Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia

Article *in* Molecular Psychiatry · May 2014

DOI: 10.1038/mp.2014.32 · Source: PubMed

Molecular Psychiatry (2014), 1–8

www.nature.com/mp

ORIGINAL ARTICLE

Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia

J Kuhn[1,17], K Hardenacke[1,17], D Lenartz[2], T Guendler[1,3,4], M Ullsperger[4,5], C Bartsch[1], JK Mai[6], K Zilles[7,8], A Bauer[7,9], A Matusch[7], R-J Schulz[10], M Noreik[10], CP Bührle[2], D Maintz[11], C Woopen[12], P Häussermann[13], M Hellmich[14], J Klosterkötter[1], J Wiltfang[15], M Maarouf[16], H-J Freund[6,18] and V Sturm[2,18]

Cholinergic neurons of the medial forebrain are considered important contributors to brain plasticity and neuromodulation. A reduction of cholinergic innervation can lead to pathophysiological changes of neurotransmission and is observed in Alzheimer's disease. Here we report on six patients with mild to moderate Alzheimer's disease (AD) treated with bilateral low-frequency deep brain stimulation (DBS) of the nucleus basalis of Meynert (NBM). During a four-week double-blind sham-controlled phase and a subsequent 11-month follow-up open label period, clinical outcome was assessed by neuropsychological examination using the Alzheimer's Disease Assessment Scale—cognitive subscale as the primary outcome measure. Electroencephalography and [^{18}F]-fluoro-desoxyglucose positron emission tomography were besides others secondary endpoints. On the basis of stable or improved primary outcome parameters twelve months after surgery, four of the six patients were considered responders. No severe or non-transitional side effects related to the stimulation were observed. Taking into account all limitations of a pilot study, we conclude that DBS of the NBM is both technically feasible and well tolerated.

Molecular Psychiatry (2014) **00,** 000–000. doi:10.1038/mp.2014.32

INTRODUCTION

Severe atrophy of the basal forebrain cholinergic system especially of the nucleus basalis of Meynert (NBM) and an ensuing reduction of cholinergic innervation of the cortex are considered part of the pathophysiological cascade in progressive Alzheimer's disease (AD).[1] Deprivation of cholinergic background tuning compromises information transmission to the cortex[2] and the significance of the cholinergic forebrain for brain plasticity has been illustrated by the reshaping of auditory receptive fields during and after stimulation of the NBM in the adult rat brain.[3]

First studies have been launched for exploring a potentially beneficial role of deep brain stimulation (DBS) of the NBM (the main cholinergic structure of the basal forebrain; Supplementary Figure S1) in AD[4] and in a case of Parkinson dementia[5,6] at the University Hospital of Cologne, Germany. Other groups explore stimulation of the fornix, due to its direct input into the hippocampus.[7–9] We present a registered clinical double-blind sham-controlled pilot investigation (Phase I) of low-frequency DBS of the NBM and its adjacent fibers.

MATERIALS AND METHODS

Patients

Four female and two male patients aged between 57 and 79 years, all of them met the diagnostic criteria for mild-to-moderate AD according to DSM-IV,[10] ICD-10,[11] and the NINCDS-ADRDA scale,[12] were recruited at the University Hospital of Cologne, Germany. Inclusion criteria were German-language fluency, stable acetylcholinesterase medication for at least three months, mini mental status examination (MMSE) scores between 18 and 26 (Table 1), and AD-typical cerebrospinal fluid changes of tau protein and amyloid beta42 levels. Written informed consent was obtained from patients and relatives, respectively. Exclusion criteria included severe mental disorders, suicidal tendencies, previous intracranial interventions, and contraindication to anesthesia, PET (positron emission tomography) or MRI (magnetic resonance imaging).

Design and ethical considerations

The study design consisted of two phases (http://clinicaltrials.gov/ct2/show/NCT01094145): a randomized sham-controlled stimulation phase of one month followed by eleven months of continued open stimulation (Figure 1). During the first phase, two weeks of stimulation (ON) were followed by two weeks without stimulation (OFF) or vice versa. The phases were separated by a 24-hour 'isolation' (washout) period to reduce effects

[1]Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany; [2]Department of Functional Neurosurgery and Stereotaxy, University of Cologne, Cologne, Germany; [3]Faculty of Economics, Otto-von-Guericke University Magdeburg, Magdeburg, Germany; [4]Center for Behavioral Brain Sciences, Magdeburg, Germany; [5]Institute of Psychology, Otto-von-Guericke University Magdeburg, Magdeburg, Germany; [6]Department of Neuroanatomy, University of Düsseldorf, Düsseldorf, Germany; [7]Institute of Neuroscience and Medicine, Research Centre Juelich, Juelich, Germany; [8]University Hospital of Psychiatry, Psychotherapy and Psychosomatics, RWTH Aachen University, Aachen, Germany; [9]Department of Neurology, Medical Faculty, University of Düsseldorf, Düsseldorf, Germany; [10]University of Cologne, Department of Geriatrics and St. Marien-Hospital, Cologne, Germany; [11]University of Cologne, Department for Radiology, Cologne, Germany; [12]University of Cologne, Institute for the History of medicine and Medical Ethics, Cologne, Germany; [13]LVR Clinic Cologne, Department of Gerontopsychiatry, Cologne, Germany; [14]University of Cologne, Institute of Medical Statistics, Informatics and Epidemiology, Cologne, Germany; [15]Department of Psychiatry and Psychotherapy, University Medical Center (UMG), Georg-August-University, Göttingen, Germany and [16]Department of Stereotaxy and Functional Neurosurgery, Klinikum Merheim, Cologne, Germany. Correspondence: Professor Dr J Kuhn, Department of Psychiatry and Psychotherapy, University of Cologne, Kerpener Strasse 62, 50937 Cologne, Germany.
E-mail: Jens.Kuhn@uk-koeln.de
[17]Shared first authorship.
[18]Shared senior authorship.
Received 5 November 2013; revised 6 February 2014; accepted 24 February 2014

Table 1. Demographic data, medication, primary outcome data and stimulation parameters

Patient	*Baseline/52 weeks*		*Medication (daily dose)*	*Target coordinates (x,y,z)*[a]	*Contacts*[b]	*Stimulation setting*[c]
	MMSE	*ADAS-cog*				
1 (Female, 79 years)	21/23	16/17	Galantamine (24 mg) Mirtazapine (15 mg)	−20, −7.1, −8.6 20.4, −6.2, −7.7	0,1,2,8,9,10	4.5 V, 150 μs, 20 Hz
2 (Female, 72 years)	22/21	23/14	Donepezil (10 mg) Mirtazapine (15 mg) Lorazepame (if required)	−23.9, −9.5, −10.0 26.5, −10.0, −7.6	0,1,2,8,9,10	2.2 V, 120 μs, 20 Hz
3 (Female, 66 years)	15/7	23/42	Galantamine (24 mg)	−26.3, −6.7, −7.1 29.3, −8.4, −6.7	0,1,2,8,9,10	4.2 V, 120 μs, 10 Hz
4 (Female, 68 years)	21/26	12/11	Donepezil (10 mg)	−28.0, −7.7, −6.6 33.2, −8.2, −6.5	0,1,8,9	3.8 V, 150 μs, 20 Hz
5 (Male, 75 years)	19/16	29/37	Memantine (20 mg) Donepezil (10 mg) Escitaloprame 5 mg)	−26.6, −7.2, −7.3 24.9, −7.2, −6.0	0,1,2,8,9,10	2.0 V, 90 μs, 20 Hz
6 (Male, 57 years)	17/19	18/18	Donepezil (10 mg)	−27.4, −7.3, −5.7 31.9, −7.0, −5.2	0,1,8,9	3.5 V, 120 μs, 20 Hz

Abbreviations: ADAS, Alzheimer's Disease Assessment Scale; MMSE, mini mental status examination. [a]Left and right hemisphere target coordinates according to Mai *et al*.[13] [b]Active monopolar contacts for the open stimulation phase. [c]Settings for the open stimulation phase. During the double-blind, crossover phase stimulation, parameters were as follows: monopolar contacts: −0, −8, 2.5 V, 90 μs, 20 Hz.

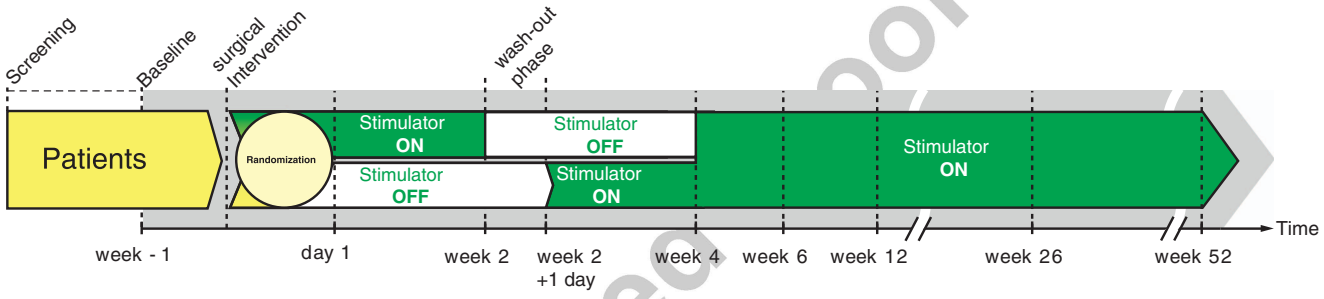

Figure 1. Design of the Meynert-Dementia-DBS-study (MeynD-DBS). During the crossover phase, two weeks of stimulation (ON with stimulation parameters as follows: −0, −8, +case, 20 Hz, 90 μs and 2.5 V) were followed by two weeks without stimulation (OFF) or vice versa. A 24-hour 'washout' period separated the phases. An open stimulation period with individualized stimulation settings followed the crossover phase.

solely due to changes in stimulation. We implemented a randomized double-blind crossover phase to control for systematic biases (that is, selection, performance and detection bias) and to anticipate the possibility of spontaneous stimulation effects. Due to ethical reasons, blinding was restricted to two weeks given the strong effects that had been observed within 24 h of blinded sham-stimulation in our first patients.[5] During the continuous open stimulation phase, stimulation parameters were set iteratively to an individual optimal level. The ethics committee of the Medical Faculty of the University of Cologne as well as the federal authority approved the study. An IDMC (independent data monitoring committee) supervised the progress, safety and efficacy of the investigation. Patients were entering the study sequentially, with each further inclusion demanding a renewed authorization by the IDMC. An independent licensed physician assessed each patient's ability to understand the research objectives and to give informed consent to treatment in a personal interview. As a standard, the MacArthur Competence Assessment Tool for Treatment (MacCat-T) was applied.[14]

Surgery, target selection and stimulation

Quadripolar electrodes (Medtronic 3387; Medtronic, Minneapolis, MN, USA) were stereotactically implanted bilaterally into the NBM (Ch4 division of the basal forebrain cholinergic system) under general anesthesia (Figure 2 and Table 1 for individual coordinates). The surgical procedures closely followed those established for other subcortical structures such as the subthalamic nucleus[15] using the Atlas of the Human Brain[13] as a basis for stereotactic planning. Ch4 was chosen as a target because (i) Ch4 contains the largest group of cholinergic neurons,[16–18] (ii) all subdivisions of Ch4 (though also of Ch3) are significantly affected by AD, and nerve growth factor (NGF)-receptor gene expression is strongly elevated in this disorder,[19,20] (iii) volume reduction in Ch4 was described as being associated with 'impaired delayed recall' in mild cognitive impaired patients.[21] In addition, markers in Ch4 correlate very well with the severity of dementia[22] as determined by praxis scores, attention/registration scores and behavioral scores.

In MR-images, the position of Ch4 was determined on the basis of its topographical relationship to compact fiber bundles. In axial slices, Ch4 projects to a field delimited by the anterior commissure and the optic tract (Supplementary Figure S1). In coronal slices, the lateral medullary lamina separating the putamen and external pallidum served as an anatomical landmark. At the level where the ventral part of this lamina is aligned with the cross section of the anterior commissure, Ch4 is roughly separated into a medial division (CH4-m), an intermediate subdivision (CH4-im), and a latero-posterior division (CH4-p).

The intermediate subdivision (Ch4-im) represents the most compact and densely packed cell cluster of the NBM complex, suggesting that large numbers of cholinergic cells would be stimulated. The posterior subdivision (Ch4-p) is the most probable source of dense innervation of the medial temporal cortex, especially the limbic and paralimbic areas including entorhinal cortex and hippocampus.

Whether the division medial or lateral to the anterior commissure (either CH4-im or CH4-p) was targeted, depended on preoperative images of the patient. In most cases, it proved impossible to insert an electrode into the preselected target (CH4-im, CH4-p) as a consequence of degenerative or otherwise pathological vascular alterations or pathological conditions such as intraparenchymal hemorrhage resulting from lesions to small vessels, sublenticular cysts or perivascular lacunae prevailing within this region. The spatial range of target areas therefore extended from CH4-im medially

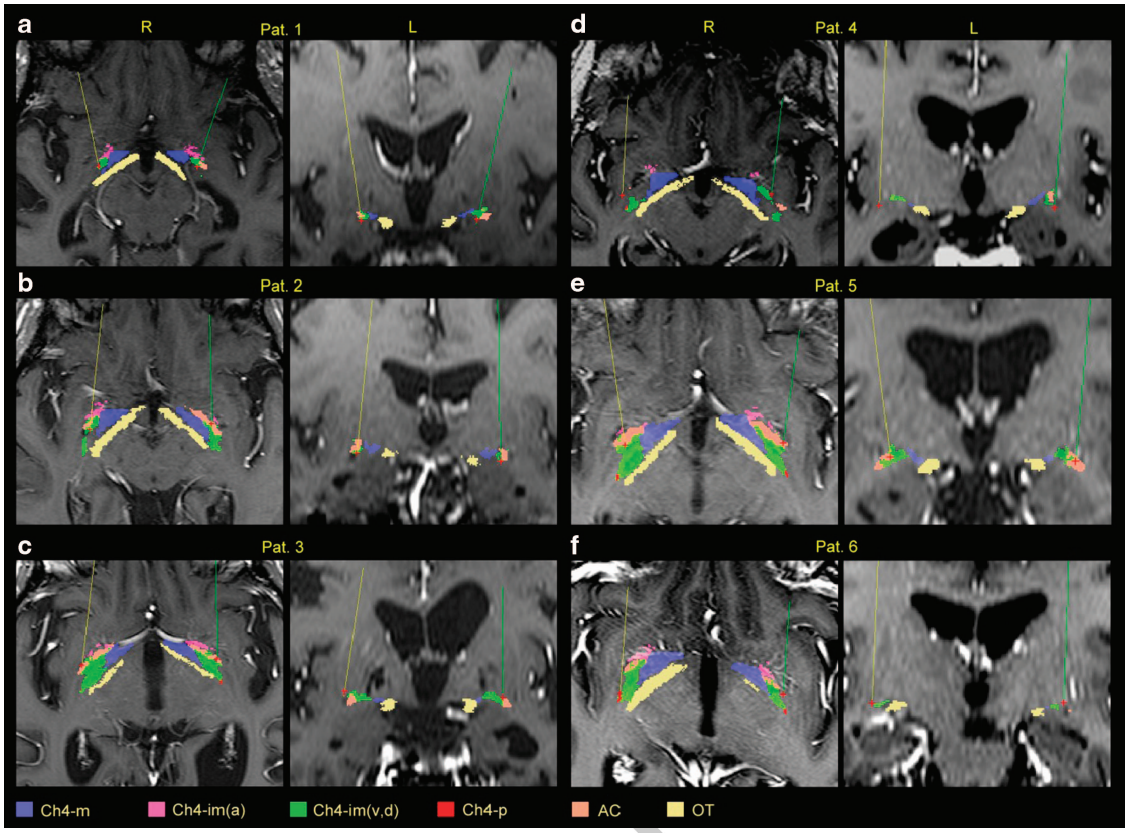

Figure 2. Localization of electrode position in the lateral and posterior portion of the NBM of the six patients. After the operation, electrode position was analyzed using a two-stage nonlinear multigrid atlas co-registration method that transformed the atlas information[13] onto the individual patient's MRI. Ch4-m, medial NBM; Ch4-im (a,v,d), intermediate NBM with anterior, ventral and dorsal divisions; Ch4-p, posterior NBM; AC, anterior commissure; OT, optic tract.

(Figure 2 and Supplementary Figure S1, patients 1 and 2) to CH-p in the subputaminal region, including the substriatal terminal island laterally (Figure 2 and Supplementary Figure S1, patient 4). (For further explanations see Supplementary Material).

Electrode positions were postoperatively confirmed by stereotactical X-ray and MRI (Supplementary Figure S2). We chose a low-frequency stimulation (20 Hz) to exert a potentially excitatory effect[23] on NBM neurons, as this frequency resembles the physiological discharge rate of NBM neurons during motor activity in freely moving animals[2] and has been shown to stimulate acetylcholine release from cortical terminals of fibers originating in the NBM in the rat brain.[24]

Neurocognitive Functioning

Primary outcome was defined as performance on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) at a 1-year follow-up assessment. Secondary outcome parameters were those assessed by the MMSE, the trail making task, the Stroop task, the verbal fluency test, subtests of the Wechsler Memory Scale (visual reproduction, figural memory, digit and spatial span), subtests of the Wechsler Adult Intelligence Scale (digit-symbol test, Mosaic test), and psychopathological tests (BDI-II and HAM-D).

Baseline assessment took place 1 week before surgery. Postoperative follow-up assessments were taken 2 weeks, 4 weeks, 6 weeks, 3 months, 6 months and 1 year after surgery (Figure 1 and Table 2; for statistical procedures see Supplementary Material).

Overall clinical response

To quantify the severity of the symptoms of dementia and to get an impression of the global functioning of the patients, we assessed the Clinical Dementia Rating before and 12 months after surgery.

Electroencephalography (EEG) analysis

In all patients, resting-state electroencephalography (EEG) was recorded preoperatively and after 1 year (see Supplementary Methods) to assess the frequency power spectrum. An initially planned cognitive task could only be completed by a subset of the patients. These data could therefore not be analyzed and are not reported.

PET

The regional metabolic rate of glucose (rCMRGlc) was determined using [^{18}F]-fluoro-desoxyglucose-PET. Patients 3, 4, 5 and 6 were examined 1 week before surgery and close to the 1-year follow-up visit after electrode implantation (with active simulation; Supplementary Material). Patient 1 was not examined. Of patient 2 no pre-operative PET was available.

Quality of life and additional parameters

Evaluation of both the patients' and their relatives' subjectively perceived quality of life was based on semi-structured interviews[25] conducted preoperatively and 1 year after surgery (see Supplementary Material), furthermore Apraxia scores, assessed with the Florida Apraxia Screening Test[26] and Goldenberg 1 and 2[27] as well as the nutritional status, assessed with the modified Mini Nutritional Assessment,[28] a 3-day eating protocol, and body mass index (see Supplementary Material) was also collected.

RESULTS

Study population

The mean age at surgery was 69.5 ± 7.7 years (s.d.). The average MMSE screening score was 20.3 ± 2.5 points, implying mild-to-moderate AD (Table 1).

Table 2. Longitudinal aggregated test data

	Baseline	*6 Weeks*	*12 Weeks*	*26 Weeks*	*52 Weeks*
Neuropsychological tests					
ADAS-cog[a]	20.2 ± 6.0	19.0 ± 10.0	20.0 ± 8.0	20.0 ± 9.0	23.2 ± 13.0
ADAS memory[a]	10.0 ± 4.1	9.8 ± 3.9	10.5 ± 3.6	10.7 ± 2.9	8.2 ± 2.3
ADAS cognitive items[a]	10.2 ± 5.5	9.3 ± 7.9	9.8 ± 5.6	9.3 ± 7.1	14.8 ± 10.9
MMSE[b]	19.2 ± 2.9	19.3 ± 4.0	18.8 ± 3.1	19.2 ± 5.3	18.7 ± 6.7
Trail making test[a] (A)	194.7 s ± 90.0	119.4 s ± 44.6	158.6 s ± 91.8	152.4s[c] ± 110.6	135.3s[d] ± 78.4
RWT formal fluency[b]	14.8 ± 5.0	11.2 ± 5.7	11.0 ± 5.3	13.5 ± 4.9	10.8 ± 6.7
RWT semantic fluency[b]	12.9 ± 4.1	14.0 ± 5.7	12.8 ± 6.5	12.7 ± 5.7	11.5 ± 7.4
RWT formal change[b]	8.5 ± 3.8	10.5 ± 8.2	8.0 ± 5.7	10.0 ± 8.9	8.0 ± 4.1
RWT semantic change[b]	7.2 ± 3.3	7.3 ± 4.2	7.5 ± 5.2	7.2 ± 4.2	7.7 ± 5.1
WAIS digit span forward[b]	4.2 ± 1.3	4.7 ± 2.0	4.5 ± 2.4	5.2 ± 1.7	5.3 ± 2.2
WAIS digit span backward[b]	3.7 ± 1.5	3.2 ± 1.8	3.7 ± 1.5	3.2 ± 2.1	3.0 ± 1.6
WAIS block span forward[b]	5.0 ± 2.8	4.8 ± 2.1	3.8 ± 2.0	3.2 ± 2.0	4.2 ± 2.6
WAIS block span backward[b]	2.0 ± 1.8	3.3 ± 2.5	2.5 ± 1.6	2.7 ± 2.7	2.8 ± 2.6
WAIS digit-symbol task[b]	14.4 ± 7.4	16.7 ± 4.3	17.3 ± 7.2	14.3 ± 6.9	10.3 ± 6.5
WMS figural memory[b]	4.0 ± 2.0	3.8 ± 1.6	4.8 ± 1.0	3.5 ± 1.9	4.2 ± 3.0
WMS mosaic task[b]	9.2 ± 7.4	13.2 ± 9.9	15.3 ± 15.3	12.5 ± 10.6	9.3 ± 10.6
Dementia test					
Clinical Dementia Rating	0.83 ± 0.3				0.83 ± 0.3
Depression tests					
BDI-II[a]	3.7 ± 3.4	2.5 ± 3.8	3.0 ± 3.3	2.8 ± 4.7	3.4 ± 5.4
HAM-D[a]	1.2 ± 0.8	1.3 ± 1.6	1.5 ± 1.8	1.2 ± 1.8	0.6 ± 0.9
Apraxia tests					
FAST[b]	15.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0	14.5 ± 1.2
Goldberg 1[b]	17.2 ± 2.9	17.3 ± 2.7	16.8 ± 3.1	15.5 ± 5.0	15.2 ± 3.9
Goldberg 2[b]	12.5 ± 4.3	14.0 ± 4.4	14.8 ± 4.3	15.7 ± 2.3	13.8 ± 5.5

Abbreviations: ADAS, Alzheimer's Disease Assessment Scale; BDI-II, Beck's Depression Inventory 2nd edition; FAST, Florida Apraxia Screening Test; HAM-D, Hamilton Depression Rating Scale; MMSE, mini mental status examination; RWT, Regensburger Wortschatz Test; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale. [a]A lower value represents a better outcome. [b]A higher value represents a better outcome. [c]One value missing. [d]Two values missing.

Study safety

The surgical procedures were well tolerated and recovery from the intervention was fast. However, two serious adverse events occurred; both were hardware-associated and resulted from malfunctioning plug-in connectors, requiring surgical revision of the respective impulse generators. One patient complained about inner restlessness at higher stimulation intensities (>5 V), no further stimulation-induced side effects were observed. All six patients completed the 12-month follow-up period. All medications were stable during the year, except for patient 2, who received Lorazepam on demand during the open stimulation phase.

Longitudinal effects on memory, cognition and global functioning

A nonsignificant increase of 3 points in the ADAS-cog score was observed after 12 months (see Figure 3a). Scores of patients 3 and 5 increased by 19 and 8 points, respectively; patients 1, 4 and 6 remained stable (changes of +1, −1 and ±0 points, respectively); and patient 2 improved by 9 points (Figure 3b and Table 1). For the memory subscale of ADAS-cog, patients 1 and 3 deteriorated by 1 and 2 points, respectively. Patients 2, 4 and 5 scores improved by 2, 4 and 8 points and patient 6 showed no change. Scores of the cognitive items subscale of ADAS-cog worsened in patients 3, 4 and 5 by 16, 3 and 16 points. The scores of patients 1 and 6 remained stable over the observation period, and patient 2 again improved by 7 points.

The mean MMSE score decreased by 0.5 points (Figure 3a). The scores of patients 2, 3 and 5 decreased by 1, 8 and 3 points, respectively, whereas those of patients 1, 4 and 6 improved by 2, 5 and 2 points, as appropriate (see Figure 3c and Table 1). Mean scores of the other tests are reported in Table 2.

The mean score of the Clinical Dementia Rating remained stable over the 12-months follow-up period (at baseline and after 12 months 0.83 points on average). After 12 months scores of DBS patients 1, 4 and 6 improved by 0.5 points, patient 2 remained stable and patients 3 and 5 deteriorated by 1 and 0.5 points, respectively.

Crossover effects

Patients 1, 4 and 6 were assigned to start the crossover phase without stimulation (OFF), and patients 2, 3 and 5 with stimulation (ON).

The mean MMSE score improved at the end of the stimulation period (two weeks stimulation ON) compared with the score at the end of the sham period (two weeks stimulation OFF) by 0.8 points, with a 95% confidence interval (CI) from −3.0 to 1.3 ($P = 0.363$; Figure 3c).

EEG

Assessed frequency power in the theta (4–8 Hz), alpha (8–12 Hz) and beta (12–30 Hz) band changed significantly only for patient 3 with a decrease in alpha power (reliable change index, RCI = −1.97; a RCI over 1.96 is comparable with a *P*-value of 0.05)[29] and an increase in theta power (RCI = 2.5). For all the other patients, EEG frequency power changes were nonsignificant (RCI < 1.5).

PET

Glucose utilization in the entire cerebrum increased in patients 4 (+2.2%), 5 (+4.9%) and 6 (+2.9%) after 1 year of DBS treatment; in

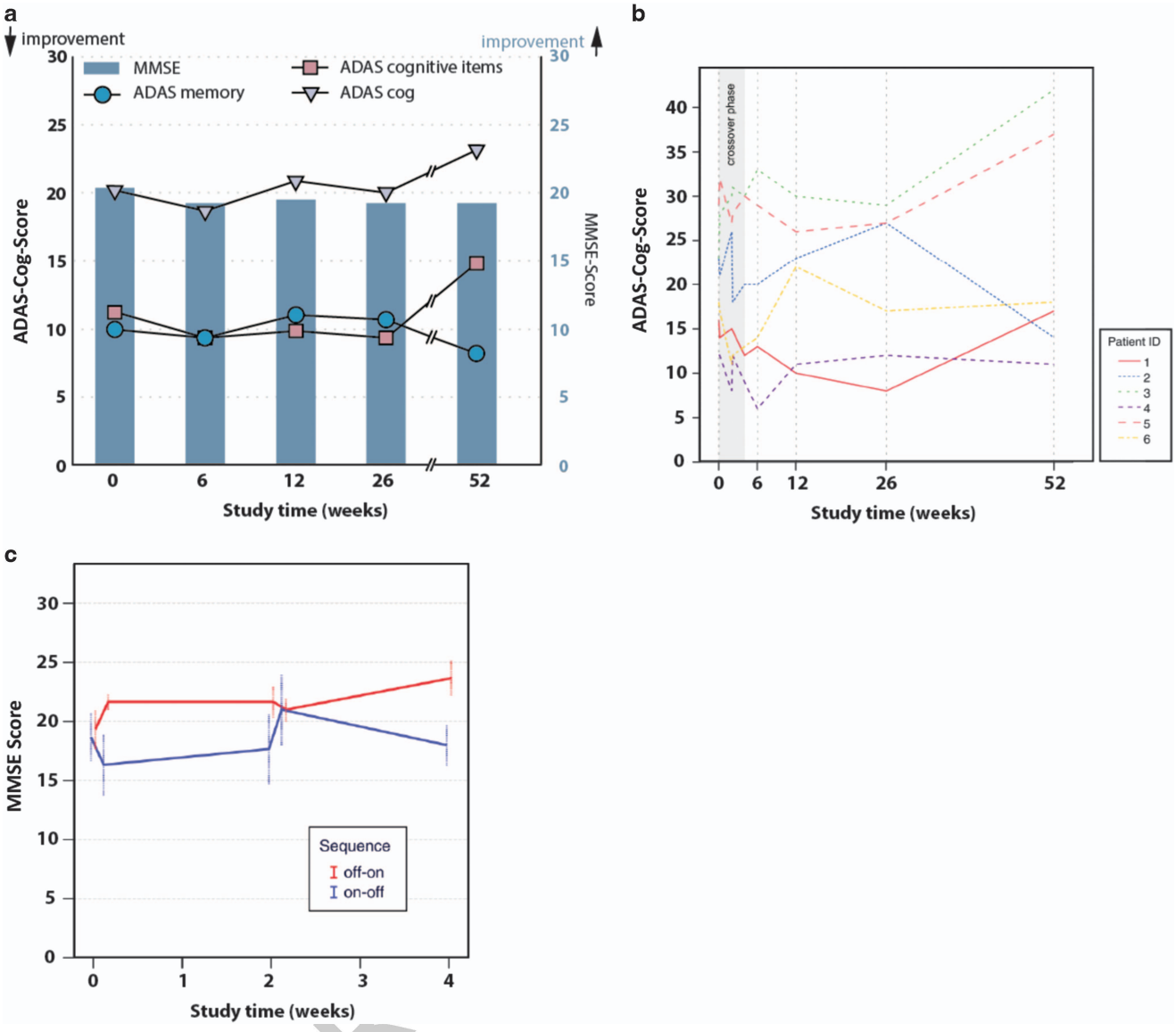

Figure 3. Longitudinal effects on memory and cognition with regard to ADAS-cog and MMSE. (**a**) Course of ADAS-cog and MMSE scores over the 52-week observation period. Improvements in ADAS-cog score are indicated by decreasing values, whereas improvements in MMSE score are reflected by increasing values. (**b**) Follow-up (52 weeks) of the individual neuropsychological abilities of the patients assessed with the primary outcome parameter ADAS-cog. (**c**) Mean MMSE score during the crossover phase. Bars denote standard error. ADAS, Alzheimer's Disease Assessment Scale; MMSE, mini mental status examination.

patient 3, rCMRGlc was constant (+0.2%). In patients 3, 4, 5 and 6, rCMRGlc changes averaged to +2.5%, $P=0.07$ in the entire cerebrum and to +1.0%, $P=0.07$ in the parietal cortex; +3.6%, $P=0.07$ in the temporal cortex and +2.7%, $P=0.07$ in the amygdalo-hippocampal region (Figure 4).

ADAS-cog and MMSE scores correlated significantly with bilateral rCMRGlc in the 3-mm circumference of the active contacts (Spearman's $\rho=1.0$; $P<0.01$) but not significantly with global cerebral, temporal and amygdalo-hippocampal rCMRGlc (Spearman's $\rho=0.8$; $P=0.2$; Supplementary Figure S3, Supplementary Figure S4, Supplementary Table S1).

Quality of life

On average the subjective quality of life (ranging from 1—bad to 10—excellent) dropped slightly from 5.7 to 5.5 after 12 months. Patients 2 and 4 reported an improvement (by 3 points and 1 point, respectively), patients 1 and 6 did not notice any changes, and patients 3 and 5 indicated a decrease (by −1 and −4 points, respectively). The relatives' estimation of the patients' quality of life also remained stable with a slight increase from 5.9 to 6.0 after 12 months.

Five patients and their relatives would opt for the treatment with DBS again. Patient 2 and the family member of patient 5 would not choose the treatment again.

DISCUSSION

This is the first Phase-I study to explore the technical feasibility of NBM-DBS in AD with a 1-year follow-up. Neurostimulation itself did not cause any adverse events. Two technical defects were fully resolved. According to their closest relatives, the patients' average quality of life did not change during the observation period.

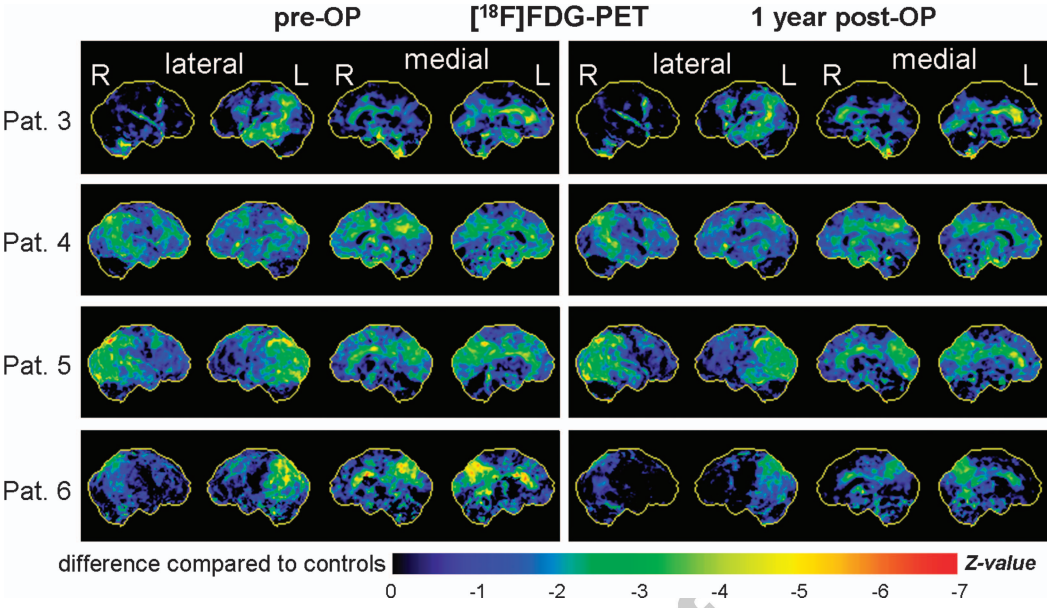

Figure 4. Cerebral glucose utilization (normalized to cerebellum) of all PET-investigated patients in relation to an age-matched control collective.[20] All patients exhibited parieto-temporal hypometabolism, which is typical for AD. Remarkably, cerebral glucose consumption improved in patients 4, 5 and 6 after 1 year of DBS treatment, whereas there was no change in patient 3. AD, Alzheimer's disease; DBS, deep brain stimulation; PET, positron emission tomography.

ADAS-cog scores worsened by an average of 3 points after 1 year of stimulation (95% CI = − 6.1 to 12.1 points, $P = 0.5$). This observation points to a rather slow disease progression, as only an increase of more than 3 points on this scale is considered clinically significant.[30] Accordingly, this change was less pronounced than the increase in ADAS-cog scores observed in an investigation of 686 comparable patients treated with anticholinergic medication; the ADAS-cog score of this cohort yielded an increase by 4.5 points per year.[31] In comparison, the ADAS-cog scores of the six patients from the first DBS Phase-I study in the fornix increased by 4.2 points over 1 year.[8] Interestingly, in the memory part of the ADAS, our patients exhibited an improvement of 1.8 points compared with baseline (Figure 3a).

The mean MMSE score remained almost stable (decreased by 0.3 points, 95% CI = − 4.5 to 5.2 points, $P = 0.9$), in contrast to a decline of 4 points per year reported for comparable pharmacologically treated patients with AD where patients lost 2.4 points on average per year.[31] On the individual level, patient 2 improved significantly which would be exceptional in AD patients,[31] three patients remained stable, patient 5 deteriorated slightly, and patient 3 worsened markedly. Long-term follow-up of patient 1, being the first to receive the treatment, is warranted, because her ADAS-cog and MMSE scores remained unchanged 3 years postoperatively, in contrast to the rapid decline of cognitive abilities and general state over the half year preceding the operation as stated by her relatives.

The scores of the patients' cognitive abilities correlated with the patients' global functioning (measured via Clinical Dementia Rating) and the subjectively perceived quality of life. Worsening of scores during the observation period was observed for patients 3 and 5 only.

Furthermore, both PET and EEG data seemed to mirror the patients' clinical course over the 1-year observation period. A global increase of 2–5% in cortical glucose metabolism, which was most pronounced in the amygdalo-hippocampal and temporal regions, was observed in three out of four patients examined by PET under DBS. There was no improvement in patient 3, who also deteriorated clinically. These results deviate from those found during the untreated course of AD, which is characterized by an average decrease of FDG uptake by 5.2% per year versus 0.9% in healthy controls.[32] Furthermore, the spectral EEG patterns failed to change substantially in five patients between pre- and postoperative conditions, which contrasts with EEG spectral changes in AD patients.[33] Only patient 3 showed a decrease in alpha power and an increase in theta power that paralleled her cognitive decline.

We can formulate three related hypotheses on the basis of these results. First, an excitatory effect of low-frequency stimulation on NBM cholinergic neurons and fibers in the vicinity of the target nucleus may increase acetylcholine release in the cortex and higher cortical acetylcholine levels are probably correlated with improved cognitive performance. This activation might be reflected by the PET results, in which rCMRGlc values within a 3-mm circumference of the active contacts correlated with cognitive functioning as well as with global cerebral, temporal and amygdalo-hippocampal rCMRGlc values. These findings are compatible with assuming both local excitation of ~~presumably~~ cholinergic cells and remote cortical effects potentially mediated by NBM output projecting to extended parts of the cortex.

Second, we cannot exclude that changes in oscillatory activity in memory-dependent circuits and hippocampal structures may also have a role in the observed effects.[34] However, it should be pointed out that there is as yet no clear-cut evidence for such an alleged mechanism. In animal experiments, low-frequency stimulation of the NBM improves particular learning mechanisms.[35]

As a third hypothesis, DBS of the NBM may promote plasticity by releasing neurotrophic factors. Although speculative, this suggestion may be plausible, as NBM neurons express the NGF. Trk-A receptor expression and NGF production is generally increased by neural activity. In addition, the basal forebrain contains various cell adhesion molecule (CD15)-expressing glial cells, which are involved in cell proliferation and plasticity.[36] Also inhibition of hippocampal neurogenesis could be demonstrated

after lesions of the projection from the NBM to the dentate gyrus. DBS in the NBM of healthy rats induced NGF synthesis locally and in the ipsilateral neocortex, an effect possibly mediated by cholinergic NBM projections.[37] In a clinical setting, stereotactically applied NGF gene delivery into the basal forebrain in eight AD patients was associated with reduced cognitive decline.[38]

Finally, this pilot study shows that bilateral low-frequency DBS of the basal forebrain in AD patients is technically feasible, may be considered a safe procedure and apparently lacks significant stimulation-induced untoward effects. Taking into account all limitations of this pilot study, the present DBS approach might slightly improve or stabilize the AD-associated symptoms in some patients. However, only further studies will be able to confirm these preliminary findings and to further elucidate if this intervention is efficient in delaying overall AD progression, ~~may be~~ by disease-modifying ~~aspects~~. Experimental results would be compatible with such an action. Preliminary results of patients recruited later in our research center support the hypothesis that beneficial effects of DBS in the NBM are more clearly apparent in younger and lesser-affected patients.

Limitations

This investigation has a number of shortcomings. Most notably the small group size of only six patients in this investigation markedly curtails its statistical power and renders generalization of the results impossible. Randomization of the patients in the crossover phase resulted in two groups that were unequally matched as to cognitive functions under baseline conditions. Furthermore, the randomized crossover phase was very short (2 weeks each, with 1 day washout). These shortcomings might at least partly be held responsible for the less convincing results of the crossover phase and future studies will most probably benefit from an extended control phase.

Inhomogeneous cell distributions, multiple fiber connections, the considerable topographical variability of the sublenticular area, as well as inter-individual differences relating to the extent and impact of neurodegeneration prohibited targeting of the NBM sub-areas on the basis of the precalculated stereotactic coordinates. Moreover, in most cases we were unable to directly impale the selected region because of vascular alterations or pathological conditions such as intraparenchymal hemorrhage resulting from lesions to small vessels, sublenticular cysts or perivascular lacunae. The spatial range of target areas therefore extended from CH4-im medially (Figure 2 and Supplementary Figure S1, patients 1 and 2) to CH-p in the subputaminal region, including the substriatal terminal island laterally (Figure 2 and Supplementary Figure S1, patient 4). Especially in patient 3—the nonresponder—preoperative MRI revealed significant general progressive vascular pathology evolving during the observation period.

Continuation of ACh-medication most likely had a confounding influence but was inevitable for ethical reasons as DBS was investigated as an add-on-therapy only in this pilot study. Whether there are future studies in which medication will be discontinued remains a topic of ethical discussions.

The use of standard cognitive tests permitted comparisons with other studies regarding the progression of the disease and the effects of medical treatment. However, this test battery might be less efficient for assessing acute stimulation effects such as those occurring in the context of the crossover period, or for example, to individually optimize stimulation parameters for each patient. Hence, an assessment of cognitive parameters, as has been conducted here, is reasonable in the context of a phase-I pilot study in which safety and feasibility are the main focus. However, future studies will demand longer follow-up periods and an extended functional assessment (for example, the Alzheimer Disease Cooperative Study ADL scale).

CONFLICT OF INTEREST

Jens Kuhn has occasionally received honoraria from AstraZeneca, Lilly, Lundbeck and Otsuka Pharma for lecturing at conferences and financial support to travel. He received financial support for studies from Medtronic Europe SARL (Meerbusch, Germany). Doris Lenartz and Juergen K. Mai received financial assistance for travel to congresses from Medtronic Europe SARL. Mohammad Maarouf has occasionally received honoraria from Medtronic Europe SARL for lecturing at conferences and consulting. Volker Sturm disclosed financial support for studies and travel to congresses, and lecture fees from Medtronic Europe SARL and Advanced Neuromodulation Systems INC. He is also a co-holder of patents on desynchronized brain stimulation and shareholder of ANM-GmbH Juelich, a company that intends to develop new stimulators. The remaining authors declare no conflict of interest.

ACKNOWLEDGMENTS

This study was supported by grants from the Marga and Walter Boll foundation and Medtronic Europe SARL.

REFERENCES

1 Grothe M, Heinsen H, Teipel SJ. Atrophy of the cholinergic basal forebrain over the adult age range and in early stages of Alzheimer's disease. *Biol Psychiatry* 2012; **71**: 805–813.
2 Buzsaki G, Bickford RG, Ponomareff G, Thal LJ, Mandel R, Gage FH. Nucleus basalis and thalamic control of neocortical activity in the freely moving rat. *J Neurosci* 1988; **8**: 4007–4026.
3 Kilgard MP, Merzenich MM. Cortical map reorganization enabled by nucleus basalis activity. *Science* 1998; **279**: 1714–1718.
4 Turnbull IM, McGeer PL, Beattie L, Pate B. Stimulation of the basal nucleus of Meynert in senile dementia of Alzheimer's type. A preliminary report. *Appl Neurophysiol* 1985; **48**: 216–221.
5 Freund HJ, 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**: 781–785.
6 Barnikol TT, Pawelczyk NB, Barnikol UB, Kuhn J, Lenartz D, Sturm V *et al.* Changes in apraxia after deep brain stimulation of the nucleus basalis Meynert in a patient with Parkinson dementia syndrome. *Mov Disord* 2010; **25**: 1519–1520.
7 Hamani C, McAndrews MP, Cohn M, Oh M, Zumsteg D, Shapiro CM *et al.* Memory enhancement induced by hypothalamic/fornix deep brain stimulation. *Ann Neurol* 2008; **63**: 119–123.
8 Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R *et al.* A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. *Ann Neurol* 2010; **68**: 521–534.
9 Hardenacke K, Kuhn J, Lenartz D, Maarouf M, Mai JK, Bartsch C *et al.* Stimulate or degenerate: deep brain stimulation of the nucleus basalis Meynert in Alzheimer's dementia. *World Neurosurg* 2012; **80**: S27.e35–S27.e43.
10 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders-DSM IV-TR*. American Psychiatric Association: Washington, DC, USA, 2000.
11 Bramer GR. International statistical classification of diseases and related health problems. Tenth revision. *World Health Stat Q* 1988; **41**: 32–36.
12 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; **34**: 939–944.
13 Mai, JK Paxinos, G Voss, T. *Atlas of the Human Brain*, 3rd revised edn. Academic Press: Amsterdam, The Netherlands, 2007, p 271.
14 Grisso T, Appelbaum PS, Hill-Fotouhi C. The MacCAT-T: a clinical tool to assess patients' capacities to make treatment decisions. *Psychiatr Serv* 1997; **48**: 1415–1419.
15 Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L *et al.* Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med* 2013; **368**: 610–622.
16 Mesulam MM, Mufson EJ, Levey AI, Wainer BH. Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. *J Comp Neurol* 1983; **214**: 170–197.
17 Pearson RC, Sofroniew MV, Cuello AC, Powell TP, Eckenstein F, Esiri MM *et al.* Persistence of cholinergic neurons in the basal nucleus in a brain with senile dementia of the Alzheimer's type demonstrated by immunohistochemical staining for choline acetyltransferase. *Brain Res* 1983; **289**: 375–379.
18 Mesulam MM, Geula C. Nucleus basalis (Ch4) and cortical cholinergic innervation in the human brain: observations based on the distribution of acetylcholinesterase and choline acetyltransferase. *J Comp Neurol* 1988; **275**: 216–240.

19 Vogels OJ, Broere CA, ter Laak HJ, ten Donkelaar HJ, Nieuwenhuys R, Schulte BP. Cell loss and shrinkage in the nucleus basalis Meynert complex in Alzheimer's disease. *Neurobiol Aging* 1990; **11**: 3–13.
20 Higgins GA, Mufson EJ. NGF receptor gene expression is decreased in the nucleus basalis in Alzheimer's disease. *Exp Neurol* 1989; **106**: 222–236.
21 Grothe M, Zaborszky L, Atienza M, Gil-Neciga E, Rodriguez-Romero R, Teipel SJ *et al.* Reduction of basal forebrain cholinergic system parallels cognitive impairment in patients at high risk of developing Alzheimer's disease. *Cereb Cortex* 2010; **20**: 1685–1695.
22 Gilmor ML, Erickson JD, Varoqui H, Hersh LB, Bennett DA, Cochran EJ *et al.* Preservation of nucleus basalis neurons containing choline acetyltransferase and the vesicular acetylcholine transporter in the elderly with mild cognitive impairment and early Alzheimer's disease. *J Comp Neurol* 1999; **411**: 693–704.
23 Benabid AL, Benazzous A, Pollak P. Mechanisms of deep brain stimulation. *Mov Disord* 2002; **17**(Suppl 3): S73–S74.
24 Kurosawa M, Sato A, Sato Y. Stimulation of the nucleus basalis of Meynert increases acetylcholine release in the cerebral cortex in rats. *Neurosci Lett* 1989; **98**: 45–50.
25 Maier F, Lewis CJ, Horstkoetter N, Eggers C, Kalbe E, Maarouf M *et al.* Patients' expectations of deep brain stimulation, and subjective perceived outcome related to clinical measures in Parkinson's disease: a mixed-method approach. *J Neurol Neurosurg Psychiatry* 2013; **84**: 1273–1281.
26 Rothi LJ, Heilman KM. Acquisition and retention of gestures by apraxic patients. *Brain Cogn* 1984; **3**: 426–437.
27 Goldenberg G. Matching and imitation of hand and finger postures in patients with damage in the left or right hemispheres. *Neuropsychologia* 1999; **37**: 559–566.
28 Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. *Nutr Rev* 1996; **54**(1 Pt 2): S59–S65.
29 Brunovsky M, Matousek M, Edman A, Cervena K, Krajca V. Objective assessment of the degree of dementia by means of EEG. *Neuropsychobiology* 2003; **48**: 19–26.
30 Schrag A, Schott JM. What is the clinically relevant change on the ADAS-Cog? *J Neurol Neurosurg Psychiatry* 2012; **83**: 171–173.
31 Gillette-Guyonnet S, Andrieu S, Nourhashemi F, Gardette V, Coley N, Cantet C *et al.* Long-term progression of Alzheimer's disease in patients under antidementia drugs. *Alzheimers Dement* 2011; **7**: 579–592.
32 Lo RY, Hubbard AE, Shaw LM, Trojanowski JQ, Petersen RC, Aisen PS *et al.* Longitudinal change of biomarkers in cognitive decline. *Arch Neurol* 2011; **68**: 1257–1266.
33 Coben LA, Danziger W, Storandt M. A longitudinal EEG study of mild senile dementia of Alzheimer type: changes at 1 year and at 2.5 years. *Electroencephalogr Clin Neurophysiol* 1985; **61**: 101–112.
34 Suthana N, Haneef Z, Stern J, Mukamel R, Behnke E, Knowlton B *et al.* Memory enhancement and deep-brain stimulation of the entorhinal area. *N Engl J Med* 2012; **366**: 502–510.
35 Boix-Trelis N, Vale-Martinez A, Guillazo-Blanch G, Marti-Nicolovius M. Induction of c-Fos expression by electrical stimulation of the nucleus basalis magnocellularis. *Neurosci Lett* 2009; **449**: 137–141.
36 Morres SA, Mai JK, Teckhaus L. Expression of the CD15 epitope in the human magnocellular basal forebrain system. *Histochem J* 1992; **24**: 902–909.
37 Hotta H, Kagitani F, Kondo M, Uchida S. Basal forebrain stimulation induces NGF secretion in ipsilateral parietal cortex via nicotinic receptor activation in adult, but not aged rats. *Neurosci Res* 2009; **63**: 122–128.
38 Tuszynski MH, Thal L, Pay M, Salmon DP, U HS, Bakay R *et al.* A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. *Nat Med* 2005; **11**: 551–555.

Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)