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# The Neurodynamic Organization of Modality-Dependent Hallucinations

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**The pathophysiology of hallucinations remains mysterious. This research aims to specifically explore the interaction between hallucinations and spontaneous resting-state activity. We used multimodal magnetic resonance imaging during hallucinations occurrence in 20 drug-free adolescents with a "brief psychotic disorder." They were furthermore compared with 20 matched controls at rest or during exteroceptive stimuli. Anatomical and functional symptom-mapping demonstrated reduced cortical thickness and increased blood oxygen level–dependent signal in modality-dependent association sensory cortices during auditory, visual, and multisensory hallucinations. On the contrary, primary-sensory-cortex recruitment was not systematic and was shown to be associated with increased vividness of the hallucinatory experiences. Spatiotemporal activity patterns in the default-mode network (DMN) during hallucinations and symptom-free periods in patients were compared with patterns measured in healthy individuals. A disengagement of the DMN was concomitant to hallucinations, as for exogenous stimulations in healthy participants. Specifically, spatial and temporal instabilities of the DMN correlated with the severity of hallucinations but persisted during symptom-free periods. These results suggest that hallucinatory experiences emerge from a spontaneous DMN withdrawal, providing a convincing model for hallucinations beyond the auditory modality.**

**Keywords:** adolescents, connectivity, cortical thickness, default-mode network, fMRI, hallucinations

## Introduction

Hallucinations are erroneous perceptions in the absence of identifiable external stimuli (Ey 1973). In schizophrenia, hallucinations are essentially explored verbally despite the fact that patients frequently have high rates of hallucinations across all sensory modalities, in adult- and early-onset disorders (Bracha et al. 1989; David et al. 2011). Anatomical and functional disturbances in sensory cortices have been proposed to be centrally involved in their pathogenesis (Allen et al. 2008; Jardri et al. 2011). However, sensory pathway lesion models poorly explain the phasic course of hallucinatory episodes. In particular, lesion theories account for persistent symptoms but do not sufficiently explain how hallucinations, which are intermittent by nature, suddenly intrude into active thought.

We propose that the intermittence of hallucinations might be related to the general concept of fluctuations in spontaneous brain activity at rest. A high degree of functional connectivity during rest characterizes several resting-state networks (RSNs). Damoiseaux et al. (2006) found auditory and visual RSNs in the human brain. These RSNs, which oscillate below 0.1 Hz (Biswal et al. 1995; Cordes et al. 2001), can be separated based on independent temporal characteristics. However, one RSN is characterized by its unique response to cognitive tasks (Fox et al. 2005). Specifically, the "default-mode network" (DMN) has high metabolic rates at rest but is typically suspended during attention-demanding tasks (Raichle et al. 2001; Fox and Raichle 2007). Conversely, "daydreaming" and "mind wandering" seem to increase DMN activity (Mason et al. 2007).

Taking this information into consideration, we would like to introduce 2 hypotheses regarding the intrusive feature of hallucinations. The first hypothesis is that hallucinations could occur first and extrinsically modulate the DMN's strength by reorienting attentional focus toward sensory expectations. This hypothesis supports the concept of a highly modulated DMN during hallucinations but with coherent low-frequency neuronal oscillations during symptom-free periods. The second hypothesis posits that the DMN is intrinsically unstable in patients who hallucinate, which causes aberrant transitions between resting and conscious sensory states. In reference to the potential role of the DMN in self-processing, both hypotheses could account for the alienness of hallucination experiences (Northoff and Qin 2011).

Although DMN activity and connectivity profiles have been explored in patients with schizophrenia, these studies provided conflicting results (Bluhm et al. 2007; Garrity et al. 2007; Zhou et al. 2007; Broyd et al. 2009; Whitfield-Gabrieli et al. 2009; Rotarska-Jagiela et al. 2010; Woodward et al. 2011) and could not disentangle which of these scenarios account for hallucinations. The lack of a definitive conclusion may notably relate to the inability of these reports to explore the online interaction between DMN and sensory cortices during various mental states, such as symptom occurrence and symptom-free periods. Potential confounding effects on resting-state values such as antipsychotic medications which may alter the DMN activity (Surguladze et al. 2007) or its functional connectivity (Achard and Bullmore 2007) also need to be adequately controlled for. The present study investigated the dynamic organization of resting-state activity during hallucinations in drug-naive participants to collect empirical evidence in favor of either of these hypotheses.

We focused on spontaneous fluctuations of brain activity using functional magnetic resonance imaging (fMRI) during wakeful rest in patients with hallucinations. To control for effects of illness duration and medication on functional measurements, we recruited only drug-free adolescents suffering from a first episode of psychosis during a period of frequent hallucinations. When participants hallucinated during a scan, an independent component analysis (ICA) of fMRI data captured

both RSN and hallucinatory activity. We specifically isolated the underpinnings of modality-dependent hallucinations and the DMN and explored their relative dynamics. Furthermore, clinical and anatomical correlation analyses were conducted in hallucinators and compared with data from matched healthy controls. A reduced cortical thickness (CT) in the key nodes mediating hallucinations may be a contributing factor to the overall weakening of the coordinated interplay between the DMN and these sensory regions. Finally, we evaluated the extent to which the severity of hallucinations altered the spatial and temporal stability of the DMN. Our findings support the theory that DMN instability is associated with aberrant sensory consciousness, independent of the underlying modality. Thus, these results are compatible with the second hypothesis presented above, that is, that phasic hallucinations emerge from a spontaneous switching off of the DMN.

## Materials and Methods

### *Participants*

This sample included 40 drug-free right-handed adolescents (Oldfield 1971), between 11 and 16 years old: 20 patients who met the "DSM-IV-TR" criteria for BPsyD (American Psychiatric Association 2000), and 20 healthy controls, matched for sex and age (see Table 1). BPsyD consists of hallucinations, delusions, or other psychotic symptoms lasting for at least 1 day but less than 1 month, with eventual return to normal premorbid functioning. It is distinguished from schizophrenia based on the duration of symptoms. The BPsyD diagnosis may evolve within the schizophrenia spectrum psychosis during the follow-up taking into account this duration criteria. A senior psychiatrist confirmed the absence of psychiatric symptoms in the control group using the Mini International Neuropsychiatric Interview (MINI-DSM-IV) (Sheehan et al. 1998). Exclusion criteria were the presence of an Axis-II diagnosis, secondary Axis-I diagnosis, neurological or sensory disorder, history of alcohol abuse, consumption of illicit psychedelic (Lysergic acid diethylamide), or dissociative drugs (Phencyclidine) based on the clinical interview and at admission urine tests or an IQ below 80. We obtained informed parental consent and assent from all participants. The local ethics committee (CPP Nord-Ouest IV, France) approved this study.

### *Symptom Assessment in the Patients Group*

An experienced psychiatrist assessed patients' symptoms using the "Positive and Negative Syndrome Scale" (PANSS) (Kay et al. 1987). We referred to the severity of hallucinations using the normalized P3-factor on the PANSS positive subscale. In addition, all included patients experienced frequent hallucinations (3–10 times/h) in auditory ($n$ = 14), visual ($n$ = 15), or both types of modalities (audiovisual, $n$ = 10). By reference to the hierarchical clustering of auditory hallucinations (Stephane et al. 2003), we specifically explored 3 dimensions of patients' hallucinatory experiences. On the day of the fMRI scan, participants completed the Visual Analogue Scales for each modality involved to address spatial location, self-other attribution and vividness of the sensory content (with anchors labeled "inside"–"outside the body"; "self-generated"–"exogenous"; and "imaginary"–"real," respectively).

**Table 1**
Participant demographic characteristics

| | Patients with BPsyD, $n$ = 20; mean ± SD | Healthy controls, $n$ = 20; mean ± SD | Group comparison, $P$ value |
|---|---|---|---|
| Age | 13.1 ± 1.8 | 12.9 ± 1.6 | 0.43 |
| Handedness ratio (R/L) | 20/0 | 20/0 | NA |
| Sex ratio (M/F) | 17/3 | 15/5 | 0.79 |
| Education[a] (years) | 7.0 ± 1.5 | 7.2 ± 1.6 | 0.27 |
| Episode duration (days) | 12.3 ± 4.9 | NA | NA |
| PANSS + subscale | 29.4 ± 5.3 | NA | NA |
| P3-item score | 5.1 ± 1.3 | NA | NA |

Note: BPsyD: Brief Psychotic Disorder according to the DSM-IV-TR classification; PANSS+: Positive and Negative Symptoms Scale–positive subscale; NA: not applicable; SD = standard deviation.
[a]Education years include elementary school.

### *Procedure*

Participants underwent a 10-min anatomical $T_1$-weighted 3D multishot turbo-field-echo scan (1.5-T Philips Achieva; 150 transverse slices, field of view = 256 $mm^2$, voxel size = 1 $mm^3$). Two successive sets of 300 blood oxygen level–dependent (BOLD) fMRI volumes were acquired (single-shot sensitivity-encoded echo-planar imaging sequence, 30 transverse slices, field of view = 240 $mm^2$, voxel size = 4 $mm^3$, repetition time = 3000 ms, echo time = 70 ms, total acquisition time = 30 min). All participants wore headphones and earplugs to attenuate scanner noise. Participants kept still in a state of wakeful rest with their eyes closed.

Following the fMRI session, each patient was interviewed regarding his or her sensory experiences during the scan. This post-fMRI interview addressed 3 characteristics of the hallucinatory experience: Q1. Which sensory modality was involved? (In the case of multisensory hallucinations, we asked the participant to specify whether separate unimodal experiences occurred during the fMRI session.) Q2. Approximately how many times did you hallucinate during recording? Q3. During which section of the fMRI session (initial, middle, or final) did you hallucinate? Participants answered Q2 and Q3 by drawing a dash for each episode over a linear scale that represented the time spent in the scanner.

### *Analysis Steps*

#### *MRI Preprocessing*

The anatomical and functional data were preprocessed and analyzed using the BrainVoyager QX v2.3 software (Brain Innovation, the Netherlands, 2011). Functional data were preprocessed using a slice scan time correction, a 3D head motion correction, smoothing using a spatial Gaussian filter (full-width at half-maximum [FWHM] = 5.0 mm), a temporal high-pass filtering with 2 sin/cos, and linear trend removal. The anatomical data were submitted to an intensity inhomogeneity correction algorithm, resampled to a 0.5 $mm^3$ resolution, and normalized in Talairach's stereotactic space (Talairach and Tornoux 1988). Data from the head tissue, subcortical structures, and cerebellum were then removed with the aim of advanced cortical segmentation processing. This segmentation was performed at the gray/white matter and the gray matter/cerebrospinal fluid boundaries. Each resulting hemisphere was submitted to a "bridge-removal" algorithm. Finally, the slice-based functional data were aligned on a high-quality 3D anatomical image.

#### *fMRI Analysis*

The fMRI signal was blindly separated using ICA in the spatial domain (Hyvarinen and Oja 2000). ICA decomposed the functional data set, while maximizing the statistical independence of the different signal sources, to extract independent spatial components (IC, See Supplementary Methods 1). Restricting the spatial ICA to portions of the matrix that include the cerebral cortex increases the reliability of the expected results (Formisano et al. 2004). The resulting "independent components spatial map" presented 3D clusters of voxels with $|Z|$ normalized values greater than 2.5. After ICA decomposition, 2 distinct procedures were applied to the data set to extract the brain activity associated with the hallucinations and the DMN. Conceptually, the first approach dedicated to "hallucinations capture" referred to a within-subject design, in which participants were their own controls between periods with and periods without hallucinations. The second approach dedicated to explore the DMN spatial stability referred more to a case–control design and compared functional measures obtained in hallucinators with those of healthy participants.

Because asking participants to report hallucinations during the fMRI session would have disrupted the DMN, we developed and validated a

new selection procedure for the individual IC that captured hallucinations. This method relied on a 3-step procedure. First, we used the "IC-fingerprint" method (De Martino et al. 2007), to select components related to a neurophysiological source for each participant (see Supplementary Methods 2). Second, we compared the IC time courses retained by this method with the temporal characteristics of the patients' descriptions of their hallucinatory experiences (Q2 and Q3). Third, we classified the ICs for each patient into sensory categories (A [auditory], V [visual], and AV [auditory + visual]) and compared them with their self-reports (Q1). A preliminary experiment validated the accuracy of the post-fMRI interview to help select the ICs that captured unpredictable sensory experiences (see Supplementary Methods 3 and Fig. S1). Next, we conducted a secondary analysis for each sensory modality by submitting individual ICs to the self-organizing group ICA algorithm (Sog-ICA; See Supplementary Methods 4) (Esposito et al. 2005). Cluster-size thresholding further corrected the random effects statistical maps for multiple comparisons (Goebel et al. 2006).

The DMN was isolated using a "goodness-of-fit" (GoF) procedure. Sog-ICA was performed on the data of the group of 20 healthy participants to obtain a spatial template of the DMN (DM template). Because these data were used to generate the DM template, it was not possible to directly conduct stability analysis in healthy participants (see Statistical Analysis). Next, we calculated the absolute spatial correlation coefficient between each participant's individual ICs and the DM template (Esposito et al. 2008). The component with the highest GoF score was assumed to be the DM component (See Supplementary Methods 5).'

*CT Analysis*

Thickness was defined as the length of the streamlines between the white/gray matter and gray matter/cerebrospinal fluid boundaries, which followed the solution gradient of the Laplace equation (Jones et al. 2000). First, CT was measured within volume spaces for each segmented cortical hemisphere. Second, the cortical surface was reconstructed and inflated for each participant. Finally, a cortex-based alignment using curvature information improved the anatomical inter-participant correspondence by mapping beyond the Talairach transformation (Fischl et al. 1999). Regions of interest (ROIs) for each participant were identified (i.e., centered on the maximum functional cortical activation coordinates associated with hallucinations; FWHM = 12 mm), and CT values were averaged over all vertices of the ROI for each subject. After checking whether the thickness values were normally distributed using the Shapiro–Wilk test, a t-test compared each ROI across groups.

*Statistical Analysis*

*Patterns of activity during hallucinations.* First, we performed a sog-ICA with a spatial threshold set to $|z| = 2.5$, $P < 0.01$, corrected by a cluster-size iterative estimation (>200 voxels). We conducted a Pearson product–moment correlation between the BOLD peaks of the hallucination-related ICs and the severity of patient hallucinations (PANSS, P3 item). Significance was set at $P < 0.05$.

Second, we explored the relationship between the DMN and the sensory cortices over time during "rest" and "hallucinations" periods (defined at the individual IC level). To explore dynamics of these networks, we normalized their fMRI signals to relative variations with respect to the mean value of the participants' individual time series (Deco et al. 2009). Hallucinations and rest periods were defined by visual inspection of the "hallucination-related" component time-course using specific criteria (Supplementary Methods 6). DMN and association sensory cortices (ASC) during these periods were compared using the Pearson product–moment correlation of their relative BOLD signal fluctuations. These findings were compared with rest and "exogenous stimulation" periods in control participants. These comparisons provided us with the means to explore the resulting collective dynamics of the brain in both physiological and pathological contexts.

*Spatial and temporal stability of the DMN.* Finally, we explored the spatial and temporal stability of the DMN as a function of hallucinations. We used "age" and "severity of hallucinations" as intraparticipant factors for these analyses. First, a linear regression analysis of the participant-specific GoF scores provided a measure of the DMN's spatial stability. Second, a spectral analysis examined the within-subject spontaneous fluctuations of the DMN over time and explored its link to hallucinations for the whole signal and for specific hallucination-free periods. For each participant, the DM component's time course was transformed to a power spectral density (PSD) using Welch's method (Childers 1978). We focused on frequencies less than 0.05 Hz because strong contributions of low BOLD oscillations commonly characterize the DMN (Cordes et al. 2001; van de Ven et al. 2004). Each PSD was standardized to its spectral sum, and PSDs within frequency bandwidths of 0–0.05 Hz were summed. A linear regression analysis was computed between low-frequency PSDs, age, and hallucination severity to explore the temporal stability of the DMN in patients with hallucinations.

## Results

### *The Neural Correlates of Uni- and Multisensory Hallucinations*

We compared individual ICs with the patients' postsession reports and classified hallucinations into 3 categories: auditory hallucinations (AH), visual hallucinations (VH), and auditory + visual hallucinations (AV-H). At the group level, the occurrence of either AH or VH was associated with increased activity within the respective associative sensory cortex (ASC; see Fig. 1*a* and Table 2). Moreover, the magnitude of ASC activation was positively correlated with hallucination severity ($r^2 = 0.56$; $P < 10^{-3}$). During A-VH hallucinations, multisensory ASCs were activated including the occipitotemporal junction (OTJ) and the superior temporal sulcus (STS) (Fig. 1*b*), which suggests sensory integration. At the participant level, we found primary sensory cortex (PSC) activations in 7 participants (i.e., striate cortex during VH and Heschl gyrus during AH), but there was no significant activation in these areas in the group analysis.

### *Primary/Association Cortices and Hallucinations*

To further investigate whether ASCs are specifically involved in the emergence of hallucinations, we explored regional gray matter loss. Patients with hallucinations, compared with healthy controls, exhibited reduced CT in visual ($t = 2.58$, $P = 0.01$) and auditory ASCs ($t = 2.74$, $P = 0.01$), whereas we did not observe differences in PSCs (Heschl gyrus, $P = 0.67$; Striate cortex, $P = 0.87$; Fig. 2). We further investigated whether activations within PSCs and ASCs were associated with specific clinical dimensions (see Supplementary Methods 7). Although we did not measure PSC activation at the group level, we found that activation of this region at the subject-level was significantly related to greater symptom vividness ($t = -2.86$, $P = 0.01$; Fig. 2), whereas we did not observe such a link for "spatial location" ($P = 0.48$) or "self/other attribution" ($P = 0.64$).

### *Interactions between Hallucinations and the Resting-state Activity*

*The Neural Dynamics of ASCs and the DMN*

An extensive exploration of the fMRI time-course of the hallucinatory and DM-ICs revealed an anticorrelation pattern between BOLD signal fluctuations in ASCs and DMN (see Fig. 3*a*). A linear correlation analysis of patients with hallucinations revealed that their BOLD signal tends to increase within ASCs when it decreases within the DMN ($r^2 = -0.36$; $P < 10^{-3}$; see Fig. 3*b*). We did not observe such a correlation between the sensory RSN, including ASCs, and the DMN during symptom-free periods.

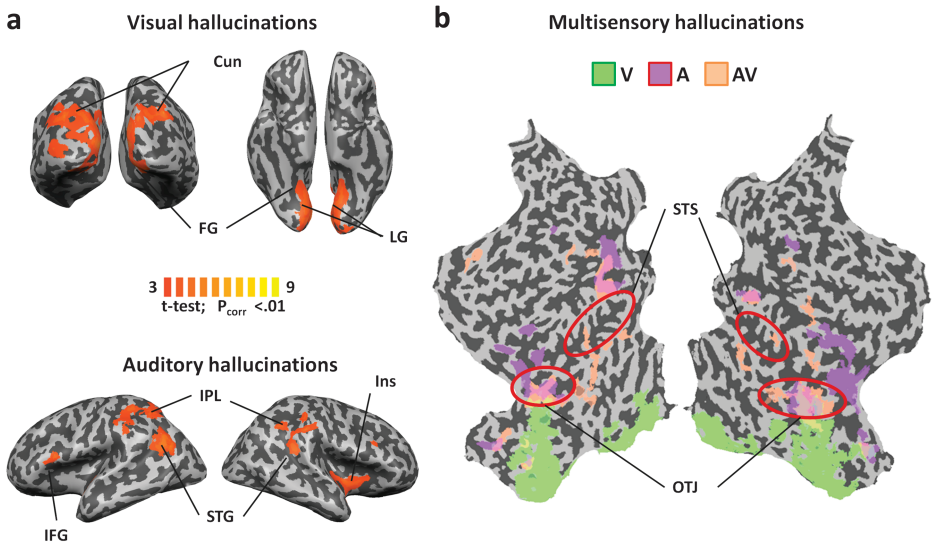


**Figure 1.** An fMRI analysis of the hallucinatory experience in 20 adolescents with brief psychosis disorder. (*a*) The bilateral ASCs activated during hallucinations: the cuneus (Cun), lingual (LG), and fusiform (FG) gyri during visual hallucinations; the anterior insula (Ins), inferior frontal gyrus (IFG), inferior parietal lobule (IPL), and superior temporal gyrus (STG) during auditory hallucinations. (*b*) An overlapping visualization of the auditory (purple), visual (green), and cross-modal (orange) components superimposed on a bilateral and flattened cortical mesh. OTJ and STS were activated during audiovisual hallucinations (AV, see Table 2). Activity in the STS was specific to multisensory hallucinations, whereas the OTJ presented a variable organization with overlaps between voxels responding to A, V, and AV inputs.

**Table 2**
The coordinates of the peak *t*- values for the cortical areas activated during hallucinations

| Cortical area | BA | Side | Talairach coordinates (mm) | | | $t_{max}$ | Cluster size ($mm^3$) |
|---|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | | |
| Auditory hallucinations | | | | | | | |
| IFG | 44 | L | −48 | 16 | 1 | 4.29 | 327 |
| AI | 13 | L | −41 | 2 | −1 | 4.66 | 3401 |
| | | R | 43 | 5 | −4 | 6.10 | 5116 |
| PG | 6 | L | −56 | 0 | 14 | 5.50 | 503 |
| STG | 21 | L | −64 | −20 | 0 | 4.32 | 942 |
| | | R | 59 | −12 | −2 | 4.56 | 787 |
| | 22 | L | −57 | −4 | −3 | 5.17 | 345 |
| MTG | 22 | L | −55 | −46 | 18 | 6.26 | 639 |
| | | R | 56 | −38 | 11 | 4.71 | 701 |
| IPL | 39 | L | −47 | −59 | 28 | 4.38 | 1341 |
| | | R | 42 | −57 | 31 | 5.39 | 994 |
| Visual hallucinations | | | | | | | |
| Cun | 18 | R | 2 | −74 | 24 | 6.09 | 4280 |
| | 19 | L | −15 | −81 | 33 | 5.26 | 6501 |
| | | R | 5 | −76 | 30 | 5.37 | 2164 |
| | 23 | L | −5 | −74 | 12 | 4.76 | 1607 |
| | 30 | R | 9 | −67 | 7 | 4.94 | 1243 |
| LG | 18 | R | 9 | −60 | 3 | 3.37 | 2890 |
| | 19 | L | −13 | −61 | 3 | 3.99 | 904 |
| FG | 37 | R | 18 | −57 | −5 | 4.01 | 628 |
| Audiovisual hallucinations | | | | | | | |
| AI | 13 | L | −43 | 1 | −1 | 3.91 | 1078 |
| | | R | 44 | 0 | −1 | 3.04 | 890 |
| OTJ | 37 | L | −49 | −62 | 11 | 5.79 | 1705 |
| | | R | 44 | −61 | 10 | 4.45 | 1984 |
| STS | 21 | L | −64 | −24 | −2 | 2.89 | 237 |
| | | R | 67 | −27 | 1 | 4.73 | 671 |
| | 22 | R | 49 | −28 | 1 | 4.40 | 256 |
| IPL | 39 | L | −47 | −59 | 31 | 3.97 | 319 |
| | | R | 49 | −59 | 28 | 3.85 | 282 |

Note: Random-effect sog-ICA results in 20 adolescents with a Brief Psychotic Disorder. BA = Brodmann areas; L = left, R = right; Talairach and Tournoux (1988) provided *x-y-z* coordinates in the normalized space; AI = anterior insula; Cun = cuneus; FG = fusiform gyrus; IFG = inferior frontal gyrus; IPL = inferior parietal gyrus; LG = lingual gyrus; MTG = middle temporal gyrus; PG = precentral gyrus; STG = superior temporal gyrus.

We discovered similar results for dynamic ASC- and DM networks in healthy controls during "exogenous stimulation" periods (see Supplementary Methods 3): BOLD signal increased within the ASCs while the participant listened to exogenous stimuli and simultaneously decreased within the DMN ($r^2 = -0.38$; $P < 10^{-3}$; see Fig. 3*c*). We did not observe a correlation between sensory RSN and the DMN during rest periods in the control group.

### *Hallucinations and the Stability of the DMN*

A multiple linear regression analysis revealed a strong relationship between the DMN GoF scores and 2 independent factors in patients with hallucinations, age, and hallucination severity ($r^2 = 0.66$, $P < 0.001$); Age showed a nonsignificant positive trend ($P = 0.08$), however, only hallucination severity predicted the DMN GoF scores with respect to the template ($P < 0.001$; see Fig. 4*a*). When hallucinations were more severe, the GoF scores decreased. In addition, we investigated the extent to which hallucination severity affects the time course of the DMN. A multiple linear regression between age, hallucination severity, and PSD values in the low-frequency bandwidth showed a significant positive relationship for the whole signal ($r^2 = 0.45$, $P = 0.006$) and for symptom-free periods ($r^2 = 0.39$, $P = 0.005$). As for the GoF scores, only hallucination severity significantly influenced PSD variation ($P < 0.01$; see Fig. 4*b*). Overall, age did not affect the spatial ($P = 0.23$) or temporal correlation ($P = 0.72$) within the DMN template. This finding is finally strengthened by the absence of relationship between DMN instability and other positive symptoms (correlation with PANSS positive subscale, $P = 0.36$).

## Discussion

Using an in-depth analysis of BOLD fluctuations in patients who suffer from BPsyDs, we discovered that hallucinatory experiences associated with hyperactivations of the ASCs occurred while the DMN was disengaged. This study's key and novel finding concern the role of DMN withdrawals in the aberrant transition between resting and active sensory states. Three lines of evidence support the pivotal role of DMN instability in

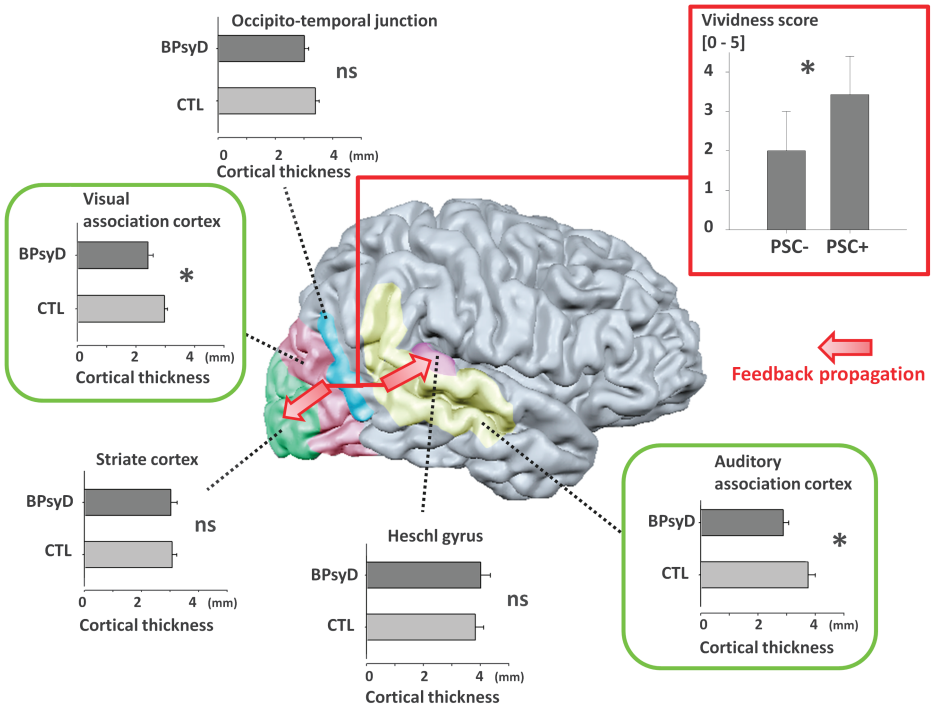


**Figure 2.** Cortical thickness analysis in adolescents with BPsyD ($n = 20$) compared to matched controls (CTL, $n = 20$). Reduced CTs were measured within the visual and auditory ASCs (green). We did not find a group difference in CT at the level of cross-modal ASCs or PSCs. Activations within these areas are associated with more vivid hallucinations (PSC+, $n = 7$), whereas no activation is associated with weaker symptoms (PSC−, $n = 13$, red). These results suggest a back propagation from the ASC to the PSC during hallucinations (red arrows), independent of sensory modality.

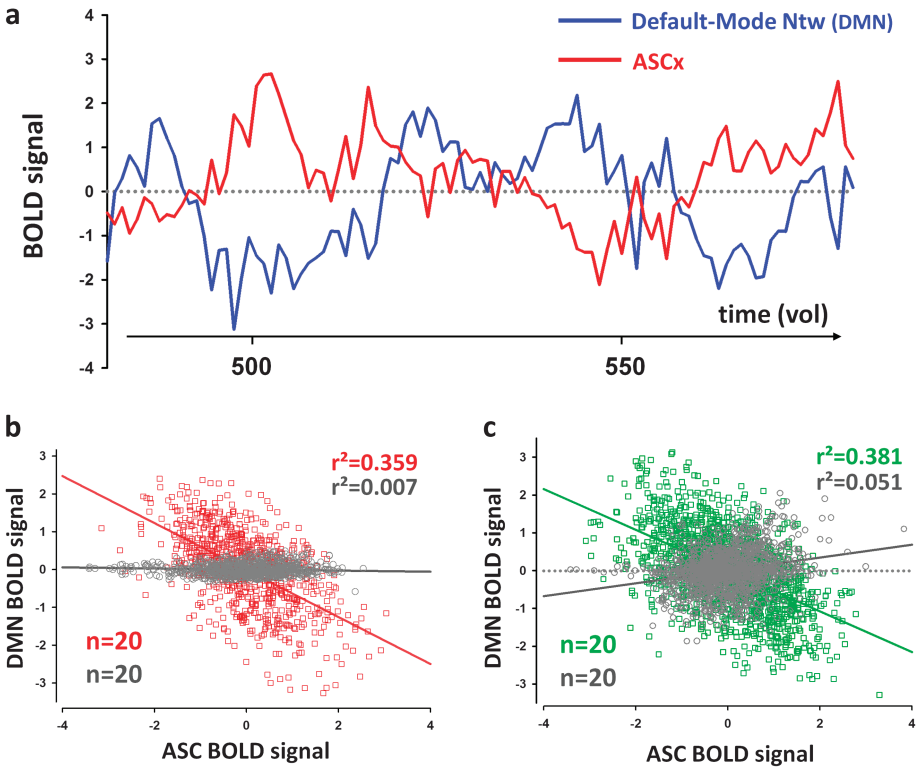


**Figure 3.** DMN dynamic at rest, during exogenous stimulation or during hallucinations. (*a*) Normalized BOLD signal fluctuations in the DMN (blue line) and ASCs (red line) in a participant with BPsyD. During hallucinations, the endogenous activity of the sensory cortices increases and is concomitant with DMN disengagement. (*b*) At the group level, a negative correlation is shown in patients with BPsyD (red plot) during hallucinations between the BOLD signal for the ASCs and the DMN. Conversely, we did not find a link between sensory RSN, encompassing ASCs, at rest within the same participants (gray plot). These patterns are similar to those in healthy controls (*c*): i.e. a negative correlation is shown between the BOLD signal in the ASCs and the DMN when exposed to exogenous stimulations (green plot), whereas we did not find a significant relationship in participants at rest (gray plot).

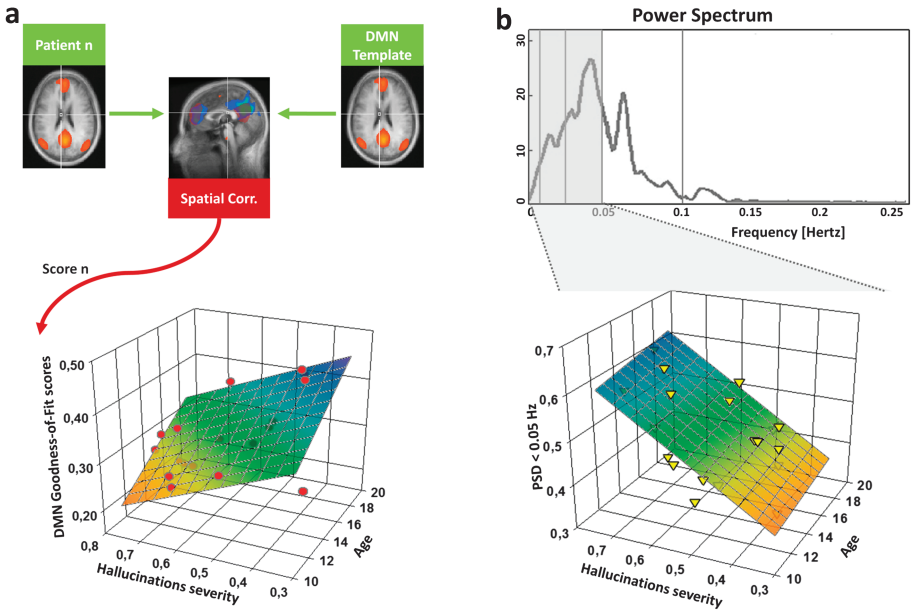


**Figure 4.** DMN spatial and temporal instability in patients with BPsyD. (*a*) According to the goodness-of-fit procedure (GoF), a template was generated from the sog-ICA of the fMRI in 20 healthy controls at rest. Next, single-participant ICAs for each of the 20 patients with BPsyD were spatially correlated with the DMN template, which allowed us to compute a GoF score. A multiple linear regression revealed a negative relationship between the GoF scores and hallucination severity (normalized P3-item of the PANSS+ subscale). Despite a developmental trend for stabilization of the DMN ($P = 0.08$), the negative correlation between GoF scores and hallucinations was independent of age in adolescents with BPsyD (regression plane: blue to yellow). (*b*) The DMN temporal dynamic exploration in patients with BPsyD also revealed a positive correlation between hallucination severity and the PSDs less than 0.05 Hz during symptom-free periods. This correlation was independent of age. Overall, these results suggest that the spatial (*a*) and the temporal stability (*b*) of the DMN decreased in the patients with the most severe psychotic symptoms.

the emergence of hallucinations: 1) the anticorrelation between ASCs and the DMN network during hallucinations, which cannot be explained by sensory RSN fluctuations; 2) the negative correlation between DM GoF scores and the severity of patients' hallucinations; and 3) the DMN's increased PSD as a function of hallucination severity, which is maintained during symptom-free periods. By recruiting drug-naive BPsyD patients, this study supports and extends previous work by controlling potentially confounding effects, such as psychotropic drug interactions with the hemodynamic signal (Achard and Bullmore 2007; Surguladze et al. 2007) and secondary progressive brain deterioration in patients with chronic hallucinations. Moreover, the validated ICA procedure allowed us to explore complex symptoms and "true" resting states because the patients were not instructed to record the beginning and end of their hallucinations during scanning while maintaining a strong accuracy. Overall, our results favor a new pathogenic hypothesis to account for hallucination emergence: intrinsic DMN instability.

We first discovered unnatural endogenous activity in modality-dependent ASCs during symptom occurrence (cf. Fig. 1). These findings are in line with the preliminary findings from 2 case reports of audiovisual hallucinatory states in schizophrenia (Silbersweig et al. 1995; Jardri et al. 2009). Two categories of multisensory ASCs recruited during audiovisual hallucinations can be distinguished (i.e., Ghazanfar and Schroeder 2006): at the border between sensory areas, the OTJ, which partially overlapped with activity patterns measured during unimodal hallucinations, and high-level multisensory cortices, such as the STS, which was specifically recruited during audiovisual hallucinations.

We furthermore demonstrated an anatomical substratum of these functional measures, with thinner modality-dependent ASCs measured in patients with hallucinations compared with healthy controls (cf. Fig. 2). Psychosis is known to be associated with a volumetric decrease of cortical structures, and early frontotemporal thinning has already been described in first-episode schizophrenia (Janssen et al. 2009; Gutierrez-Galve et al. 2010). However, this is the first report of a specific link between ASC changes and hallucinations at a very early stage of drug-naive psychosis. This result supports a predisposition toward modality-dependent hallucinations in our sample, in accordance with recent findings showing a link between reduced CTs in the superior temporal gyrus and vulnerability to auditory–verbal hallucinations in schizophrenia patients and their healthy relatives (Oertel-Knöchel et al. forthcoming). At this stage, complementary longitudinal measurements in this sample are still required to distinguish between 2 possible explanations for cortical thinning: gray matter loss and delayed development of these areas. Following CT longitudinally in this diagnostic group would also allow for examining whether these structural changes are reversible when symptoms abide or whether they persist in those who later convert to schizophrenia. Finally, the secondary and cross-modal sensory cortices identified in our study are known involved in complex object perception, whereas PSCs are responsible for the perception of single aspects, such as tone or luminance (Mesulam 1998). Despite an absence of correlation with spatial location, source attribution, or vividness, ASC activation during hallucinations might reflect the phenomenological content of the pathological experiences lived by the participants, as, for example, the type of object perceived (e.g., a face) in accordance with the seminal findings obtained in patients with the Charles Bonnet syndrome (Ffytche et al. 1998).

In addition, this finding extends previous reports regarding PSCs: whereas some brain imaging studies have failed to identify Heschl gyrus (i.e., auditory PSC) activations during AH

(Shergill et al. 2000; Sommer et al. 2008), others have reported its activation (Dierks et al. 1999; van de Ven et al. 2005), which calls into question the exact role of this structure in hallucinations. The present experiment showed inconsistent activations of PSCs in patients with hallucinations that did not survive a second-order analysis. This finding is consistent with results from a meta-analysis of the hallucinatory state (Jardri et al. 2011). Furthermore, we did not find a difference in CT in the PSCs between patients and controls. Taken together, these findings support the idea that hallucinations do not require PSC activation and that PSCs activations are related to specific clinical features, such as the vividness of hallucinations (Cf. Fig. 2). Even if this is beyond the scope of this experiment, it is possible that hyperactivation measured in the PSC might arise from a back propagation of ASC activity, which was shown to be systematically involved. The findings regarding the major role of ASCs in hallucinations immediately raise a new question: from where does this abnormal increase in sensory activity come?

By showing that hallucinations are linked to a fluctuating DMN, our results create an important link between 2 fields of research in neuroscience: spontaneous brain activity at rest and perception in a pathological context. BOLD dynamic analysis in all participants revealed that uncorrelated sensory cortex and DMN fluctuations characterized rest periods. Conversely, we observed an anticorrelation pattern characterized by decreased activity in the DMN that accompanies ASC overactivity during both hallucinations periods in patients and exogenous stimulation periods in controls (cf. Fig. 3). These hallucination-related ICs encompassing ASCs are thus distinguishable from the sensory RSN. Disengagement of the DMN during goal-directed behaviors, as shown in the exogenous stimulation condition, is common in the literature (Raichle et al. 2001; Fox et al. 2005). We provided the first evidences for a comparable dynamic pattern during hallucinatory experiences, with the noteworthy exception that PSC recruitment was unnecessary for hallucinations to occur.

After demonstrating the phasic and mutual influences between the DMN and ASCs, we conducted additional analyses to investigate 2 possible explanations for hallucinations. Despite a current lack of direct evidence for causality (i.e., correlation does not imply causation), a few points can be made. Let us assume that the patients' DMN functions properly but that hallucinations regularly disturb this network. If this scenario is the case, then the DMN should exhibit a reduced spatial stability, evidenced here by the low range of GoF scores (0.23–0.47) that are negatively correlated with hallucination severity (see Fig. 4*a*), but not a disturbed temporal dynamic at rest because low-frequency oscillations are a physiological characteristic of RSNs (Cordes et al. 2001; van de Ven et al. 2008). However, such a hypothesis cannot explain the finding that increased oscillations below 0.05 Hz at rest are maintained during symptom-free periods (see Fig. 4*b*). Even if a longitudinal fMRI follow-up of the DMN spatial and temporal stability after psychotic remission is now required to fully clarify such a relationship, the results of our study support an intrinsic and global instability of the DMN in hallucinators relative to controls (Northoff and Qin 2011). A recent fMRI experiment conducted in healthy volunteers exposed to psilocybin also supports the role of the DMN instability in the psychedelic state (characterized by frequent hallucinations), that is, the main effect of psilocybin was not observed directly on sensory cortices but was shown in association with a significant decrease in the coupling between key connectors of the DMN (Carhart-Harris et al. 2012). This finding illuminates the conclusions derived from previous studies of hallucinatory states by suggesting that the unpredictable phasic course of hallucinations may result from DMN instability. The stronger and larger oscillations of spontaneous brain activity measured in the present study may also account for the decrease in the signal-to-noise ratio in the sensory cortices (Winterer et al. 2000). This finding is in accordance with the more general hypothesis that hallucinations and the neural processing of exteroceptive stimuli compete for common neurophysiological mechanisms (David et al. 1996; Woodruff et al. 1997; Plaze et al. 2006; Ford et al. 2009).

Although science still lacks an accurate description of the DMN's cognitive functions, there is growing evidence that the DMN is associated with memory (Spreng et al. 2009) and self-referential processing (Gusnard 2005). Synchronously, coactivated brain areas including the anterior and posterior cingulate cortex (ACC and PCC, respectively), the lateral and inferior parietal cortex and the bilateral hippocampal/parahippocampal gyri (PHC) constitute the DMN (Greicius et al. 2009). Notably, these brain areas are not homogeneously affected in schizophrenia (Rotarska-Jagiela et al. 2010); low-frequency fluctuations have been shown to increase in the PHC and ACC. Previous accounts of hallucinations have stressed the potential cognitive role of these structures, including PHC involvement in abnormal memory retrieval (Hoffman et al. 2008; Diederen et al. 2010) and ACC involvement in the misattribution of sensory events to external sources (Allen et al. 2007; Fletcher and Frith 2009). Our findings particularly fit with these current theories of hallucinations and integrate them into a coherent framework.

It had been argued that hallucinations might reflect the output of memory-based sensory experiences within a current context (Copolov et al. 2003). PHC, known to "presensitize" association cortices to link a given input with a representation in memory (Bar 2007), could contribute to such a mechanism. Interestingly, brain imaging studies investigating cortical activations prior to the onset of AH effectively revealed that the PHC was deactivated (Diederen et al. 2010), and this effect was shown to be associated with memory recall (Weis et al. 2004). Despite an absence of activation of the PHC during hallucinations in our sample, we argue that the abnormal instability of this structure (which is part of the DMN) might trigger dispersed storage sites within modality-dependent ASCs, thereby causing hallucinations. Another crucial component of a psychotic experience is the difficulty for patients with hallucinations to adequately determine the origin of a given stimulus, thereby causing a misattribution of internal events to external sources. The ACC, which is involved in inferential processes, seems to be a key node of source monitoring (Allen et al. 2005, 2007). The predictive coding framework, which postulates that the more a stimulus is predictable, the more likely it is to have been generated internally (Fletcher and Frith 2009), also captures source monitoring. Taken together, the sudden disengagement of the DMN involves the ACC and constitutes a mechanism that increases the predictive coding errors that contribute to a faulty appraisal of the stimulus origin.

In conclusion, this study approaches the issue of DMN aberrations in BPsyD from different angles and employs a series of compatible analyses to present a new principle that governs the intrusive nature of hallucinations with regard to how the DMN and ASCs interact during these symptoms. This report

provides a coherent pathophysiological account for the emergence of auditory, visual, and audiovisual hallucinations. From a developmental perspective, it is now well known that the progressive strengthening of long-range connections during development contributes to the stabilization of temporally correlated neural activity between regions of the DMN from childhood (Fair et al. 2008) to late adolescence (Stevens et al. 2009). At the molecular level, this phenomenon also relies on the maturation of γ-aminobutyric acidergic transmission involved in neural synchrony of large cellular assemblies (Uhlhaas and Singer 2010). Recent studies proposed that such an increase within network connectivity that occurs during normal development may be compromised in schizophrenia (Woodward et al. 2011). Our findings build upon prior studies by showing that DMN spatiotemporal instability is related to hallucinations in the earliest stages of drug-naive psychosis. The fact that this effect persists after correcting for age effectively suggests a prepubertal origin of these instabilities, and the maturational processes of late adolescence are insufficient to compensate for this. A longitudinal exploration of early-onset hallucinations in both benign and clinical pediatric populations is now required to identify neurodevelopmental influences on these symptoms. Further studies will also have to determine if instabilities of the DMN are the consequence of a primary dysfunction of this network or of disrupted coordination between the DMN and other RSNs, such as the salience network that has been recently proposed to be involved in switching between the DMN and task-related states in healthy subjects (Cole et al. 2010; Menon and Uddin 2010).

## Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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## Notes

Author Contributions: R.J., P.T., and D.P. designed the study. R.J. and P.D. recruited the participants. R.J., C.D., and D.P. collected the data. R.J. made the fMRI and CT analyses. All the authors participated in the results interpretation, the manuscript redaction, and approved its final version. *Conflict of Interest* : None declared.

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