McKie S, Deakin JF, Elliott R. Neuronal correlates of theory of mind and empathy: A functional magnetic resonance imaging study in a nonverbal task. *Neuroimage* Aug 22 2006;29(1):90-98.

54. Reniers RL, Vollm BA, Elliott R, Corcoran R. Empathy, ToM, and self-other differentiation: an fMRI study of internal states. *Social Neuroscience* Feb 2014;9(1):50-62.

55. Van Overwalle F, Baetens K, Marien P, Vandekerckhove M. Social cognition and the cerebellum: a meta-analysis of over 350 fMRI studies. *NeuroImage* Feb 1 2014;86:554-572.

56. Sylvester CY, Wager TD, Lacey SC, Hernandez L, Nichols TE, Smith EE, Jonides J. Switching attention and resolving interference: fMRI measures of executive functions. *Neuropsychologia* 2003;41(3):357-370.

57. Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nature reviews Neuroscience* Mar 2011;12(3):154-167.

58. Fusar-Poli P, Rocchetti M, Sardella A, et al. Disorder, not just state of risk: meta-analysis of functioning and quality of life in people at high risk of psychosis. *The British Journal of Psychiatry: the journal of mental science* Sep 2015;207(3):198-206.

59. Isaac C, Januel D. Neural correlates of cognitive improvements following cognitive remediation in schizophrenia: a systematic review of randomized trials. *Socioaffective neuroscience & psychology* 2016;6:30054.

60. Peyroux E, Franck N. RC2S: A Cognitive Remediation Program to Improve Social Cognition in Schizophrenia and Related Disorders. *Frontiers in human neuroscience* 2014;8:400.

61. Sun D, Stuart GW, Jenkinson M, et al. Brain surface contraction mapped in first-episode schizophrenia: a longitudinal magnetic resonance imaging study. *Molecular Psychiatry* Oct 2009;14(10):976-986.

62. Fornito A, Yucel M, Patti J, Wood SJ, Pantelis C. Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophrenia research* Mar 2009;108(1-3):104-113.

63. Haast RA, Kiliaan AJ. Impact of fatty acids on brain circulation, structure and function. *Prostaglandins Leukot Essent Fatty Acids* Jan 2015;92c:3-14.

64. Kang JX, Gleason ED. Omega-3 Fatty acids and hippocampal neurogenesis in depression. *CNS Neurol Disord Drug Targets* Jun 2013;12(4):460-465.

65. Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume. *Neurobiology of Aging* Sep 2014;35 Suppl 2:S20-28.

66. Phillips C, Baktir MA, Srivatsan M, Salehi A. Neuroprotective effects of physical activity on the brain: a closer look at trophic factor signaling. *Frontiers in Cellular Neuroscience* 2014;8:170.

67. Hennebelle M, Champeil-Potokar G, Lavialle M, Vancassel S, Denis I. Omega-3 polyunsaturated fatty acids and chronic stress-induced modulations of glutamatergic neurotransmission in the hippocampus. *Nutrition Reviews* Feb 2014;72(2):99-112.

68. van der Gaag M, Smit F, Bechdolf A, French P, Linszen DH, Yung AR, McGorry P, Cuijpers P. Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups. *Schizophrenia research* Sep 2013;149(1-3):56-62.

69. Eack SM, Greenwald DP, Hogarty SS, Cooley SJ, DiBarry AL, Montrose DM, Keshavan MS. Cognitive enhancement therapy for early-course schizophrenia: effects of a two-year randomized controlled trial. *Psychiatric Services* Nov 2009;60(11):1468-1476.

70. Eack SM, Hogarty GE, Cho RY, Prasad KM, Greenwald DP, Hogarty SS, Keshavan MS. Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: results from a 2-year randomized controlled trial. *Archives of general psychiatry* Jul 2010;67(7):674-682.

71. Hartmann JA, Yuen HP, McGorry PD, Yung AR, Lin A, Wood SJ, Lavoie S, Nelson B. Declining transition rates to psychotic disorder in "ultra-high risk" clients: Investigation of a dilution effect. *Schizophrenia research* Jan 2016;170(1):130-136.

Table 1

Sample characteristics

Measure	Baseline			Follow-up			Baseline vs follow-up
	n	*Mean*	*SD*	*n*	*Mean*	*SD*	*p value*
Age	109	19.5	3.6	109	28.7	4.7	<0.001
IQ				102	99.9	19.4	
BPRS psychotic subscale	107	8.9	2.9	108	6.9	3.7	<0.001
SANS total	108	18.7	12.6	108	11.4	13.9	<0.001
SOFAS				109	67.2	15.8	
GAF	108	59.5	12.3	109	64.1	15.3	<0.006
QLS social functioning				108	36.6	10.6	
QLS vocational functioning				108	22.7	8.5	
Intake criteria	*n*	*%*					
APS only	53	48.6					
BLIPS only	10	9.2					
Vulnerability only	19	17.4					
APS + BLIPS	6	5.5					
APS + vulnerability	17	15.6					
BLIPS + vulnerability	1	0.9					
APS + BLIPS + vulnerability	3	2.8					

Note. BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; SOFAS, Social and Occupational Functioning Assessment Scale; GAF, Global Assessment of Functioning; QLS, Quality of Life Scale; APS, attenuated psychotic symptoms; BLIPS, brief limited intermittent psychotic symptoms; SD, standard deviation.

Table 2

Association between lower baseline grey matter density *and poor functional outcome (SOFAS, QLS)*

Region	BA	Left/right	Cluster size	MNI coordinates			*p*-value
				x	*y*	*z*	
Association with SOFAS scores							
Medial prefrontal cortex	10	L	1952[a]	-9	51	16	0.017
Medial prefrontal cortex	10			0	50	16	0.018
Medial prefrontal cortex	9			0	44	25	0.018
Cingulate gyrus	32	R	1352[b]	14	14	28	0.021
Anterior cingulate	32	R		16	24	25	0.021
Anterior cingulate	33	R		4	8	25	0.030
Anterior cingulate	32	L	945[c]	-12	36	9	0.028
Anterior frontal cortex	10	L		-12	34	-6	0.031
Subcallosal gyrus	25	L		-9	22	-11	0.034
Declive		L	142	-57	-58	-23	0.033
Association with QLS social functioning scores							
Medial prefrontal cortex	10	L	229	-4	51	16	0.033
Medial prefrontal cortex	9	L		-2	45	24	0.044

Note. The coordinates represent the loci of the local maxima within each distinct anatomical region in Montréal Neurological Institute (MNI) space. All clusters are FWE corrected for multiple comparisons using TFCE. Cluster sizes are indicated in number of voxels. BA, Brodmann Area. [a] This cluster extended further into BA 47, 32 and 6. [b] This cluster extended further into BA 24. [c] This cluster extended further into BA 9, 24 and the caudate.

Table 3

Association between lower baseline grey matter density *and increased negative symptoms (SANS) at follow-up*

Region	BA	Left/right	Cluster size	MNI coordinates			*p*-value
				x	*y*	*z*	
Medial prefrontal cortex	9		3353[a]	0	45	24	0.010
Cingulate gyrus	32	R		15	15	30	0.012
Anterior cingulate	32	R		16	24	25	0.012
Precentral gyrus	6	R	100	51	-3	40	0.043
Orbitofrontal cortex	11	L	40	-9	27	-9	0.048
Anterior cingulate	32	L		-10	34	-6	0.048
Anterior cingulate	25	L	38	-4	14	-11	0.049
Caudate		L		-3	9	-3	0.049
Cingulate gyrus	23	R	3	10	-16	33	0.050

Note. The coordinates represent the loci of the local maxima within each distinct anatomical region in MNI space. All clusters are FWE corrected for multiple comparisons using TFCE. Cluster sizes are indicated in number of voxels. BA, Brodmann Area. [a] This cluster extended further into BA 6 and 8.

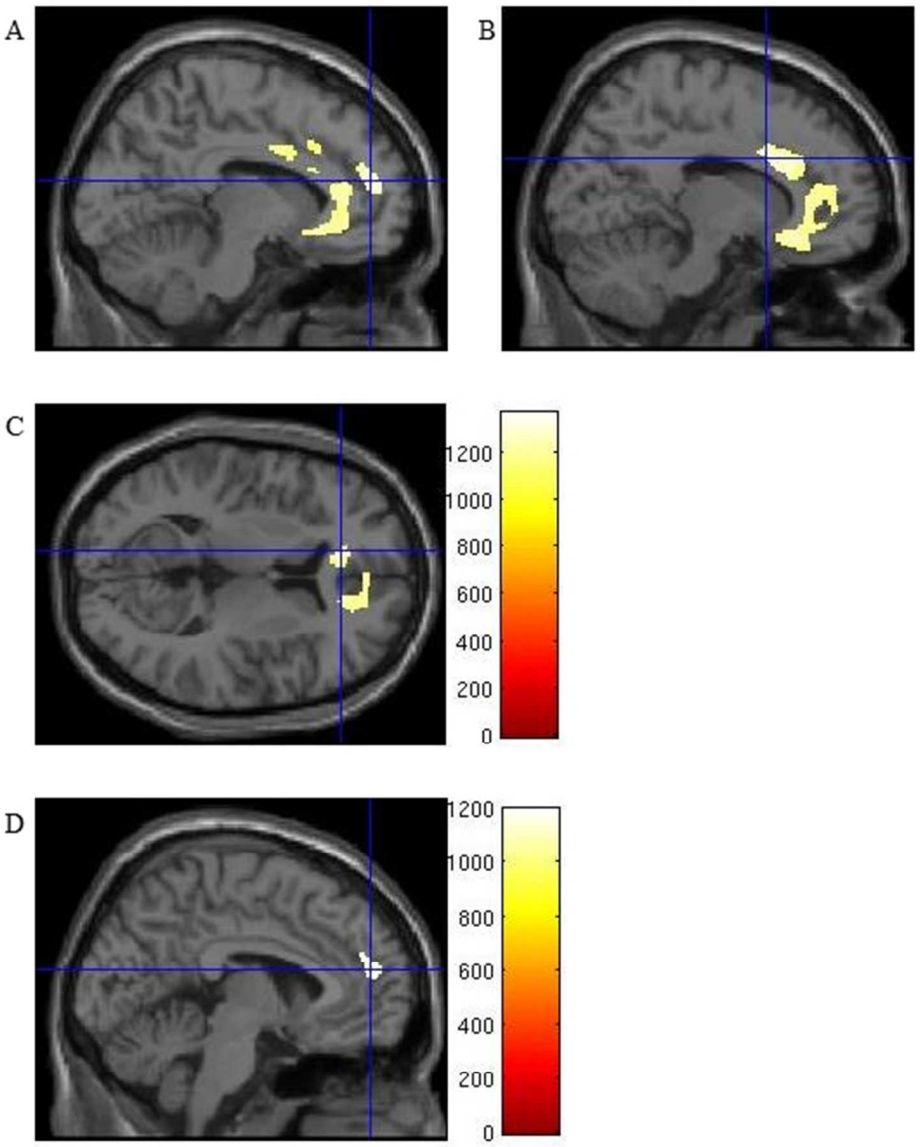
Figure Legends

Figure 1. Association between lower baseline grey matter density and poor functional outcome.

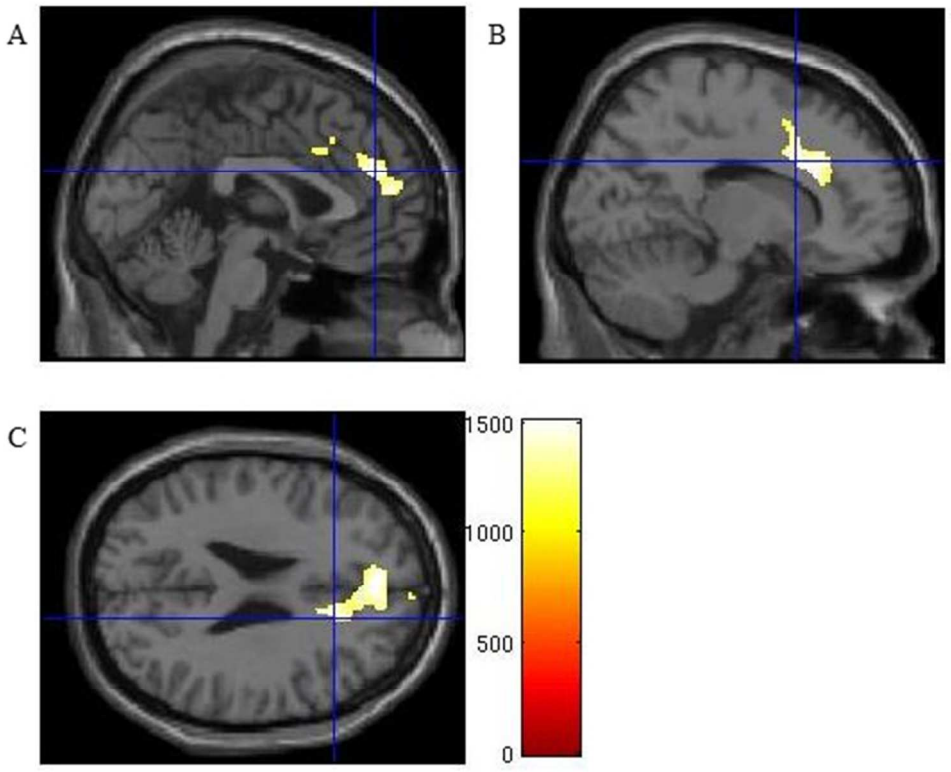
TFCE-enhanced images displaying areas of lower baseline grey matter density associated with poor functional outcome as indicated by lower scores on the Social and Occupational Functioning Assessment Scale (SOFAS) (a, b, c) and social functioning subscale of the Quality of Life Scale (QLS) (d) at follow-up. Threshold at $p<0.05$ FWE corrected. Crosshairs at a) medial prefrontal cortex [-9 51 16], b) cingulate gyrus [14 14 28], c) anterior cingulate [-12 36 9], d) medial prefrontal cortex [-4 51 16]. Colour bars show TFCE-enhanced t-statistic.

Figure 2. Association between lower baseline grey matter density and increased negative symptoms at follow-up.

TFCE-enhanced images displaying areas of lower baseline grey matter density associated with increased negative symptoms as indicated by higher scores on the Scale for the Assessment of Negative Symptoms (SANS) at follow-up. Threshold at $p<0.05$ FWE corrected. Crosshairs at a) medial prefrontal cortex [0 45 24], b) cingulate gyrus [15 15 30], c) anterior cingulate [16 24 25]. Colour bar shows TFCE-enhanced t-statistic.



145x183mm (96 x 96 DPI)



148x122mm (96 x 96 DPI)

Supplementary material

Data analysis - preprocessing

Images processed using VBM8 were written out to 1.5x1.5x1.5mm isotropic voxels in standard anatomical space (Montreal Neurological Institute, http://www.bic.mni.mcgill.ca/brainweb) and segmented into grey matter, white matter and cerebrospinal fluid. Data quality and homogeneity of the images were checked. Data of three participants were excluded from further analyses due to the mean covariance between the volumes being more than two standard deviations from the mean of the group. The modulated normalised images were smoothed with an 8mm Full-Width at Half-Maximum Gaussian kernel. Employing the General Linear Model, statistical analysis was performed on a voxel-by-voxel basis.

Sample characteristics

GAF scores at baseline did not correlate with SOFAS or QLS scores at follow-up but did show a weak positive correlation with GAF scores at follow-up (r=0.19, $p<0.05$, $d=0.33$). SOFAS scores at follow-up showed a weak negative correlation with SANS scores at baseline (r=-0.24, $p<0.05$, $d=3.39$) but no significant correlation was found with baseline GAF or BPRS psychotic subscale scores. SOFAS scores at follow-up furthermore showed a strong positive correlation with follow-up scores of GAF (r=0.94, $p<0.001$, $d=5.36$), QLS social functioning (r=0.76, $p<0.001$, $d=2.35$), and QLS vocational functioning (r=0.74, $p<0.001$, $d=2.20$). SANS scores at baseline correlated significantly with GAF scores at baseline (r=-0.49, $p<0.001$, $d=3.29$), and furthermore GAF (r=-0.27, $p<0.01$, $d=3.24$) and QLS vocational functioning (r=-0.22, $p<0.05$, $d=0.37$) at follow-up. There was no association with QLS social functioning or IQ at follow-up. SANS scores at follow-up correlated significantly with SOFAS (r=-0.71, $p<0.001$, $d=3.75$), GAF (r=-0.69, $p<0.001$, $d=3.61$), QLS social functioning (r=-0.71, $p<0.001$, $d=2.03$), QLS vocational functioning (r=-0.58, $p<0.001$, $d=0.98$), and IQ (r=-0.22, $p<0.05$, $d=5.24$) at follow-up. IQ at follow-up (available for n=102) showed a weak positive correlation with SOFAS scores at follow-up (r=0.24, $p<0.05$, $d=0.50$) and GAF scores at follow-up (r=0.27, $p<0.01$, $d=0.57$) but was not significantly related to QLS scores.

Of the 38 participants who transitioned to psychosis by the time of follow-up, 14 had a diagnosis of schizophrenia, 5 bipolar disorder with psychotic features, 1 schizoaffective disorder, 5 psychotic disorder NOS, 5 MDD with psychotic features, 3 delusional disorder, 2 substance induced psychotic disorder, 2 brief psychotic disorder and for 1 participant the specific diagnosis was not available. Those with a diagnosis of schizophrenia (n=14) did not have a significant worse outcome than those with a differential diagnosis. Neuroleptic and antidepressant medication use at baseline was documented for 70 (64%) of the 109

participants. Of these participants, 1 (1%) reported taking neuroleptics and 11 (16%) reported antidepressant use while the remainder (n=58, 83%) reported no use of neuroleptics or antidepressants. At follow-up, 29 participants (27%) reported taking medication for psychiatric problems for some of the period between baseline and follow-up while 22 participants (20%) reported to have been on medication most of the time. 23 (21%) participants received low-dose neuroleptics (risperidone) and 1 (1%) received low-dose lithium as trial treatment at PACE after study entry. 55 participants (50%) reported receiving non-pharmacological treatment. Overall, 79 participants (72%) received either (n=36) or both (n=43) forms of treatment in the period between baseline and follow-up. Those who received neuroleptic medication in the period between baseline and follow-up scored significantly lower on all functioning measures at both baseline and follow-up than those who did not receive any neuroleptic medication (Table A1).

Table A1

Functioning scores for those who received neuroleptic medication in the period between baseline and follow-up and those who did not receive any neuroleptic medication during this time

Measure	Neuroleptics since entry at PACE			No neuroleptics since entry at PACE			Neuroleptics vs no neuroleptics
	n	*Mean*	*SD*	*n*	*Mean*	*SD*	*p value*
	Baseline						
GAF	24	54.0	10.7	74	61.4	11.7	<0.008
	Follow-up						
SOFAS	24	56.2	17.1	75	71.2	13.8	<0.001
GAF	24	53.5	16.0	75	67.8	13.8	<0.001
QLS social functioning	23	31.3	13.4	75	38.1	9.3	<0.05
QLS vocational functioning	23	17.9	9.9	75	24.6	7.2	<0.006

Note. GAF, Global Assessment of Functioning; SOFAS, Social and Occupational Functioning Assessment Scale; QLS, Quality of Life Scale; SD, standard deviation.

Table A2

Association between lower baseline grey matter density and poor functional outcome (SOFAS) including symptom severity (SANS and BPRS psychotic subscale scores) at baseline as nuisance variables.

Region	BA	Left/right	Cluster size	MNI coordinates			*p*-value
				x	*y*	*z*	
Medial prefrontal cortex	10	L	42	-8	52	15	0.049
Declive		L	11	-56	-60	-23	0.040

Note. The coordinates represent the loci of the local maxima within each distinct anatomical region in MNI space. All clusters are FWE corrected for multiple comparisons using TFCE. Cluster sizes are indicated in number of voxels. BA, Brodmann Area; SOFAS, Social and Occupational Functioning Assessment Scale; SANS, Scale for the Assessment of Negative Symptoms; BPRS, Brief Psychiatric Rating Scale.

Table A3

Association between lower baseline grey matter density and absolute decline in functioning (GAF)

Region	BA	Left/right	Cluster size	MNI coordinates			*p*-value
				x	*y*	*z*	
Middle frontal gyrus	46	R	232	48	21	30	0.042
Inferior frontal gyrus	45	R		44	16	19	0.044
Inferior frontal gyrus	9	L	13	-45	-3	27	0.047

Note. The coordinates represent the loci of the local maxima within each distinct anatomical region in MNI space. All clusters are FWE corrected for multiple comparisons using TFCE. Cluster sizes are indicated in number of voxels. BA, Brodmann Area.

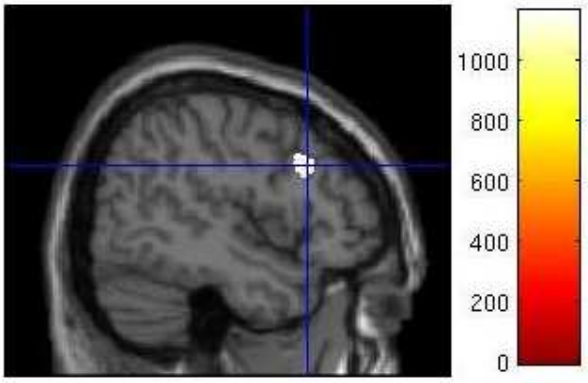


Figure A1. Association between lower baseline grey matter density and absolute decline in functioning (GAF).

TFCE-enhanced image displaying the area of lower baseline grey matter density associated with functional decline as indicated by lower absolute change scores on the Global Assessment of Functioning scale (GAF). Threshold at $p<0.05$ FWE corrected. Crosshairs at middle frontal gyrus [48 21 30]. Colour bar shows TFCE-enhanced t-statistic.