Neuroscience robotics for controlled induction and real-time assessment of hallucinations

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Although hallucinations are important and frequent symptoms in major psychiatric and neurological diseases, little is known about their brain mechanisms. Hallucinations are unpredictable and private experiences, making their investigation, quantification and assessment highly challenging. A major shortcoming in hallucination research is the absence of methods able to induce specific and short-lasting hallucinations, which resemble clinical hallucinations, can be elicited repeatedly and vary across experimental conditions. By integrating clinical observations and recent advances in cognitive neuroscience with robotics, we have designed a novel device and sensorimotor method able to repeatedly induce a specific, clinically relevant hallucination: presence hallucination. Presence hallucinations are induced by applying specific conflicting (spatiotemporal) sensorimotor stimulation including an upper extremity and the torso of the participant. Another, MRI-compatible, robotic device using similar sensorimotor stimulation permitted the identification of the brain mechanisms of these hallucinations. Enabling the identification of behavioral and a frontotemporal neural biomarkers of hallucinations, under fully controlled experimental conditions and in real-time, this method can be applied in healthy participants as well as patients with schizophrenia, neurodegenerative disease or other hallucinations. The execution of these protocols requires intermediate-level skills in cognitive neuroscience and MRI processing, as well as minimal coding experience to control the robotic device. These protocols take ~3 h to be completed.

Introduction

Hallucinations are defined as aberrant perceptual experiences that take place in the absence of corresponding external stimuli. They can occur in a single (i.e., auditory) or multiple sensory modalities (i.e., auditory and visual), and their content may be simple or complex. Insight into the aberrant origin of hallucinatory experiences (i.e., recognizing the hallucination as a false perception by the patient) may be lost in some individuals [1,2]. Hallucinations occur in 5–10% of the general population, in the absence of any diagnosed disease or disorder[3], are more frequent in the elderly[4,5] and have been reported in up to 50% following bereavement[6,7]. Hallucinations are also of medical importance and are reported in various clinical populations. For example, hallucinations are prominent clinical features in patients with psychiatric and neurodegenerative diseases, such as schizophrenia[8], dementia with Lewy bodies (DLB)[9] and Parkinson's disease[10]. However, the sensory modality, frequency and severity of hallucinations differs across these conditions.

Schizophrenia is a psychiatric disorder with symptoms typically starting in late adolescence or early adulthood, and includes psychotic symptoms such as hallucinations, delusions and thought disorder, often requiring lifelong treatment[8]. Hallucinations are among the most frequent symptoms in schizophrenia, and predominantly consist of auditory hallucinations (voices, defined as auditory verbal hallucinations (AVHs); 60–80% of patients[11]), but other hallucinations such as visual hallucinations may also occur (simple visual patterns, people, animals; 30–50% (ref. [11])). A frequent but less investigated hallucination in schizophrenia is the presence hallucination (PH; 46% (ref. [12]) defined as the vivid sensation that another person is nearby when no one is actually present and can neither be seen nor heard[13]).

In neurodegenerative disease, hallucinations are most frequently observed in DLB, the second most common neurodegenerative dementia following Alzheimer's disease[14–16]. Visual hallucinations occur in ~80% of such patients and have been identified as one of the three core features for the

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diagnosis of DLB (also including parkinsonian motor symptoms and cognitive decline)[14]. PH and AVH are less frequent, and both are described in 20–40% of patients with DLB[17–19].

Although Parkinson's disease is primarily defined as a movement disorder (i.e., rigidity, tremor and bradykinesia), approximately half of the patients with Parkinson's disease suffer from hallucinations, which increase in frequency and severity as the disease progresses. Visual hallucinations, PH and auditory hallucinations have been described in 30–60% (refs. [10,20]), 25–42% (refs. [21,22]) and 5–15% (ref. [18]) of patients with Parkinson's disease, respectively. Hallucinations in Parkinson's disease are associated with and have been argued to be putative predictors of major negative clinical outcomes such as delusions, cognitive decline and dementia, as well as earlier home placement and a higher risk of mortality. Moreover, there is growing consensus that hallucinations in Parkinson's disease form a continuum progressing throughout the disease[10,22,23], with the typical scenario starting with the so-called minor hallucinations (PH, passage hallucinations (brief images of a person or animal passing sideways, within the peripheral visual field) and visual illusions) with preserved cognition that evolves towards visual hallucinations and cognitive decline and dementia. Because of the earlier onset of minor hallucinations (i.e., they may occur in some cases even before motor symptoms[24]) and their likely transition towards visual hallucinations, it has been argued that minor hallucinations, including PH, may be an early indicator of a more severe form of Parkinson's disease[22,25].

Despite the elevated frequency and clinical importance of hallucinations in several neurological and psychiatric diseases (e.g., refs. [10,11]), hallucination research is hampered by the low number of devices and experimental approaches for hallucination induction. Previous attempts to elicit hallucinations, such as drug-induced hallucinations or those induced by automatized visual stimulation (i.e., flicker-induced hallucinations), mostly failed to induce clinically relevant hallucinations (i.e., resembling those experienced by patients in daily life). These methods also do not induce specific hallucinations with clear onset and offset, but rather complex multisensory hallucinations with highly variable onsets–offsets. Moreover, the intensity of such induced hallucinations may vary and can be associated with more severe alterations of consciousness (i.e., clouding of consciousness, delirium and agitation) that limit their impact for clinical, legal and ethical reasons (for more details, see 'Comparison with other methods').

Hallucinations are subjective and private experiences, and current methods to investigate and evaluate spontaneous hallucinations are based on self-reports and interpretations of those reports by investigators, known to be associated with several limitations. Verbal reports and graphical depictions often only capture some aspects of conscious experience and are prone to the well-known participant and experimenter biases[26,27], which may be exacerbated in patient populations. Reporting hallucinations is further affected by the fear of stigmatization, which often causes patients to refrain from reporting them openly to caregivers and clinicians[23]. The unpredictable and spontaneous appearance of hallucinations, often outside the hospital or research setting, further complicates their study. Finally, it is very unusual for research to be able to investigate the hallucination of a given participant in real-time, that is, while the person is undergoing a hallucinatory experience.

Another major shortcoming is that hallucination research is biased towards research in patient populations, despite the demonstration that they can also occur in healthy individuals[3]. Investigating how hallucinations arise in the nervous system of healthy individuals, in parallel with patient studies, will improve our possibilities of understanding the actual mechanisms underlying hallucinatory perceptions; because healthy individuals do not have confounding medical variables present in most patients, such as medications, comorbidities, neuropsychological deficits or impairments of consciousness[28]. Therefore, laboratory-based methods and procedures allowing the repeated, safe, controlled and real-time induction of well-defined hallucinations are critical to determine their behavioral and brain mechanisms and to develop new diagnostic and prognostic tools for different disorders characterized by hallucinations.

Development of the protocol

By integrating clinical observations and recent advances in cognitive neuroscience in healthy participants with robotics, we have designed a new method able to induce a specific, clinically relevant, hallucination in healthy participants: PH. Such robot-induced PH (riPH) were induced repeatedly and in real-time in the laboratory or in different clinic settings and were controlled by a robotic device across several experimental conditions. The method for riPH was developed and first investigated in
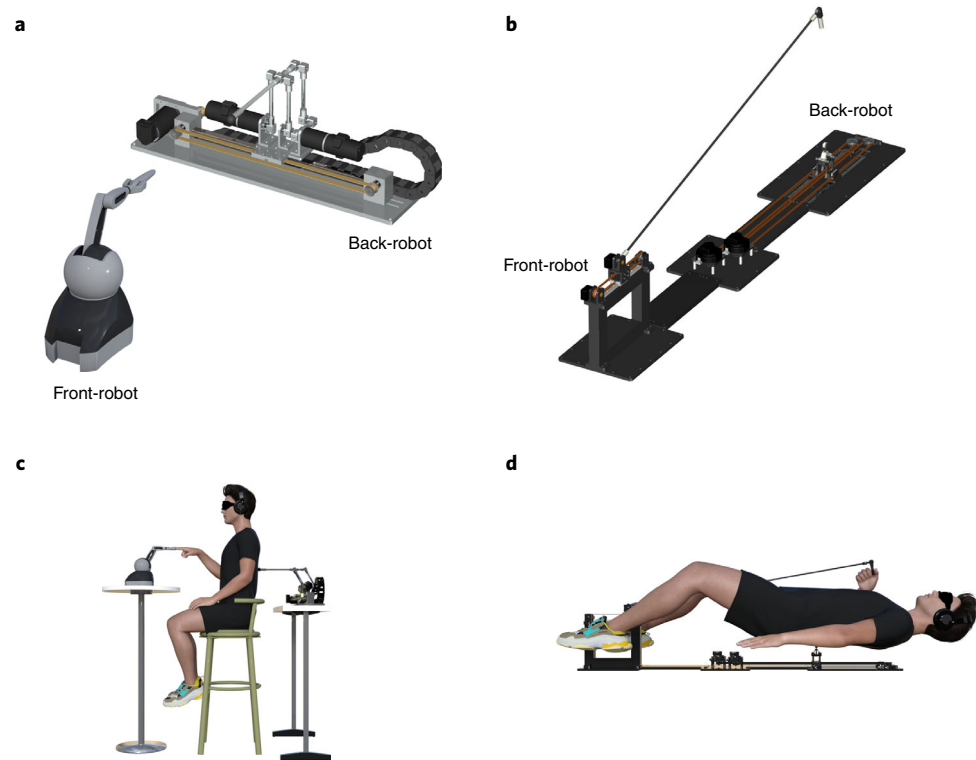
Fig. 1 | Robotic setup. a, Behavioral robotic device. **b**, MR-compatible robotic device. **c**, Behavioral setup allowing the induction of riPH, depending on the sensorimotor condition. **d**, MR setup allowing the induction of riPH, depending on the sensorimotor condition. The participant is lying on the back-robot (the plank on which the participant is laying on has been removed from the illustration to avoid hiding the back-robot).

healthy participants[29–31] and subsequently tested in patients with Parkinson's disease[31] and schizophrenia[32].

Previous work suggested that hallucinations such as AVH, but also related sensations such as loss of agency and passivity experiences, may be associated with altered sensory prediction of self-generated actions[33,34] and the inability to update or increase the precision of this prior[2]. Impairments in sensory prediction and sensorimotor integration have also been associated with PH in patients with neurological disorders[29,35,36]. Furthermore, invasive electrical stimulation (in a patient undergoing presurgical epilepsy evaluation) of the temporoparietal cortex, which is associated with sensorimotor integration, resulted in the repeated and the controlled induction of PH[37], and damage to temporoparietal cortex and related regions has been associated with PH and sensorimotor deficits[29], corroborating the important role of altered sensorimotor processing in PH of neurological origin.

By integrating these clinical observations with the human neuroscience of own-body perception in healthy participants (i.e., refs. [38–40]) and advances in robotics, we developed the following robotic method and sensorimotor procedure for PH induction (Fig. 1). Participants are asked to perform repetitive movements to operate a robot placed in front of them (front-robot), which is combined with a back-robot providing tactile feedback (i.e., touches or strokes) to the participants' backs[41]. When such sensorimotor stimulation and tactile feedback are delivered with a delay between a participant's hand movements and the tactile feedback they receive on their back (i.e., asynchronous condition), they reported riPH (Fig. 2a,b)[29,31,32,42]. We further observed that an increase in such asynchronous delays (increase in sensorimotor conflict) increases the probability to induce an riPH[31] (Fig. 2c). However, when the tactile feedback is delivered synchronously with the participant's hand movements (synchronous control condition, but with a spatial conflict between the movement in front and touch feedback delivered on the back), participants did not experience riPH, but instead reported control sensations (e.g., illusory self-touch), compatible with previous works on own-body perception[38,39,43–46].

More recently, the robotic method and procedure were adapted for clinical research and it was shown that patients with Parkinson's disease and preexisting symptomatic PH (PD–PH) have a
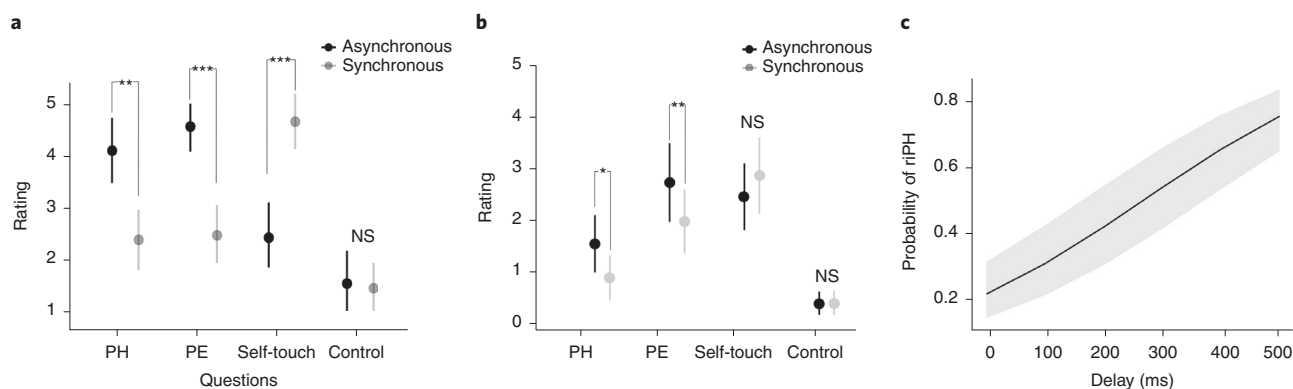
Fig. 2 | Behavioral results of the robotic sensorimotor stimulation. a, Questionnaires' results, showing a significant induction of riPH (and other illusions) during the condition with strongest sensorimotor conflict (results from ref. [29]). The dots indicate the mean ratings; the error bars indicate the 95% confidence interval. Data were analyzed fitting cumulative link mixed model. **b**, Questionnaire results using the MR-compatible robotic device (results from ref. [31]). The dots indicate the mean ratings; the error bars indicate the 95% confidence interval. Data were analyzed fitting cumulative link mixed model. **c**, riPH is modulated as a function of the sensorimotor delay. Data were analyzed fitting a binomial generalized linear mixed models. The thicker line indicates the mean of the fitted models; the shaded area indicates the 95% confidence interval. The questions are the following: (1) PH: 'I had the impression that someone was standing close to me, behind or next to me'; (2) passivity experience (PE): 'I had the impression that someone else was touching my back'; (3) self-touch: 'I had the impression that I was touching my back'. Asterisks indicate significant differences across sensorimotor conditions, for the indicated question. NS, not significant.

higher sensitivity to the riPH method, compared with patients with Parkinson's disease without preexisting symptomatic PH. In addition, PD–PH patients could experienced riPH to one side of their body and not only on their back (i.e., where the robotic tactile feedback was actually applied). Some patients directly likened the riPH with their symptomatic PH (~40%). These findings reveal relevant phenomenological similarities between such experimentally controlled riPH and the same patients' preexisting symptomatic PH that are often experienced by patients to one side of their body and of the same intensity: the conscious experience associated with riPH shares characteristics with spontaneously occurring symptomatic PH[31].

Overall, these results demonstrate that specific sensorimotor conflicts, including bodily signals from the arm and trunk, are sufficient to induce mild to moderate riPH, linking PH to the misperception of the source and identity of sensorimotor signals of one's own body. These data also show that riPH shares phenomenological characteristics with symptomatic PH. Moreover, riPHs were induced safely and repeatedly and were robotically controlled across experimental conditions, which has not been achieved before. This enables the repeated real-time assessment of a specific hallucination compared with standard assessments based on the retrospective evaluation of spontaneously occurring hallucinations that may have occurred days (or months before) and only a limited number of times. The assessment of riPH can be based on established procedures in human neuroscience, including among others hallucination proneness (measured with questionnaire or implicit measures (see below for more details)), qualitative measures (phenomenological description of the hallucination, e.g., spatial location) and behavioral readouts (e.g., drift in self-location, numerosity estimation).

By adapting the robotic technology[29], sensorimotor method and experimental protocol to the MRI environment, it has also been possible to identify the brain network associated with riPH in greater detail and in healthy participants[31]. Robotic sensorimotor stimulation activated a network of brain regions consisting of the inferior frontal gyrus (IFG), anterior insula, medial prefrontal cortex and the posterior part of the superior temporal sulcus (pSTS), especially in the asynchronous condition (Fig. 3). Moreover, additional research showed that these regions were partially overlapping with brain regions associated with the symptomatic PH of neurological origin (caused by stroke or focal epilepsy)[29]. This anatomical overlap (between the riPH fMRI network in healthy participants and the PH network in patients with neurological disorders suffering from non-parkinsonian neurological illnesses) allowed us to define a common cortical PH network that included the pSTS, the IFG and the ventral premotor cortex. We confirmed the relevance of this latter network in patients with Parkinson's disease by observing a disruption within this common PH network, describing altered connectivity between the left IFG and left pSTS. This disruption was found only in patients with Parkinson's disease with preexisting symptomatic PH, but not in patients with Parkinson's disease without such PH, revealing pathological cortical sensorimotor processing related to a specific hallucination in Parkinson's disease.
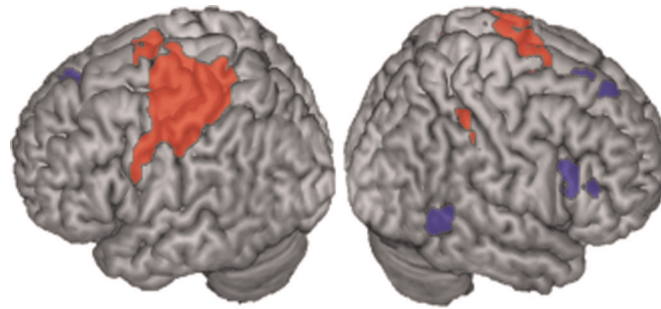
Fig. 3 | Brain network of riPH. Brain activations in the asynchronous > synchronous contrast (blue), showing the brain regions more activated in the asynchronous condition compared with the synchronous condition (results from ref. [31]). In red, the conjunction analysis asynchronous > [motor + touch] ∩ synchronous > [motor + touch] is shown (results from ref. [31]).This conjunction contrast highlights the brain regions involved in the spatial sensorimotor conflict between the sensorimotor movement of the hand in front space and the feedback in the back, independent of the sensorimotor delay.

Collectively, these results on riPH show that the robotic procedure can be used to induce specific hallucinatory states in realtime, repeatedly, and under controlled conditions in patients with Parkinson's disease and in healthy individuals. The hallucinatory states are associated with a specific brain network that is disrupted in patients with Parkinson's disease with preexisting symptomatic PH. The possibility to study a clinically relevant hallucination in healthy individuals will further allow research to progress faster (avoiding limitations due to patient recruitment and testing) and to identify the mechanisms and brain networks without clinical confounds (medications, comorbidities, neuropsychological deficits or impairments of consciousness) present in many patient populations. Investigating a specific hallucination in real-time also allows a reduction in confounds arising from recollecting and interpreting complex subjective reports about hallucinations that have occurred outside the controlled laboratory environment and also facilitates the real-time study of the neural correlates of specific hallucinations and their potential as hallucination biomarkers, which is very challenging for spontaneously occurring hallucinations (which are often associated with other clinical confounds).

Applications of the method

Schizophrenia, a psychiatric disorder with a worldwide prevalence of ~1% (ref. [47]), is characterized by psychotic symptoms that require lifelong treatment[8]. AVHs are the most prevalent hallucination experienced in schizophrenia and have been suggested to arise from abnormal sensorimotor prediction[2,48] and, among others, the inability to update the priors associated with these sensorimotor signals[2].

We recently adapted our robotic protocol that induces riPH to the investigation of the relation between sensorimotor stimulation and auditory voice perception[49]. Evidence from healthy participants[49] showed that conflicting sensorimotor stimulation applied with the robotic method resulted in systematic and predictable errors in voice perception. Similarly, results from patients with psychiatric disorders who have early psychosis showed a selectively reduced accuracy in auditory–verbal (self–other) discrimination during conflicting sensorimotor stimulation applied with the robotic method, especially in individuals suffering from so-called first-rank symptoms, including AVH and delusions[32].

These results confirm an association between altered sensorimotor processes and auditory–verbal misattribution that is typically observed in schizophrenia. Recent neuroimaging results corroborated and extended these behavioral findings by showing that the common PH network (as described above) in a large group of patients with early psychosis was characterized by alterations of the common PH network and its connectivity with Heschl's gyrus, a brain region linked to auditory perception and auditory–verbal hallucinations[50]. More work is needed to directly investigate the behavioral and brain mechanisms of symptomatic PH and riPH in schizophrenia[12] and how the sensorimotor PH mechanisms relate to those of AVH, delusions and related cognitive functions in schizophrenia, as recently shown for the psychosis-related phenomenon of thought insertion[42].

DLB, a neurological disorder, and the second most common dementia subtype[51], is typically characterized by hallucinations, which are one of the three defining symptoms for DLB diagnosis.

Despite the high prevalence of PH in DLB, very little is known about the brain mechanisms underlying this specific hallucination in DLB, as past research has predominantly focused on visual hallucinations. By adapting our robotic sensorimotor procedure to patients with DLB, we may be able to further elucidate the (aberrant) brain mechanisms of PH and also determine overlapping and distinct PH mechanisms by comparing PH in patients with DLB versus those of patients with Parkinson's disease and healthy controls[31]. This would provide us with additional information on the neural causes of symptomatic PH and how this depends on disease type, and eventually aid in differential diagnosis among PH of neurodegenerative origin. Recent work allowed us to demonstrate that patients with DLB and symptomatic PH are characterized by alterations in the common PH network[52]. Additional research is required to investigate whether these PH-related alterations precede those associated with visual hallucinations (one of the key symptoms of DLB), as observed for Parkinson's disease. Finally, hallucinations, including PH, in patients with Parkinson's disease have been associated with cognitive decline[10], and riPH will help the investigation of such associations in patients with DLB, requiring longitudinal clinical research.

Hallucinations are not only associated with psychiatric or neurodegenerative disease but are also experienced by the general population in the absence of any diagnosed disease or disorder[3]. For instance, 20% of individuals over 60 years of age have reported experiencing hallucinations[4,53], and PH have been observed in 5% of those individuals. Whether these events are indicative of the onset of mild cognitive decline or are limited to specific events such as traumatic events (bereavement[53]) is still unknown. However, tremendous current research efforts are dedicated to the early detection of dementia, its distinction from normal age-related decline and the early distinction between cognitive decline in Alzheimer's disease versus DLB and other dementias[54,55]. We suggest that the adaptation and further integration of the described riPH procedure with other psychophysical, neuropsychological, clinical and neuroimaging techniques may help early detection and differentiation of clinical early dementia from normal aging, by adding a hallucination–psychosis dimension to current cognitive evaluations.

Comparison with other methods

Alternative methods and procedures able to induce hallucinations by using experimental methods have been described, but are sparse and suffer from several limitations. Flicker-induced hallucinations[56,57], Ganzfeld-induced hallucinations[58] or visual/sensory deprivation[59,60] are among some of the most well-known methods. Although these methods are relatively effective in inducing hallucinations in healthy participants, they have been mostly used to investigate visual hallucinations and have limitations. The experimental control over the specific content of such induced hallucinations, as well as their onset and offset, is very low. Thus, there are multiple characteristics of the induced visual hallucinations (color, form and motion) that are very heterogeneous, which in addition typically change unpredictably over time. Such methods generally do not allow for the repeated induction of a hallucination within a short time period. Moreover, these methods do not seem to induce hallucinations that are comparable to those experienced by patients with neurological or psychiatric disorders (e.g., for flickering stimuli, see ref. [61]). Other procedures have employed conditioning-induced hallucinations by paring visual and auditory stimuli to evoke hallucinations in one or the other modality[62,63]. While this method is more reliable than the other procedures presented in this section, the time needed to induce such hallucinations can be relatively long, and the hallucinations induced are currently restricted to simple stimuli (e.g., tone or flash) and, therefore, rarely match the phenomenology of clinical hallucinations.

Other methods to induce and study hallucinations in healthy participants exist, but many of these have potentially serious side effects. For instance, it is possible to induce a range of complex hallucinations by pharmacological interventions (for a review, see ref. [64]). Substances like ketamine, lysergic acid diethylamide (LSD), phosphoryloxy-N,N-dimethyltryptamine (psilocybin) or N,N-dimethyltryptamine (DMT) have been investigated intensively in the past and have received renewed interest[64,65]. By combining such pharmacological interventions with behavioral, electro-encephalography and neuroimaging data, it has been possible to identify some of the brain mechanisms associated with drug-induced hallucinations. For instance, visual hallucinations have been associated with abnormal activation of the 5-hydroxytryptamine (serotonin) type 2A (5-HT2A) receptors[63]. These findings are of high relevance for the development of new pharmacological treatments aiming at treating hallucinations. However, pharmacological studies suffer from similar shortcomings as noted above for flicker- and Ganzfeld-induced hallucinations (i.e., onset, offset,

repetition in a short time frame, content, etc.). Moreover, higher doses may induce very intense hallucinations that may be associated with impairments of consciousness, making the real-time description and investigation (very) challenging. Lower doses, on the other hand, probably fail to induce hallucinations[63]. In addition, in most cases of drug-induced hallucinations, a large range of visual, auditory, somatosensory and other hallucinations are generally reported simultaneously, making the investigation of specific drug-induced hallucinations difficult. Drug-induced hallucinations also raise several ethical concerns (such as inducing uncontrolled psychotic episodes in healthy participants or providing psychoactive drugs to patients without being able to predict the reaction to the substance) that are not, or at least less, present in other hallucination-inducing techniques.

Finally, another method inducing hallucinations is based on invasive electrical stimulation of the brain, but can be applied only in highly specialized clinical settings and proposed to specific patient populations (for example, to patients with epilepsy undergoing invasive presurgical evaluation). Thus, electrical stimulation of specific brain regions has been shown to induce PH[37], simple and complex hallucinations[66], visual hallucinations[67], AVH[67], vestibular hallucinations[68,69] and somatosensory hallucinations[70]. Hallucinations induced by invasive brain stimulation can be considered the gold standard of linking brain circuits to hallucinations, owing to their high spatial resolution, full control of the stimulation and hallucination onset and offset, and the repeated induction of highly specific hallucinations, including PH[37]. However, this powerful approach is limited to rare patient explorations, requires a neurosurgical intervention and is not applicable for systematic experimental research in healthy people and other non-neurosurgical populations.

Experimental design

To experimentally investigate riPH, we have developed several distinct experimental procedures (1) based on comparing asynchronous versus synchronous sensorimotor stimulation conditions, (2) additionally manipulating somatosensory force feedback ('virtual back' in front of the participant) and (3) based on the determination of sensorimotor delay dependency.

General experimental procedure (for behavioral and brain imaging studies)

Robotic sensorimotor stimulation is administered with a robotic system[30,41] consisting of two robotic components (front-robot and back-robot) that we previously have used to induce PH[29,31,32,42]. Participants are asked to insert their index finger in the front-robot and carry out repeated poking movements while they receive tactile cues on their back, delivered by the back-robot (Fig. 1). Such sensorimotor stimulation includes motor, tactile and proprioceptive signals from the upper limb moving the front-robot and additional tactile signals from the back-robot. At the beginning of the experiment, after having explained and inspected the robotic setup, participants are instructed to perform several poking movements (in the synchronous condition) to become familiar with the robotic device, the movements and the tactile feedback. During the experimental conditions, participants are instructed to perform arm movements at a frequency of ~1 Hz (1 poke per second), and to explore their whole back with their movements (Fig. 4). Participants must be instructed not to count the time between pokes nor the number of pokes, but do the movement as learned during the training. During the sensorimotor stimulation, participants are either blindfolded or asked to keep their eyes closed for the remainder of the experiment. In addition, participants are exposed to continuous pink (or white) noise through headphones.

Spatiotemporal sensorimotor stimulation

This experimental protocol (Fig. 5) enables the investigation of riPH as well as other bodily experiences (self-touch, passivity experience, etc.)[29,31,32,42]. This protocol (spatiotemporal sensorimotor stimulation) has the advantage of being of very short duration and can therefore be done by most participants, including patients where time may be limited. The back stroking is applied either synchronously (0 ms delay; control condition) or asynchronously (500 ms delay) with respect to the movement performed by the participant with the front-robot.

The versatility of the robotic system provides the possibility to apply the touch feedback from the back-robot not only to the back, but also to other body parts (e.g., the hand). Because PH is associated with a misinterpretation of the global (trunk-centered) self[29], stimulating the hand should not induce riPH, but it can induce other illusions such as loss of agency or passivity experience (i.e., the illusion of being touched by someone else)[48,71]. It can therefore be used as control experimental conditions. The delays of 0 ms and 500 ms have been motivated by prominent work in sensorimotor and
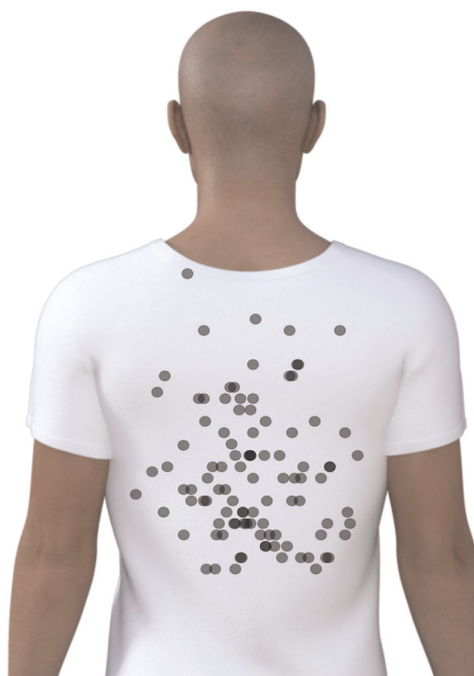
Fig. 4 | Example of back exploration done for the behavioral experiment. Each dot indicates a point in which the back-robot applied touch on the back of the participant.

multisensory integration and sense of agency, as well as the forward model of motor control that has been applied to bodily illusions[43,72–76] and hallucinations[48].

For behavioral experiments, the sensorimotor stimulation lasts 2 consecutive minutes for each of the experimental conditions (synchronous and asynchronous). In total, the experiment generates two datasets: (1) synchronous, 2 min; (2) asynchronous, 2 min, for a total of 4 min, with ~120 pokes per dataset (the value will vary depending on the participant's poking frequency). For fMRI experiments, the sensorimotor stimulation is reduced to 30 s. The order of the conditions must be randomized across participants. The assessment of riPH and other specific bodily illusions is done through explicit measures (for questionnaire, see Supplementary Table S1 and refs. [29,31,32,42]) or implicit measures such as self-location[29] or numerosity estimation[29] that are administered immediately after each condition. Self-location is quantified using the mental ball-throwing task, during which participants are asked to estimate (by pressing a button) the time that a ball they are holding in their hands would take to reach the wall if they were to throw it. Numerosity estimation is quantified asking participants to judge to how many people they feel close. Importantly, the participant must stay blindfolded during these tasks.

Somatosensory force feedback
This experimental protocol extends the spatiotemporal sensorimotor stimulation protocol and allows one to test how the induced PH depends on the force that participants apply at the front-robot and consequently receive on their back by the back-robot. The front-robot allows manipulation of the somatosensory force feedback (force conditions) that is applied on the back of the participant. Specifically, using an impedance control, a 'virtual wall' with a stiffness of 1.0 N/mm can be created with the front-robot. The virtual wall consists in a force applied by the front-robot in the opposite direction to the force done by the arm extension; this occurs only when the front-robot reaches the predefined coordinate in which the virtual wall is located. Hence, the participant will be able to extend the movement to a predefined distance (i.e., position of the virtual wall, after which the robot will stop the movement as if there was a 'virtual' wall beyond which no movement is possible. The force feedback also includes a mechanical stop occurring (synchronously or asynchronously) to the touch that the participant received on the back[29]. As for the spatiotemporal sensorimotor stimulation, riPH can be assessed with implicit and explicit measures.
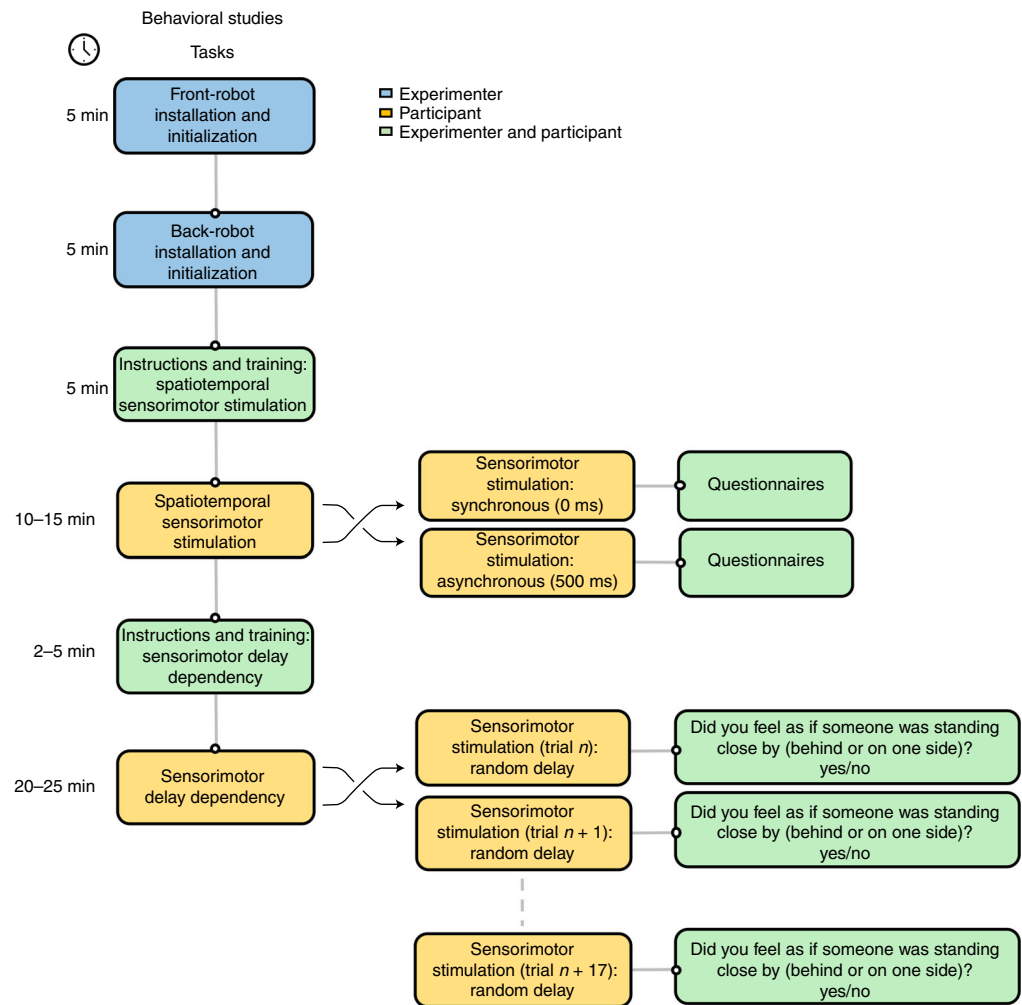
Fig. 5 | The experimental workflow for behavioral experiments is divided into three principal stages. First, initialization of the front and back-robot and installation of the participant is performed by the researcher (blue). Next, participants (yellow) will be given instructions and a short training session to familiarize themselves with the robotic setup and its use. Before starting the first experiment (i.e., 'Spatiotemporal sensorimotor stimulation'), participants are asked to wear headphones and a blindfold. In our previous work[31], the synchronous (0 ms) and asynchronous (500 ms) conditions were each performed for 2 min, each followed by a short questionnaire to assess the intensity of PH and other mental states. The arrow crossing indicates that the two experimental conditions must be randomized in order across participants. Finally, the researcher will instruct the participant on how to perform the second part of the study (i.e., 'Sensorimotor delay dependency'). In our previous work[31], the 'Sensorimotor delay dependency' task was repeated three times (18 trials per block, delays 0–500 ms). In total, each delay (between 0 and 500 ms, steps of 100 ms, six delays tested) was randomly repeated nine times. Thus, the total number of trials across all sessions and delays was 54. Experimental parameters can be adapted on the basis of the research questions and needs.

Sensorimotor delay dependency

This experimental protocol (Fig. 5) allows the assessment of the proneness to induced hallucinations (e.g., PH), and how this depends on the degree of the delay of the applied sensorimotor conflict. Compared with the spatiotemporal sensorimotor stimulation experimental protocol described above, here we use a two-alternative (yes/no) experimental paradigm, in which participants are asked to perform the poking movement (and receive the stimulation on the back) and then report (verbally), on a trial-by-trial basis, whether they experienced the hallucination or not (question: 'Did you feel as if someone was standing close by (behind you or on one side)?'), without opening their eyes. Compared with the experiment mentioned above, the trials here are shorter, lasting only ~10 s (longer or shorter duration are possible). Accordingly, here we can repeat the hallucination induction over many more trials as well as test several controlled experimental parameters (such as the delay, the position of the tactile feedback on the back, the presence/absence of the virtual wall, the duration

of the trials, etc.). In our previous work testing the effect of delay[31], in total, participants were exposed to three experimental blocks, and each block was composed of 18 trials consisting in random order of the different delay conditions. In total, each delay (between 0 and 500 ms, steps of 100 ms, six delays tested) was randomly repeated nine times. Thus, the total number of trials across all sessions and delays was 54. We note that the number of trials (as well as the other parameters) can be adapted on the basis of the experimental question and/or the population tested.

On each sensorimotor stimulation trial, the temporal delay between the movement and the stroking on the back is randomly chosen between 0 and 500 ms (with 100 ms steps)[31]. Larger delays (any delay) are also possible (maximum 3999 ms). The beginning of each trial in the delay protocol of our method is indicated by an acoustic signal (e.g., 400 Hz tone, 100 ms duration), and after this tone, the participant will start performing the poking movements. Once the number of pokes reaches the desired number (automatically counted using the force sensors; for example, six[31]), two consecutive tones (400 Hz, 100 ms duration) indicate to the participant to stop moving the robot and to verbally answer yes/no to the riPH question. To limit possible confounds, the investigators must always be placed as far as possible from the participant, and in front (not on the back or side) during the whole experiment. The order of the delays must be fully randomized. All the experimental parameters (e.g., delays, number of repetitions, etc.) can be adapted to the experimental needs. Similar to what is described above, we can manipulate the somatosensory force feedback and the body part stimulated.

Using different delays (presented randomly) has several advantages and provides the possibility to integrate several features from psychophysics into hallucination research and identify:

1   The type of association between delays and the induced PH;
2   A difference in sensitivity to the sensorimotor task between groups of participants (e.g., groups of patients) as indicated by a difference in slope of the fitted regression;
3   A difference in the propensity to reporting 'yes' (bias) would be reflected as a main effect of group (rather than a difference in slope).

fMRI protocol

To experimentally assess the brain mechanisms of PH (Fig. 6), we use an MR-compatible robotic system[30] to generate sensorimotor conflicts in a similar manner as described above, but adapted to the supine body position in the scanner. The front-robot consists of a rod attached on a revolution joint, itself attached to a slider allowing the participant to move in the X (along the body) and Z (towards the body) directions. The movement of the carbon-fiber rod is electronically translated into movements of the back-robot. The back-robot is composed of an effector that touches the participant on its back through stroking and tapping movements. Furthermore, its shape was adapted to the space inside the scanner, and a wooden mattress structure was specifically designed with a central slit to allow the tip of the back-robot to touch the back of the participants. The performance of the robotic system has been previously validated inside a 3 T and 7 T MR scanner with a vendor-supplied spherical phantom (Siemens)[31].

Comparable to the behavioral experiments described above, participants are blindfolded and are wearing headphones in order to receive the auditory cues to start (one tone) and stop the movement (two consecutive tones). During the fMRI session, in addition to the experimental conditions (see below for details) the anatomical T1-weighted image is also acquired for each participant (Fig. 6).

Spatiotemporal sensorimotor stimulation

Participants are asked to move the front-robot in a self-paced manner while receiving sensory feedback on their back either synchronously to the movement (synchronous condition) or with a

Fig. 6 | Experimental workflow for the fMRI experiment. First, the fMRI robotic system is installed and initialized by the researcher (blue). Then ▶ participants are laid (with earplugs, headphones and blindfold) in the MR bed on a mattress below which the back-robot is installed. Next, participants (yellow) receive the instructions and short training with the robotic setup, before starting the first experimental run (i.e., 'Spatiotemporal sensorimotor stimulation'). In our previous work[31], the synchronous (0 ms) and asynchronous (500 ms) conditions were given in randomized order and lasted 30 s each, followed by rest. The arrow crossing indicates that the two experimental conditions must be randomized in order across participants. Each condition was repeated eight times. The anatomical image is then acquired followed by a second experimental run (i.e., 'Spatiotemporal sensorimotor stimulation'). The control tasks (i.e., in the motor control task, participants are only moving the front-robot without receiving any sensory feedback on the back; in the touch control task, participants do not perform any movement but are touched on the back) are acquired (eight repetitions for each task). Finally, after the fMRI acquisition is terminated (but participants are still in the scanner), the participant will be asked to perform again 30 s of movement in each condition (i.e., asynchronous and synchronous) and will be asked to answer verbally to a short questionnaire that assesses the intensity of PHs and other mental states. Experimental parameters can be adapted on the basis of the research questions and needs.

Neuroimaging (fMRI) study

Tasks

Experimenter
Participant
Experimenter/participant
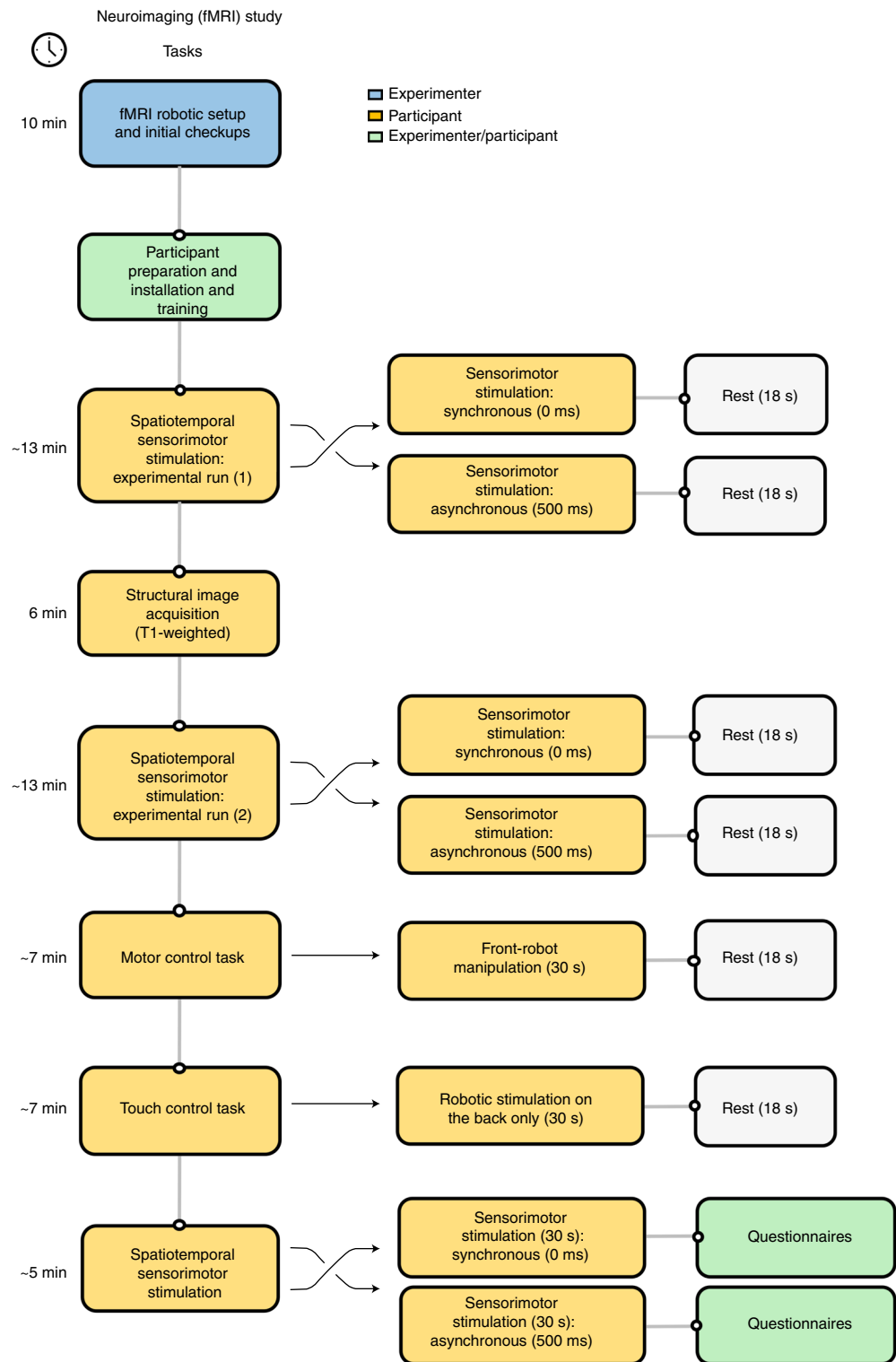
delay of 500 ms (asynchronous condition). Depending on the research question, different delays can be used in the paradigm. The fMRI experimental design is a task-based block design. Participants perform two runs of 12 min each, during which they repeatedly have to move the front-robot for 30 s (16 repetitions per condition in total), followed by 18 s of rest. Conditions are presented in a randomized order.

Two additional control conditions are recorded:

1   In a touch control task, only the sensory feedback is applied (touch only; no movement done by the participant);

2   In a motor control task, only the movement is performed (no touch is applied on the back).

In the motor control task, participants are asked to manipulate the front-robot in the same manner as during the two experimental runs (with the asynchronous and synchronous condition); however, in this condition they do not receive any tactile feedback on the back. Conversely, during the touch control task, participants do not perform any movement with their right hand but receive tactile feedback on their back (from a prerecorded sequence).

The experiment always starts with the two experimental runs and continues with the touch control tasks and ends with the motor control task. For each of the robotic stimulation periods, the movement parameters of the robotic system along the X and Z axes are recorded at a frequency of 100 Hz.

From this, there would be a minimum of four datasets of functional images (two experimental runs) in the example used consisting of 320 functional images each, and two control tasks consisting of 160 functional images each and one T1-weighted image resulting from each experiment.

Expertise needed to implement the protocol

A mechatronic engineer (engineer trained in integrating mechanical and electronic engineering systems, which includes robotics and computer systems) with some experience in cognitive neuroscience might be necessary for the building and maintaining of the robotic devices. Details on how to build the robotic devices have been previously published (for the behavioral robot, see ref. [41]; for the MRI robot, see ref. [30]).

Materials

Participants

- Any individual able to perform the task can be enrolled in the studies ▲ CRITICAL Obtain informed consent from the participants (in agreement with local regulations) before starting any part of the experimental procedure. For the MRI protocol, participants must not present any contraindications (Supplementary Table 2). ▲ CRITICAL Obtain informed consent from the participants, and conduct an anamnestic interview to verify the inclusion criteria (these can vary depending on the researchers' interest) and collect the demographic data (age, sex and handedness through the Edinburg Handedness Inventory[77]).

Equipment
Behavioral protocol
A schematic illustration of the setup is shown in Fig. 1a,c.

- Front- and back-robot. The details for assembly can be found in ref. [41]. In this reference, the front-robot is a PHANToM Omni (SensAble), referred to as the master device. PHANToM Omni was recently renamed Touch USB by the manufacture 3D Systems. The back-robot is referred to as slave device. The back-robot is linearly driven in the Y direction by a toothed-belt drive mechanism using a DC motor (RE 40, Maxon). The movements in X and Z directions are generated by a parallel-link mechanism based on two harmonic drive motors (RH-8D 6006, Harmonic Drive Systems). A load cell (ELPF-TIM-50N, Measurement Specialties) is attached on the tip of the end link so as to give force feedback to the master device.
- Desktop computer with Visual Studio 2012 (Microsoft) installed
- A custom-made controller (motor driver) for controlling the robotic device with serial communication function
- Headphones
- Blindfold
- Questionnaire (Supplementary Table 1)

MRI protocol equipment: a schematic illustration of the setup is shown in Fig. 1b,d. ▲ CRITICAL All neuroimaging data must be organized according to the Brain Imaging Data Structure (BIDS)-compliant (https://bids.neuroimaging.io/) specifications[78].

- MRI scanner, the protocol has been implemented using a 3 T Siemens Magnetom Prisma MRI scanner using whole-brain echo-planar imaging (EPI) sequences measuring the BOLD activity[31]
- Sequences: for the functional images, we used whole-brain EPI with the following parameters: 43 continuous slices, field of view (FOV) 230 mm, repetition time (TR) 2.5 s, time to echo (TE) 30 ms, flip angle 90°, in-plane resolution $2.5 \times 2.5\,mm^2$ and slice thickness 2.5 mm. We used a 64-channel head

coil. The two experimental runs contained 320 volumes, and the control conditions (in which there are only eight repetitions per condition) included 160 volumes. For each participant, an anatomical image was recorded using a T1-weighted MPRAGE sequence (TR 2.3 s, TE 2.32 ms, inversion time 900 ms, flip angle 8°, 0.9 mm isotropic voxels, 192 slices per slab and FOV 240 mm)

- MR-compatible front- and back-robotic system. The details for assembly can be found in ref. [30]. To be compatible with the MRI environment, the components need to be made of nonmagnetic materials, such as polyacetal, brass or aluminum. In the reference, two ultrasonic motors with optical encoders (USR60-E3T, Shinesi Corp.), timing belts and pulleys to linearly drive two sliders set on aluminum low-profile guide systems (NK-02-17-1-300, igus) were used. The movements of the two sliders were constrained by a parallel-link mechanism, so the horizontal (X direction) and vertical (Z direction) movements of a contact part are achieved by driving the sliders in the same and opposite directions, respectively. The device is designed to be placed inside the gantry of MRI scanner, so it is better if the contact part is small so that the movement does not disturb the homogeneity of the magnetic field. Moreover, the ultrasonic motors are located far from the isocenter of the MRI scanner to reduce the influence (noise and distortion) of the electrical field on the MR images as much as possible. The dimensions of the prototype device were 880 mm long, 215 mm wide and 116.5 mm (maximum) high
- Desktop computer with Visual Studio (Microsoft; and platform toolset V110) installed and a data acquisition card (NI PCIe-6323, National Instruments) for controlling the robotic device
- The computer should also have MATLAB 2020 (or more recent versions) with the Instrument Control toolbox (toolbox part of MATLAB) and the psychtoolbox installed (freely available)
- Headphones
- Blindfold

Software

For the preprocessing, the SPM12 toolbox (Wellcome Department of Cognitive Neurology, Institute of Neurology, UCL, London, UK) running in MATLAB is needed (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). ▲ CRITICAL This protocol is intended to be run on a modern workstation running an up-to-date Microsoft Windows. ▲ CRITICAL Scripts to control the robotic device are provided on GitLab: https://gitlab.epfl.ch/fbernasc/roboticsph.

Procedure 1: response measured by results of questionnaire

▲ CRITICAL The procedure does not require a specific directory structure or file-naming convention. However, users should modify the scripts when interacting with the software so that the naming conventions and preprocessing pipelines match (the BIDS naming convention should be favored).

Behavior

▲ CRITICAL It is important that, during the experimental part, the researcher(s) are in front of the participant (not on the back or the side, to avoid confounds on the illusions, especially PH), at a minimal distance of 2 m. The back-robot should be placed against a wall, making it impossible that someone is located on the back. The distance between the left and right sides of the robot to the wall should be equivalent (to avoid confounds on the reported location of the riPH). Although the participant will wear a blindfold, if possible, the light should be dimmed. The chair must be without a backrest (or with a very low backrest to not block the touch feedback applied by the back-robot) and have a height that allows the participant to easily touch the whole back surface with the back-robot. The initial position of the participant and the front- and back-robot is illustrated in Fig. 1c.

Robotic setup and initial checkups ● Timing 10 min

1 Install and initialize the front-robot (Touch USB (3D systems)).
   - Connect the USB cable to the computer (or Ethernet cable if you do not use the USB version of the Touch USB)
   - Connect the power supply
   - Open the Touch Setup application, and follow the instructions displayed on screen
     ? TROUBLESHOOTING
   - Press the 'Save configuration' button; the software will close automatically
     ? TROUBLESHOOTING

2   Install and initialize the back-robot.
    • Connect the USB cable and the power cable, and switch the electric box on
    • Make sure you screw the correct rod at the back of the robot (depending on if you want to do a back- or hand-poking experiment) and open the corresponding controller application (HapticGroup_BackPocking_V5.1, or later version, if available; can be found here at https://gitlab.epfl.ch/fbernasc/roboticsph.git) to calibrate the back-robot position according to the participant
    • Make sure the front-robot and the back-robot are in their resting position (Supplementary Fig. 1), and make sure the subject chair (and the subject) is not too close to the robot to avoid blocking its initialization motion
    • Start the initialize process ('Sampler (S)', then 'ON'; then in the pop-up window press 'Initialization')
    ? TROUBLESHOOTING
    • Press the 'i' key. The robot starts moving to find the hard stops, and then it goes to its initial position
    ? TROUBLESHOOTING
    • Once the robot stops the movement and the pop-up window indicates the successful initialization, stop the process ('Sampler (S)', then 'OFF' or alternatively press right click of the mouse)
    • Start the initialize process ('Sampler (S)', then 'ON', then in the pop-up window 'Experiment')
    • Select 'Condition 1' for heaving the virtual wall or 'Condition 3' for no virtual wall (see 'Somatosensory force feedback')
    • If needed, adjust the height of the robot (unscrew the vertical moving support and push the complete robot upward/downward, then screw it back)
        At the end of the whole experiment, stop the process ('Sampler (S)', then 'OFF' or alternatively press right click of the mouse)

Spatiotemporal sensorimotor stimulation
Setup ● Timing 5 min
▲ CRITICAL   Before starting the experiment, the participant must be trained on how to use the robotic device. To this aim, the participant will be asked to perform a few movements in the synchronous condition with the eyes closed, at a frequency of ~1 Hz, and to explore the whole back (Fig. 4). Participants must be instructed not to count the time between pokes nor the number of pokes, but do the movement as learned during the training. The researcher can correct and guide the participants movement at this stage.

3   Prepare research subject for the robotic sensorimotor task (blindfold, headphones); robot should already be switched on and initialized (see critical point above).
4   Provide instructions to participants (see critical point above).
5   Make the participant do a few movements with the robotic devices, to make him/her understand how to control the robotic device and what resembles the touch on the back (habituation phase) applied by the back-robot.

Data collection ● Timing 15 min
6   Perform the first sensorimotor stimulation (one sensorimotor condition pseudo-randomly chosen, e.g., synchronous).
    • Execute the function by typing the following into a MATLAB command-line terminal: 'PH_Experiments'. This will open a guided user interface (GUI; Fig. 7) that is already populated with default values for a standard experiment, for example, a single trial using 0 ms delay, for a total trial duration of 120 s, and one single trial (in 'Nb trials')
    • Edit the default values so that they are consistent with the chosen condition
    • Press 'Launch' to start the experiment
7   Remove the blindfold, and ask the person to fill in the questionnaire to assess the intensity of illusions (Supplementary Table 1).
8   Take a short break to allow the participant to rest (usually several minutes, but can be adapted to the individual participant).
9   Perform the second sensorimotor stimulation (the other sensorimotor condition pseudo-randomly chosen, e.g., asynchronous).
    • In the GUI, which should still remain open, change the delay to the other delay (e.g., 500 ms). The default values can still be changed according to the experiment's need
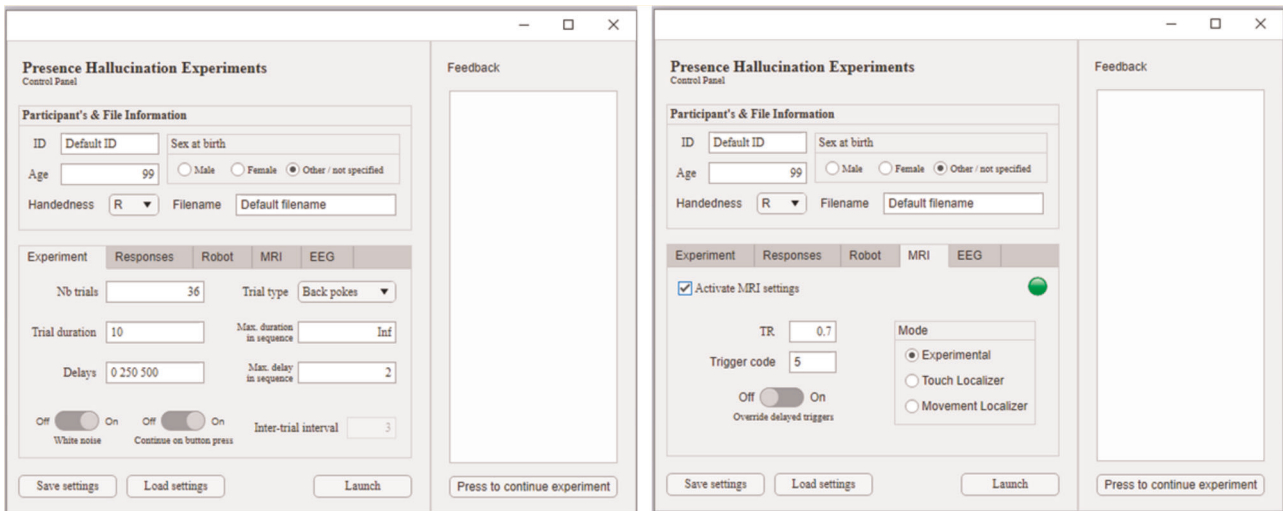   • Press 'Launch' to start the experiment again

Fig. 7 | GUI for behavioral experiments. Left: view of the GUI with default values to conduct behavioral experiments. Each parameter can be adapted depending on the experimental needs. Positioning the cursor on the parameter icon will provide additional information on the role of the selected parameter. Right: GUI displaying the MRI settings. View of the GUI with default values to conduct behavioral experiments. Each parameter can be adapted depending on the experimental needs. Positioning the cursor on the parameter icon will provide additional information on the role of the selected parameter. By selecting 'Activate MRI settings' it will be possible to conduct MRI experiments.

10   Remove the blindfold, and ask the person to fill in the questionnaires to assess the intensity of illusions (Supplementary Table 1).

Sensorimotor delay dependency
Setup ● **Timing 5 min**
11   Prepare research subject for robotic sensorimotor task as described in Steps 3–5 above.

Data collection ● **Timing 20–25 min**
12   Perform sensorimotor stimulation.
   • Execute the function by typing the following into a MATLAB command-line terminal: 'PH_Experiments'. This will open a GUI (Fig. 7) that is already populated with default values for a standard experiment
   • Update these values so that they appropriate for the current task. This can be done manually or by loading a file. For example, load the provided file 'Settings_SensorimotorDelayDependency.m' using the button 'Load settings' in the main page. This will prepare the GUI for this particular experiment. For example, delays randomly chosen among 0, 250 and 500 ms, 36 repetitions in total, and a total duration of 10 s for each trial. These default values can also be changed depending on what is needed

      The duration of each experimental session will vary on the basis of the number of delays, repetitions and duration of each trial.
13   Remove blindfold, and take a break for a few minutes.
14   Repeat sensorimotor stimulation (with the same parameters defined in Step 12 above).
15   Remove blindfold, and take a break for a few minutes.
16   Repeat sensorimotor stimulation (with the same parameters defined in Step 12 above).
17   Remove blindfold.

Procedure 2: response measured by fMRI

▲ **CRITICAL**   Before starting the experiment, the participant must be trained on how to use the robotic device. To this aim, the participant will be asked to perform a few movements in the synchronous condition with the eyes closed, at a frequency of ~1 Hz, and explore the whole space. The researcher can correct and guide the participant's movement at this stage.
If the user's MRI data are BIDS compliant (https://bids.neuroimaging.io/), few modifications (e.g., modifying the scripts to recognize the user's functional files) will be necessary.

fMRI robotic setup and initial checkups ● Timing 10 min

1   Install the robotic system on the scanner bed, and connect the different cables with the two motors and the front-robot (Supplementary Fig. 2). Make sure to plug them in by properly following the labels.

2   Verify that the contact part of the back-robot is located at the center of the slide of the back-robot as well as the slider of the front-robot. The contact part of the back-robot has to have both 'legs parallel' (Supplementary Fig. 3). If it is not the case, manually change the front-robot slider to the middle, and for the back-robot, a recalibration would be needed in Step 10.

3   Verify that all screws are tight; if some are too loose, they need to be fixed. The same applies if the screws are too tight.
    ! CAUTION Only use MR-compatible equipment to tighten or loosen screws in the robotic system; alternatively, take the robotic system out of the MR platform to do this step.

4   Open the code 'HapticGroup' and launch it to open the GUI interface using Visual Studio 2010 by pressing F5 + Ctrl. This will open the GUI interface, and an information window will appear saying either that 'joypad is connected' or that 'Joypad is disabled'; click 'OK'.

5   Initialize the robotic position by going to 'Initialization (I)', then 'Initialize NI card' and then 'Initialization (I)' and 'Zero-volt output'.

6   Turn on the control box.

7   Initialization of the devices: go on 'Experiment (E)', then 'Device1/2: initialization', and then click 'OK' without changing the parameters.

8   If the front and back robots were not in the correct position (from Step 4), change their position now:
    • The front robot can be moved to the middle by hand if not done previously
    • For the back-robot contact part, use the key '1' and '2' to move the first motor and the keys '3' and '4' to move the second motor. The contact part should be located in the middle of the slider (Supplementary Fig. 3)
    • When this is done, press 'enter' to save these initial positions and then 'Experiment (E)', 'Sampler OFF'

9   Select the input device, by going to 'Experiment (E)', 'Select input device (front-robot)' and then 'Device 1-Passive'.

10 Select the output device by going to 'Experiment (E)', 'Select output device (back-robot)' and then 'Device 2 -Position control'.
    The robotic system is ready to be started.

Participant preparation ● Timing 10–15 min

▲ CRITICAL   This orientation procedure is done before the experiment itself starts.

11 Complete and verify the MR safety questionnaire (the participant has to remove all metallic objects and is reminded of the magnetic field present in the MR).

12 Start the robotic device. On starting, you will see 'Experiment (E)', 'Sampler ON', and a window will appear to confirm the chosen input and output devices. Click 'Yes' if it is correct.

13 When the participant enters the MR scanner, explain the instructions for the task. Provide additional general information regarding the MR scanner (e.g., loud noise, earplugs necessary and emergency button).

14 Set the participant up on the mattress.

15 Ensure that the participant feels the back robot on their back and that the movement performed with the hand is done correctly.

16 Make sure that the participant is blindfolded, puts on the earplugs and headphones, and has access to the MR emergency button (which is placed on the chest).

17 Provide support to the elbows to reduce the amount that the head moves when the participant moves the robot. Tell them to limit their movement to a wrist movement to avoid moving the shoulder and hence the head.

fMRI acquisition ● Timing ~1 h to 1 h 10

18 When the participant enters the MR scanner, remind them of the instructions.

19 Execute the function by typing the following into a MATLAB command-line terminal: 'PH_Experiments'. This will open the GUI.

20 In the experiment tab, turn off the 'Continue on button press', and set the number of trials to 8, the trial duration to 30, the delays to '0 500', the trial type to 'seconds' and 'Inter-trial interval' to 18.

21 Go to the MRI tab. In the example shown in Fig. 7, the repetition time was set to 2.5 s, and the MRI trigger was set to '5'. Modify the MRI trigger to the appropriate value for your configuration. The number of trials, trial duration, inter-trial interval and the other experimental parameters will

still follow the parameters input in the Experiment tab. Note, however, that using MRI settings will force 'Trial type' to be 'Seconds'. Change the default values as appropriate for the experiment.

22   While the subject is performing the task, make sure that the robotic system is moving properly and not blocked by inspecting visually in the Visual Studio interface that the 'Slave Angle[rad]' is changing.
     ? TROUBLESHOOTING

23   Record the T1-weighted anatomical image.

24   Perform a second run of the robotic stimulation experiment.
     • Remind the participant of the instructions
     • If you have not closed the GUI, you may simply press 'Launch' again; otherwise, reopen the GUI by typing 'PH_Experiments' in the command line as in Step 9
     ? TROUBLESHOOTING

25   Perform the 'touch control task' experiment after reminding the instructions to the participant. In this task, an image is acquired while the person's back is touched by the back robot.
     • While maintaining all experimental parameters, navigate to the MRI tab and select 'Touch Localizer' under the mode panel
     • Relaunch the experiment
     ? TROUBLESHOOTING

26   Perform the 'motor control task' experiment after reminding the participant of the instructions. In this task, an image is acquired while the person pokes the front-robot, with no other stimulus.
     • While maintaining all experimental parameters, navigate to the MRI tab and select 'Motor Localizer' under the mode panel
     • Relaunch the experiment
     ? TROUBLESHOOTING

27   Switch the scanner off, and repeat the two experiments.
     • Using the software, choose 'PH_Experiments' and change 'Trial duration' time to 30 s and select 2 as number of trials
     • Record the outcome using the behavioral questionnaire

28   On the Visual Studio interface, click on 'Experiment(E)', then on 'Sampler OFF'. When closing the program, a window will appear to reset the initial position of the back robot; click on 'Yes'.

29   Turn off the control box.

30   Take the subject out the MRI, and remove the head coil, blindfold, headphones and earplugs.

fMRI preprocessing ● Timing ~3–4 h

31   Once acquired, check that the functional and structural images are converted in BIDS format[78].
     ▲ **CRITICAL STEP** This format is required, because if the user's MRI data are BIDS compliant (https://bids.neuroimaging.io/), few modifications (e.g., modifying the scripts to recognize the user's functional files) will be necessary.

32   Apply a standard preprocessing pipeline to the images, including the following steps:
     • Correction of the functional images for slice timing
     • Spatial realignment of the functional images
     • Co-registration of the anatomical image with the mean functional image and segmentation of the anatomical image into gray matter, white matter and cerebrospinal fluid tissue.
     • Normalization to the Montreal Neurological Institute brain template of both functional and anatomical images.
     • Smoothing with a Gaussian kernel with full-width half-maximum of 6 mm of the functional images.
     • Assess head motion by performing a framewise displacement calculation[79].
     • Use filters to remove low-frequency confounds. The two experimental runs are filtered with a high-pass filter at 1/300 Hz, while the two control tasks are filtered with a high-pass filter at 1/100 Hz.

33   Activation contrasts: apply a general linear model analysis to the functional images from both the experimental runs and the control tasks, for each subject. Model as regressors the following parameters:
     • For the experimental runs, the two different conditions (i.e., synchronous and asynchronous), and in the control tasks, the robotic task (either corresponding to the participant's movement or to the robotic stimulation on the back)
     • The auditory cues (lasting 1 s)
     • The six motion parameters for each run

34 Also model as parametric modulators the total amount of movement performed during the conditions in which the participant is moving the front robot (i.e., asynchronous, synchronous and motor task condition). If you want to do exactly what we did, then threshold the results with a threshold of $P < 0.001$ at voxel level and then family-wise error corrected (FWE-corrected ($P < 0.05$) for multiple comparison.

Troubleshooting

Procedure 1
Step 1 (front-robot (PHANToM Omni (SensAble)) installation and initialization)

Serial connection error
Error description: Serial connection ERROR message displayed when opening the controller application.
Cause: The controller application was not able to find the communication port (COM) port corresponding to the driver electronic, or the driver is not answering.

Solutions:
a) Open windows devices manager under 'port (COM & LPT)', and check if the device 'Silicon Labs CP210x…' is listed. If not, make sure the electric box is on and the USB cable is plugged (if a USB hub is used, make sure it is on). You can try changing USB port.
b) If the device is listed, make sure its driver is installed. If properly installed, the device should be listed as shown in the image below (except for COM number that may be different). If the icon is a yellow '!' or '?', the driver is not installed. The driver is in the installation folder [.. \Haptic-Group_tool_set_Backup\ Installer\CP210x_driver\ CP210xVCPInstaller_x64.exe].
c) If you use Windows 7 or 8, it is possible that Windows automatically installed a version of the driver that does not support a high baud rate. You can check the version in the device manager:
• Right click → Property → driver tab. If the version is 10.X.X.X or above, change it to 6.X.X.X
• If not already done, install the CP210xVCPInstaller_x64.exe given in the installation folder. Then, in the device manager, right click → Property → driver tab → update driver → Search driver on my computer → choose among a list, then select version 6.X.X.X
d) If you use HapticGroup_V3_1 or lower version, the COM port of the electric box must have the lowest ID, so if other COM ports are used, make sure the lowest ID is attributed to the electric driver (if not, change it).

Front-robot (PHANToM Omni) cannot be opened
Error description: When enabling the sampler (during initialization or experiment), the controller application tells you it cannot connect to the master devices.
Cause: The front-robot was not properly initialized, or you forgot to close the front-robot application.
Solutions:
a) Turn off and on the front-robot, wait for a few seconds and redo the initialization using the 'Touch Setup' software. If you use the old version of the software, do not forget to press the 'apply' button before closing the application. Make sure you closed the 'Setup' application before running the controller application.
b) In some cases, if you have a USB version of the front-robot, the controller application cannot connect to it (although the setup phase works fine). Currently, there is no available solution. You should use the Ethernet version of the front robot or use a different computer.

Step 2 (back-robot installation and initialization)

The robot does not move smoothly

Error description: When you do a smooth continuous trajectory with the front robot, the motion of the poking robot is 'jumpy'. There are two possible causes:
Cause 1: The serial communication with the poking robot has too much (and too variable) delay. This is because the communication is done with a USB virtual COM port, and if the same USB controller is shared among multiple peripherals, the delay increases.

Solution 1:

a) If you are using a USB hub to connect both the front robot and the robot (and if you have enough free USB ports directly on the computer), try removing the hub and connect both directly to the computer. If you have a laptop with one USB-3 port (the blue one), use this port for the robot (alternatively, if you use a USB-3 hub for both the robot and front robot, connect the hub to this port). If you have other USB peripherals connected to the computer, remove them.

b) In some cases, this problem is more pronounced when the computer is in low power mode. The low power mode is usually the default mode on a laptop if it is running on battery; thus, make sure your laptop is connected to its power supply.

Cause 2: This is less likely, but if the computer is performing some heavy tasks (for example, software installation or antivirus scan), the control loop cannot be run with 2 ms sample time.
Solution 2: Kill those tasks while you are using the robot.

Motion is different between front and back-robot and/or bad virtual wall orientation

Error description: The virtual wall is not in a good position (not vertical or not flat), and/or the displacements of the poking robot do not match the front robot (even if you are not touching the boundary of the workspace). For example, a straight motion of the input corresponds to a curved one of the outputs, or a horizontal one corresponds to a 'not horizontal' one.
Cause: The front- or back-robot has not been properly calibrated
Solution: Go back to the initialization mode, plug (for 3 s), and unplug the pen of the front-robot (you should hear a click when the pen is correctly pluged). Then reset the initial position of the complete system by redoing the calibration (press the 'i' key).

The relative position between front and back-robot changes (drifts) during the experiment
Error description: After the initialization, the motion of the poking robot corresponds to the motion of the front-robot (for example, a straight-line trajectory of the input corresponds to the same straight line of the output), but during the experiment the relative position changes (the same straight trajectory of the input corresponds to a different trajectory of the output). There are two possible causes:
Cause 1: The position of the front-robot is drifting during the experiment because one of its position sensors is damaged.
Diagnosis of the problem: To make sure this is the problem, close everything, open the front-robot application and redo the initialization/calibration of the front-robot. Once this is done, stay in the front-robot application (where you have the 3D representation of the device) and do some motion. You should see that the position of the 3D model and the position of the real device are drifting apart.

Solution 1: No solutions; you need to change the front-robot.

Causes 2: The position of the robot is drifting during the experiment because one of the couplings (of axis 1 or 3) is not properly tightened.
Diagnosis of the problem: Initialize the system (the same way you do usually). Then, before starting the experiment, set the motor current of axis 1 and 3 to the maximum value (5.5 A) and click 'apply the change' (do not click 'overwrite default', or if you may forget to change back the value next time you use the system). Once the experiment is running, do not touch the front-robot, and, by hand, force changes the position of the poking robot (front-back and vertical motion; no need to move it sideways). If the robot does not come back to its initial position when you release it, one of the couplings is not tight.
Solution 2: Stop the experiment, and tighten the corresponding screw.

Procedure 2, Step 25–27
The back-robot does not move anymore
It is possible that the motors stop moving properly during the experiment. When this happens, go to 'Experiment (E)', 'Sampler OFF' and then turn off the controller (motor driver). Wait a few seconds and turn them on again before starting the initialization again: 'Experiment (E)', 'Sampler ON'.

Anticipated results

Behavior
Spatiotemporal sensorimotor stimulation
On the basis of our previous results[31,32,42], we predict that in the condition of asynchronous sensorimotor stimulation (compared to the synchronous sensorimotor stimulation) a participant will experience a stronger riPH and stronger passivity experience (feeling of being touched by someone else) in both the behavioral (Fig. 2a) and the MRI settings (Fig. 2b). Concerning the implicit measures of riPH, during the asynchronous stimulation, participants may also show a drift in self-location in the backward direction and have a tendency to overestimate the number of individuals close by (numerosity estimation)[29]. In the synchronous sensorimotor stimulation (compared to the asynchronous sensorimotor stimulation), we predict that the participants will experience a stronger sensation of touching themselves (self-touch), despite extending their arms in front of their bodies. The synchronous sensorimotor stimulation and stimulation with force feedback are further associated with a drift of the subject's body toward the front position and lower estimation of individuals close by (compared with the asynchronous condition)[29]. Generally, the absence of a force feedback results in stronger riPH in the asynchronous condition. On the basis of our previous findings[31], we expect that patients with Parkinson's disease and PH are more sensitive (higher ratings in the questionnaire) to riPH, and in some of these patients, the phenomenology of the riPH resembles what they experience in daily life.

Sensorimotor delay dependency
On the basis of our previous results[31], we expect that the probability to report/experience a riPH increases with the increase of the sensorimotor conflict (i.e., the longer the delay between movement and touch on the back) (Fig. 2c). In addition, we expect that patients with Parkinson's disease and PH (versus patients without PH) show a higher sensitivity to the riPH already with 0 ms delay (as indicated by the higher intercept) and a stronger sensitivity to the delays (as indicated by the steeper slope)[31].

fMRI
On the basis of our previous findings[31], we expect that the contrast asynchronous > synchronous (i.e., showing brain regions more activated in the asynchronous condition compared with the synchronous condition) will activate the right pSTS, the IFG, the right anterior insula and the right medial prefrontal cortex.

Regarding the control tasks, we expect that the action of moving the front robot (motor control task) will result in activations in a large cortical–subcortical network including contralateral sensorimotor cortex (depending which hand the participant uses during the robotic stimulation), putamen and thalamus and bilateral premotor cortex, supplementary motor area, parietal operculum (secondary somatosensory cortex, supramarginal gyrus) and ipsilateral cerebellum. We expect that the experience of being touched on the back (touch control task will activate the bilateral parietal operculum including supramarginal gyrus, secondary somatosensory cortex and superior temporal gyrus.

We also expect, on the basis of our previous findings[31], that the conjunction analysis (asynchronous > [motor + touch] ∩ synchronous > [motor + touch]) will reveal a subcortical–cortical network in the left sensorimotor cortex, bilateral supplementary motor area, right inferior parietal cortex, left putamen and right cerebellum. This contrast highlights the brain regions involved in the spatial sensorimotor conflict between the sensorimotor movement of the hand in front space and the feedback in the back, independent of the sensorimotor delay.

For the subjective questionnaire assessing the riPH (in the dataset example assessed at the end of the scanning session), we predict that in the condition of asynchronous sensorimotor stimulation a participant will experience a stronger riPH and stronger passivity experience (feeling of being touched by someone else).

Although the MRI robotic approach has not been yet applied to patients with Parkinson's disease, on the basis of our previous findings[31], we expect that patients with Parkinson's disease and PH would have higher activity in the pSTS and IFG compared with patients with Parkinson's disease without PH in the asynchronous versus synchronous condition since both of these regions were identified as part of the PH network (for more details, see ref. [31]). We would expect the same in DLB with PH compared with patients without PH. Regarding the control tasks, we would expect no difference in activations between the patients (Parkinson's disease or DLB) with or without PH.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

MRI data are available on zenodo.org (https://zenodo.org/record/4423384#.YkKyHDWxVmN). Behavioral data can be found on GitLab (https://gitlab.epfl.ch/fbernasc/np-p210507a.git).

Code availability

The codes to control the robots have been uploaded to GitLab (https://gitlab.epfl.ch/fbernasc/roboticsph.git).

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Author contributions

The study and the protocol were designed by F.B., E.B., G.R. and O.B. The robotic system and codes for controlling it were designed by M.H and J.L. H.D. developed the code for the GUI allowing to adapt the behavior of the robots depending on the experimental conditions. J.P. adapted the questionnaire for the assessment of the illusions induced by the robotic device. The manuscript was written by F.B., E.B. and O.B. All authors approved the final version of the manuscript.

Competing interests

O.B., G.R. and M.H. are inventors on patent US 10,286,555 B2 held by the Swiss Federal Institute (EPFL) that covers the robot-controlled induction of the feeling of a presence (presence hallucination). O.B. and G.R. are inventors on patent US 10,349,899 B2 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 co-founders and shareholders of Metaphysiks Engineering SA, a company that develops immersive technologies, including applications of the robotic induction of presence hallucinations that are not related to the diagnosis, prognosis or treatment of Parkinson's disease. O.B. is a member of the board and shareholder of Mindmaze SA.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41596-022-00737-z.

Correspondence and requests for materials should be addressed to Olaf Blanke.

Related links
Key references using this protocol
Blanke, O. et al. *Curr. Biol.* **24**, 2681–2686 (2014): https://doi.org/10.1016/j.cub.2014.09.049
Serino, A. et al. *iScience* **24**, 101955 (2021): https://doi.org/10.1016/j.isci.2020.101955
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Stripeikyte, G. et al. *Schizophr. Bull.* (2021): https://doi.org/10.1093/schbul/sbab031

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	The fMRI data is available via https://zenodo.org/deposit/4423384
Data analysis	For the fMRI data analysis, SPM12 toolbox (Wellcome Department of Cognitive Neurology, Institute of Neurology, UCL, London, UK) running on matlab was used.

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Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	The manuscript describes a new robotic procedure and method to study hallucinations in different populations.
Research sample	The manuscript reuses the fMRI dataset from Bernasconi, Blondiaux et al., 2021 at https://zenodo.org/deposit/4423384
Sampling strategy	Not applicable
Data collection	No data were collected for this study. The manuscript reuses the fMRI dataset from Bernasconi, Blondiaux et al., 2021 at https://zenodo.org/deposit/4423384
Timing	Not applicable
Data exclusions	No data were excluded for the analysis
Non-participation	No participants dropped out.
Randomization	Participants were not allocated into experimental groups

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☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	The manuscript reuses the fMRI dataset from Bernasconi, Blondiaux et al., 2021 at https://zenodo.org/deposit/4423384
Recruitment	not applicable
Ethics oversight	The fMRI study was approved by the Cantonal Ethics Committee of Geneva (Commission Cantonale d'Ethique de la Recherche sur l'Être Humain - CCER)

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Magnetic resonance imaging

Experimental design

Design type	task functional MRI and block design

Design specifications	2 experimental blocks including two conditions (asynchronous and synchronous) of 30 sec with 20 sec rest (among those 0.5 sec and 1.5 sec are the "start" auditory cue and "stop" auditory cue). Each block lasts 12 min (8 repetition per conditions). The control tasks include one condition each (either robotic manipulation or robotic stimulation on the back) of 30 sec and also 20 sec of rest (including 0.5 sec and 1.5 sec are the "start" auditory cue and "stop" auditory cue). Those tasks lasted around 7 min (8 repetitions per condition).
Behavioral performance measures	The movement parameters of the front robot along the X and Z axis are recorded at a frequency of 100 Hz. Questionnaire data is also assessed after the scanning session.

Acquisition

Imaging type(s)	functional and structural
Field strength	3T
Sequence & imaging parameters	Users can adapt this part as the robotic procedure does not depend on the MR sequence used. The data used in the current manuscript (Bernasconi, Blondiaux et al., 2021) uses the following sequences: - For the functional images, we used a whole brain echo-planar imaging (EPI) with the following parameters: 43 continuous slices, FOV=230mm, TR=2.5s, TE=30ms, flip angle=90°, in-plane resolution=2.5x2.5mm2, slice thickness=2.5mm. We used a a 64-channel head-coil. The two experimental runs contained 320 volumes and the control conditions (in which there is only 8 repetitions per condition) included 160 volumes. - anatomical image was recorded using a T1-weighted MPRAGE sequence (TR=2.3s, TE=2.32 ms, Inversion time=900ms, flip angle=8°, 0.9mm isotropic voxels, 192 slices per slab and FOV=240mm).
Area of acquisition	whole brain

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software	Standard SPM12 preprocessing pipeline is applied to the images, which includes the following steps: first the functional images are corrected for slice timing and are spatially realigned. Then, the anatomical image is then co-registered with the mean functional image and segmented into grey matter, white matter and cerebro-spinal fluid (CSF) tissue. Finally, the anatomical and the functional images are normalized to the Montreal Neurological Institute (MNI) brain template. Functional images are then smoothed with a Gaussian kernel with full-width half-maximum of 6mm. The two experimental runs were filtered with a high-pass filter at 1/300 Hz to remove low frequency confounds, while the two control tasks were filtered with a high-pass filter at 1/100 Hz.
Normalization	Normalised
Normalization template	MNI template
Noise and artifact removal	Head motion is assessed based on framewise displacement (FD) calculation.
Volume censoring	Not applicable

Statistical modeling & inference

Model type and settings	Mass univariate with fixed effects for the first and second level analysis
Effect(s) tested	Effect of interest: asynchronous condition > synchronous condition For the control conditions: motor task > baseline and touch task > baseline Conjunction analysis: asynchronous > [motor + touch] ∩ synchronous > [motor + touch]

Specify type of analysis: ☒ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference (See Eklund et al. 2016)	Cluster-wise P = 0.001
Correction	FWE-corrected threshold of P = 0.05

Models & analysis

n/a	Involved in the study
☒ ☐	Functional and/or effective connectivity
☒ ☐	Graph analysis
☒ ☐	Multivariate modeling or predictive analysis