Corticolimbic brain anomalies are associated with cognitive subtypes in psychosis: A longitudinal study

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Abstract

Background. Earlier studies examining structural brain abnormalities associated with cognitively derived subgroups were mainly cross-sectional in design and had mixed findings. Thus, we obtained cross-sectional and longitudinal data to characterize the extent and trajectory of brain structure abnormalities underlying distinct cognitive subtypes ("preserved," "deteriorated," and "compromised") seen in psychotic spectrum disorders.

Methods. Data from 364 subjects (225 patients with psychotic conditions and 139 healthy controls) were first used to determine the relationship of cognitive subtypes with cross-sectional measures of subcortical volume and cortical thickness. To probe neurodevelopmental abnormalities, brain structure laterality was examined. To examine whether neuroprogressive abnormalities persist, longitudinal brain structural changes over 5 years were examined within a subset of 101 subjects. Subsequent discriminant analysis using the identified brain measures was performed on an independent subject group.

Results. Cross-sectional comparisons showed that cortical thinning and limbic volume reductions were most widespread in "deteriorated" cognitive subtype. Laterality comparisons showed more rightward amygdala lateralization in "compromised" than "preserved" subtype. Longitudinal comparisons revealed progressive hippocampal shrinkage in "deteriorated" compared with healthy controls and "preserved" subtype, which correlated with worse negative symptoms, cognitive and psychosocial functioning. Post-hoc discrimination analysis on an independent group of 52 subjects using the identified brain structures found an overall accuracy of 71% for classification of cognitive subtypes.

Conclusion. These findings point toward distinct extent and trajectory of corticolimbic abnormalities associated with cognitive subtypes in psychosis, which can allow further understanding of the biological course of cognitive functioning over illness course and with treatment.

Introduction

Management of cognitive impairments in psychosis is an urgent issue [1]. Cognitive impairments in psychosis are strongly associated with disability and poor daily functioning, impede treatment adherence and response to psychosocial rehabilitation treatments, and are more enduring than key psychotic symptoms [2]. However, present antipsychotics do not adequately treat cognitive deficits and potential pharmacological cognitive enhancers show modest favorable effects [3]. While cognitive remediation therapies have reported some positive outcome, the treatment effects are still low-to-moderate [4], in part because individual treatment responses can be variable and is influenced by differing cognitive profiles, psychopathology, and illness course.

Given the impetus to look for better cognitive-enhancing interventions in psychosis [5,6], there is a need for better understanding about the neural substrates underlying variability in degree and trajectory of cognitive impairments. Individuals with psychosis can be stratified into three cognitive subtypes, based on the extent of cognitive decline from the expected level of cognitive functioning and the timing at which it occurs [7–9]. The "deteriorated" cognitive subtype presents with impaired current but normal premorbid cognitive performance, suggestive of progressive decline in cognition over the course of illness. The second "compromised" cognitive subtype exhibits both impaired current and premorbid cognitive performance, suggestive of compromised cognitive function early in life. A third "preserved" cognitive subtype presents relatively intact premorbid and current cognitive abilities compared with healthy individuals.

Although many studies have linked structural brain abnormalities to impaired cognitive performance in psychotic spectrum disorders [10–13], the underlying neurobiology of the three cognitive subtypes is still not entirely clear. To date, earlier studies which had compared brain structural measures among cognitive subtypes in psychotic conditions were mainly cross sectional in design and reported mixed findings [14–16] in terms of the extent of underlying brain anomalies. To the best of our knowledge, none have specifically examined the use of identified putative brain measures to classify cognitive subtypes in an independent subject group.

Based on extant literature, the present study thus has a few aims and hypotheses. First, we aimed to compare cross sectional brain subcortical volumes and cortical thickness across the three cognitive subtypes and hypothesized that "deteriorated" cognitive subtype would have greater subcortical and cortical abnormalities compared with "preserved" cognitive subtype. Second, we aimed to study abnormal brain laterality measures as indices of neurodevelopmental aberrations and hypothesized that differences in laterality indices of specific brain structures are associated with "compromised" compared with "preserved" cognitive subtype. Third, we examined neuroprogressive brain changes over time and hypothesized that they are associated with "deteriorated" compared with "preserved" cognitive subtype. Finally, we tested the reliability of the classification of cognitive subtypes using the identified brain structures on an independent smaller group of subjects.

Materials and Methods

Participants

Two hundred twenty-five clinically stable outpatients with psychotic conditions (schizophrenia or schizoaffective disorder: $n = 164$; bipolar disorder with psychotic features: $n = 46$; and brief psychotic disorder: $n = 15$) were recruited from the Institute of Mental Health from 2010 to 2017. Their diagnoses were based on clinical interviews, medical records and verified by the Structured Clinical Interview for DSM-IV (patient version) by board certified psychiatrists in the hospital. One hundred thirty-nine healthy controls were recruited from the community, affiliated academic centers and through word-of-mouth concurrently and were screened using Structured Clinical Interview for DSM-IV (nonpatient version) to rule out any formal Axis I disorders. Controls with first-degree relatives with Axis 1 disorders were excluded.

Inclusionary criteria for all participants included an age range of 21–65 years and fluency in the English language (which is the main working language within the country and the primary medium of instruction in school). Exclusionary criteria included history of neurological or neurodevelopmental disorders including intellectual disability, substance, or alcohol dependence/abuse 6 months before the study or magnetic resonance imaging (MRI) contraindications. Of the 364 participants, 52 formed the independent subject group. Participants in the independent subject group ($n = 52$) were recruited using the same inclusion/exclusion criteria. All the study procedures were approved by the National Healthcare Group Institutional Review Board. Written informed consent was obtained from all subjects.

Cognitive subtyping and clinical measures

For cognitive subtyping, we adopted the approach in which the estimated premorbid intellect as well as the discrepancy between present level of cognitive functioning and the expected level of

cognitive functioning as predicted by premorbid cognitive estimates were considered [14,15]. We aligned the cut-off thresholds with previous studies in that subjects were considered "preserved" if (a) their estimated premorbid cognition were above the 10th percentile of healthy controls and (b) the difference between their present cognitive and premorbid cognitive abilities were less than 0.8 standard deviation (SD) [14,15]. The remaining patients (i.e., those with an estimated premorbid cognition less than 10th percentile or the discrepancy between present cognitive and premorbid cognitive abilities were more than 0.80 SDs below their predicted level) were considered cognitively impaired. Cognitively impaired patients were stratified into "deteriorated" and "compromised" groups if their estimated premorbid cognitive abilities were above or below the 10th percentile of the healthy subjects' distribution, respectively [14,15].

The composite score from all the six subtests of the Brief Assessment of Cognition (BAC), standardized to normative data of 595 subjects from our local community [17] was used to evaluate the present level of cognitive functioning. BAC evaluates multiple domains of verbal memory and learning, working memory, speed of processing, verbal fluency, and executive function [18]. For longitudinal assessments, an alternate form of BAC was administered to minimize practice effects.

The Wide Range Achievement Test—Reading Subtest III (WRAT-3) was used to appraise premorbid cognitive abilities [19]. We had tested several models with various predictors to obtain the best fit of expected level of cognitive functioning in healthy reference subjects. WRAT-3 together with age and gender were the strongest predictors of expected level of cognitive abilities. Symptom severity and psychosocial functioning were evaluated using the Positive and Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning (GAF) respectively.

Image acquisition, processing, and quality control

Data from MRI structural scans and follow-up scans used to conduct the primary analyses were acquired on the same 3-T scanner (Philips Achieva (Eindhoven, The Netherlands)) at the National Neurological Institute, with no major hardware or software updates in between the follow-up duration. T1 weighted MPRAGE scans for a cohort of 315 individuals were collected using Philips Achieva scanner (180 axial slices of 0.9 mm thickness with no gap, (FOV) Field of View = 230×230 mm^2; (TR)Repetition Time = 7.2 s, (TI) Inversion Time = 856 ms, (TE)Echo Time = 3.8 ms, (FA)Flip Angle = 8°, voxel size = $0.9 \times 0.9 \times 0.9$ mm^3). A three-step image quality control process was applied for images acquired from the initial 367 subjects (228 patients and 139 healthy controls). First, images were inspected for motion artifact at the time of acquisition and scanning was repeated if necessary. Second, independent researchers visually inspected the raw DICOM structural images of individuals scanned before preprocessing. Of the original data collected, two were excluded after failing visual inspection for motion artifacts (ringing and ghosting); another one subject was excluded due to abnormally enlarged and anomalous shaped ventricles. The three excluded were patients with schizophrenia. Third, after preprocessing, the images were subjected to another round of quality check using guidelines by the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium (http://enigma.ini.usc.edu).

Image pre-processing was performed using FreeSurfer version 5.3 (http://surfer.nmr.mgh.harvard.edu). Additional specialized longitudinal processing to reduce within-subject morphological variability resulting from cross-sectional image processing biases/scanner-related measurements [20] as detailed in our earlier paper

[21] was performed prior to longitudinal analyses. Outcome measures extracted for subsequent analyses include global brain measures of intracranial volume (ICV), total brain volume (TBV), total gray matter, subcortical gray matter volume, total cortical white matter, and regional brain measures of subcortical region volumes and cortical thickness.

Statistical analysis

Analyses were performed using open-source R software version 3.3.0. Before hypotheses testing, quantile–quantile plots and Shapiro–Wilks tests of each outcome measure were performed to determine normal distribution. Plots of residuals versus fitted values were also performed after regression analysis to ensure homoscedasticity.

Analyses of demographics, cognitive, clinical and baseline global brain variables

Chi-squared or analysis-of-variance (ANOVA) tests were used to analyze demographics, cognitive and clinical variables, followed by post-hoc Tukey's tests upon main effect of subtype. For global brain measures, an analysis-of-covariance (ANCOVA) was performed, adjusting for age and gender, followed by post-hoc Tukey's tests. Another ANCOVA was performed with ICV as an additional covariate [14].

Cross-sectional analyses of regional outcome measures (subcortical volume, cortical thickness, and their laterality indices)

To examine the relationship of cognitive subtypes on the subcortical volume and cortical thickness in the 312 individuals, an ANCOVA was performed with cognitive subtype, age, gender, ICV, and years of education as independent variables, followed by Bonferroni correction for the multiple brain regions tested. Post-hoc tests were conducted using simultaneous inference in general parametric models, with Tukey's test to correct for the 6 pairwise group comparisons. Cohen's f^2 values (local effect size, i.e., effect size of an individual variable within a multivariate model) were also calculated for various predictors including cognitive subtype. To determine subtype differences in lateralization, similar ANCOVA analyses were performed, with laterality indices of subcortical volume and cortical thickness $(\text{Measure}_{left} - \text{Measure}_{right})/(\text{Measure}_{left} + \text{Measure}_{right})$ as the dependent variables; cognitive subtype, age, gender, years of education, and handedness as independent variables.

Secondary sensitivity analysis

Because the effect of cognitive subtypes could confounded by variability in age and diagnosis, we sought to substantiate the findings by performing identical analyses on a more homogeneous subset of participants, that is limiting the age group of all subjects to 21–45 years of age and confining the patients to those with a primary diagnosis of schizophrenia. This particular cohort is comprised of 105 healthy controls and 109 patients (see Supplementary Table S3).

Longitudinal analyses

To examine whether the brain trajectories differed among subset of 101 individuals with follow-up data (see participant characteristics in Supplementary Table S1), a linear mixed-effects model described in our previous study [21] was fitted, fixed effects included the interaction between cognitive subtype and time (number of years between baseline and follow-up scan), cognitive subtype, time, age at baseline, gender, ICV, and years of education, random effects included individual intercept and slope. Significant testing was performed using ANOVA, followed by Bonferroni correction for the multiple brain regions tested. Post-hoc pair-wise group comparisons were performed using Wald tests to compute asymptotic Chi-squared statistics, with *p*-values adjusted for between-group multiple comparisons using the Holm–Bonferroni method.

A posteriori longitudinal brain-clinical/cognitive correlations

Consequent to the findings of significant volume trajectory abnormalities in a cognitive subtype, regression analysis described in our previous study [22] was conducted to determine whether standardized rates of volume change (adjusted for ICV, baseline age, gender, antipsychotic dosage, and years of education) were associated with standardized rates of change in measures (adjusted for age, gender, antipsychotic dosage, and years of education) of cognition (BAC composite), symptoms (PANSS and GAF symptoms) and social/occupational functioning (GAF disability).

Classification of cognitive subtypes on an independent dataset using putative imaging markers

To explore whether putative discriminative variables, that is outcome measures that showed significant between-group differences in the main cross-sectional dataset could predict group classification in an independent sample cohort (see participant characteristics in Supplementary Table S2), linear discriminant analysis was performed, which separates the classes (cognitive subtypes) by maximizing the centers of the combined predictor data and minimizing the variation within each class of data [23].

Results

Baseline sociodemographic, cognitive, and clinical characteristics

These baseline data including the cross-sectional comparisons are summarized in Table 1. Generally, the three cognitive subtypes did not significantly differ among and from the healthy controls in gender and handedness. "Deteriorated" and "compromised" cognitive subtypes received less years of education than healthy controls. While patient groups also did not differ in in antipsychotic dosage, severity of symptoms, or duration of illness, the "compromised" subjects were older and showed later onset of illness compared with other cognitive subtypes.

Global brain measures

There was significant cognitive subtype main effect on absolute TBV but not ICV. "Deteriorated" subjects had smaller absolute TBV than healthy controls. Subtype effects were also significant for all global measures after adjusting for ICV; relative to healthy controls, "deteriorated" and "preserved" cognitive subtypes showed lower TBV and total cortical gray matter volume, and "deteriorated" cognitive subtype showed lower total subcortical gray matter and total cortical white matter volume.

Regional brain measures

Table 2A shows significant subtype effects on limbic structures and lateral ventricles. Smaller bilateral hippocampal volume was found in "deteriorated" compared with healthy and "preserved" cognitive subtype, and "compromised" compared with healthy controls.

Table 1. Characteristics of cohort of 312 individuals with psychosis and healthy comparison individuals.

	Healthy	Preserved	Deteriorated	Compromised	χ^2 or F value (d.f.)	p value
Demographics						
N	125	79	69	39	–	
Gender	77 m, 48 f	41 m, 38 f	38 m, 31 f	21 m, 18 f	2.17 (3)	0.54
Age (years)	32.82 (9.73)	31.66 (8.20)	30.93 (8.14)	39.98 (10.78)	9.28 (3, 308)	<0.001[a]
Education (years)	14.83 (2.57)	12.98 (2.53)	11.4 (2.25)	10.76 (3.09)	40.01 (3, 308)	<0.001[b]
Handedness	118 R, 7 L	72 R, 7 L	67 R, 2 L	37 R, 1 L, 1 A	10.26 (6)	0.11
Cognitive measures						
WRAT3-reading	49.51 (4.83)	51.08 (4.18)	49.81 (4.41)	38.69 (6.14)	65.51 (3, 230)	<0.001[c]
BAC verbal memory	0.39 (0.93)	−0.29 (0.91)	−1.60 (1.06)	−1.45 (1.09)	49.66 (3, 230)	<0.001[d]
BAC digit sequencing	0.15 (1.09)	−0.03 (0.96)	−1.55 (0.96)	−1.39 (1.37)	40.52 (3, 230)	<0.001[d]
BAC token motor task	−0.08 (0.90)	−0.72 (0.94)	−1.31 (1.01)	−1.49 (1.37)	18.51 (3, 230)	<0.001[d]
BAC verbal fluency	1.58 (1.77)	−0.31 (0.99)	−1.43 (0.93)	−1.44 (0.90)	73.88 (3, 230)	<0.001[d]
BAC symbol coding	0.27 (1.06)	−0.71 (0.84)	−2.02 (1.03)	−1.77 (1.17)	58.80 (3, 230)	<0.001[d]
BAC tower of london	0.41 (0.72)	0.16 (0.92)	−1.74 (2.26)	−1.22 (2.47)	22.74 (3, 230)	<0.001[d]
BAC composite	0.45 (0.65)	−0.31 (0.41)	−1.61 (0.67)	−1.46 (0.88)	127.12 (3, 230)	<0.001[d]
Clinical measures						
Primary diagnosis (SS, BPD, BD)	–	54 SS, 5 BPD and 20 BD	51 SS, 3 BPD, 15 BD	21 SS, 7 BPD, 11 BD	8.20 (4)	0.19
Age onset of illness	–	25.93 (7.93)	25.55 (6.83)	32.57 (10.44)	10.85 (2, 184)	<0.001[e]
Antipsychotic dosage (daily CPZ equivalent)	–	266.93 (341.51)	213.73 (206.76)	174.85 (145.61)	1.75 (2, 184)	0.18
Duration of illness in years	–	5.34 (5.92)	4.90 (5.07)	7.17 (8.02)	1.80 (2, 184)	0.17
PANSS Positive	–	9.43 (3.14)	10.32 (3.48)	10.59 (4.55)	1.79 (2, 184)	0.17
PANSS Negative	–	8.62 (3.35)	8.91 (3.03)	9.62 (4.01)	1.13 (2, 184)	0.33
PANSS General psychopathology	–	19.68 (3.80)	20.90 (3.90)	21.41 (7.44)	2.07 (2, 184)	0.13
GAF (total)	–	57.84 (20.13)	50.72 (17.8)	57.67 (19.1)	2.97 (2, 184)	0.05
GAF (symptoms)	–	60.35 (20.38)	54.0 (18.65)	60.95 (19.24)	2.46 (2, 184)	0.08
GAF (disability)	–	58.86 (19.94)	51.46 (17.61)	59.1 (18.79)	3.42 (2, 184)	0.04
Global neuroimaging measures (mm^3)						
ICV	1,273,904.18 (172,173.01)	1,251,065.74 (204,242.05)	1,274,967.84 (189,960.44)	1,245,999.79 (205,469.40)	0.43 (3, 308)	0.73
TBV	1,083,476.16 (101,868.70)	1,050,581.08 (104,775.77)	1,046,533.01 (101,992.179)	1,028,841.59 (105,186.97)	5.94 (3, 306)	<0.001[f]
					15.79 (3, 305)	<0.001[g]
Total cortical GM	590,094.80 (55,748.96)	570,013.2 (57,411.9)	565,622.2 (55650.72)	555,236.1 (56,064.83)	9.2 (3, 306)	<0.001[h]
					18.26 (3, 305)	<0.001[i]

Table 1. (Continued).

	Healthy	Preserved	Deteriorated	Compromised	χ² or F value (d.f.)	p value
Total subcortical GM	60,419.86 (5,534.18)	59,676.20 (5,460.11)	59,193.04 (5304.19)	57,204.26 (5,367.33)	5.72 (3, 306)	<0.001
					9.20 (3, 305)	<0.001[j]
Total cortical WM	446,413.77 (49,758.77)	431,357.67 (49,635.21)	430,700.40 (49415.81)	426,478.42 (52,152.60)	3.59 (3, 306)	<0.05
					6.95 (3, 305)	<0.001[k]

Abbreviations: A, ambidextrous; BD, bipolar disorder with history of psychosis; BAC, brief assessment of cognition; BPD, brief psychotic disorder; C, Chinese; CPZ, chlorpromazine equivalent daily doses; f, females; GM, gray matter; H, healthy control; I, Indian; ICV, intracranial volume; L, left; M, malay; m, Males; O, other ethnicities; R, right; SS, schizophrenia spectrum (i.e., schizophrenia, schizoaffective disorder and schizophreniform); PANSS, Positive and Negative Syndrome Scale; TBV, total brain volume; WM, white matter; WRAT3, Wide Range Achievement Test 3 (Reading subtest).

Measures of continuous variables are indicated by mean ± standard deviation. Post-hoc tests indicate

[a]C older than the H, P and D ($p < 0.001$).

[b]H received more years of education compared with all the patient subtypes ($p < 0.001$), and P received more years of education compared with D ($p < 0.005$) and C ($p < 0.001$).

[c]C performed worse than H, P, and D on WRAT3 ($p < 0.001$).

[d]H and P performed better than D and C subjects on all BAC subtests ($p < 0.001$). No significant group differences were found between D and C. H performed better than P in verbal memory, token motor task, verbal fluency, symbol coding, and composite scores ($p < 0.01$).

[e]C had a higher age onset of illness than P and D ($p < 0.001$). No significant group differences were found between P and D. After adjusting for effects of age and gender, post-hoc Tukey's tests indicate

[f]D showed lower TBV than H ($p < 0.05$).

[g]D and P showed lower total cortical GM than H ($p < 0.05$). When ICV was adjusted for besides age and gender, post-hoc Tukey's tests indicate

[h]P and D showed lower TBV than H ($p < 0.05$).

[i]P and D showed lower total cortical GM than H ($p < 0.001$).

[j]D showed lower total subcortical GM than H ($p < 0.05$).

[k]D showed lower total cortical WM than H ($p < 0.01$).

Smaller left amygdala volume was seen in "compromised" compared with healthy and "preserved" cognitive subtype. Smaller thalamic volume and enlarged ventricles were found in "deteriorated" and "preserved" subtypes compared with healthy controls.

Table 2B shows the effect of cognitive subtype on cortical thickness measures. Among the cognitive subtypes, "deteriorated" showed the most widespread cortical thinning across the four lobes relative to healthy controls. "Preserved" showed similar patterns of cortical thinning compared to "deteriorated" subtype within the prefrontal regions (pars orbitalis, pars opercularis, pars triangularis, rostral middle frontal gyrus, medial and lateral orbitofrontal gyri; temporal regions (middle and superior temporal gyri, banks of superior temporal sulcus), lateral occipital gyrus and inferior parietal cortex, but not in the lingual gyrus and superior frontal gyrus as seen in "deteriorated" cognitive subtype. "Compromised" subtype showed most limited cortical thining relative to healthy controls that was restricted to the lingual gyrus and lateral orbitofrontal gyrus.

Secondary analysis on the cohort more homogenous for age and diagnosis revealed similar pattern of findings as above, with strong local effect sizes for cognitive subtypes (Supplementary Table S4), suggesting that the cognitive subtypes contributed more to the variances in group-based volumes rather than diagnosis or age.

Lateralization measures

"Compromised" showed significantly increased rightward amygdalar lateralization when compared with healthy ($p = 0.033$) and "preserved" cognitive subtype ($p = 0.021$).

Longitudinal comparisons

The subtype-by-time interaction effect was significant only in the hippocampus, after adjusting for multiple comparisons. Figures 1A, B indicates that this effect was driven by progressive bilateral hippocampal volumetric decline in "deteriorated" compared with healthy ($p = 0.00061$ for left hippocampus; $p = 0.00018$ for right hippocampus) and "preserved" ($p = 0.017$ for left hippocampus; $p = 0.036$ for right hippocampus) cognitive subtype. No significant subtype-by-time effects on cortical thickness measures.

A posteriori longitudinal brain-behavioral correlations

In "deteriorated" individuals, progressive volume decline of hippocampus correlated with less improvement in the BACS composite score over time (left: $p = 0.017$; right not significant: $p = 0.12$), worse GAF disability scores i.e. psychosocial and occupational functioning (left: $p = 0.035$; right: $p = 0.027$) and greater severity of negative symptoms (left: $p = 0.012$; right not significant: $p = 0.50$), general psychopathology (left: $p = 0.05$; right: $p = 0.036$) but not positive symptoms (Figure 1C).

Cognitive subtype classification based on putative markers:

A composite index of the above putative neuroimaging measures associated with the cognitive subtypes (i.e., bilateral volumes of the hippocampus, lateral ventricles, thalamus, ICV to adjust for brain size) and amygdala laterality measure without demographic or clinical variables) classified an independent cohort of patients with schizophrenia with an accuracy of 90% for healthy controls, 83% for "preserved," 73% for "deteriorated," and 75% for "compromised" cognitive subtypes, with an overall accuracy of 71%.

Table 2. Effects of cognitive subtypes on (a) volumes of subcortical regions and (b) thickness of cortical regions in the cohort of 312 subjects of patients with psychosis and healthy comparison controls.

(A) Subcortical regions	F and p-values of ANCOVA test of cognitive subtype; Cohen's f^{2a}	Post-hoc pairwise tests[b]					
		P vs. H	D vs. H	C vs. H	D vs. P	C vs. P	C vs. D
Hippocampus							
Left	$F_{3, 304} = 13.43, p = 2.96e-08\#; f^2 = 0.08$	$\beta = -63.40$, SE = 47.44, $t = -1.34$, $p = 0.54$	$\beta = -262.14$, SE = 53.77, $t = -4.88$, $p < 0.001$***	$\beta = -121.98$, SE = 65.38, $t = -1.87$, $p = 0.24$	$\beta = -198.73$, SE = 53.10, $t = -3.74$, $p = 0.0012$***	$\beta = -58.57$, SE = 65.15, $t = -0.90$, $p = 0.80$	$\beta = 140.16$, SE = 65.63, $t = 2.14$, $p = 0.14$
Right	$F_{3, 304} = 11.82, p = 2.42e-07\#; f^2 = 0.07$	$\beta = -63.35$, SE = 50.23, $t = -1.26$, $p = 0.58$	$\beta = -215.04$, SE = 56.94, $t = -3.77$, $p = 0.001$**	$\beta = -188.20$, SE = 69.23, $t = -2.72$, $p = 0.034$*	$\beta = -151.69$, SE = 56.22, $t = -2.69$, $p = 0.0.35$*	$\beta = -124.85$, SE = 68.98, $t = -1.81$, $p = 0.27$	$\beta = 26.84$, SE = 69.49, $t = 0.39$, $p = 0.98$
Amygdala							
Left	$F_{3, 304} = 10.0, p = 2.66e-06\#; f^2 = 0.007$	$\beta = 0.005$, SE = 0.02, $t = 0.0, p = 0.10$	$\beta = -0.51$, SE = 0.03, $t = -1.65$, $p = 0.21$	$\beta = -0.01$, SE = 0.04, $t = -2.98, p = 0.01$*	$\beta = -0.5$, SE = 0.03, $t = -1.67, p = 0.33$	$\beta = -0.01$ SE = 0.04, $t = -2.99, p = 0.015$*	$\beta = -0.59$, SE = 0.4, $t = -1.62$, $p = 0.37$
Right	$F_{3, 304} = 3.27, p = 0.021$						
Thalamus							
Left	$F_{3, 304} = 5.98, p = 0.00057\#; f^2 = 0.04$	$\beta = -250.7$, SE = 118.2, $t = -2.12$, $p = 0.15$	$\beta = -394.8$, SE = 134.0, $t = -2.95$, $p = 0.018$*	$\beta = -143.6$, SE = 162.9, $t = -0.88$, $p = 0.81$	$\beta = -144.2$, SE = 132.3, $t = -1.09$, $p = 0.69$	$\beta = 107.1$, SE = 162.4, $t = 0.66$, $p = 0.91$	$\beta = 251.2$, SE = 163.6, $t = 1.54$, $p = 0.41$
Right	$F_{3, 304} = 17.80, p = 1.15e-10\#; f^2 = 0.08$	$\beta = -300.68$, SE = 80.31, $t = -3.74$, $p = 0.001$**	$\beta = -344.84$, SE = 91.03, $t = -3.79$, $p = 0.001$**	$\beta = -197.97$, SE = 110.68, $t = -1.79$, $p = 0.28$	$\beta = -44.16$, SE = 89.88, $t = -0.49$, $p = 0.96$	$\beta = 102.71$, SE = 110.29, $t = 0.93$, $p = 0.79$	$\beta = 146.87$, SE = 111.10, $t = 1.32, p = 0.55$

(B) Thickness of cortical regions	F and p-values of ANOVA test of cognitive subtype; Cohen's f^{2a}	Post-hoc pairwise tests[b]					
		P vs. H	D vs. H	C vs. H	D vs. P	C vs. P	C vs. D
Banks of the superior temporal sulcus							
Left	$F_{3, 249} = 9.23, p = 8.21E-06\#; f^2 = 0.09$	$\beta = -0.07$, SE = 0.02, $t = -3.28, p = 0.006$**	$\beta = -0.13$, SE = 0.03, $t = -5.09, p < 0.001$***	$\beta = -0.06$, SE = 0.03, $t = -1.91, p = 0.22$	$\beta = -0.06$, SE = 0.03, $t = -2.25, p = 0.11$	$\beta = 0.01$, SE = 0.03, $t = 0.36$, $p = 0.98$	$\beta = 0.07$, SE = 0.03, $t = 2.12$, $p = 0.15$
Right	$F_{3, 285} = 9.40, p = 6.03E-06\#; f^2 = 0.08$	$\beta = -0.06$, SE = 0.02, $t = -2.47, p = 0.07$	$\beta = -0.1$, SE = 0.03, $t = -3.66, p = 0.0017$**	$\beta = -0.07$, SE = 0.03, $t = -1.94, p = 0.21$	$\beta = -0.04$, SE = 0.03, $t = -1.51, p = 0.43$	$\beta = 0$, SE = 0.03, $t = -0.14, p = 1.0$	$\beta = 0.04$, SE = 0.03, $t = 1.09$, $p = 0.69$
Cuneus							
Left	$F_{3, 303} = 6.15, p = 0.0004\#; f^2 = 0.05$	$\beta = -0.06$, SE = 0.02, $t = -3.1, p = 0.01$*	$\beta = -0.04$, SE = 0.02, $t = -1.91, p = 0.22$	$\beta = -0.04$, SE = 0.03, $t = -1.47, p = 0.45$	$\beta = 0.02$, SE = 0.02, $t = 0.85, p = 0.83$	$\beta = 0.02$, SE = 0.03, $t = 0.76$, $p = 0.87$	$\beta = 0$, SE = 0.03, $t = 0.08, p = 1.0$
Right	$F_{3, 304} = 6.24, p = 0.0004\#; f^2 = 0.05$	$\beta = -0.04$ SE = 0.02, $t = -2.21, p = 0.12$	$\beta = -0.06$, SE = 0.02, $t = -2.91, p = 0.020$*	$\beta = -0.04$, SE = 0.02, $t = -1.56, p = 0.40$	$\beta = -0.02$, SE = 0.02, $t = -0.95, p = 0.77$	$\beta = 0.0$, SE = 0.02, $t = 0.05, p = 1.0$	$\beta = 0.02$, SE = 0.02, $t = 0.83$, $p = 0.84$
Inferior parietal cortex							
Left	$F_{3, 304} = 6.06\ p = 0.00051\#; f^2 = 0.05$	$\beta = -0.05$, SE = 0.02, $t = -2.63, p = 0.04$*	$\beta = -0.06$, SE = 0.02, $t = -2.79, p = 0.03$*	$\beta = -0.01$, SE = 0.02, $t = -0.61, p = 0.93$	$\beta = -0.01$, SE = 0.02, $t = -0.45, p = 0.97$	$\beta = 0.03$, SE = 0.02, $t = 1.31$, $p = 0.55$	$\beta = 0.04$, SE = 0.02, $t = 1.67$, $p = 0.34$

Table 2. (*Continued*).

(B) Thickness of cortical regions	F and p-values of ANOVA test of cognitive subtype; Cohen's f^{2a}	Post-hoc pairwise tests[b]					
		P vs. H	D vs. H	C vs. H	D vs. P	C vs. P	C vs. D
Right	$F_{3,\,304} = 5.32$, $p = 0.0014$						
Lateral occipital gyrus							
Left	$F_{3,\,305} = 9.31$, $p = 6.62E\text{-}06\#$; $f^2 = 0.08$	$\beta = -0.07$, SE = 0.02, $t = -3.86$, $p = 0.00077^{***}$	$\beta = -0.09$, SE = 0.02, $t = -4.27$, $p = 0.00013^{***}$	$\beta = -0.05$, SE = 0.03, $t = -1.93$, $p = 0.21$	$\beta = -0.02$, SE = 0.02, $t = -0.86$, $p = 0.83$	$\beta = 0.02$, SE = 0.03, $t = 0.87$, $p = 0.82$	$\beta = 0.04$, SE = 0.03, $t = 1.56$, $p = 0.40$
Right	$F_{3,\,305} = 6.23$, $p = 0.00040\#$; $f^2 = 0.05$	$\beta = -0.06$, SE = 0.02, $t = -2.98$, $p = 0.016^{*}$	$\beta = -0.08$, SE = 0.02, $t = -3.62$, $p = 0.0019^{**}$	$\beta = -0.02$, SE = 0.03, $t = -0.85$, $p = 0.83$	$\beta = -0.02$, SE = 0.02, $t = -0.99$, $p = 0.75$	$\beta = 0.04$, SE = 0.03, $t = 1.32$, $p = 0.55$	$\beta = 0.06$, SE = 0.03, $t = 2.11$, $p = 0.15$
Lateral orbitofrontal gyrus							
Left	$F_{3,\,305} = 14.43$, $p = 8.15E\text{-}09\#$; $f^2 = 0.10$	$\beta = -0.07$, SE = 0.02, $t = -3.32$, $p = 0.0057^{**}$	$\beta = -0.08$, SE = 0.02, $t = -3.53$, $p = 0.0027^{**}$	$\beta = -0.11$, SE = 0.03, $t = -3.73$, $p = 0.0014^{**}$	$\beta = -0.01$, SE = 0.02, $t = -0.59$, $p = 0.93$	$\beta = -0.04$, SE = 0.03, $t = -1.33$, $p = 0.54$	$\beta = -0.02$, SE = 0.03, $t = -0.84$, $p = 0.83$
Right	$F_{3,\,304} = 13.48$, $p = 2.79E\text{-}08\#$; $f^2 = 0.09$	$\beta = -0.05$, SE = 0.02, $t = -2.32$, $p = 0.093$	$\beta = -0.09$, SE = 0.02, $t = -4.18$, $p < 0.001^{***}$	$\beta = -0.09$, SE = 0.03, $t = -3.29$, $p = 0.0060^{**}$	$\beta = -0.05$, SE = 0.02, $t = -2.16$, $p = 0.14$	$\beta = -0.04$, SE = 0.03, $t = -1.62$, $p = 0.36$	$\beta = 0$, SE = 0.03, $t = 0.13$, $p = 1.0$
Lingual gyrus							
Left	$F_{3,\,304} = 11.14$, $p = 5.89E\text{-}07\#$; $f^2 = 0.09$	$\beta = -0.05$, SE = 0.02, $t = -2.85$, $p = 0.02^{*}$	$\beta = -0.07$, SE = 0.02, $t = -3.37$, $p = 0.0045^{**}$	$\beta = -0.08$, SE = 0.02, $t = -3.28$, $p = 0.006^{**}$	$\beta = -0.02$, SE = 0.02, $t = -0.86$, $p = 0.82$	$\beta = -0.03$, SE = 0.02, $t = -1.23$, $p = 0.60$	$\beta = -0.01$, SE = 0.02, $t = -0.53$, $p = 0.95$
Right	$F_{3,\,304} = 6.62$, $p = 0.00024\#$; $f^2 = 0.05$	$\beta = -0.05$, SE = 0.02, $t = -2.54$, $p = 0.055$	$\beta = -0.06$, SE = 0.02, $t = -2.69$, $p = 0.037^{*}$	$\beta = -0.04$, SE = 0.03, $t = -1.58$, $p = 0.39$	$\beta = -0.01$, SE = 0.02, $t = -0.45$, $p = 0.97$	$\beta = 0.01$, SE = 0.02, $t = 0.26$, $p = 0.99$	$\beta = 0.02$, SE = 0.03, $t = 0.62$, $p = 0.92$
Medial orbital frontal gyrus							
Left	$F_{3,\,304} = 8.61$, $p = 1.68E\text{-}05\#$; $f^2 = 0.06$	$\beta = -0.07$, SE = 0.02, $t = -3.42$, $p = 0.0037^{**}$	$\beta = -0.07$, SE = 0.02, $t = -3.2$, $p = 0.0081^{**}$	$\beta = -0.0$, SE = 0.03, $t = -1.08$, $p = 0.70$	$\beta = 0$, SE = 0.02, $t = -0.17$, $p = 1.0$	$\beta = 0.04$, SE = 0.03, $t = 1.41$, $p = 0.49$	$\beta = 0.04$, SE = 0.03, $t = 1.54$, $p = 0.41$
Right	$F_{3,\,304} = 11.82$, $p = 2.42e\text{-}07\#$; $f^2 = 0.05$	$\beta = -0.05$, SE = 0.02, $t = -2.31$, $p = 0.096$	$\beta = -0.1$, SE = 0.03, $t = -3.97$, $p < 0.001^{***}$	$\beta = -0.05$, SE = 0.03, $t = -1.67$, $p = 0.34$	$\beta = -0.05$, SE = 0.03, $t = -1.93$, $p = 0.21$	$\beta = 0$, SE = 0.03, $t = 0.01$, $p = 1$	$\beta = 0.05$, SE = 0.03, $t = 1.58$, $p = 0.39$
Middle temporal gyrus							
Left	$F_{3,\,299} = 4.41$, $p = 0.005$						
Right	$F_{3,\,304} = 11.25$, $p = 5.11E\text{-}07\#$; $f^2 = 0.08$	$\beta = -0.07$, SE = 0.02, $t = -3.17$, $p = 0.0086^{**}$	$\beta = -0.11$, SE = 0.02, $t = -4.47$, $p < 0.001^{***}$	$\beta = -0.06$, SE = 0.03, $t = -2.02$, $p = 0.18$	$\beta = -0.04$, SE = 0.02, $t = -1.66$, $p = 0.35$	$\beta = 0.01$, SE = 0.03, $t = 0.3$, $p = 0.99$	$\beta = 0.05$, SE = 0.03, $t = 1.64$, $p = 0.35$
Pars opercularis							
Left	$F_{3,\,305} = 11.42$, $p = 3.98E\text{-}05\#$; $f^2 = 0.06$	$\beta = -0.07$, SE = 0.02, $t = -3.44$, $p = 0.0036^{**}$	$\beta = -0.07$, SE = 0.02, $t = -3.19$, $p = 0.0085^{**}$	$\beta = -0.05$, SE = 0.03, $t = -1.85$, $p = 0.25$	$\beta = 0$, SE = 0.02, $t = -0.14$, $p = 1.0$	$\beta = 0.02$, SE = 0.03, $t = 0.65$, $p = 0.92$	$\beta = 0.02$, SE = 0.03, $t = 0.76$, $p = 0.87$

Table 2. (*Continued*).

(B) Thickness of cortical regions	F and p-values of ANOVA test of cognitive subtype; Cohen's f^{2a}	Post-hoc pairwise tests[b]					
		P vs. H	D vs. H	C vs. H	D vs. P	C vs. P	C vs. D
Right	$F_{3, 305} = 9.90$, $p = 3.00E\text{-}06$#; $f^2 = 0.07$	$\beta = -0.07$, SE = 0.02, $t = -2.98$, $p = 0.016*$	$\beta = -0.11$, SE = 0.02, $t = -4.28$, $p < 0.001***$	$\beta = -0.07$, SE = 0.03, $t = -2.15$, $p = 0.14$	$\beta = -0.04$, SE = 0.02, $t = -1.66$, $p = 0.34$	$\beta = 0$, SE = 0.03, $t = 0.01$, $p = 1.0$	$\beta = 0.04$, SE = 0.03, $t = 1.35$, $p = 0.53$
Pars orbitalis							
Left	$F_{3, 305} = 11.42$, $p = 4.04E\text{-}07$#; $f^2 = 0.09$	$\beta = -0.13$, SE = 0.03, $t = -4.32$, $p < 0.001***$	$\beta = -0.16$, SE = 0.03, $t = -4.75$, $p < 0.001***$	$\beta = -0.13$, SE = 0.04, $t = -3.24$, $p = 0.0071**$	$\beta = -0.03$, SE = 0.03, $t = -0.93$, $p = 0.79$	$\beta = 0$, SE = 0.04, $t = -0.11$, $p = 1.0$	$\beta = 0.03$, SE = 0.04, $t = 0.64$, $p = 0.92$
Right	$F_{3, 305} = 6.72$, $p = 0.0002113$#; $f^2 = 0.05$	$\beta = -0.11$, SE = 0.03, $t = -3.72$, $p = 0.0016**$	$\beta = -0.15$, SE = 0.03, $t = -4.61$, $p < 0.001***$	$\beta = -0.12$, SE = 0.04, $t = -2.87$, $p = 0.022*$	$\beta = -0.04$, SE = 0.03, $t = -1.33$, $p = 0.54$	$\beta = -0.01$, SE = 0.04, $t = -0.18$, $p = 1.0$	$\beta = 0.04$, SE = 0.04, $t = 0.9$, $p = 0.80$
Pars triangularis							
Left	$F_{3, 305} = 10.19$, $p = 2.07E\text{-}06$#; $f^2 = 0.08$	$\beta = -0.06$, SE = 0.02, $t = -2.91$, $p = 0.020*$	$\beta = -0.1$, SE = 0.03, $t = -4.13$, $p < 0.001***$	$\beta = -0.08$, SE = 0.03, $t = -2.63$, $p = 0.04*$	$\beta = -0.04$, SE = 0.02, $t = -1.57$, $p = 0.39$	$\beta = -0.02$, SE = 0.03, $t = -0.53$, $p = 0.95$	$\beta = 0.02$, SE = 0.03, $t = 0.75$, $p = 0.88$
Right	$F_{3, 304} = 9.56$, $p = 4.72E\text{-}06$#; $f^2 = 0.08$	$\beta = -0.07$, SE = 0.02, $t = -3.47$, $p = 0.0032**$	$\beta = -0.11$, SE = 0.02, $t = -4.85$, $p < 0.001***$	$\beta = -0.07$, SE = 0.03, $t = -2.29$, $p = 0.10$	$\beta = -0.04$, SE = 0.02, $t = -1.79$, $p = 0.28$	$\beta = 0.01$, SE = 0.03, $t = 0.23$, $p = 1.0$	$\beta = 0.05$, SE = 0.03, $t = 1.68$, $p = 0.33$
Rostral middle frontal gyrus							
Left	$F_{3, 305} = 3.35$, $p = 0.02$						
Right	$F_{3, 305} = 7.52$, $p = 7.16E\text{-}05$#; $f^2 = 0.06$	$\beta = -0.06$, SE = 0.02, $t = -3.34$, $p = 0.0051**$	$\beta = -0.09$, SE = 0.02, $t = -4.26$, $p < 0.001***$	$\beta = -0.05$, SE = 0.03, $t = -2.01$, $p = 0.18$	$\beta = -0.03$, SE = 0.02, $t = -1.31$, $p = 0.55$	$\beta = 0.01$, SE = 0.03, $t = 0.41$, $p = 0.98$	$\beta = 0.04$, SE = 0.03, $t = 1.47$, $p = 0.45$
Superior frontal gyrus							
Left	$F_{3, 305} = 6.84$, $p = 0.00018$#; $f^2 = 0.06$	$\beta = -0.04$, SE = 0.02, $t = -1.81$, $p = 0.27$	$\beta = -0.09$, SE = 0.02, $t = -3.47$, $p = 0.0033**$	$\beta = -0.05$, SE = 0.03, $t = -1.65$, $p = 0.35$	$\beta = -0.05$, SE = 0.02, $t = -1.88$, $p = 0.24$	$\beta = -0.01$, SE = 0.03, $t = -0.33$, $p = 0.99$	$\beta = 0.04$, SE = 0.03, $t = 1.19$, $p = 0.63$
Right	$F_{3, 305} = 7.89$, $p = 4.38E\text{-}05$#; $f^2 = 0.06$	$\beta = -0.05$, SE = 0.02, $t = -2.34$, $p = 0.089$	$\beta = -0.11$, SE = 0.02, $t = -4.57$, $p < 0.001***$	$\beta = -0.05$, SE = 0.03, $t = -1.73$, $p = 0.30$	$\beta = -0.06$, SE = 0.02, $t = -2.52$, $p = 0.06$	$\beta = 0$, SE = 0.03, $t = -0.03$, $p = 1.0$	$\beta = 0.06$, SE = 0.03, $t = 2.01$, $p = 0.18$
Superior temporal gyrus							
Left	$F_{3, 303} = 6.95$, $p = 0.00015$						
Right	$F_{3, 305} = 12.0$, $p = 0.192E\text{-}07$##; $f^2 = 0.09$	$\beta = -0.07$, SE = 0.02, $t = -3.46$, $p = 0.0033**$	$\beta = -0.11$, SE = 0.02, $t = -4.62$, $p < 0.001***$	$\beta = -0.06$, SE = 0.03, $t = -2.16$, $p = 0.13$	$\beta = -0.04$, SE = 0.02, $t = -1.56$, $p = 0.40$	$\beta = 0.01$, SE = 0.03, $t = 0.35$, $p = 0.98$	$\beta = 0.05$, SE = 0.03, $t = 1.62$, $p = 0.37$

Abbreviations: β, beta coefficients; C, compromised; D, deteriorated; H, healthy; P, preserved; SE, standard error.

[a]f^2 effect sizes of 0.02, 0.15, and 0.35 are considered small, medium, and large, respectively.

[b]Post-hoc tests, with multiple comparison adjusted p-values of * < 0.05, ** < 0.01, or *** < 0.001 shown.
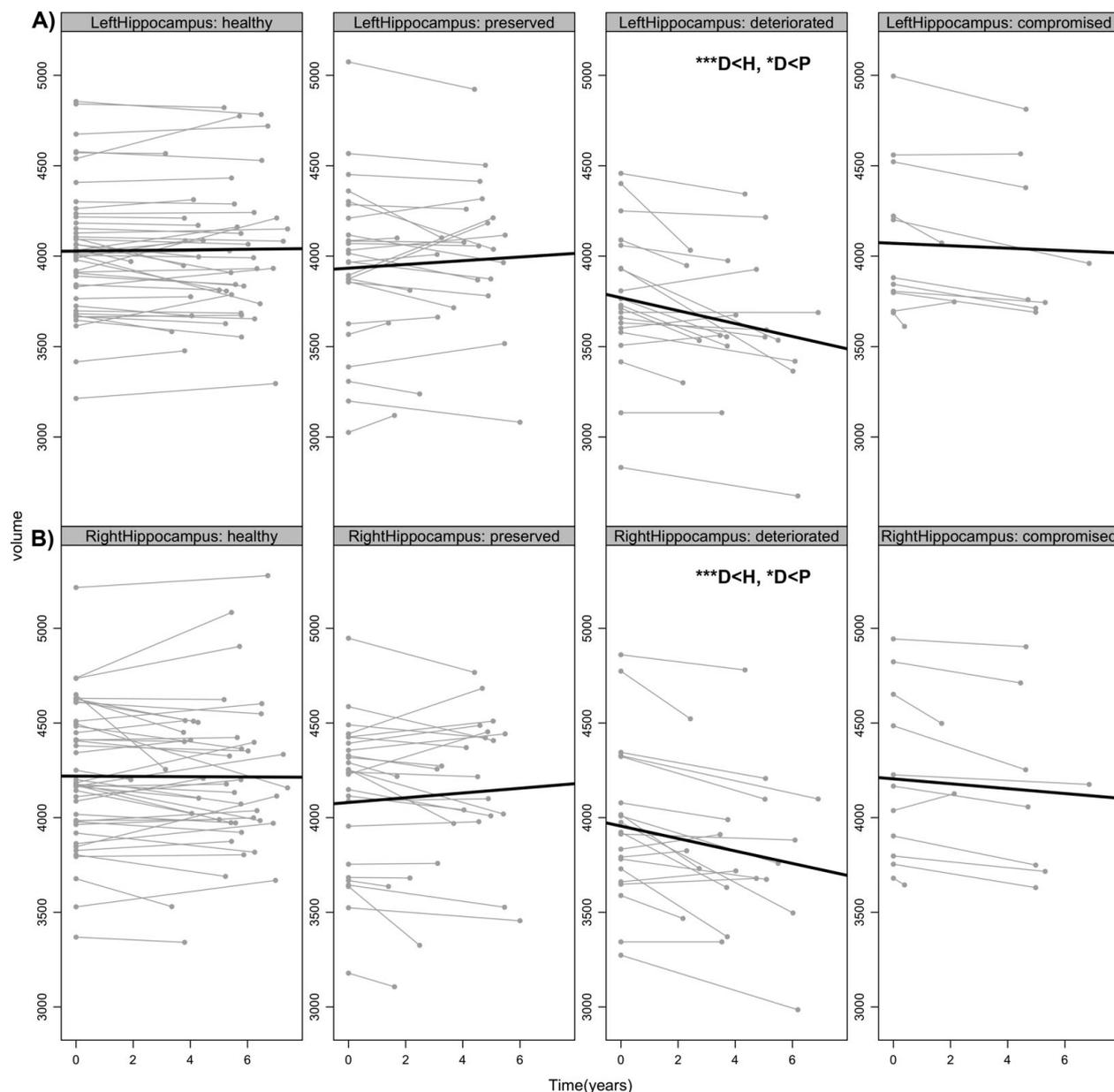
Figure 1. Hippocampal volume changes across the cognitive subtypes and healthy controls over time: a longitudinal snapshot. Spaghetti plots indicate progressive volume decline over time in the (A) left hippocampus and (B) right hippocampus in "deteriorated" cognitive subtype compared with "preserved" subtype and healthy individuals. (C) Within the "deteriorated" cognitive subtype, left hippocampal volume decline correlated with less improvements in cognitive composite scores (higher scales indicate better performance over time) and worse negative symptoms. Volume decline in both the left and right hippocampi also correlated with worse general psychopathology and psychosocial and occupational functioning. ***$p < 0.001$, *$p < 0.05$.

Discussion

The current study found shared and distinct corticolimbic abnormalities among the cognitive subtypes. Cortical thinning, ventricular enlargements and limbic volume reductions were the most widespread in "deteriorated" cognitive subtype and were the most limited in "compromised" cognitive subtype compared with healthy controls. Lateralization of brain regions did not differ among the groups, apart from the amygdala, which showed more pronounced rightward lateralization in "compromised" compared with healthy controls and "preserved" cognitive subtype. Progressive shrinkage of the hippocampus was associated with "deteriorated" subtype compared with healthy controls and "preserved"

subtype; the hippocampal shrinkage correlated with worsening cognitive and psychosocial functioning, and increasing severity of negative symptoms.

The nature and extent of brain structure abnormalities in our cross-sectional findings were consistent with some but not all prior findings. First, no group differences in ICV were found which was similar to findings of an earlier study [16]. Second, we found that "deteriorated" cognitive subtype exhibited the largest extent of gray matter reductions in measures of total cortical gray matter and total subcortical gray matter when compared with healthy controls, in contrast with an earlier finding that "compromised" subtype exhibited the largest extent of gray matter reductions [15,16]. Third, relatively extensive brain tissue loss was observed in "preserved"
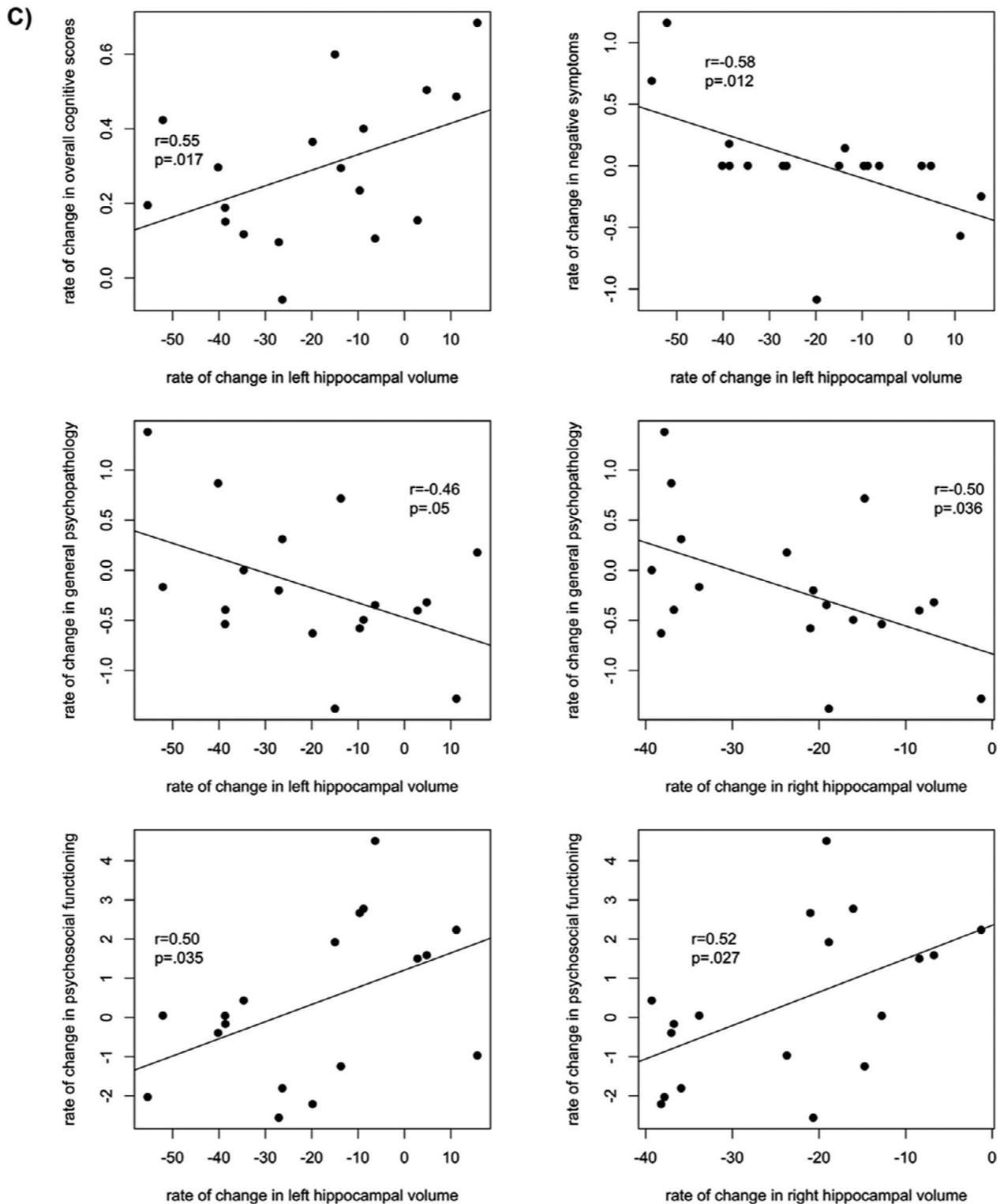
Figure 1. Continued

cognitive subtype, which was in line with previous literature [14,16,24,25]. One possible explanation to account for the absence of direct relationship between brain pathology and clinical manifestation could be cognitive reserve [26]. Cognitive reserve is posited as an active process in psychosis, in which efficiency in neural networks and/or recruitment of alternative networks can compensate for the loss of brain tissue [27]. Education is a known neuroprotective factor contributing to cognitive reserve [27] and in this present study "preserved" received more years of education than "compromised" and "deteriorated." Another possible explanation

could be the effects of the type, duration of use and dosages of antipsychotics, which have been linked to brain tissue loss [13,28,29]. Although not markedly significant, we note that "preserved" received relatively higher antipsychotic dose than the other groups. Conversely, the duration of untreated psychosis—found to differentially affect the general cognitive abilities of patients with low premorbid IQ and high premorbid IQ [30]—may also exert differential effects on frontal and temporal regions of the brain [31,32].

We noted generally an absence of group lateralization differences in regional subcortical and cortical thickness measures except the amygdala. "Compromised" showed increased rightward amygdala lateralization, which was driven by a differentially smaller left amygdala, compared with "preserved" and healthy controls. Longitudinally, this pattern of abnormal amygdala lateralization did not change. The amygdala continues to grow non-linearly throughout infancy into adolescence, reaching maximal volume at 9–11 years of age [33], and has recently been shown to be an area of ongoing postnatal neurogenesis [34]. Different cognitive roles have been posited for the left and right amygdala, with the left being involved in deliberate evaluation and the right involved in subliminal and more rapid affective responses relevant in psychosis [35,36].

Besides laterality differences, "compromised" showed the most limited cortical thinning and ventricular enlargement among the subtypes. Brain atrophy was also relatively spared in "compromised." This begets the question of why brain changes are more circumscribed in "compromised" than "preserved." One explanation could be that the progression of brain changes in "compromised" are later in onset. Another explanation could be that "compromised" had taken the "first hit" in cognitive impairments earlier in life, hence subsequent onslaught of disease-related effects had affected this subtype to a lesser degree than the other two.

In contrast, the hippocampal shrinkage, and to a certain extent thalamic shrinkage, in "deteriorated" is suggestive of more dynamic and aggressive brain changes occurring in this subtype. The progressive loss of hippocampal volume is on top of the reduction in hippocampal volume in "deteriorated" when compared to healthy and "preserved" at baseline, the latter finding by itself consistent with a previous study, which though did not include comparisons with the "compromised" cognitive subtype [37]. The observed relationship between the brain changes and cognitive performances are consistent with a large-scale study of schizophrenia spectrum conditions spanning over 18 years showing that only a subset of the patients showed progressive brain changes, and which correlated most closely with cognitive impairments [13]. Previously, we had also reported progressive hippocampal loss accompanying decline across all symptom domains in a schizophrenia cohort [21]. This additional subtyping of cognitive profile now revealed that the hippocampal shrinkage correlated with worsening negative symptoms and global psychopathology but not positive symptoms in "deteriorated" cognitive subtype. This could be attributed to the clinical overlap between cognitive dysfunction and phenomenology such as poverty of speech, deficits with abstract thinking and poor attention in negative syndrome of schizophrenia [38]. Cognitive difficulties also affect daily functioning [2], and may explain the observed association between hippocampal reduction in "deteriorated" subtype and declining psychosocial and occupational functioning.

We then used our main findings (namely limbic structures, lateral ventricular volumes, and amygdala laterality index) to predict the cognitive subtypes within a small independent cohort of subjects. The overall accuracy was 71% which suggest that further elucidation of specific brain substrates underlying cognitive subtypes in psychosis is warranted, which could be monitored for changes with clinical management (pharmacological or non-pharmacological) over time. A previous trial of a 2-year cognitive enhancement therapy reported left amygdala volume increase and greater left hippocampal volume preservation [5]. Another trial of auditory cognitive training reported a correlation between thalamic volume change and cognitive improvements in the intervention group [6] which highlights the need to account for brain measures associated with cognitive subtype in psychosis at baseline and longitudinally.

Our findings should be interpreted within the confines of several limitations. First, the cognitive profiling heavily relied on a cross-sectional tool of reading ability for assessing premorbid cognitive abilities. Second, the findings between cognitive subtypes and brain pathology are associational; the study design cannot whether the brain reductions already present in the different subtypes are because of stunted neurodevelopment, accelerated neurodegeneration, diminished neuroplasticity, or due to confounding effects of poor lifestyle choices or cumulative antipsychotic exposure. Also, our longitudinal analyses were based on a modest sample size. Future prospective studies may want to extend the age range starting from adolescence which could proffer further insights into brain structural changes underlying cognitive subtypes. Additional imaging modalities of structural or resting-state functional connectivity could potentially provide richer information on multimodal cerebral networks associated with cognitive subtypes.

In conclusion, our present findings pointed toward distinct extent and trajectory of corticolimbic structure abnormalities associated with cognitive subtypes in psychosis, which may allow better biological understanding of the course of cognitive functioning with treatment over time.

Supplementary Materials. To view supplementary material for this article, please visit http://dx.doi.org/10.1192/j.eurpsy.2020.36.

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