

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
14
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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35

36 The current study aimed to further investigate the structural alterations associated
37
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
41
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
45
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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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 BPRS³⁷, negative symptoms using the Scale for the Assessment of Negative Symptoms (SANS⁴¹), and GAF³⁴ for functioning. During the follow-up assessment, baseline measures were re-administered and the Social and Occupational Functioning Assessment Scale (SOFAS⁴²) and Quality of Life Scale (QLS⁴³) 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-R⁴⁴) proposed by Ward⁴⁵. 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 (WASI⁴⁶) was used to measure IQ at follow-up. Transition to frank psychosis was established using the CAARMS³⁹ 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 30°, 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 30°, 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 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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1
2
3 of a percentage change score and an absolute change score. The SOFAS does not assess
4
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
8
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
20
21 with functional outcome^{23,27}, density associations with negative symptoms and IQ measured
22
23 at follow-up were additionally examined, along with density associations with positive
24
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

33
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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46

47 -Table 1-
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51 Primary analysis

52
53 Lower than average baseline grey matter density was significantly associated with
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55 lower SOFAS scores at follow-up. This association was found in large clusters in medial
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2
3 prefrontal cortex, right cingulate gyrus extending into anterior cingulate, left anterior
4
5 cingulate extending into anterior frontal cortex and subcallosal gyrus, and left cerebellar
6
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
34
35 scores at follow-up and therefore subsequent analyses focussed on grey matter density
36
37 associations only.
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44

45 -Table 2, Figure 1-
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48

49 **Exploratory analyses**

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51 No significant association was found between baseline grey matter density (lower or
52
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
4
5 decline in GAF score over follow-up (supplementary materials Table A3, Figure A1).
6

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

20 Significantly lower baseline grey matter density was observed in a large cluster
21 extending from medial prefrontal cortex into cingulate gyrus and anterior cingulate, and
22
23 clusters in right precentral and cingulate gyrus, left orbitofrontal cortex extending into
24
25 anterior cingulate, and left anterior cingulate extending into caudate in association with
26
27 higher SANS scores at follow-up (Table 3, Figure 2). Further exploratory analyses revealed
28
29 that this association was not driven by a particular SANS subscale. There was no significant
30
31 association between higher baseline grey matter density and SANS scores at follow-up.
32
33
34
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36 No significant association was observed between baseline grey matter density and IQ
37
38 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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47 Discussion

48 This study investigated the association between baseline grey and white matter
49
50 density and functional outcome 2.4 to 12.9 years after identification as UHR for psychosis.
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52 Lower baseline grey matter density in large clusters in bilateral frontal and limbic regions and
53
54 left cerebellar declive were associated with poorer functional outcome. These findings were
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1
2
3 independent of transition status or persistence of the at-risk mental state at follow-up
4
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.

40
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,
20
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
54
55 memory, processing speed and attention, and verbal fluency), but not global cognitive
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1
2
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
10
11 see our recent paper on attenuated psychotic symptoms in this sample³⁰) or general low
12
13 functioning at follow-up.
14

15
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 remediation^{59,}
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.
49
50 The next step should therefore involve implementation and evaluation of the efficacy of
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1
2
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
8 A limitation of the current study is the long recruitment period spanning the years
9
10 1993-2006. During this period, changes in recruitment, treatment and operationalisation of
11
12 the UHR criteria took place at the PACE clinic. As these changes did not fully account for the
13
14 decline in transition rates that has been observed over the years, and other factors may have
15
16 had additional impact⁷¹, they were not controlled for in the current study. A further limitation
17
18 is the time to follow-up; this varied widely from 2.4 to 12.9 years after baseline assessment
19
20 and may have had an impact on functional outcome. Participants scanned at the 3T scanner
21
22 were recruited later, resulting in a shorter follow-up period for this sample than data acquired
23
24 on the 1.5T scanner. To control for this, length of the follow-up period and field strength of
25
26 scanner were specified as nuisance variables in all analyses. However, as there are likely to
27
28 be a number of sample differences over the recruitment periods⁷¹, including over the period
29
30 where data were obtained at 1.5T, this makes any direct comparison between 1.5T and 3T
31
32 data far less informative. Finally, only limited information was available regarding
33
34 participants' treatment at baseline and during the period between baseline and follow-up
35
36 making it difficult to control for the potential impact of this factor in our analyses. Future
37
38 research would do well to record these factors in more detail and control for them in
39
40 subsequent analyses.
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45
46 Taken together, the current findings provide novel evidence that those with the
47
48 poorest functional outcomes have the lowest grey matter densities at identification as UHR,
49
50 regardless of transition status or persistence of the at-risk mental state. These findings
51
52 increase our understanding of psychotic illnesses and their causes and once replicated and
53
54 validated may increase our ability to predict which UHR individuals are at greatest risk of
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56 having the poorest functional outcome. This may enable us to target interventions for this
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1
2
3 group accordingly. Moreover, the current findings provide scope for application in the wider
4
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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Table 1

Sample characteristics

Measure	Baseline			Follow-up			Baseline vs follow-up <i>p value</i>
	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	
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	<i>n</i>	<i>%</i>					
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.

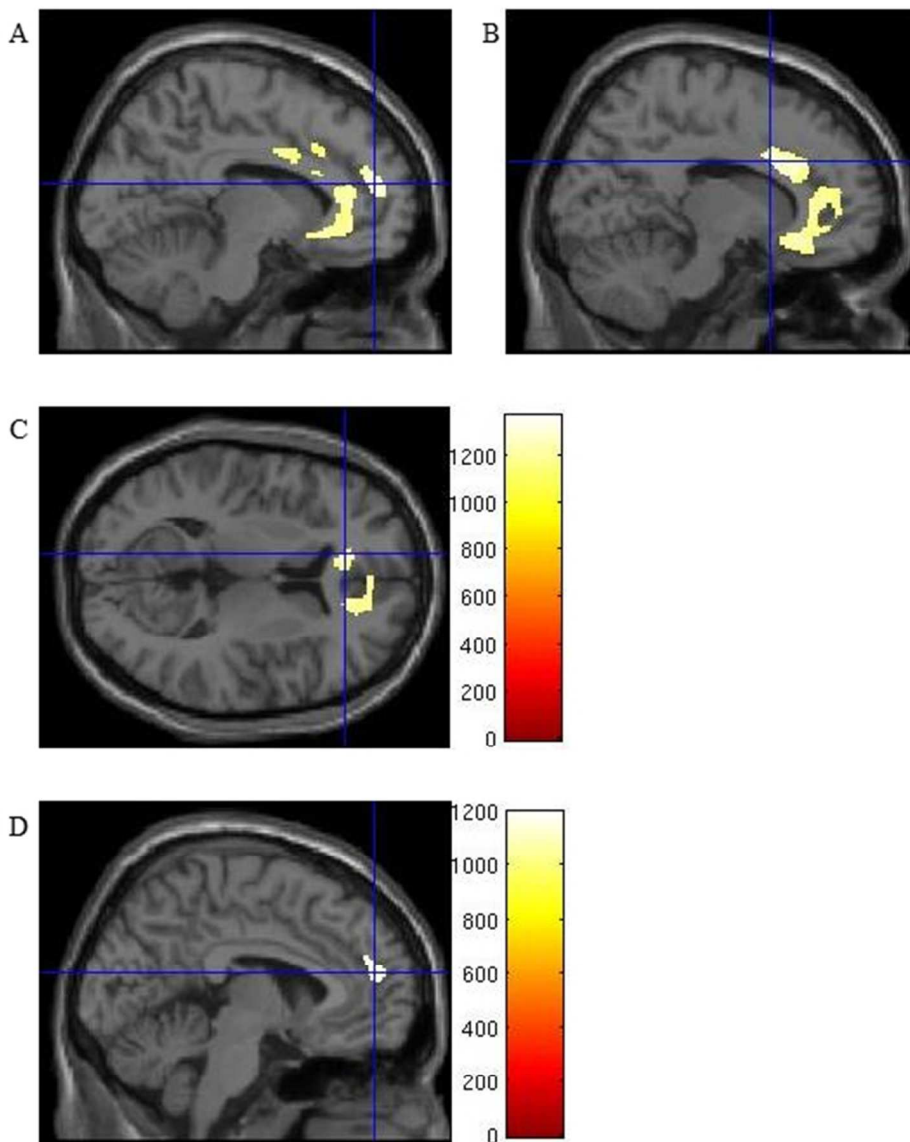
Figure Legends

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.

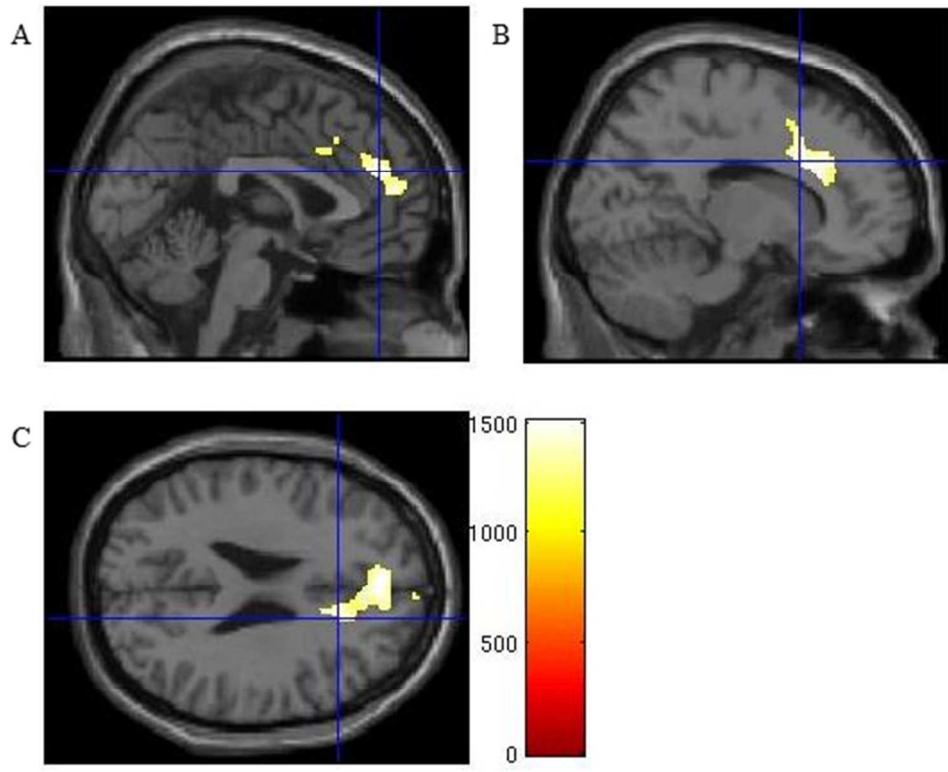
TFCE-enhanced images displaying areas of lower baseline grey matter density associated with increased negative symptoms as indicated by higher scores on the Scale for the Assessment of Negative Symptoms (SANS) at follow-up. Threshold at $p < 0.05$ FWE corrected. Crosshairs at a) medial prefrontal cortex [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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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

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3 participants. Of these participants, 1 (1%) reported taking neuroleptics and 11 (16%) reported
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5 antidepressant use while the remainder (n=58, 83%) reported no use of neuroleptics or
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7 antidepressants. At follow-up, 29 participants (27%) reported taking medication for
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9 psychiatric problems for some of the period between baseline and follow-up while 22
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11 participants (20%) reported to have been on medication most of the time. 23 (21%)
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13 participants received low-dose neuroleptics (risperidone) and 1 (1%) received low-dose
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15 lithium as trial treatment at PACE after study entry. 55 participants (50%) reported receiving
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17 non-pharmacological treatment. Overall, 79 participants (72%) received either (n=36) or both
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19 (n=43) forms of treatment in the period between baseline and follow-up. Those who received
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21 neuroleptic medication in the period between baseline and follow-up scored significantly
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23 lower on all functioning measures at both baseline and follow-up than those who did not
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25 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.

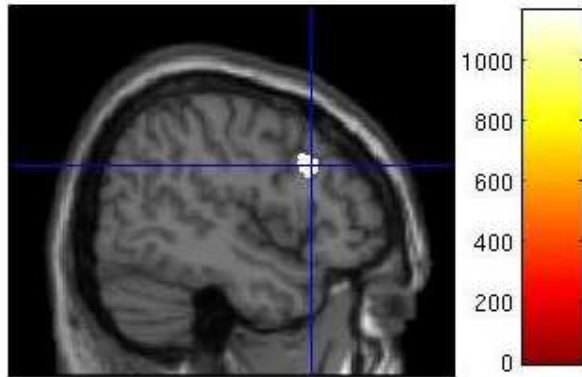
Table A3

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.



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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.