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

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

Running head: Neuroanatomical predictors of functional outcome

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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 psychosis¹. 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 volume²⁻⁴) may arise during or even before the onset phase of psychosis⁵⁻⁸. These brain changes have a demonstrated relationship with transition to psychosis^{5, 9-12} and may serve as biomarkers for onset of illness¹³ and inform intervention efforts¹⁴.

However, the majority of UHR individuals do not transition to psychosis¹⁵ and despite this, many still show poor psychosocial functioning at follow-up¹⁶⁻¹⁹. 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 vulnerability²⁰ 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 individuals²⁶.

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3 Research in UHR individuals^{16, 27, 28} has shown that reduced neurocognitive
4
5 performance on measures of verbal learning and memory, processing speed and attention, and
6
7 verbal fluency predicts poor functional outcome. Functional outcomes also appear to be
8
9 associated with a history of childhood maltreatment, regardless of transition status²⁹, and non-
10
11 resolving attenuated psychotic symptoms^{30, 31}. The limited research on associated brain
12
13 functioning shows that poorer social functioning as measured by the Social Attainment
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15 Survey³² can be predicted by increased activation in anterior cingulate and left inferior frontal
16
17 gyrus during performance of a reasoning language processing task³³. Likewise, poor
18
19 functioning as indicated by low Global Assessment of Functioning (GAF³⁴) scores has been
20
21 predicted by increased left inferior frontal and insula activation during performance of a
22
23 verbal fluency task and lower thalamic glutamate levels³⁵. On the structural level, lower
24
25 baseline fractional anisotropy (FA) in the hippocampus and inferior longitudinal fasciculus in
26
27 UHR individuals has been shown to predict deterioration in social and role functioning at 15
28
29 month follow-up³⁶. These latter studies have been limited by the small UHR samples and
30
31 short follow-up period (6-24 months) for assessment of functional outcome.
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36 The current study aimed to further investigate the structural alterations associated
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38 with poor functional outcome in a larger sample of UHR individuals followed over the
39
40 medium- to long-term. We adopted a voxel-based morphometry approach to investigate
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42 whether grey and white matter brain density of individuals at UHR for psychosis could
43
44 predict functional outcome 2.4 to 12.9 years later, and if this association would be related to
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46 transition status. Based on the findings described above, we predicted that lower densities in
47
48 frontal and temporal regions at baseline would be associated with poorer psychosocial
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50 functioning at follow-up.
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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 (BPRS³⁷)/Comprehensive Assessment of Symptoms and History (CASH³⁸)/GAF³⁴ and the Comprehensive Assessment of At-Risk Mental States (CAARMS³⁹). 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

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2
3 assessments of this sample took place between 2.4 and 12.9 (mean=9.2, SD=2.5, median=9.8)
4
5 years after study entry at PACE.
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8

9 10 **Assessments**

11
12 Participants underwent clinical assessment and MRI at baseline. Clinical assessment
13
14 included assessment of positive symptoms using the BPRS³⁷, negative symptoms using the
15
16 Scale for the Assessment of Negative Symptoms (SANS⁴¹), and GAF³⁴ for functioning.
17
18 During the follow-up assessment, baseline measures were re-administered and the Social and
19
20 Occupational Functioning Assessment Scale (SOFAS⁴²) and Quality of Life Scale (QLS⁴³)
21
22 were used as indices of functional outcome. For participants recruited before the year 2000
23
24 (n=73, 67% of the current sample), IQ at follow-up was measured using subtests of the
25
26 Wechsler Adult Intelligence Scale-Revised (WAIS-R⁴⁴) proposed by Ward⁴⁵. These subtests
27
28 are information, picture completion, block design, arithmetic, digit span, similarities and digit
29
30 symbol. For participants recruited from the year 2000 onwards (n=36, 33% of the current
31
32 sample), the full Wechsler Abbreviated Scale of Intelligence (WASI⁴⁶) was used to measure
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34 IQ at follow-up. Transition to frank psychosis was established using the CAARMS³⁹ or the
35
36 state public mental health records when CAARMS data were not available.
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43 **MRI acquisition**

44
45 80% (n=87) of the T1-weighted MRI scans were obtained using a 1.5T GE Signa MR
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47 scanner: 124 slices of 1.5mm thickness, TR=1.43s, TE=3.3ms, flip angle 30°, matrix
48
49 256x256, FOV 24cm. The remaining 20% (n=22) of the T1-weighted MRI scans were
50
51 obtained using a 3T GE LX Horizon Scanner: 124 slices of 2mm thickness, TR=3.6s,
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53 TE=9ms, flip angle 30°, matrix 410x410, FOV 20cm.
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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 threshold⁴⁷. 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

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2
3 of a percentage change score and an absolute change score. The SOFAS does not assess
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5 social and role functioning separately and therefore the QLS was additionally employed. The
6
7 QLS is based on self-report but has the advantage that its items can be factored into social
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9 functioning, vocational functioning and engagement⁴⁸. Data on this measure was available for
10
11 108 participants and scores on the social and vocational functioning scales were used to
12
13 investigate if density associations were more specifically associated with either social- or
14
15 vocational functioning.
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19 Given that negative symptoms and general cognitive ability are strongly associated
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21 with functional outcome^{23,27}, density associations with negative symptoms and IQ measured
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23 at follow-up were additionally examined, along with density associations with positive
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25 symptoms at follow-up. Available follow-up data were as follows; SANS n=107, IQ n=102,
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27 and BPRS positive n=105.
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32 Results

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34 Characteristics of the sample are presented in Table 1. Of the 109 participants, 38
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36 (35%) had transitioned to psychosis by the time of follow-up. The average length of time to
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38 conversion was 622 days (SD=719 days). Of those who had not transitioned to psychosis by
39
40 the time of follow-up, 27 (38%) met APS or BLIPS criteria. Further details about the sample
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42 are presented in the supplementary materials.
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48 -Table 1-
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52 Primary analysis

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54 Lower than average baseline grey matter density was significantly associated with
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56 lower SOFAS scores at follow-up. This association was found in large clusters in medial
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3 prefrontal cortex, right cingulate gyrus extending into anterior cingulate, left anterior
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5 cingulate extending into anterior frontal cortex and subcallosal gyrus, and left cerebellar
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7 declive (Table 2, Figure 1). These areas of association were lower in size when symptom
8
9 severity (SANS and BPRS psychotic subscale scores at baseline) were additionally added as
10
11 nuisance variables (supplementary materials Table A2). To determine whether this pattern
12
13 was being driven by the individuals who had transitioned to psychosis at follow-up (note,
14
15 transition status at follow-up was entered as a nuisance variable in all analyses), a secondary
16
17 analysis was conducted. A comparison of the relationship of baseline grey matter with
18
19 functional outcome in the identified bilateral frontal and limbic areas, and left declive, in
20
21 those who had transitioned to psychosis at follow-up (n=37) with those who had not (n=69)
22
23 revealed no significant differences. The same comparison for those who had not transitioned
24
25 to psychosis but met APS or BLIPS criteria at follow-up (n=27) with those who had not
26
27 transitioned to psychosis and did not meet APS or BLIPS criteria at follow-up (n=42)
28
29 revealed no significant differences either. There was no significant association between
30
31 higher baseline grey matter density and lower SOFAS scores at follow-up. There was no
32
33 significant association between baseline white matter density (lower or higher) and SOFAS
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35 scores at follow-up and therefore subsequent analyses focussed on grey matter density
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37 associations only.
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45 -Table 2, Figure 1-
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49 **Exploratory analyses**

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51 No significant association was found between baseline grey matter density (lower or
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53 higher) and baseline GAF score or percentage change in GAF score. Lower baseline grey
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2
3 matter density in middle and inferior frontal gyri was, however, significantly associated with
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5 decline in GAF score over follow-up (supplementary materials Table A3, Figure A1).
6

7
8 Lower baseline grey matter density in left medial prefrontal cortex was significantly
9
10 associated with lower social functioning scores on the QLS at follow-up (Table 2, Figure 1).
11
12 There was no significant association between higher baseline grey matter density and social
13
14 functioning scores on the QLS at follow-up. No significant association was observed between
15
16 baseline grey matter density (lower or higher) and vocational functioning scores on the QLS
17
18 at follow-up.
19

20
21 Significantly lower baseline grey matter density was observed in a large cluster
22
23 extending from medial prefrontal cortex into cingulate gyrus and anterior cingulate, and
24
25 clusters in right precentral and cingulate gyrus, left orbitofrontal cortex extending into
26
27 anterior cingulate, and left anterior cingulate extending into caudate in association with
28
29 higher SANS scores at follow-up (Table 3, Figure 2). Further exploratory analyses revealed
30
31 that this association was not driven by a particular SANS subscale. There was no significant
32
33 association between higher baseline grey matter density and SANS scores at follow-up.
34
35

36
37 No significant association was observed between baseline grey matter density and IQ
38
39 at follow-up or between baseline grey matter density and positive symptoms at follow-up.
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43 -Table 3, Figure 2-
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46 47 48 **Discussion**

49
50 This study investigated the association between baseline grey and white matter
51
52 density and functional outcome 2.4 to 12.9 years after identification as UHR for psychosis.
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54 Lower baseline grey matter density in large clusters in bilateral frontal and limbic regions and
55
56 left cerebellar declive were associated with poorer functional outcome. These findings were
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2
3 independent of transition status or persistence of the at-risk mental state at follow-up
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5 (although in this regard we were only powered to detect a large effect and replication in
6
7 larger samples is required). We did not observe an association between larger baseline grey
8
9 matter density and poorer functional outcome, and there was no association between baseline
10
11 white matter density (lower or higher) and functional outcome. Lower baseline grey matter
12
13 density in middle and inferior frontal gyri was associated with absolute decline in
14
15 functioning. When social and vocational functioning were investigated separately, poorer
16
17 social functioning at follow-up was associated with lower baseline grey matter density in an
18
19 area of left medial prefrontal cortex that overlapped with the medial prefrontal region
20
21 observed for the association with functional outcome. Even though both social and vocational
22
23 functional scores on the QLS showed a strong relationship with functioning as measured by
24
25 the SOFAS, vocational functioning at follow-up was not associated with baseline grey matter
26
27 density. Exploration of the association between baseline grey matter density and increased
28
29 negative symptoms at follow-up revealed areas of lower density in bilateral frontal and limbic
30
31 regions that partially overlapped with those observed in the association with functional
32
33 outcome. No association was found between baseline grey matter density and IQ or positive
34
35 symptoms at follow-up.
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41 The findings regarding QLS social functioning do advocate for a key role for social
42
43 dysfunction in the poor functional outcomes in this sample. Both the anterior and medial
44
45 prefrontal regions have been shown to play an important role in emotion processing⁴⁹, and in
46
47 social abilities such as self-referential processing^{50, 51}, empathy, Theory of Mind and
48
49 perspective taking⁵²⁻⁵⁴. The brain areas observed in the association of baseline grey matter
50
51 density and SOFAS scores at follow-up support this suggestion as recruitment of the anterior
52
53 cingulate has been associated with performance of emotional tasks with cognitive demand
54
55 and emotional recall/imagery⁴⁹. Lower baseline grey matter density of the decline was
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1
2
3 associated with poorer functional outcome but not with increased negative symptoms at
4
5 follow-up, providing additional support for the suggestion that social dysfunction may
6
7 underlie poorer functional outcome in the current sample. The cerebellum has been
8
9 implicated in social-cognitive functioning in that it provides domain-general executive and
10
11 semantic support⁵⁵, consistent with findings of higher cerebellar activity when executive
12
13 resources are demanded to support mentalizing in contexts with a high level of abstraction⁵⁵.
14
15 It needs noting that the current SOFAS findings represent an overall association between
16
17 lower baseline grey matter density and poorer psychosocial outcome that includes social and
18
19 role functioning. While many of the observed areas respond to social cognitive paradigms,
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21 they may also have involvement in so called ‘cold cognition’ paradigms in which rational
22
23 reasoning takes prominence over emotions^{56, 57}.
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27
28 The observed partial overlap in brain areas that showed lower grey matter density at
29
30 baseline in association with poorer functional outcome and increased negative symptoms
31
32 illustrates the strong association between negative symptoms and functional outcome on both
33
34 the conceptual and neural level and is consistent with the manifestation of cognitive deficits,
35
36 affective disturbances, social isolation and school failure as suggested by the first dimension
37
38 of vulnerability of the CASIS model²⁰.
39

40
41 The brain areas that show lower grey matter density in association with poorer
42
43 functional outcome as assessed by the SOFAS do not include the dorsolateral prefrontal
44
45 cortex, suggesting that changes in baseline density of this brain area and associated cognitive
46
47 impairments are not associated with poorer functioning in later years. This is consistent with
48
49 our failure to observe an association between baseline grey matter density and estimated IQ at
50
51 follow-up as an approximate measure of general cognitive ability. This is also in line with our
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53 earlier finding¹⁶ which showed that specific neurocognitive domains (verbal learning and
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55 memory, processing speed and attention, and verbal fluency), but not global cognitive
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3 impairment, predicted poor functional outcome. In contrast, the area observed in association
4
5 with decline in GAF score in the period between baseline and follow-up does overlap with
6
7 the dorsolateral prefrontal cortex. Lower densities observed in this association may, however,
8
9 reflect worse symptomatic outcome rather than cognitive impairment (for further discussion
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11 see our recent paper on attenuated psychotic symptoms in this sample³⁰) or general low
12
13 functioning at follow-up.
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16 The current findings support recent statements that treatment should not only be
17
18 focussed on those who will develop above threshold psychotic symptoms but also on those
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20 with poor functional outcome^{23, 25, 58}. Moreover and consistent with the current findings,
21
22 treatments that specifically target social impairments, such as social cognitive remediation⁵⁹,
23
24 ⁶⁰, could be a way of alleviating long-term social disability and distress. Lower grey matter
25
26 densities as observed in the current study are commonly found in first-episode psychosis^{6, 7, 61}
27
28 and chronic schizophrenia^{2, 62}. Detection of these structural alterations as early as the at-risk
29
30 mental state supports early intervention approaches in those with a prospective diagnosis of
31
32 psychosis but also in those with a prospective diagnosis of non-psychotic disorders that are
33
34 associated with poor functional outcome. Evidence is emerging that interventions involving
35
36 exercise or the administration of essential fatty acids alter brain structure⁶³⁻⁶⁷ and a recent
37
38 meta-analysis has shown that these efforts, as well as administration of neuroleptics and
39
40 cognitive behavioural therapy, may show efficacy in preventing or delaying transition⁶⁸.
41
42 Cognitive enhancement therapy in patients with schizophrenia or schizoaffective disorder has
43
44 been shown to not only improve neurocognitive functioning⁶⁹, but to also have
45
46 neuroprotective properties as demonstrated by preservation and even increase of grey matter
47
48 density in limbic areas⁷⁰. Early intervention using these techniques may preserve function²¹.
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50 The next step should therefore involve implementation and evaluation of the efficacy of
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3 psychosocial interventions in individuals at UHR for psychosis to reverse the structural
4
5 alterations that may lead to poorer psychosocial functioning.

6
7 A limitation of the current study is the long recruitment period spanning the years
8
9 1993-2006. During this period, changes in recruitment, treatment and operationalisation of
10
11 the UHR criteria took place at the PACE clinic. As these changes did not fully account for the
12
13 decline in transition rates that has been observed over the years, and other factors may have
14
15 had additional impact⁷¹, they were not controlled for in the current study. A further limitation
16
17 is the time to follow-up; this varied widely from 2.4 to 12.9 years after baseline assessment
18
19 and may have had an impact on functional outcome. Participants scanned at the 3T scanner
20
21 were recruited later, resulting in a shorter follow-up period for this sample than data acquired
22
23 on the 1.5T scanner. To control for this, length of the follow-up period and field strength of
24
25 scanner were specified as nuisance variables in all analyses. However, as there are likely to
26
27 be a number of sample differences over the recruitment periods⁷¹, including over the period
28
29 where data were obtained at 1.5T, this makes any direct comparison between 1.5T and 3T
30
31 data far less informative. Finally, only limited information was available regarding
32
33 participants' treatment at baseline and during the period between baseline and follow-up
34
35 making it difficult to control for the potential impact of this factor in our analyses. Future
36
37 research would do well to record these factors in more detail and control for them in
38
39 subsequent analyses.
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45 Taken together, the current findings provide novel evidence that those with the
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47 poorest functional outcomes have the lowest grey matter densities at identification as UHR,
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49 regardless of transition status or persistence of the at-risk mental state. These findings
50
51 increase our understanding of psychotic illnesses and their causes and once replicated and
52
53 validated may increase our ability to predict which UHR individuals are at greatest risk of
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55 having the poorest functional outcome. This may enable us to target interventions for this
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2
3 group accordingly. Moreover, the current findings provide scope for application in the wider
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5 context of mental health, by increasing our understanding of those who show poor
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7 functioning but never transition to frank psychotic illness, and may suggest a shift of focus to
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9 functioning rather than distinct diagnostic categories.
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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.

Reniers et al. - NEUROANATOMICAL PREDICTORS OF FUNCTIONAL OUTCOME 18

- 1
2
3 8. Pantelis C, Velakoulis D, McGorry PD, et al. Neuroanatomical abnormalities before
4 and after onset of psychosis: a cross-sectional and longitudinal MRI comparison.
5
6 *Lancet* Jan 25 2003;361(9354):281-288.
7
- 8
9 9. Dazzan P, Soulsby B, Mechelli A, et al. Volumetric abnormalities predating the onset
10 of schizophrenia and affective psychoses: an MRI study in subjects at ultrahigh risk of
11 psychosis. *Schizophrenia Bulletin* Sep 2012;38(5):1083-1091.
12
13
- 14 10. Garner B, Pariante CM, Wood SJ, et al. Pituitary volume predicts future transition to
15 psychosis in individuals at ultra-high risk of developing psychosis. *Biological*
16 *Psychiatry* Sep 1 2005;58(5):417-423.
17
18
- 19 11. Koutsouleris N, Meisenzahl EM, Davatzikos C, et al. Use of neuroanatomical pattern
20 classification to identify subjects in at-risk mental states of psychosis and predict
21 disease transition. *Archives of general psychiatry* Jul 2009;66(7):700-712.
22
23
- 24 12. Walterfang M, McGuire PK, Yung AR, et al. White matter volume changes in people
25 who develop psychosis. *British Journal of Psychiatry* Sep 2008;193(3):210-215.
26
27
- 28 13. Pantelis C, Yucel M, Bora E, Fornito A, Testa R, Brewer WJ, Velakoulis D, Wood
29 SJ. Neurobiological markers of illness onset in psychosis and schizophrenia: The
30 search for a moving target. *Neuropsychology Review* Sep 2009;19(3):385-398.
31
32
- 33 14. Wood SJ, Pantelis C, Velakoulis D, Yucel M, Fornito A, McGorry PD. Progressive
34 changes in the development toward schizophrenia: studies in subjects at increased
35 symptomatic risk. *Schizophrenia Bulletin* Mar 2008;34(2):322-329.
36
37
- 38 15. Nelson B, Yuen HP, Wood SJ, et al. Long-term follow-up of a group at ultra high risk
39 ("prodromal") for psychosis: the PACE 400 study. *JAMA Psychiatry* Aug
40 2013;70(8):793-802.
41
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Reniers et al. - NEUROANATOMICAL PREDICTORS OF FUNCTIONAL OUTCOME 19

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2
3 **16.** Lin A, Wood SJ, Nelson B, et al. Neurocognitive predictors of functional outcome
4 two to 13 years after identification as ultra-high risk for psychosis. *Schizophrenia*
5 *research* Oct 2011;132(1):1-7.
6
7
- 8
9 **17.** Addington J, Cornblatt BA, Cadenhead KS, et al. At clinical high risk for psychosis:
10 outcome for nonconverters. *The American Journal of Psychiatry* Aug
11 2011;168(8):800-805.
12
13
- 14 **18.** Salokangas RK, Nieman DH, Heinimaa M, et al. Psychosocial outcome in patients at
15 clinical high risk of psychosis: a prospective follow-up. *Social Psychiatry and*
16 *Psychiatric Epidemiology* Feb 2013;48(2):303-311.
17
18
- 19 **19.** Brandizzi M, Valmaggia L, Byrne M, Jones C, Iwegbu N, Badger S, McGuire P,
20 Fusar-Poli P. Predictors of functional outcome in individuals at high clinical risk for
21 psychosis at six years follow-up. *Journal of Psychiatric Research* Jun 2015;65:115-
22 123.
23
24
- 25 **20.** Cornblatt BA, Lencz T, Smith CW, Correll CU, Auther AM, Nakayama E. The
26 schizophrenia prodrome revisited: a neurodevelopmental perspective. *Schizophrenia*
27 *Bulletin* 2003;29(4):633-651.
28
29
- 30 **21.** Pantelis C, Wannan C, Bartholomeusz CF, Allott K, McGorry PD. Cognitive
31 intervention in early psychosis - preserving abilities versus remediating deficits.
32 *Current Opinion in Behavioral Sciences* 2015;4:63-72.
33
34
- 35 **22.** Schultze-Lutter F. Subjective symptoms of schizophrenia in research and the clinic:
36 the basic symptom concept. *Schizophrenia bulletin* Jan 2009;35(1):5-8.
37
38
- 39 **23.** Lin A, Wood SJ, Yung AR. Measuring psychosocial outcome is good. *Curr Opin*
40 *Psychiatry* Mar 2013;26(2):138-143.
41
42
- 43 **24.** Lin A, Nelson B, Yung AR. 'At-risk' for psychosis research: where are we heading?
44 *Epidemiology and Psychiatric Sciences* Dec 2012;21(4):329-334.
45
46
47
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Reniers et al. - NEUROANATOMICAL PREDICTORS OF FUNCTIONAL OUTCOME 20

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2
3 25. Yung AR, Nelson B, Thompson A, Wood SJ. The psychosis threshold in Ultra High
4 Risk (prodromal) research: is it valid? *Schizophrenia research* Jul 2010;120(1-3):1-6.
5
6
- 7 26. Lin A, Wood SJ, Nelson B, Beavan A, McGorry P, Yung AR. Outcomes of
8 nontransitioned cases in a sample at ultra-high risk for psychosis. *American Journal*
9 *of Psychiatry* 2014.
10
11
- 12 27. Cotter J, Drake RJ, Bucci S, Firth J, Edge D, Yung AR. What drives poor functioning
13 in the at-risk mental state? A systematic review. *Schizophrenia research* Nov
14 2014;159(2-3):267-277.
15
16
- 17 28. Carrion RE, McLaughlin D, Goldberg TE, Auther AM, Olsen RH, Olvet DM, Correll
18 CU, Cornblatt BA. Prediction of functional outcome in individuals at clinical high
19 risk for psychosis. *JAMA Psychiatry* Nov 2013;70(11):1133-1142.
20
21
- 22 29. Yung AR, Cotter J, Wood SJ, McGorry PD, Thompson A, Nelson B, Lin A.
23 Childhood maltreatment and transition to psychotic disorder independently predict
24 long term functioning in young people at Ultra High Risk for psychosis.
25 *Psychological Medicine* 2015;45(16):3453-3465.
26
27
- 28 30. Croyley VL, Lin A, Nelson B, et al. Baseline grey matter volume of non-transitioned
29 "ultra high risk" for psychosis individuals with and without attenuated psychotic
30 symptoms at long-term follow-up. *Schizophrenia research* May 29 2015.
31
32
- 33 31. Kambeitz-Illankovic L, Meisenzahl EM, Cabral C, et al. Prediction of outcome in the
34 psychosis prodrome using neuroanatomical pattern classification. *Schizophrenia*
35 *research* Mar 26 2015.
36
37
- 38 32. Goldstein MJ. Further data concerning the relation between premorbid adjustment and
39 paranoid symptomatology. *Schizophrenia Bulletin* 1978;4(2):236-243.
40
41
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60
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.

Reniers et al. - NEUROANATOMICAL PREDICTORS OF FUNCTIONAL OUTCOME 22

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2
3 41. Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS):
4 conceptual and theoretical foundations. *British Journal of Psychiatry Supplement* Nov
5 1989(7):49-58.
6
7
- 8
9 42. Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM-IV: a review of
10 measures of social functioning. *The American Journal of Psychiatry* Sep
11 1992;149(9):1148-1156.
12
13
- 14 43. Heinrichs DW, Hanlon TE, Carpenter WT, Jr. The Quality of Life Scale: an
15 instrument for rating the schizophrenic deficit syndrome. *Schizophrenia Bulletin*
16 1984;10(3):388-398.
17
18
- 19 44. Wechsler D. *Wechsler Adult Intelligence Scale-Revised*. New York: Psychological
20 Corporation; 1981.
21
22
- 23 45. Ward LC. Prediction of verbal, performance, and full scale IQs from seven subtests of
24 the WAIS-R. *Journal of Clinical Psychology* Jul 1990;46(4):436-440.
25
26
- 27 46. Wechsler D. *Wechsler Abbreviated Scale of Intelligence (WASI) manual*. San
28 Antonio, TX: Psychological Corporation; 1999.
29
30
- 31 47. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of
32 smoothing, threshold dependence and localisation in cluster inference. *Neuroimage*
33 Jan 1 2009;44(1):83-98.
34
35
- 36 48. Shtasel DL, Gur RE, Gallacher F, Heimberg C, Cannon T, Gur RC. Phenomenology
37 and functioning in first-episode schizophrenia. *Schizophrenia Bulletin*
38 1992;18(3):449-462.
39
40
- 41 49. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a
42 meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* Jun
43 2002;16(2):331-348.
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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.

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57
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60
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.

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42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
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60
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.

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Table 1

Sample characteristics

Measure	Baseline			Follow-up			Baseline vs follow-up p value
	n	Mean	SD	n	Mean	SD	
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.

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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			<i>p</i> -value
				<i>x</i>	<i>y</i>	<i>z</i>	
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.

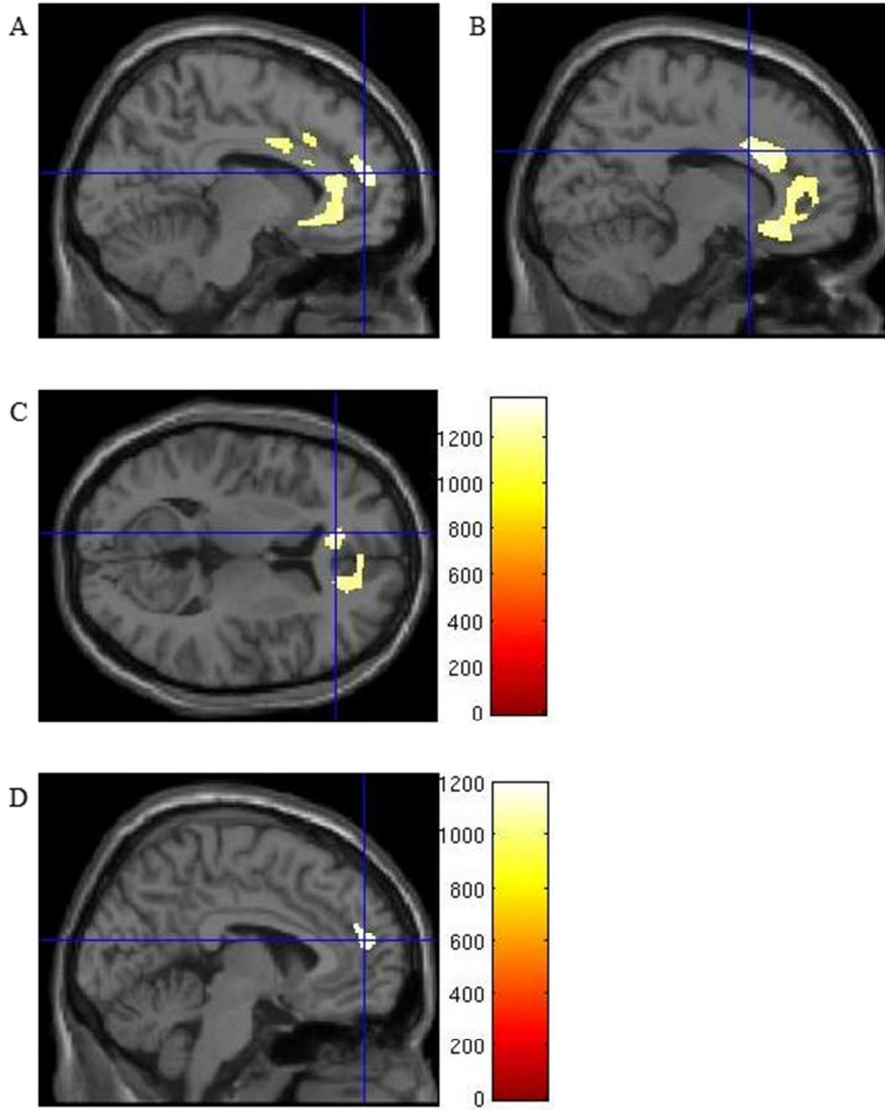
Figure Legends

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.

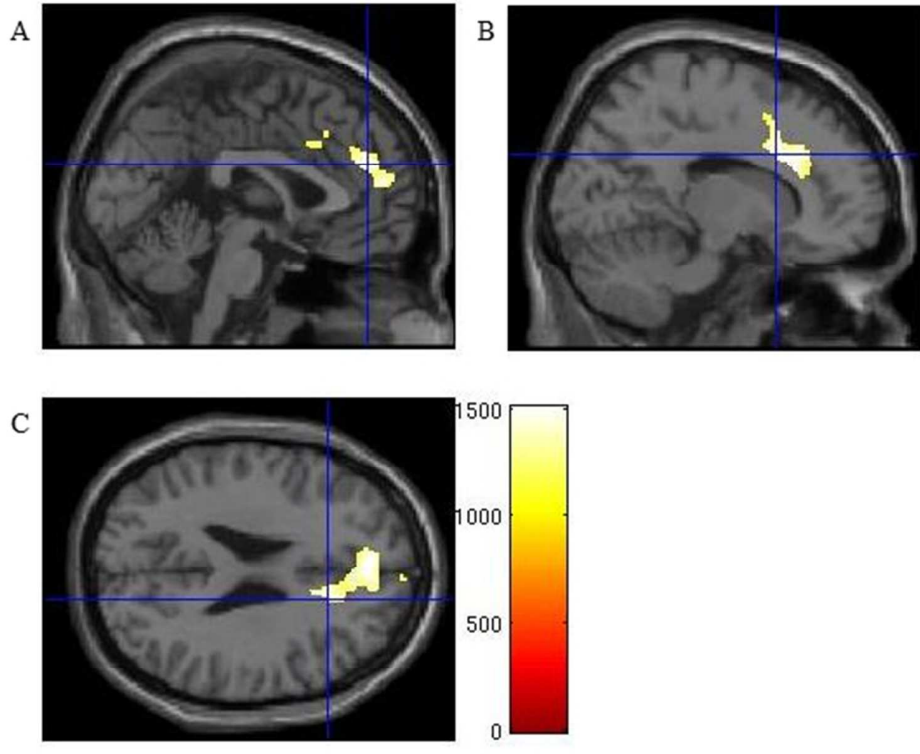
TFCE-enhanced images displaying areas of lower baseline grey matter density associated with increased negative symptoms as indicated by higher scores on the Scale for the Assessment of Negative Symptoms (SANS) at follow-up. Threshold at $p < 0.05$ FWE corrected. Crosshairs at a) medial prefrontal cortex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



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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

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

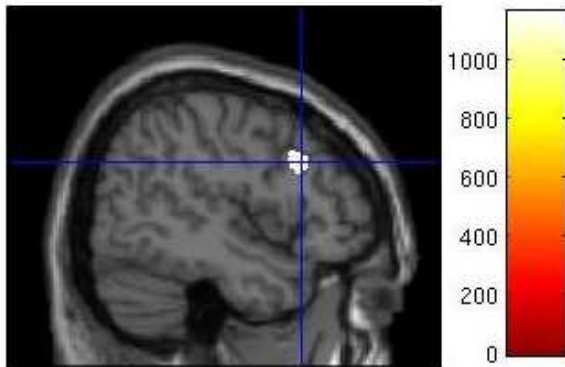


Figure A1. Association between lower baseline grey matter density and absolute decline in functioning (GAF).

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.