REGULAR RESEARCH ARTICLE

Voice Hearing in Borderline Personality Disorder Across Perceptual, Subjective, and Neural Dimensions

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Abstract

Background: Auditory verbal hallucinations (AVH) commonly occur in the context of borderline personality disorder (BPD) yet remain poorly understood. AVH are often perceived by patients with BPD as originating from inside the head and hence viewed clinically as “pseudohallucinations,” but they nevertheless have a detrimental impact on well-being.

Methods: The current study characterized perceptual, subjective, and neural expressions of AVH by using an auditory detection task, experience sampling and questionnaires, and functional neuroimaging, respectively.

Results: Perceptually, reported AVH correlated with a bias for reporting the presence of a voice in white noise. Subjectively, questionnaire measures indicated that AVH were significantly distressing and persecutory. In addition, AVH intensity, but not perceived origin (i.e., inside vs outside the head), was associated with greater concurrent anxiety. Neurally, fMRI of BPD participants demonstrated that, relative to imagining or listening to voices, periods of reported AVH induced greater blood oxygenation level-dependent activity in anterior cingulate and bilateral temporal cortices (regional substrates for language...
Auditory verbal hallucinations (AVH) commonly occur in the context of borderline personality disorder (BPD) yet remain poorly understood. We investigated the perceptual, subjective, and neural expressions of AVH by using an auditory detection task, experience sampling and questionnaires, and functional neuroimaging, respectively. Perceptually, reported AVH correlated with a bias for reporting the presence of a voice in white noise. Subjectively, questionnaire measures indicated that AVH were significantly distressing and persecutory. In addition, AVH intensity, but not perceived origin (i.e., inside vs outside the head), was associated greater concurrent anxiety. Neurally, participants showed patterns of activation that resemble those in other groups experiencing hallucinations. Neurally, participants showed patterns of activation that resemble those in other groups experiencing hallucinations (e.g., the involvement of cingulate and language cortices). By describing AVH in BPD at multiple levels of assessment, we showed a similarity between the experience in BPD to other groups, thus demonstrating the need for the experience to be considered a treatment priority.

Significance Statement
Auditory verbal hallucinations (AVH) commonly occur in the context of borderline personality disorder (BPD) yet remain poorly understood. We investigated the perceptual, subjective, and neural expressions of AVH by using an auditory detection task, experience sampling and questionnaires, and functional neuroimaging, respectively. Perceptually, reported AVH correlated with a bias for reporting the presence of a voice in white noise. Subjectively, questionnaire measures indicated that AVH were significantly distressing and persecutory. In addition, AVH intensity, but not perceived origin (i.e., inside vs outside the head), was associated with greater concurrent anxiety. Neurally, participants showed patterns of activation that resemble those in other groups experiencing hallucinations. Neurally, participants showed patterns of activation that resemble those in other groups experiencing hallucinations (e.g., the involvement of cingulate and language cortices). By describing AVH in BPD at multiple levels of assessment, we showed a similarity between the experience in BPD to other groups, thus demonstrating the need for the experience to be considered a treatment priority.

Introduction
Patients diagnosed with borderline personality disorder (BPD) show a pattern of behavior characterized by impulsivity and instability in interpersonal relationships, self-image, and emotional states (American Psychiatric Association, 1994). Contemporary emphasis is placed on emotional instability (BPD is encompassed within emotionally unstable personality disorder); however, psychotic symptoms are extremely common, reflected in the original view that the diagnosis was on the “border” between psychosis and neurosis. Between 50% and 90% of patients with BPD report hearing voices that other people do not hear (Yee et al., 2005; Kingdon et al., 2010). Importantly, such auditory verbal hallucinations (AVH) are a risk factor for suicide plans, attempts, and hospitalization (Miller et al., 1993; Zonnenberg et al., 2016).

Despite their high prevalence and apparent importance, the central relevance of AVH to patients with BPD is often clinically undervalued. Because patients with BPD often report AVH as originating from an “inner location” (as opposed to the outside world), the veracity and significance of AVH may be questioned: these experiences are often labelled as “pseudo-hallucinations” (Wing et al., 1974). Empirical studies, however, show the concept of pseudohallucinations has low construct validity and reliability (Copolov et al., 2004; Daalman et al., 2011). Indeed, many clinicians find the term confusing, with inconsistency in its usage (Berrios and Dening, 1996). Overall, the concept is poorly predictive of diagnosis or clinical characteristics (van der Zwaard and Polak, 2001). However, the notion that AVH in BPD represent pseudohallucinations persists and fuels a hesitancy to consider the experience as comparable—in severity or validity—with AVH in schizophrenia (Mustafa, 2020). The current study was motivated to reappraise this issue through enhanced understanding of AVH in BPD.

In patients with schizophrenia and related psychotic disorders, AVH are linked to cognitive psychological mechanisms that include externalizing biases in source monitoring (Brookwell et al., 2013; Griffin and Fletcher, 2017). This refers to the tendency to misattribute internally generated cognitive events to external sources (Bentall and Slade, 1985; Hoffman, 1986; Fraser, 1993; Larsen and Woodward, 2007). In auditory yes-no signal detection tasks, participants report perceived presence or absence of an ambiguous auditory stimulus (either very faint or embedded within white noise). Signal detection theory (Green and Swets, 1966) can be applied to quantify perceptual sensitivity (the probability of detecting a signal correctly, given the probability of a false alarm; see The Relationship Between Signal Detection and AVH and response bias (the tendency to report “signal” vs “noise”). This latter variable is particularly interesting here because it potentially informs us of how an ambiguous stimulus is interpreted or evaluated (Peters et al., 2016). Patients with psychosis, and even hallucination-prone non-clinical individuals, tend to over-report the presence of auditory targets (exhibit a liberal response bias) yet typically show no reliable differences in perceptual sensitivity (Bentall and Slade, 1985; Barkus et al., 2007; Waters et al., 2012). In fact, liberal biases in auditory detection appear primarily associated with AVH and not the presence of a psychiatric diagnosis (Powers et al., 2017), indicating a relationship between voice-hearing and the evaluation of ambiguous (external) auditory signals. Within the current study, we tested if liberal auditory responses bias without corresponding deficits in auditory sensitivity (i.e., the profile reported in people with a psychosis diagnosis) is also seen in people with a diagnosis of BPD.

Functional neuroimaging has been used to investigate neural correlates of AVH in patients with schizophrenia: AVH are linked to multiple functional alterations (Čurtić-Blake et al., 2017) yet most consistently with hyperactivity in language-related temporal lobe regions (Allen et al., 2008; Jardri et al., 2011; Kühn and Gallinat, 2012; Orlov et al., 2018). It is unclear if AVH-driven neural activity is similar in patients with BPD to patients with schizophrenia.

The current study aimed to advance understanding of the cognitive, subjective, and neurophysiological mechanisms underlying AVH in BPD patients. An auditory yes-no detection task was used
to assess whether psychosis-like response profiles are associated with AVH severity in BPD. Structured ratings characterized the subjective experience of AVH (e.g., distressing and persecutory; and perceived internal or external origin) and their relation to other clinical symptoms (including anxiety). Functional magnetic resonance imaging (fMRI), in a symptom-capture design, determined neural correlates of AVH compared with hearing external auditory voice stimuli and cues imagined experiences of voices. Lastly, we used resting-state fMRI to map associations between interregional functional connectivity and AVH symptom severity. By approaching AVH at these 3 levels of description, we provide a detailed profile and deeper understanding of AVH in patients with BPD. The outcomes of this study can be evaluated against published findings regarding hallucinatory phenomena in other diagnostic groups across the psychosis spectrum.

MATERIALS AND METHODS

Participants

Fifty-two participants with diagnosis of BPD (n females = 42, n males = 10) with a mean age of 34 years (SD = 10.9) were recruited from the Sussex and Kent regions (UK) with the assistance of the Sussex Voices Clinic, Sussex Partnership NHS Foundation Trust and Kent & Medway NHS & Social Care Partnership Trust. Diagnosis of schizophrenia was part of the exclusion criteria. To ensure they were voice hearers, participants were required to have experienced persistent AVH over the past 6 months. For full demographics and inclusion/exclusion criteria, see supplementary Materials.

Three participants withdrew from the study after they were recruited but before taking part in the first phases, so they did not provide any data. One additional participant, who completed later phases of the study, did not complete the initial clinical phase. Therefore, 48 participants first attended the clinical assessment phase, where questionnaires and interviews (face-to-face and online) were completed (see Clinical Assessment). The next phase of the study, a signal detection task (see Signal Detection Task), was completed by 22 participants (M age = 33 years, SD = 10.8; n females = 16, n males = 6). The final phase, a neuroimaging task (see Neuroimaging Assessment), was completed by 30 participants (M age = 32.9 years, SD = 10.3; n females = 26, n males = 4).

Ethical approval was obtained from South Central Berkshire “B” Research Ethics Committee via the National Research Ethics System ID: 234 904, with sponsorship from Sussex Partnership NHS Foundation Trust and Brighton and Sussex Medical School Research Governance and Ethics Committee. All data acquisition methods used were in accordance with international, national, and institutional guidelines. All participants gave informed consent following Declaration of Helsinki guidelines.

Behavioral Assessments

The behavioral assessment phase included the clinical characterization of patients using structured interviews and questionnaires (see Clinical Assessment Phase), followed by the signal detection task (see Signal Detection Task) completed by participants in another session.

Clinical Assessment Phase

First, participants completed a series of semi-structured interviews: (1) the Positive and Negative Syndrome Scale for Schizophrenia, (2) Psychotic Symptoms Rating Scale—Auditory Hallucinations, and (3) Brief Negative Symptom Scale. Next, they completed a series of online questionnaires using Qualtrics (Qualtrics, 2013). Notably, they completed the Brief Symptom Impact Scale (BSIS; designed for the current study) and the Revised Beliefs About Voices Questionnaire (Chadwick et al., 2000).

The BSIS is a 10-item measure of impact of AVH, relative to other symptoms, containing items corresponding to the 9 diagnostic criteria for BPD (e.g., identity disturbance, impulsivity, etc., see supplementary Materials), alongside 1 item relating to voice hearing. Participants ranked these 10 items in order of current negative impact (in terms of distress and/or ability to function), where 1 = “generally affects me most” and 10 = “generally affects me least.” BSIS-Voices refers to the ranked score of the AVH item.

The Revised Beliefs About Voices Questionnaire is a 35-item self-report questionnaire measuring beliefs about the malevolent, benevolent, and omnipotence of voices alongside behavioral and emotional responses to voices. Items are rated on a 4-point ordinal scale ranging from 0 (disagree) to 3 (strongly agree). A recent factor analysis identified the 2 beliefs subscales assessing “persecutory beliefs about voices” (12 items [e.g., “My voice is persecuting me for no good reason”]; potential range of scores 0–36) and “benevolence beliefs” (6 items [e.g., “My voice wants to help me”]; potential range of scores 0–18) (Strauss et al., 2018).

Signal Detection Task

Participants completed a computer-based task in which they detected the presence or absence of a human voice embedded in auditory noise and rated their subjective decision confidence (Fig. 1A). Participants completed 200 self-paced trials (total time ranging between 15 and 25 minutes), grouped into 5 blocks of 40, which commenced when the participants pressed the space key. Trials began with the onset of a fixation cross of variable duration (200–400 ms). Subsequently, 1500 ms of white noise was presented binaurally through stereo headphones at 50% of maximum speaker output. In 50% of trials, a 200-ms voice clip with gradual onset and offset was inserted into the noise at a random time. This stimulus comprised an androgynous voice articulating the syllable “ba.” Following offset of the auditory white noise there was a fixed 300-ms period of silence followed by a response prompt. Participants then reported (5-second window) whether a voice stimulus was present (left arrow key) or absent (right arrow key). After, participants indicated whether they were confident (left arrow key) or not confident (right arrow key). Participants were offered breaks between blocks. Task difficulty was matched across participants using a calibration paradigm (Fig. 1B, detailed account in supplementary Materials), whereby the volume of the signal was adjusted using a standard psycho-physical “staircase” procedure (Levitt, 1971). This accounted for natural variation in auditory acuity across individuals.

The Relationship Between Signal Detection and AVH

To investigate the relationship between signal detection outcome measures and AVH symptoms, we examined how participants’ response bias and perceptual sensitivity related to AVH symptom severity (BSIS). We quantified participants’ biases towards reporting hearing a voice in noise using Signal Detection Theory (Green and Swets, 1966) to measure decision threshold c, also referred to as response bias. Response bias c represents the amount of “voice” evidence required to report that a voice was present. When c takes the value 0, participants are unbiased.
Negative values (arising from an increase in hit and false alarm rates) correspond to a bias towards reporting “voice,” and positive values (arising from a decrease in hit and false alarm rates) correspond to a bias towards reporting “no voice.” This measure is theoretically independent of task performance (perceptual sensitivity $d'$). We calculated bias $c$ and sensitivity $d'$ as follows:

\[
\text{hit rate} = \frac{\text{hits} + 0.5}{\text{hits} + \text{misses} + 1} \tag{1}
\]

\[
\text{false alarm rate} = \frac{\text{false alarms} + 0.5}{\text{false alarms} + \text{correct rejections} + 1} \tag{2}
\]

\[
c = -0.5 \times (Z(\text{hit rate}) + Z(\text{false alarm rate})) \tag{3}
\]

\[
d' = Z(\text{hit rate}) - Z(\text{false alarm rate}) \tag{4}
\]

where $Z$ is the standard $z$-score. Hit rate/false alarm rate here reflects the probability of reporting “voice present” when a voice was present/absent. The addition of 0.5 to hits (report “present” on voice-present trials), misses (report “absent” on voice-present trials), false alarms (report “present” on voice-absent trials), and correct rejections (report “absent” on voice-absent trials) corresponded to a correction for the possibility of empty cells (e.g., no false alarms).

We aimed to assess the relationship between participants’ response bias ($c$), perceptual sensitivity ($d'$), and their AVH symptom severity (BSIS-Voices). Pearson correlations were conducted in R (V 1.3.1093) (Team, 2015) to assess the relationship between AVH symptom severity and both response bias and perceptual sensitivity.

**Assessing the Extent to Which AVH Were Perceived as Distressing and Persecutory**

To categorize the subjective experience of AVH, we analyzed questionnaire-based measures of AVH at the state (distress) and trait (persecutory) level. We report descriptive statistics on (1) responses to the in-scanner distress item (Table 1, Question 2), and (2) responses to BAVQ-Persecutory and BAVQ-Benevolent.
Table 1. Questions for Participants at Each Probe Instance During Rest and Task fMRI

<table>
<thead>
<tr>
<th>Question</th>
<th>Label</th>
<th>AVH</th>
<th>Distress</th>
<th>Not at all distressing</th>
<th>Yes</th>
<th>Completely distressing</th>
</tr>
</thead>
<tbody>
<tr>
<td>I heard my voice/s</td>
<td></td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How distressing did your voice/s feel?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How loud were your voice/s?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What proportion of the time were you hearing your voice/s?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Where did your voices sound like they were coming from?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I felt anxious</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: AVH, auditory verbal hallucinations.

Questions 2-5 were only asked if participants responded positively to question 1.

subscales. Because these 2 subscales have differing ranges, scores were transformed to span a 1–10 range.

NEUROIMAGING ASSESSMENTS

Scanning Protocol and Preprocessing

Patients completed 1 structural scan and four 8-minute functional scans. The task details of the functional scans are in 3.2.

Preprocessing of functional imaging datasets was performed using FMRIPREP [RIID:SCR_016216], a Nipype [RIID:SCR_002502] based tool (Esteban et al., 2019). Detailed information regarding scanning parameters and preprocessing procedures can be found in the Supplementary Materials.

Neuroimaging Task Paradigms

Each participant completed 4 runs within the fMRI task protocol. The first run was a resting-state scan in which the participant lay with eyes open for 8 minutes. On-screen instructions stated "if you hear your voice/s, press the THUMB button when your voice/s start/stop." The participant then completed 3 randomized task runs. Each 8-minute run consisted of 5 blocks of 10 trials. Each block was 1 of 3 conditions (fixation-cross; externally presented verbal stimuli; cued imaginary verbal stimuli). Blocks were pseudo-randomized within-runs and fixed across participants. To ensure instances of AVH were recorded throughout the task, during all conditions, the participant was reminded (after condition-specific instructions) to report the onset and offset of an AVH using the thumb button.

In the first condition, the participant fixated on a cross, and there were no additional instructions other than to indicate the presence of AVH. In the second condition, auditory verbal stimuli were played through headphones, and the participant was instructed to press a button with their index finger on the onset and offset of these stimuli. These stimuli consisted of spoken word sentences. Stimuli were constructed to mimic typical hallucinatory content. For example, one stimulus said "Oi, can you hear me? I’m not going anywhere." Stimulus content was derogatory, ambiguous, or neutral and were from third- and second-person perspectives. Stimulus duration varied from 1.17 to 5.36 seconds (M = 3.42, SD = .84). Volume was root mean square normalized. More details of voice stimuli can be seen in the supplementary Materials. In the third condition, the participant was instructed, when cued, to imagine voices. The participant was told "whenever the cross turns RED, press the FINGER button, and imagine hearing your voices . . . whenever the cross turns BLACK, press the FINGER button again, and relax." To help perform this task, the participant wrote down 5 examples of things their voices say, prior to scanning.

Table 2. Model Specifications for the 4 Linear Mixed Models

<table>
<thead>
<tr>
<th>Model name</th>
<th>Model specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model intensity</td>
<td>Anxiety - 1 + AVH intensity + (1</td>
</tr>
<tr>
<td>Model location</td>
<td>Anxiety - 1 + AVH location + (1</td>
</tr>
<tr>
<td>Model both</td>
<td>Anxiety - 1 + AVH intensity + AVH location + (1</td>
</tr>
<tr>
<td>Model reduced</td>
<td>Anxiety - 1 + (1</td>
</tr>
</tbody>
</table>

Abbreviation: AVH, auditory verbal hallucinations.

During all functional runs, a white fixation cross was presented centrally on a grey screen. The cross turned red during conditions 2 and 3 when stimuli were present. It did not change color during the fixation-cross condition. During all runs, the lower portion of the screen also displayed the phrase "MY VOICEs ARE . . ." beneath which the words PRESENT and ABSENT were shown. When the participant indicated the presence of AVH, the word PRESENT turned white and ABSENT turned grey.

Experience Sampling Protocol

At the end of each run, the participant was asked a series of questions (Table 1) on a visual analogue scale relating to AVH occurring in the previous time period. The participant was invited to "use the THUMB and FINGER button to move the slider" left and right, respectively. Questions 2 to 5 were only asked if the participant responded positively to question 1. The participant was given 5 seconds to answer each question.

Experience Sampling and Behavioral Data Analysis

Principal Component Analysis—Principal component analysis (PCA) with varimax rotation was performed (using SPSS, V25, IBM Corp, 2017) on responses to the 4 questions relating to descriptions of AVH (questions 2–5; Table 1). Component extraction was based on analysis of the correlation matrix. Components with Eigenvalues >1 were retained. As there were only 4 items, PCA was not used simply for dimension reduction: PCA also allows for a compact description of the linear relationship between item responses to identify “patterns of experience” (components). Importantly, this analysis produces scores describing how well each observation is described by the given components. Linear Mixed Model on PCA Factor Scores and Anxiety—The influence of different components of the AVH experience on clinically relevant changes in affect were then investigated using in-scanner anxiety ratings. To determine how AVH experience sampling principal components correlated with the run-by-run anxiety ratings reported in the scanner, we constructed linear mixed models of these the run-by-run data for all participants together by (Table 2), using the package lme4.
of functional connectivity between clusters of activation identified by the AVH > external + imagined contrast and other voxel clusters across the whole cortex covaried with AVH symptom severity (BSIS-Voices). The seeds used during this analysis were binarized masks of significant task clusters of the AVH > external + imagined contrast (contrast 10, Table 2). Details on the location of these clusters can be seen in the results section (Fig. 4C). Using FSL, the mean signal across all the voxels within each mask for the resting-run was computed to derive the seed time series. This time series was used as the explanatory variable at the first-level analyses, along with the nuisance regressors corresponding to those used in the task GLM. At the second-level (group) analysis, AVH symptom severity scores (BSIS-Voices) were entered as a covariate. Age and overall head movement (mean framewise displacement) were also included as nuisance regressors.

Group-level maps were thresholded the same as the previous analysis. Twenty-six participants reported hearing voices during this resting scan (via button press), so analysis was conducted on single runs from 26 participants.

Data Availability

All group level task-based and resting-state functional neuroimaging data are freely available in unthresholded format on neurovault.org (Gorgolewski et al., 2015; https://identifiers.org/neurovault:collection:9410).

RESULTS

Relationship Between AVH Symptom Severity, Response Bias, and Perceptual Sensitivity

We examined the relationship between AVH symptom severity (BSIS-Voices) and signal detection theory measures of response bias (c) and perceptual sensitivity (d’) using 2 Pearson’s correlations. These tested if symptom severity (across the 21 individuals who completed both signal detection and relevant questionnaire measures) varied with differences in response bias and/or perceptual sensitivity.

The first correlation (Fig. 2A) revealed greater AVH symptom severity (as indicated by lower BSIS-Voices scores) was associated with a more liberal response bias (as indicated by more negative values of c) (r(19) = .65, P = .001, 95% CI [0.31, 0.85]). In other words, participants with more severe AVH symptoms exhibited a stronger bias towards reporting “voice present.” In contrast, the second correlation (Fig. 2B) indicated that AVH symptom severity was not significantly associated with perceptual sensitivity (r(19) = −.18, P = .443, 95% CI [−0.57, 0.28]).

Levels of Distress and Persecutory Beliefs in Hallucinations

AVH experiences were shown to be distressing: a mean in-scanner distress score (Question 2, Table 1) of 61.72 was reported across the 21 participants who indicated via Question 1 (Table 2) that they experienced AVH in the previous (task and rest) run (n responses = 60, SD = 25.50). When looking at responses to questions during the clinical assessment phase, participants rated their voices to be more persecutory than benevolent (measured by BAVQ-Persecutory and BAVQ-Benevolent, respectively). After rescaling both subscales to be on a 1–10 scale, scores were higher for persecutory beliefs (n = 33, M = 4.56, SD = 2.57) than benevolent beliefs (n = 33, M = 1.41, SD = 2.00).

(Bates et al., 2015) in R. To test goodness-of-fit, individual models were compared with reduced models using a chi-squared test (R function ANOVA).

General Linear Model Voxel-Based fMRI Analysis

First-Level Analysis—Functional neuroimaging data analyses was conducted using FSL’s FLAME (Woolrich et al., 2001, 2004; Smith et al., 2004). General linear modeling (GLM) was conducted to ascertain which voxels’ blood oxygenation level–dependent (BOLD) signal was associated with the experimental regressors of interest over the 3 non-rest functional runs. At the individual participant (first) level, for each run, 3 event-related boxcar regressors were modeled that corresponded to timing of button presses for (1) external voices, (2) imagined voices, and (3) AVH. Each regressor was convolved with a double gamma function to model the hemodynamic response. See supplementary materials for details on nuisance regressors. Overall, 10 contrasts were computed at this first level (Table 3) to isolate activity related to each of the 3 event types. Notably, contrast 8 (AVH > external) highlighted activity associated with periods of AVH relative to activity elicited by the perception of externally presented voices. Contrast 9 (AVH > imagined) highlighted activity associated with periods of AVH while removing activity associated with imagining voices. Contrast 10 (AVH > external + imagined) highlighted activity associated with periods of AVH while removing activity associated with both tasks.

Higher-Level Analyses—A fixed-effect design was conducted to average runs within each participant. Individual participant data were then entered into a higher-level group analysis using a mixed-effects design. Higher-level contrasts were computed to extract the group average of these second-level parameter estimates. Group-level maps were thresholded with a cluster-wise level. Due to analytical limitations, only functional runs in which active AVH were reported via button presses were included in this analysis. This equated to a total of 43 (out of 81) task runs from 17 participants out of the 30 participants who completed this phase of the study. After accounting for missing data, 41 runs were entered in higher-level group analyses.

Resting-State Seed-Based Functional Connectivity Analysis

Seed-based functional connectivity analyses were conducted on the resting-state data. Here we explored how the strength

Table 3. Full List of Contrasts Computed at the First-Level GLM

<table>
<thead>
<tr>
<th>Number</th>
<th>Name</th>
<th>AVH</th>
<th>External</th>
<th>Imagined</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>External</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Imagined</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>AVH</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>External &gt; imagined</td>
<td>0</td>
<td>1</td>
<td>−1</td>
</tr>
<tr>
<td>5</td>
<td>External &gt; AVH</td>
<td>−1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Imagined &gt; external</td>
<td>0</td>
<td>−1</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Imagined &gt; AVH</td>
<td>−1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>AVH &gt; external</td>
<td>1</td>
<td>−1</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>AVH &gt; imagined</td>
<td>1</td>
<td>0</td>
<td>−1</td>
</tr>
<tr>
<td>10</td>
<td>AVH &gt; external + imagined</td>
<td>2</td>
<td>−1</td>
<td>−1</td>
</tr>
</tbody>
</table>

Abbreviations: AVH, auditory verbal hallucinations; GLM, general linear modeling.
Relationship Between AVH Intensity, AVH Location, and Anxiety

To characterize the relationship between different descriptive aspects of the AVH experience, PCA was performed on the responses to AVH questions obtained during the neuroimaging experiment. A total 21 (out of 30) participants reported hearing voices (positive answers to “I heard my voice/s”) on 60 out of 111 (task and rest) runs. Therefore, 60 observations of responses to Questions 2 to 5 were collected. PCA was performed on these observations and 2 components were extracted. The first component (named AVH intensity, accounted for 47.11% of variance) captured AVH described as prevalent (Table 1, Question 2; component loading = 0.82), loud (Question 3, 0.85), and distressing (Question 4, 0.70). The second component (AVH location, accounted for 25.51% of variance) captured AVH perceived as coming from outside the head (Question 5; loading = 0.99). The item loadings on each of these components are represented as word clouds in Fig. 3.

We tested whether AVH intensity was associated with anxiety by fitting the intensity model [anxiety ~ 1 + AVH intensity + (1|patient)] to the anxiety reports. Goodness-of-fit was compared with a reduced model [anxiety ~ 1 + (1|patient)] that did not include the factor of intensity. The inclusion of intensity significantly improved goodness-of-fit (X^2(1)=6.74, P = .009) and was such that higher intensity was associated with increased reported anxiety (β = 8.36).

We repeated this process for AVH location, comparing the location [anxiety ~ 1 + AVH location + (1|patient)] and reduced model. While intensity was associated with anxiety ratings, this was not the case for location. Goodness-of-fit was not improved by modeling this fixed effect (β = -2.18, X^2(1)=0.36, P = .549). Together, these results indicate that AVH rated as prevalent, loud, and distressing (greater AVH intensity) were associated with significantly greater levels of anxiety. AVH location had no significant association with anxiety levels.

VOXEL-BASED GLM RESULTS

A GLM was conducted on the task-based fMRI data to reveal the neural correlates of AVH. Group-level maps are presented in Figure 2. The relationship between signal detection theory response bias, perceptual sensitivity, and auditory verbal hallucinations (AVH) symptom severity. (A) Scatterplot showing the positive relationship between response bias (c') and hallucination symptom severity (BSIS-Voices), where 1 = AVH are the least severe of my symptoms and a negative (c') pertains to a liberal response bias. (B) Scatterplot showing no relationship between perceptual sensitivity (d') and AVH symptom severity (BSIS-Voices).

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Figure 3. Dimensions of auditory verbal hallucinations (AVH) experience extracted using principal components analysis (PCA). Word clouds depicting the loading of the 4 question items on the 2 components. Each word represents 1 question (Table 1, questions 2-5). The size of the word represents the magnitude of its loading. The color of the word represents the direction of loading (red = positive, blue = negative). (A) AVH intensity component. (B) AVH location component.

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Figure 4. It shows that for all 3 contrasts, there were significant clusters of activation for AVH. Of primary interest is anterior cingulate cortex, which exhibited higher BOLD during AVH compared with external and imagined voices (P < .002). In addition, BOLD was higher in paracingulate gyrus (P < .001) and in left middle (P < .001) and right superior temporal gyrus (P < .004) during AVH compared with imagined voices alone. For more details, see supplementary Table 1.

The statistical map for the significant rostral anterior cingulate cluster (ACC) resulting from the AVH > imagined + external contrast was binarized into a mask and used as a seed in the subsequent resting-state functional connectivity analysis.

RESTING-STATE SEED-BASED FUNCTIONAL CONNECTIVITY

Seed-based functional connectivity analysis was conducted on resting-state runs to assess how the strength of connectivity between the ACC seed and the whole brain varied with AVH symptom severity (BSIS-Voices). As illustrated in Figure 5, greater AVH symptom severity was associated with less ACC-insula (right) (P < .001), ACC-insula (left) (P < .001), and ACC-parahippocampal gyrus (P < .001) resting-state functional connectivity. For more details, see supplementary Table 2.
DISCUSSION

The common experience of AVH by patients with BPD is a poorly understood phenomenon. In clinical practice, AVH in BPD are often described as pseudohallucinations, casting doubt on the significance, and even validity, of the patient’s experience. The term pseudohallucinations conflates symptom phenomenology with categorical diagnostic distinction between personality disorder and psychotic illnesses (notably schizophrenia). Consequently, there is hesitancy for some researchers and clinicians to consider AVH in BPD as comparable with those in schizophrenia. However, the present study reinforces evidence that the AVH experience in BPD is comparable with other patients across the psychosis spectrum in terms of the cognitive mechanisms, subjective experience, and neural substrates.

We demonstrated that patients with BPD who experience more severe AVH show a greater propensity (were more liberal) to report an auditory signal—here, detecting a voice in white noise. With increasing AVH severity, there was a decrease in response bias, indicating a greater tendency towards reporting false alarms (i.e., erroneous hear a voice) in the signal detection task. No association was observed between voice hearing symptomatology (as quantified using BSIS-V) and perceptual sensitivity (d’), suggesting that those with more severe symptoms were not better or worse at detecting voices. This same pattern is also reported in signal detection studies of patients on the psychosis spectrum and in non-clinical individuals who experience hallucinations (Rappaport et al., 1972; Bentall and Slade, 1985; Hoffman, 1986; Fraser, 1993; Larøi and Woodward, 2007; Vercammen et al., 2008; Brookwell et al., 2013; Griffin and Fletcher, 2017).

We demonstrated that AVH in patients with BPD are associated with adverse subjective experiences: AVH were reported by patients with BPD, on a trait level, to be more persecutory than benevolent and, on a state level, to evoke marked subjective distress. This endorses earlier findings that AVH experience in BPD causes high levels of distress through derogatory, negative, and critical content (Hepworth et al., 2013; Pearse, 2014). Moreover, these affective qualities are very similar to those ascribed to AVH experience in schizophrenia (Slotema et al., 2012). Ascertaining which aspects of the AVH experience are coupled to heightened anxiety levels has important clinical implications. Here, we observed that anxiety levels increased with increasing intensity (loudness, prevalence, distress) of AVH, but there was no significant relationship with the location (internal or external) of AVH perception. The perception of an AVH as originating from within the head is 1 key factor proposed to distinguish a pseudohallucination from “true” hallucinations. However, we showed that AVH with an “inner” location are no less anxiety-provoking than those with an “outer” location. This challenges the clinical relevance of the pseudo/real distinction (based on perceived location) in terms of the affective impact of AVH. Phenomenologically, the interior/exterior distinction might retain other etiological relevance (Anthony, 2004), yet the...
prefix pseudo- undermines the clinical credibility of those experiencing inner AVH. Whether an AVH is “heard” is arguably a more suitable way of determining whether it is real (Hunter, 2004). Our results suggest that the reported intensity, rather than their location, should inform assessment of the clinical impact of hallucinations in BPD, particularly in relation to negative affective symptoms.

We used fMRI to characterize and compare AVH-related regional brain activity to listening to externally presented sentences and imagining similar auditory verbal content. Relative to both the listening and imagination tasks, AVH elicited greater activity within rostral ACC and adjacent prefrontal cortex. ACC activation is previously reported to distinguish hallucinating patients (with schizophrenia) from non-hallucinating controls (Jardri et al., 2011). Moreover, real-time modulation of ACC activity (using fMRI neurofeedback) in patients with schizophrenia was reported to evoke changes in both AVH severity and mood, suggesting a causal role of ACC activation in affect-laden hallucinatory experience (Dyck et al., 2016).

AVH experience was also associated with greater activity within lateral temporal cortices, considered specialized for language processing. The right middle temporal gyrus and left posterior superior temporal gyrus (STG) showed higher activity when the participants experienced AVH than when imagining that they were hearing a similar voice. These regions, identified as core structures within a functional network supporting speech and human voice processing (Belin et al., 2000; Hickok and Poeppel, 2007), have also been proposed as neural substrates underlying AVH. For example, individuals who experience AVH (but without psychosis) exhibit higher levels of resting-state functional connectivity between left and right STG than matched controls (Diederen et al., 2013). Even in silence, neural activity within left temporal language regions (including STG) shows endogenous fluctuations in concert with changes in ACC activation (Hunter et al., 2006), suggesting a functional coupling between temporal and cingulate regions. Taken together, these results suggest that the observed activity within language and cingulate regions associated with AVH may reflect a mechanism through which AVH are generated, through dysfunctional cingulo-temporal connectivity.

Symptom-capture studies of AVH echo the involvement of temporal language regions: meta-analyses support greater activation in STG and adjacent temporo-parietal language regions during AVH experience in patients with schizophrenia (Curcic-Blake et al., 2017). There also seems to be a causal relationship between AVH and STG, because transcranial magnetic stimulation to temporo-parietal cortex reduces AVH severity (Hoffman et al., 2007; Kindler, 2013). Furthermore, a proof-of-concept neurofeedback study reported reductions in psychotic symptoms and AVH distress when STG activity was volitionally downregulated (Orlov et al., 2018). Thus, the current study’s observations are consistent with suggestions of a central role of language-specialized temporal cortices in AVH experience.

**Figure 5.** The results of resting-state seed-based functional connectivity analysis, using auditory verbal hallucinations (AVH) symptom severity (BSIS-Voices) as a group level covariate. The binarized seed is shown on the left. To the right are the 3 significant clusters. The area associated with the coordinates in question is based on the most probable Harvard-Oxford label. Abbreviations: L, left hemisphere; R, right hemisphere. Statistical maps are cluster corrected at Z=2.3, P=0.05.

<table>
<thead>
<tr>
<th>Area</th>
<th>Mid insula cortex (R)</th>
<th>Parahippocampal Gyrus (Posterior, L)</th>
<th>Mid-ventral insula cortex (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X (mm)</td>
<td>35.5</td>
<td>-14.5</td>
<td>-40.5</td>
</tr>
<tr>
<td>Y (mm)</td>
<td>-8.5</td>
<td>-38.5</td>
<td>-12.5</td>
</tr>
<tr>
<td>Z (mm)</td>
<td>5.5</td>
<td>-12.5</td>
<td>-4.5</td>
</tr>
<tr>
<td>p</td>
<td>8.76e-11</td>
<td>8.9e-05</td>
<td>16e-04</td>
</tr>
</tbody>
</table>
In summary, the task-based fMRI analysis showed that dorsal and rostral ACC activity was associated with AVH, while resting-state analysis suggest that the rostral ACC may work in conjunction with the insula to bring about the emergence of AVH in a manner that varies with AVH severity.

Among other things, the dorsal and rostral ACC are implicated in the control of internal physiological arousal and its integration with deployment of attentional, cognitive, and behavioral resources (Criticly et al., 2003, 2005, Critchley, 2005). Moreover, the ACC has been shown to work in concert with the insula, theoretically to enable the dynamic integrative control of internal bodily state (Medford and Critchley, 2010). This representation enables physiological arousal states to be matched with perceptual, cognitive, and affective processing and associated behaviors (Craig, 2009; Seth and Tsakiris, 2018). Moreover, this interoceptive representation is posited to be a crucial reference for intact self-awareness (Tsakiris et al., 2007; Craig, 2009; Critchley and Harrison, 2013). Neurological damage to insula regions can contribute to anosagnosic denial of paralysis and somatoparaphrenia (Vallar and Ronchi, 2009), and insula activity has been found to predict the modulation of illusory experiences of body ownership in the rubber hand illusion (Tsakiris et al., 2007). Accordingly, the aberrant ACC—insula connectivity observed in the current study may be indicative of a dysfunction in the integrity of biological self-hood and thus give rise to self-disturbance. In turn, this may manifest as dissociative and psychotic experiences, including problems with source monitoring and, by extension, hallucinations. A link between physiological arousal states and AVH has been established by a recent study using an experience sampling (ecological momentary assessment) study with heart rate monitoring of patients with schizophrenia (Kimhy et al., 2017). Periods of heightened cardiac autonomic arousal (including the withdrawal of vagally mediated heart rate variability) predict transitory increases in auditory hallucinations. This evidence lends support to this hypothesis that physiological arousal and its interoceptive representation, relying on processing in the ACC and insula, may play an important role in AVH.

LIMITATIONS

To our knowledge, this study represents the largest multimethod investigation of AVH in well-characterized patients with BPD. However, we did not study parallel control groups of non-clinical individuals (including “voice-hearers”) or patients with diagnoses of schizophrenia. Consequently, inferences concerning the similarity of BPD experience of AVH to other patient groups draw on measures of symptom variation across our patient group and from comparison with published evidence. The absence of a control group also means we are unable to determine if the titration levels in the signal detection paradigm are atypical. Our findings motivate the need to compare AVH in BPD with other populations susceptible to AVH. Another constraint, shared by similar studies, is the general use of temporally static measures of data analysis. Distinct extrinsic and intrinsic factors may trigger a hallucination, yet other factors may contribute to sustaining and/or stopping it. Neu rally, this may include dynamic reconfigurations of functional brain networks at different time points within a hallucination. Here, we used static post hoc measures of neural connectivity, thereby emphasizing stronger and temporally more stable interactions. A richer understanding of neural correlates of AVH may be achieved if future investigations apply dynamic analytic methods [e.g., sliding windows or Hidden Markov Models (Chen et al., 2017)] that capture time-varying functional states over shorter temporal windows. Lastly, the BSIS-Voices measure assesses voice hearing in relation to other symptoms, arguably making it a more holistic measure of BPD experience assessed from the patient’s perspective (Hayward et al., 2021). The BSIS, completed by the majority of patients, corresponds significantly to established scales such as the PSYRATS (r(30) = -.42, P = .02) and hence was chosen as our primary measure to assess voice hearing. For consistency with prior literature, we repeated the behavioral analysis (i.e., how signal detection measures relate to AVH severity) using PSYRATS. Both measures demonstrated a significant positive relationship between criterion (bias) and AVH symptomatology (see supplementary Material).

CONCLUSION

The current study characterized AVH experience in BPD over cognitive, subjective, and neural levels. Critically, across all 3 levels of assessment, our findings highlight the broad similarity of AVH experience in patients with BPD to reported AVH experience of non-clinical and clinical groups across the psychosis spectrum. Our findings challenge the categorization of AVH in BPD as pseudohallucinations and highlight the need to reconceptualize the phenomenology and clinical impact of AVH in BPD for consideration as a priority treatment target. Insights from the neural level of assessment allude to the possible dependence of AVH on physiological arousal states and their control. Future research is needed, ideally incorporating neuroimaging with concurrent physiological assessment, to investigate dynamic interoceptive mechanisms underlying the expression of hallucinations.

Supplementary Materials

Supplementary data are available at International Journal of Neuropsychopharmacology (IJNPPY) online.

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Interest Statement

None.

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