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Neural correlates of personal space regulation in psychosis: role of the inferior parietal cortex

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Regulation of interpersonal distance or "personal space" (PS; the space near the body into which others cannot intrude without eliciting discomfort) is a largely unconscious channel of non-verbal social communication used by many species including humans. PS abnormalities have been observed in neuropsychiatric illnesses, including schizophrenia. However, the neurophysiological basis of these abnormalities remains unknown. To investigate this question, in this study, functional magnetic resonance imaging (fMRI) data were collected while individuals with psychotic disorders (PD; $n = 37$) and demographically-matched healthy control (HC) subjects ($n = 60$) viewed images of faces moving towards or away from them. Responses of a frontoparietal-subcortical network of brain regions were measured to the approaching versus the withdrawing face stimuli, and resting-state fMRI data were also collected. PS size was measured using the classical Stop Distance Procedure. As expected, the PD group demonstrated a significantly larger PS compared to the HC group ($P = 0.002$). In both groups, a network of parietal and frontal cortical regions showed greater approach-biased responses, whereas subcortical areas (the striatum, amygdala and hippocampus) showed greater withdrawal-biased responses. Moreover, within the PD (but not the HC) group, approach-biased activation of the inferior parietal cortex (IPC) and functional connectivity between the IPC and the ventral/limbic striatum were significantly correlated with PS size. This study provides evidence that PS abnormalities in psychotic illness involve disrupted function and connectivity of the PS network. Such brain-behavior relationships may serve as objective treatment targets for novel interventions for schizophrenia and related psychotic illnesses.

Molecular Psychiatry (2025) 30:3008–3017; https://doi.org/10.1038/s41380-025-02906-4

INTRODUCTION

Social dysfunction in schizophrenia has been linked to impairments in motor behaviors that are involved in non-verbal social communication, such as facial expressions, gestures, and other forms of 'body language" [1, 2], including the regulation of interpersonal distance or "personal space" [3–9]. Personal space is defined as the physical distance one prefers to maintain from another person [10]. Intrusions into personal space typically lead to subjective and physiological discomfort [11, 12]. Thus personal space is essentially a safety zone around the body that plays a role in defending the body from harm [13–15]. It also provides one avenue for non-verbal communication of social cues, related to conveying trust, familiarity, and social hierarchy [10, 16–18]. In humans, personal space preferences are influenced by a range of cultural and social factors [19, 20], but remain relatively stable within individuals over repeated measurements, when such environmental factors are controlled [21].

Numerous studies have found that personal space requirements are greater, by about 30% on average, in individuals diagnosed with schizophrenia [22], compared to the typical interpersonal distances observed in healthy populations [23]. However, the neurophysiological mechanisms underlying this consistent finding remain unclear. One model of understanding the regulation of personal space can be derived from studies of brain regions involved in monitoring the space near the body that have been conducted in both non-human primates [13–15, 24] and humans [9, 25, 26]. Personal space regulation involves a specific network of parietal and frontal cortical areas [27], plus interconnected portions of the striatum [28] and other emotion-processing areas such as the amygdala [29].

Although personal space is often found to be enlarged in schizophrenia, there is also much variation in the interpersonal distances observed among individuals with schizophrenia [3, 7, 30] and in non-clinical populations [21, 25]. Previous work has found that the preferred size of personal space, as well as the "permeability" of personal space boundaries, are associated with psychological characteristics related to social drive and motivation, as well as overall social functioning [9, 25]. Other studies have found associations between interpersonal distances and various symptoms of psychopathology, such as anxiety [31–33] and paranoia [2, 34], as well as insecure attachment [35] and loneliness [36, 37]. A better understanding of the function of the brain regions involved in monitoring the space near the body and their associations with personal space-related behavior may clarify the role that this neural system plays in psychopathology [22].

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Received: 17 April 2024 Revised: 14 November 2024 Accepted: 21 January 2025
Published online: 3 February 2025

Thus in the current study, we aimed to measure the functioning of the network of brain regions that contribute to personal space regulation in both healthy individuals and those with diagnoses of psychotic disorders, testing the hypothesis that variation in the activity and connectivity of this neural system is linked to variation in personal space preferences [9, 25].

MATERIALS AND METHODS

Participants

Recruitment. Forty subjects with a diagnosis of a psychotic disorder (PD) and sixty demographically-matched healthy control (HC) subjects were enrolled in this study (see Table 1 for demographic characteristics of the two groups). HC subjects were recruited via advertisements in online community forums and postings on research portals (https://rally.massgeneralbrigham.org). PD patients receiving treatment within the MGH Psychosis Clinical and Research Program (PCRP) were invited to participate after expressing interest. In addition, some PD subjects were recruited via online advertisements.

Ethics approval and consent to participate. Before enrollment, written informed consent to participate in the study was obtained from all subjects, in accordance with the Declaration of Helsinki. All study procedures were approved by and carried out in accordance with the guidelines and regulations set forth by the Massachusetts General Brigham Institutional Review Board (study protocol #2016P002569).

Inclusion criteria. All subjects were between 18 and 50 years of age and proficient in English, with no lifetime history of substance dependence, no current or history of substance abuse within the past six months, and no unstable medical illnesses. All subjects had normal, or corrected to normal, vision (as determined by the Snellen test). Inclusion/exclusion criteria included standard MRI contraindications (claustrophobia, metal in the body), and potential subjects with any current or past neurological illnesses, a history of seizures, stroke, or head injury resulting in prolonged loss of consciousness and/or neurological sequelae were excluded. Additionally, potential healthy control subjects were excluded if they had a history of a PD, or a first- or second-degree relative with a history of a PD. All subjects included in the PD group had a confirmed history of one or more psychotic episode(s), with no clinically significant changes in symptoms for at least four weeks prior to enrollment into the study. Any potential PD subject who was determined to have a PD diagnosis due to another medical condition or a substance/medication was excluded from participation. All diagnoses were determined initially using medical records and then confirmed using the Mini International Neuropsychiatric Interview (MINI) [38].

In this study, we used a Research Domain Criteria (RDoC) [39] based approach, including subjects with diagnoses of either non-affective or affective psychoses, in order to increase variation in personal space behavior across the sample and thus the power to detect dimensional relationships between behavioral characteristics and brain function. The minimum required sample size for this study was estimated based on the effects achieved in previous studies using the same fMRI paradigm [9, 25].

Clinical characterization

Schizophrenia symptom severity in the PD group was measured using the Positive and Negative Syndrome Scale (PANSS) [40], with a five-factor model derived from a consensus of published PANSS items factor analyses [41]. For all subjects, social motivation/anhedonia and social withdrawal were also assessed. Social anhedonia was measured using the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) [42]. Social withdrawal was measured using the self-report Time Alone Questionnaire (TAQ) [9, 25].

Personal space measurements. On the same day of the scan session, personal space size was measured using the Stop Distance Procedure (SDP) [43–45], a highly validated and reliable procedure (kappa ~ 0.8) [10] for measuring personal space characteristics. The "passive" version of the procedure was conducted as follows: In a neutral laboratory setting, a confederate (unknown to the subject, typically a research assistant) stood 3 meters from the subject, facing the subject. The confederate then began slowly walking directly towards the subject, while maintaining a neutral facial expression and eye contact with the subject. The subject was instructed before the beginning of the procedure to stop the confederate at two points: first when they felt "slightly uncomfortable", i.e., when their personal space boundary had just been reached ("the distance at which you would normally have a conversation with a person you have just met"); second when they felt "very uncomfortable", i.e., when their personal space boundary had definitely been crossed. These distances were measured 6 times each with a male and female confederate, and the confederate order (male vs. female) was counter-balanced across subjects.

The first stop distance (Distance 1, D1) represents personal space size. The second stop distance (Distance 2, D2) is used to calculate a normalized ratio [100 – (D2 x 100) / D1] ranging from 0–100, indicating the subject's ability to tolerate personal space intrusions (the "permeability" of personal space). Low and high permeability scores correspond, respectively, to a

Table 1. Demographic and clinical characteristics of study.

	HC (n = 60)	PD (n = 37)	Test statistic	P
Gender (% female)	35.0	29.7	X^2 (1, N = 97) = 0.288	0.592
Age (yrs)	26.12 (5.53)	27.81 (6.24)	t(95) = −1.395	0.166
Parental Education (yrs)	15.58 (3.33)	15.78 (2.86)	t(95) = −0.304	0.762
Full-Scale IQ	109.92 (7.44)	106.71 (9.75)	t(95) = 1.822	0.072
PANSS 5 Factor: Positive factor (4 items)	—	2.47 (0.18)		—
PANSS 5 Factor: Negative factor (6 items)	—	2.20 (0.16)		—
PANSS 5 Factor: Disorganized factor (3 items)	—	2.15 (0.14)		—
PANSS 5 Factor: Excited factor (4 items)	—	1.58 (0.10)		—
PANSS 5 Factor: Depressed factor (3 items)	—	2.69 (0.18)		—
Illness Duration (yrs)	—	7.49 (6.03)		—
CPZ equivalents (mg)	—	253.93 (352.83)		—

Variables-of-interest are listed in left-most column for the Healthy Control (HC) and Psychotic Disorder (PD) groups, with the mean (standard deviation) and between-group difference significance (independent t-test) provided. Variables include: gender (percentage of females), mean age (years), mean parental education (years), mean full-scale intelligence quotient (IQ; American National Adult Reading Test score), and, for the PD group only, mean scores on the Positive and Negative Syndrome Scale (PANSS) Five Factor subscales (positive, negative, disorganized, excited, and depressed), mean illness duration (years), and mean chlorpromazine (CPZ) equivalents. The 37 PD subjects whose data were included in the analyses (subjects were excluded if found to have brain structural abnormalities (1 PD excluded) or very poor task performance during scanning (2 PD excluded); see Supplementary Materials for exclusion criteria) had the following primary diagnoses: schizophrenia ($n = 17$), schizoaffective disorder (n = 9), and bipolar disorder with psychotic features ($n = 11$). The participants of the PD group were treated with the following antipsychotic medications: 43.2% ($n = 16$) aripiprazole, 13.5% ($n = 5$) clozapine, 13.5% ($n = 5$) olanzapine, 21.6% ($n = 8$) none, and the remaining 18.9% ($n = 7$) were being treated with one of the following medications: risperidone, quetiapine, lurasidone*, ziprasidone*, perphenazine, haloperidol, cariprazine, or paliperidone palminate (* same individual).

low or high tolerance for (or high and low discomfort with) personal space intrusions [23].

MRI data acquisition

MRI data were acquired in each subject at a single time point on a research-dedicated 3 T Siemens Prisma scanner, using a 64-channel head coil during a single scan session. The following scans were acquired: a single T1-weighted 3D multi-echo MPRAGE scan sequence [46], Blood Oxygenation Level-Dependent (BOLD) data during eight task runs, followed by two runs of whole-brain resting-state BOLD data collection. See the Supplemental Methods for the specific parameters of each scan.

Functional MRI ("Looming") paradigm. Within each functional task run, subjects viewed images of human faces (8 female and 8 male; with neutral facial expressions) which either increased in size ("approaching") or decreased in size ("withdrawing") over the course of each 16 s trial (referred to hereafter as the "looming" trial, i.e., either approaching or withdrawing), resulting in a 2×2 experimental design (Face Gender (2) x Looming Direction (2); Fig. 1A), similar to previous studies [9, 25, 26, 47]. Each functional run included a total of 16 trials, with 16 s blank (neutral gray) fixation blocks presented at the beginning and end of each functional run. Face gender and looming trial type (approach or withdrawal) was randomized and counter-balanced within each functional run (see Supplemental Methods for further details).

In-scanner attentional task. While maintaining central fixation throughout each Looming task functional run, subjects were instructed to covertly attend to other areas of the screen and report whenever they detected a dot appearing at a random location on the screen. During each 16 s trial, a dot appeared 3 times, with the duration between subsequent dot presentations randomly varying between 3,429 ms and 4,571 ms. Additionally, the duration of each dot presentation varied randomly between 366 ms and 1,486 ms, with the dot size scaled with eccentricity (i.e., with a larger diameter when presented further from central fixation). Subjects responded using their right index finger to press a key on the response box provided when detecting a dot.

Resting-state fMRI. Within each resting-state functional run, subjects viewed a mid-level uniform gray screen with a fixation cross presented at the center. Subjects were instructed to maintain central fixation throughout each run, and to do their best to stay awake and alert.

MRI data analysis

Standard, well-validated methods were used for cortical reconstruction of the anatomical scan of each subject [48] and data quality assurance for all of the MRI data [49] (see the supplemental methods for details). The boundaries of four frontoparietal cortical a priori regions-of-interest (ROIs), within the dorsal and ventral premotor cortex and the inferior and superior parietal cortex, were defined in a previously collected dataset [50] ($n = 130$) which was also collected using the Looming task paradigm. In addition, five subcortical ROIs, within the medial temporal lobe (the amygdala and hippocampus) and striatum (the cognitive, default mode and limbic sectors), were defined using two atlases [51, 52] (see Supplemental Methods for further details).

BOLD data preprocessing. All whole-brain BOLD data (task and resting-state) were preprocessed using the Freesurfer Functional Analysis Stream (FS-FAST, version 6). Preprocessing steps included standard motion correction procedures, slice timing correction, and boundary-based registration [53] to transform BOLD time-series data from native functional to anatomical volume and cortical surface space. Volumetric spatial smoothing was applied at twice the isotropic voxel resolution (task fMRI: FWHM = 5 mm; resting-state fMRI: FWHM = 4 mm).

Task fMRI data analysis. To identify significant activation during the Looming task, the first-level analysis employed a univariate general linear model (GLM) fit to the event-related BOLD time series data acquired over all runs passing quality assurance steps. The GLM included a canonical SPM hemodynamic response function, head motion (6 parameters) and scanner drift as nuisance regressors, and excluded any time points identified as outliers (see data quality assurance procedures in the Supplementary Materials). Of primary interest were the GLM contrast effect size (CES) maps generated when contrasting all approaching face trials versus all withdrawing face trials (i.e., approach vs. withdrawal). Subsequently, a group-level analysis was performed to identify regions where the group-wise CES maps were significantly different from zero, with the resulting significance maps thresholded at $P < 0.0001$, then subjected to permutation testing (cluster-wise $P < 0.05$; 1000 permutation trials) to correct for multiple comparisons. The group-wise CES maps were also subjected to a ROI-based analysis, using ROIs defined independently of the current dataset. Between-group differences were examined using whole-brain (vertex- and voxel-wise) comparisons, and 2×2 (Looming Task Condition (2): Approach, Withdrawal; Group Type (2): Healthy Control, Psychotic Disorder) ANOVA statistical tests.

Resting-state functional data analysis. Using the resting-state scans, a seed-based functional connectivity analysis was conducted, with a focus on the functional connectivity of the inferior parietal cortex, a central node of the personal space network [9, 25, 54, 55]. See the Supplemental Methods for additional details about this analysis.

Statistical analyses. Group differences in personal space measurements were assessed using independent sample t-tests (two-sided test performed; equal variance between populations not assumed) using Bonferroni corrections. Two-way between-subjects ANOVAs were performed to test for any differences in ROI-averaged BOLD activation (approach vs. withdrawal) and across groups (HC vs. PD groups). Significant effects were further investigated using pairwise t-tests. Pearson's correlations were assessed between ROI-based task fMRI measures and personal space measures (testing a priori predictions based on previous work [9]). Specifically, we tested whether the activation and connectivity of the inferior parietal cortex, a key node of the personal space network, were correlated with the size of personal space in either group [9]. Additional exploratory correlations were conducted between fMRI measures (task and resting-state connectivity strength) and clinical measures of symptom severity and functioning.

RESULTS

Personal space measures

As expected, mean personal space size of the PD group ($n = 37$) was significantly larger than that of the HC group ($n = 60$; $t(95) = -3.155$, $P = 0.002$; PD: 107.2 cm +/− 50.6; HC: 79.4 cm +/− 36.1; mean +/− standard deviation; see Supplementary Fig. 1A). Consistent with this, the PD group also demonstrated a significantly lower permeability of personal space (tolerance for personal space intrusions) compared to the HC group ($t(95) = 2.770$, $P = 0.007$; PD: 43.9% +/− 12.9; HC: 52.0% +/− 14.5; see Supplementary Fig. 1B). Because personal space size and permeability tend to be strongly associated (i.e., negatively correlated, as in the current data: PD: $r = -0.64$, $P < 0.001$; HC: $r = -0.47$, $P < 0.001$), the subsequent analyses focused on personal space size only. Findings related to personal space permeability are reported in the Supplementary Results.

Looming paradigm fMRI results

When measuring BOLD responses to approaching compared to withdrawing faces (Fig. 1A) in the four primary cortical ROIs of the personal space-monitoring network, significant main effects (approach > withdrawal) were found within inferior parietal ($F(1190) = 6.684$, $P = 0.011$; Fig. 1B) and superior parietal ($F(1190) = 4.004$, $P = 0.047$; Fig. 1C) cortex, with similar trends in ventral premotor ($F(1190) = 3.729$, $P = 0.055$) and dorsal premotor ($F(1190) = 2.886$, $P = 0.09$) cortex (see Fig. 1D, E), as well as the four ROIs combined ($F(1190) = 4.874$, $P = 0.029$). No significant main effects of group or significant group-by-condition interactions were observed in these four regions (see Supplementary Table 3). Follow-up cortical surface-based analyses showed similar results (Fig. 1F, G; Supplementary Fig. 2 and Supplementary Tables 4 & 5).

At the subcortical level, with the exception of a main effect of group within the amygdala ($F(1190) = 5.998$; $P = 0.015$), there were no significant main effects of looming or group or any significant interactions, within the a priori subcortical ROIs

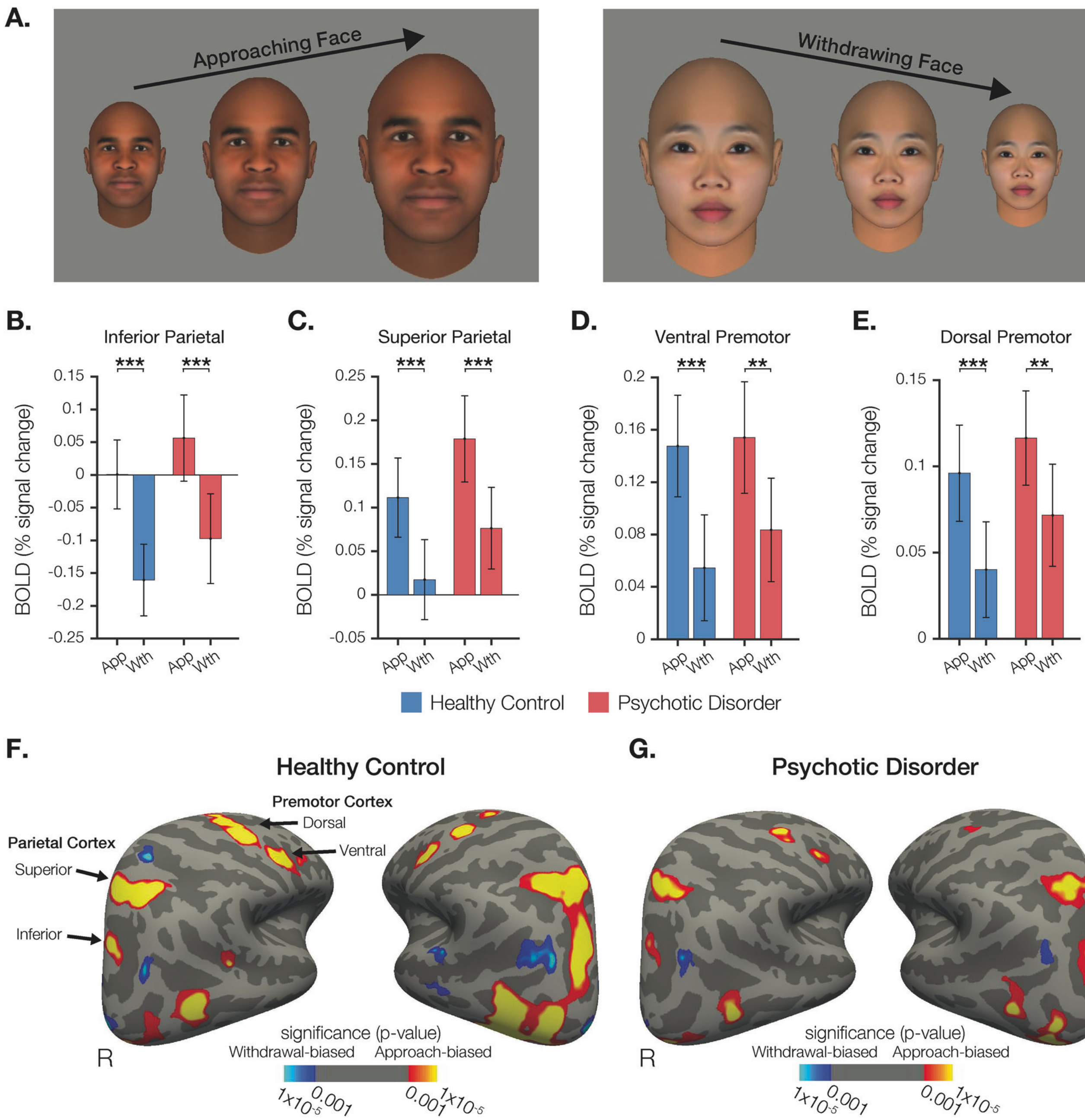

Fig. 1 Experimental stimuli and looming-related BOLD activation within cortical areas. A Examples of the Looming paradigm stimuli. Each unique face was presented at central fixation while either increasing (approach condition) or decreasing (withdrawal condition) in size over the course of a 16 s block. The functional contrast of approach > withdrawal was computed in the analyses. **B–E** Bar graphs depicting mean BOLD signal level (% change from baseline) for each looming condition (App = approaching faces; Wth = withdrawing faces) and group (Healthy Control group in blue, $n = 60$; Psychotic Disorder group in red, $n = 37$) within each cortical personal space network region-of-interest (ROI), averaged over the right and left hemispheres. Error bars represent one standard error of the mean (** $P < 0.01$; *** $P < 0.001$, for the approach vs. withdrawal paired t-test comparison). **F**, **G** Cortex-wide activation (approach > withdrawal) maps for the HC ($n = 60$) and PD ($n = 37$) groups, respectively, are displayed, with posterior views of the significance maps (display threshold: $P < 0.001$, vertex-wide corrected), overlaid on inflated cortical surface models derived from a common space brain template (fsaverage) for the left and right hemispheres (for additional views see Supplementary Figure 3). Black arrows denote cortical ROI locations, defined using an independent fMRI dataset (see Supplementary Figure 1).

(Fig. 2A–E), or across the combination of all five subcortical ROIs (Supplementary Table 3). The main effect of group in the amygdala was due to significantly larger overall responses (both approach and withdrawal) in the HC group compared to the PD group.

Follow-up subcortical voxel-wise analyses identified significant looming-related (withdrawal > approach) clusters within the hippocampus and amygdala in the HC group, and significant clusters in the hippocampus, limbic striatum, and default mode striatum in the PD group (Supplementary Tables 6 & 7). In summary, in contrast to the significant approach > withdrawal activation observed in the cortical personal space network, activation in these subcortical areas showed the reverse pattern, with withdrawal > approach activation (Fig. 2F, G).

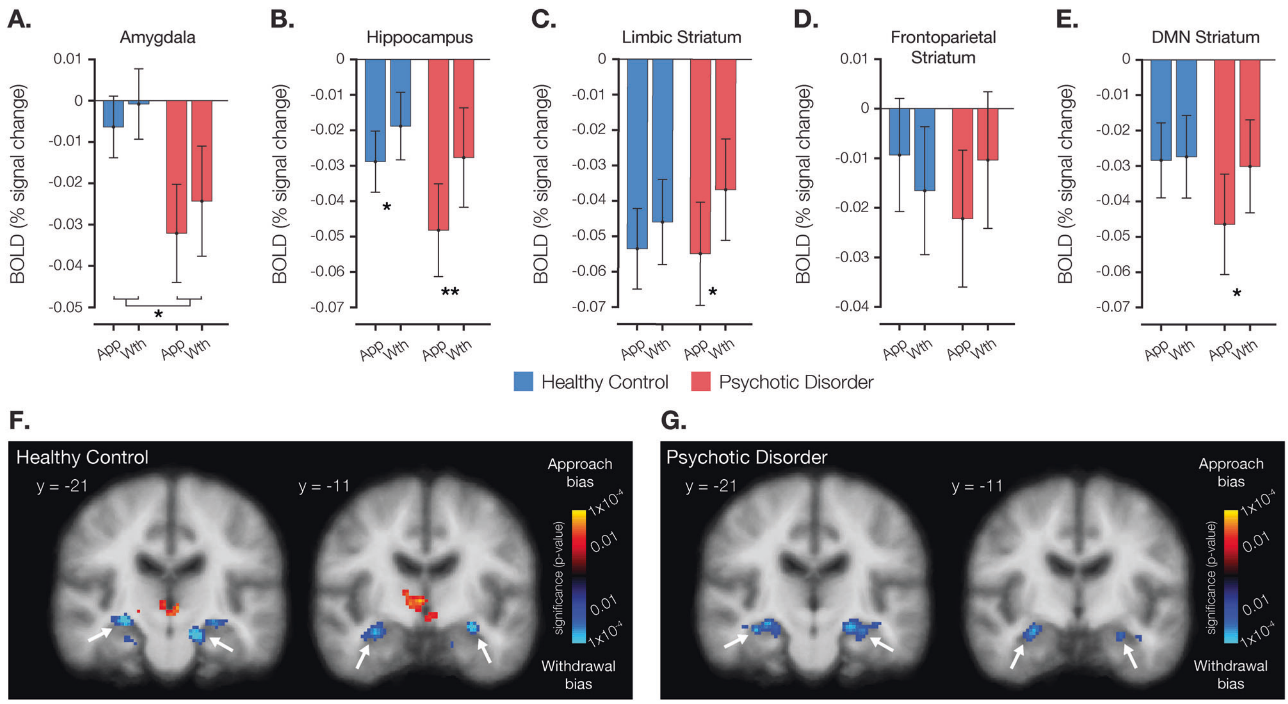

Fig. 2 Looming-related BOLD activation within subcortical areas. A–E Bar graphs of mean BOLD signal level (% change from baseline) for each condition (App = approaching faces; Wth = withdrawing faces) and group (Healthy Control group in blue, $n = 60$; Psychotic Disorder in red, $n = 37$) within each subcortical personal space network ROI are shown (averaged over the right and left hemispheres). Error bars represent one standard error of the mean (* $P < 0.05$; ** $P < 0.01$, for the approach vs. withdrawal paired t-test comparison, and group difference two-sample t-test in panel A). **F, G** Whole-brain activation (approach > withdrawal) maps for the Healthy Control and Psychotic Disorder groups, respectively, are displayed, with representative coronal slices overlaid with significance maps (display threshold: $P < 0.01$; subcortical volume-corrected) revealing significant effects in the hippocampus and amygdala in both groups.

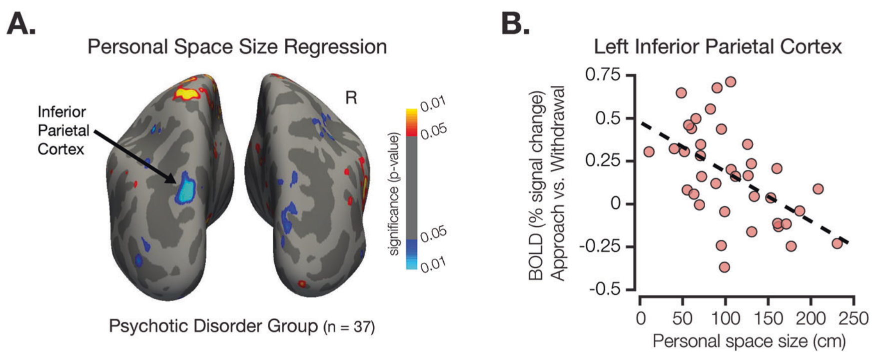

Fig. 3 Association between personal space size and looming BOLD activation within inferior parietal cortex. A The cortex-wide significance map ($P < 0.05$, uncorrected) for the secondary regression analysis examining the association between personal space size and looming activation for the PD group is shown. The cluster within the left inferior parietal cortex is 228 mm^2 in size with a peak P-value of 0.0001 ($z = -3.983$). **B** A scatter plot displaying the association between personal space size and mean BOLD signal level (% change from baseline) for the looming functional contrast (approach > withdrawal) within the significant left inferior parietal cortex cluster (see black arrow in panel A) found in the PD group only is shown. Red circles represent individual datapoints for the Psychotic Disorder ($n = 37$) group. The dashed black line represents the linear regression ($r = -0.53$, $P < 0.001$).

Dimensional relationships: looming activation and personal space

Next, we tested for the predicted dimensional association between personal space behaviors and looming-related activation of the inferior parietal cortex, based on prior work identifying this region as a key node of the personal space network [9, 14, 15, 25]. A significant negative correlation between personal space size and looming activation (approach > withdrawal) of the inferior parietal cortex was found in the PD group, but not in the HC group (PD: $r = -0.33$, $P = 0.044$; HC: $r = -0.14$, $P = 0.294$), with lower inferior parietal cortex approach > withdrawal activation associated with a larger personal space size. This ROI-based finding was further confirmed and localized using whole brain regression, with significant clusters found within the inferior parietal ROI (Fig. 3A; Supplementary Fig. 3), with the most significant cluster in the left inferior parietal cortex in the PD group (Fig. 3B). Moreover, the ROI analyses revealed that no other cortical region within the personal space network showed this association.

Functional connectivity of inferior parietal cortex

We then measured the functional connectivity of the inferior parietal cortex, to identify other regions in its network that may

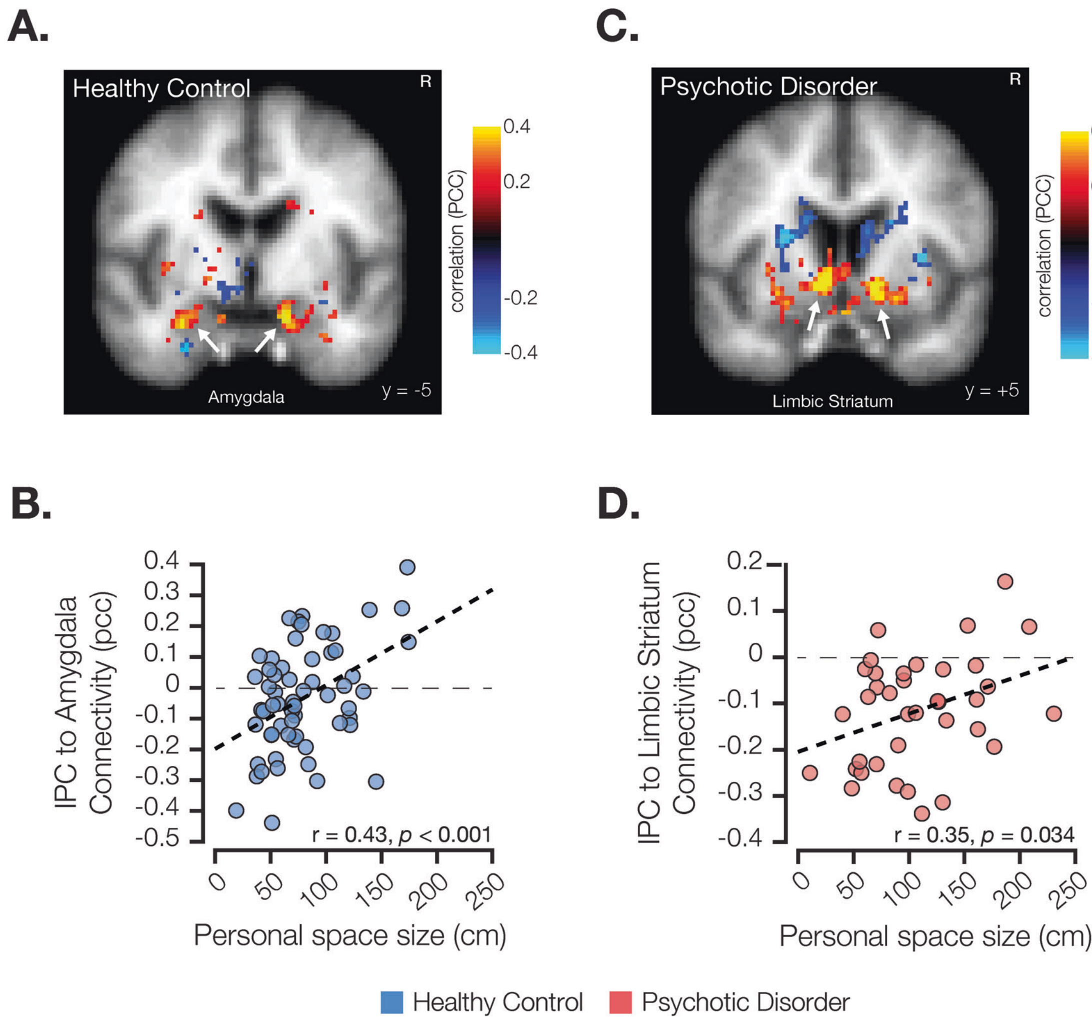

Fig. 4 Associations between personal space size and inferior parietal cortex functional connectivity strength. A, C Representative coronal slice from MNI atlas space overlaid with partial correlation coefficient maps (display threshold: *pcc* > 0.1; uncorrected) resulting from inferior parietal cortex seed-based functional connectivity for: (A) the Healthy Control group (n = 60) with white arrows indicating clusters within the amygdala, and (C) the psychotic disorder group (n = 37) with white arrows indicating clusters within the limbic striatum. **B, D** Scatter plots displaying the association between personal space size measurements and inferior parietal cortex functional connectivity with the amygdala in the Healthy Control group (B), and with the limbic striatum in the Psychotic Disorder group (D). Colored circles represent individual datapoints for the Healthy Control (blue, $n = 60$) and Psychotic Disorder (red, $n = 37$) groups.

influence personal space regulation. The inferior parietal cortex showed significant positive connectivity with the three other personal space cortical ROIs bilaterally in both the HC and PD groups (superior parietal cortex, and dorsal and ventral premotor cortices; Supplementary Table 8). A follow-up cortical surface-based analysis showed a similar pattern of findings for the HC group, but only two of these three regions survived cluster correction in the PD group (all ROIs except the ventral premotor area; Supplementary Fig. 4). In addition, significant anticorrelations between the inferior parietal cortex seed and the a priori subcortical ROIs were observed in both the HC and PD groups (with the exception of the amygdala in the HC group; Supplementary Fig. 5). There were no between-group differences (HC vs. PD) in inferior parietal cortex connectivity with these cortical and subcortical regions (Supplementary Table 8). Lastly, the functional connectivity between the cortical (4 ROIs combined) and subcortical (5 ROIs combined) personal space networks was significantly anti-correlated in both groups (HC: $t(59) = -12.465$, $P < 0.001$; PD: $t(36) = -6.864$, $P < 0.001$; Supplementary Fig. 5I), with no between-group differences ($t(95) = -0.569$, $P = 0.571$).

Dimensional relationships: functional connectivity and personal space

We next tested whether the functional connectivity of the inferior parietal cortex to the nodes of the cortical and subcortical personal space network was correlated with personal space size. Differences between the two groups in the strength of the correlations were assessed using the Fisher's z statistic. In the HC group, but not the PD group, personal space size was correlated with inferior parietal-ventral premotor connectivity (HC: $r = 0.28$, $P = 0.030$; PD: $r = -0.23$, $P = 0.170$; Fisher's $z = 2.41$, $P = 0.016$) and with inferior parietal-amygdala connectivity (HC: $r = 0.43$, $P = 0.001$; PD: $r = -0.01$, $P = 0.965$; Fisher's $z = 2.17$, $P = 0.03$; Fig. 4A, B). In contrast, in the PD group, but not the HC group, personal space size was correlated with inferior parietal-limbic striatum connectivity (HC: $r = -0.10$, $P = 0.440$; PD: $r = 0.35$, $P = 0.034$; Fisher's $z = -2.15$, $P = 0.032$; Fig. 4C, D).

Exploratory associations with clinical measures

When correlations between subscale scores for the five symptom factors of the PANSS [41] and personal space size were examined in the PD group, the severity of disorganized symptoms (but not the other four symptom clusters) was significantly associated with a larger personal space size ($r = 0.36$, $P = 0.028$; Supplementary Fig. 6A). This association was largely driven by two of the three items of the disorganized symptom factor, the conceptual disorganization ($r = 0.38$, $P = 0.020$), and poor attention ($r = 0.36$, $P = 0.028$) items (but not the abstract thinking difficulty item, $r = 0.14$, $P = 0.423$). Of the ten PANSS items not included in the five-factor model, the disturbance of volition item was also associated with a larger personal space size ($r = 0.41$, $P = 0.012$). In addition, personal space size was correlated with social anhedonia in the HC group but not the PD group (HC group: $r = -0.27$, $P = 0.034$; PD group: $r = 0.08$, $P = 0.644$).

Similarly, within the PD group, inferior parietal cortex activation was significantly correlated with the severity of disorganized symptoms ($r = -0.35$, $P = 0.036$; Supplementary Fig. 6B) and disturbance of volition ($r = -0.33$, $P = 0.044$) but not any other clinical measure.

Lastly, none of findings observed in the PD group were associated with potential confounds such as antipsychotic dose or duration of illness.

DISCUSSION

Summary of main findings

In this study, we examined a network of cortical and subcortical regions that responds to face images that appear to move towards or away from participants, crossing personal space boundaries in both conditions, in healthy individuals and in those with psychotic disorders. In addition to the previously described cortical personal space network, which exhibits greater responses to approaching compared to withdrawing stimuli [9, 25, 55–57], we also found that specific subcortical areas (e.g. the amygdala, hippocampus, and the limbic and default network subdivisions of the striatum [52]) show preferential responses to withdrawing compared to approaching stimuli. There were no significant differences on average in the magnitude of responses of any of these regions between the healthy and psychotic disorder groups, except in the amygdala, which showed significantly larger overall responses in the healthy control group compared to the psychotic disorder group, consistent with prior findings [58, 59].

The central findings of this study are that the size of personal space was negatively correlated with looming-related activation of the inferior parietal cortex and the functional connectivity strength of the inferior parietal cortex with the limbic striatum in the psychotic disorder group, but not in the control group. In contrast, in the healthy control, but not the psychotic disorder, group, personal space size was correlated with inferior parietal cortex functional connectivity to the ventral premotor area and the amygdala. These distinct patterns of responses and functional connectivity in the healthy and psychotic disorder groups suggest that social dysfunction in psychotic illness, as manifested by one change in behavior, an increased personal space requirement, could potentially be measured and monitored using the functioning of this specific neural system (as well as personal space-related behavior) as a quantitative marker.

Approach vs. withdrawal response biases

In both groups of subjects, predominantly approach-biased responses were observed in the cortical personal space network, whereas mainly withdrawal-biased responses were observed in subcortical regions. The pattern of responses of the cortical personal space network is consistent with evidence from studies conducted in non-human primates suggesting that attending to an incoming, potentially threatening stimulus is an essential function of the frontoparietal nodes of the personal space network. Studies in non-human primates show that, following detection of a stimulus that may be on a collision course with the body, this network triggers automatic, stereotyped motor responses to such stimuli, such as swatting and retraction of vulnerable body parts [13–15].

The function of the subcortical withdrawal-biased responses is less clear, but these responses may accompany a deactivation of the approach-biased cortical network [60], analogous to the well-known reciprocal relationship between the activity of the task-positive and default mode networks during cognitively-demanding versus introspective tasks [61, 62]. Indeed, we found that the activity of these cortical and subcortical personal space networks were strongly anti-correlated in both the healthy control and psychotic disorder groups. We speculate that these withdrawal-biased subcortical regions may process information about physically proximal stimuli that are important for understanding their behavioral relevance, but not needed to defend the body from imminent harm, such as episodic memories, reward-related information and other personally salient associations [63].

These two types of responses may be maintained in a certain state of balance, both locally within particular brain areas, as well as between critical cortical and subcortical sites. In a recent fMRI study conducted in healthy subjects at high spatial resolution (7 Tesla MRI, 1.1 mm isotropic), we recently identified predominantly approach-biased patches, as well as some withdrawal-biased patches, that were radially-distributed throughout the cortical depth of inferior parietal cortex (putative personal space-related "columns") [26]. Based on these "mesoscale" findings regarding the functional organization of the inferior parietal cortex, we hypothesize that the communication between approach and withdrawal -biased columns, or the integration of their input by another region in the personal space circuitry (e.g., the limbic striatum), may be altered in individuals with aberrant personal space regulation. Future studies can test this possibility using high resolution fMRI.

In a prior preliminary study, we found that responses of a functionally-defined portion of the dorsal parietal cortex was positively correlated (rather than negatively correlated, as in the current study) with personal space size in a small sample of people with schizophrenia [9]. The heterogenous meso-scale topography of approach- and withdrawal-biased patches within the inferior parietal cortex may explain why the direction of correlation between personal space size and looming-related activation could be inconsistent in small functionally-defined regions, compared to the constrained, objectively defined regions-of-interest examined in the current study. Such discrepancies may also arise from the process of averaging over multiple individuals, each with a unique anatomical configuration of approach and withdrawal -biased columns within a large parietal cortex region-of-interest comprised of predominantly approach-biased areas. Follow-up work can identify the precise relationship between personal space behaviors and the distinct approach and withdrawal -biased circuits of this network.

In addition, the strength of the functional connectivity of the inferior parietal cortex with the limbic striatum was associated with a larger personal space in individuals with psychotic disorders, suggesting that dysregulated communication between the limbic striatum, a region that has been consistently implicated in the pathophysiology of schizophrenia [64–67], and the inferior parietal cortex may play a role in personal space enlargement in psychotic disorders.

The neural basis of personal space

One of the central findings of this study is the association observed in the psychotic disorder group between the size of personal space and the magnitude of responses of the inferior parietal cortex, with similar associations found for the permeability of personal space (i.e., the degree of tolerance to personal space intrusions). These associations were also evident, but at a weaker level, in the healthy control group and full sample, suggesting that this relationship may be present across populations.

The personal space network was originally characterized in non-human primates based on the discovery of multi-sensory neurons in the ventral intraparietal (VIP) area within the dorsal parietal cortex and in the ventral premotor cortex (PMv); these neurons showed specific responses to objects that were close to or moving towards the body [14, 68–71]. The neurons of this network have multimodal receptive fields in which visual, tactile and/or auditory inputs are aligned with each other in a body-centered reference space [72–74]. Interoceptive and proprioceptive information also contribute to personal space processing [69, 75]. Moreover, stimulating neurons in VIP and PMv elicits defensive movements (e.g., a swatting motion and eye closing), presumably for the purpose of protecting the face and body from incoming threats [15]. Human fMRI studies have since revealed a wider network of regions beyond VIP, PMv, and the putamen, that may be involved in monitoring the space near the body and responding to stimuli within that space [56, 57].

Weaker (or less differentiated) inferior parietal cortex responses to approaching versus withdrawing face stimuli in individuals who prefer to maintain a larger personal space may be related to a diminished engagement of the approach-biased neurons within this area when encountering approaching conspecifics. These approach-biased neurons in the inferior parietal cortex may be chronically overactivated in some individuals, leading to persistently elevated states of arousal unmodulated by specific incoming stimuli. Ultimately, these persistent arousal states may result in a need to maintain and monitor a greater amount of physical space near the body. This proposed model can be tested in future studies which identify the approach-biased and withdrawal-biased columns within inferior parietal cortex and the arousal responses that occur in response to personal space intrusions in each individual. Pupilometry data obtained from in-scanner eye-tracking measurements could serve as an objective measure of arousal state, while eye position data, along with a titrated attentional task (e.g., using a staircasing procedure), could be used to account for or eliminate effects of attentional modulation across individuals.

Symptom correlations

Prior studies have observed associations between personal space characteristics (size and/or permeability) and the severity of negative symptoms, social anhedonia, and social withdrawal [9, 50, 55]. Consistent with these previous findings, we observed a correlation between personal space size and social anhedonia in the healthy control group in the current study. In contrast, in the psychotic disorders group, the size of personal space was correlated with levels of disorganization and disturbance of volition, rather than negative symptoms. However, the negative and disorganized symptom factors of the five-factor PANSS model are highly correlated with each other [41], and prior evidence suggests that these two symptom dimensions are somewhat linked [76–78].

In fact a range of symptoms have been found to correlate with personal space measurements in prior studies, including positive symptoms (e.g., paranoia [2, 34]), negative symptoms [9], and anxiety [31–33]. One possible interpretation of these varied findings is that a more fundamental "trait-level" abnormality is associated with disrupted personal space boundaries, such as a disturbance of an awareness of the bodily 'self' [79–81], which is partially manifested as expressions of different symptom states, perhaps depending on the phase of illness or other interacting traits, in psychotic illnesses.

Also, unlike in our prior studies of personal space in psychotic disorders [9, 55], the psychotic disorder group in the current study included individuals with diagnoses of affective psychosis (e.g., bipolar disorder and schizoaffective disorder, bipolar type) in addition to patients with non-affective psychosis (e.g., schizophrenia or schizoaffective disorder, depressive type). This design was based on an RDoC-informed [39] approach; we aimed to test the hypothesis that changes in the function of the personal space network are linked to transdiagnostic personal space dysregulation, rather than to a particular disorder such as schizophrenia. The brain-behavior associations identified here broadly support this model.

CONCLUSIONS

Understanding the functional organization of the personal space network in the human brain may provide a general model of neural systems that span lower-level sensory processes and associative functions that underlie social behaviors. In addition, brain-behavior associations, such as the links observed here between the activity and functional connectivity of the inferior parietal cortex and personal space preferences, may be used as objective markers of illness or risk for illness, potentially serving as targets of treatments or indicators of treatment response or prognosis [82].

DATA AVAILABILITY

All data of this study are available on the NIMH Data Archive as part of the "Neural mechanisms of social distance in psychosis" collection (ID# 2519).

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AUTHOR CONTRIBUTIONS

DH and RT contributed substantially to the conception and design of the study. LV, MA, CJ, AH, ND and JM contributed substantially to the data acquisition. LV, MA, and DH conducted the analyses and interpretation of the data. LV and DH wrote the first draft of the manuscript and DH, ND, RT, MA, CJ, AH and JM provided comments on subsequent manuscript revisions. All authors approved the final version of the manuscript.

FUNDING

This research was funded by National Institutes of Health grant R01MH109562 (DJH), and supported by grants 1S10RR023043, 1S10RR023401, and P41EB015896 for shared resources and imaging resources provided by the Athinoula A. Martinos Center for Biomedical Imaging.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41380-025-02906-4.

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