Imagine that: elevated sensory strength of mental imagery in individuals with Parkinson’s disease and visual hallucinations

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Visual hallucinations occur when our conscious experience does not accurately reflect external reality. However, these dissociations also regularly occur when we imagine the world around us in the absence of visual stimulation. We used two novel behavioural paradigms to objectively measure visual hallucinations and voluntary mental imagery in 19 individuals with Parkinson’s disease (ten with visual hallucinations; nine without) and ten healthy, age-matched controls. We then used this behavioural overlap to interrogate the connectivity both within and between the major attentional control networks using resting-state functional magnetic resonance imaging. Patients with visual hallucinations had elevated mental imagery strength compared with patients without hallucinations and controls. Specifically, the sensory strength of imagery predicted the frequency of visual hallucinations. Together, hallucinations and mental imagery predicted multiple abnormalities in functional connectivity both within and between the attentional control networks, as measured with resting-state functional magnetic resonance imaging. However, the two phenomena were also dissociable at the neural level, with both mental imagery and visual misperceptions associated with specific abnormalities in attentional network connectivity. Our results provide the first evidence of both the shared and unique neural correlates of these two similar, yet distinct phenomena.

1. Introduction

It is easy to take visual perception for granted. For the overwhelming majority of people, conscious perception seems to mirror the external world with high validity. However, individuals with a variety of neuropsychiatric disorders regularly experience situations in which this relationship breaks down and they experience something that is not there—an ‘hallucination’. Although these symptoms are associated with varying and extensive pathology [1,2], the precise neural mechanisms underlying hallucinations remain a mystery, due largely to the inherent difficulties associated with reproducibly eliciting hallucinatory symptoms in the research setting.

Work in Parkinson’s disease (PD) has been able to bridge this issue. Recent conceptual advances suggest that visual hallucinations in PD are related to an inability to rapidly and flexibly use attention [3]. More specifically, impaired recruitment of exogenous attention networks has been proposed as a contribution to visual hallucinations [3], leading to an over-reliance on endogenous attention systems, which are ill-equipped to interpret the contents of exogenous perceptual abnormalities.

These mechanistic insights have been largely driven by the creation of a novel behavioural paradigm capable of reproducibly eliciting visual hallucinations [4]. Known as the Bistable Percept Paradigm (BPP; figure 1b), this task requires participants to view a series of stable and bistable monochromatic images and subsequently identify any ‘hidden’ items they perceive. PD patients that experience visual hallucinations in daily life are far more likely to perceive
Figure 1. Relationship between mental imagery and visual hallucinations: (a) binocular rivalry—subjects view a different monocular pattern in each eye (right eye = horizontal stripes (red online); left eye = vertical stripes (green online)), however their perceptual experience vacillates back and forth between the two; and (b) BPP—participants view a series of monochromatic images and have to determine whether they are stable (e.g. a tree) or bistable (e.g. a tree with the silhouettes of faces etched into the trunk). In our experiment, subjects spent 5 s imagining either pattern prior to a brief stimulus presentation, effectively priming the conscious perception of the imagined stimulus; (c) there was a strong positive correlation \( r = 0.632, p = 0.002 \) between impaired performance on the BPP \((y\text{-axis—percentage of misperceptions})\) and the strength of imagery on binocular rivalry \((x\text{-axis—percentage of trials with strong influence of imagery of perception})\). The correlation remains significant after removing the single outlier; and (d) hallucinators (PD + VH) had higher mental imagery strength than healthy controls \( (HC; t = 2.1, p = 0.046) \) and patients without hallucinations \( (PD - VH; t = 3.2, p = 0.006) \). (Online version in colour.)

Then use this information to interrogate patterns of functional connectivity within the resting brain.

2. Material and methods

(a) Participants

Nineteen adults with PD (mean age = 68.4 years; 70% males) and 10 age-matched healthy controls (mean age = 67.9 years; 70% males) were recruited from the Parkinson’s Disease Research Clinic at the Brain and Mind Research Institute at the University of Sydney. Demographic details for the patients with PD are presented in table 1.

(b) Neuropsychological tests

Performance data are included in table 1. None of the patients showed evidence of clinical dementia [7]. The Montreal Cognitive Assessment (MoCA) was used as general measure of cognition [8] and the Beck Depression Inventory (BDI-II) was used to assess for the presence of affective disturbance [9]. To explore the role of attentional set-shifting (the ability to shift attention between competing targets), all patients performed the Trail Making Test (TMT) parts A and B [10], allowing for the calculation of a difference score \( \text{TMT}_{B-A} \).

(c) Bistable percept paradigm

The BPP was programmed using EPrime Software (Psychology Software Tools, USA) and consisted of a battery of 40 monochromatic images that were classified a priori as either stable or bistable images [4]. As shown in figure 1b, bistable images contained two or more interpretations (e.g. silhouette of faces within a landscape
so as to minimize any pre-existing eye bias (see [6] for details).

The strength of the two stimuli was adjusted on a case-by-case basis were presented in an annulus around a fixation spot. The relative luminance of both Gabor patterns was 7.8 cd m\(^{-2}\). Both patterns (e) Strength of mental imagery

To investigate the effects of imagery on rivalry, subjects were instructed to imagine one of the two rivalry patterns (a green-vertical or red-horizontal grating) during the blank intervening period (6 s) between rivalry presentations (750 ms). During rivalry presentations, participants were instructed to indicate which image was dominant by pressing the corresponding keys (‘1’ = green, ‘2’ = equal mix and ‘3’ = red). The specific image that each patient was cued to imagine on each trial was randomized, with an equal number of red and green cues. Each patient performed two blocks of trials, each containing 40 trials. The percentage of trials in which the imagined pattern matched subsequent reported rivalry pattern was taken as our measure of imagery strength (see [12,13] for definitions of imagery strength).

Mock rivalry displays were also included to ensure that there was no bias related to demand characteristics [14]. If participants’ responses were due to demand characteristics, we would expect to see priming (higher than 50%) for mock trials. Analysis of mock trials demonstrated that participants displayed no decisional bias, with the average priming of mock trials not being significantly different from chance (PD: mean \(50.46 \pm 2.5\); \(t = 0.8\), \(p = 0.430\); controls: mean = 50.46 \(\pm 1.4\); \(t = 1.0\), \(p = 0.350\)).

### Statistical analysis

Owing to the lack of a consensus gold standard for the diagnosis of visual hallucinations [15], we opted to split the cohort of patients using scores on the BPP [3,4]. Demographic variables were compared between groups using independent-samples \(t\)-tests. Pearson correlation coefficients were used for continuous data and a Hotelling’s \(t\)-test was used to compare correlation coefficients. Scores on both outcomes measures showed strong internal consistency (BPP: \(r = 0.560\), \(p = 0.005\); imagery: \(0.381\), \(p = 0.047\)). All behavioural data analysis was performed using SPSS v. 20 (Chicago, IL, USA), all analyses used an \(\alpha\) of 0.05 and were one-tailed.

### Neuroimaging analysis

The 19 individuals with PD also underwent a single 10-min resting-state scan in which patients were instructed to lie still with their eyes open and to let their minds wander freely. Images were acquired on a General Electric 3 Tesla MRI (General Electric, Milwaukee, USA). T2*-weighted echo planar functional images were acquired in sequential order with repetition time (TR) = 3 s, echo time (TE) = 32 ms, flip angle 90°, 32 axial slices covering the whole brain, field of view = 220 mm, interslice gap = 0.4 mm and raw voxel size = 3.9 \(\times\) 3.9 \(\times\) 4 mm\(^3\) thick. T1-weighted images were also acquired, consisting of a set of 126 adjacent axial cuts parallel to the anterior commissure–posterior commissure line, with a slice thickness of 1.5 mm and a voxel size of 1 \(\times\) 1 \(\times\) 1 mm\(^3\).

Preprocessing and analysis were conducted using Statistical parametric mapping software (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/

<table>
<thead>
<tr>
<th></th>
<th>BPP +</th>
<th>BPP −</th>
<th>controls</th>
<th>(p)-value</th>
</tr>
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<tr>
<td>(N)</td>
<td>10</td>
<td>9</td>
<td>10</td>
<td></td>
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<tr>
<td>age</td>
<td>69.5 ±8</td>
<td>67.1 ±7</td>
<td>63.5 ±8</td>
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<td>MoCA</td>
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<td>27.6 ±2</td>
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<td>BDI-II</td>
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<td>8.9 ±7</td>
<td>7.9 ±7</td>
<td>0.197</td>
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<tr>
<td>disease duration</td>
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<td>4.4 ±3</td>
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<tr>
<td>UPDRS III</td>
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<td>32.0 ±15</td>
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<td>0.780</td>
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<td>DDE, mg d(^{-1})</td>
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<td>512.5 ±225</td>
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<td>0.100</td>
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<tr>
<td>imagery strength</td>
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<td>48.4 ±5</td>
<td>52.3 ±4</td>
<td>0.006</td>
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<td>TMTB–A</td>
<td>110.5 ±88</td>
<td>39.6 ±20</td>
<td>43.1 ±15</td>
<td>0.025</td>
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Table 2. Coordinates for regions of interest.

<table>
<thead>
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<th>network</th>
<th>MNI coordinates</th>
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<tr>
<td>dorsal attention network</td>
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<tr>
<td>bilateral superior parietal lobule</td>
<td>±27 – 52 57</td>
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<tr>
<td>bilateral frontal eye fields</td>
<td>±25 – 8 54</td>
</tr>
<tr>
<td>default mode network</td>
<td></td>
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<tr>
<td>midline precuneus</td>
<td>0 – 73 40</td>
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<tr>
<td>midline medial prefrontal cortex</td>
<td>0 59 10</td>
</tr>
<tr>
<td>bilateral hippocampal formation</td>
<td>±22 – 22 – 22</td>
</tr>
<tr>
<td>ventral attention network</td>
<td></td>
</tr>
<tr>
<td>bilateral anterior insula</td>
<td>±42 24 – 20</td>
</tr>
<tr>
<td>bilateral dorsal anterior cingulate cortex</td>
<td>±12 26 28</td>
</tr>
<tr>
<td>visual network</td>
<td></td>
</tr>
<tr>
<td>bilateral occipital cortex</td>
<td>±8 – 94 4</td>
</tr>
</tbody>
</table>

Regions of interest (ROIs) for the study were defined according to previously published coordinates [4,16] and mapped onto known hubs within the putative attention control networks (see table 2). Pre-processed images were imported into the Functional Connectivity (conn) toolbox (http://www.nitrc.org/projects/conn) in SPM8, which allowed for the calculation of both within- and between-network connectivity (see electronic supplementary materials for details).

To assess the shared neural correlates between mental imagery and visual hallucinations, we performed a series of multiple regression analyses in which each individual subject’s BPP error score and their strength of mental imagery was correlated with a measure of impaired attentional set-shifting (r = 0.441, p = 0.060); however, this relationship was not observed between medication dose and impaired BPP scores (r = 0.190, p = 0.211). In addition, each of the significant effects described above remained following partial correlation with dopaminergic equivalence scores.

3. Results
(a) Association between mental imagery and bistable percept paradigm error score
Across all PD patients, there was a strong positive correlation between the strength of mental imagery and impaired performance on the BPP (r = 0.704, p = 0.001), which was not observed in control subjects (r = −0.151, p > 0.500) (figure 1c). In addition, both of the primary outcome measures were positively correlated with a measure of impaired attentional set-shifting (r = 0.457, p = 0.05 and r = 0.763, p < 0.001, respectively) and a multiple regression involving all three factors was strongly significant (F2,16 = 12.2, p < 0.001), accounting for almost 60% of the variance in the BPP error score (R2 = 0.59). Finally, the relationship between imagery strength and misperceptions appeared to be driven by the frequency of misperceptions in stable images (r = 0.632, p = 0.002), rather than any perceptual abnormalities in the bistable images (r = 0.037, p = 0.877) and the difference between the two correlations was significant (t = 2.16, p < 0.05). Each of these results remained significant after the removal of the three non-hallucinators who self-reported minor misperceptions (all ps < 0.05).

The group of subjects in our study with impaired performance on the BPP displayed significantly stronger mental imagery (t = 3.17, p = 0.006), which was also higher than that observed in control subjects (t = 2.25, p = 0.037) (figure 1d). Catch trials in the imagery task showed no decisional bias (t = 0.82, p = 0.430), ensuring our measure was perceptual.

Importantly, none of the outcome measures in our study were correlated with impaired visual acuity, general cognitive deficits, the severity of motor symptoms or the duration of disease, all factors that have been previously proposed as causative factors in visual hallucinations [2,5]. There was a trend towards a correlation between mental imagery and the level of dopaminergic medication dose (r = 0.441, p = 0.060); however, this relationship was not observed between medication dose and impaired BPP scores (r = 0.190, p = 0.211). In addition, each of the significant effects described above remained following partial correlation with dopaminergic equivalence scores.

(b) Resting-state functional connectivity
A multiple regression using the frequency of misperceptions on the BPP as well as the strength of mental imagery predicted increased connectivity within the ventral attention network (R = 0.636, F2,16 = 5.45, p = 0.008) and default mode network (R = 0.492, F2,16 = 2.57, p = 0.049) (figure 2), suggestive of a relative over-reliance on endogenous attention networks in hallucinators (figure 3). The two measures also predicted decreased connectivity between the dorsal and ventral attention networks (R = 0.542, F2,16 = 5.34, p = 0.030), the ventral attention and visual networks (R = 0.632, F2,16 = 5.34, p = 0.008) and the dorsal attention and visual networks (R = 0.552, F2,16 = 3.51, p = 0.025), implicating decreased between-network connectivity in the neurobiological mechanism of both mental imagery and visual hallucinations. However, given the presence of reduced imagery strength in non-hallucinators (relative to healthy controls), it bears mention that these connectivity deficits may have been due to reduced imagery performance in the non-hallucinator group.

The severity of BPP visual hallucinations alone predicted increased connectivity within the ventral attention network (R = 0.585, p = 0.004) and the default mode network (R = 0.493, p = 0.0160), as well as impaired connectivity between the ventral and dorsal attention networks (R = −0.430, p = 0.033). By contrast, the strength of mental imagery did not predict any of these relationships (R < 0.400), but instead was related to the degree of impaired connectivity between the ventral attention and visual networks (R = −0.496, p = 0.015). Neither measure predicted the strength of impairment between the dorsal attention and visual networks (R < 0.400). After removing the three non-hallucinators who self-reported infrequent misperceptions, we observed similar effects, however the correlation between the BPP error score and impaired DAN–VAN connectivity was only significant at trend levels (R = −0.455, p = 0.08).

4. Discussion
To our knowledge, these results provide the first evidence that links visual misperceptions and visual hallucinations with the influence of mental imagery on conscious perception. Although previous studies have investigated these concepts indirectly in other disorders [6,17], the novel measures used here offer a more objective method for observing the
Pathophysiological effects of visual misperceptions in PD, as they do not rely solely on introspection and self-report. Importantly, the BPP is able to avoid this issue, providing an objective measure of visual misperceptions and hallucinations in susceptible patients with PD [4]. Together, these results suggest that mental imagery and visual misperceptions (which we demonstrate are strongly related to the presence of clinically defined visual hallucinations) may be differing manifestations of a similar neurobiological mechanism, with the former due to a voluntary process and the latter the result of an involuntary, pathological process.

Although visual misperceptions and mental imagery are distinct phenomena, we provide evidence to suggest that they share a common neurobiological mechanism. Namely, both behavioural phenomena were predictive of increased connectivity within the ventral attention and default mode networks, as well as impaired connectivity between the ventral attention, dorsal attention and visual networks (figure 2). Consistent with previous predictions [3,6], these results suggest that visual hallucinations arise in the context of impaired coordination between exogenous attentional networks and the primary visual cortex, whereby attention towards exogenous stimuli is less effective. Without the usual exogenous attentional alerts to novel or unexpected stimuli, ambiguities in visual processing might be rendered open to exaggerated endogenous interpretations. Such an over-reliance on internal interpretations might allow the evolution of small ambiguities in visual processing to grow into more salient and even autobiographical interpretations [7,18]. Importantly, this mechanism is consistent with accounts of mental imagery [5,8], which similarly propose that top–down influences over primary visual cortex underlie the capacity to imagine visual images [9,19]. Together, these results highlight the possibility of a common neural mechanism underlying both visual hallucinations and mental imagery.
Despite overlap in the neurobiological mechanisms of misperceptions and mental imagery, misperceptions and imagery are not identical processes, differing distinctly in regard to volitional control and also in the way they are experienced. Hence, it is not surprising that we observed some dissociable patterns of brain connectivity between the two behavioural measures. Specifically, the severity of misperceptions was strongly predictive of increased within-network connectivity in endogenous networks and impaired connectivity between the dorsal and ventral attention networks, whereas the strength of mental imagery was associated with impaired interactions between the ventral attention network and the visual network. This dissociation highlights the fact that, although imagery strength and hallucinations likely share a common neurobiological mechanism, they also reflect distinct processes. For instance, recent imaging studies have implicated increased activity within cortical regions used for attention [10,20], whereas visual hallucinations in PD have been related to impaired interactions between neural systems involved in the attentional modulation of perception [4,16,21,22].

Imagery and visual misperceptions were also associated with varying degrees of within-network connectivity. However, these resting-state differences appeared to be driven most strongly by the severity of visual misperceptions (figure 2). These results are consistent with the notion that patients with visual hallucinations are unable to recruit activity within networks subserving exogenous attention, and instead rely on other attentional networks, such as the ventral attention and default mode networks, to compensate for this deficiency. Interestingly, the default mode network is commonly associated with self-referential processes [4,23] and endogenous attention [4,24], including periods of task-independent thought, or ‘mind wandering’ [11,18,25]. Given the lack of exogenous attention demonstrated by patients with hallucinations in both behavioural [4,6] and neuroimaging studies [6,16], the association with increased default-mode connectivity could reflect an over-reliance on endogenous networks to interpret and inform the current contents of perceptual experience. Together, these data help to clarify the pathophysiological mechanism of visual hallucinations, which might occur paroxysmally due to impaired communication between attentional and perceptual systems (figure 3) [3,12,16]. That is, abnormal activity in the visual cortex may be misinterpreted due to faulty interactions with frontoparietal networks normally used to focus exogenous attention [2,3,14,21,22]. However, hallucinations in PD are often of complex objects (such as faces or people), suggesting that these perceptual abnormalities only occur once neural activity in the primary visual system interacts with the ventral visual stream [21,22], suggesting that hallucinations are due to a combination of impaired visual input with concomitant exogenous attentional dysfunction [3,28]. This accords with recent investigations into pareidolia—visual misperceptions closely related to hallucinations [29]—which are similarly mediated by top–down attentional control mechanisms [30,31]. This is an exciting avenue for future research, which should seek to determine whether unprovoked hallucinations occur due to a top–down priming from ventral temporal structures or to emergent activity within primary visual cortex.

Previous investigations have suggested that mental imagery may be decreased in patients suffering from visual hallucinations in the context of Charles Bonnet syndrome or dementia [32,33]. Although seemingly in contrast to our findings, there are crucial task-based differences relative to this study. These prior studies measured attentional ability applied within a mental image, whereas we directly assessed the sensory strength of mental imagery [13].

Many of the findings here have also been demonstrated in other neuropsychiatric disorders with visual hallucinations and illusions. For example, patients with either schizophrenia [34] or post-traumatic stress disorder [35,36] have been shown to have increased resting activity within the ventral attention network and report more vivid mental imagery [37,38]. In addition, both disorders have displayed impairments in cognitive flexibility [39,40]. Furthermore, default mode network over-activity [41] and dissociation with cognitive control regions [42] have also been reported in patients with schizophrenia. Intriguingly, hallucinations in disorders classically associated with primary retinal impairment, such as Charles Bonnet Syndrome, are also associated with visual attentional impairments [32,33], suggesting a common neural mechanism for hallucinations across all disorders [2,43]. Future studies should thus be designed to delineate the precise combination of deficits across attentional and perceptual domains that lead to the manifestation of visual hallucinatory symptoms across the broad range of neuropsychiatric disorders.

In conclusion, our data suggest a possible overlap in the neurological mechanisms supporting mental imagery and those that are dysfunctional in visual hallucinations, as demonstrated in PD.

**Ethics statement.** All participants with PD were diagnosed according to UKPD Brain Bank Criteria. Permission for the study was obtained from the local research ethical committee and all patients gave written informed consent.

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