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Short communication

Oscillatory activity and cortical coherence of the nucleus basalis of Meynert in Parkinson's disease dementia

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ABSTRACT

Background: Deep brain stimulation (DBS) of the nucleus basalis of Meynert (NBM) is a new potential treatment for Parkinson's Disease dementia (PDD) and other types of dementia. To get a better understanding of this structure, its local neurophysiological properties and cortical connectivity patterns were studied.
Methods: We simultaneously recorded DBS local field potentials (LFPs) and electroencephalography (EEG) in two patients with PDD. Both patients had DBS electrodes in the internal globus pallidus (GPi) with one or more distal contacts close to or inside the NBM. Measurements were obtained during routine battery replacement. The distance of DBS contacts to the NBM were calculated using CT-MRI fusion.
Results: Delta (1–4 Hz) oscillations were more prominently present in the NBM region than in its vicinity, whereas temporal coherence in the theta (4–8 Hz) range was less outspoken.
Conclusion: These neurophysiological characteristics, if also proven in larger cohorts, might help to map the NBM more precisely during electrode implantation.

1. Introduction

The nucleus basalis of Meynert (NBM), located in the basal forebrain, is emerging as a potential target of DBS for Parkinson's disease dementia (PDD) and Alzheimer's disease (AD). The NBM predominantly contains cholinergic neurons and plays an important role in cognition, particularly attention [1]. In PD the NBM progressively degenerates, which results in a decreased cholinergic input to the cortex [2]. Preliminary evidence indicates that cholinergic input from the degenerating NBM might be enhanced by low-frequency (20 Hz) stimulation of the NBM [3]. Furthermore, experimental evidence from rodents and preliminary human research indicates improved cognition after low-frequency stimulation of the NBM [4].

Accurate positioning of DBS electrodes in the NBM region is challenging because of the horizontally oriented anatomy, in combination with focal degeneration and interregional functional disparities [5]. Intra-operative neurophysiological mapping may therefore help to target the NBM. As an initial attempt, exploratory measurement of local field potentials (LFP) was performed in two PDD patients with DBS electrodes implanted near the NBM. Also, NBM connectivity to cortical areas was investigated using simultaneous electroencephalography (EEG) recordings.

2. Materials & methods

2.1. Patients

A 70-year-old male and a 73-year-old female had been diagnosed with Parkinson's disease (PD) for 17 and 25 years, respectively. Both patients were received bilateral DBS (Medtronic 3387) of the GPi approximately three years (see Supplementary Table 1) before cognitive symptoms, including short-term memory deficits, attentional fluctuation, and bradyphrenia became progressively prominent. The diagnosis of PDD was based on the onset of

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cognitive symptoms in the presence of PD with no other likely cause. The cognitive symptoms fulfilled the criteria for a major neuro-cognitive disorder due to PD according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V). The results of cognitive screening are provided in Supplementary Table 1. During a regular replacement of the DBS Internalised Pulse Generator (IPG) (ActivaPC Medtronic) under local anesthesia, a 2-min recording of LFP and EEG signals was performed. This was performed during the standard procedure of checking impedances during the exposure of the DBS leads, which required the same manipulation of the DBS cables. For this reason subjects were not exposed to any risk, neither was the surgery prolonged. For this reason no ethical approval needed to be obtained.

2.2. Anatomical position of the DBS contacts

The stereotactic coordinates of the four contacts of the DBS-electrode and the coordinates of the NBM in relation with the anterior-commissural point were determined using the Talairach stereotactic coordinate system [6]. With BrainLAB software (BrainLAB, Heimstetten, Germany) post-implantation CT images were fused with preoperative 3T-MRI images. The stereotactical coordinates of the DBS contacts were projected onto the *Atlas of The Human Brain*, where the NBM was defined as the basal nucleus (BC) [7]. By using this method, a 3-dimensional vector of the center of each bipolar LFP to the center of the NBM was measured. DBS contacts that either had their center inside the NBM or less than the size of one DBS contact (2 mm) away from the center of the NBM were regarded as candidates for NBM assessment. Bipolar LFPs were dichotomised based on this distance to the NBM.

2.3. Data acquisition

Simultaneous EEG and LFP resting state recording was performed after disconnection of the IPG. EEG signals were acquired through eleven Ag/AgCl electrodes placed in frontal (F3, F4, Fz), temporal (T3, T4), central (C3, C4, Cz), and parietal (P3, P4, Pz) areas according to the International 10–20 system. Additional electrodes were used to monitor ocular movement, masseter muscle activity, and ECG. All impedances were below 5 kΩ. LFP data were acquired in a monopolar way from all the four contacts. EEG and LFP signals were recorded (Schwarzer AHNS 40/44-channel PSG amplifier, Schwarzer, Munich, Germany) at a sampling rate of 1000 Hz using Brain-RT 2014 software (OSG Bvba, Rumst, Belgium).

2.4. Off-line data analyses

EEG and LFP data were visually inspected and 1-min artifact-free epochs were selected for and subsequently imported to Brain Vision Analyzer 2.1 (Brain Products GmbH, München, Germany) and in-house software written in LabVIEW (National Instruments, Austin, TX, USA) for re-referencing and preprocessing. EEG data was source-reconstructed by comparing the raw EEG signal with its four neighboring EEG signals (local average). In order to avoid influences of cortical signals, monopolar LFP data was re-referenced by subtracting data from adjacent contacts, thus creating three bipolar channels (0–1, 1–2, 2–3) for each lead.

2.5. Spectral and coherence analysis

Spectral analyses were performed in BrainVision Analyzer 2.1 (Brain Products GmbH, München, Germany). Bipolar LFP signals were band-pass filtered with an eight-order Butterworth filter at 0.5–100 Hz band. Spectral analysis was applied on a 15-sec artifact-free LFP epoch for each bipolar channel using fast Fourier transformation with 10% Hanning window. The spectral peak powers of delta (1–4 Hz), theta (5–8 Hz), alpha (9–13), beta (14–30 Hz) and gamma (31–100 Hz) were subsequently determined and normalized over the range between 1 and 100 Hz.

The signal coherence between each bipolar LFP channel and four different cortical areas of its corresponding side (F3/4, C3/4, T3/4, P3/4) was calculated using in-house written software in LabVIEW (National Instruments, Austin, TX, USA). A minimum 60-sec resting-state EEG and bipolar LFP signal was filtered off-line with a high-pass filter of 2 Hz, 48 dB/octave. The coherence values (range 0–1) between 1 and 100 Hz were calculated for each frequency band using medians.

2.6. Statistical Analysis

Spectral peak power of bipolar LFPs was compared for each frequency band between the NBM and non-NBM using two-sample *t*-tests. Data was checked for normality using the Kolmogorov-Smirnov test. Multiple comparisons were corrected by applying the false discovery rate. The median of coherence was obtained for both the frequency band and location. The combination of the cortical region and frequency band was compared between the NBM and non-NBM contacts using the two-sample *t*-test. Spearman rank correlation coefficient was used for correlations between the distance to the NBM, as well as spectral peak power or coherence.

3. Results

3.1. Anatomical localization

Three of the sixteen DBS contacts (four contacts for each lead) were located less than 2 mm from the NBM. The three contacts were contact 0 and 1, which are the two most distal contacts of the left lead of patient 1, and contact 4, which is the most distal contact of the right lead of patient 2 (Fig. 1). Other electrodes were identified in several structures proximal to the NBM, including the GPi, the globus pallidus externa (GPe), the internal capsule (IC), the putamen, and the anterior commissure. The distances of the center of heach bipolar LFP and the NBM are listed in Supplementary Table 2.

3.2. Spectral analysis

The mean of normalized peak power of each frequency band from each bipolar contact of four brain hemispheres is shown in Fig. 2A. Normalized peak power of the delta band (1–4 Hz) was higher inside than outside the NBM ($p < 0.001$, Fig. 2A). Furthermore, the distance of the middle of the bipolar contact pairs (i.e. the value between the two contacts) to the NBM correlated *negatively* with delta peak power ($\rho = -0.72$, $p = 0.007$).

3.3. EEG-LFP coherence

Overall, the peak of coherence between bipolar LFPs and cortical areas was most prominently seen in the temporal theta range (Fig. 2 B/C). DBS contacts inside the NBM showed significantly less coherence in the temporal theta band than DBS contacts outside the NBM (Fig. 2 D/E). The distance of bipolar LFP channel to the NBM was found to be *positively* correlated with the median of coherence within theta band between LFP end temporal EEG ($\rho = 0.6$; $p = 0.03$).

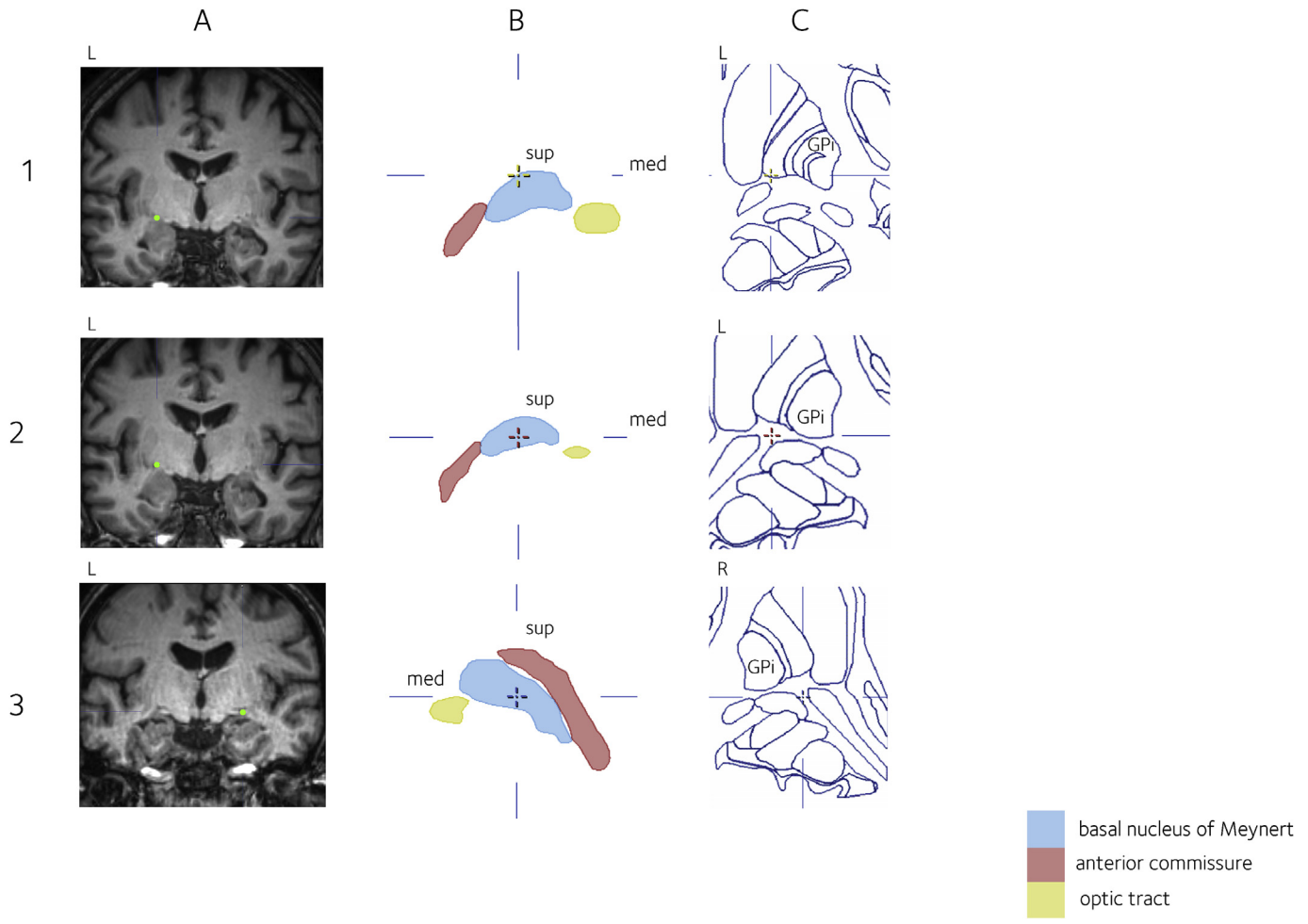

Fig. 1. Location of the three DBS contacts in the nucleus basalis of Meynert (NBM). Each row represents one of these contacts. Row 1 and 2: the two most ventral contacts on the left from patient 1 (contact 0 and 1). Row 3: the most ventral contact on the right from patient 2 (contact 4). Columns A-C show three methods of depicting the localization of each contact. A: based on the co-registration of the post-operative CT to pre-operative MRI in coronal setting B: based on demarcation of the NBM and its surrounding structures according to patients' individual MRI. C: based on the stereotactic atlas of the human brain [7]. Sup = superior, Med = medial, GPi = Globus pallidus interna.

4. Discussion

The present pilot study describes the oscillatory activity of the NBM region, in combination with its connectivity to central, frontal, parietal and temporal cortical areas. Our data indicate that delta oscillations are more prominent in the NBM region than outside. The other finding was that temporal coherence in the theta range was less outspoken in the NBM region than outside the NBM.

The local delta activity in the NBM region is comparable with previously reported findings of local oscillatory activity describing peak NBM activity in delta band during the resting-state LFP recording in PDD and dementia with Lewy Bodies (DLB) [8]. Although the anatomical connections of the NBM are well established and involve many cortical regions, including the frontal region, our coherence profiles did not show prominent frontal coherence from either the bipolar LFPs in the NBM region or the LFPs of structures proximal to the NBM. The latter also has frontal connections according to recent findings in healthy volunteers [3,9]. Theoretically, the absence of these functional connections might be the result of the cholinergic degeneration of the NBM in PDD, although cholinergic nuclear imaging studies suggest a more prevalent occipital-frontal gradient of cortical cholinergic denervation [10]. Interestingly, the cortical coherence was most prominent within the theta band in the temporal areas, which might be in line with very recent finding, that theta power in the temporal region was a powerful marker for PDD [11]. Since this coherence was virtually absent in the NBM region, one might speculate that such aberrant activity might also result from cholinergic degeneration.

4.1. Limitations

The current pilot study has several limitations. Firstly, the DBS leads were not intentionally targeted to the NBM region. However the distance to the NBM was reliably observed within the size of a DBS contact point for three contacts. This was consistently shown by transposing the contact coordinates onto patients' individual MRIs as well as onto the stereotactic atlas of the human brain (Fig. 1). Next to this, since only resting-state data was obtained in the intra-operative setting, no specific conclusion could be drawn about possible dynamic changes of the NBM and cortical activity in cognitive processing. Furthermore, although bipolar LFP recordings are less subjected to record signals from adjacent areas than monopolar LFP recordings, there still might be an influence of these areas. Finally and most importantly, our pilot study only involved two patients (four hemispheres), which limits the external validity of our findings.

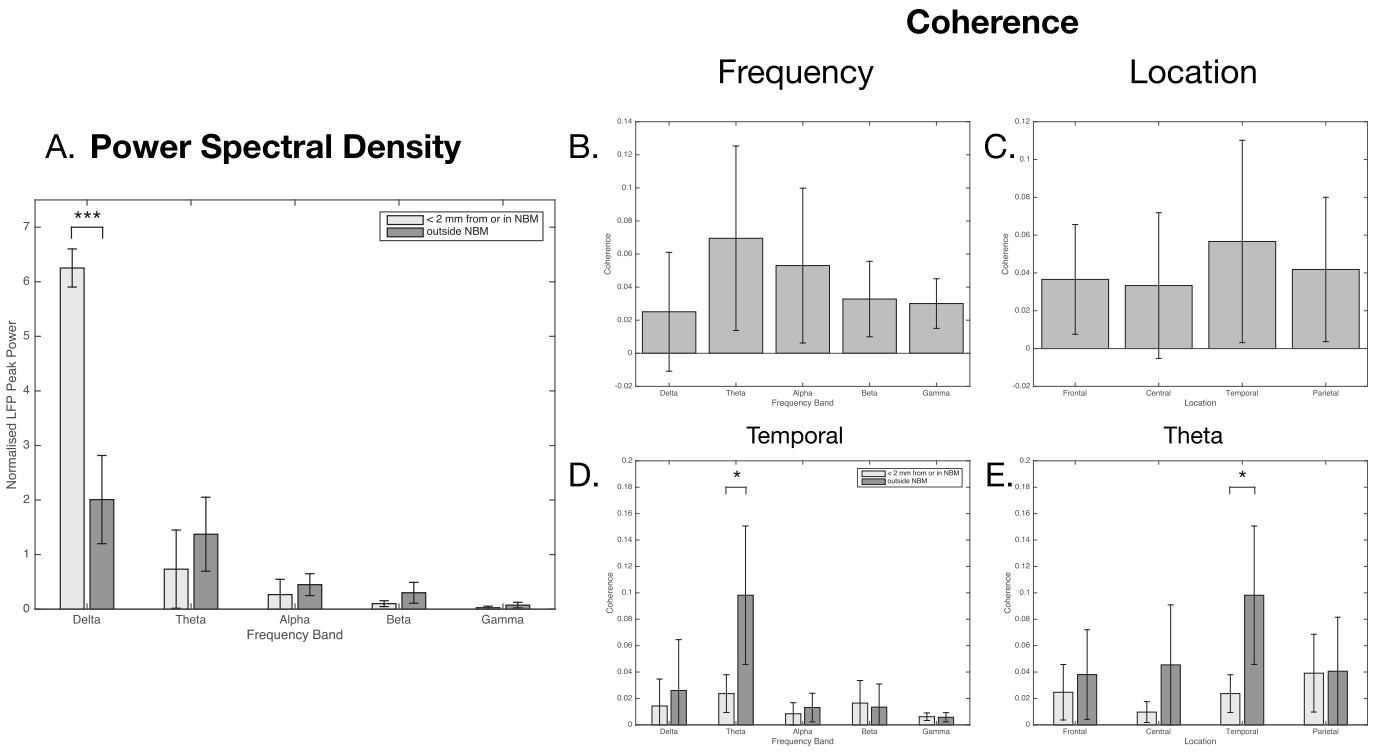

Fig. 2. A. Differences in power spectral density between DBS contacts inside or outside the NBM. Means and standard deviations of normalized peak power of delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–100 Hz) bands are shown. **B.** Median coherence profiles of frontal, central, temporal and parietal regions for the different frequency bands. **C.** Median coherence profiles of the different frequency band for the different cortical regions. **D.** Differences in coherence profile of contacts in and outside the NBM for the different frequency bands in the temporal region. **E.** Differences in coherence profile of contacts in and outside the NBM for the different regions in the theta band. *** = $p < 0.001$, * = $p < 0.05$. NBM = nucleus basalis of Meynert; LFP = local field potential.

5. Conclusion

The current pilot study provides insight into the neurophysiological characteristics of the NBM in PDD, which showed increased low-frequency activation in the NBM region and decreased temporal cortical connectivity compared to its proximal structures, including the GPi. Additionally, data were published recently in which NBM subregions were characterized using MRI-diffusion tensor imaging (DTI) [12]. In the future neurophysiological data may be combined with this new imaging techniques, to further investigate the anatomical position and function of the NBM, guiding implantations of DBS-NBM electrodes. This is of special relevance since the anatomical delineation of the NBM is compromised in cases of degeneration.

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Author roles

Research project: A. Conception, B. Organization, C. Execution;
Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
Manuscript: A. Writing of the first draft, B. Review and Critique.
M.N.: 1B, 1C, 2C, 2B, 3A
D.L.M.O.: 1B, 1C, 2C, 2B, 3B
J.M.C.v.D.:1A, 3B
J.C.v.Z.: 1C, 3B
A.K.K.: 1C, 2B
G.D.: 1C, 3B
T.v.L.: 1A, 3B
M.B.: 1A, 1B, 1C, 2A, 2B, 2C

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.03.024.

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