Title: Neural Circuitry of Novelty Salience Processing in Psychosis Risk: Association with Clinical Outcome

Abbreviated title: Hippocampal circuits and psychosis risk

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ABSTRACT

Psychosis has been proposed to develop from dysfunction in a hippocampal-striatal-midbrain circuit, leading to aberrant salience processing. Here, we used functional magnetic resonance imaging (fMRI) during novelty salience processing to investigate this model in people at clinical high-risk (CHR) for psychosis according to their subsequent clinical outcomes. Seventy-six CHR participants as defined using the Comprehensive Assessment of At-Risk Mental States (CAARMS) and 31 healthy controls (HC) were studied while performing a novelty salience fMRI task that engaged an *a priori* hippocampal-striatal-midbrain circuit of interest. The CHR sample was then followed clinically for a mean of 59.7 months (~5 years), when clinical outcomes were assessed in terms of transition (CHR-T) or non-transition (CHR-NT) to psychosis (CAARMS criteria): during this period, 13 individuals (17%) developed a psychotic disorder (CHR-T) and 63 did not. Functional activation and effective connectivity within a hippocampal-striatal-midbrain circuit were compared between groups. In CHR individuals compared to HC, hippocampal response to novel stimuli was significantly attenuated (P=0.041 family-wise error corrected). Dynamic Causal Modelling revealed that stimulus novelty modulated effective connectivity from the hippocampus to the striatum, and from the midbrain to the hippocampus, significantly more in CHR participants than in HC. Conversely, stimulus novelty modulated connectivity from the midbrain to the striatum significantly less in CHR participants than in HC, and less in CHR participants who subsequently developed psychosis than in CHR individuals who did not become psychotic. Our findings are consistent with preclinical evidence implicating hippocampal-striatal-midbrain circuit dysfunction in altered salience processing and the onset of psychosis.

INTRODUCTION

The inappropriate attribution of salience to what would normally be irrelevant or neutral stimuli is a robust feature of psychotic disorders, and is linked to altered subcortical dopaminergic signaling[1, 2]. Whilst there are a number of animal models that attempt to describe the pathology and development of psychosis (e.g., chronic phencyclidine models, prenatal immune activation models (for review, see [3]), a particularly influential model proposes that psychosis develops when hippocampal dysfunction drives increased subcortical dopamine activity through descending projections to the striatum.[4, 5] Neuroimaging studies of reward salience suggest that salience processing and associated neural hippocampal-striatal-midbrain responses are perturbed in both patients with psychosis[6, 7] and individuals at clinical high-risk (CHR) for psychosis[8-11], and that this is associated with positive symptoms[11]. In this context, although novelty has been less investigated as a dimension of salience than reward in psychosis[12], preclinical evidence indicates that dopaminergic neurons in the midbrain code the salience of unexpected stimuli and respond to novel stimuli[13, 14]. The first aim of the present study was to examine hippocampal-striatum-midbrain circuit activation and effective connectivity in CHR individuals. We assessed activation using functional magnetic resonance imaging (fMRI) in conjunction with a novelty salience paradigm based on a task that had previously elicited robust hippocampal-striatal-midbrain responses[15], and employed Dynamic Casual Modeling (DCM)[16] to assess effective connectivity within this circuit.

While previous neuroimaging studies had reported altered activation and connectivity in a hippocampal-striatal-midbrain circuit during reward salience processing in CHR individuals[8, 11], the extent to which these findings are specific to the CHR subset who later develop psychosis has yet to be investigated. Our second aim was to address this issue by examining the relationship between activation and

connectivity within this circuit and the subsequent onset of a psychotic disorder. We therefore followed up our CHR participants to determine their clinical outcome.

Our primary hypothesis was that during novelty salience processing, hippocampal-striatal-midbrain circuit activation would be attenuated[6, 7, 11] in CHR individuals compared to healthy controls. We also examined how pure novelty salience processing altered effective connectivity in this circuit. Our second prediction was that these alterations would be particularly evident in the CHR subgroup who subsequently developed psychosis.

METHODS

Participants

A total of 116 participants were recruited into the study. Ethical approval was obtained from the National Health Service UK Research Ethics Committee, and all participants provided written informed consent.

CHR participants (n=85) were recruited from four different clinical sites in England: OASIS (Outreach and Support in South London)[17], part of the South London and Maudsley NHS Trust; CAMEO, part of the Cambridge and Peterborough NHS Trust; the West London Early Intervention Service; and the Coventry and Warwick Warwickshire Partnership NHS Trust. All participants underwent clinical assessments and MRI scanning at King's College London (KCL) by two trained researchers (CS and BQ). CHR signs and symptoms for inclusion were assessed with the Comprehensive Assessment of At-Risk Mental States (CAARMS)[18]. Exclusion criteria were past/present diagnosis of psychotic disorders, past/present/familiar history of neurological illness, substance abuse/dependence according to DSM-5 criteria[19] or contraindication to scanning.

Healthy controls (HC, n=31) were recruited from the same geographical areas as CHR participants. None had a personal/familial history of psychiatric/neurological disorder or were using prescription medication as assessed via self-report. Additional exclusion criteria for all participants involved self-reporting illicit substance use in the week prior to scanning or alcohol use in the 24 hours prior to scanning.

Clinical Measures

On the day of the MRI scan, the following measures were collected at KCL by trained raters: psychopathology using the CAARMS[18], anxiety and depression symptoms using the Hamilton Anxiety and Depression Scales (HAM-A/HAM-D) [20], Premorbid IQ was estimated with the National Adult Reading Test (NART)[21]. Handedness was assessed using the Annett Handedness Scale[22]. Participants provided information on tobacco (cigarettes/day), alcohol (units/day), and cannabis use (0=no use, 1=experimental use, 2=occasional use, 3=moderate use, 4=severe use).

Novelty Salience Task

All participants underwent fMRI scanning on a 3T GE scanner at KCL using an event-related novelty salience task adapted from Bunzeck and Duzel[15]. Participants completed three 6-min runs of a visual oddball paradigm (Figure 1A). In each of the three runs, there were 80 standards (same picture in 73% of trials), 10 target oddballs (same picture in 9% of trials, requiring a button press at each presentation), 10 neutral oddballs (same picture in 9% of trials), and 10 novel oddballs (a unique picture in 9% of trials representing a “pure novel stimulus”[15]), yielding a total of 360 stimuli across the entire 18-min experiment (240 standards, 30 target oddballs, 30 neutral oddballs and 30 novell oddballs). All pictures depicted black-and-white outdoor scenes.

The target stimulus, used solely to assess engagement with the task as in the original study[15] (there was no measure of accuracy during novelty processing), was presented at the start of the experimental session for 4.5s. Participants were asked to press a button with their right index finger every time it appeared (30 presentations in total). During the experiment, pictures were presented for 500ms followed by a white fixation cross on a gray background with an inter-stimulus interval of 2.7s, jittered between -300ms and +300ms (uniformly distributed).

Clinical Follow-Up

The entire CHR sample was followed up subsequent to scanning to determine clinical outcome (transition/non-transition to psychosis). The mean interval between baseline and follow-up assessments was 59.7 months (SD=15.4 months). Transition to psychosis was determined using CAARMS Psychosis Threshold criteria[18] and confirmed with the Structured Clinical Interview for Diagnosis[19], administered by a psychiatrist trained in its use.

Image Acquisition and Preprocessing

See Supplement for details on fMRI acquisition and preprocessing.

Statistics

Demographic, clinical and behavioral data

Analyses of demographic data were performed in SPSS 24 (http://www-01.ibm.com/software/uk/analytics/spss/). The effect of group on these measures was examined using independent samples *t*-tests for parametric data and Chi-square tests for non-parametric data. To examine the relationship between fMRI activation and transition to psychosis, the CHR sample was divided into two groups at follow-up: a transition to psychosis group (CHR-T) and a non-transition to psychosis group (CHR-NT). Analysis of behavioral data were performed in SPSS 24 for reaction time

(RT), target recognition and error rates using separate two-sample *t*-tests: HC vs. CHR and CHR-NT vs. CHR-T. Significant effects are reported at P<0.05 with Bonferroni post-hoc correction as appropriate (demographic data: age, sex, IQ, years of education, handedness, tobacco, alcohol, cannabis, antipsychotics and antidepressant use – p<0.05/10 = p<0.005; clinical data: CAARMS positive, negative, total, GAF, HAM-A and HAM-D – p<0.05/6 = p<0.008; behavior: targetness, errors and RT – p<0.05/3 = p<0.017).

fMRI data analysis

Statistical analysis of the fMRI data was conducted using the general linear model in SPM12. Separate regressors of interest were specified for each trial type: Standard, Target, Neutral and Novel. Realignment parameters (x, y, z, pitch, roll, yaw) were included in all first-level models as covariates of no interest to account for variance associated with head movement. All regressors were convolved with a canonical hemodynamic response function during the 500ms in which trials were presented. One contrast image was generated for each participant to examine activation related to pure stimulus novelty by contrasting all novel oddball trials against neutral oddball trials[15] and was then submitted to second-level analysis.

For between-group comparisons between HC and CHR participants, a two-sample *t*-test was performed using the first-level novel>neutral contrast images, covarying for age. We used an initial cluster defining threshold of P<0.001 uncorrected to then enforce a voxel-wise height threshold of family-wise error (FWE) P<0.05 after small volume correction (SVC) for region-of-interest (ROI) analyses,[23, 24] using a pre-specified bilateral mask comprising the hippocampus, striatum and midbrain. The striatum was chosen on the basis of its role in the aberrant salience hypothesis[2] and previous fMRI studies documenting salience–related responses in this region[25]. The hippocampus was chosen based on preclinical evidence for its

central role in psychosis through the regulation of dopamine signaling,[4] and prior work indicating a relationship between aberrant hippocampal activity and the CHR state[(e.g.,26, 27)]. The midbrain was chosen since novel stimuli are associated with fMRI activations in this region as shown by Bunzeck and Duzel's study using this task in healthy volunteers[15]. The ROI mask was built using the WFU_Pitckatlas toolbox and comprised predefined anatomical masks of the striatum (caudate, pallidum, putamen) and the hippocampus from the automated anatomical labelling atlas, and a 6-mm sphere around the midbrain (ventral tegmental area/substantia nigra, VTA/SN) coordinates reported in the study with healthy volunteers[15] (only right-sided as in Bunzeck & Duzel[15], *xyz*: 8, -20, -18) (Figure 1B).

To investigate the relationship between functional activation in response to novelty and transition to psychosis, a two-sample *t*-test was specified in SPM (CHR-NT vs CHR-T), adjusting for age. The same ROI mask and significance threshold as above were applied (P_{FWE}<0.05 after SVC). Potential confounding effects of substance use (alcohol, tobacco, cannabis) and levels of anxiety/depression (HAM-A/HAM-D) on the regions showing significant novelty-related group differences were examined with an additional ANCOVA in SPSS. Exploratory whole-brain voxel-wise analysis of fMRI data (comparing all CHR to HC subjects and CHR-NT to CHR-T subjects) is reported in the Supplement.

Dynamic Casual Modeling (DCM)

Volumes of interest and time-series extraction

Based on preclinical evidence[4, 5] and data from a previous study of the task in healthy volunteers[15], we used DCM12 in SPM12 to compute effective connectivity within a circuit comprising the hippocampus, the striatum and the midbrain (Figure 3A). The volumes of interest (VOIs) for these regions were defined using the maximally activated coordinates in the second-level fMRI analysis within our masked

regions (Figure 1B), following published rules for the application of DCM[28]. The VOI for the hippocampus was extracted from the group-level fMRI difference between CHR versus HCs (*xyz*: 38 -16 -14). As there was no significant group-level difference in either the striatum or midbrain, we used the coordinates of the task effect of novel>neutral across all participants with an 8-mm sphere for each region, allowing the center of the sphere to move to the nearest supra-threshold voxel (*xyz*: striatum, 28 20 -2; VTA/SN, 14 -24 -16; P_{UNC}<0.05).

Group comparisons with parametric empirical Bayes (PEB)

PEB, included in SPM12, allows evaluating group effects and between-subjects variability on DCM parameters (HC vs CHR; CHR-NT vs CHR-T). PEB for DCM is performed by comparing the posterior density of any (reduced) model in terms of the posterior of its parent or full model. The first step is to estimate a full model (i.e., with every connection switched 'on') for every subject. Then, a nested model is constructed (i.e., with certain conditions switched 'off), which allows the expression of the posterior density of any (reduced) model in terms of the posterior of its parent or full model. This process affords an efficient way to evaluate posterior densities under empirical priors. It is then possible to apply Bayesian model reduction to the posterior densities over the second-level parameters to find out where between-subject effects are expressed.[29] Results are given by the group effect on the Posterior Probabilities (P) and the Bayesian Confidence Interval. Group differences were thresholded with a P>0.5 obtained as recommended by DCM's developers (https://arxiv.org/pdf/1902.10604.pdf) and following Kass & Raftery.[30] Although comparing Bayes Factor to P-values is not straightforward, it could be argued that it is equivalent to P<0.05.[31] The present study examined how the connections between the anterior hippocampus, ventral striatum and VTA/SN were modulated by stimulus novelty (novel>neutral oddball trials) by generating a second model space which included a full model, to then create four different models with each connection

switched 'off' (nested models) (Figure 3A). Group differences were then verified by comparing the evidence between the full model and the nested model. Group variables were de-meaned before being entered in the PEB model, to account for the different sample sizes of our study groups. Age was included as a covariate on all PEB analyses.

Additional exploratory analyses within the CHR group and its subgroups according to transition status were conducted to examine potential associations between severity of positive prodromal symptoms and fMRI response to novelty / DCM connectivity strengths (eFigure 1 in Supplement).

RESULTS

Demographic and clinical data

Nine CHR participants were excluded from the final analyses due to incomplete fMRI data (n=3), or excessive movement (n=6). The analyzed sample thus comprised 76 CHR participants and 31 HCs. Detailed examination of potential movement confounds is reported in the Supplement (eTable 1 and eFigure 2).

All of the CHR participants met the CAARMS Attenuated Psychotic Symptoms criteria[32]. A minority additionally fulfilled the BLIPS (n=5) or schizotypal personality disorder/familial risk criteria (n=2). At the time of scanning, most (67/76; 88%) CHR participants were naïve to antipsychotic medication. The remainder were taking low doses of antipsychotics (<1.5mg haloperidol equivalents per day). The majority of CHR participants were also anti-depressant free at the time of scanning (48/76; 63%).

The HC and CHR groups did not differ significantly in gender, handedness, estimated IQ, years of education, alcohol, or cannabis use. However, the CHR group

was younger and smoked more tobacco. As would be expected, they showed higher levels of anxiety and depressive symptoms (HAM-A/HAM-D scores) and had lower levels of overall functioning compared to HCs (GAF score) (Table 1).

Thirteen of the CHR participants (17%) developed a psychotic disorder within the follow-up period of 59.7 months (CHR-T), while 63 participants did not (CHR-NT). There were no significant differences in demographic or clinical variables at baseline between these groups (Table 1).

Behavioral Data

The groups did not differ in their engagement with the fMRI task (mean RT or recognition of target stimuli; eTable 2 in the Supplement).

fMRI data

Effect of task

Across groups, pure stimulus novelty was associated with activation in the anterior hippocampus, ventral striatum and midbrain bilaterally (P_{FWE}<0.05 after SVC; Table 2, Figure 2A).

Group differences: all CHRs vs HCs

In CHR participants, relative to HC, pure stimulus novelty (novel>neutral oddball trial) was associated with significantly less activation in the anterior portion of the right hippocampus than in HCs (P_{FWE}=0.041; *xyz*=38 -16 -14; Z=3.42, Hedges' g=0.543; Figures 2B/2C). There were no areas where CHR participants showed greater activation than HC. These findings remained unchanged after adding sex as additional covariate of no interest in the analysis (HC > CHR: right hippocampus, P_{FWE}=0.033; xyz=38 -16 -14; Z=3.49, Hedges' g=0.544; CHR > HC no suprathreshold voxels).

Because resting-state neuroimaging studies in CHR groups have reported increased hippocampal perfusion/metabolism[26, 27, 33, 34], we tested whether the reduced activation of the right anterior hippocampus in CHR relative to HC during pure stimulus novelty reflected an increased response to the neutral comparator stimuli that fMRI studies traditionally use[35]. This supplementary analysis involved the contrast of neutral oddballs versus standards, reflecting activation related to unexpected, as opposed to novel stimuli, and revealed an increased hippocampal response in CHR relative to HC at a lenient threshold (P=0.004 uncorrected, x y z=36 -24 -16; k_E = 20; z = 2.66; Hedges' g=0.186; Figure 1).

Group differences: transition to psychosis

There were no significant differences in activation between the CHR-T subgroup and either the CHR-NT subgroup or HCs. However, as in the total CHR sample, a lower right anterior hippocampal response to novel>neutral stimuli was evident when CHR-NT were compared with HC (P_{FWE}=0.018; *xyz*=38 -16 -14; Z=3.68, Hedges' g=0.626). These findings remained unchanged after additionally adjusting the analysis for sex (HC > CHR-NT: right hippocampus, P_{FWE}=0.013; xyz=38 -16 -14; Z=3.76, Hedges' g=0.488; HC <> CHR-T or CHR-NT <> CHR-T: no suprathreshold voxels). Clinical follow-up information (transition/non-transition) was not available for 6 of the 76 CHR individuals; repeating the transition analysis with these 6 individuals excluded from the CHR-NT group did not change the results (HC > CHR-NT: right hippocampus, P_{FWE}=0.019; xyz=38 -16 -14; Z=3.64, Hedges' g=0.621; HC <> CHR-T or CHR-NT <> CHR-T: no suprathreshold voxels).

Analysis of potential confounders

A secondary analysis assessed the potentially confounding effects of substance use (alcohol, cigarettes and cannabis) and levels of anxiety/depression (HAM-A/HAM-D)

on the group difference in right anterior hippocampus activation. The group effect remained significant ($F_{1,80}$=5.486, P=0.022, Hedges' g=0.742) (eTable 3 in the Supplement). We also examined whether antipsychotic medication could have affected the results by repeating the analysis after the 9 CHR participants who were receiving antipsychotics had been excluded from the SPM design. Again, the group difference in the right anterior hippocampus remained significant (P_{FWE}=0.042; *xyz*=38, −18 −14; Z=3.43, Hedges' g=0.591). Finally, comparing CHR participants with (n=28) versus CHR participants without (n=48) antidepressants showed no suprathreshold effects at P_{FWE}<0.05.

Exploratory whole-brain fMRI results (comparing all CHR with HC subjects and CHR-NT with CHR-NT subjects) are reported in the Supplement (eTable 4, eFigure 3).

Effective connectivity: all CHRs vs HCs

For the comparison of HC vs CHR groups, PEB revealed group differences in the modulatory effect of pure stimulus novelty on hippocampal-striatal-midbrain connections. The CHR group showed relatively reduced connectivity from VTA/SN to striatum (P:0.52), but greater connectivity from hippocampus to striatum (P:0.64) and from VTA/SN to hippocampus (P:0.68) (Figure 3B). These findings remained largely unchanged after additionally adjusting the analysis for sex (VTA/SN to hippocampus P:0.74; hippocampus to striatum P:0.63; although VTA/SN to striatum P:0.47).

Effective connectivity: transition to psychosis

Comparison of the CHR participants who subsequently developed psychosis and those who did not by PEB analysis also revealed a group difference: the CHR-T subgroup showed reduced connectivity from VTA/SN to striatum compared to the CHR-NT subgroup (P:0.51) (Figure 3C). This finding remained unchanged after additionally adjusting the analysis for sex (P:0.53). Repeating this analysis excluding

the 6 individuals for which follow-up clinical information was not available revealed that the reduced connectivity in CHR-T individuals from VTA/SN to striatum remained significant (P:0.71), and a further connectivity decrease was observed for the backward connection from the striatum to the VTA/SN (P:0.75) (eFigure 4).

DISCUSSION

Our first major finding was that participants at CHR for psychosis showed an altered anterior hippocampal response during pure stimulus novelty processing, suggesting that salience dysregulation is not only present in patients with psychosis, but is also evident before its onset. The result was not attributable to effects of age, treatment with antipsychotic or antidepressant medication, substance use, anxiety/depression symptoms, or differential behavioral engagement with the fMRI task. Complementary whole-brain analysis showed no significant between-group differences (as shown in the Supplement), suggesting that during 'pure stimulus novelty' processing regions outside our *a priori* hippocampal-striatal-midbrain mask would not be differentially engaged by CHR individuals. The second major finding came from applying a circuit-based approach to examine functional coupling within a hippocampus–striatal–midbrain circuit during salience processing. CHR subjects showed significantly reduced effective connectivity from the midbrain to the striatum compared to controls, but greater connectivity from the hippocampus to the striatum and from the midbrain to the hippocampus. The reduction in midbrain-striatal connectivity in the whole sample was also evident in the subgroup who later became psychotic compared to the subgroup who did not. Overall, the results support previous reports that altered salience-related response in the hippocampus is associated with psychosis risk,[8, 11] and suggest that the subsequent development of psychosis may rather be based on circuit-based connectivity disruptions.

According to a well-validated neurodevelopmental animal model, the methylazoxymethanol acetate (MAM) model, increased tonic activity of the ventral/anterior hippocampus leads the ventral striatum to disinhibit the midbrain via inhibition of the ventral pallidum, which increases the number of spontaneously active midbrain dopamine neurons[4, 36]. Human imaging evidence has been largely consistent with this model[37]. Resting cerebral blood volume (CBV) or flow (CBF) is elevated in the anterior hippocampus of patients with schizophrenia[33, 34, 38, 39] and CHR individuals[26, 27, 34]. Higher levels of CBV/CBF are positively associated with psychotic symptoms in CHR subjects[33] and with subclinical psychotic-like experiences in schizotypal individuals[40]. Furthermore, CHR subjects show elevated striatal dopamine function[41, 42], an association between striatal dopamine function and reduced hippocampal activation during a memory task[43], and altered hippocampal glutamate levels[44, 45]. In turn, altered hippocampal glutamate levels have been related to abnormal hippocampal activation during a memory task in CHR[46]. Our findings extend this literature by showing that hippocampal dysregulation is also evident when CHR individuals process novelty salience.

An important consideration in the interpretation of fMRI data is that increases and decreases in BOLD response depend on (i) the direction of the change in regional brain activity relative to the baseline for both the control and the task condition, (ii) the way in which the control condition and the condition of interest are compared, (iii) comparing groups which may have different baseline states[35, 47]. Our novelty salience paradigm was adapted from that employed by Bunzeck and Duzel[15] showing that the VTA/SN preferentially responds to stimulus novelty over other forms of stimulus salience. The contrast between novel and neutral oddballs allowed quantification of neural response to what the authors called “pure stimulus novelty”, as opposed to rareness/deviance *per se*[15]. Our results suggest that the reduced response to pure stimulus novelty in the right anterior hippocampus in CHR

individuals may be driven by increased response to the control condition comprising neutral stimuli (albeit at an uncorrected level).

In terms of effective connectivity within this circuit, relative to controls, CHR subjects showed greater modulation by pure stimulus novelty in the connection from hippocampus to striatum and from midbrain to hippocampus. While this analysis also indicated reduced modulation of connectivity from midbrain to striatum in CHR individuals, this effect was no longer significant once sex was adjusted for in the analysis, suggesting a potential relationship between midbrain-striatal connectivity and sex in the CHR state which merits further research. Overall, these findings suggest that, in CHR subjects, afferent and efferent connectivity of the hippocampus were increased, consistent with disrupted interactions within a hippocampal-striatal-midbrain circuit being associated with increased risk for psychosis. This pattern of dysconnectivity would be in line with the maximal tonic activation of dopamine neuron firing hypothesized to occur in psychosis, thought to obscure salience-driven increases in population activity of mesostriatal dopamine neurons[36], leading to all stimuli being inappropriately registered as salient. This could account for the increased response to non-novel stimuli, and the attenuation of the hippocampal response to salient stimuli, observed in the CHR group.

Although the later onset of psychosis in CHR subjects was not associated with significant differences in hippocampal activation, this subgroup showed reduced modulation by pure stimulus novelty of the effective connectivity from midbrain to striatum compared to CHR subjects who did not become psychotic. As a similar alteration in midbrain-striatal connectivity was also evident in the total CHR sample relative to controls (above), this suggests that among the changes in connectivity seen in the CHR sample, alterations in communication from midbrain to striatum may be particularly relevant to the subsequent onset of psychosis. This would be

consistent with PET studies in CHR subjects showing elevated midbrain and striatal dopamine function linked to later transition to psychosis[42, 43]. An alternative explanation relates to a 'ceiling effect' for hippocampal activity and subcortical connectivity in dopamine-related regions; the lower hippocampal response to novel versus non-novel stimuli could reflect a reduced signal-to-noise ratio in the comparison between these two conditions in CHR individuals, supported by the (uncorrected) hyper-responsivity to the neutral comparator condition. This notion is consistent with previous findings on emotional salience in CHR groups that lower responses to emotional stimuli are driven by increased responses to the neutral, non-emotional condition[48-52], and by reports of increased resting hippocampal perfusion in CHR[26, 27, 33, 34]. Taken together, these results suggest that increased baseline activity/tonic dopamine signaling within this circuitry may render CHR/CHR-T individuals less able to 'effectively' distinguish between novel (salient) and non-novel (non-salient) stimuli.

Despite studying a relatively large sample of CHR subjects, the number in the CHR-T subgroup was small; the findings in this subgroup should therefore be interpreted with caution, and warrant replication in larger samples. Previous imaging studies of salience processing in CHR individuals relative to HCs have found significant differences in activation of the hippocampal-striatal-midbrain circuit in the context of reward/motivational salience[8, 11], but not novelty or emotional salience. A possible explanation for this discrepancy might relate to modest sample sizes in previous studies, as we included a relatively large CHR sample (n=76). Additional sources for discrepancies might relate to the use of different salience task paradigms, tapping on different dimensions of salience processing. More specifically, Roiser et al.[11] used the Salience Attribution Task (SAT), a monetary reward task measuring adaptive and aberrant motivational salience. In contrast, Winton-Brown et al.[8] used the Salience Integration Task (SIT), a monetary incentive delay task in

which conditions were manipulated to examine reward (monetary), novelty (with half of the trials as pre-familiarized and the other half as novel), and aversion (with half of the pictures as emotionally aversive). Given that salience is a multifaceted construct[12], and that novelty salience had not been studied in relation to transition to psychosis, we used a task paradigm known to robustly isolate the specific processing of novelty[15]. In terms of findings, Roiser et al. focused on the dorsolateral prefrontal cortex, hippocampus and midbrain, and found that the magnitude of aberrant motivational salience attribution was positively correlated with ventral striatal responses to non-salient cue features[11]. Winton-Brown et al. focused on the hippocampus, striatum and midbrain, and found significant group differences with CHR subjects showing greater activation than HC to reward-predicting stimuli in the ventral pallidum and in the midbrain/hippocampus, while they did not observe any significant effects for novelty or emotional salience[8]. In the present study, using a specific 'pure stimulus novelty' salience task, we observed a significant difference in hippocampal responsivity between HC and CHR individuals. Finally, Roiser et al.[11] had shown an abnormal association between hippocampal response to motivational salience and dopamine synthesis capacity in a smaller sample of CHR individuals. Given that the hippocampus is central to the processing of novelty salience,[53] it would be interesting to determine whether the hippocampal alteration we detected during novelty processing is also abnormally associated with dopamine synthesis capacity in CHR individuals.

In summary, **t**he data from the present study indicate both perturbed hippocampal activation and hippocampal-striatal-midbrain effective connectivity in the context of novelty salience in people at CHR for psychosis, and that the later onset of psychosis is associated with alterations in midbrain-striatal connectivity. These findings are consistent with data from preclinical models of psychosis

implicating alterations in a hippocampal–striatal-midbrain circuit in the development of psychosis.

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COMPETING INTERESTS

Dr. Grace receives consulting fees from Johnson & Johnson, Lundbeck, Pfizer, GSK, Merck, Takeda, Dainippon Sumitomo, Otsuka, Lilly, Roche, Asubio, and Abbott; and receives research funding from Lundbeck, Lilly, Autifony, Alkermes and Johnson & Johnson. Dr Howes has received investigator initiated research funding from and/or participated in advisory/speaker meetings organized by Astra- Zeneca, Autifony, BMS, Eli Lilly, Heptares, Jansenn, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand and Roche. Neither Dr Howes or his family have been employed by or have holdings/a financial stake in any biomedical company. The other authors declare no competing financial interests.

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FIGURE LEGENDS

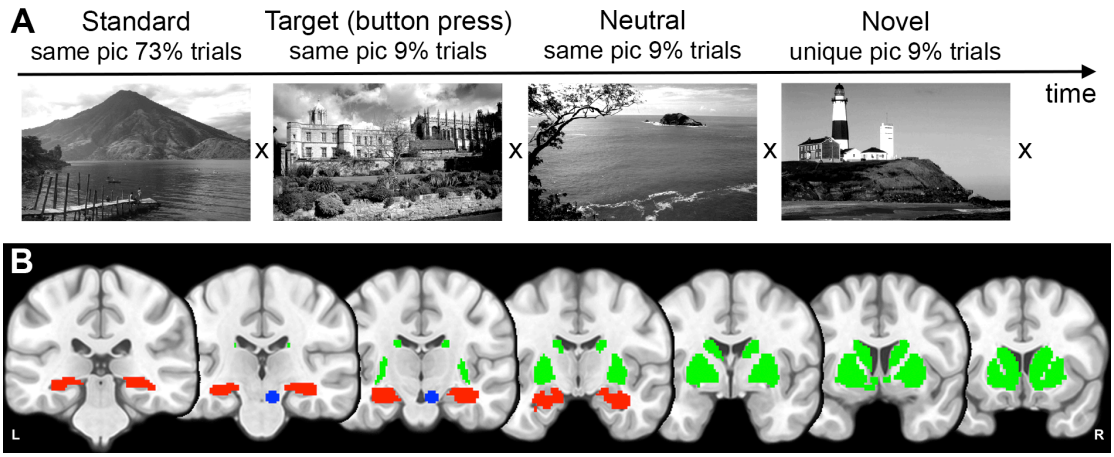

Figure 1. (A) Task paradigm. (B) Region-of-interest mask used for small volume correction on the fMRI analysis. Red = hippocampus; green = striatum; blue = midbrain. L = left hemisphere; R = right hemisphere.

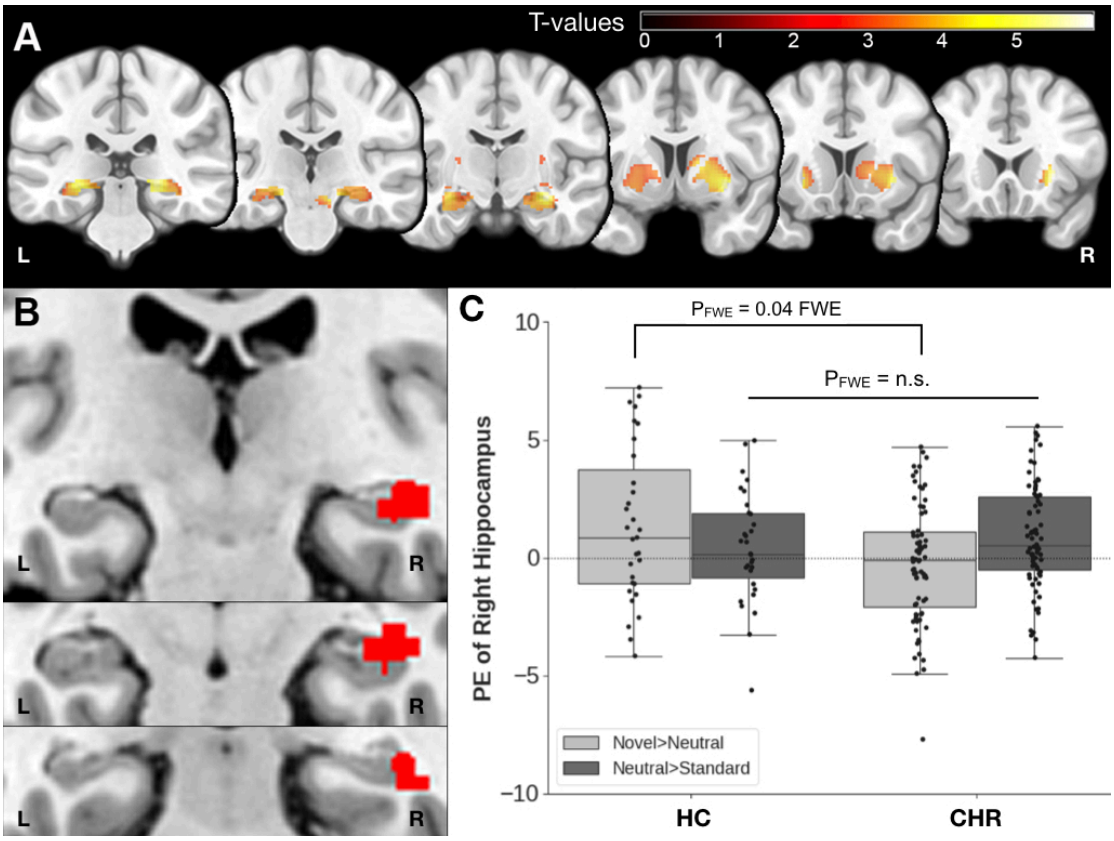

Figure 2. (A) Novel > Neutral oddball trials across groups, and (B) Between-group clinical high risk (CHR) versus healthy control (HC) results in right hippocampus for the contrasts of novel > neutral oddballs with activation superimposed on a standard T1 template. (C) Boxplots show mean hippocampal activation in each group for novel > neutral (pure stimulus novelty) and neutral > standard (stimulus rareness/deviance). L = left hemisphere; R = right hemisphere.

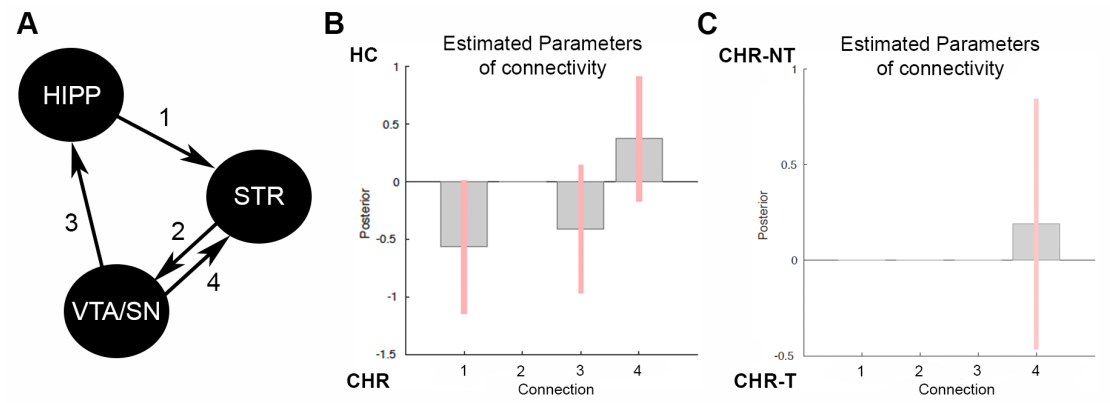

Figure 3. (A) DCM model. (B) Group effects on PEB models between HC and CHR. (C) Group effects on PEB models between CHR-NT and CHR-T. Gray bars show posterior probabilities for model evidence. Pink bars represent the Bayesian 95% confidence interval.

TABLES

Table 1. Demographic and questionnaire data.

Measure	HC (n=31)	CHR (n=76)	*g or V*	P	CHR-NT (n=63)	CHR-T (n=13)	*g or V*	P
Age (years)	25.0 (4.1)	22.46 (3.6)	0.677	**0.003**	22.7 (3.8)	21.9 (2.6)	0.220	0.488
Gender (male/female)	15/16	42/34	0.063	0.518	36/27	6/7	0.083	0.468
NART IQ	104.9 (13.7)	103.5 (14.6)	0.097	0.669	103.6 (15.6)	103.1 (8.2)	0.034	0.878
Years of education	15.8 (3.5)	14.6 (2.2)	0.455	0.071	14.6 (2.2)	14.5 (2.5)	0.044	0.907
CAARMS								
Positive score	-	10.1 (4.1)	-		9.7 (3.9)	11.8 (4.7)	0.520	0.102
Negative score	-	5.1 (4.1)	-		5.1 (4.1)	4.8 (4.3)	0.073	0.785
Total score	-	42.3 (22.4)	-		42.1 (21.9)	43.2 (25.5)	0.050	0.873
GAF score	92.9 (5.0)	58.0 (9.5)	4.124	**<0.001**	58.5 (9.7)	55.3 (8.5)	0.336	0.272
HAM-A score	3.4 (4.2)	18.4 (11.2)	1.542	**<0.001**	17.5 (10.4)	22.8 (14.2)	0.477	0.173
HAM-D score	1.7 (3.5)	17.6 (11.1)	1.662	**<0.001**	17.0 (11.1)	20.3 (11.2)	0.297	0.396
Tobacco (cigarettes/day)	1.9 (3.4)	6.3 (9.0)	0.563	**0.001**	7.2 (9.6)	2.1 (3.6)	0.573	0.074
Alcohol (units/day)	1.7 (2.2)	1.6 (3.4)	0.032	0.964	1.8 (3.6)	0.9 (0.7)	0.272	0.426
Cannabis (median [range])[a]	0 [0-3]	0 [0-4]	0.146	0.703	0 [0-4]	0 [0-4]	0.147	0.811
Antipsychotic medication (n)	-	9 (12%)	-	-	8 (13%)	1 (8%)	0.058	0.611
Antidepressant medication (n)	1 (3.2%)	28 (37%)	0.343	**<0.001**	25 (40%)	3 (23%)	0.130	0.258
Right-handed (n)	26 (90%)	64 (85%)	0.187	0.162	52 (83%)	12 (92%)	0.090	0.434

[a] 0=never, 1=experimental use, 2=occasional use, 3=moderate use, 4=severe use.

CAARMS, Comprehensive Assessment for the At-Risk Mental State; CHR, clinical high risk; CHR-NT, clinical high-risk non-transition; CHR-T, clinical high-risk transition; GAF, Global Assessment of Functioning scale; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; HC, healthy controls; NART, National Adult Reading Test. g or V, Hedges' g or Cramer's V.

Table 2. Random Effects Analysis for Novel Oddballs versus Neutral Oddballs Across and Within Groups in the hippocampal-striatal-midbrain region of interest.

Brain Area	MNI Coordinates			*k*	*T*	*Z*	Voxel-wise P_{FWE}
	x	*y*	*z*				
Across all participants (n=107)							
R anterior hippocampus	32	-12	-14	568	5.52	5.16	<0.001
L hippocampus	-26	-30	-6	560	4.77	4.53	0.001
R midbrain	12	-24	-16	50	4.37	4.18	<0.001
R ventral putamen	28	20	-2	963	5.91	5.47	<0.001
R dorsal pallidum	18	4	6		4.25	4.07	0.008
R ventral caudate	14	8	6		4.15	3.98	0.012
L ventral putamen	-26	14	-4	540	4.28	4.10	0.008
HC (n=31)							
R anterior hippocampus	32	-14	-14	542	4.89	4.62	<0.001
L hippocampus	-22	-34	-6	552	3.96	3.82	0.011
R midbrain	14	-18	-14	5	3.22	3.13	0.014
R ventral putamen	32	4	-8	42	3.77	3.64	0.019
CHR (n=76)							
R hippocampus	22	-32	-2	18	3.63	3.51	0.031
R midbrain	12	-24	-16	24	4.00	3.85	0.002
R ventral putamen	28	20	-2	247	5.57	5.20	<0.001
L ventral putamen	-26	14	-6	19	3.68	3.56	0.024
CHR-NT (n=63)							
R midbrain	12	-24	-16	17	3.59	3.48	0.005
R ventral putamen	28	20	-2	124	5.43	5.08	<0.001
CHR-T (n=13)							
No suprathreshold voxels							

L, left; R, right. CHR, clinical high risk; CHR-NT, clinical high-risk non-transition; CHR-T, clinical high-risk transition; HC, healthy controls.

SUPPLEMENTARY INFORMATION

Title: Neural Circuitry of Novelty Salience Processing in Psychosis Risk: Association with Clinical Outcome

Gemma Modinos[1,2*], Paul Allen[3,1*], Andre Zugman[4], Danai Dima[2,5], Matilda Azis[1], Carly Samson[1], Ilaria Bonoldi[1], Beverly Quinn[6], George GW Gifford[1,], Sophie E Smart[1,], Mathilde Antoniades[1], Matthijs G. Bossong[7], Matthew R Broome[8], Jesus Perez[5,9,10], Oliver D. Howes[1], James M. Stone[2], Anthony A. Grace[11], Philip McGuire[1]

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Supplementary Methods

fMRI acquisition and preprocessing

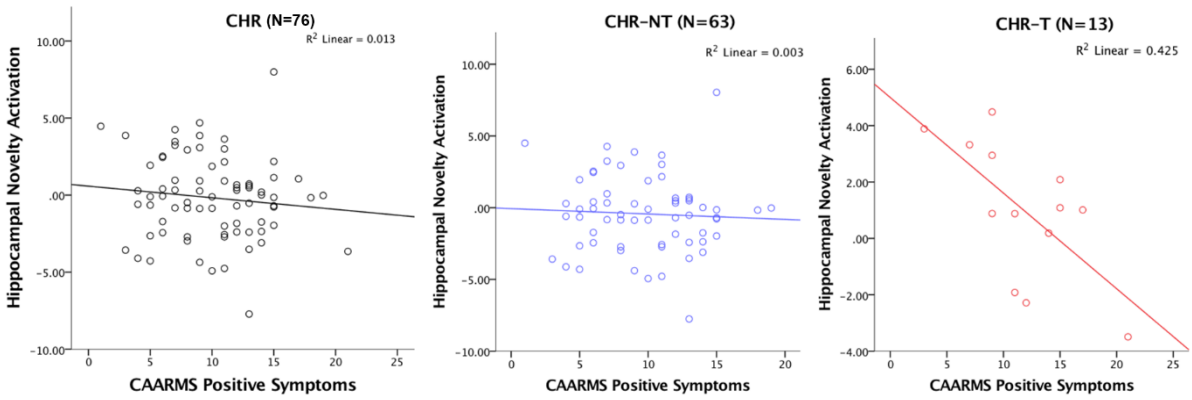
Echo-planar images sensitive to blood oxygenation level-dependent (BOLD) contrast were acquired to measure hemodynamic responses on a General Electric Signa HDx TwinSpeed 3T scanner (Milwakee, Wisconsin) at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology & Neuroscience (King's College London). Acquisition parameters were as follows: repetition time (TR): 2000 ms; echo time (TE), 30 ms; flip angle, 75°; slice thickness, 3 mm; field of view (FoV), 240; 39 axial sections collected with sequential (top-down) acquisition and 3.3-mm interslice gap). Structural data were acquired by means of a three-dimensional T1-weighted magnetization prepared rapid acquisition gradient-echo sequence (TR = 6.98 ms, TE = 2.85 ms, voxel size = 1.05 × 1.05 × 1.2 mm, FoV = 260 mm, flip angle = 11°, inversion time = 400 ms). Three clinical high risk (CHR) subjects had to be excluded because of failure to complete the fMRI task. Functional MRI data were preprocessed using the SPM12 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm12). After slice timing, realignment,

segmentation, co-registration and stereotaxic normalization (2x2x2 mm^3), images were spatially smoothed using an 8-mm full-width at half-maximum Gaussian filter and a high pass filter (128 s). Excessive movement was considered at 43 mm of translation and 3 degrees of rotation in any axis; six clinical high risk (CHR) subjects exceeded this threshold and were therefore removed from the final analysis.

Results

Relationship between pure stimulus novelty activation / DCM connectivity and psychotic symptoms

Exploratory correlations between fMRI parameter estimates extracted from regions showing significant novelty-related group differences and severity of positive prodromal symptoms (summary scores of CAARMS unusual though content, non-bizarre ideas, perceptual abnormalities and disorganized speech) were tested with Pearson correlation analysis in SPSS. Within the CHR-T group, activation parameters in the right anterior hippocampus during novelty processing were significantly negatively correlated with CAARMS positive symptoms (r=-0.652, p=0.016) (eFigure 1). There were no significant correlations in the CHR group as a whole (r=-0.115, p=0.324) or in the CHR-NT group (r=-0.055 p=0.671).



eFigure 1. Scatterplots depicting a significant inverse correlation between right hippocampal response to Neutral > Standard and severity of CAARMS positive symptoms within CHR-T the group (left), which was absent in the CHR-NT group (middle) and the CHR group as a whole (right).

Finally, correlations between severity of positive symptoms and connectivity strengths were assessed with using a PEB model with the CAARMS positive symptom as a regressor. PEB results of this type of analysis results in estimation of the effect size and probability for that effect. For this analysis, we included only the CHR sample. We have thresholded results at P>0.5 (weak probability). In the total CHR sample, there was a positive effect between the strength of modulation of the forward connection from the VTA/SN to the hippocampus and the severity of CAARMS positive symptoms (effect size: 0.04; P: 0.57), and a negative association between connectivity from the hippocampus to the striatum and CAARMS positive symptoms (effect size: -0.07; P: 0.69). The negative effect between hippocampus to striatum connectivity and positive symptoms was also evident in CHR-NT subjects (Effect size: -0.06 P: 0.66). In the CHR-T group, there were effects of CAARMS positive symptoms in VTA/SN to Striatum (effect size: -0.05; P: 0.55) and in VTA/SN to hippocampus (effect size: 0.09; P:0.72).

Examining Potential Movement Confounds

We used movement parameters for each trial in each of the three runs for each subject to compare movement between groups. For the final sample of 31 healthy controls (HC) and 76 CHR subjects (of which 13 became CHR-T and 63 CHR-NT), mean incremental (frame-to-frame) movement and group *t*-test results for each translation axis (x, y, z) and rotation axis (pitch, roll, yaw) averaged across the three task runs are summarized in eTable 1.

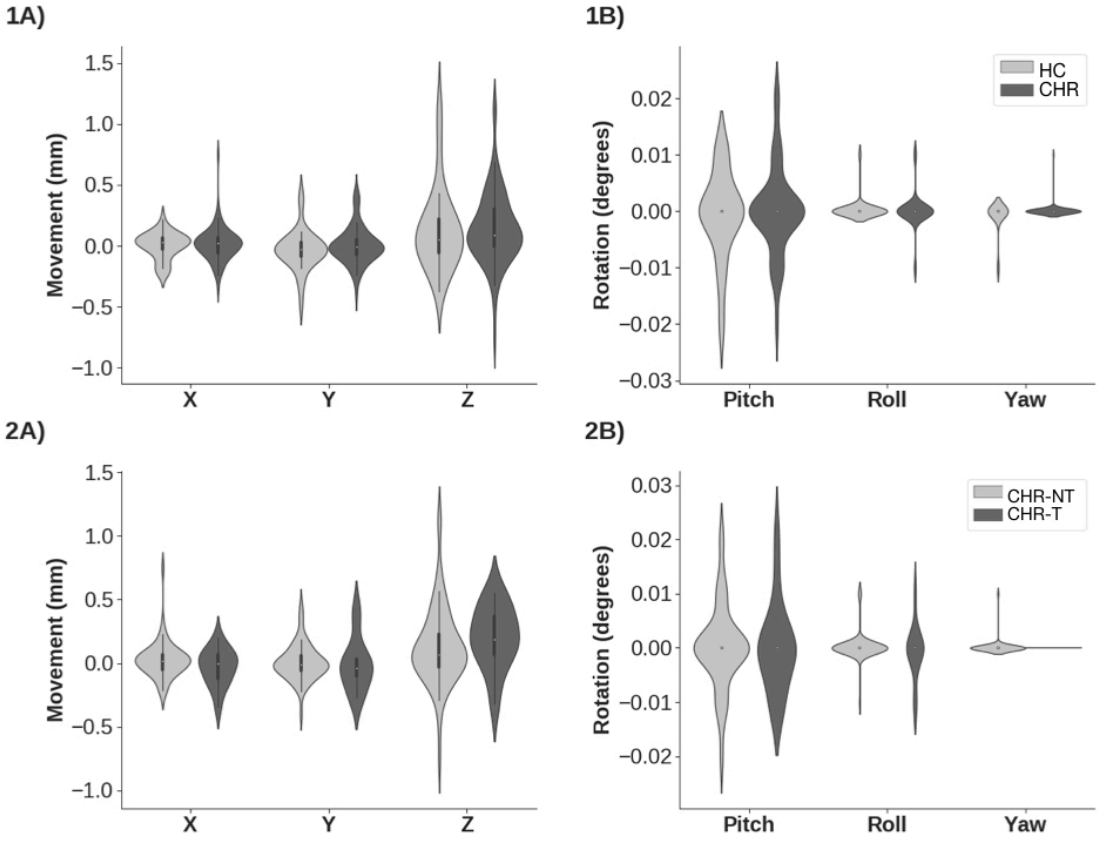
	HC (n=31)		**CHR (n=76)**				**CHR-NT (n=63)**		**CHR-T (n=13)**			
	Mean	**SE**	**Mean**	**SE**	**g**	**p**	**Mean**	**SE**	**Mean**	**SE**	**g**	**p**
x	0.0042	0.11	0.0167	0.14	0.095	0.662	0.0264	0.14	-0.0305	0.14	0.406	0.189
y	-0.0316	0.16	0.0051	0.15	0.240	0.273	0.0076	0.14	-0.0087	0.22	0.105	0.752

z	0.1357	0.34	0.1414	0.30	0.018	0.931	0.1285	0.31	0.2036	0.25	0.249	0.412
pitch	-0.0003	0.01	0.0004	0.01	0.07	0.679	0.0003	0.01	0.0005	0.01	0.02	0.935
roll	0.0001	0.00	0.0003	0.00	0.07	0.852	0.0003	0.00	0.0000	0.00	0.02	0.720
yaw	-0.0004	0.00	0.0005	0.00	0.07	0.034*	0.0004	0.00	0.0006	0.00	0.02	0.808

eTable 1. Incremental movement.

* $P < 0.05$. g, Hedges' g.

There was a difference between HC and CHRs in the yaw dimension ($p = 0.034$); therefore, movement parameters (x, y, z, pitch, roll, yaw) were included in all first level fMRI models as covariates of no interest to rule out variance associated with head movement. There were no significant differences between HC and CHRs in any of the other axis/dimensions, as well as no significant differences in any of the movement parameters between CHR-NT and CHR-T.



eFigure 2: Violin plots showing mean incremental (frame-to-frame) movement by each translation (x, y, z: 1A and 2A) and rotation axis (pitch, roll, yaw: 1B and 2B)

averaged across the 3 task runs by group (HC vs CHR total, 1A and 1B; CHR-NT vs CHR-T, 2A and 2B).

Behavioral Results.

Reaction time (RT)

Behavioral analysis of RTs revealed that mean reaction times (RT) did not differ significantly between the groups (eTable 2).

Target recognition

Target stimuli detection was nearly perfect across all participants, with a mean hit rate >95% and a very low error rate of <7%, with no significant between-group differences (eTable 2).

eTable 2. Behavioral results for the novelty salience task.

Measure	HC (n=31)	CHR (n=76)	g	p	CHR-NT (n=63)	CHR-T (n=13)	g	p
Targetness (%)	96.3	96.3	0.009	0.964	96.3	96.1	0.032	0.924
Errors (%)	4.7	6.5	0.157	0.457	6.6	5.5	0.101	0.760
Reaction Time (mean, SD)	561.7 (83.6)	568.7 (97.8)	0.074	0.731	566 (90.3)	583.3 (135.6)	0.177	0.592

Targetness = percent correct hits on target stimuli. Errors = false alarms + missed hits. CHR, clinical high risk; CHR-NT, clinical high-risk non-transition; CHR-T, clinical high-risk transition; HC, healthy controls. g, Hedges' g.

Analysis of potential confounders

A univariate ANCOVA in SPSS with the individual right hippocampal parameter estimates of activation to Novel > Neutral as dependent variable, Group as between-subjects factor, and alcohol use, cigarettes, cannabis use, HAM-A and HAM-D

scores as covariates showed that the group effect remained significant ($F_{1,80}$ = 5.486, p = 0.022, Cohen's d = 0.742). Further details are provided in eTable 3 below.

eTable 3. Univariate ANCOVA results.

Tests of Between-Subjects Effects

Dependent Variable: Right_Hippocampus

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	97.902[a]	6	16.317	2.091	0.064
Intercept	7.851	1	7.851	1.006	0.319
cigarettes_current	7.331	1	7.331	0.939	0.336
Alcohol_current	7.495	1	7.495	0.960	0.330
cannabis_current	1.028	1	1.028	0.132	0.718
HAMA	11.619	1	11.619	1.489	0.226
HAMD	6.203	1	6.203	0.795	0.376
Baseline_Group	42.816	1	42.816	5.486	**0.022**
Error	577.565	74	7.805		
Total	690.048	81			
Corrected Total	675.466	80			

a. R Squared = .145 (Adjusted R Squared = .076)

Whole-brain analysis

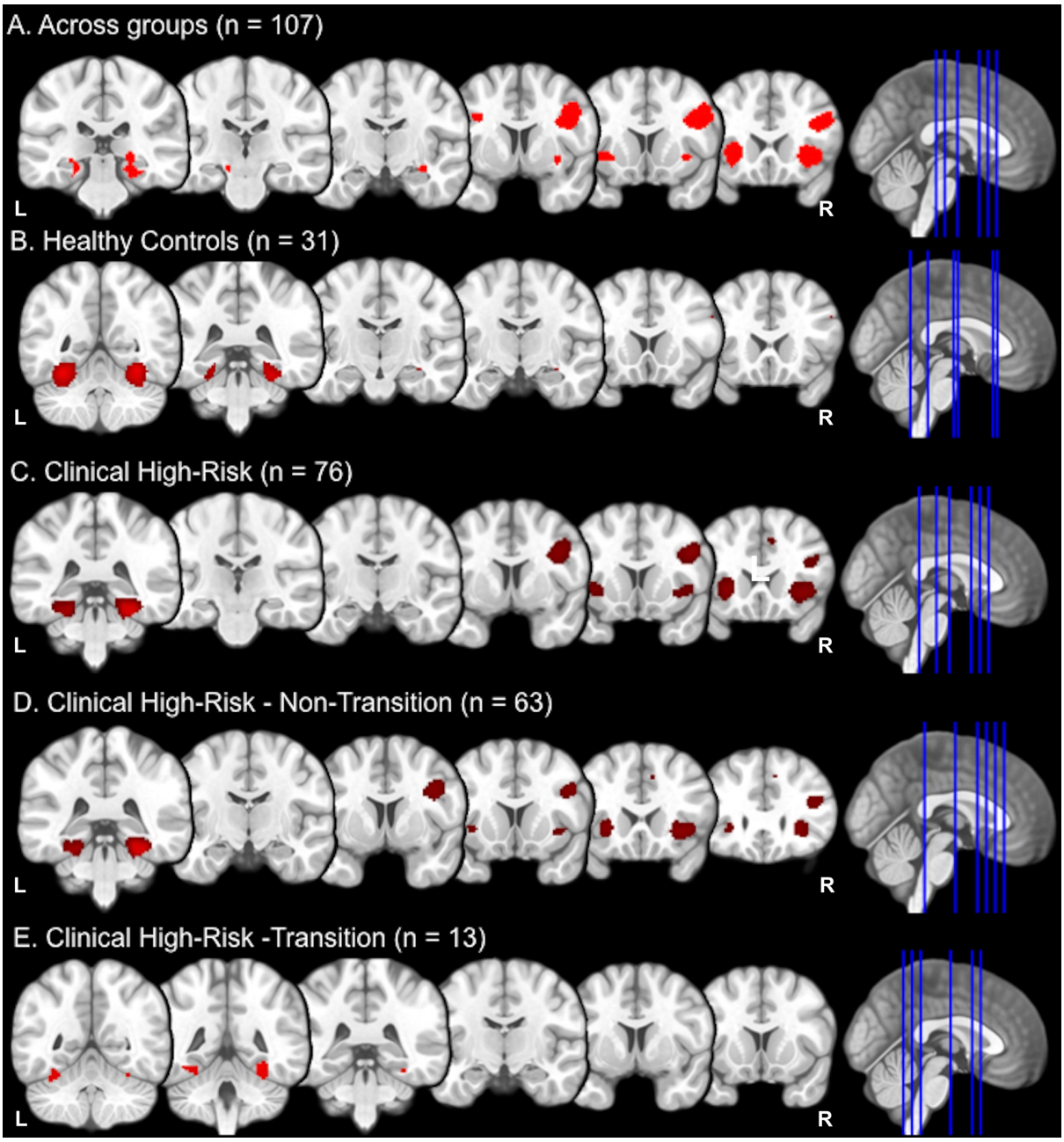
Across groups and at the whole-brain level, pure stimulus novelty was associated with activation in the fusiform gyrus/occipital lobes and insula bilaterally, right hippocampus, putamen, inferior frontal gyrus/middle frontal gyrus, medial frontal gyrus and middle temporal gyrus, and with the left inferior parietal lobule (voxel-wise p_{FWE}<0.05, eTable 4, eFigure 3). At the whole brain level, there were no regions that showed between-group differences in the CHR as a whole relative to the HC group, or in the CHR-NT relative to the CHR-T group.

eTable 4: Random Effects Analysis for Novel Oddballs versus Neutral Oddballs Across and Within Groups at the Whole-Brain Voxel-wise Level. The x, y, z

coordinates of local maxima are listed according to the MNI coordinate system. All results voxel-wise p<0.05 FWE corrected.

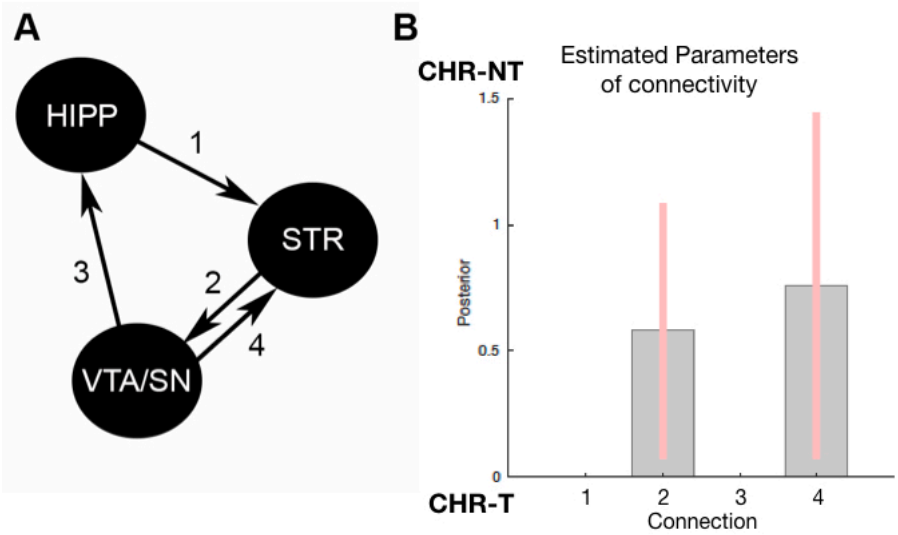
Brain Area	MNI Coordinates			*k*	*T*	*Z*	Voxel-wise *pFWE*
	x	*y*	*z*				
Across all participants (n=107)							
R fusiform gyrus	28	-46	-14	4959	13.10	*Inf*	<0.001
R middle occipital gyrus	36	-78	9		8.33	7.27	<0.001
R superior occipital gyrus	20	-94	-6		8.05	7.08	<0.001
L fusiform gyrus	-30	-48	-20	3730	11.69	*Inf*	<0.001
L inferior occipital gyrus	-18	-94	-6		9.52	*Inf*	<0.001
L middle occipital gyrus	-36	-86	-2		9.40	*Inf*	<0.001
R inferior frontal gyrus	44	12	28	1367	6.88	6.23	<0.001
R middle frontal gyrus	48	32	22		6.41	5.87	<0.001
L insula	-30	22	-2	388	6.64	6.05	<0.001
R insula	32	22	-2	613	6.63	6.04	<0.001
R hippocampus	32	-12	-14		5.52	5.16	0.002
R putamen	32	4	-8		5.24	4.93	0.004
L inferior parietal lobe	-28	-58	42	130	6.09	5.62	<0.001
R medial frontal gyrus	8	30	42		5.70	5.30	0.001
R middle temporal gyrus	58	-40	-10	20	5.35	5.02	0.003
R middle frontal gyrus	40	46	14	23	4.91	4.65	0.015
HC (n=31)							
R fusiform gyrus	30	-48	-16	1114	7.79	6.90	<0.001
R calcarine gyrus	20	-94	-6		5.90	5.47	<0.001
L fusiform gyrus	-32	-50	-20	971	4.82	6.56	<0.001
L lingual gyrus	-30	-82	-16		4.97	4.70	0.012
L middle occipital gyrus	-16	-92	-6	455	7.23	6.49	<0.001
L inferior occipital gyrus	-28	-92	-8		5.39	5.05	0.003
R middle occipital gyrus	36	-78	8	71	5.00	4.73	0.011

R hippocampus	32	-14	-14	7	4.89	4.63	0.016
R inferior frontal gyrus	54	20	30	5	4.74	4.50	0.026
CHR (n=76)							
R fusiform gyrus	28	-46	-14	3809	12.13	*Inf*	<0.001
R middle occipital gyrus	34	-72	20		8.25	7.22	<0.001
L fusiform gyrus	-30	-48	-16	2912	10.23	*Inf*	<0.001
L middle occipital gyrus	-34	-88	-2		8.48	7.37	<0.001
R inferior frontal gyrus	44	12	30	954	6.68	6.08	<0.001
R insula	36	20	-4	622	6.58	6.00	<0.001
L insula	-28	24	0	415	6.57	5.99	<0.001
R medial frontal gyrus	8	28	42	44	5.01	4.73	0.011
L inferior parietal lobe	-30	-56	40	26	4.99	4.72	0.011
CHR-NT (n=63)							
R fusiform gyrus	28	-46	-14	3363	10.93	*Inf*	<0.001
R middle occipital gyrus	34	-72	20		7.94	7.00	<0.001
L fusiform gyrus	-30	-48	-18	1266	9.05	7.74	<0.001
L middle occipital gyrus	-34	-88	-2	1109	8.21	7.18	<0.001
L inferior occipital gyrus	-20	-94	-8		6.41	5.86	<0.001
R insula	34	20	-4	405	6.04	5.58	<0.001
R inferior frontal gyrus	40	8	30	378	5.78	5.37	0.001
R middle frontal gyrus	42	30	20	175	5.55	5.18	0.001
R medial frontal gyrus	10	24	42	16	4.79	4.54	0.021
CHR-T (n=13)							
R fusiform gyrus	30	-44	-14	170	5.45	5.10	0.002
L cerebellum lobule 6	-36	-54	-24	124	4.95	4.68	0.012
L fusiform gyrus	-32	-48	-16		4.91	4.64	0.015



eFigure 3: Random Effects Analysis for Novel Oddballs versus Neutral Oddballs Across and Within Groups at the Whole-Brain Voxel-wise Level. (A) across groups, (B) within HCs, (C) within CHRs, (D) within CHR-NT, (E) within CHR-T. Activation maps are superimposed on a standard T1 template. All results voxel-wise $p<0.05$ FWE corrected. L = left hemisphere; R = right hemisphere.

Effective connectivity: transition to psychosis excluding CHR subjects for whom clinical outcome information could not be obtained



eFigure 4. (A) DCM model. (B) Group effects on PEB models between CHR-NT (n=57) and CHR-T (n=13). Gray bars show posterior probabilities for model evidence. Pink bars represent the Bayesian 95% confidence interval.