

PARKINSON'S DISEASE

Robot-induced hallucinations in Parkinson's disease depend on altered sensorimotor processing in fronto-temporal network

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Hallucinations in Parkinson's disease (PD) are disturbing and frequent non-motor symptoms and constitute a major risk factor for psychosis and dementia. We report a robotics-based approach applying conflicting sensorimotor stimulation, enabling the induction of presence hallucinations (PHs) and the characterization of a subgroup of patients with PD with enhanced sensitivity for conflicting sensorimotor stimulation and robot-induced PH. We next identify the fronto-temporal network of PH by combining MR-compatible robotics (and sensorimotor stimulation in healthy participants) and lesion network mapping (neurological patients without PD). This PH-network was selectively disrupted in an additional and independent cohort of patients with PD, predicted the presence of symptomatic PH, and associated with cognitive decline. These robotics-neuroimaging findings extend existing sensorimotor hallucination models to PD and reveal the pathological cortical sensorimotor processes of PH in PD, potentially indicating a more severe form of PD that has been associated with psychosis and cognitive decline.

INTRODUCTION

The vivid sensation that somebody is nearby when no one is actually present and can neither be seen nor heard [sense of presence or presence hallucinations (PHs)] has been reported from time immemorial and found its way into the language and folklore of virtually all cultures (1–3). After anecdotal reports of PH by extreme mountaineers (4), solo sailors, and shipwreck survivors (5), PHs have also been described in a variety of medical conditions including schizophrenia (1, 6), epilepsy, stroke, brain tumors (3, 7, 8), and Parkinson's disease (PD) (9–11).

Whereas PHs are very rare manifestations in most medical conditions, they are more frequent in PD and may occur as a recurrent neuropsychiatric complication, affecting many patients on a weekly and in few on a daily basis (9). Thus, PHs occur in about 50% of patients with PD (9–12) and are generally grouped with so-called

minor hallucinations, which include, next to PHs, passage hallucinations (rapid perception of a person or animal passing sideways in the periphery of the visual field) and visual illusions (visual misperceptions of objects) (10). Minor hallucinations are prevalent, may manifest early (10, 11)—often preceding the onset of unisensory traditional hallucinations such as structured visual hallucinations (VH), auditory, or tactile hallucinations (13)—and may even be experienced, by one-third of patients, before the onset of the first motor symptoms (14).

Hallucinations in PD increase in frequency and severity with disease progression and are one of the most disturbing non-motor symptoms (10, 11, 15). Hallucinations in PD are associated with major negative clinical outcomes such as chronic psychosis, cognitive decline, and dementia, as well as higher mortality (9, 10, 13, 16, 17). Although these associations have mostly been observed for unisensory traditional hallucinations, growing clinical evidence suggests that they may also be valid for PH. This is clinically relevant also because PHs often appear before unisensory traditional hallucinations (10). Yet, despite their high prevalence and association with major negative clinical outcome, PHs (and other minor hallucinations) remain underdiagnosed (10, 11), because of patients' reluctance to report minor hallucinations and clinicians' failure to ask about them (18, 19).

Several important studies have investigated visual and cognitive brain mechanisms in patients with PD and with hallucinations, revealing distributed structural changes in visual cortex (in lateral and ventral occipito-temporal areas, in fusiform gyrus, and visual parietal areas) but also retinal changes (20). Moreover, several visual deficits have been observed in PD including contrast sensitivity (21, 22), visuo-spatial attention (23), color vision (22), and biological motion perception (24) and have been described as possible alterations leading to hallucinations (24). We note, however, that these studies mostly focused on patients with structured visual hallucinations (20) or did

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not evaluate minor hallucinations, including PH. Comparable studies are rare or lacking for PH (or other minor hallucinations), and, accordingly, very little is known about the location and distribution of early brain changes and behavioral consequences in patients with PD and PH and how they may associate with more severe and disabling structured visual hallucinations and cognitive deficits (10, 25).

Early neurological work investigated PH after focal brain damage and classified PH among disorders of the body schema, suggesting that they are caused by abnormal self-related bodily processes (8, 26). More recent data corroborated these early findings and induced PH repeatedly by invasive electrical stimulation of a cortical region involved in sensorimotor processing (3). By integrating these clinical observations with human neuroscience methods inducing bodily illusions (27–30), we have designed a method able to robotically induce PH (robot-induced PH or riPH) in healthy participants (31). This research demonstrated that specific sensorimotor conflicts, including bodily signals from the arm and trunk, are sufficient to induce mild to moderate PH in healthy participants, linking PH to the misperception of the source and identity of sensorimotor signals of one's own body.

Here, we adapted our robotic procedure to patients with PD and elicited riPH, allowing us to characterize a subgroup of patients that is highly sensitive to the sensorimotor procedure and to identify their aberrant sensorimotor processes. We next determined the common PH-network (cPH-network) in frontal and temporal cortex, by combining magnetic resonance (MR)-compatible robotics in healthy participants with a brain network analysis in neurological patients without PD but with PH. Last, we recorded resting-state functional magnetic resonance imaging (fMRI) data in a new and independent sample of patients with PD and identified pathological functional connectivity patterns within the cPH-network, which were predictive for the occurrence of PD-related PH.

RESULTS

riPH in patients with PD (asynchronous versus synchronous stimulation)

Previous studies observed that most patients with PD who experience PH report them as neutral and not distressing (except when occurring for the first time), and usually short lasting. Moreover, PHs are typically felt beside or behind the patient's body (rarely, also in an adjacent room) (9). In the current experiment, the semi-structured interview data confirmed that symptomatic PH (sPH) in 54% of the patients were neutral or positive, and in 62% of the patients, sPHs were of undetermined gender. In 69%, the presence was felt either on the side of the patient's body and/or on the back (for other variables, see table S1). Collectively, these results are compatible with previously reported sPH in PD (9).

On the basis of the semi-structured interview, 26 patients with PD were grouped into those who reported sPH (PD-PH; $n = 13$) and those without sPH (PD-nPH; $n = 13$) (Supplementary Materials; tables S2 and S3). Patients were asked to actuate a robotic device and were exposed to repetitive sensorimotor stimulation that has been shown to induce PH in healthy participants in a controlled way (30). We first assessed whether robotic sensorimotor stimulation induces PH in patients with PD and whether such riPHs differ between PD-PH and PD-nPH, hypothesizing that patients with PD-PH are more sensitive to the robotic procedure. All patients were treated with antiparkinsonian medications, and there was no significant (all

permutation, $P > 0.05$) difference in medication between the two groups of patients (table S2).

In the robotic sensorimotor paradigm, participants were asked to perform repetitive movements to operate a robot placed in front of them, which was combined with a back robot providing tactile feedback to patients' backs (Fig. 1A). On the basis of previous data (28, 31, 32), tactile feedback was delivered either synchronously with patients' movements (synchronous control condition with a spatial conflict between movement in front and touch on the back) or with a 500-ms delay (asynchronous condition) associated with an additional spatio-temporal sensorimotor conflict shown previously to induce PH (fig. S3) (31).

The robotic procedure was able to induce PH in patients with PD. The PD-PH group rated the intensity of riPH higher than the PD-nPH group (main effect of Group: permutation $P = 0.01$) (Fig. 1B). Confirming the general importance of conflicting asynchronous sensorimotor stimulation (31) for riPH, both subgroups gave higher PH ratings in the asynchronous versus synchronous condition (main effect of Synchrony: permutation $P = 0.045$) (Fig. 1C). By adding Gender as covariate of no interest to our analysis, we observed similar results to those we reported above. Gender did not significantly influence (permutation $P = 0.6$) riPH ratings. We confirm the enhanced sensitivity to the sensorimotor robotic stimulation (permutation $P = 0.04$, main effect of Group) and the importance of the conflicting sensorimotor stimulation to riPH (permutation $P = 0.028$, main effect of Synchrony). Montreal Cognitive Assessment (MoCA) score did not significantly influence (permutation $P = 0.06$) the ratings, and we confirmed the enhanced sensitivity to the sensorimotor robotic stimulation (permutation $P = 0.037$, main effect of Group) and the importance of the conflicting sensorimotor stimulation to riPH (permutation $P = 0.038$, main effect of Synchrony). Other robot-induced bodily experiences (such as illusory self-touch) also confirmed previous findings (31), and no significant (all permutation $P > 0.05$; tables S4 and S5) differences between PD-PH and PD-nPH were observed for the control items (see tables S4 and S5). These results show that PH can be safely induced by the present robotic procedure under controlled conditions in patients with PD. Such riPHs were modulated by sensorimotor stimulation with asynchronous robotic stimulation resulting in higher ratings in all tested groups, and PD-PH (versus PD-nPH) reported stronger riPH, linking the patients' usual sPH to experimental riPH and showing that PD-PHs were more sensitive to our robotic procedure.

Post-experiment debriefing revealed that 38% of PD-PH reported riPH comparable (or even stronger) in intensity to the patients' usual sPH in daily life. One patient from PD-PH group, for example, described his riPH as "an adrenaline rush. Like something or someone was behind me, although there is no possibility to have someone behind" (movie S1 and the Supplementary Materials). All such instances were reported after asynchronous stimulation. Another patient from the PD-PH group reported that he could feel the robot-induced presence on the side (not on the back) and added (after being asked to compare sPH and riPH): "It is slightly similar, but it is not exactly the same because the presence (symptomatic) is all of a sudden, while here (the riPH) it is built-up." Although the riPH was strong felt, another patient from the PD-PH group noted that the riPH lacked some aspects of his sPH. He described that "when I feel the sPH, it's like a chewing gum with a lot of taste, while here (the riPH) it was still like chewing gum but without the taste." Another patient from PD-PH group reported that "I honestly have the impression to

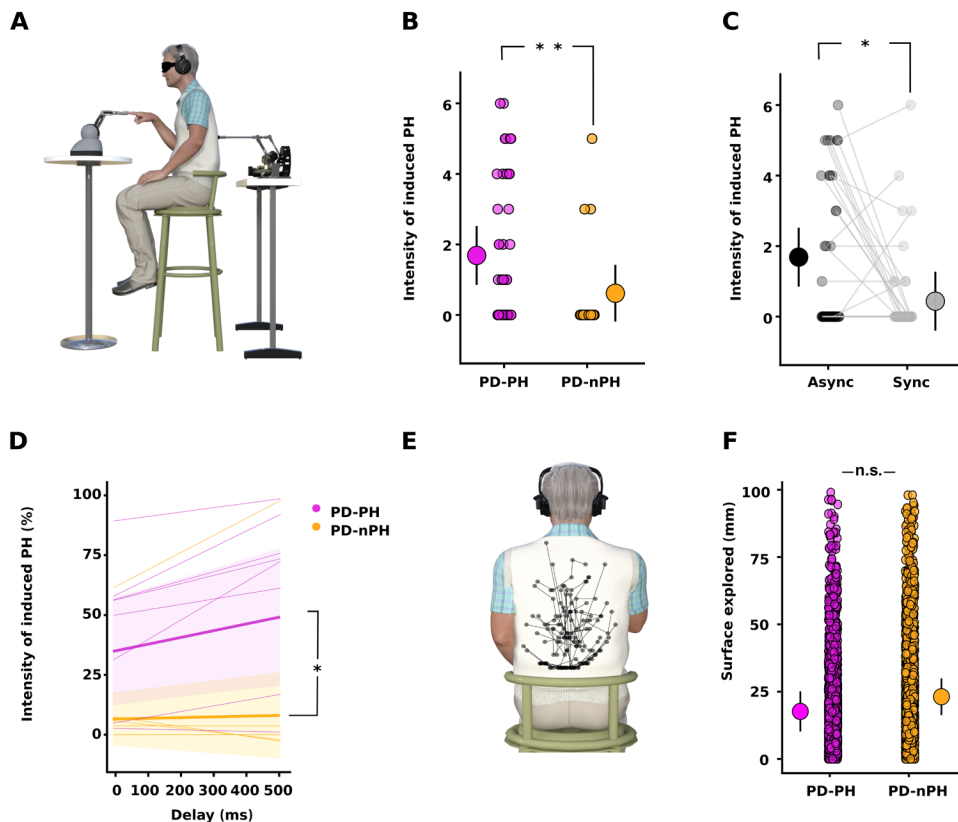


Fig. 1. riPH in patients with PD. (A) Experimental setup. During the asynchronous condition, the sensorimotor feedback on the participants’ backs was delayed by 500-ms or with a random delay (0 to 500 ms, steps of 100 ms). (B) riPH in patients with PD (asynchronous versus synchronous stimulation). Each dot indicates the individual rating of the intensity of the riPH [PD-PH (purple) and PD-nPH (orange)]. The dots with the bar on the left and right sides indicate the mixed-effects linear regression between PD-PH and PD-nPH. Error bar represents 95% confidence interval. $**P \leq 0.01$. (C) riPH in patients with PD (asynchronous versus synchronous stimulation). Each dot indicates the individual rating of the intensity of the riPH. The dots with the bar on the left and right sides indicate the mixed-effects linear regression between asynchronous (black) and synchronous (gray) sensorimotor stimulation. Error bars represent 95% confidence interval. $*P \leq 0.05$. (D) riPHs in patients with PD-PH depend on sensorimotor delay. riPH as a function of delay. The thicker line indicates the mean of the fitted models, the shaded area indicates the 95% confidence interval, and thinner lines indicate single participant fit. (E) riPHs in patients with PD-PH depend on sensorimotor delay. Example of movements that were executed by one patient during sensorimotor stimulation. (F) Mixed-effects linear regression between the Euclidean distance between pokes for PD-PH (purple) and PD-nPH (orange). Error bar represents 95% confidence interval. n.s., not significant.

have someone behind me.” Just after the stimulation and opening her eyes, she added, “I was surprised to see you all in front of me.”

Moreover, PD-PH experienced riPH on their side (and not only on their back, where tactile feedback was applied), revealing a further phenomenological similarity between riPH and patients’ usual sPH (9) and suggesting that we induced a mental state that mimics sPH. Analyzing all trials for which a participant positively rated the riPH during the robotic procedure (value of >0 on Likert scale) we found that the PD-PH group reported ($n = 14$) a higher number of lateralized riPH [chi-square: $P = 0.001$, $\chi^2(1) = 11.27$] than PD-nPH ($n = 1$). The PD-PH group riPH reported riPH either to the side ($n = 14$) or behind them ($n = 6$), with no predominant location [chi-square: $P = 0.11$, $\chi^2(1) = 3.22$]. The very few instances in patients with PD-nPH did not differ (behind: $n = 2$; lateralized: $n = 1$) [chi-square: $P = 1$, $\chi^2(1) = 0.33$]. For both groups of patients, the most affected side by PD did not influence the location of the

riPH (all $P > 0.05$) (also see table S5). In summary, these data reveal that riPH can be safely induced by the present procedure, is stronger in patients who report sPH (PD-PH), and shares phenomenological similarities with PD-related sPH.

riPH in patients with PD (sensorimotor delay dependency)

Previous work investigated the effects of systematically varied sensorimotor conflicts (delays) on somatosensory perception, enabling the induction and modulation of different somatic experiences and illusions (32–34). Sensorimotor processing and the forward model of motor control (35, 36) are prominent models of hallucinations (37, 38), and it has been proposed that deficits in predicting sensory consequences of actions cause abnormal perceptions and hallucinations (37–39). Next, we assessed whether riPHs depend on the degree of conflict applied during sensorimotor stimulation, by inserting different delays between the movements of the front robot (capturing movements of the forward-extended arm) and the back robot (time of tactile feedback on the back). In each trial, participants were exposed to a randomly chosen delay (0 to 500 ms, steps of 100 ms). After each trial, participants were prompted whether they experienced an riPH or not (Yes/No response). We investigated whether the intensity of riPH increases with increasing delays (showing that PHs are modulated by increasing spatio-temporal conflicts) and whether PD-PH have a higher spatio-temporal delay sensitivity than PD-nPH.

As predicted, the results show that the intensity of riPH increased with increasing spatio-temporal conflict (main effect of Delay: permutation $P = 0.014$) and that this

delay dependency differed between the two patient groups, showing a higher delay sensitivity in patients of PD-PH group (interaction Group*Delay: permutation $P = 0.039$) (Fig. 1D, fig. S1, and the Supplementary Materials). We also confirmed that patients from the PD-PH group experienced stronger riPH than those from the PD-nPH group (main effect of Group: permutation $P = 0.016$; Fig. 1D). We measured the movements performed by all participants during the task, allowing us to analyze whether PD-PH and PD-nPH moved differently, calculating the interpoke interval [time between the end of the touch on the back (poke n) and the beginning of the following poke $n + 1$] and the spatial distance between successive pokes (poke n and poke $n + 1$). The analysis of movement data excluded differences in movement patterns (neither temporal nor spatial aspects) between the two subgroups of patients. There is no difference in the interpoke interval between PD-PH and PD-nPH (permutation $P = 0.29$). Average duration of the interpoke interval for PD-PH was 2.06 ± 1.97 s

(means \pm SD) and 1.55 ± 2.26 s for PD-nPH (means \pm SD). The duration of each poke did not differ between PD-PH and PD-nPH (permutation $P = 1$). The average duration of the poke duration for PD-PH was 0.75 ± 5.24 s (means \pm SD) and 0.73 ± 2.82 s (means \pm SD) for PD-nPH (fig. S2, A and B). Spatial analysis of the movement revealed no difference in the distance between the pokes between PD-PH and PD-nPH (permutation $P = 0.3$). Average surface exploration for PD-PH was 17.83 ± 18.4 mm (means \pm SD) and 23.89 ± 21.05 mm for PD-nPH (means \pm SD). Movement control analyses (Fig. 1, E and F; fig. S2; and table S6) allowed us to exclude that the observed differences in riPH ratings between patient groups are due to differences in movements of the arm and related tactile feedback during the robot actuation. In addition, the differences in riPH between PD-PH and PD-nPH are not likely to be explained by differences in demographic or clinical variables (including anti-parkinsonian medication, motor impairment, gender, and cognitive functions; all permutation $P > 0.05$; table S2).

On the basis of previous results using robotics and conflicting sensorimotor stimulation (32–34), these data reveal abnormal perceptual processes in PD-PH when exposed to different sensorimotor conflicts, characterized by experiencing stronger riPH and higher sensorimotor sensitivity. These findings are compatible with an alteration of sensorimotor brain processes associated with the forward model and its role in hallucinations in PD-PH (37, 38, 40).

Brain mechanisms of riPH in healthy participants using MR-compatible robotics

We first performed a behavioral pilot study in a mock scanner with the new MR-compatible robot ($n = 24$ participants; Supplementary

Materials) where we showed that PH is induced in asynchronous conditions [main effect of Synchrony: permutation $P < 0.001$ with higher ratings in two asynchronous conditions compared to the synchronous condition, post-hoc test: [$t(46) = 4.14, P < 0.001$ and $t(46) = 2.92, P = 0.00053$, respectively]]. In line with prior work (30), we found that asynchronous robotic stimulations were associated with higher passivity experience than the synchronous stimulation [main effect of Synchrony: permutation $P < 0.001$; post-hoc test: $t(46) = 2.16, P = 0.035$, and $t(46) = 4.75, P < 0.001$, for two asynchronous conditions; Supplementary Materials]. The other robot-induced bodily experiences and control items did not show any main effect of Synchrony on the ratings (table S7).

On the basis of these behavioral pilot data, we exposed 25 new healthy participants to asynchronous and synchronous robotic stimulation while recording fMRI (Fig. 2A, movie S2, and fig. S3). Our behavioral data replicated previous results (31, 41), and we found that asynchronous versus synchronous robotic stimulation induces stronger PH (main effect of Synchrony: permutation $P = 0.008$; Fig. 2B) and another bodily experience (passivity experience; table S8) but did not modulate control items (all permutation $P > 0.08$; Supplementary Materials and table S8). riPHs were also not related to movement differences across conditions (permutation $P = 0.99$; Fig. 2C), confirming that sensorimotor stimulation (and not movement differences) applied with the MR-compatible robot modulated PH intensity across conditions.

To identify the neural mechanisms of riPH, we conducted two different fMRI analyses that are complementary and of equal importance: we investigated (i) the brain regions that were more activated during the asynchronous versus synchronous condition (spatio-temporal

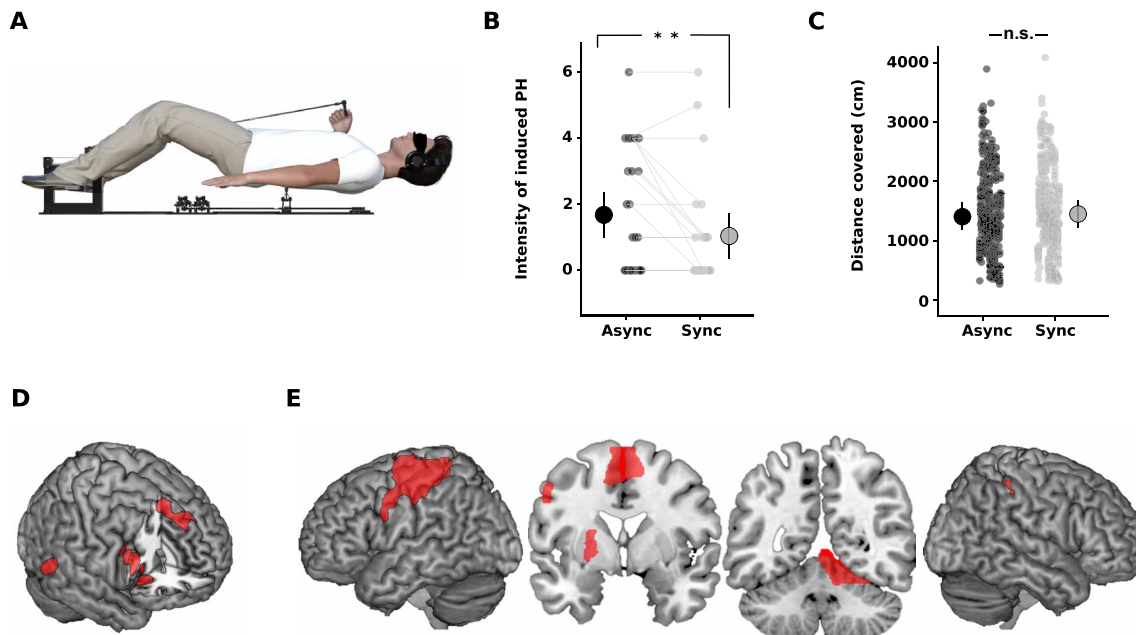


Fig. 2. Neuroimaging results of riPH (healthy participants). (A) MR-compatible robotic system is shown. Participants were instructed to move the front robot with their right hand, and the back robot delivered the touch to the participant's back either synchronously or asynchronously (500-ms delay between their movement and the sensory feedback received on the back). (B) Asynchronous versus synchronous condition induced stronger riPH. Each dot indicates the individual rating of the intensity of the riPH in healthy participants. The dots with the bar on the left and right sides indicate the mixed-effects linear regression between asynchronous (black) and synchronous (gray) sensorimotor stimulation. Error bar represents 95% confidence interval. $**P \leq 0.01$. (C) Movement data from the fMRI experiment. Each dot indicates the individual movement for each trial and participant. The dots with the bar on the left and right sides indicate the mixed-effects linear regression between asynchronous (black) and synchronous (gray) sensorimotor stimulation. (D) Brain regions sensitive to the delay. (E) Brain areas present in the conjunction analysis: asynchronous $>$ [motor + touch] \cap synchronous $>$ [motor + touch]. The coronal slices are at $Y = -1$ and $Y = -53$. There was no anatomical overlap between both networks (D and E).

sensorimotor conflict; asynchronous > synchronous and synchronous > asynchronous contrasts) and (ii) the brain regions more activated by both of the sensorimotor conditions (synchronous and asynchronous) versus two control conditions (motor and touch) (conjunction analysis, asynchronous > [motor + touch] \cap synchronous > [motor + touch]). The conjunction analysis enabled us to capture the brain regions that reflect the spatial sensorimotor conflict between the sensorimotor movement of the hand in front space and the feedback in the back, which is independent of the right-hand movements (motor control), independent of the tactile feedback (touch control), and independent of whether asynchronous or synchronous stimulation was carried out. The asynchronous versus synchronous contrast enabled us to detect changes related to the additional spatio-temporal contrast between the hand movement and the tactile feedback (fig. S4). Regions more activated during asynchronous versus synchronous sensorimotor stimulation were restricted to cortical regions (Fig. 2D and table S9) and included the inferior frontal gyrus (IFG), anterior insula, medial prefrontal cortex, and the posterior part of the middle temporal gyrus (pMTG; bordering on angular gyrus and adjacent occipital cortex). The synchronous > asynchronous contrast did not show any significant (all $P > 0.05$) brain activations. We also correlated riPH or passivity experiences ratings with the brain regions activated more during the asynchronous condition compared with the synchronous condition, and found no significant correlation (all $P > 0.05$ after correcting for multiple comparisons). Conjunction analysis (asynchronous > [motor + touch] \cap synchronous > [motor + touch]) (fig. S5) revealed a subcortical-cortical network in the left sensorimotor cortex [contralateral to the hand moving the robot, including primary motor (M1), somatosensory cortex (S1), and adjacent parts of the premotor cortex (PMC) and superior parietal lobule], bilateral supplementary motor area (SMA), right inferior parietal cortex (IPS), left putamen, and right cerebellum (Fig. 2E and table S10). Activations from the conjunction analysis (Fig. 2E) also did not correlate with PH or passivity experiences ratings (all P values of >0.05 after correcting for multiple comparisons).

Collectively, these fMRI results constitute a delineation of the neural underpinnings of riPH in healthy participants that is unrelated to movement differences across conditions and is distinct from activations in the two control conditions. The neural underpinnings of riPH reveal a network of brain regions that have been shown to be involved in sensorimotor processing and in agency [such as M1-S1, pMTG (42, 43), PMC (34, 44), SMA (43, 45), and IPS (29, 46), as well as the cerebellum (42, 47) and putamen].

cPH-network for sPH and riPH

To determine neural similarities between riPH and sPH and confirm the sensorimotor contribution to sPH, we first applied lesion network mapping analysis (48) and identified network connectivity mapping in neurological patients without PD, in whom sPHs were caused by focal brain damage, and then determined the cPH-network between the riPH and sPH. Lesion network mapping (48) extends classical lesion symptom mapping by considering each lesion as a seed region of interest (ROI) and computing its connectivity map [in normative resting-state fMRI data, publicly available database, using 126 healthy participants; (49)] (fig. S6).

This analysis revealed that all lesions had functional connectivity with the bilateral posterior superior temporal gyrus/temporo-parietal junction, bilateral middle cingulate cortex, bilateral insula, and right IFG, constituting the sPH network (Fig. 3A; for all regions, see table S11), and did not overlap with connectivity patterns of a control hallucination network, in which the same method was applied to a control group of 11 patients suffering from structured visual hallucinations (50) (Supplementary Materials and table S12). Further analysis showed that the brain lesions causing sPH were more strongly connected with the riPH network (as defined in healthy participants) than the lesions causing control hallucinations [difference between the two groups of lesions: $t(18) = 2.74$, $P = 0.013$; fig. S7]. The sPH network was defined as those PH regions that were not overlapping with the control hallucination-derived network. We then determined whether there were any common brain regions between the sPH network (neurological patients without PD) and the riPH network (healthy participants). For this, we performed an overlap between both networks, which identified the cPH-network consisting of three regions, including right IFG, right pMTG, and left ventral PMC (vPMC; two almost continuous PMC clusters; considered as one ROI for the following analysis) (Fig. 3B; Supplementary Materials). Additional bootstrap analysis showed that the Dice coefficient is stable and consistent with the original Dice value of 0.037 (mean Dice coefficient = 0.0327; SD = 0.012; Supplementary Materials). Last, we also intersected the 19 overlap maps and found consistent selection of the three key regions (vPMC, IFG, and pMTG).

These data show that riPH and sPH overlap in several brain regions, even if both types of PH differ in several aspects such as frequency, intensity, and trigger mechanism, supporting a link between sensorimotor robotics-inducing hallucinatory states with neuroimaging in healthy participants and neurological patients. These data further corroborate that riPH and sPH are not related to the tactile hallucinations by showing that the cPH-network does not

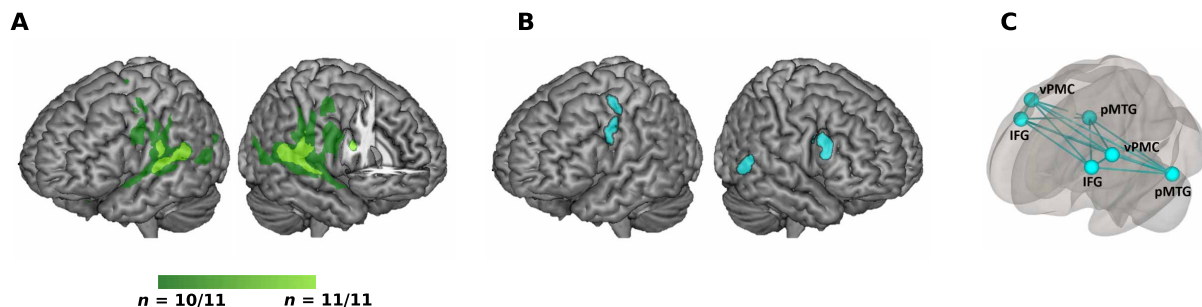


Fig. 3. sPH network and cPH-network. (A) sPH network connectivity in neurological nonparkinsonian patients. (B) Common regions between the riPH network and sPH network (cPH-network) were found in three regions: left ventral premotor cortex (vPMC), right inferior frontal gyrus (IFG), and right posterior middle temporal gyrus (pMTG). (C) Schematic display of the cPH-network projected bilaterally.

include key tactile brain regions (for example, S1), compatible with previous data for PH induced by invasive electrical stimulation (3) and lesion overlap analysis in neurological patients with sPH [insula and posterior temporoparietal cortex; (31)].

Functional connectivity analysis in cPH-network in patients with PD

To assess the relevance of the cPH-network for sPH experienced by patients with PD in daily life, we analyzed resting-state fMRI data in a new group of 30 patients with PD (table S13). We investigated whether functional connectivity within the cPH-network (projected bilaterally; Fig. 3C) differed between PD-PH ($n = 15$) and PD-nPH ($n = 15$). On the basis of the disconnection hypothesis of hallucinations (51), evidence of decreased connectivity for hallucinations of psychiatric origin (38), and aberrant functional connectivity in patients with PD and minor hallucinations including PH (25), we predicted that the functional connectivity within the cPH-network differs between the two groups of patients and that the connectivity within the cPH-network is reduced in PD-PH versus PD-nPH. We found the functional connectivity within the cPH-network, predicted with 93.7% accuracy whether a patient was clinically classified as PD-PH (κ : 0.86, permutation $P = 0.004$, using linear discriminant analysis; see Materials and Methods). Moreover, within the cPH-network, the functional connectivity between the left IFG and left pMTG contributed mostly to the classification of the two subgroups (Supplementary Materials and table S14). PD-PH had reduced left IFG-pMTG connectivity (permutation $P < 0.0001$; Fig. 4, A and B). These changes were selective because (i) the same analysis in a control network (fig. S8) (same size and same number of connections) did not predict the occurrence of hallucinations based on the functional connectivity (accuracy: 27.7%, κ : -0.43, permutation $P = 0.24$) and (ii) no changes in functional connectivity were observed when analyzing the whole-brain connectivity. To assess that the

prediction analyses above were not biased by the algorithm used, we conducted an additional analysis, using Random Forest (RF), and found that RF also significantly (accuracy: 87.5%, κ : 0.74, permutation $P = 0.039$) predicts whether a patient with PD is PD-PH or PD-nPH based on the cPH-network, and that the variable mostly contributing to the classification performance is the left IFG-left pMTG connection (table S15). The difference in connectivity between PD-PH and PD-nPH cannot be explained by differences in demographic or clinical variables (including antiparkinsonian medication, motor impairment, gender, or cognitive functioning; all permutation $P > 0.05$; table S13). These data show that reduced fronto-temporal connectivity within the cPH-network distinguishes patients with PD and sPH from those without hallucinations, in accordance with the disconnection hypothesis of hallucinations (51–53).

Functional disconnection within the cPH-network and cognitive decline in patients with PD and PH

It has been suggested that PHs (and minor hallucinations) are indicative of a more severe and rapidly advancing form of PD, evolving toward structured visual hallucinations and psychosis (10, 54), as well as faster cognitive deterioration including dementia (13, 55–57). We therefore tested whether functional connectivity between the left IFG-pMTG within the cPH-network relates to cognitive dysfunction in the present patients with PD-PH. Results show that stronger decreases in the left IFG-pMTG connectivity are associated with stronger cognitive decline [PD-Cognitive Rating Scale (CRS); (58)], reflecting differences in frontal-subcortical function ($P = 0.01$, $\rho = 0.69$; Fig. 4C), but not on posterior-cortical function ($P = 0.66$, $\rho = -0.15$; fig. S9) (the two correlations differ significantly: $t = 3.87$, $P < 0.01$). These results reveal an association between fronto-subcortical cognitive alterations and specific decreases in fronto-temporal connectivity within the cPH-network in PD-PH, compatible with a more severe form of PD associating PH and cognitive decline.

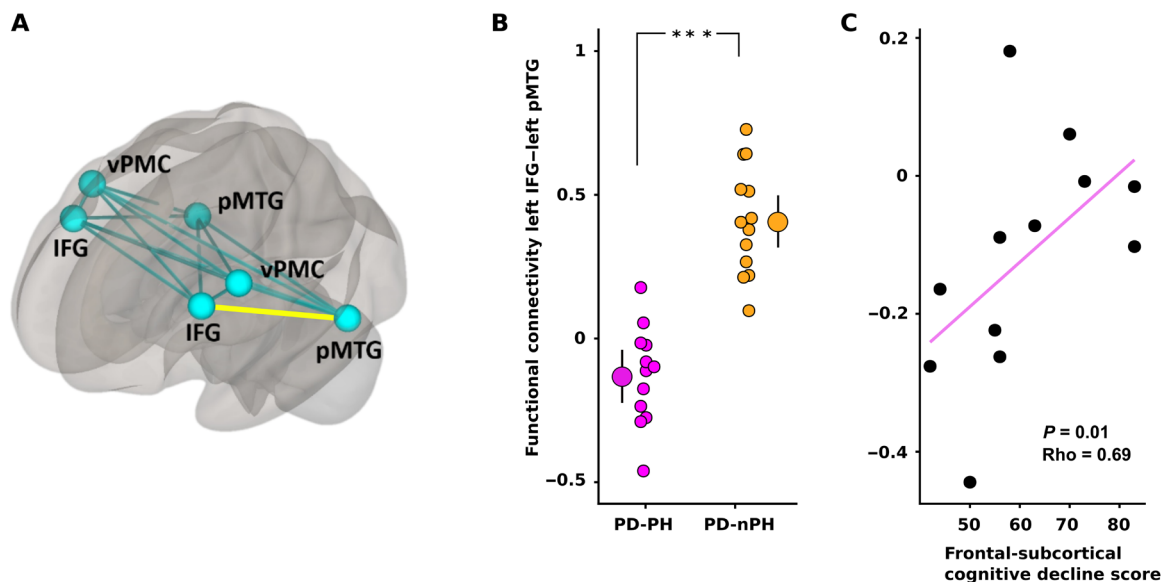


Fig. 4. Functional connectivity in the sensorimotor network. (A) Connections showing differences in functional connectivity between PD-PH versus PD-nPH within the cPH-network are shown (yellow). (B) Mixed-effects linear regression between the functional connectivity for PD-PH (purple) and PD-nPH (orange) between left IFG and left pMTG is shown. Error bar represents 95% confidence interval, and the dot represents the mean functional connectivity. Dots represent the functional connectivity for each patient. *** $P \leq 0.001$. (C) Degree of functional disconnection is correlated with the cognitive decline (frontocortical subscore of PD-CRS) in PD-PH.

DISCUSSION

Having developed a robotic procedure that can induce PH in patients with PD under safe and controlled sensorimotor conditions, we report that patients with PD and sPH are highly sensitive to the procedure and reveal abnormal sensorimotor mechanisms that may lead to PH. Using MR-compatible robotics in healthy participants combined with lesion network mapping analysis in patients with sPH of neurological non-parkinsonian origin, we identify the common network associated with PH and show that fronto-temporal connectivity within this cPH-network is selectively disrupted in a new and independent sample of patients with PD. Disruption of the cPH-network was only found in patients with PD suffering from sPH (PD-PH), and the degree of this disruption was further associated with the severity of cognitive decline.

The present behavioral findings show that stronger sensorimotor conflicts result in stronger riPH, supporting and extending previous evidence in favor of an alteration of self-related sensorimotor processing as a fundamental mechanism underlying PH (31, 41). We show that this mechanism is especially vulnerable in PD-PH, revealed by their stronger bias and sensitivity when exposed to conflicting sensorimotor stimulation. These results extend the sensorimotor forward model to PHs in PD-PH (37, 38, 40) and support earlier evidence in neurological patients (without PD) that have classified PH among disorders of body schema and have further associated PH with altered sensorimotor self-monitoring (3, 7, 8). Altered sensorimotor monitoring has also been reported in research on psychosis of psychiatric origin, suggesting that hallucinations are based on aberrant sensorimotor processes (32, 38, 39) leading to a misattribution of self-generated actions to others (patients' failure to ignore irrelevant stimuli that result from their own actions are erroneously processed as being externally generated). Our findings cannot be related to a general response bias related to PD because riPHs were absent or weaker in PD-nPH and because the control items showed no effects in any of the participant groups.

It could be argued that our procedure may have induced a mere tactile hallucination or misperception. However, this is not the case because our procedure manipulated specific sensory and motor mechanisms, which did not only involve tactile stimulation on the back but also involved additional proprioceptive, tactile, and motor cues (from the upper limb), as well as additional robotically controlled spatiotemporal cues (related to the incongruency between these proprioceptive-tactile-motor signals). Tactile cues alone are not sufficient to induce riPH: If riPHs were tactile hallucinations or misperceptions, then every experimental condition (even the synchronous condition) should lead to PH because they also contain tactile cues. However, this was neither the case in our study nor in previous work (31, 41) (Supplementary Materials).

By including fMRI data from healthy participants experiencing riPH and from patients with sPH suffering from nonparkinsonian neurological illnesses, we mapped common brain structures between both types of PH, which we showed to be selectively disrupted in patients with PD and sPH. The imaging results within this cPH-network revealed that aberrant functional connectivity decreases between fronto-temporal regions that have been associated with outcome processing of sensorimotor signals and the forward model (53, 59), further linking PH in PD to the fronto-temporal hallucination disconnection model (51, 53, 60) that has associated hallucinations with aberrant sensorimotor processes and a disruption of the fronto-temporal communication (60, 61).

Although not tested directly, we argue that the present cPH-network and reported disruption may also be of relevance for patients with PD suffering from other minor hallucinations or structured visual hallucinations. Thus, the implication of the pMTG in PD-PH is in line with previous work showing impairments within the dorsal attentional networks and default mode network (DMN) for minor hallucinations (25) and structured visual hallucinations (62, 63) that have both been shown to involve the pMTG region. More brain imaging work and longitudinal studies in patients with PD are needed, directly investigating the potential common and distinct brain networks involved in PH and visual hallucinations, especially with respect to attentional and DMN networks.

Our finding shows that the decreased fronto-temporal connectivity within the cPH-network is associated with stronger cognitive decline of PD-PH in frontosubcortical (but not posterior-cortical) functions, lending support to clinical suggestions about the importance of PH (and other minor hallucinations) as a major risk factor not only for the occurrence of structured visual hallucinations and psychosis (54) but also for a more severe and rapidly advancing form of PD (10, 13, 55, 57). Because the phenomenology of riPH resembles those of sPH in PD-PH, and the PD-PH group was found to be more sensitive to the riPH, the present procedure provides researchers and clinicians with objective possibilities to assess the occurrence and intensity of subjective hallucinatory phenomena by quantifying delay sensitivity. This includes the possibility to induced online, repeatedly, and under controlled conditions hallucinatory states in patients with PD, as well as the association of these measures with cPH-network activity. This is not possible in current clinical practice that is based on clinically important but post-hoc interviews between physician and patient, often about hallucinations that have occurred many days or weeks ago and that many patients hesitate to speak about (18). The detection of specific behavioral and imaging changes associated with specific hallucinatory states that are observed online during the robotic procedure might improve the quantification and prediction of a patient's proneness to PH, potentially for other minor and traditional hallucinations and psychosis, and may facilitate targeted pharmacological interventions that limit side effects (64).

There are several limitations to our findings. First, to investigate the brain mechanisms of riPH in healthy participants, we only used 0- and 500-ms delays (and two control conditions) instead of the multiple delay conditions tested in the behavioral experiment. The use of several conditions of sensorimotor conflict in future imaging work will likely allow us to define more fine-grained layers of the riPH brain network. Second, the brain mechanisms of sPH in parkinsonian versus other neurological origins (such as epilepsy, stroke, or brain tumor) may differ in some aspects. Therefore, future neurological research should investigate these separately, even though patients with focal brain damage causing PH are very rare. Third, future work should record fMRI while patients with PD are exposed to the robotic device and procedure, allowing to determine the brain networks related to riPH in PD and to assess how this relates to alterations observed using resting-state fMRI. Last, to further corroborate the relevance of PH in psychosis and cognitive decline, future work should assess longitudinally the clinical evolution of patients with PD and PH.

MATERIALS AND METHODS**Study design**

Objectives of the study were to (i) investigate the possibility to induce robot-controlled PH in patients with PD; (ii) assess potential

differences in sensitivity to riPH in different subgroups of patients with PD; (iii) assess the role of sensorimotor processes (delay dependency) of riPH using robotics; (iv) determine the neural network of PH (cPH-network), by combining MR-compatible robotics in healthy participants with brain network analysis in neurological patients without PD but with PH; and (v) predict patients' hallucinatory state based on pathological functional connectivity patterns within the cPH-network during resting-state fMRI. For each experiment, each participant underwent the same experimental procedures, and conditions were randomly presented to the participant. The sample size was not predetermined through statistical methods. The investigators were not blinded to the experimental conditions during experiments and the analyses.

General experimental procedure *riPH in patients with PD*

To investigate riPH, we adapted the experimental method and device of our previous research (31). Briefly, sensorimotor stimulation was administered with a robotic system consisting of two robotic components (front robot and back robot) that has previously been used to induce PH. For each experimental session, we applied the following conditions: synchronous sensorimotor stimulation and asynchronous sensorimotor stimulation (consisting of an additional temporal delay between the front robot and the back robot; Fig. 1A). During the sensorimotor stimulation, participants were always asked to keep their eyes closed and were exposed to continuous white noise through headphones (for more details, see the Supplementary Materials).

riPH in patients with PD (asynchronous versus synchronous stimulation)

Participants were asked to insert their index finger in the haptic front robot and carry out repeated poking movements, whereas they received tactile cues on their backs, delivered by the back robot. Thus, sensorimotor stimulation included motor, tactile, and proprioceptive signals from the upper limb moving the front robot and additional tactile signals from the back robot. Stroking was applied either synchronously (0-ms delay) or asynchronously (500-ms delay) (Synchrony: asynchronous versus synchronous). In addition, we measured the effect of the side of the body (hand moving the front robot) that was most strongly affected by PD versus the other hand (Side) to investigate whether the hemisphere predominantly affected by PD influenced riPH (65, 66). The factors (Synchrony; Side) and the order of testing were randomized across participants. Each participant randomly started with one side first, for which the two Synchrony conditions (random order) were tested, and then the second side was tested with the two Synchrony conditions (random order). In total, each participant performed four sessions (one per condition) lasting 2 min each. At the end of each of the four sensorimotor stimulation conditions, participants filled a questionnaire (six questions) adapted from (31) to measure riPH and other induced illusions. Participants were asked to indicate, on a seven-point Likert scale, how strongly they felt the sensation described by each item [from 0 (not at all) to 6 (very strong)]. For further details, see the Supplementary Materials.

riPH in patients with PD (sensorimotor delay dependency)

We applied a Yes/No task, after sensorimotor stimulation, in which participants were asked to report whether they experienced PH or not, on a trial-by-trial basis. On each sensorimotor stimulation trial, the delay between the movement and the stroking on the back was randomly chosen from a delay between 0 and 500 ms (steps of 100 ms).

The trial started with an acoustic signal (400-Hz tone and 100-ms duration) indicating the beginning of the trial: At this point, the participant started with the poking movements. Once the number of pokes reached a total of six (automatically counted), two consecutive tones (400 Hz and 100-ms duration) indicated to the participant to stop the movements and to verbally answer Yes/No to the PH question [question: "Did you feel as if someone was standing close by (behind you or on one side)?"]. The investigators were always placed >4 m away and in front of the participants during the experiment. Each participant was asked to perform three sessions of 18 trials (three repetitions per delay; see the Supplementary Materials).

Brain mechanisms of riPH in healthy participants using MR-compatible robotics

The experimental procedure was based on a pilot experiment performed in a mock scanner (see the Supplementary Materials). Participants were blindfolded during the task and received auditory cues through earphones to start (one beep) and to stop (two beeps) the movement. The paradigm was implemented using an in-house software (ExpyVR, <http://lnco.epfl.ch/expyvr>), and Visual studio 2013 interface (Microsoft) was used to control the robotic system.

Participants underwent two runs of 12 min each, during which they repeatedly had to move the front robot for 30 s with their right hand followed by 20 s of rest for a total of 16 repetitions per condition (eight repetitions for the motor and touch control conditions) (fig. S3). Synchronous and asynchronous conditions were randomized across runs. The questionnaire was presented at the end of the scanning session and after a randomized repetition of 30 s of each condition. The questionnaire was based on the pilot experiment and a previous study (31). More detail about the experimental procedure is given in the Supplementary Materials. fMRI data acquisition and data analysis are described in the Supplementary Materials.

Participants *riPH in patients with PD*

All participants provided written informed consent before the experiments. The study was approved by the Cantonal Ethics Committee of Geneva (Commission Cantonale d'Ethique de la Recherche sur l'Être Humain), the Cantonal Ethics Committee of Vaud. Participants consisted of patients with PD ($n = 26$) and age-matched healthy controls (HC; $n = 21$). On the basis of an extensive semi-structured interview (conducted after the experimental sessions) about hallucinations (including sPH), patients with PD were separated into two subgroups: patients who reported sPH as part of their PD (PD-PH) ($n = 13$) and patients without sPH (PD-nPH) ($n = 13$). Patients were considered as having sPH if they answered affirmatively to the question that previous investigators have used: "Do you sometimes feel the presence of somebody close by when no one is there?" The hallucinated presence could be located behind, on the side (left or right) of the patient, or in another room and was generally not seen (2, 3, 7, 9, 31). All patients who were included presented idiopathic PD diagnosed by trained neurologists. No patient was suffering from a neurological disorder other than PD (more details in the Supplementary Materials).

Brain mechanisms of riPH in healthy participants using MR-compatible robotics

None of the healthy participants had a history of neurological or psychiatric disorders. All participants provided written informed consent before the experiment. The study was approved by the Cantonal Ethics Committee of Geneva (Commission Cantonale d'Ethique de la

Recherche sur l'Être Humain). Twenty-five healthy participants (10 females; mean age \pm SD, 24.6 ± 3.7 years old; age range, 18 to 32 years old; Edinburg Handedness Inventory mean index, 64.8 ± 23.7 ; range, 30 to 100) took part in the experiment.

Functional connectivity analysis in cPH-network in patients with PD

Thirty patients were prospectively included from a sample of outpatients regularly attending the Movement Disorders Clinic at Hospital de la Santa Creu i Sant Pau (Barcelona) based on the fulfilling of Movement Disorder Society (MDS) new criteria for PD. Informed consent to participate in the study was obtained from all participants. The study was approved by the local Ethics Committee. Patients were included if the hallucinations remained stable during the 3 months before inclusion in the study. More details are provided in the Supplementary Materials.

Statistical analyses

riPH in patients with PD (asynchronous versus synchronous stimulation)

Each question was analyzed with linear mixed-effects models [lme4 and lmerTest both R packages; (67, 68)]. Models were performed on the subjective ratings in each of the four conditions with Synchrony (synchronous versus asynchronous), Groups (PD-PH versus PD-nPH and PD-PH versus HC), and Side as fixed effects and random intercepts for each participant. The significance of fixed effects was estimated with a permutation test [5000 iterations; predictmeans (69) R package].

riPH in patients with PD (sensorimotor delay dependency)

To investigate how the degree of sensorimotor conflict modulates PH, we analyzed the behavioral responses as a function of different delays (0 to 500 ms, steps of 100 ms) across groups (PD-PH versus PD-nPH). Trials were averaged for each delay and participant. Here, the data were analyzed with a linear model, fitted for each participant independently. We assessed (i) the main effect of the delay (on the intensity of riPH) with a permutation test (5000 iterations) between slopes of the individual fit versus zero, (ii) the difference between the slopes of PD-PH versus PD-nPH with a permutation test between the slopes of the two subgroups, and (iii) the main effect of group with a permutation test on the intercepts between the two subgroups.

Brain mechanisms of riPH in healthy participants using MR-compatible robotics

Questionnaire data were analyzed in the same way as in the riPH in patients with PD experiment. Synchrony (synchronous and asynchronous) was used as a fixed effect and the participants as random intercepts.

fMRI activation contrasts. The experimental runs were submitted to a general linear model analysis. In all runs, the periods corresponding to a given robotic stimulation (synchronous, asynchronous, motor condition, and touch condition; fig. S3) and the periods corresponding to the auditory cues were modeled as separated regressors. The six realignment parameters were modeled for each run as regressors of no interest. To avoid confounding effects due to the amount of movement performed in each trial, the quantity of movement of the front robot (synchronous and asynchronous for the experimental runs and movement condition for the motor localizer; see above) was included as parametric modulators of each condition.

Group-level analyses were performed using the contrasts defined for each participant. To determine which brain regions were involved in sensorimotor conflicts (spatio-temporal conflict and fixed spatial

conflict), the following contrasts were computed: asynchronous > [motor + touch] and synchronous > [motor + touch]. A conjunction between those two contrasts (asynchronous > [motor + touch] \cap synchronous > [motor + touch]) was performed to identify the regions involved in the fixed spatial sensorimotor conflicts. For the experimental runs, *t* tests (asynchronous > synchronous and synchronous > asynchronous) were performed to assess brain activations during a specific sensorimotor conflict. Results were thresholded at $P < 0.001$ at voxel level, and only the clusters surviving $P < 0.05$ family-wise error rate (FWE)-corrected for multiple comparisons were reported as significant. The obtained clusters were labeled using the Automated Anatomical Labeling (AAL) atlas (70) and the Anatomy toolbox (71).

Lesion network mapping analysis. To identify the brain regions functionally connected to each lesion location causing PH in neurological patients, we used lesion network mapping analysis (48, 72). Briefly, this method uses normative resting-state data from 151 healthy participants obtained from the publicly available enhanced Nathan Kline Institute Rockland Sample (49) and the lesion locations as seed ROI. The fMRI acquisition parameters are described in the Supplementary Materials.

The resting-state data were analyzed using the CONN-fMRI Functional Connectivity toolbox (v.18.a, www.nitrc.org/projects/conn) (73). The lesion masks were used as seed ROIs, and their mean time course was extracted and correlated to all other brain voxels. Each lesion seed yielded a brain network thresholded at $P < 0.001$ ($t \pm 3.37$) with $P < 0.05$ whole-brain FWE peak level corrected. The 11 networks were then binarized and overlapped to determine the regions of shared positive and negative correlations (fig. S6). The network overlap was thresholded at 90% (at least 10 of 11 cases) with a minimal cluster extent of 50 voxels. This procedure was repeated with the structured visual hallucinations lesions (Supplementary Materials).

Functional connectivity analysis in cPH-network in patients with PD

Regions of interest. The cPH-network [right pMTG ($x = 54$, $y = -54$, and $z = 0$), the right IFG ($x = 51$, $y = 18$, and $z = 29$), and the left vPMC ($x = -53$, $y = 1$, and $z = 37$) were transposed bilaterally to ensure that the cPH-network is not affected by any effects of movement-related laterality of activation observed in the riPH networks (Fig. 3B). Clusters were built using FSL (<https://fsl.fmrib.ox.ac.uk/fsl/>). A control network was derived by shifting each region ($x \pm 0/20$; $y + 30$; $z - 15$) of the cPH-network (fig. S8). This approach allowed controlling for the exact same shape and number of voxels as original cPH-network areas. fMRI data acquisition and data analysis are described in the Supplementary Materials.

Whole-brain connectivity. To investigate the whole-brain functional connectivity differences between the patient groups, a hypothesis-free (voxel-to-voxel) approach using the CONN toolbox was applied (see the Supplementary Materials for more details).

Patient classification based on functional connectivity in the cPH network. To assess whether the functional connectivity of the cPH network predicted if a patient was clinically classified PD-PH (or PD-nPH), we conducted a leave-one-out cross-validation procedure with a linear discriminant analysis [using Caret R packages; (74)]. Each possible connection within the cPH-network was used as a variable for the classifier. To ensure that the κ value was above chance level, we conducted a permutation test (5000 iterations). At each iteration, functional connectivity values were permuted between subgroups, and the cross-validation procedure was repeated.

Post hoc analyses for the between-group differences were performed using a permutation tests (5000 iterations) on the connection, which mostly contributed to the decoding. Connectivity outliers (8.75% of all data points) were identified on the basis of 1.5 interquartile range from the connectivity median value for each connection.

Functional disconnection within the cPH-network and cognitive decline in patients with PD and PH

To assess whether the functional disconnection is associated with cognitive decline in the PH-PH group, we computed a Spearman two-tailed correlation analyses between the functional connectivity within cPH-network areas (we selected the functional connectivity that explained mostly the classification of the patient) and the neuropsychological measures of the PD-CRS. One correlation was calculated for the frontal-subcortical PD-CRS score and one for the parietal-cortical score. Difference between these two correlations was assessed using the Steiger Tests [psych R package; (75)]. In the Supplementary Materials, the raw data for experiments with less than 20 samples are reported (data file S1).

SUPPLEMENTARY MATERIALS

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Materials and Methods

Fig. S1. riPH (patients with PD and HC).

Fig. S2. Analysis of the movement patterns during the sensorimotor stimulation.

Fig. S3. The different conditions assessed with MR-compatible robotic system.

Fig. S4. Sensorimotor conflicts present in the robotic experiment.

Fig. S5. riPH network.

Fig. S6. Lesion network mapping analysis.

Fig. S7. Lesion connectivity with the riPH network.

Fig. S8. Control regions for the resting-state fMRI analysis of patients with PD.

Fig. S9. Correlation between functional connectivity and posterior-cortical cognitive score.

Table S1. Phenomenology of the sPH in PD.

Table S2. Clinical variables for PD-PH and PD-nPH.

Table S3. Clinical variables for PD-PH and HC.

Table S4. Mean ratings for all questions and experimental conditions.

Table S5. Statistical results for the ratings for all questions (from asynchronous versus synchronous stimulation) and experimental conditions.

Table S6. Statistical results for sensorimotor delay dependency, when comparing PD-PH and HC.

Table S7. Mean ratings for all questions used in the mock scanner experiment.

Table S8. Mean ratings for all questions of the fMRI questionnaire.

Table S9. Spatiotemporal sensorimotor conflict PH regions.

Table S10. Robotically induced brain activations.

Table S11. sPH-derived network.

Table S12. visual hallucination (VH)-derived network.

Table S13. Clinical variables for PD-PH and PD-nPH.

Table S14. Patients' classification based on functional connectivity and linear discriminant analysis algorithm.

Table S15. Patients' classification based on functional connectivity and RF algorithm.

Movie S1. MRI robot.

Movie S2. Reports from patients with PD and PH after riPH.

Data file S1. Raw data for experiments with less than 20 samples.

References (76–87)

[View/request a protocol for this paper from Bio-protocol.](#)

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of the feeling of a presence) held by the Swiss Federal Institute (EPFL) that covers the robot-controlled induction of the feeling of a presence (PH). O.B. and G.R. are inventors on patent US 10,349,899 B2 (Title: System and method for predicting hallucinations) held by the Swiss Federal Institute (EPFL) that covers a robotic system for the prediction of hallucinations for diagnostic and therapeutic purposes. O.B. and G.R. are cofounders and shareholders of Metaphysics Engineering SA, a company that develops immersive technologies, including applications of the robotic induction of PHs that are not related to the diagnosis, prognosis, or treatment of PD. O.B. is member of the board and shareholder of Mindmaze SA. P.K. reports personal fees from Boston Scientific, outside the submitted work. **Data and materials availability:** Matlab and R code are available on https://gitlab.epfl.ch/fbernasc/sensorimotor_hallucinations_pd.git; behavioral and MRI data are available on zenodo.org (<https://zenodo.org/deposit/4423384>). All the remaining data are present in the main text or the Supplementary Materials.

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Robot-induced hallucinations in Parkinson's disease depend on altered sensorimotor processing in fronto-temporal network

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Grasping hallucinations in PD

Nearly half of the patients with Parkinson's disease (PD) experience hallucinations, and recent studies have shown that hallucinations are associated with negative cognitive outcome and higher mortality. Now, Bernasconi *et al.* used a robotic method to induce hallucinations in patients with PD to study the mechanisms behind this symptom. The authors identified a subgroup of patients with increased sensitivity to hallucinations and used magnetic resonance to show that frontotemporal connectivity, associated with hallucinations in healthy participants, was disrupted in patients with PD suffering from hallucinations. The results might improve diagnosis of hallucinations in patients with PD and facilitate the development of targeted therapies.

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