Anterior Hippocampal–Cortical Functional Connectivity Distinguishes Antipsychotic Naïve First-Episode Psychosis Patients From Controls and May Predict Response to Second-Generation Antipsychotic Treatment

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Background: Converging evidence implicates the anterior hippocampus in the proximal pathophysiology of schizophrenia. Although resting state functional connectivity (FC) holds promise for characterizing anterior hippocampal circuit abnormalities and their relationship to treatment response, this technique has not yet been used in first-episode psychosis (FEP) patients in a manner that distinguishes the anterior from posterior hippocampus. ***Methods:*** We used masked-hippocampal-group-independent component analysis with dual regression to contrast subregional hippocampal–whole brain FC between healthy controls (HCs) and antipsychotic naïve FEP patients ($N = 61$, 36 female). In a subsample of FEP patients ($N = 27$, 15 female), we repeated this analysis following 8 weeks of second-generation antipsychotic treatment and explored whether baseline FC predicted treatment response using random forest. ***Results:*** Relative to HC, untreated FEP subjects displayed reproducibly lower FC between the left anteromedial hippocampus and cortical regions including the anterior cingulate and insular cortex ($P < .05$, corrected). Anteromedial hippocampal FC increased in FEP patients following treatment ($P < .005$), and no longer differed from HC. Random forest analysis showed baseline anteromedial hippocampal FC with four brain regions, namely the insular–opercular cortex, superior frontal gyrus, precentral gyrus, and postcentral gyrus predicted treatment response (area under the curve = 0.95). ***Conclusions:*** Antipsychotic naïve FEP is associated with lower FC between the anterior hippocampus and cortical regions previously implicated in schizophrenia. Preliminary analysis suggests that random forest models based on hippocampal FC may predict treatment response in FEP patients, and hence could be a useful biomarker for treatment development.

Key words: first-episode psychosis/hippocampus/insula/cingulate/antipsychotic/resting state

Introduction

Hippocampal abnormalities are among the most consistent biological findings in schizophrenia.[1–5] The hippocampal formation is a heterogeneous region, containing distinct subcomponents including the dentate gyrus, cornu ammonis subfields, and subiculum; in addition, the function, gene expression, and anatomical connectivity of these subcomponents vary along the anterior–posterior hippocampal axis.[6–8] Converging evidence points toward involvement of anterior hippocampal structures in ultrahigh-risk (UHR) and first-episode psychosis (FEP) stages of the illness. Previous work in UHR and FEP subjects reported that reduced volume and higher resting blood flow are localized to the anterior hippocampus.[9–14] Further, rodent ventral (homologous to human anterior) hippocampal neurons are affected by rodent models of psychosis, eg, the methylazoxymethanol acetate model, such that the interactions of these neurons with subcortical and prefrontal regions involved in salience attribution are altered in a manner that could contribute to psychotic symptoms and cognitive deficits in human.[15,16] Therefore, characterizing hippocampal interactions with extrinsic brain regions may provide biomarkers useful for developing early interventions in FEP.

Resting state functional connectivity (FC), a measure of interregional coherence in low-frequency fluctuations in the BOLD (blood-oxygen-level-dependent) functional magnetic resonance imaging

(fMRI) signal, has frequently been used to study brain network abnormalities in schizophrenia, including predicting response to antipsychotic medication in FEP patients.[17,18] To date, few studies have characterized FC of the hippocampus in antipsychotic naïve FEP patients by using techniques that differentiate FC along the anterior–posterior axis; however, several studies have assessed hippocampal–brain FC in chronic schizophrenia patients, both unmedicated and medicated.[19–21]

In this study, we aimed to characterize subregional hippocampal–whole brain FC in antipsychotic naïve FEP subjects using masked-hippocampal-group-independent component analysis (ICA) with dual regression.[22] This data-driven technique reproducibly segments the hippocampus into independent components (ICs) that occupy distinct subregions along the anterior–posterior axis and display distinct patterns of whole brain FC.[22,23] Resting state functional magnetic resonance imaging (fMRI) scans were acquired in a cohort of FEP patients at baseline, prior to commencing second-generation antipsychotic (SGA) medication, and following 8 weeks of this treatment; healthy control (HC) participants matched for age and gender were scanned at the same intervals. We hypothesized that relative to HC, unmedicated FEP patients would show altered anterior hippocampal–whole brain FC. As an exploratory analysis, we assessed the effect of SGA medication on hippocampal FC, and used a random forest (RF) model to determine whether baseline hippocampal FC could predict response to SGA treatment.

Methods and Materials

Study Design, Setting, Participants, and Antipsychotic Medication

Data were acquired as part of a larger study ascertaining FEP biomarkers, from which results were previously published.[2] Between March 5, 2013, and October 8, 2014, individuals with non-affective FEP were recruited from the Shanghai Mental Health Centre early psychosis program. HCs group matched by age and sex were recruited by advertisement. Eligible FEP participants met criteria for schizophrenia or schizophreniform disorder but not for any other Axis I disorder, according to a full Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (SCID *DSM-IV-TR*), were psychotropic medication naive, and were experiencing a first-episode of psychosis. Baseline ("T1") clinical and neuroimaging assessments were made prior to FEP patients commencing SGA medication according to standard clinical practice; follow-up ("T2") assessments occurred following 8 weeks of this treatment (see table 1 and supplementary methods for medication details). Eligible HCs, also psychotropic medication naïve, were assessed with the SCID (*DSM-IV-TR* non-patient version) to exclude any Axis I disorder. All participants provided written informed consent, were between 16 and 40 years old, were Mandarin-speaking Han Chinese individuals living in the Shanghai metropolitan area, were right-handed, had completed at least 9 years of school, were medically stable, were free from substance abuse (according to

Table 1. Subject Demographics and Symptoms

	FEP Group A Baseline (n = 27)	FEP Group A Week 8 (n = 27)	P Value (Baseline vs Week 8)	FEP Group B Baseline (n = 34)	Healthy Controls (n = 27)	P Value (FEP A vs B or also vs HC)
Mean (*SD*) or No.						
Age, years	24.11 (7.19)			25.85 (8.53)	24.46 (7.18)	> .05
Sex						> .05
Female	15			21	14	
Male	12			13	12	
Education level, years	11.81 (3.58)			12.12 (2.51)	12.69 (2.49)	> .05
Handedness						> .05
Right	27			34	25	
Left	0			0	1	
DUP, weeks	24.44 (16.52)			27.16 (27.28)		> .05
Daily CPZ average dose, mg	N/A	488 (275.88)		N/A	N/A	N/A
Treatment duration, days	1.2 (1.94)¤			1.8 (2.17)	N/A	> .05
BPRS total score	52.56 (13.2)	33.15 (7.23)	< .001	44.44 (9.26)	N/A	< .01
BPRS positive score	20.74 (5.07)	10 (3.54)	< .001	18.74 (12.33)	N/A	> .05
SANS composite score	21.4 (20.51)	15.48 (12.53)	< .05	18.24 (14.32)	N/A	> .05

Note: All but 2 patients were antipsychotic naïve. FEP, first-episode psychosis; HCs, healthy controls; DUP, duration of untreated psychosis; CPZ, chlorpromazine; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; N/A, not applicable.

self-report) and suicidal ideation, and had no contraindications to MRI. The study was approved by institutional review boards at Shanghai Mental Health Center and NYU School of Medicine. Symptom assessment scales included the Brief Psychiatric Rating Scale (BPRS) and the Scale for the Assessment of Negative Symptoms (SANS), see supplementary methods for details.

Image Preprocessing, Masked Hippocampal Group ICA, and Dual Regression

See supplementary methods for details on all methods including acquisition parameters, preprocessing methods, as for following sections. Potential motion artifacts were controlled for by strict exclusion criteria and artifact removal according to Power et al.[24] Masked hippocampal group ICA (GICA) and dual regression analyses were used to identify hippocampal ICs and map their whole brain FC, respectively. GICA is a commonly used data-driven technique in which group fMRI BOLD data concatenated across subjects is decomposed into a set of independent (uncorrelated and non-Gaussian) components, each characterized by a group-level spatial map and time course.[25] *Masked GICA* identifies ICs within a masked brain region; dual regression then measures their extrinsic FC in a multivariate manner.[22,26] Masked hippocampal GICA and whole brain dual regression were performed using the mICA Toolbox (v.1.14) as in previous studies.[22,23] This freely available software (www.nitrc.org/projects/mica/) streamlines implementation of FSL Melodic and Dual Regression on select brain regions. An additional Toolbox function was used to calculate split-half reproducibility (Pearson spatial correlation coefficient) of hippocampal ICs.

To establish internal reproducibility of FEP vs HC differences in hippocampal–whole brain FC, the FEP sample was split into 2 groups: 1) FEP A subjects with both T1 and T2 data available, and 2) FEP B, subjects with T1 data only. Masked hippocampal GICAs were created with data merged from all subject groups and time points relevant to each contrast, so that common ICs were used in subsequent dual regression analyses to calculate hippocampal–whole brain FC (see supplementary figure S1 GICAs 5, 7, and 8). To ensure this approach was justified, ie, that distinct group and time data yielded hippocampal ICs with a similar spatial configuration and reproducibility, GICAs were first performed within each separate group (supplementary figure S1, GICAs 1–4 and 6).

Group and Time Contrasts

Group and time contrasts in hippocampal–whole brain FC were calculated with unpaired *t* tests (paired for time contrasts), using FSL Randomise with 1000 permutations. Contrasts included the main effects of group (FEP A vs HC across time) and time (T1 vs T2 across HC and FEP A subjects), followed by the simple effects of group (FEP A or FEP B vs HC) at each time, and time within each group (T1 vs T2 within FEP A or HC subjects), see supplementary figure S1. Within the resulting difference maps, areas of significance were identified by threshold-free cluster enhancement,[27] thresholded at $P < .05$ and corrected for family-wise error (FWE) rate. Clusters greater than 10 voxels were reported. The Dice similarity coefficient (DSC) was used to calculate the FEP A vs FEP B reproducibility of FEP vs HC differences in hippocampal–whole brain FC. To determine the directional basis of group and time effects, mean *z* scores for all significant voxels were analyzed by 2-way ANOVA with follow-up *t* tests. Within-group whole brain FC of hippocampal ICs that were significantly different between groups was calculated for these, and neighboring ICs, and one sample *t* tests were used to compare this FC between ICs. To assess baseline FC relationships to symptoms, appropriate hippocampal–whole brain voxelwise regressions were calculated using methods as earlier.

Prediction of Treatment Response

To predict treatment response in FEP A subjects, a RF model using baseline FC features was used to classify patients into "responders" vs "nonresponders". Responders were subjects with a 35% or greater reduction in BPRS total score at T2 relative to T1 (ΔBPRS total >35%); nonresponders had ΔBPRS total <35%. This threshold was based on a median split in baseline BPRS total score. The RF model used 40 baseline FC features—ie, 40 brain regions of interest (ROIs)—to classify patients into these groups. Resulting predictive FC features were those associated with the largest area under the curve (AUC) of the receiver operating characteristic curve (ROC). The following analyses were performed to examine relationships to treatment response. First, the Kolmogorov test, which differentiates samples based on empirical distributions rather than means, was used to compare baseline FC between responders and nonresponders; second, multiple regressions including left anteromedial (LAM) FC scores from all predictive areas were calculated to determine whether baseline FC and T2-T1 change in FC predicted treatment response (ΔBPRS total or positive, as SANS did not change). To compare RF results with those from univariate analyses, voxelwise regressions were performed to identify brain regions in which baseline FC or T1-T2 change in FC correlated with ΔBPRS total or positive, and successive thresholds ($P < .05$, FWE corrected; $P < .05$ uncorrected, or $P < .10$, uncorrected) were used to identify the highest threshold at which at least 10 significant voxels overlapped with the relevant ROI.

Results

Patient Characteristics

From 66 FEP subjects imaged at baseline, 61 met preprocessing criteria (5 were excluded due to excessive motion). Of these, 27 subjects had both T1 and T2 data (FEP A subjects), 34 subjects had T1 data only (FEP B). Twenty-seven HC subjects were selected to be age and gender matched to FEP A subjects. As shown in table 1, FEP A, FEP B, and HC subjects did not differ in age or gender composition. FEP A subjects had significantly higher symptom severity (BPRS total and BPRS positive) compared to FEP B subjects, but did not differ in other characteristics. In FEP A subjects, there was a significant reduction in BRPS total and positive scores following treatment; however, negative symptoms (SANS) did not significantly change.

Masked Hippocampal GICA

Results from masked hippocampal GICA analyses in all subjects agreed with previous studies in healthy subjects,[22,28] i.e., each hippocampus contained five ICs with a similar organization in each hemisphere: one in the posterior (Post), one in the mid (Mid), and three in the anterior hippocampus (anterior, Ant; anteromedial, AM; and anterolateral, AL), (see figure 1). The z_{max} for each IC was both consistent with previous studies, and similar between groups and times (supplementary table S1). Likewise, split-half reproducibility was similar at baseline between HC subjects (Pearson spatial correlation coefficient, $r = .77$), FEP A subjects ($r = .78$), and FEP B subjects ($r = .74$).

Hippocampal–Whole Brain FC

There were no significant effects of group or time at the whole brain level for subjects with follow-up (FEP A and HC), $P > .05$, corrected. There was, however, a significant effect of group at baseline: antipsychotic naïve FEP patients had lower FC between the LAM hippocampal IC and cortical areas in the default mode[29] and salience networks,[30] including the left anterior and mid-posterior insular and opercular cortices, the posterior, mid and anterior cingulate cortices, and the precentral and postcentral gyri (figure 2 and supplementary tables S2A and B). This group difference was highly reproducible between FEP A and B subjects in that the LAM IC was independently identified in both contrasts, and for areas that differed to HC in LAM–brain FC, the DSC was 0.71, indicating good reproducibility. Additional brain areas that were significant in the FEP B vs HC contrast included the right anterior and posterior insular and opercular cortices, the bilateral superior temporal gyrus and superior frontal gyrus (SFG). Baseline FC in FEP subjects was not significantly correlated with baseline BPRS total, positive, or SANS composite scores, $P < .05$, corrected.

At time 2, following 8 weeks of SGA treatment in FEP A subjects, hippocampal–whole brain FC did not differ from HC, even when the threshold was relaxed to $P < .05$, uncorrected. Longitudinal analysis with a 2-way ANOVA of mean z scores within the group difference
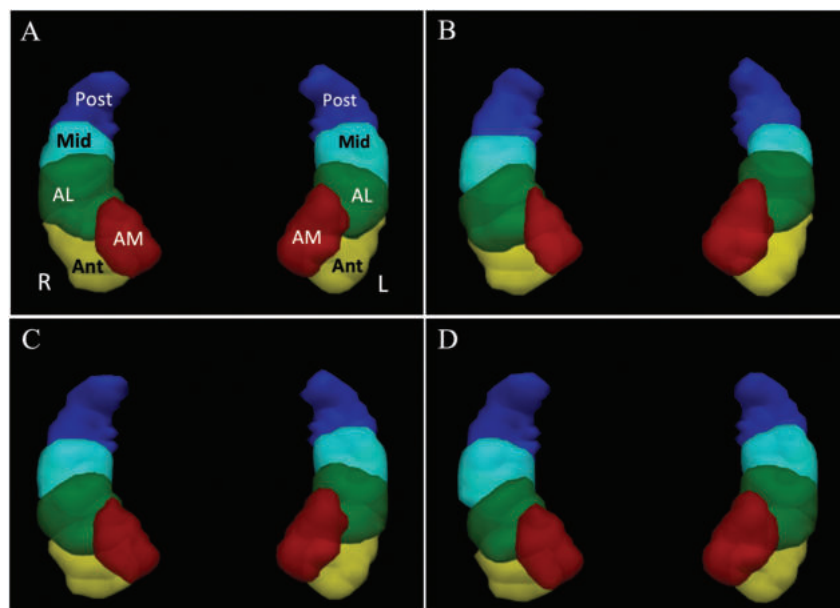

Fig. 1. Independent components (ICs) from masked hippocampal group ICA. Isosurfaces of z scores (thresholded 0.5–30) representing the probability of belonging to one of the 10 ICs are shown in a superior view of the masked bilateral hippocampi in MNI space. (A) Healthy controls (HCs). Each IC in the left (L) and right (R) hippocampus is labeled according to its relative position in the hippocampus. AM, anteromedial; Ant, anterior; AL, anterolateral; Mid, middle; and Post, posterior. (B) FEP group A, (C) HC + FEP group A, (D) HC + FEP group B. ICA, independent component analysis; FEP, first-episode psychosis.
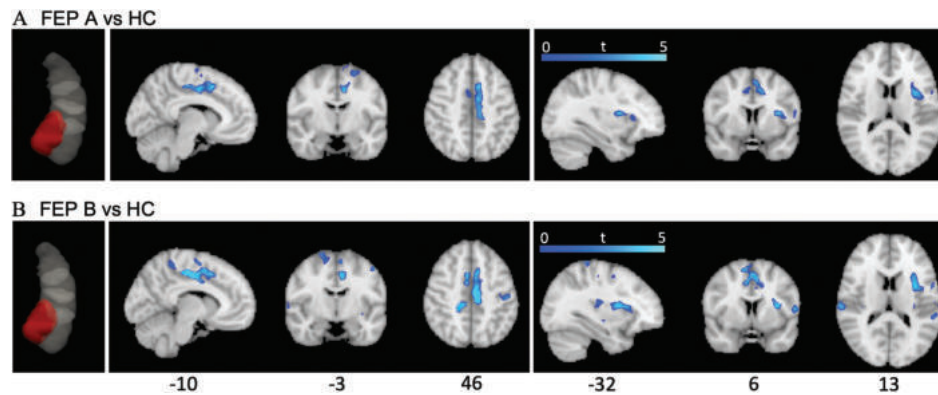
Fig. 2. Differences in hippocampal–whole brain connectivity between antipsychotic naïve FEP subjects and healthy controls (HCs). (A) FEP group A subjects compared to HCs. The left anteromedial (LAM) hippocampal IC from the group FEP A + HC sample is shown in red in leftmost figure inset. Areas of reduced functional connectivity (FC) in FEP A vs HC subjects are shown to the right. (B) FEP Group B subjects compared to HC. The LAM hippocampal IC from the group FEP B + HC sample is shown in red in leftmost figure inset. Areas of reduced FC in FEP B vs HC subjects are shown to the right. IC, independent component; FEP, first-episode psychosis. For color, please see the figure online.

map (from T1) showed a significant group × time interaction, $F(1,104) = 16.36$, $P < .00l$ (see supplementary figure S2). Follow-up t tests showed that at T1, FC in FEP A subjects was lower than that in HC. Within FEP A subjects, FC increased from T1 to T2 ($P < 0.005$). By contrast, in HC subjects FC *decreased* from T1 to T2.

Baseline within-group whole brain FC was examined for the LAM IC, and adjacent (left anterolateral and left anterior) ICs in all FEP subjects (figure 3 and supplementary table S3A), and in HC, supplementary table S3B. For both groups, LAM–brain FC included the dorsal anterior cingulate cortex (dACC) and posterior cingulate cortex (PCC), medial prefrontal cortex, and subcortical areas including the amygdala, midline thalamus, ventral and dorsal striatum, and ventral tegmental area (VTA) (identified using masks from[31]), among other areas. In FEP subjects, comparison of whole brain FC between ICs in FEP subjects showed the anteromedial IC had relatively greater FC with the VTA, bilateral amygdala, medial prefrontal cortex, and subcallosal ACC, compared with anterolateral and anterior ICs (supplementary table S5).

Prediction of Treatment Response

Random forest prediction of membership to responder vs nonresponder categories resulted in an ROC AUC of 0.95 and classification accuracy of 0.89 (see figure 4). Of the 40 RF features, 4 were predicted correct classification, namely the right SFG (MNI x, y, z: 16, −6, 66), left precentral gyrus (PreCG) (−42, −12, 64), right posterior insular–opercular cortex (InsOperc) (36, −14, 20), and left postcentral gyrus (PCG) (−62, −4, 30), ranked in decreasing variable importance score according to the Gini index. The Kolmogorov test of equality for the distributions of responders vs nonresponders showed that responders had significantly higher LAM FC with the InsOperc and SFG, with a trend toward higher FC
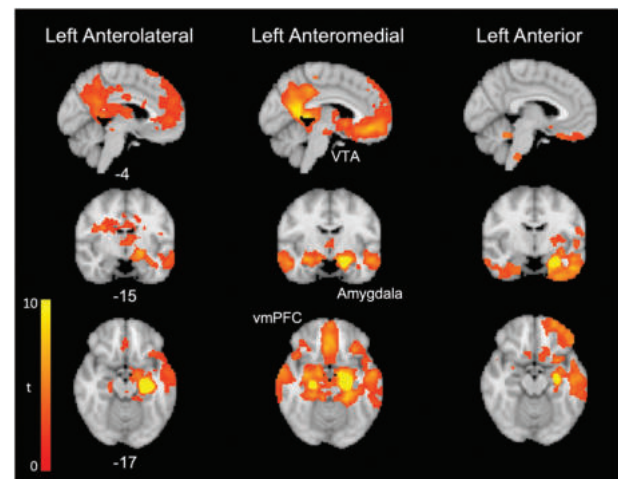

Fig. 3. Whole brain functional connectivity of anterior hippocampal independent components (ICs). Mean whole brain functional connectivity for the left anterolateral, left anteromedial, and left anterior hippocampal ICs is shown for FEP group A patients at baseline. FEP, first-episode psychosis; VTA, ventral tegmental area; vmPFC, ventromedial prefrontal cortex.

with the PreCG, whereas PCG FC did not differ between groups (figure 4). Simultaneous multiple linear regression including baseline LAM FC scores from all 4 predictive brain regions significantly predicted ΔBPRS total score ($P < .001$), where InsOperc had a significant positive β coefficient (supplementary table S5, supplementary figure S3). In addition, ΔBPRS positive score was also predicted by the model ($P < .001$), where both InsOperc and SFG had significant positive β coefficients. For equivalent T2-T1 *change* in FC scores, the overall model was significant for both ΔBPRS total and positive scores ($P < .01$), with a significant negative β coefficient for InsOperc (supplementary table S5). These results indicate that greater treatment responses in both BPRS total and positive

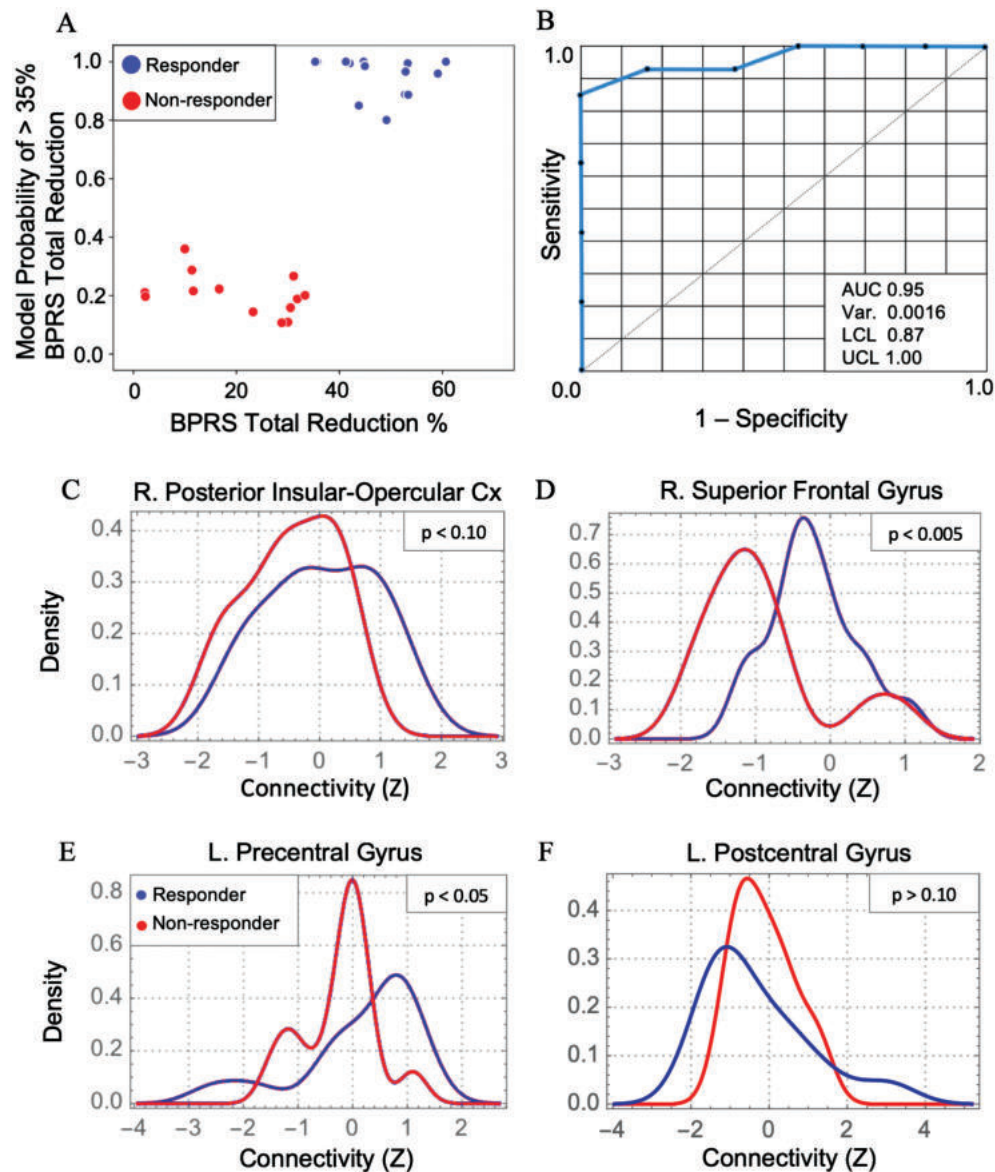**Fig. 4.** Random forest (RF) prediction of treatment response. (A) RF model probability of "response" (reduction in BPRS total score >35). (B) Receiver operating curve for the RF model. (C–F) Plots show density distributions of left anteromedial hippocampal functional connectivity with the 4 brain regions that were predictive in the RF model. *P* values from Kolmogorov tests of distribution equality. Var, variance; LCL, lower confidence limit; UCL, upper confidence limit; R., right; L., left; Cx, cortex; AUC, area under the curve; BPRS, Brief Psychiatric Rating Scale.

scores were correlated with a greater T1 to T2 decrease in LAM-right posterior insular-opercular cortex FC, and a greater baseline potential for this decrease to occur.

Parallel univariate voxelwise analysis showed neither baseline LAM–brain FC, nor T1 to T2 change in FC were significantly correlated with symptom improvement (ΔBPRS positive or total score) at $P < .05$, corrected. However, at $P < .05$, uncorrected, baseline FC in an area of voxels overlapping the InsOperc ROI was positively correlated with both ΔBPRS total and positive scores (supplementary figure S4); in addition, a greater decrease in FC from T1 to T2 was positively correlated with both ΔBPRS total and positive scores (not shown in figure).

At $P < .10$, these same relationships were observed for the SFG and PreCG ROIs (supplementary figure S4), but not for the PCG ROI.

Discussion

Masked Hippocampal Group ICA

In this study, we used masked hippocampal GICA with dual regression to characterize hippocampal–brain resting state FC in unmedicated FEP patients, and to examine the effects of SGA treatment. We report the first use of Masked hippocampal GICA with dual regression in a neuropsychiatric disorder. Despite the critical

need to differentiate FC along the anterior–posterior hippocampal axis, there is no consensus on what config-uration of subregional ROIs would best discern hetero-geneity within the human hippocampus. Rodent models are unsuitable given expansion of the anterior hippo-campus in primate evolution[7,32,33]; a binary anterior vs posterior division[8] masks known differences between the anteromedial and anterolateral hippocampus,[22,32–35] and multiple small ROIs are unlikely to be reproducible.[36] By contrast, masked hippocampal GICA segments the hip-pocampus with a data-driven technique, yielding repro-ducible ICs consistent with rodent-human topology, ie, greater functional heterogeneity in the anterior vs pos-terior hippocampus.[6] We used a dimensionality of 10 ICs based on previous studies[22,28]; also, the resulting ICs are appropriate to the current spatial resolution (80–200 voxels per IC). Hippocampal ICs in FEP subjects had a similar configuration and reproducibility to those in HCs, meaning dual regression could be performed within a group space.

FEP–Control Differences in Anterior Hippocampal–Brain FC

We report, to the best of our knowledge, the first study of FC between the hippocampus and extrinsic brain in an antipsychotic naïve FEP sample. Patients had re-producibly lower FC between an anterior hippocampal subregion and brain areas previously implicated in schiz-ophrenia, as discussed later. That 2 independently con-ducted data-driven analyses converged on the LAM hippocampal IC supports the validity of this finding, and warrants discussion of this subregion's function and anatomical connectivity. The anteromedial human hippocampus is homologous to the caudoventral tip of the rodent hippocampus (vHipp), because the anterior tip of the human hippocampus inverts medially to form the uncus in embryological development.[32,33] The vHipp and functionally connected brain regions, including the VTA, midline thalamus, nucleus accumbens, amygdala, and infralimbic cortex, are implicated in rodent models of psychosis, substantiating the theory that inappropriate vHipp activation drives aberrant salience via interactions with the VTA.[16,37] The anteromedial IC displayed rela-tively stronger FC with these brain areas, as in previous studies,[22] consistent with greater poly- and monosynaptic anatomical connectivity.[38–42] Although subcortical areas did not differ between FEP and controls in the resting state, aberrant anteromedial FC could nonetheless func-tionally affect these circuits, so these findings support the potential importance of this hippocampal subregion in human psychotic disorders.

This is the first report of subregional hippocampal–brain FC in an antipsychotic naïve unmedicated FEP sample. Our entirely data-driven analysis showed repro-ducibly lower FC in FEP patients relative to controls

in the PCC, dACC and insular cortex, core hubs of the default mode,[29] and salience[30] networks. The question of how the anterior hippocampus functionally interacts with the salience network in FEP is of interest given ab-errant salience monitoring is a core feature of psychosis, and the anterior hippocampus plays a key role in sali-ence attribution: in humans, it activates in response to mismatch or novelty,[43,44] co-activates with the anterior insula during threat appraisal,[45] and has strong FC with subcortical nodes involved in salience processing[22,46,47]; in rodents, the ventral hippocampus modulates salience according to context via interactions with the amygdala and prefrontal cortical areas.[45,48,49] Although the salience network and isolated nodes (dACC and insular cortex) have been previously reported to show altered within net-work FC (typically hypoconnectivity) relative to controls in UHR,[50,51] antipsychotic naïve FEP,[52,53] and chronic medicated schizophrenia patients,[54–58] few studies have assessed hippocampal FC with this network. Current findings suggest relative hypoconnectivity between the anterior hippocampus and cortical hubs in the salience network in unmedicated FEP patients. Results add to previous studies in unmedicated mixed FEP and chronic patients,[21] and medicated chronic psychosis spectrum patients.[19,20] These studies were not directly comparable given their use of either whole anterior and posterior ROIs,[19,20] or three 6-mm diameter ROIs in the posterior, mid, and anterolateral hippocampus[21]; also their univar-iate calculation of FC is known to produce less unique patterns of brain FC compared to the current multivar-iate FC with dual regression[59]; nonetheless previous and current findings overlapped in several regards, including hypoconnectivity between the hippocampus and dACC in patients relative to controls.[19–21]

Time/Treatment Effects

Few studies have examined the effects of antipsychotics on hippocampal FC in schizophrenia, none in a wholly FEP sample. We did not find a main effect of treatment/time at the whole brain voxelwise level; however, within areas that differed between patients and controls, namely the cingulate and insular-opercular cortex, FEP patients displayed a significant increase in mean FC following treatment. This suggests that the remediation of patient-control differences at T2 partially resulted from increased FC in this region in patients, in addition to the T1 to T2 *decrease* observed in HC. This latter finding may reflect attenuation of novelty in controls at follow-up and aug-mentation of novelty after treatment in FEP patients, consistent with previous reports showing greater novelty-related fMRI activation in the anterior hippocampus of medicated patients compared with unmedicated patients or controls.[60,61] Owing to a lack of clinical equipoise, pla-cebo controls are not typically included in FEP treat-ment studies. This finding suggests that for the anterior

hippocampus, control of novelty may be necessary to isolate time from medication effects. Overall, exploratory findings are broadly consistent with previous reports showing SGA treatment in FEP patients was associated with increased FC in brain areas within the salience and default mode networks,[17,62] and add to regional blood flow findings[63–65] in showing hippocampal function is altered by antipsychotic treatment, emphasizing the importance of isolating medication effects. Underlying mechanisms may include direct interactions with D2 dopaminergic receptors in the hippocampus,[66] and improved integrity in white matter tracts arising from the hippocampus.[67]

Treatment Response Prediction

We report the first exploratory use of RF to predict treatment response in schizophrenia patients; a previous study used a different machine-learning method for this purpose.[68] We used RF techniques previously associated with the highest accuracy in diagnostic classification,[69] including an out-of-bag estimate to reduce the probability of overfitting, and recursive feature elimination (Gini index). Mechanistic analyses of predictive RF features suggest that *higher* baseline LAM–right posterior InsOperc cortex FC and a greater T1-T2 *decrease* in this FC predicted both BPRS total and positive symptom reduction, despite lower (mostly anterior) insular FC in FEP A patients relative to controls, and an increase following treatment. A previous study in unmedicated FEP patients found that higher insula-Heschl's gyrus FC was associated with increased positive symptoms despite concurrent hypoconnectivity relative to controls, similar to the current finding (reduced FC associated with positive symptom treatment response).[52] This is the first study of anterior hippocampal–insula FC in unmedicated FEP patients. Although the diverse and incompletely understood roles of both these brain areas preclude simple interpretations of FC directionality, findings merit further study. In general, univariate voxelwise analyses of baseline and T1-T2 FC change scores converged on similar areas and correlations with treatment response, but at significance levels that did not survive correction for multiple comparisons. Overall, these exploratory findings suggest that RF analysis based on hippocampal–brain FC may be useful for predicting treatment outcomes in antipsychotic naïve FEP patients.

There were several limitations to the current study. We regard the RF analysis as exploratory owing to the small sample size and lack of a replication sample. We did not explore how hippocampal FC might relate to improvement in negative symptoms, given these did not change with treatment in this study. In addition, we used a relatively stringent univariate test of group differences, which is limited in detecting nonlinear interactions. This approach allowed us to report results of masked hippocampal ICA with dual regression, (a novel technique), in a manner

that could be compared with previous studies; future machine-learning based analyses may be used to classify FEP patients vs HC using this technique. Regarding posterior hippocampal FC, our results contrast with previous reports[20,21] in finding no group differences. This may be because ICA assigns mutually exclusive time courses to ICs,[59] and the relatively stronger FC of anterior ICs with areas such as the PCC masks posterior FC[22]; therefore, univariate analysis may be more appropriate for measuring posterior hippocampal FC.

In summary, we used a data-driven analysis to show that unmedicated FEP patients had reproducibly lower FC between the LAM hippocampus and cortical regions associated with the salience network, compared with controls. Future multimodal neuroimaging studies may elucidate how this hypoconnectivity relates to anterior hippocampal hyperactivity[70] and reduced volume.[2] Our exploratory findings suggest that altered FC may be remediated by SGA treatment, and that associated patterns of FC may predict relevant response with high accuracy. Further studies in external FEP populations may validate these findings.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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unmedicated patients with schizophrenia. *JAMA Psychiatry.* 2013;70(12):1294–1302.

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