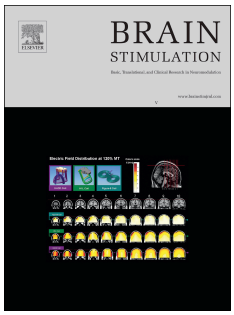
Journal Pre-proof



Bilateral Nucleus Basalis of Meynert Deep Brain Stimulation for dementia with Lewy bodies A Randomised Clinical Trial

James Gratwicke, Ludvic Zrinzo, Joshua Kahan, Amy Peters, Una Brechany, Ann McNichol, Mazda Beigi, Harith Akram, Jonathan Hyam, Ashwini Oswal, Brian Day, Laura Mancini, John Thornton, Tarek Yousry, Sebastian J. Crutch, John-Paul Taylor, Ian McKeith, Lynn Rochester, Jonathan M. Schott, Patricia Limousin, David Burn, Martin N. Rossor, Marwan Hariz, Marjan Jahanshahi, Thomas Foltynie

PII: S1935-861X(20)30089-9

DOI: https://doi.org/10.1016/j.brs.2020.04.010

Reference: BRS 1719

To appear in: *Brain Stimulation*

Received Date: 10 November 2019

Revised Date: 2 March 2020

Accepted Date: 15 April 2020

Please cite this article as: Gratwicke J, Zrinzo L, Kahan J, Peters A, Brechany U, McNichol A, Beigi M, Akram H, Hyam J, Oswal A, Day B, Mancini L, Thornton J, Yousry T, Crutch SJ, Taylor J-P, McKeith I, Rochester L, Schott JM, Limousin P, Burn D, Rossor MN, Hariz M, Jahanshahi M, Foltynie T, Bilateral Nucleus Basalis of Meynert Deep Brain Stimulation for dementia with Lewy bodies A Randomised Clinical Trial *Brain Stimulation*, https://doi.org/10.1016/j.brs.2020.04.010.

Bilateral Nucleus Basalis of Meynert Deep Brain Stimulation for dementia with Lewy bodies
A Randomised Clinical Trial

James Gratwicke[a], Ludvic Zrinzo[a], Joshua Kahan[a], Amy Peters[a], Una Brechany[c], Ann McNichol[c], Mazda Beigi[f], Harith Akram[a], Jonathan Hyam[a], Ashwini Oswal[a], Brian Day[a], Laura Mancini[e], John Thornton[e], Tarek Yousry[e], Sebastian J Crutch[b], John-Paul Taylor[d], Ian McKeith[d], Lynn Rochester[c], Jonathan M Schott[b], Patricia Limousin[a], David Burn[c], Martin N Rossor[b], Marwan Hariz[a], Marjan Jahanshahi[a]*; Thomas Foltynie[a]*

*Shared senior authorship

Author affiliations:
[a]Department of Clinical & Movement Neurosciences, UCL Institute of Neurology and The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK
[b]Dementia Research Centre, UCL Institute of Neurology and The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK
[c]Biomedical Research Building, Newcastle University & Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[d]Newcastle University & Northumberland, Tyne and Wear NHS Foundation Trust, Newcastle upon Tyne, UK
[e]Lynsholm Department of Neuroradiology, The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK
[f]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Corresponding author: Professor T Foltynie, MRCP, PhD, Unit of Functional Neurosurgery (Box 146), The National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK (t.foltynie@ucl.ac.uk), +44 (0) 203 448 8726

Manuscript word count: 3355

Abstract

Background: Dementia with Lewy bodies (DLB) is the second most common form of dementia. Current symptomatic treatment with medications remains inadequate. Deep brain stimulation of the nucleus basalis of Meynert (NBM DBS) has been proposed as a potential new treatment option in dementias.

Objective: To assess the safety and tolerability of low frequency (20 Hz) NBM DBS in DLB patients and explore its potential effects on both clinical symptoms and functional connectivity in underlying cognitive networks.

Methods: We conducted an exploratory randomised, double-blind, crossover trial of NBM DBS in six DLB patients recruited from two UK neuroscience centres. Patients were aged between 50-80 years, had mild-moderate dementia symptoms and were living with a carer-informant. Patients underwent image guided stereotactic implantation of bilateral DBS electrodes with the deepest contacts positioned in the Ch4i subsector of NBM. Patients were subsequently assigned to receive either active or sham stimulation for six weeks, followed by a two week washout period, then the opposite condition for six weeks. Safety and tolerability of both the surgery and stimulation were systematically evaluated throughout. Exploratory outcomes included the difference in scores on standardised measurements of cognitive, psychiatric and motor symptoms between the active and sham stimulation conditions, as well as differences in functional connectivity in discrete cognitive networks on resting state fMRI.

Results: Surgery and stimulation were well tolerated by all six patients (five male, mean age 71.33 years). One serious adverse event occurred: one patient developed antibiotic-associated colitis, prolonging his hospital stay by two weeks. No consistent improvements were observed in exploratory clinical outcome measures, but the severity of neuropsychiatric symptoms reduced with NBM DBS in 3/5 patients. Active stimulation was associated with

functional connectivity changes in both the default mode network and the frontoparietal network.

Conclusion: Low frequency NBM DBS can be safely conducted in DLB patients. This should encourage further exploration of the possible effects of stimulation on neuropsychiatric symptoms and corresponding changes in functional connectivity in cognitive networks.

Trial registration number: NCT02263937

Keywords: deep brain stimulation, nucleus basalis of Meynert, dementia with Lewy bodies, cholinergic networks, functional brain networks.

Introduction

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia and is associated with the highest morbidity and caregiver burden of any dementia syndrome [1–3]. It is characterised by prominent deficits in attention, executive functions and visuoperceptual abilities, while mnemonic abilities are less impaired [4–6]. These cognitive impairments are accompanied by fluctuating cognition, neuropsychiatric symptoms, REM sleep behaviour disorder and parkinsonism, highlighting the phenotypic overlap with Parkinson's disease dementia (PDD) [4,7]. Current treatment in DLB is limited to symptomatic therapies, including cholinesterase inhibitors (ChEIs) and N-methyl D-aspartate receptor antagonist medications. These provide only modest benefits [8,9], and there is an unmet need for more effective treatments.

DLB is mainly caused by deposition of pathognomonic Lewy body inclusions in the cerebral cortices, however recent research has shown that the underlying pathology of the condition extends beyond this to include contributions from amyloid plaques, neurofibrillary tangles and cerebral microbleeds [10–13],while an expanding number of genetic factors also contribute [14–18]. Given this complex underlying pathologic milieu, pharmacologic therapies targeting isolated aspects of the disease process may have limited impact. An alternative strategy may be electrical neuromodulation of upstream cognitive networks. We previously proposed that the nucleus basalis of Meynert (NBM) in the basal forebrain represents a key cognitive node to target in dementia given that it is the main source of cholinergic innervation to cortex, and is strongly implicated in arousal, attention, memory and perceptive functions [19–21]. Furthermore, degeneration of NBM and consequent loss of corticopetal cholinergic innervation is strongly associated with the development of cognitive and behavioural deficits in Lewy-body dementias (DLB and PDD) [22–25].

We recently investigated the safety and potential symptomatic effects of neuromodulation of the NBM in PDD patients using low frequency deep brain stimulation (DBS); in that patient group the therapy was found to be safe and well-tolerated, and there were beneficial effects on neuropsychiatric symptoms, in particular a reduction in complex visual hallucinations in some patients [26]. Given that DLB and PDD share a common phenotype and underlying pathophysiology (although subtle differences exist [27]), neuromodulation of NBM might represent a potential novel therapy in DLB patients as well. We therefore aimed to evaluate the safety, tolerability and potential symptomatic effects of NBM DBS in DLB patients in a randomised double-blind exploratory clinical trial.

Materials and methods

Trial design

We conducted a randomised, double-blind, crossover trial, with two principle aims: (1) to evaluate the general safety and tolerability of our NBM DBS procedure in DLB patients. (2) to compare scores on a battery of standardised cognitive, psychiatric and motor tests pre-operatively and repeated after six weeks of bilateral NBM DBS and six weeks of sham DBS (Figure 1).

All patients completed a full battery of baseline assessments (see below) prior to undergoing surgery. An early post-operative abbreviated assessment battery was conducted with each patient one week after pulse generator implantation (Figure 1) to assess the impact of the surgical procedure alone. Three weeks later patients attended for 24 hours and were screened for the effects of stimulation in an open label manner, using the Wechsler Adult Intelligence Scale-IV (WAIS-IV) digit span as an objective measure. Low frequency monopolar stimulation at 20 Hz with pulse-width 60 µs was used to allow comparison with the results of our previously published trial in PDD patients [26]. As there is no precedent for selecting optimum stimulation voltage for the NBM target we used digit span score to screen for potential beneficial effects at different voltages. Digit span is a brief test of working memory and attention, with multiple permutations. It can therefore be administered multiple times in a short session without inducing fatigue or being confounded by learning effects. Optimum stimulation voltages were defined as those producing highest digit span scores with the lowest energy, without side-effects (to avoid unblinding) and these were adopted for the blinded phase. DBS was subsequently turned off for two weeks (washout period). Patients were subsequently randomised into the simulation off-first or on-first group for the subsequent six weeks. Following this DBS was turned off in all patients during another two-week washout period. Patients were then switched over to the opposite condition for a further six weeks. A full battery of assessments was repeated at the end of each six-week period, except for measures of IQ (Figure 1). The general safety and tolerability of the surgical

procedure and subsequent stimulation were systematically monitored throughout the trial period.

Trial participants

DLB patients who met the following eligibility criteria were recruited from two neurological referral centres (London and Newcastle) in the UK: fulfilled criteria for the diagnosis of probable DLB [7]; were appropriate candidates for DBS surgery aside from the co-existence of dementia; aged 50-80 years; able to give written informed consent; CAFS (Clinician Assessment of Fluctuation Scale [28]) score 2-12; MMSE (Mini-Mental State Examination) score 21-27; MRI brain imaging showing minimal atrophy and no abnormality which would compromise compliance with the protocol; living at home with a carer-informant; willing to comply with the trial protocol. All patients were already receiving ChEI medication at the time of recruitment, the dose of which was continued unchanged throughout the trial. In addition, several of the patients were taking medications with mild anticholinergic properties (Patient B was taking mirtazapine and sertraline, Patient C was taking amitriptyline and Patient F was taking venlafaxine, Table 1). Likewise, the doses of these medications were continued unchanged throughout the trial. Keeping the doses of all medications with cholinergic effects constant throughout the trial period ensured that any clinical effects seen during this period were solely a result of NBM DBS.

Randomisation

Patients were randomly assigned to either the stimulation off-first group (sham stimulation for six weeks, followed by active stimulation for six weeks) or the stimulation on-first group (vice versa) (Figure 1). Patients were recruited into each group in a counterbalanced order using computer-generated pairwise randomisation (following order of

enrolment). Both the patients and the clinicians performing trial assessments were blind to stimulation condition. An unblinded member of the trial team at each site (TF and UB) were responsible for randomisation allocation and spent the same time adjusting each patient's stimulator at the start of both active and sham stimulation periods in order to preserve patient blinding.

Surgical procedure

Enrolled patients underwent stereotactic implantation of bilateral DBS electrodes (model 3389, Medtronic, Minneapolis, MN, USA). A frontal entry point, on or posterior to the coronal suture allowed a trajectory that avoided sulci and ventricles while enabling optimal placement of the deepest contact/s in the Ch4i subsector of NBM. This anatomical target represents the widest and thickest portion of the NBM and is thus readily visible on MRI scans to enable image-guided implantation. Furthermore, the most widespread cortical projections from the NBM originate in this portion of the nucleus, and thus stimulation here has the potential to exert the greatest biological effects [21]. We selected a target for our deepest contacts which was a few millimetres more anteromedial in Ch4i compared to that used in our previous trial of NBM DBS in PDD [26]. The Ch4i subsector is larger here, giving the highest probability of successful contact placement. The average trajectory in the sagittal plane was 0–10 degrees anterior to a line perpendicular to the anterior commissure – posterior commissure line, and in the coronal plane was 0-5 degrees lateral to the same. Individual stereotactic axial and coronal proton-density MRI scans were obtained for each patient, on which the pallidum, optic tract, anterior commissure and the adjacent NBM were visible (1.5T Siemens Espree, PDw Turbo Spin-echo; 1.0 x 1.0 x 2.0 mm; TR 4000ms TE 13ms). These images were then used to guide stereotactic electrode implantation into the NBM. Consequently, microelectrode recording was not necessary. Surgery was performed

under general anaesthesia using a Leksell model G stereotactic frame. We have previously published full details of our neurosurgical procedure [29,30]. The accuracy of DBS lead contact location was confirmed immediately with intraoperative stereotactic MRI (we have previously published full details of this methodology [26]). An Activa PC implantable pulse generator (Medtronic, Minneapolis, MN, USA) was implanted into each patient one week later in a second procedure under general anaesthesia.

Outcomes

Due to the small sample size of this pilot trial all outcomes were exploratory. However, at each visit we prioritised an abbreviated battery of cognitive assessments in order to minimise the impact of patient fatigue on these particular measures. This was because these assessments were the most specific measures of function in individual cognitive domains, and due to this they were also the most taxing measures. These 'primary' outcome measures comprised: the Hopkins Verbal Learning Test - revised (HVLT-R), WAIS-IV digit span, verbal fluency, Posner's covert attention test, Simple and Choice Reaction Times and the CAFS.

At baseline and at the end of each blinded stimulation condition all patients underwent a full battery of assessments, which comprised both the abbreviated cognitive battery and the following additional validated assessments ('secondary' outcome measures): MMSE; Mattis Dementia Rating Scale-2; short recognition memory for faces; WAIS-IV arithmetic and letter-number sequencing; trail making test; colour-word interference test; WAIS-IV symbol search and digit-symbol coding; Florida apraxia screening test; Benton judgement of line orientation; Sustained attention to response test; MDS Unified Parkinson's Disease Rating Scale; Freezing of Gait Questionnaire; Scales for Outcomes in Parkinson's Disease (SCOPA)-Autonomic symptoms; Starkstein Apathy Scale; The Neuropsychiatric

Inventory (NPI); the Blessed dementia scale; Hamilton depression scale; Hamilton anxiety scale; the North-East visual hallucinations interview; clinical global impression of change scale; Quality of life – Alzheimer's disease scale; Mayo fluctuations composite scale; Zarit burden interview. In addition, adverse events were systematically recorded throughout the trial period.

Statistics

This was a pilot trial without the power to assess efficacy and all outcome measures were principally exploratory. Statistical comparisons were performed solely as a means of screening which measures might be prioritised in future trials and are not corrected for multiple comparisons. Two-tailed Wilcoxon signed ranks tests were used to compare scores on- vs off- stimulation when the distribution of differences was symmetrical, and two-tailed Sign tests otherwise. For transparency in the inter-individual variability in outcomes, data for all patients are presented in the supplementary materials. Data were analysed using Statistical Package for the Social Sciences (SPSS) version 24.0 software.

Functional MRI

All patients underwent scanning with functional MRI (fMRI) at the end of each blinded six-week condition to investigate the effects of NBM DBS on functional connectivity in the default mode network (DMN) and frontoparietal network (Methods in supplementary materials).

Study Approval

The study was sponsored by UCL and performed at the National Hospital for Neurology and Neurosurgery, London, UK and the Clinical Ageing Research Unit at

Newcastle University, UK. The trial conformed to the Seoul revision of the Declaration of Helsinki (2008) and Good Clinical Practice guidelines and was approved by the East of England Research Ethics Committee. All enrolled participants were determined to have capacity to provide informed consent by an independent neuropsychologist, prior to providing written informed consent.

Results

Patient Characteristics and Surgery

Between May 2014, and February 2016, we assessed 15 DLB patients and enrolled six into the study (five male, mean age 71.33 years (SD 3.67)) all of whom proceeded to NBM DBS implantation. Table 1 summarises their characteristics, the stereotactic coordinates of their active NBM contacts and their individual stimulation parameters during the blinded period. The most ventral active contact was successfully placed in the Ch4i subsector of NBM in each patient (Figure 2 in supplementary materials). In the two patients with a second active contact per hemisphere (Patients B and E), this was located on the NBM/GPi border. All six patients completed the blinded crossover phase and were included in all analyses.

At the end of the trial period (prior to unblinding) we asked each patient and their caregiver independently which condition they thought had been active stimulation and which they thought had been sham. Overall, just as many patients and caregivers alike identified the correct order of conditions as did not, consistent with random guessing across both groups.

Therefore, it appears that blinding was not compromised by any side-effects of NBM DBS during the trial.

Safety and tolerability

Only one serious adverse event occurred during the trial period: Patient D developed antibiotic-associated Clostridium difficile colitis after IPG implantation (as a result of prophylactic cefuroxime administered intra-operatively), which necessitated a prolongation of hospital stay by two weeks while he completed an extended course of antibiotic therapy and recovered. Once fully recovered there were no ongoing sequelae and no long-term extra morbidity. Table 3 in the supplementary materials lists all adverse events. Both surgical procedures were well-tolerated and all patients were ambulatory within 24 hours following each individual surgery. Two patients experienced mildly increased confusion and paranoia immediately after electrode implantation surgery, which responded to reassurance and resolved within 48 hours in both cases. All patients were fatigued in the post-operative period following both surgeries and consequently most failed to complete the one-week post-operative assessment battery. Consequently, it is difficult to judge the extent to which our surgical procedure had any specific adverse effects on cognitive performance in the immediate post-operative period.

Exploratory outcomes

There was no significant change in any of the scales in either the abbreviated cognitive battery or the additional assessments, either when comparing active NBM DBS to sham, or when comparing pre- and post-operative assessments (all $p>0.05$). Group results for all patients are presented in Table 2, and individual results in Tables 4-8 in supplementary materials. Of note, there was no clear dose-response relationship between voltage and digit

span; some patients appeared to perform better at higher voltages and others at lower, regardless of side-effects.

In parallel with our previous findings in PDD patients, the most notable finding within this cohort was a trend for improvement at group level in NPI total scores with NBM DBS (Table 2). At baseline patients had a median NPI total score of 15 points (range 1-37), while scores were 21 points (range 1-44) at the end of the sham stimulation period, and 9 points (range 1-30) at the end of the active stimulation period. Scrutinising the individual scores (Table 6 in supplementary materials), 3 patients had reduced NPI scores with NBM DBS on compared with baseline and sham stimulation, while 2 patients were essentially unchanged compared with baseline. Notably 4 patients had worse NPI scores during sham stimulation compared with baseline. (NB Patient D's NPI results were excluded from these analyses because his carer became unwell and was admitted to hospital, meaning there was no reliable informant to complete his NPI during the blinded period. Therefore, all NPI group analyses only include five patients).

Resting state fMRI

Four of the six patients were able to complete the fMRI study protocol correctly. The other two were too somnolent and too agitated respectively. Activity throughout the DMN was readily identifiable in all four patients with both active and sham NBM DBS. Given the small numbers, we conducted separate group analyses using a fixed effects design, and then repeated it using a random effects design (see Methods in the supplementary materials). Our

fixed effects group analysis detected a statistically significant decrease in connectivity between the posterior cingulate cortex of the DMN and the right inferior parietal lobule associated with active stimulation (Table 9 and Figure 3 in supplementary materials). However, using our random effects analysis no significant differences in DMN functional connectivity were detected. Our fixed effects group analysis of the frontoparietal network (which includes both the dorsal and ventral attention networks) detected stimulation-associated increases in functional connectivity between the left intraparietal sulcus and the left inferior frontal gyrus, and the left superior parietal lobule (precuneus), and the right paracingulate gyrus (Table 9 and Figure 4 in supplementary materials). Stimulation-associated reductions in functional connectivity were detected between the left intraparietal sulcus and the left middle temporal gyrus. Repeating this analysis using a random effects design yielded no statistically significant differences in functional connectivity.

Discussion

DBS electrode implantation and low frequency (20Hz) stimulation of the NBM was safe and well tolerated in the six DLB patients in this study. Dementia is considered a contraindication to DBS [31], yet this study provides further evidence that well-selected patients with cognitive and psychiatric symptomatology can still consent to and tolerate DBS without serious adverse events or significant cognitive deterioration, in experienced centres. This complements prior studies in AD [32,33] and PDD [26], and should reassure further exploratory studies of DBS for cognitive network neuromodulation in dementia.

In accordance with our previous study in PDD patients [26], there was no significant change in cognitive outcomes associated with NBM stimulation, but again there was a suggestion of possible improvement in neuropsychiatric symptoms. Strong associations have been shown between degeneration of the NBM and its cholinergic projections and the development of neuropsychiatric symptoms in dementia [34], particularly in Lewy body dementias [22]. Thus the combined results of both trials provide support to the hypothesis that NBM stimulation might modulate cholinergic transmission to relieve such symptoms [21]. However, it must be noted that the NPI is a composite scale assessing 12 different psychiatric symptoms (delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night-time behaviour disturbances, and appetite and eating abnormalities), and the biological substrates underlying each of these will vary. Therefore, although cholinergic neuromodulation may have influenced some of these psychiatric symptoms to bring about the improvement in composite score, the exact degree to which any of these individual specific symptoms was affected is not clear from the result. Of note, patients were maintained on ChEI therapy throughout both trials, therefore any symptomatic effects of NBM DBS are in addition to those achieved with pro-cholinergic medication.

It is important to note that we had to exclude Patient D's NPI results from our analysis, and therefore the present results are based on only five patients compared to six in the PDD trial. Furthermore, comparison of NPI scores between baseline and stimulation switched OFF in this study suggests a possible decline in NPI scores, raising the possibility of either a negative effect of the surgical procedure itself, and/or a rebound effect following withdrawal of NBM DBS, in those patients receiving NBM DBS ON during the first trial period. Additionally, while the possible improvement in neuropsychiatric symptoms with NBM DBS ON in the DLB patients was not dissimilar to the corresponding caregiver distress scores (Table 2), this did not translate into subjective improvements in quality of life for either patients or carers, which remained unchanged (Table 7 in supplementary materials). Finally, while NBM DBS switched ON was generally beneficial compared with NBM DBS switched OFF or baseline in terms of NPI scores, there was no convincing, consistent advantage seen in scales assessing depression, anxiety or apathy.

Interestingly, we did observe a clinical change in vigilance in Patient D, who displayed marked cognitive fluctuation and frank daytime somnolence both at baseline and during sham stimulation, precluding his ability to perform many of the assessments at these time points (see Tables 4-8 in supplementary materials). However, during the blinded on-stimulation condition he was much more alert and attentive, and consequently able to engage with and complete all assessments. This was also reflected in the objective improvement in his CAFS score with NBM DBS (8 points) compared to both off-stimulation and baseline (both 12 points respectively, see Table 4 in supplementary materials). The rest of our clinical results were similar to those seen in the previous PDD trial: patients' performance on many cognitive tests remained unchanged, and in some instances may have slightly worsened with stimulation.

Our fMRI analyses revealed that within our case series, there was a decrease in functional connectivity between the posterior cingulate cortex and the right inferior parietal cortex, both key nodes of the DMN. Our analysis of the frontoparietal network revealed increased functional connectivity between the intraparietal sulcus, inferior frontal gyrus and superior parietal lobule, and reduced connectivity with the middle temporal gyrus. These regions have been implicated in attentional control [35], and have also been demonstrated to show altered functional connectivity in patients with DLB [36,37]. Whether the observed bidirectional changes in functional connectivity in these brain networks with NBM DBS are beneficial or detrimental cannot be determined, however they show that NBM DBS did induce biological effects in these cognitive networks. However, when both analyses were repeated using a random effects design, these results were no longer significant, perhaps unsurprising given the small sample size involved. The results of our fixed effects analyses should therefore be considered exploratory findings, that cannot be generalised beyond our cohort, and thus currently of unclear significance that will require further evaluation and replication. In addition, our analyses were restricted to the DMN and frontoparietal networks, thus we cannot exclude the possibility that significant changes occurred in other brain networks due to NBM DBS.

The results of our exploratory outcome measures should not be interpreted as evidence for or against efficacy, solely as “hypothesis-generating” to assist the design and planning of future trials. As mentioned above, all patients continued ChEI therapy during the trial, and potential physiological effects of NBM DBS on the cholinergic system, and consequent clinical effects, may have been partially masked by the ongoing exposure to these medications. In addition, we did not include a non-operated, randomised control group of DLB patients, and so cannot comment on whether NBM DBS made any difference to the expected rate of progression of cognitive deficits during the trial period. Furthermore, the

period of active simulation was relatively short. Given that the therapeutic effects of DBS in certain neurological conditions such as dystonia only develop after several months of continuous stimulation [38] it remains possible that a longer period of stimulation in this trial might have produced greater clinical effects.

For the purposes of uniformity across patients in both our trials in DLB and PDD, we chose to investigate the effects of continuous low frequency (20 Hz) NBM stimulation only, however the scientific rationale for this is limited [21,39]. A recent study of NBM DBS in primates suggests that continuous stimulation may actually have an inhibitory effect on cognition, whereas intermittent stimulation may improve performance [40]. Future trials of NBM DBS should therefore consider the use of a titration schedule investigating cognitive responses to different frequencies, pulsewidths and modes (continuous/intermittent) of NBM DBS. However, implementing this would likely require a longer study with a greater frequency of assessment visits, which might be difficult for dementia patients to comply with. Future studies could also utilise cholinergic imaging using positron emission tomography to investigate whether NBM DBS does indeed increase corticopetal cholingeric output.

Conclusion

This pilot trial shows that NBM DBS is safe and well tolerated in carefully selected DLB patients. Furthermore, active stimulation was shown to induce changes in functional connectivity in cognitive networks in this patient group. These findings encourage further exploration of neuromodulation of cognitive networks as a therapy in dementia. However, no significant clinical effects were seen in this study, and therefore whether the search for potential symptomatic benefits ultimately justifies a surgical intervention in patients with dementia will always require well informed patient-centred discussions. Finally, although clinical and economic thresholds for DBS to be considered cost effective in the management

of Alzheimer's dementia have been estimated to be relatively low [41], the life expectancy of DLB patients is comparatively shorter [3]. Whether earlier intervention at a time when NBM degeneration would be less pronounced might yield greater clinical effects (as well as improved cost effectiveness) will also need to be explored.

Acknowledgements

We thank all the patients who participated in this trial and their partners, as well as their referring clinicians.

Contributors

JG, MJ, JK and TF designed the research. JG, LZ, AP, UB, AM, JK, BD, LM, JH, DB, MH, PL, MJ and TF conducted the study and acquired the data. JG, MJ, JK and TF analysed the data and wrote the manuscript. All authors commented on the final version of the manuscript. TF and JG had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, and the decision to submit for publication.

Funding

This study was supported by the UK Department of Health NIHR Biomedical Research Units at both Queen Square and Newcastle University/ Newcastle upon Tyne Hospitals NHS Foundation Trust and was sponsored by UCL. The work was undertaken at UCL/UCLH in London, UK, and the University of Newcastle in Newcastle upon Tyne, UK. The Unit of Functional Neurosurgery, UCL Institute of Neurology, Queen Square, London, is supported by the Parkinson's Appeal and the Monument Trust.

Financial disclosures

JG reports honoraria from Medtronic, UCB Pharmaceuticals, Britannia Pharmaceuticals and Bial. JT report grants and personal fees from Medtronic. LZ and MH report honoraria and travel expenses from Medtronic and Boston Scientific for speaking at meetings. JH reports honoraria from Medtronic and St Jude Medical. PL reports honoraria from Medtronic, St Jude Medical and Boston Scientific. BD reports personal fees from Takeda Development Centre Europe Ltd. TF reports honoraria from Medtronic, St Jude Medical, Profile Pharma, Bial, Abbvie Pharmaceuticals, UCB Pharmaceuticals and Oxford Biomedica. JMS has received research funding and PET tracer from AVID Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly). He has consulted for Roche, Eli Lilly, Biogen and Merck, received royalties from Oxford University Press and Henry Stewart Talks, given education lectures sponsored by Eli Lilly and serves on a Data Safety Monitoring Committee for Axon Neuroscience SE. MR reports other fees from Servier and Merck. AP, UB, AM, MB, HA, AO, TY, JPT, IMK, LR, DB and JK declare no competing interests.

REFERENCES

[1] Ricci M, Guidoni SV, Sepe-Monti M, Bomboi G, Antonini G, Blundo C, et al. Clinical findings, functional abilities and caregiver distress in the early stage of dementia with Lewy bodies (DLB) and

Alzheimer's disease (AD). Arch Gerontol Geriatr 2009;49:10–3. https://doi.org/10.1016/j.archger.2008.10.001.

[2] Boström F, Jönsson L, Minthon L, Londos E. Patients with dementia with lewy bodies have more impaired quality of life than patients with Alzheimer disease. Alzheimer Dis Assoc Disord 2007;21:150–4. https://doi.org/10.1097/WAD.0b013e318065c4a9.

[3] Price A, Farooq R, Yuan J-M, Menon VB, Cardinal RN, O'Brien JT. Mortality in dementia with Lewy bodies compared with Alzheimer's dementia: a retrospective naturalistic cohort study. BMJ Open 2017;7:e017504. https://doi.org/10.1136/bmjopen-2017-017504.

[4] McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor J-P, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 2017;89:88–100. https://doi.org/10.1212/WNL.0000000000004058.

[5] McKeith I, Mintzer J, Aarsland D, Burn D, Chiu H, Cohen-Mansfield J, et al. Dementia with Lewy bodies. Lancet Neurol 2004;3:19–28.

[6] Ferman TJ, Smith GE, Boeve BF, Graff-Radford NR, Lucas J a, Knopman DS, et al. Neuropsychological differentiation of dementia with Lewy bodies from normal aging and Alzheimer's disease. Clin Neuropsychol 2006;20:623–36. https://doi.org/10.1080/13854040500376831.

[7] McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–72. https://doi.org/10.1212/01.wnl.0000187889.17253.b1.

[8] Wang H-F, Yu J-T, Tang S-W, Jiang T, Tan C-C, Meng X-F, et al. Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. J Neurol Neurosurg Psychiatry 2015;86:135–43. https://doi.org/10.1136/jnnp-2014-307659.

[9] Stinton C, McKeith I, Taylor J-P, Lafortune L, Mioshi E, Mak E, et al. Pharmacological Management of Lewy Body Dementia: A Systematic Review and Meta-Analysis. Am J Psychiatry 2015;172:731–42. https://doi.org/10.1176/appi.ajp.2015.14121582.

[10] Jellinger K a., Attems J. Does striatal pathology distinguish Parkinson disease with dementia and dementia with Lewy bodies? Acta Neuropathol 2006;112:253–60. https://doi.org/10.1007/s00401-006-0088-2.

[11] Ballard C, Ziabreva I, Perry R, Larsen JP, O'Brien J, McKeith I, et al. Differences in neuropathologic characteristics across the Lewy body dementia spectrum. Neurology 2006;67:1931–4. https://doi.org/10.1212/01.wnl.0000249130.63615.cc.

[12] Edison P, Rowe CC, Rinne JO, Ng S, Ahmed I, Kemppainen N, et al. Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography. J Neurol Neurosurg Psychiatry 2008;79:1331–8. https://doi.org/10.1136/jnnp.2007.127878.

[13] Gungor I, Sarro L, Graff-Radford J, Zuk SM, Tosakulwong N, Przybelski S a., et al. Frequency and topography of cerebral microbleeds in dementia with Lewy bodies compared to Alzheimer's disease. Parkinsonism Relat Disord 2015;21:1101–4. https://doi.org/10.1016/j.parkreldis.2015.07.008.

[14] Zarranz JJ, Alegre J, Gómez-Esteban JC, Lezcano E, Ros R, Ampuero I, et al. The New Mutation, E46K, of α-Synuclein Causes Parkinson and Lewy Body Dementia. Ann Neurol 2004;55:164–73. https://doi.org/10.1002/ana.10795.

[15] Ohtake H, Limprasert P, Fan Y, Onodera O, Kakita a., Takahashi H, et al. -Synuclein gene alterations in dementia with Lewy bodies. Neurology 2004;63:805–11. https://doi.org/10.1212/01.WNL.0000139870.14385.3C.

[16] Piscopo P, Marcon G, Piras MR, Crestini a., Campeggi LM, Deiana E, et al. A novel PSEN2 mutation associated with a peculiar phenotype. Neurology 2008;70:1549–54. https://doi.org/10.1212/01.wnl.0000310643.53587.87.

[17] Nalls M a, Duran R, Lopez G, Kurzawa-Akanbi M, McKeith IG, Chinnery PF, et al. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. JAMA Neurol 2013;70:727–35. https://doi.org/10.1001/jamaneurol.2013.1925.

[18] Guerreiro R, Ross OA, Kun-Rodrigues C, Hernandez DG, Orme T, Eicher JD, et al. Investigating the genetic architecture of dementia with Lewy bodies: a two-stage genome-wide association study. Lancet Neurol 2018;17:64–74. https://doi.org/10.1016/S1474-4422(17)30400-3.

[19] Goard M, Dan Y. Basal forebrain activation enhances cortical coding of natural scenes. Nat Neurosci 2009;12:1444–9. https://doi.org/10.1038/nn.2402.

[20] Kalmbach A, Hedrick T, Waters J. Selective optogenetic stimulation of cholinergic axons in neocortex. J Neurophysiol 2012;107:2008–19. https://doi.org/10.1152/jn.00870.2011.

[21] Gratwicke J, Kahan J, Zrinzo L, Hariz M, Limousin P, Foltynie T, et al. The nucleus basalis of Meynert: A new target for deep brain stimulation in dementia? Neurosci Biobehav Rev 2013;37:2676–88. https://doi.org/10.1016/j.neubiorev.2013.09.003.

[22] Barrett MJ, Blair JC, Sperling SA, Smolkin ME, Druzgal TJ. Baseline symptoms and basal forebrain volume predict future psychosis in early Parkinson disease. Neurology 2018;90:e1618–26. https://doi.org/10.1212/WNL.0000000000005421.

[23] Ray NJ, Bradburn S, Murgatroyd C, Toseeb U, Mir P, Kountouriotis GK, et al. In vivo cholinergic basal forebrain atrophy predicts cognitive decline in de novo Parkinson's disease. Brain 2018;141:165–76. https://doi.org/10.1093/brain/awx310.

[24] Grothe MJ, Schuster C, Bauer F, Heinsen H, Prudlo J, Teipel SJ. Atrophy of the cholinergic basal forebrain in dementia with Lewy bodies and Alzheimer's disease dementia. J Neurol 2014:1939–48. https://doi.org/10.1007/s00415-014-7439-z.

[25] Perry EK, Curtis M, Dick DJ, Candy JM, Atack JR, Bloxham C a, et al. Cholinergic correlates of cognitive impairment in Parkinson's disease: comparisons with Alzheimer's disease. J Neurol Neurosurg Psychiatry 1985;48:413–21. https://doi.org/10.1136/jnnp.48.5.413.

[26] Gratwicke J, Zrinzo L, Kahan J, Peters A, Beigi M, Akram H, et al. Bilateral Deep Brain Stimulation of the Nucleus Basalis of Meynert for Parkinson Disease Dementia: A Randomized Clinical Trial. JAMA Neurol 2018;75:169–78. https://doi.org/10.1001/jamaneurol.2017.3762.

[27] Goldman JG, Williams-Gray C, Barker R a, Duda JE, Galvin JE. The spectrum of cognitive impairment in Lewy body diseases. Mov Disord 2014;29:608–21. https://doi.org/10.1002/mds.25866.

[28] Walker MP, Ayre GA, Cummings JL, Wesnes K, McKeith IG, O'Brien JT, et al. The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale. Two methods to assess fluctuating confusion in dementia. Br J Psychiatry 2000;177:252–6. https://doi.org/10.1192/bjp.177.3.252.

[29] Foltynie T, Zrinzo L, Martinez-Torres I, Tripoliti E, Petersen E, Holl E, et al. MRI-guided STN DBS in Parkinson's disease without microelectrode recording: efficacy and safety. J Neurol Neurosurg Psychiatry 2011;82:358–63. https://doi.org/10.1136/jnnp.2010.205542.

[30] Holl EM, Petersen EA, Foltynie T, Martinez-Torres I, Limousin P, Hariz MI, et al. Improving targeting in image-guided frame-based deep brain stimulation. Neurosurgery 2010;67:437–47. https://doi.org/10.1227/NEU.0b013e3181f7422a.

[31] Foltynie T, Hariz MI. Surgical management of Parkinson's disease. Expert Rev Neurother 2010;10:903–14. https://doi.org/10.1586/ern.10.68.

[32] Kuhn J, Hardenacke K, Lenartz D, Gruendler T, Ullsperger M, Bartsch C, et al. Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia. Mol Psychiatry 2015;20:353–60. https://doi.org/10.1038/mp.2014.32.

[33] Lozano AM, Fosdick L, Chakravarty MM, Leoutsakos J-M, Munro C, Oh E, et al. A Phase II Study of

Fornix Deep Brain Stimulation in Mild Alzheimer's Disease. J Alzheimers Dis 2016;54:777–87. https://doi.org/10.3233/JAD-160017.

[34] van Dalen JW, Caan MWA, van Gool WA, Richard E. Neuropsychiatric symptoms of cholinergic deficiency occur with degradation of the projections from the nucleus basalis of Meynert. Brain Imaging Behav 2016. https://doi.org/10.1007/s11682-016-9631-5.

[35] Vossel S, Geng JJ, Fink GR. Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. Neuroscientist 2014;20:150–9. https://doi.org/10.1177/1073858413494269.

[36] Peraza LR, Kaiser M, Firbank M, Graziadio S, Bonanni L, Onofrj M, et al. FMRI resting state networks and their association with cognitive fluctuations in dementia with Lewy bodies. NeuroImage Clin 2014;4:558–65. https://doi.org/10.1016/j.nicl.2014.03.013.

[37] Schumacher J, Peraza LR, Firbank M, Thomas AJ, Kaiser M, Gallagher P, et al. Functional connectivity in dementia with Lewy bodies: A within- and between-network analysis. Hum Brain Mapp 2018;39:1118–29. https://doi.org/10.1002/hbm.23901.

[38] Tisch S, Rothwell JC, Limousin P, Hariz MI, Corcos DM. The physiological effects of pallidal deep brain stimulation in dystonia. IEEE Trans Neural Syst Rehabil Eng 2007;15:166–72. https://doi.org/10.1109/TNSRE.2007.896994.

[39] Freund H-J, Kuhn J, Lenartz D, Mai JK, Schnell T, Klosterkoetter J, et al. Cognitive functions in a patient with Parkinson-dementia syndrome undergoing deep brain stimulation. Arch Neurol 2009;66:781–5. https://doi.org/10.1001/archneurol.2009.102.

[40] Liu R, Crawford J, Callahan PM, Terry A V., Constantinidis C, Blake DT. Intermittent Stimulation of the Nucleus Basalis of Meynert Improves Working Memory in Adult Monkeys. Curr Biol 2017;27:2640-2646.e4. https://doi.org/10.1016/j.cub.2017.07.021.

[41] Mirsaeedi-Farahani K, Halpern CH, Baltuch GH, Wolk D a., Stein SC. Deep brain stimulation for Alzheimer disease: a decision and cost-effectiveness analysis. J Neurol 2015:1191–7. https://doi.org/10.1007/s00415-015-7688-5.

Legends for the figures:

Figure 1. Study Design: Black arrows indicate study time-points, green arrows indicate assessments at those time points as per protocol. All six patients who underwent surgery completed the double-blind phase of the protocol.

Table 1: Baseline clinical characteristics of the DLB patients, and parameters used during the blinded stimulation period

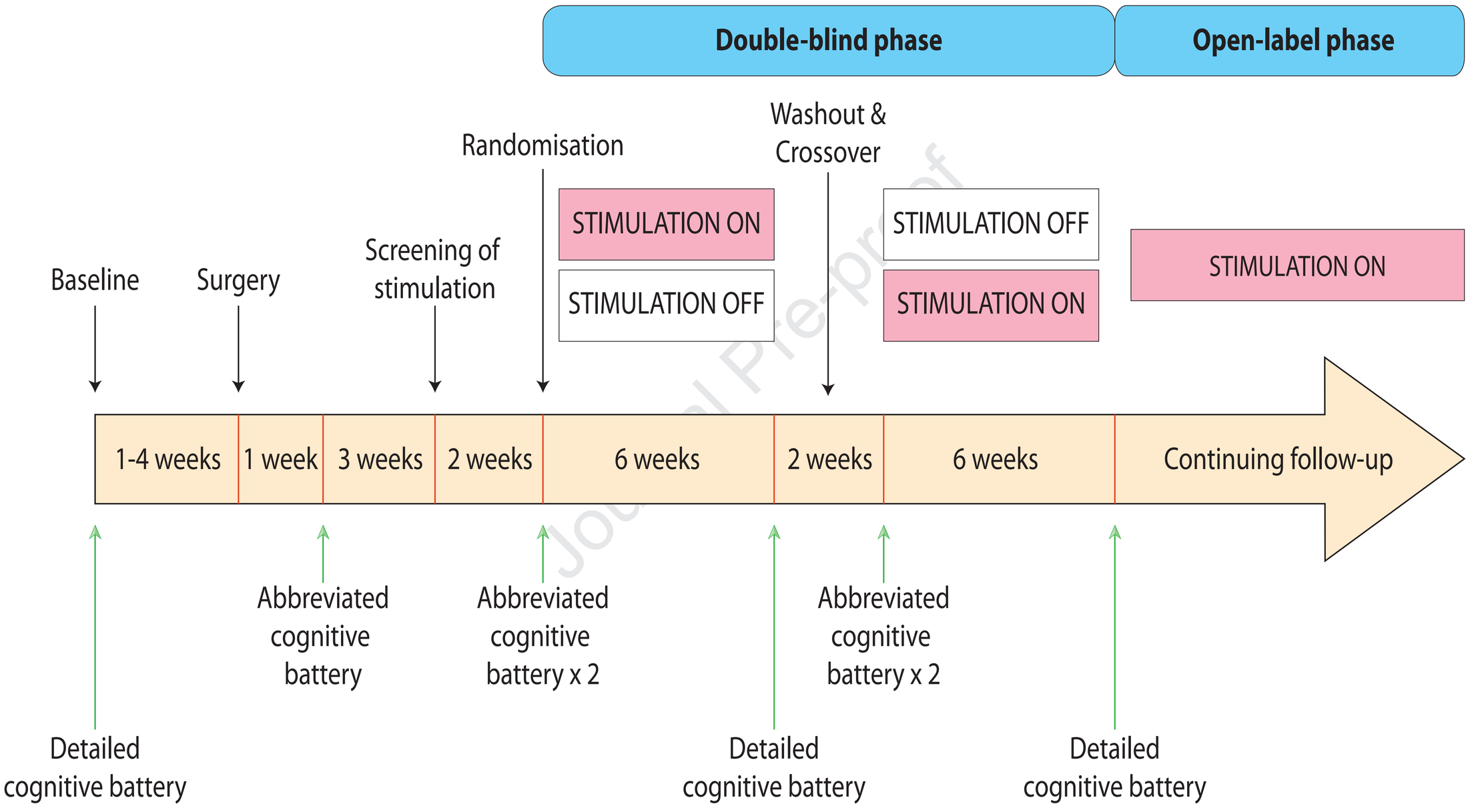
Patient	Sex	Age at surgery (yrs)	Disease duration (yrs)	UPDRS Part III (motor) score	Visual hallucinations	CAFS score	TOPF estimated premorbid IQ	WASI measured current IQ (95% CI)	MMSE	Mattis Dementia Rating Scale 2 (Raw, Scaled)	Co-morbidities	Concomitant medications at enrolment (total daily doses)	Daily levodopa equivalent dose (LED, mg/day)†	Daily total cholinesterase inhibitor dose (mg/day)	Active contacts (monopolar)	Stereotactic coordinates (x,y,z)◊	Stimulation parameters
A	M	65	5	35	No	12	92	83 (78-89)	23	126, Scaled 5 (moderately impaired)	Hypertension, appendicectomy, osteoarthritis, hiatus hernia	Half Sinemet CR 125 mg BD, Donepezil 10 mg ON, Enalapril 15 mg OM, Indapamide 1.5 mg OM, Clonazepam 1 mg ON	187.5	10	1, 9	-20.4, 5.5, -5.3; 18.5, 6.6, -5.4	2.5V, 60us, 20Hz
B	M	73	4	42	No	9	102	90 (85-96)	23	121, Scaled 4 (moderately impaired)	Coronary artery disease, cateracts.	Rivastigmine 4.5 mg BD, Sinemet Plus 125 mg TDS, Mirtazepine 45 mg ON, Sertraline 100 mg OM, Sotalol 40 mg BD, Amlodipine 5mg BD, Aspirin 75 mg OM, Atorvastatin 20 mg ON	375	9	0, 1, 8, 9	-21.4, 9.2, -4.5; 20.5, 8.8, -4.2	2.5V, 60us, 20Hz
C	F	73	10	24	Yes	2	101	90 (85-96)	21	123, Scaled 5 (moderately impaired)	Anxiety, vulvodynia	Sinemet 250 mg QDS, Rivastigmine 9.5 mg/24h, Amytriptylline 125 mg ON, Domperidone 10 mg QDS, HRT, Lansoprazole 30 mg OM	1000	9.5	0,8	-17.3, 7.7,-5.3; 16.8,7.6, -4.7	3.0V, 60us, 20 Hz
D	M	69	5	64	Yes	12	91	69 (65-76)	22	103, Scaled 2 (severely impaired)	Sciatica	Madopar 125 mg TDS, Madopar CR 125 mg ON, Rivastigmine 3 mg QDS, Ezetimibe 10 mg OD, Tamsulosin 400 mcg OD	468.75	12	0, 8	-19.1, 9.7, -7.5; 21.4, 11.5,-7.3	2.5V, 60us, 20Hz
E	M	75	3	20	Yes	12	NC	65 (61-72)	24	82, Scaled 2 (severely impaired)	Macular degeneration, coeliac disease, COPD	Donepezil 10 mg ON, Sinemet 62.5 mg OM, ventolin inhaler, seretide inhaler	62.5	10	0, 1, 8, 9	-18.8, 7.4,-4.6; 18.0,8.8,-4.9	3.5V, 60us, 20Hz
F	M	73	4	16	No	12	96	90 (85-96)	24	125, Scaled 5 (moderately impaired)	Nil	Donepezil 10 mg ON, Venlafaxine MR 150 mg OM	0	10	0,8	-18.9, 4.2, -8.0; 19.7, 5.7, -7.3	2.0V, 60us, 20Hz
Group Mean		**71.33**	**5.17**	**33.50**		9.83	**96.40**	**81.17**	**22.83**	**113.33**			**348.96**	**10.08**		**-19.3, 7.3, -5.9**	
SD		**3.67**	**2.48**	**17.80**		4.02	**5.03**	**11.37**	**1.17**	**17.53**			**365.73**	**1.02**		**19.2, 8.2, -5.6**	

Disease duration was estimated by examining the patient's medical notes and collateral history from the caregiver to determine the time at which cognitive decline began to interfere with occupational or social function. The Mattis Dementia Rating Scale 2 Scaled score is corrected for age but not education. Patient E had very poor vision due to severe macular degeneration which impaired his completion of all visuoperceptual tasks, therefore WASI, MMSE and Mattis DRS-2 scores likely underestimate his cognitive ability. He is also alexic and so could not complete the TOPF. CAFS = Clinician Assessment of Fluctuations Scale. COPD = chronic obstructive pulmonary disease. CR = controlled release preparation. SD = standard deviation. TOPF = Test of Premorbid Function. UPDRS = Movement Disorders Society unified Parkinson's disease rating scale. † LED calculation as per protocol in [31]. ◊ Mean stereotactic co-ordinates of the deepest active contact in left and right hemispheres respectively, with reference to the mid-commissural point of the AC-PC plane.

Table 2: Group level primary and selected secondary exploratory outcome measures

	Group median *(interquartile range)*						Median difference in scores (DBS ON vs OFF)	p value
	Baseline		DBS OFF		DBS ON			
Primary outcome measures								
Hopkins Verbal Learning Test Revised (T scores)								
Total recall	31.00	*(15.00)*	27.00	*(6.00)*	26.00	*(13.00)*	3.00	0.416
Delayed Recall	33.00	*(12.00)*	31.00	*(9.00)*	24.00	*(14.00)*	0.00	0.581
Retention	38.00	*(5.00)*	42.00	*(31.00)*	27.00	*(31.00)*	-8.00	0.500
Recognition discrimination index	40.00	*(22.00)*	30.00	*(25.00)*	35.00	*(14.00)*	6.00	0.916
WAIS-IV digit span (raw scores)								
Digits forwards (range 0-16)	8.00	*(2.50)*	10.00	*(1.00)*	9.00	*(1.00)*	0.00	0.276
Digits backwards (range 0-14)	7.00	*(1.75)*	8.00	*(4.00)*	6.00	*(2.00)*	-1.00	0.336
Digits sequencing (range 0-16)	5.00	*(1.75)*	6.00	*(1.00)*	5.00	*(4.00)*	0.00	0.285
D-KEFS Verbal Fluency Test (scaled scores)								
Letter Fluency	9.00	*(2.00)*	8.00	*(1.00)*	7.00	*(4.00)*	-1.00	0.683
Category Fluency	4.00	*(3.00)*	4.00	*(5.00)*	4.00	*(6.00)*	0.00	1.000
Category Switching Total Correct	3.00	*(4.00)*	2.00	*(2.00)*	3.00	*(4.00)*	0.00	0.414
Posner's covert attention test								
Total accuracy (0-100%)	91.00	*(24.00)*	93.00	*(46.00)*	88.00	*(37.00)*	-3.00	0.500
CANTAB Reaction Time Test								
Simple Reaction Time (ms)	547.00	*(405.50)*	521.00	*(98.00)*	435.00	*(435)*	-72.00	0.600
Choice Reaction Time (ms)	493.00	*(105.5)*	469.00	*(99.00)*	424.00	*(203.50)*	-35.00	0.715
Clinician Assessment of Fluctuations Scale	12.00	*(3.00)*	12.00	*(6.00)*	10.00	*(4.00)*	-2.00	0.625
Selected secondary outcome measures								
Mini-Mental State Examination (MMSE)	23.00	*(2.00)*	25.00	*(4.00)*	24.00	*(1.00)*	-2.00	0.102
Mattis Dementia Rating Scale 2 (raw score)	122.00	*(22.00)*	126.00	*(46.00)*	122.00	*(25.00)*	0.00	0.596
Neuropsychiatric Inventory								
Total score (0-144)	15.00	*(11.00)*	21.00	*(19.00)*	9.00	*(14.75)*	-13.00	0.066
Caregiver distress score (0-60)	10.00	*(8.00)*	15.00	*(12.25)*	4.00	*(9.00)*	-4.00	0.068
Hallucinations subscale (0-12)	1.00	*(4.00)*	0.00	*(2.00)*	0.00	*(0.00)*	0.00	0.655

All scaled scores/T scores are age-adjusted. Posner task total accuracy is % of presented targets correctly responded to. Higher scores are better on all tests, except for measures of reaction time, Clinician Assessment of Fluctuations Scale scores and Neuropsychiatric Inventory subscales, in which lower scores are better. In the Hopkins Verbal Learning Test Revised the ability to access newly learned information is assessed by the percentage of words retained after a twenty-minute delay from those in a previously learnt 12 word list (retention). A list of 24 randomly ordered words is subsequently read, containing both the original 12 target words and 12 non-target words, and the patient must identify which were the target words – this provides a measure of retention in memory that is relatively free from the influence of effortful memory search and retrieval (recognition – discrimination index).



Highlights:

- Novel therapeutic strategies for dementia are urgently needed.
- Deep brain stimulation of the nucleus basalis of Meynert has been proposed.
- This intervention was well tolerated in patients with dementia with Lewy bodies
- It may impact upon neuropsychiatric symptoms
- Stimulation possibly induced functional connectivity changes in cognitive networks.

CRediT Roles

James Gratwicke: Conceptualisation, Methodology, Investigation, Formal analysis, Writing – Original Draft, Writing – Review & Editing, Visualisation. **Ludvic Zrinzo:** Conceptualisation, Methodology, Investigation, Writing – Review & Editing, Supervision. **Joshua Kahan:** Conceptualisation, Methodology, Investigation, Formal analysis, Writing – Original Draft, Visualisation. **Amy Peters:** Investigation. **Una Brechany:** Investigation. **Ann McNichol:** Data Curation. **Mazda Beigi:** Investigation. **Harith Akram:** Investigation. **Jonathan Hyam:** Investigation. **Ashwini Oswal:** Methodology, Investigation, Formal analysis. **Brian Day:** Investigation. **Laura Mancini:** Methodology, Investigation. **John Thornton:** Project administration. **Tarek Yousry:** Project administration. **Sebastian J Crutch:** Writing – Review & editing. **John-Paul Taylor:** Writing – Review & editing. **Ian McKeith:** Writing – Review & editing. **Lynn Rochester:** Methodology, Writing – Review & editing. **Jonathan M Schott:** Methodology, Writing – Review & editing. **Patricia Limousin:** Conceptualisation, Methodology, Investigation, Writing – Review & Editing. **David Burn:** Conceptualisation, Methodology, Investigation, Writing – Review & Editing. **Martin N Rossor:** Conceptualisation, Writing – Review & Editing, Supervision, Project administration, Funding acquisition. **Marwan Hariz:** Conceptualisation, Methodology, Investigation, Writing – Review & Editing. **Marjan Jahanshahi:** Conceptualisation, Methodology, Writing – Review & Editing, Supervision. **Thomas Foltynie:** Conceptualisation, Methodology, Investigation, Validation, Data Curation, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.