

Electrical stimulation induced self-related auditory hallucinations correlate with oscillatory power change in the default mode network

Jing Yang^{1,2,†}, Lu Shen^{1,2,†}, Qiting Long², Wenjie Li², Wei Zhang^{3,4}, Qi Chen^{1,2,*}, Biao Han^{1,2,*}

¹Center for Studies of Psychological Application, South China Normal University, No.55, West of Zhongshan Avenue, Tianhe District, 510631, Guangzhou, China,

²School of Psychology, South China Normal University, No. 55, West of Zhongshan Avenue, Tianhe District, 510631, Guangzhou, China,

³Department of Neurology, Beijing Tsinghua Changgung Hospital, Litang Road No. 168, Changping District, 102218, Beijing, China,

⁴Epilepsy Center, Shanghai Neuromedical Center, Gulang Road No. 378, Putuo District, 200331, Shanghai, China

*Corresponding authors: Biao Han, School of Psychology, South China Normal University, No.55, West of Zhongshan Avenue, 510631, Guangzhou, China.

Email: biao.han@m.scnu.edu.cn; Qi Chen, School of Psychology, South China Normal University, No.55, West of Zhongshan Avenue, 510631, Guangzhou, China.

Email: qi.chen27@gmail.com

†Jing Yang and Lu Shen contributed equally to this work

Self-related information is crucial in our daily lives, which has led to the proposal that there is a specific brain mechanism for processing it. Neuroimaging studies have consistently demonstrated that the default mode network (DMN) is strongly associated with the representation and processing of self-related information. However, the precise relationship between DMN activity and self-related information, particularly in terms of neural oscillations, remains largely unknown. We electrically stimulated the superior temporal and fusiform areas, using stereo-electroencephalography to investigate neural oscillations associated with elicited self-related auditory hallucinations. Twenty-two instances of auditory hallucinations were recorded and categorized into self-related and other-related conditions. Comparing oscillatory power changes within the DMN between self-related and other-related auditory hallucinations, we discovered that self-related hallucinations are associated with significantly stronger positive power changes in both alpha and gamma bands compared to other-related hallucinations. To ensure the validity of our findings, we conducted controlled analyses for factors of familiarity and clarity, which revealed that the observed effects within the DMN remain independent of these factors. These results underscore the significance of the functional role of the DMN during the processing of self-related auditory hallucinations and shed light on the relationship between self-related perception and neural oscillatory activity.

Key words: self; auditory verbal hallucination; electrical stimulation; neural oscillations; default mode network.

Introduction

The self, a concept of great significance, has garnered extensive attention and investigation from philosophers and psychologists over the course of history. Psychological exploration of the self dates back to the early days of the discipline (James 1890), and cognitive neuroscientists have been intrigued by the neural underpinnings of the self since the late 1990s (Craig et al. 1999). Notably, when information is self-related, such as self-relevant traits and personal experiences, individuals consistently demonstrate superior memory retention and more effective cognitive processing compared to information that is other-related (Kesebir and Oishi 2010; Sui et al. 2012; Liu et al. 2016; Yin et al. 2019). These findings have led to the proposal of a specific brain mechanism dedicated to processing self-related information (Gillihan and Farah 2005; Christoff et al. 2011; Sui and Gu 2017). Despite the acknowledged importance of self-related information processing, the precise neural mechanisms underlying this cognitive process remain a subject requiring further investigation.

The default mode network (DMN) has emerged as a key player in the representation and processing of self-related information within the human brain. A wealth of neuroimaging research has consistently demonstrated a strong association between the self and the DMN, particularly involving specific subregions like the medial prefrontal cortex (mPFC) and posterior cingulate

cortex (PCC) (Gillihan and Farah 2005; Qin and Northoff 2011; Menon 2023). To illustrate, studies employing functional magnetic resonance imaging (fMRI) have steadfastly revealed heightened activity within the mPFC and PCC during tasks involving self-referential judgments (Kelley et al. 2002; Heatherton et al. 2006; Mitchell et al. 2006; Whitfield-Gabrieli et al. 2011; Davey et al. 2016; Wen et al. 2020; Levorsen et al. 2023). Furthermore, disruptions to the mPFC during a shape-label matching task have been shown to eliminate the prioritization of arbitrary self-related stimuli in working memory (Yin et al. 2021). Additionally, temporary interference with PCC diminishes the recall of items previously encoded as self-related (Lou et al. 2004). Despite the extensive evidence anchoring the self to the DMN, the specific neural oscillatory mechanisms within the DMN and their intricate connection to self-related processing remain unclear due to inherent methodological limitations.

Electrical brain stimulation (EBS) is a powerful technique routinely used in clinical practice to evaluate patients with epilepsy and for specific brain tumor resection (Berger and Rostomily 1997; Duffau 2001; Jayakar et al. 2016). This method involves focal stimulation of the cerebral cortex, which has long been known to elicit or interfere with specific and complex behaviors and experiences, making it a valuable tool for investigating the neural basis of perception, thought, and behavior

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(Bartholow 1874; Penfield and Boldrey 1937; Brindley and Lewin 1968; Dobelle and Mladejovsky 1974; Ojemann et al. 1989). During EBS, electrical discharges are delivered to targeted brain regions in awake human subjects, enabling the mapping of functional involvement in sensation, movement, language, memory, and other cognitive functions (Ojemann et al. 2003). Contrary to most neuroimaging studies, which may not directly assess the necessity of specific brain regions in cognitive functions, EBS provides direct observations about the necessity of stimulated regions for the studied perceptual or behavioral functions (Penfield and Jasper 1954). Classical EBS studies have offered invaluable evidence on the localization of functions in the human brain, such as the somatosensory homunculus in the primary sensory cortex (Penfield and Boldrey 1937; Penfield 1958), and have provided crucial insights into the potential involvement of different cortical regions in human conscious experiences (Penfield and Jasper 1954). Recently, researchers utilized EBS to induce auditory hallucinations and illusions in epileptic patients and found that specific brain regions, including the superior temporal gyrus and the insula, were associated with these auditory phenomena (Jaroszynski et al. 2022).

In this study, we employed EBS to investigate the activity within the DMN concerning the generation and processing of self-related auditory perception, with a specific focus on neural oscillations. To achieve this, we examined EBS data from patients who experienced auditory verbal hallucinations during electrical stimulation at specific brain sites, while simultaneously recording brain signals from other sites. These hallucinations were categorized as self-related or other-related. After removing EBS artifacts, we directly compared the power changes in different frequency bands within DMN recording sites to understand the oscillatory mechanisms involved in self-related auditory perception. To ensure the validity of our findings, we controlled for potential confounding factors in auditory hallucinations. We compared self-related and other-related hallucinations for familiar and clear auditory hallucinations separately, excluding familiarity and clarity as confounding factors. Our hypothesis posited that the observed differences in oscillatory power between self-related and other-related hallucinations would offer valuable insights into the neural mechanisms governing the generation and processing of self-related auditory perception within the DMN.

Materials and methods

Subjects

From a larger patient pool consisting of 62 individuals with drug-resistant epilepsy who had undergone intracranial electrode implantation and subsequent electrical stimulation, seven patients (four females, mean age: 26.3 yrs, see Table 1) exhibiting electrical stimulation-induced auditory hallucinations were selected for this study. The selection of patients was based on specific inclusion criteria: (i) experiencing auditory hallucinations of human voices exclusively during electrical stimulation, (ii) absence of significant structural abnormalities observed in their structural MRI scans, (iii) no history of previous brain surgery before the implantation of stereoencephalography (sEEG) electrodes, (iv) absence of any other neurological, psychiatric, or developmental disorders apart from epilepsy, (v) normal hearing abilities, and (vi) attainment of seizure-free status following the surgical intervention to exclude any potential abnormal data associated with ongoing seizures. It is important to note that all procedures were not specifically performed for the purpose of this study, but rather as part of a pre-surgical evaluation conducted

for clinical purposes. All patients provided written informed consent to allow the utilization of their data, and the experimental procedures conducted in this study received approval from the Ethics Committee of the School of Psychology at South China Normal University. sEEG recordings were obtained from these patients during the period spanning August 2018 to November 2019.

Electrical stimulation and intracranial recording

Depending on the clinical need, semi-rigid platinum/iridium depth electrodes with 7 to 19 contacts each (0.8 mm diameter, 2 mm length, and 1.5 mm spacing) were implanted. After implantation, the patients were monitored for about 2 wks in their hospital rooms. During this time, professional physicians performed electrical stimulation mapping on some brain regions while sEEG signals and simultaneous videos were recorded. This mapping aimed to identify the functional aspects of different brain areas, crucial for surgical planning. sEEG was recorded using a 256-channel Nihon Kohden Neurofax 1200A Digital System with bipolar montage and a sampling rate of 2,000 Hz. Electrical stimulation was administered using the Nihon Kohden Cortical Stimulator (Model MS-120BK-EEG), a constant current device delivering rectangular pulses. The stimulation operated at a frequency of approximately 48 Hz and a pulse width of 0.3 ms. Biphasic waveforms were employed at each site, incorporating cathodic and anodic phases with alternating polarities. This design ensured symmetrical stimulation, with equal durations and amplitudes for both cathodic and anodic phases, resulting in an effective stimulation rate of approximately 24 Hz in one polarity and approximately 24 Hz in the opposite polarity. Each stimulation session had a duration of 3 s. Notably, no ground return was utilized during the stimulation process. Patients were queried about their experiences after each stimulation without knowing when the stimulation began or ended. The stimulation current commenced at 0.4 mA and incrementally increased until meeting one of the predefined criteria: the report of a hallucination or subjective sensation, the observation of a behavioral response, or reaching the maximum current threshold of 5 mA.

Stimulations that induced auditory verbal hallucinations were included in the study. In order to investigate the effect of “self-related hallucinations,” the hallucinations were first classified based on their association with the self. Hallucinations were labeled as “self-related” if the voices or content directly connected to the individual experiencing them, such as familiar voices (e.g. family members, teachers) or personally relevant information (e.g. discussions about seizures or surgery success rates). Conversely, hallucinations were classified as “other-related” if the voices or content were unrelated to the individual’s personal experiences, including voices from video games, unfamiliar individuals, or indistinct phrases. To differentiate the impact of self-relevance from the effects of clarity and familiarity, the clarity and familiarity of the auditory hallucinations was assessed. Hallucinations were categorized as “clear” if the content was easily understandable and memorable to the individual, with information that could be accurately described. Conversely, hallucinations were labeled as “unclear” if the content was vague, indistinct, or difficult to recall (Table 2). To determine familiarity, hallucinations were labeled as “familiar” if they were recognized and associated with known individuals, contexts, or experiences. This included voices of family members, friends, characters from media that the individual could identify, or even unknown voices that the individual felt familiar with. In contrast, hallucinations were labeled

Table 1. Demographic information.

Subject	Age	Gender	Identified Epileptogenic Zone
sub-1	24	Male	Supramarginal gyrus, Rostral middle frontal gyrus
sub-2	29	Female	Amygdala, Hippocampus
sub-3	21	Male	Amygdala, Hippocampus
sub-4	44	Female	Amygdala, Hippocampus
sub-5	15	Female	Insula, Precentral gyrus
sub-6	13	Male	Amygdala, Temporal pole
sub-7	38	Female	Fusiform gyrus

as “unfamiliar” when the voices or content were in unfamiliar languages, or the content was entirely new and unrelated to the person’s prior experiences (Table 2). Trials conducted at these sites with similar currents that did not result in auditory hallucinations were included in the no hallucination condition.

Data preprocessing and analyses

To locate the stimulation and recording sites, both post-implant CT scans and pre-implant T1-weighted structural MRI were co-registered to pre-implant CT scans in functional MRI of the brain software library (FSL) (Jenkinson et al. 2012) for each subject, and the contacts were located using the sEEG assistant (Narizzano et al. 2017) based on 3D Slicer (Fedorov et al. 2012). The midpoints of the two contacts where the electrical stimulus was applied or the electrical signal was recorded were then designated as the stimulation or recording sites. The sites were then projected to the nearest vertex using intracranial electrode visualization (iELVis) (Groppe et al. 2017) on the individual cortical surface obtained by FreeSurfer (Destrieux et al. 2010). The locations of the stimulation sites were determined using their nearest vertices based on the Desikan–Killiany Atlas (Desikan et al. 2006). Recording sites with obvious epileptic artifacts were first removed, and the remaining sites with nearest vertices located in either early auditory areas, including primary auditory cortex (A1), lateral belt (LBelt), medial belt (MBelt), para belt (PBelt), and retro-insular (RI), or auditory association areas, including auditory area 4 (A4), auditory area 5 (A5), temporal region A area 2 (TA2), superior temporal sulcus (STSdp, STSda, STSvp, and STSva), and superior temporal gyrus area A were designated as auditory recording sites based on the Human Connectome Project cortical parcellation (Glasser et al. 2016). Using a similar method, recording sites with nearest vertices located in the default mode network based on Yeo’s 7-network parcellation and not assigned as auditory recording sites were designated as default mode network recording sites (Yeo et al. 2011). For visualization, the coordinates of stimulation and recording sites were also converted into the montreal neurological institute (MNI) space using FreeSurfer and a standard cortical template was used.

To remove electrical stimulation artifacts, a template subtraction method based on unsupervised dictionary learning (Caldwell et al. 2020) was used. Specifically, we first performed a bipolar re-referencing of the continuous raw data. Next, raw data during electrical stimulation were epoched and the stimulation onset was assigned as time 0. Individual pulse artifacts induced by electrical stimulation within each of these epochs were then detected. A dictionary of artifact templates was learned using the Hierarchical Density-Based Spatial Clustering of Applications with Noise (HDBSCAN) algorithm (Campello et al. 2013). Then, by comparing each individual pulse artifact to the dictionary, their closest template can be determined. Finally, the recovered

signals were obtained by subtracting the closest template from the raw signals for each individual pulse artifact. Examples that encompass raw traces during the resting (−5 to −2 s relative to the stimulation onset), raw traces during electrical stimulation (−0.5 to 2.5 s relative to the stimulation onset), the recovered traces after template subtraction, and their respective spectrograms were shown in the Supplementary Material (Fig. S1).

The recovered signals were subjected to time-frequency analysis using Morlet wavelets (Frequency: 2–150 Hz, 5–42 cycles) to extract their components. Subsequently, we implemented a z-score baseline correction for each trial, utilizing a baseline time window spanning from 0.4 to 0.02 s before the stimulus. To remove electrical stimulation artifacts without introducing filtering artifacts, time-frequency data centered on multiples of 24 Hz were directly eliminated with a ± 2 Hz bandwidth. Recording sites with extreme high post-stimulus signals (average absolute event-related potentials (ERP) $> 30 \mu\text{V}$ in the 0.1 to 2.5 s range) were excluded. Power change, representing the difference between auditory hallucination and no hallucination conditions, was computed. The averaged power change was computed by grouping into four frequency bands (theta: 4–8 Hz; alpha: 8–14 Hz; beta: 14–30 Hz; gamma: 30–150 Hz) and averaged over time (0.1 to 2.5 s). Recording sites displaying extremely high power changes (average absolute power change > 10 in the 0.1 to 2.5 s range for the theta, alpha, beta, or gamma bands) were also excluded from the analysis. These steps were taken to analyze the time-frequency dynamics associated with auditory hallucinations, while ensuring artifact removal and capturing meaningful power changes in specific frequency ranges.

Statistical analyses

Statistical analyses were performed using custom MATLAB scripts. Mixed-design analysis of variance (ANOVA) was employed to compare stimulation currents between self-related and other-related hallucinations. Significance testing of post-stimulation power changes was conducted using a permutation test. Firstly, the averaged power change was computed by taking the difference between auditory hallucination and no hallucination conditions, and grouping it into four frequency bands. Subsequently, 1,000 permutations were generated by shuffling the data between auditory hallucination and no hallucination conditions, creating a null distribution of power changes. P-values were obtained by comparing the observed power changes to the null distribution, assigning a significance level of 0.001 to the most extreme observed changes. Similarly, to assess the significance of the difference in post-stimulation power changes between self-related and other-related hallucinations across all conditions, the difference in averaged power changes between these groups was computed. Permutations were performed by shuffling the data between self-related and other-related

Table 2. Details of electrical stimulation and subjective reports of auditory hallucinations.

No.	Subject	Stimulation location	Auditory hallucinations described by patients	Self-relevance	Familiarity	Clarity
1	sub-1	Right superior temporal	Heard my biology teacher saying in my left ear “the seizures are in the insula and frontal lobes”	Self-related	Familiar	Clear
2	sub-1	Right superior temporal	Heard a woman’s voice in my left ear, the voice was familiar, the content was not clear.	Other-related	Familiar	Unclear
3	sub-1	Right superior temporal	Heard a human voice in a video game that I used to play in my left ear.	Other-related	Familiar	Unclear
4	sub-1	Right superior temporal	Heard a human voice in a video game that I used to play in my left ear.	Other-related	Familiar	Unclear
5	sub-2	Left superior temporal	Heard a phrase, but don’t remember the content.	Other-related	Unfamiliar	Unclear
6	sub-2	Left superior temporal	Heard someone saying, “It’s out.”	Other-related	Unfamiliar	Clear
7	sub-2	Left superior temporal	Heard someone saying, “It’s out.”	Other-related	Unfamiliar	Clear
8	sub-3	Left superior temporal	Heard a woman speak with a familiar voice in Mandarin in my right ear, and the content was not clear.	Other-related	Familiar	Unclear
9	sub-3	Left superior temporal	Heard a woman speak with a familiar voice in Mandarin in my right ear, and the content was not clear.	Other-related	Familiar	Unclear
10	sub-3	Left superior temporal	Heard a woman speak with a familiar voice in Mandarin in my right ear, and the content was not clear.	Other-related	Familiar	Unclear
11	sub-3	Left superior temporal	Heard a woman I didn’t know speak in Mandarin in my right ear, and the content was not clear.	Other-related	Unfamiliar	Unclear
12	sub-4	Left superior temporal	Heard a woman’s voice in my right ear, the content was not clear.	Other-related	Unfamiliar	Unclear
13	sub-4	Left superior temporal	Heard a woman saying in my right ear, “What is the job?”	Other-related	Unfamiliar	Clear
14	sub-4	Left superior temporal	Heard two people talking, the content was not clear.	Other-related	Unfamiliar	Unclear
15	sub-4	Left superior temporal	Heard a woman’s voice in my right ear, the content was not clear.	Other-related	Unfamiliar	Unclear
16	sub-5	Right superior temporal	Heard my father’s voice in my left ear, the content was not clear	Self-related	Familiar	Unclear
17	sub-5	Right superior temporal	Heard my younger brother’s voice in my left ear, the content was not clear	Self-related	Familiar	Unclear
18	sub-5	Right superior temporal	Heard my grandmother’s voice in my left ear, the content was not clear	Self-related	Familiar	Unclear
19	sub-5	Right superior temporal	Heard my younger brother and my grandmother’s voice, the content was not clear	Self-related	Familiar	Unclear
20	sub-6	Right middle temporal	Heard the phrase: “What the hell do you want to do”	Self-related	Unfamiliar	Clear
21	sub-6	Right middle temporal	Heard a family member or someone on TV saying, “What the hell do you want to do? Are you still yourself?”	Self-related	Familiar	Clear
22	sub-7	Left fusiform	Heard Prof. Wang (one of the attending doctors) saying, “The success rate of this surgery is . . . , you should accept the treatment.”	Self-related	Familiar	Clear

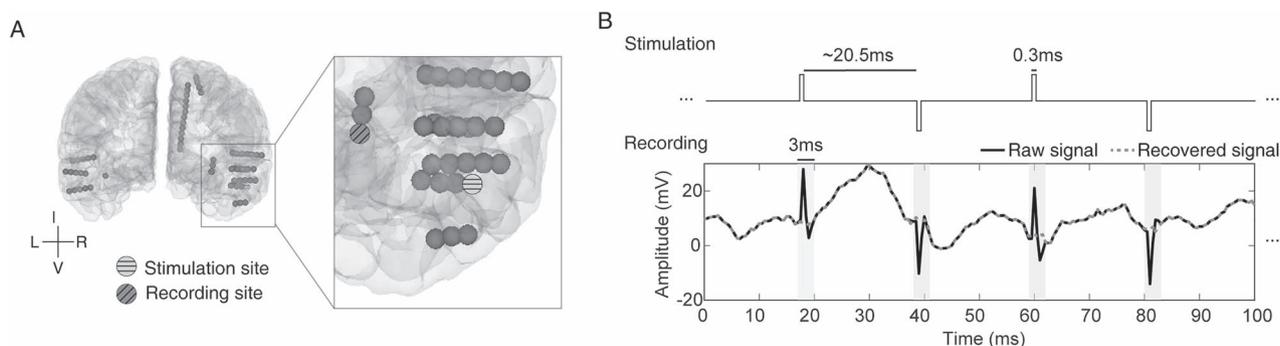


Fig. 1. Electrical stimulation and intracranial recording. (A) It shows the visualization of a stimulation site and a recording site from one example subject. Note that the stimulation and recording sites do not indicate the exact location of the electrode contacts, but rather the midpoint of the two contacts where the electrical stimulation was applied or the electrical signals were recorded. L: Left; R: Right; D: Dorsal; V: Ventral. (B) It shows examples of the electrical stimulation profile, the recorded raw signal, and the recovered signal. The electrical stimulation profile illustrates the voltage difference between two concurrently stimulated contacts. The recovered signal was extracted by removing the artifacts of the electrical stimulation in the artifact window (gray).

hallucinations for 1,000 times, generating a null distribution of power changes. *P*-values were calculated by comparing the observed differences to the null distribution. A statistic was considered significant if it exceeded the 95th percentile of the null hypothesis distribution ($\alpha = 0.05$) and underwent false discovery rate (FDR) correction.

Results

Within the context of pre-surgical evaluations carried out for clinical purposes, patients who had undergone intracranial recording procedures were specifically queried regarding their perceptual experiences during electrical stimulations. In the present study, aimed at investigating auditory hallucinations and their neural underpinnings in terms of self-relevance, we included seven patients who reported experiencing auditory verbal hallucinations subsequent to electrical stimulation. During the application of electrical stimulation to designated stimulation sites, resulting in the generation of auditory verbal hallucinations, simultaneous recording of brain signals took place at recording sites (Fig. 1A). The stimulations were administered at a rate of approximately 24 Hz in one polarity and approximately 24 Hz in the opposite polarity, which introduced electrical stimulation artifacts in the recording sites. These artifacts were then mitigated to extract the recording site signal using the HDBSCAN algorithm (Campello et al. 2013) (Fig. 1B). Among the patients, a total of 22 stimulations targeting the superior temporal area and fusiform area successfully induced auditory verbal hallucinations at critical current levels (Fig. 2A). To facilitate comparison, trials with lower yet comparable stimulation currents that did not induce auditory hallucinations were employed as the “no hallucination” condition. Based on the content of the hallucinations or the identity of the voices, the hallucinations induced at different stimulation sites were further classified as either self-related ($n = 8$) or other-related ($n = 14$). In instances where patients reported which ear they heard the hallucinations, the experience was contralateral to the hemisphere of stimulation (for example, stimulation at the left superior temporal area resulted in hallucinations being heard in the right ear).

Due to variations in stimulation currents between auditory hallucination and no hallucination conditions across different stimulation sites, it is plausible that these currents might contribute to the observed differences in neural activity between self-related and other-related hallucinations. To address this potential

confounding factor, we conducted a mixed-design ANOVA on the stimulation currents. The within-factor of the ANOVA compared auditory hallucination conditions with no hallucination conditions, while the between-factor compared self-related hallucinations with other-related hallucinations. The results indicated a significant main effect for auditory hallucination versus no hallucination ($F(1, 20) = 212.743, P = 4.029 \times 10^{-12}$), indicating a difference in stimulation currents between the two conditions. Importantly, there was no significant main effect for self-related versus other-related hallucinations ($F(1, 20) = 2.341, P = 0.141$), and no interaction effect was observed ($F(1, 20) = 0.253, P = 0.620$) (Fig. 2B). These findings suggest that any observed effects related to self-relevance in auditory hallucinations cannot be attributed to differences in stimulation currents between the self-related and other-related conditions.

Self-related auditory hallucinations correlate with alpha and gamma power change in the default mode network

Given that there were no significant differences in stimulation currents between self-related and other-related hallucinations, we conducted a direct comparison of post-stimulation power changes within the default mode network. These power changes were quantified as the difference in neural oscillatory power between auditory hallucination and no hallucination conditions. A total of 308 recordings were collected during auditory hallucination conditions, along with an equal number of 308 recordings during no hallucination conditions, all from recording sites within the default mode network. Among the auditory hallucination conditions, 58 recordings were associated with self-related hallucinations, while 250 recordings were associated with other-related hallucinations. All the recording sites in the DMN are illustrated in Fig. 3A.

As patients were questioned about their experiences after each stimulation session, the exact onset and offset of hallucinatory experiences remained uncertain. Consequently, our initial analysis focuses on the power changes throughout the entire stimulation period (from 0.1 to 2.5 s after the stimulation onset), excluding only segments containing noticeable stimulation onset or offset artifacts. Using a permutation test, we observed significant results in different frequency bands. In the theta and alpha bands, the post-stimulation power changes were significantly negative for other-related hallucinations (theta-band: $M = -0.723 \pm 0.132$, mean \pm SEM, $P = 0.006$; alpha-band:

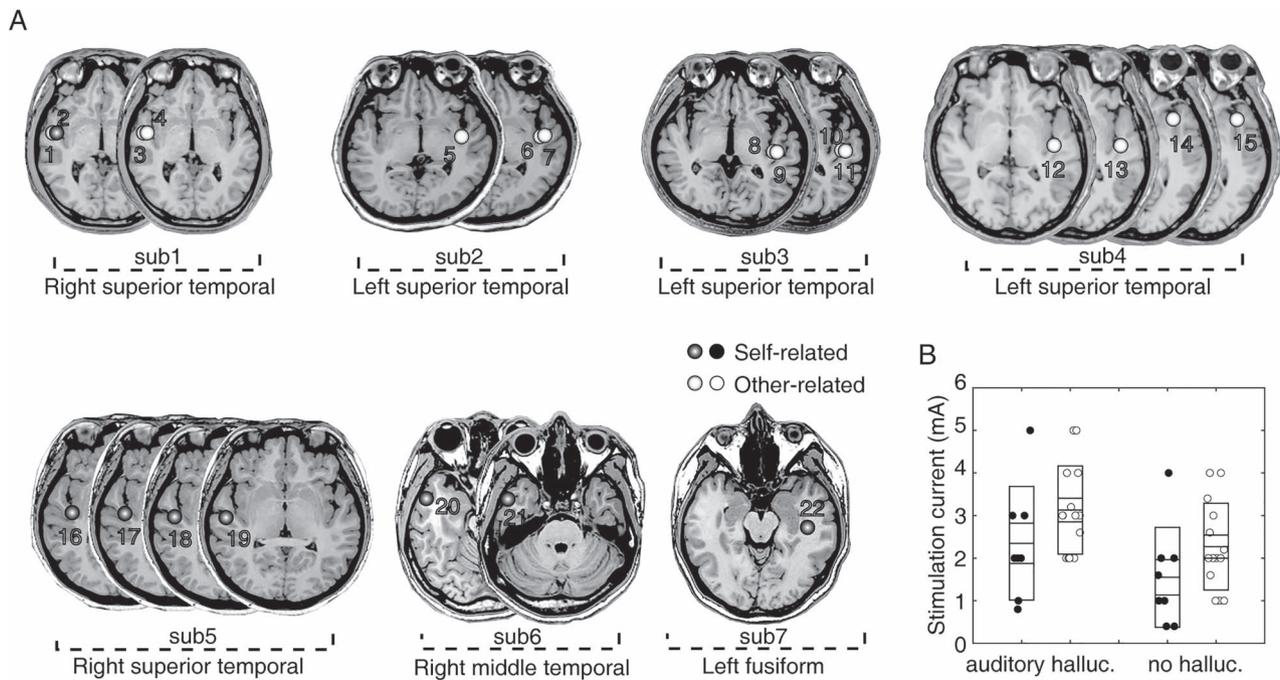


Fig. 2. (A) Location of the stimulation site. It shows all stimulation sites mapped on individual brains for self-related and other-related auditory hallucinations. The no hallucination condition included trials without hallucinations but with a similar stimulation current. No stimulation sites induced both self- and other-related hallucinations. The stimulation sites do not indicate the exact location of the electrode contacts, but rather the midpoint of the two contacts where the electrical stimulation was applied. (B) It shows the stimulation currents at these sites in the auditory hallucination and no hallucination conditions.

$M = -0.687 \pm 0.087$, $P = 0.001$, FDR corrected), but not for self-related hallucinations (theta-band: $M = -0.475 \pm 0.221$, $P = 0.265$; alpha-band: $M = 0.774 \pm 0.220$, $P = 0.080$; Fig. 3B). In the beta and gamma frequency bands, the power changes for self-related or other-related hallucinations did not show significant results ($P > 0.05$, Fig. 3B).

Crucially, the power changes observed in self-related hallucinations were significantly greater in the alpha ($M = 1.462 \pm 0.152$, $P = 0.001$, FDR corrected) and gamma bands ($M = 0.507 \pm 0.085$, $P = 0.018$, FDR corrected) compared to other-related hallucinations, indicating a significant functional role of oscillatory power within the default mode network during self-related auditory hallucinations (Fig. 3B). The time-frequency map of the power changes, depicted in Fig. 3C, revealed a broadband and persistent increase in activity in the gamma and alpha band oscillations for self-related hallucinations compared to other-related hallucinations in the default mode network. Figure 3D further illustrates the comparison of power changes over time between self-related and other-related hallucinations, providing additional insights into the temporal dynamics of these power changes. These findings highlight the involvement of specific oscillatory patterns and their differential modulation in the processing of self-related auditory information within the default mode network.

To ensure that observed effects were not solely due to subject-related variance, we conducted several additional analyses. Firstly, we focused on Subject 1, who uniquely experienced both self-related and other-related hallucinations. Subject 1 contributed 7 recordings for self-related auditory hallucinations and 15 recordings for other-related auditory hallucinations. Our comprehensive analysis of this subject revealed a significant increase in power changes within the alpha frequency band for self-related auditory hallucinations compared to other-related auditory hallucinations (mean \pm SEM: 3.509 ± 0.663 ; $P = 0.007$,

FDR corrected, see Fig. S2). Conversely, no significant differences in power changes were observed within the theta, beta, and gamma bands when comparing self-related to other-related hallucinations (all P s > 0.05). Additionally, to address subject-related variance comprehensively, we employed Linear Mixed Model (LMM) analyses. Specifically, we designed and compared two models to scrutinize the impact of subject-related variance on the “self-relevance” effect for both alpha-band and gamma-band power changes. One model exclusively considered the variation in power change related to subject-related variance, while the other model extended the analysis to encompass both subject-related variance and self-relevance (see Supplementary Material). The model comparison indicated a significant difference or a trend of significance between the two models in the alpha band ($\chi^2(1) = 9.517$, $P = 0.002$) and in the gamma band ($\chi^2(1) = 3.423$, $P = 0.064$).

To further investigate the temporal dynamics of the observed effect, we segmented the entire time span (0.1 to 2.5 s) into four segments: 0.1–0.7, 0.7–1.3, 1.3–1.9, and 1.9–2.5 s. Applying the same statistical analysis methods to each segment, we assessed the differences in power changes between self-related and other-related auditory hallucinations. Notably, we observed significantly higher power changes in the alpha band between 1.3–1.9 s ($M = 2.187 \pm 0.184$, $P = 0.001$; FDR corrected) and 1.9–2.5 s ($M = 1.323 \pm 0.212$, $P = 0.014$; FDR corrected), as well as in the gamma band between 1.3–1.9 s ($M = 0.599 \pm 0.089$, $P = 0.005$; FDR corrected) and 1.9–2.5 s ($M = 0.577 \pm 0.089$, $P = 0.017$; FDR corrected) during self-related hallucinations compared to other-related hallucinations (Fig. S3). No significant differences in power changes for the theta and beta bands were observed in all time segments (all P s > 0.05).

To explore whether the observed effects were consistent across all DMN subregions, we visually examined the recording

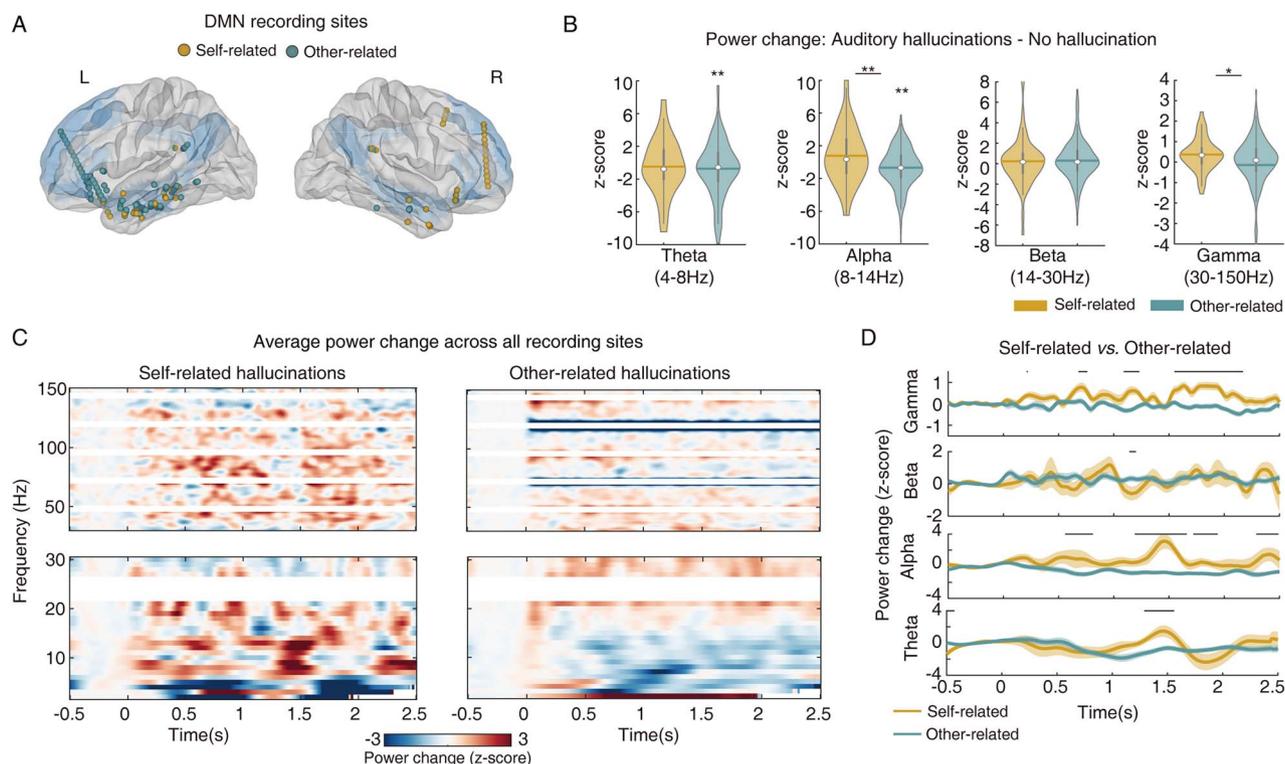


Fig. 3. (A) Visualization of all recording sites within the default mode network mapped on a standard average brain, representing self-related and other-related auditory hallucinations. Note that the recording sites do not indicate the exact location of the electrode contacts, but rather the midpoint of the two contacts where the electrical signals were recorded. (B) Comparison of the average power change in theta (4–8 Hz), alpha (8–14 Hz), beta (14–30 Hz), and gamma (30–150 Hz) bands between self-related and other-related auditory hallucinations. (C) Time-frequency results displaying the average power changes for self-related and other-related auditory hallucinations across all recording sites in the DMN. (D) Comparisons of average power changes over time between self-related and other-related auditory hallucinations across all recording sites in the DMN. Time point 0 corresponded to the initiation of electrical stimulation. Time points with a significance level of $P < 0.05$ (uncorrected) between the two categories are indicated by the horizontal black bar for visualization purposes. Shaded areas and error bars represent ± 1 standard error. L: Left hemisphere; R: Right hemisphere. * $P < 0.05$; ** $P < 0.01$ (FDR corrected).

sites within the DMN and divided it into five subregions (see Table S1 and Fig. S4): mPFC, ventrolateral prefrontal cortex (vlPFC), temporoparietal junction (TPJ), temporal cortex (TC), and posteromedial cortex (PMC). PMC was excluded from our analysis due to the limited number of recording sites. For the remaining four subregions, we employed LMM analyses and designed and compared two models: one considering only the fixed effect of self-relevance, and the other extending the analysis to include the fixed effects of both self-relevance and subregions. Model comparison results revealed a significant difference between the two models in the gamma band ($\chi^2(3) = 14.995$, $P = 0.002$), but not in the alpha band ($\chi^2(3) = 6.042$, $P = 0.109$). To further elucidate the effect profiles in different subregions, we conducted direct comparisons of post-stimulation power changes in the theta, alpha, beta, and gamma bands within the mPFC, vlPFC, TPJ, and TC (Fig. S5). The results revealed that, compared to other-related hallucinations, self-related hallucinations exhibited significantly greater power changes in the alpha band ($M = 1.804 \pm 0.368$, mean \pm SEM; $P = 0.019$, FDR corrected) and the gamma band ($M = 0.564 \pm 0.093$, $P = 0.003$, FDR corrected) in the mPFC. However, no significant differences were observed in the vlPFC and TC in either the alpha or gamma band (all P s > 0.05). In the TPJ, power changes in self-related hallucinations were significantly greater in the alpha band ($M = 3.574 \pm 0.680$, $P = 0.012$, FDR corrected) but not in the gamma band ($P > 0.05$). Notably, there were no significant differences in the theta and beta bands across all subregions, with the exception of the beta band power change

in the TC ($M = -1.236 \pm 0.156$, $P = 0.011$, FDR corrected). These findings suggest a degree of consistency in the observed effects across all DMN subregions in the alpha band, whereas such consistency was not evident in the gamma band.

Exclusion of familiarity as confounding factors in the effects of self-related hallucinations

To address the potential confounding factor of familiarity in the effects of self-related hallucinations, we conducted a control analysis. The classification of “self-related hallucinations” is primarily based on the direct connection of voices or content to the individual experiencing the auditory hallucinations. Nevertheless, there is a possibility of overlap with the concept of familiarity, which could influence the observed outcomes. To account for this, we carefully labeled hallucinations as “familiar” ($n = 13$) if they were recognized and associated with known individuals, contexts, or experiences or “unfamiliar” ($n = 9$) if they were not (see Table 2). This allowed us to specifically compare self-related and other-related hallucinations within the context of familiarity and examine whether the observed results remained consistent. By focusing on auditory hallucinations that evoked a sense of familiarity, we aimed to determine if the factor of familiarity significantly contributed to the observed outcomes. By conducting this control analysis, the potential confound of familiarity was effectively mitigated, thereby enhancing the validity of the findings. For the control analysis, a total of 139 recordings were obtained during familiar auditory hallucination conditions, with an equal number

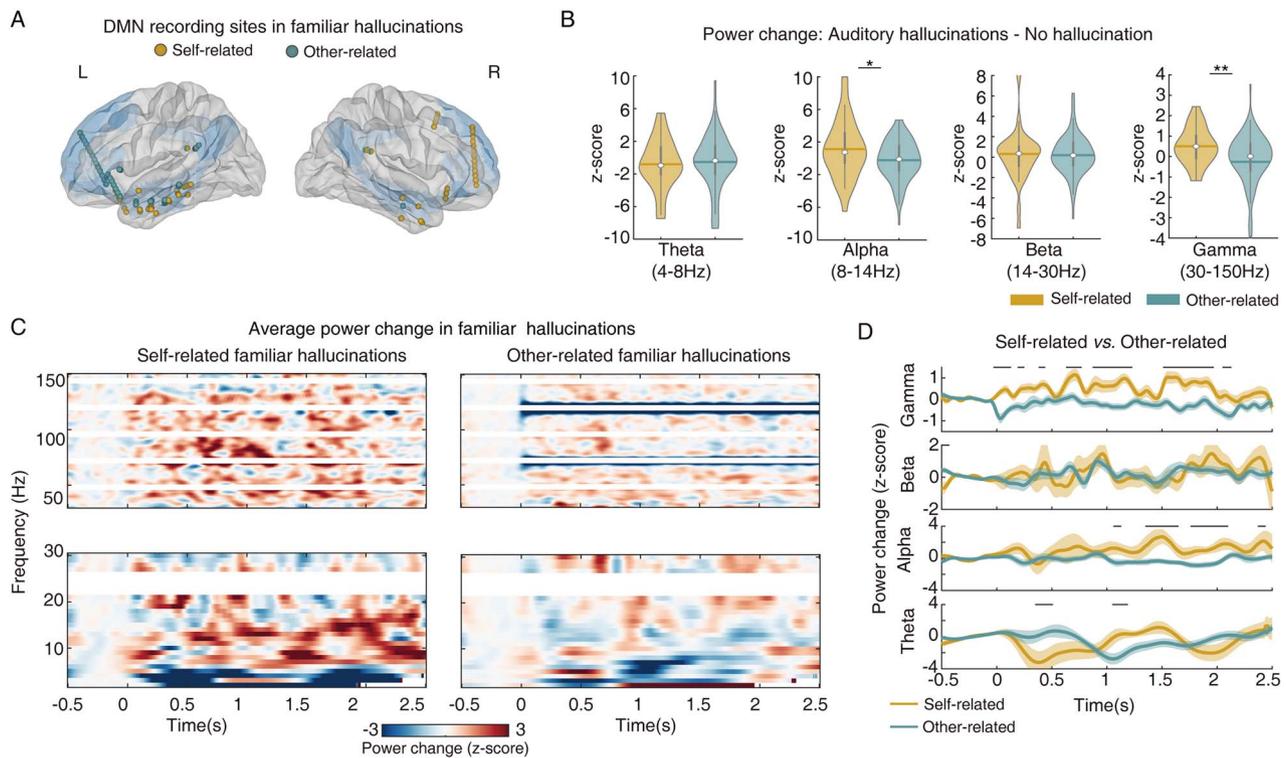


Fig. 4. (A) Visualization of all recording sites within the default mode network mapped on a standard average brain, illustrating self-related familiar and other-related familiar auditory hallucinations. Note that the recording sites do not indicate the exact location of the electrode contacts, but rather the midpoint of the two contacts where the electrical signals were recorded. (B) Comparison of the average power change in theta (4–8 Hz), alpha (8–14 Hz), beta (14–30 Hz), and gamma (30–150 Hz) bands between self-related familiar and other-related familiar auditory hallucinations. (C) Time-frequency results depicting the average power changes for self-related familiar and other-related familiar auditory hallucinations within the DMN during familiar hallucinations. (D) Comparative analysis of average power changes over time between self-related familiar and other-related familiar auditory hallucinations within the DMN during familiar hallucinations. Time point 0 corresponded to the initiation of electrical stimulation. Time points with a significance level of $P < 0.05$ (uncorrected) between the two categories are indicated by the horizontal black bar for visualization purposes. Shaded areas and error bars represent ± 1 standard error. L: Left hemisphere; R: Right hemisphere. * $P < 0.05$; ** $P < 0.01$ (FDR corrected).

of 139 recordings during no hallucination conditions, all extracted from recording sites within the default mode network. Among the auditory hallucination conditions, 36 recordings were linked to self-related hallucinations, while 103 recordings were associated with other-related hallucinations (Fig. 4A).

Employing a similar statistical approach, we investigated and compared the post-stimulation power changes within the default mode network for familiar auditory hallucinations. The results revealed no significant power change in the theta, alpha, beta, and gamma bands for either self-related familiar or other-related familiar hallucinations (all P s > 0.05). Notably, power changes during self-related familiar hallucinations were significantly higher in the alpha ($M = 1.361 \pm 0.238$, $P = 0.013$, FDR corrected) and gamma bands ($M = 0.761 \pm 0.121$, $P = 0.008$, FDR corrected) compared to other-related familiar hallucinations (Fig. 4B). The time-frequency results (Fig. 4C) and time-resolved comparison (Fig. 4D) exhibited a consistent pattern, similar to the comparison between self-related and other-related hallucinations depicted in Fig. 3. To further account for the influence of self-relevance, particularly when incorporating the variable of familiarity, LMM analyses were employed. Specifically, we formulated and compared two models for both alpha-band and gamma-band power changes (see Supplementary Material). One model exclusively considered the variation in power change related to the fixed-effect variable familiarity, while the other model extended the analysis to include both the fixed-effect variables familiarity and self-relevance. The model comparison revealed

a significant difference or a trend of significance between the two models in the alpha band ($\chi^2(1) = 9.260$, $P = 0.002$) and the gamma band ($\chi^2(1) = 3.545$, $P = 0.059$). These findings indicate that, even after excluding the influence of familiarity, oscillatory power in the alpha and gamma bands within the default mode network continues to play a crucial role in generating self-related hallucinations. Thus, we can exclude familiarity as a confounding factor in the effects of self-related hallucinations, further supporting the notion that self-related processes have distinct neural underpinnings in the default mode network.

Exclusion of clarity as confounding factors in the effects of self-related hallucinations

In addition, we considered the potential impact of clarity on self-related auditory hallucinations. Since self-related hallucinations are directly connected to the experiencing individual, they may involve more recognizable content. This raised concerns about potential overlap with clarity, as clearer hallucinations might be more easily recognized and associated with the self, potentially biasing the results. In order to disentangle the influence of self-relevance from the effects of clarity, the hallucinations were further categorized based on whether they were clear ($n = 7$) or unclear ($n = 15$) (see Materials and Methods, Table 2). Then, we conducted a comprehensive control analysis focusing on two distinct categories of auditory hallucinations: self-related clear hallucinations and other-related clear hallucinations, within the

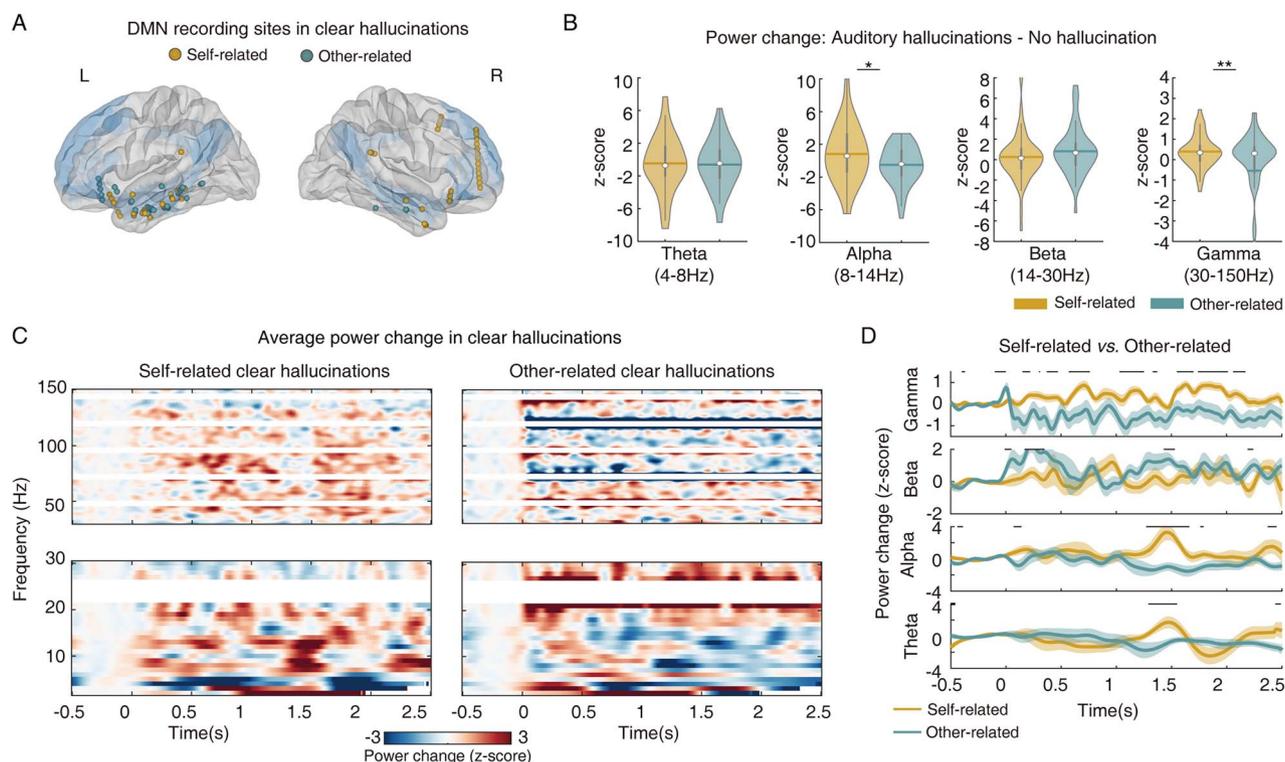


Fig. 5. (A) Visualization of all recording sites within the default mode network mapped on a standard average brain, depicting self-related clear and other-related clear auditory hallucinations. Note that the recording sites do not indicate the exact location of the electrode contacts, but rather the midpoint of the two contacts where the electrical signals were recorded. (B) Comparison of the average power change in theta (4–8 Hz), alpha (8–14 Hz), beta (14–30 Hz), and gamma (30–150 Hz) bands between self-related clear and other-related clear auditory hallucinations. (C) Time-frequency results depicting the average power changes for self-related clear and other-related clear auditory hallucinations within the DMN during clear hallucinations. (D) Comparative analysis of average power changes over time between self-related clear and other-related clear auditory hallucinations across all recording sites within the DMN during clear hallucinations. Time point 0 corresponded to the initiation of electrical stimulation. Time points with a significance level of $P < 0.05$ (uncorrected) between the two categories are indicated by the horizontal black bar for visualization purposes. Shaded areas and error bars represent ± 1 standard error. L: Left hemisphere; R: Right hemisphere. * $P < 0.05$; ** $P < 0.01$ (FDR corrected).

default mode network. By examining hallucinations that are both self-related and clearly recognized, we aimed to isolate the specific contribution of self-relevance in auditory perception, while excluding the potential influence of content clarity. A total of 106 recordings were obtained during clear auditory hallucination conditions, along with an equal number of 106 recordings during no hallucination conditions. Among the clear auditory hallucinations, 55 recordings corresponded to self-related clear hallucinations and 51 recordings corresponded to other-related clear hallucinations (Fig. 5A and Table 2).

Utilizing a similar statistical approach, we examined and compared post-stimulation power changes within the default mode network for clear auditory hallucinations. The analysis revealed no significant power changes in the theta, alpha, beta, or gamma band for either self-related clear or other-related clear hallucinations (all P s > 0.05). Notably, there were significantly greater power changes in the alpha ($M = 1.334 \pm 0.294$, $P = 0.023$, FDR corrected) and gamma bands ($M = 0.938 \pm 0.179$, $P = 0.008$, FDR corrected) during self-related clear hallucinations compared to their other-related counterparts (Fig. 5B). The time-frequency results (Fig. 5C) and the time-resolved comparison (Fig. 5D) exhibited a similar pattern as the comparison between self-related and other-related hallucinations illustrated in Fig. 3. To further address the potential influence of self-relevance, especially when considering the variable of clarity, we employed LMM analyses. We formulated and compared two models for both alpha-band and gamma-band power changes (see Supplementary Material). One model

exclusively considered the variation in power change related to the fixed-effect variable clarity, while the other model extended the analysis to include both the fixed-effect variables clarity and self-relevance. The model comparison revealed a statistically significant difference between the two models in both the alpha band ($\chi^2(1) = 4.259$, $P = 0.039$) and the gamma band ($\chi^2(1) = 6.841$, $P = 0.008$). This suggests distinct neural underpinnings of self-related processes in auditory perception, even after excluding the potential confounding factor of content clarity.

Through this rigorous control analysis, we effectively ruled out clarity as a confounding factor in the observed effects of self-related hallucinations. These findings provide compelling evidence supporting the notion that oscillatory power in the alpha and gamma bands within the default mode network plays a critical functional role in generating self-related auditory hallucinations. The exclusion of clarity as a confounding factor enhances the validity and robustness of our previous results and highlights the unique neural mechanisms associated with self-related processes in auditory perception.

Discussion

In order to investigate the neural oscillatory mechanisms underlying self-related auditory perception, we collected data from a total of seven patients who experienced auditory verbal hallucinations following electrical stimulation. In line with recent investigations in electrical stimulation-induced auditory

hallucinations (Jaroszynski et al. 2022), our study observed successful induction of auditory verbal hallucinations through targeted stimulation of the superior temporal area and fusiform area, with the perceived hallucinations manifesting contralateral to the hemisphere of stimulation. In total, we recorded and categorized 22 instances of hallucinatory experiences, distinguishing between self-related and other-related conditions. By comparing changes in neural oscillatory power within the DMN between self-related and other-related auditory hallucinations, our findings indicate significant increases in power changes in the alpha and gamma frequency bands during self-related hallucinations compared to other-related ones. To validate our primary results, we conducted controlled analyses for factors of familiarity and clarity, revealing that the observed effects within the DMN remain independent of these factors. Our results underscore the significant functional role of alpha and gamma oscillatory power within the DMN during the processing of self-related auditory hallucinations.

Existing literature has extensively established the DMN's engagement in self-reference tasks (Gillihan and Farah 2005; Qin and Northoff 2011; Kolvoort et al. 2020; Qin et al. 2020). For instance, previous positron emission tomography studies have demonstrated heightened activity in the medial frontal area when participants engaged in self-reflection upon trait adjectives, as opposed to considering traits of others or unrelated topics (Craik et al. 1999; D'Argembeau et al. 2005). Correspondingly, earlier fMRI investigations, alongside recent replications with different techniques, have consistently highlighted the increased activation of both the mPFC and the PCC during judgments involving self-related or other-related trait adjectives (Heatherston et al. 2006; Whitfield-Gabrieli et al. 2011; Lipsman et al. 2014; Davey et al. 2016; Wolff et al. 2018; Wen et al. 2020; Levorsen et al. 2023; Wolman et al. 2023). Transcranial magnetic stimulation research has indicated that transient interference with PCC function impairs the recall of items encoded with self-relevance (Lou et al. 2004). In a singular-case lesion study, a patient with extensive damage to the medial prefrontal areas demonstrated significant deficits in the accuracy and consistency of personal trait knowledge, with no analogous impact on knowledge of other individuals' traits (Marquine et al. 2016). A three-layer topographic model of self was also constructed based on the empirical findings (Qin et al. 2020). Building upon these discoveries and capitalizing on the exceptional occasion to simultaneously administer electrical stimulation and record neural activity in human subjects, our study has definitively validated the DMN's role in processing self-related information while unveiling its distinct oscillatory profile.

In intracranial studies, the involvement of the DMN gamma band neural oscillations in self-related processes remains a topic of debate. For instance, investigations focusing on the human PMC have demonstrated that self-episodic statements (e.g. "I used a computer today") and self-semantic statements (e.g. "I use a computer often") elicit a significantly higher gamma response compared to rest conditions and math tasks (Dastjerdi et al. 2011; Foster et al. 2012). However, no significant increase in gamma activity was observed for self-judgment statements (e.g. "I am smart") when compared to rest conditions or math tasks. Similarly, a recent electrocorticography study revealed that judgments related to self or others did not show differences in high-frequency broadband power, but distinct differences in peak and offset latencies were observed, with other-mentalizing evoking significantly later responses than self-mentalizing across

the entire DMN (Tan et al. 2022). Our current study contributes to this body of knowledge by showing a significant increase in gamma activity during self-related auditory verbal hallucinations compared to other-related auditory verbal hallucinations. Given that auditory verbal hallucinations involve the perception of hearing voices or sounds that are not present in the external environment, memory processes may play a role. Memories of past conversations, experiences, or inner dialogues could potentially contribute to the auditory verbal hallucinations (West 1962; Jones 2010; Northoff and Qin 2011; Northoff 2014; Alderson-Day et al. 2016; Wengler et al. 2020). Thus, it is plausible that some form of memory activation, which may not necessarily be true memory, serves as a prerequisite for gamma band neural activity in self-related processes.

Furthermore, our research has unveiled a distinct and significant role played by alpha-band oscillations within the DMN in processes closely tied to the self. Electroencephalography (EEG) studies have demonstrated the specialized function of alpha waves in self-referential cognitive tasks. To illustrate, when comparing traits related to oneself versus those related to others, the activation of self-referential traits was linked to a heightened synchronization of alpha-band activity specifically centered over the central brain region (Mu and Han 2010). In a different vein, investigations have indicated that the anticipatory alpha-band activity within the lower frequency range (8–9 Hz) was observed prior to the presentation of stimuli that participants perceived as deeply self-associated (Bai et al. 2016). Additionally, the realm of alpha band oscillations has been linked to the creation of illusory self-location induced by virtual reality scenarios (Lenggenhager et al. 2011). Nonetheless, the inherent limitations of EEG in spatial resolution make it challenging to pinpoint the precise source of such alpha-band responses. In our current study, leveraging the capabilities of intracranial recordings that provide both high temporal and spatial resolutions, we have identified increased alpha-band oscillations during instances of self-related auditory hallucinations within the DMN. These findings strongly imply a distinctive role for DMN alpha-band activity in processes involving the self. In conjunction with the observed increased gamma band activity in the DMN, our results propose a positive correlation between alpha and gamma-band activity within the DMN during self-related processes. Notably, considering the robust connection between gamma-band activity and BOLD signals (Conner et al. 2011; Han et al. 2023), this aligns with a study revealing that transcranial stimulation of alpha oscillations using high-definition alpha-frequency transcranial alternating current stimulation resulted in increased BOLD activity within the DMN (Clancy et al. 2022).

Various theoretical frameworks propose distinct neural networks' involvement in processing self-related stimuli (Humphreys and Sui 2016). However, recent alternative perspectives challenge this notion, suggesting that self-processing might not rely on specialized mechanisms, but instead emerge from domain-general cognitive processes (Golubickis and Macrae 2023). They posit that rather than recruiting specialized mechanisms, the self may leverage domain-general cognitive processes. For instance, self-related processes could capitalize on top-down signals from the prefrontal and parietal cortices, known to enhance the processing of task-relevant stimuli (Buschman and Kastner 2015). The phenomenon of self-prioritization might find its explanation in the engagement of the frontoparietal attentional system (Dixon et al. 2018). While our study's findings did not provide direct evidence for distinct neural networks in self-related

processes, they did reveal a departure from the expected top-down attentional network pattern. Specifically, our study identified a noteworthy increase in gamma band neural oscillations in DMN during self-related auditory hallucinations. This contradicts the anticipated correlation between top-down control and reduced DMN activity (Miller et al. 2009). Moreover, it is noteworthy that a reduction in alpha-band power traditionally signifies heightened attentional engagement (Klimesch et al. 1998). Contrarily, in the context of self-related processes, we observed an augmentation in alpha band activity. This evidence leads us to propose that self-related processes involve a more complex mechanism than the conventional top-down attentional control.

This study does have some limitations and potential factors that should be taken into consideration. Several of these limitations are connected to the method of intracranial recording used in the research. These encompass the utilization of participants with epilepsy, resulting in inconsistent brain coverage across the participant cohort. Furthermore, the application of electrical stimulation led to the emergence of electrical artifacts. Although we took measures to address these limitations and minimize their impact on our results, they could not be entirely eliminated. To enhance the credibility of our findings, it would be valuable to replicate the study using healthy participants, leveraging the latest advancements in source-space EEG/magnetoencephalography (MEG) techniques. In addition, it is noteworthy that, apart from subject 1, the instances of auditory verbal hallucinations were predominantly self-related or other-related in nature. This circumstance necessitated the utilization of a fixed-effect style analysis, which, by its very design, carries limitations on generalizability, confining our conclusions to the specific conditions and participant cohorts examined in this study. Moreover, the results from Subject 1, while aligning with our primary findings in the alpha band, diverged in the gamma band. The precise reason for this discrepancy remains uncertain and may be attributed to the possible absence of an effect in the gamma band or the limited sample size, leading to reduced statistical power. These limitations may stem from the rarity of our dataset, where, among 62 cases in our patient pool, only seven individuals reported auditory hallucinations. Notably, out of approximately 900 stimulations conducted within this subset, auditory hallucinations were elicited in only 22 instances. Nevertheless, it is essential to investigate self-related versus other-related hallucinations in individual subjects for a deeper understanding in future research. Throughout the study, rigorous attempts were made to control for potential confounding variables. Notably, demographic factors such as age and gender exhibited no significant differences among participants (data not shown). Stimulation currents were similar between the self-related and other-related hallucinations and the absence of auditory or visual stimuli during electrical stimulation ruled out bottom-up stimulus discrepancies as contributors to the observed results. Factors related to familiarity and clarity were also carefully controlled. Despite these efforts, it's important to recognize that certain uncontrolled confounding variables might still impact the results. Given the nature of the data, achieving perfect matching of all relevant factors is nearly impossible. For instance, modulation occurs from the amygdala and hippocampus to the DMN (Marek et al. 2013; Kaplan et al. 2016). Signals from these areas have the potential to interfere with DMN activity. Consequently, variables such as autobiographical memory may conceivably influence the observed self-related effect.

In summary, employing electrical stimulation and intracranial recordings in humans, we explored how the DMN contributes to

generating and processing self-related auditory perception. Our results reveal that self-related hallucinations exhibit stronger positive power changes in both alpha and gamma oscillations compared to other-related hallucinations within the DMN. These findings not only offer novel insights into the DMN's role in self-related processes but also shed light on the relationship between self-related perception and neural oscillatory activity.

Author contributions

Jing Yang (Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Visualization, Writing—original draft), Lu Shen (Investigation, Methodology, Project administration), Qiting Long (Data curation, Methodology), Wenjie Li (Formal analysis, Investigation), Wei Zhang (Data curation, Investigation, Supervision) Qi Chen (Funding acquisition, Methodology, Resources, Supervision), and Biao Han (Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing—original draft, Writing—review & editing)

Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

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