Visual cortical excitability in dementia with Lewy bodies
John-Paul Taylor, Michael Firbank and John T. O’Brien

Summary
Alterations in the visual system may underlie visual hallucinations in dementia with Lewy bodies (DLB). However, cortical excitability as measured by transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) activation of lower visual areas (V1–3) to visual stimuli appear normal in DLB. We explored the relationship between TMS-determined phosphene threshold and fMRI-related visual activation and found a positive relationship between the two in controls but a negative one in DLB. This double dissociation suggests a loss of inhibition in the visual system in DLB, which may predispose individuals to visual dysfunction and visual hallucinations.

Declaration of interest
None.

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Dementia with Lewy bodies (DLB) is characterised by complex visual hallucinations. Previously, we used the threshold for eliciting phosphenes with occipital transcranial magnetic stimulation (TMS) as a measure of visual cortical excitability. Although this threshold correlated with the severity and frequency of visual hallucinations in DLB, overall excitability was similar between DLB and controls, suggesting that early visual areas are functionally intact in DLB. This was supported by our finding of an unaltered cortical activity in the early visual system (V1, V2/V3), as measured by blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI), in DLB. BOLD haemodynamic response has been suggested to be related to synaptic activity in terms of input and local processing, as well as to neuronal spiking arising from sensory stimulation, and thus may represent the activity in both excitatory and inhibitory neuronal populations. In contrast, the neuronal discharge consequent to TMS is likely to be dependent on the relative balance of excitatory and inhibitory activity within the area of stimulation. Therefore a positive relationship between BOLD activity in the early visual system and phosphene threshold may suggest that inhibition outweighs excitation, whereas a negative relationship may indicate the opposite. In this paper we report the interrelationship between fMRI BOLD activity of the early visual system and visual cortical excitability as measured using TMS, using previously published data from patients with DLB and hallucinations and from controls.

Results
The DLB and control groups were similar in terms of age, gender and visual acuity. Unified Parkinson’s Disease Rating Scale (UPDRS)Ⅱ motor scores were significantly higher and cognitive test and visuoperceptual task scores significantly lower in the DLB group (online Table DS1).

Phosphenes were elicited in a similar proportion of the control (17/19, 90%) and DLB groups (14/17, 82%; Fisher exact test, P = 0.66). Across groups, phosphene thresholds were similar (control group: median 70.7%, interquartile range (IQR) = 44.0%; DLB group: median 77.2%, IQR = 36.0%, Mann–Whitney U-test 115.5, P = 0.23).

There were no differences in V1 or V2/V3 BOLD magnitude between the control and DLB groups for checkerboard stimulus (V1: control group, mean 0.41 (s.d. = 0.36); DLB group, mean 0.57 (s.d. = 0.30), P = 0.16. V2/V3 control group: mean 0.68 (s.d. = 0.36); DLB group mean 0.71 (s.d. = 0.29), P = 0.83).

Similarly, there were no perfusion differences in V1 (ml/100 g/min: control group, mean 33.3 (s.d. = 9.6); DLB group, mean 28.0 (s.d. = 10.5), P = 0.20) or V2/V3 (control group, mean 32.1 (s.d. = 8.4), DLB group, mean 27.0 (s.d. = 7.6), P = 0.15) between groups. However, there were significant positive correlations between the magnitude of the BOLD response (V1 and V2/V3) to the checkerboard stimulus and phosphene thresholds in the control group and a significant negative relationship in the DLB group in both V1 and V2/V3 (V1: control group, ρ = 0.48, P = 0.04; DLB group, ρ = −0.71, P = 0.002. V2/V3: control group, ρ = 0.64, P = 0.003; DLB group, ρ = −0.57, P = 0.02, online Fig. DS1). These relationships remained significant (P<0.05) even with the removal of non-responders (i.e. those participants with a phosphene threshold greater than 100% of the stimulator output) except for phosphene threshold v. V2/V3 in the DLB group. In TMS responders (i.e. those experiencing phosphenes) BOLD activity was significantly lower in the control group in V1 compared with the DLB group (control group, mean 0.40 (s.d. = 0.37); DLB group, mean 0.65 (s.d. = 0.25), P = 0.04).

Differences in the slopes for the control v. DLB group for V1 and V2/V3 were highly significant (Fisher r-to-z transformation: V1, z = 3.78, P < 0.001, V2/V3, z = 3.76, P < 0.001). BOLD activity was significantly lower in V1 and trending lower in V2/V3 in those in the DLB group who were on cholinesterase inhibitors (V1: mean 0.45 (s.d. = 0.24); V2/V3: mean 0.62 (s.d. = 0.10)) compared

Method
Details of participant selection, neuropsychological and neuropsychiatric assessment, fMRI and TMS testing are described fully elsewhere. In the current analysis, we selected participants who had undergone both fMRI and occipital TMS. In brief, 16 participants who met criteria for probable DLB and who experienced visual hallucinations at least once in the month before TMS/fMRI testing were recruited from a community-dwelling population of patients, along with 19 controls. The study was approved by the local ethics committee. The DLB diagnosis was made independently by two experienced senior clinicians. Occipital TMS and neuroimaging evaluations were conducted within 2 weeks of each other.

TMS and imaging protocols are described in the online supplementary methods.
with those in the DLB group not taking these agents (V1: mean 0.82 (s.d. = 0.28), P = 0.02; V2/V3: mean 0.88 (s.d. = 0.33), P = 0.10) although phosphate thresholds were similar, as was cerebral perfusion in V1 and V2/V3 between the DLB group on and off cholinesterase inhibitors (phosphate threshold: mean 76.7% (s.d. = 20.2%) v. 78.2% (s.d. = 21.1%), P = 0.90. Perfusion (ml/100g/min): V1, mean 27.1 (s.d. = 9.7) v. 30.4 (s.d. = 13.7), P = 0.62; V2/V3, mean 27.4 (s.d. = 7.3) v. mean 25.8 (s.d. = 9.4), P = 0.73). There was no association between global cognitive function in the DLB group and phosphate threshold, BOLD activity or cortical perfusion in V1 or V2/V3 (P > 0.13).

Discussion

We report a significant positive relationship between phosphate threshold and BOLD activity in early visual areas (V1, V2/V3) in our controls, which suggests that the greater an individual’s inherent visual cortical excitability, the smaller the visual cortical activation in response to a simple checkerboard stimulus. This observation implies that individuals with sensitive visual systems in the face of ‘upstream’ pathology in the visual system thus leading to a maintenance of the phosphate threshold within a normative range and possibly improved bottom-up visual processing, but at the cost of increasing the risk of visual hallucination occurrence, as evidenced by our previous work linking phosphate threshold with visual hallucination frequency and severity.

In summary, our findings of a double dissociation suggest a marked deviance in visual neuronal processing between patients with DLB who hallucinate versus healthy controls. Whether this represents a specific loss of inhibitory drive in the visual cortex of people with DLB and what role cholinergic function plays remains to be clarified; neurochemical post-mortem studies or novel spectroscopic imaging assessing for example gamma-amino-butyric acid-ergic tone may be helpful in this regard.

References

3 Logothetis NK. What we can do and what we cannot do with fMRI. Nature 2008; 453: 869–78.
### Table DS1  Demographic, cognitive and motor characteristics of participants included in study

<table>
<thead>
<tr>
<th></th>
<th>Control group (n= 19)</th>
<th>Dementia with Lewy bodies group (n= 16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years: mean (s.d.)</td>
<td>77.6 (7.1)</td>
<td>81.3 (5.6)</td>
<td>0.10</td>
</tr>
<tr>
<td>Males:females: n</td>
<td>11:8</td>
<td>8:8</td>
<td>0.74</td>
</tr>
<tr>
<td>Unified Parkinson’s Disease Rating Scale, motor subscale: mean (s.d.)</td>
<td>0.9 (1.6)</td>
<td>35.0 (13.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mini-Mental State Examination,13 mean (s.d.)</td>
<td>29.0 (1.2)</td>
<td>18.7 (5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cambridge Cognitive Examination (CAMCOG),14 mean (s.d.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>96.5 (3.4)</td>
<td>63.7 (14.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Executive subscore</td>
<td>22.1 (3.4)</td>
<td>9.9 (4.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Memory subscore</td>
<td>23.6 (2.1)</td>
<td>15.4 (4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visual acuity, decimalised: mean (s.d.)</td>
<td>0.64 (0.29)</td>
<td>0.55 (0.26)</td>
<td>0.33</td>
</tr>
<tr>
<td>Visuoperceptual score, % correct: mean (s.d.)</td>
<td>39.8 (0.4)</td>
<td>30.6 (6.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinician Assessment of Fluctuation,15 mean (s.d.)</td>
<td>–</td>
<td>8.3 (4.4)</td>
<td>N/A</td>
</tr>
<tr>
<td>One Day Fluctuation Assessment Scale,15 mean (s.d.)</td>
<td>–</td>
<td>6.7 (4.7)</td>
<td>N/A</td>
</tr>
<tr>
<td>Neuropsychiatry inventory,14 hallucinations subscale: median (IQR)</td>
<td>–</td>
<td>2.5 (4.5)</td>
<td>N/A</td>
</tr>
<tr>
<td>On cholinesterase inhibitor, n</td>
<td>–</td>
<td>11</td>
<td>N/A</td>
</tr>
<tr>
<td>On anti-Parkinsonian medication, n</td>
<td>–</td>
<td>4</td>
<td>N/A</td>
</tr>
<tr>
<td>L-dopa dose equivalent, mg:16 mean (s.d.)</td>
<td>–</td>
<td>145.8 (72)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A, not applicable.

a. For comparison of data in control participants v. participants with dementia with Lewy bodies (DLB) independent student t-tests were used for continuous data and Pearson chi-squared for categorical data. Results in bold are significant.

b. Calculated equivalent L-dopa dose in those in the DLB group on dopaminergic medication.

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**Fig. DS1** Scatter plots showing phosphene threshold plotted against V1 blood oxygen level-dependent (BOLD) activity (a) and V2/V3 BOLD activity (b) in response to checkerboard stimulation in dementia with Lewy body (DLB, n = 16) and control (n = 19) groups.

Relationship between phosphene threshold and V1 BOLD activity in the control group was positive (r = 0.48, P = 0.04) and negative in the DLB group (r = −0.71, P = 0.002) and this was also the case for phosphene threshold v. V2/V3 BOLD activity (control group, r = 0.64, P = 0.008; DLB group, r = −0.57, P = 0.02). Linear fits to data (dashed = control group, solid = DLB group) are shown for illustrative purposes.

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### Additional references


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