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Interventionelle neurophysiologische Untersuchungen zu sensorischen, kognitiven und emotionalen Funktionen der Basalganglien

Habilitationsschrift

zur Erlangung der Venia Legendi für die

Fächer Neurologie und Klinische Neurowissenschaften

an der Hohen Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

Vorgelegt von

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Düsseldorf 2016

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Dr. med. Lars Wojtecki

Düsseldorf, Oktober 2016

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Zusammenfassung

Die Basalganglien und der Thalamus stellen ein mit der Hirnrinde eng in Kommunikation stehendes Netzwerk dar. In dieser Habilitationsschrift wurden *neurophysiologische* Korrelate nicht-motorischer Funktionen der Basalganglien und des Thalamus untersucht. Zu den untersuchten nicht-motorischen Funktionen gehören hier kognitive Funktionen, insbesondere Exekutivfunktionen und kognitive Kontrolle, die somatosensorische Verarbeitung und die Verarbeitung von Emotionen. Ein Schwerpunkt der eigenen Arbeiten war hierbei die Untersuchung von niederfrequenten neuronalen Oszillationen als physiologisches Korrelat der integrativen Aufgabe der Basalganglien und Mittel der *long-range* Kommunikation. Methodisch wurden zwei wesentliche Pfeiler dargestellt, die bei Patienten, die mit Tiefer Hirnstimulation (THS) behandelt werden, zum Einsatz kommen. Einerseits das Modulieren der Gehirnaktivität durch gezielte elektrische Impulse und das Untersuchen der daraus resultierenden behavioralen Folgen, andererseits das Modulieren des Verhaltens oder des sensorischen *Inputs* mit verschiedenen Paradigmen und das Untersuchen der daraus resultierenden lokalen, neuronalen (oszillatorischen) Aktivität mittels invasiver elektrophysiologischer Ableitungen (lokale Feldpotentiale; LFP).

Zunächst wurde für die Parkinson-Krankheit (THS des Nucleus subthalamicus; STN) gezeigt, dass Aspekte des Sprechens und ihrer exekutiv-kognitiven Komponente durch die THS beeinflusst werden können. Hinsichtlich der exekutiven Kontrolle von Sprache (Wortflüssigkeit) zeigte sich eine Modulierbarkeit derart, dass sich die Performanz durch die Frequenzeinstellung beeinflussen ließ. Entgegen der therapeutischen hochfrequenten Einstellung scheint eine niederfrequente (Alpha-Theta) Stimulation kognitive Funktionen zu verbessern. Die frequenzabhängige Modulation der Performanz zeigte sich insbesondere auch bei einer rhythmusabhängigen kognitiven Funktion, nämlich bei der Einschätzung von Zeiträumen (*interval timing*). Eigene Arbeiten zur Placebo-Forschung zeigten, dass der Wirkung auf exekutiv-kognitive Funktionen auch ein konditionaler Lernprozess zu Grunde liegt, der offensichtlich für Kognition und Motorik gegenläufig sein kann. Dies entspricht dem Modell über getrennte motorische und kognitive Netzwerke der Basalganglien, welche sich selektiv und frequenzabhängig durch die THS beeinflussen

lassen. Im Weiteren wurde gezeigt, dass auch die motorischen Schablonen des emotionalen Ausdrucks (am Beispiel des pathologischen Lachens und Weinens) durch STN –Stimulation moduliert werden können – wahrscheinlich durch Beeinflussung ponto-zerebellärer Netzwerke. Für die Stimulation des Pallidums (Globus pallidus internus / externus; GPi / GPe) bei der Huntington-Krankheit wurde dargelegt, dass die THS in der Lage ist, das Kardinalsymptom Chorea zu unterdrücken, ohne dabei wesentliche kognitive Nebenwirkunken auszulösen. Vielmehr zeigte sich sogar bei der Stimulation des GPe ein positiver Effekt auf die kognitive Kontrolle (Fehlermonitoring), wofür über dies mittels Elektroenzephalographie ein elektrophysiologisches Korrelat gezeigt wurde. Mittels Ableitung von LFP aus den Zielgebieten STN, GPi und Thalamus wurde schließlich dargelegt, dass niederfrequente Oszillationen an verschiedenen nicht-motorischen Funktionen beteiligt sind. Es zeigte sich, dass der STN und frontale kortikale Areale bei der exekutiven Kontrolle von Sprache eine funktionelle Rolle spielen. Hierbei scheinen lokale und *long-range* Synchronisationen niederfrequent oszillierender neuronaler Cluster eine Rolle zu spielen. Die positiven Effekte der niederfrequenten Stimulation des STN auf die Wortflüssigkeit werden somit vermutlich durch Aktivierung entsprechender Alpha-Theta-Oszillationen in assoziativen STN-Subarealen vermittelt. Die Alpha-Theta-Oszillationen können als rhythmische Signatur zum *gating* des adäquaten Verhaltens über ein subthalamisch-präfrontales Netzwerk verstanden werden. Für die somatosensorische Verarbeitung (als integrative Rolle der Basalganglien) zeigten Ableitungen aus dem GPi ebenfalls Hinweise auf die Rolle der niederfrequenten Oszillationen. Schließlich wurde für den zentralen Thalamus gezeigt, dass niederfrequente Oszillationen bei der Verarbeitung emotionaler und kognitiv relevanter Reize eine funktionelle Relevanz haben.

Zusammenfasend unterstreichen die vorgelegten Arbeiten, dass das Netzwerk von Basalganglien, Thalamus und Kortex eine generelle Instanz zur Modulation von Verhalten darstellt. Diese Funktion geht dabei über die Bahnung, Hemmung oder Feinabstimmung von Bewegungen weit hinaus, sondern bezieht sich auf alle Aspekte von der Integration sensorischer Information, bis hin zur Modulation eines adäquaten behavioralen Outputs des menschlichen Verhaltens.

Abkürzungsverzeichnis

CSD	*current source density*
COV	*coefficient of variation*
CRN/Nc	*correct-related negativity*
CT	*central thalamus*
EEG	Elektroenzephalographie
ERN	*error-related negativity*
FA	*fusiform face area*
FFT	Fast Fourier Transformation
fMRT	funktionelle Kernspintomographie
GPe	Globus pallidus externus
Gpi	Globus pallidus internus
HD	*Huntington´s Disease*, Morbus Huntington
Hz	Hertz
LFP	lokales Feldpotential
MEG	Magnetoenzephalographie
MP	Morbus Parkinson
MRT	Kernspintomographie
ms	Millisekunden
OFC	orbitofrontaler Kortex
PET	Positronenemissionstomographie
PLC	*pathological laughter and crying*
SNc	Substantia nigra, pars compacta
SNr	Substantia nigra, pars reticulata
SPS	*sensory palmar stimulation*
STN	*subthalamic nucleus*, Nucleus subthalamicus
THS	Tiefe Hirnstimulation
UHDRS	Unified Huntingtońs Disease Rating Scale
UPDRS	Unified Parkinsońs Disease Rating Scale
VF	*verbal fluency*
VTA	ventrales tegmentales Areal

1 Einleitung

In der vorliegenden Habilitationsschrift werden neurophysiologische Untersuchungen vorgelegt, die sich mit den Basalganglien des Menschen beschäftigen. Klassischerweise werden die Basalganglien als Regelkreis der Bewegungskoordination gesehen. Die hier dargestellten Arbeiten haben jedoch deren nicht-motorische Funktionen und korrespondierende neurophysiologische Korrelate im Fokus und unterstreichen die moderne Interpretation der Basalganglien als generellen Regelkreis für die Integration sensorischer Information und die darauf basierende Anpassung des Verhaltens. Zum Verständnis der unten dargestellten eigenen Arbeiten werden zunächst anatomische, physiologische und technisch-methodische Grundlagen erläutert.

1.1 Die Basalganglien: Struktur, Funktion, Konnektivität

Die Basalganglien sind eine Gruppe subkortikal gelegener Hirnkerne, die als funktionelle Einheit fungieren. Sie befinden sich bihemisphärisch an der Basis des Vorderhirns und sind eng mit dem zerebralen Kortex, dem Thalamus und anderen Hirnregionen verknüpft. Ihre Strukturen umfassen das Striatum (bestehend aus Nucleus caudatus und Putamen), den Globus pallidus (internus: GPi; externus: GPe), die Substantia nigra (Pars compacta: SNc; pars reticulata: SNr) und den Nucleus subthalamicus (STN). Die Basalganglien erhalten Afferenzen aus annähernd allen Kortexarealen und fungieren als zentrale Schaltstelle, unter anderem für das extrapyramidal-motorische System. Sie ermöglichen eine kontrollierte und zielführende Verhaltenssteuerung durch Integration kortikaler und subkortikaler Information und die anschließende Rückkopplung über den Thalamus an die entsprechenden Rindenareale. Ein vereinfachtes Schema geht davon aus, dass kortikale Afferenzen zum Striatum projizieren. Von dort aus gelangen Projektionen direkt (*direct pathway*) über Ausgangsstationen (SNr und GPi) zum Thalamus und schließlich zurück zum Kortex, oder sie führen indirekt (*indirect pathway*) über die modulierend zwischengeschalteten Instanzen des GPe und STN. Ferner besteht ein *hyperdirect pathway* vom Kortex direkt zum STN (Nambu et al., 2002). Man geht von verschieden funktionellen Untereinheiten der Basalganglien aus, die mit entsprechenden

Kortexarealen in Verbindung stehen: Eine motorische Untereinheit zum präzentralen Kortex, eine okulomotorische, zum frontalen und supplementären Augenfeld, eine limbische zum zingulären und medialen orbitofrontalen Kortex und eine kognitiv-assoziative zum dorsolateralen präfrontalen und lateralen orbitofrontalen Kortex (Alexander et al., 1990). Die beiden zuletzt genannten Untereinheiten sind derzeit Gegenstand intensiver Forschung und Fokus der vorliegenden Habilitationsschrift. Sie sind an der Steuerung von Emotionen und der Feinabstimmung von Exekutivfunktionen beteiligt, indem sie wahrscheinlich sensorischen *Input* und Verhaltens*output* adjustieren. Unter Exekutivfunktionen versteht man kognitive Prozesse, die für die zielbezogene Kontrolle von Handlungen verantwortlich sind. Sie sind eng an das Frontalhirn und dessen Vernetzung mit den oben genannten subkortikalen Strukturen gekoppelt. Zu den Exekutivfunktionen gehören (willentliche) Planung von Handlungssequenzen, flexibler Wechsel zwischen Bewegungen, Auswahl (Priorisierung) von Bewegungen im Hinblick auf übergeordnete Ziele, Unterdrückung automatisierter Reaktionen sowie Abschirmung von Absichten gegen konkurrierende Impulse (Karnath and Thier, 2012). Funktionell bauen die Basalganglienareale, je nach Funktion, wahrscheinlich temporäre elektrisch oszillierende Verbindungen untereinander und mit den relevanten kortikalen Arealen auf. Dieses Konzept ist in Abbildung 1 dargestellt (Péron et al., 2013). Funktionelle Kopplungen finden zwischen neuronalen Clustern statt, deren elektrophysiologisch messbare oszillatorische Aktivität *in Phase* synchronisiert ist. Synchronisationen können zwischen gleich schnell schwingenden (z.B. Beta-Frequenz: 13-30-mal pro Sekunde; Hertz; Hz), oder auch zwischen zwei verschieden schnell schwingenden Oszillatoren auftreten (*cross frequency coupling*).

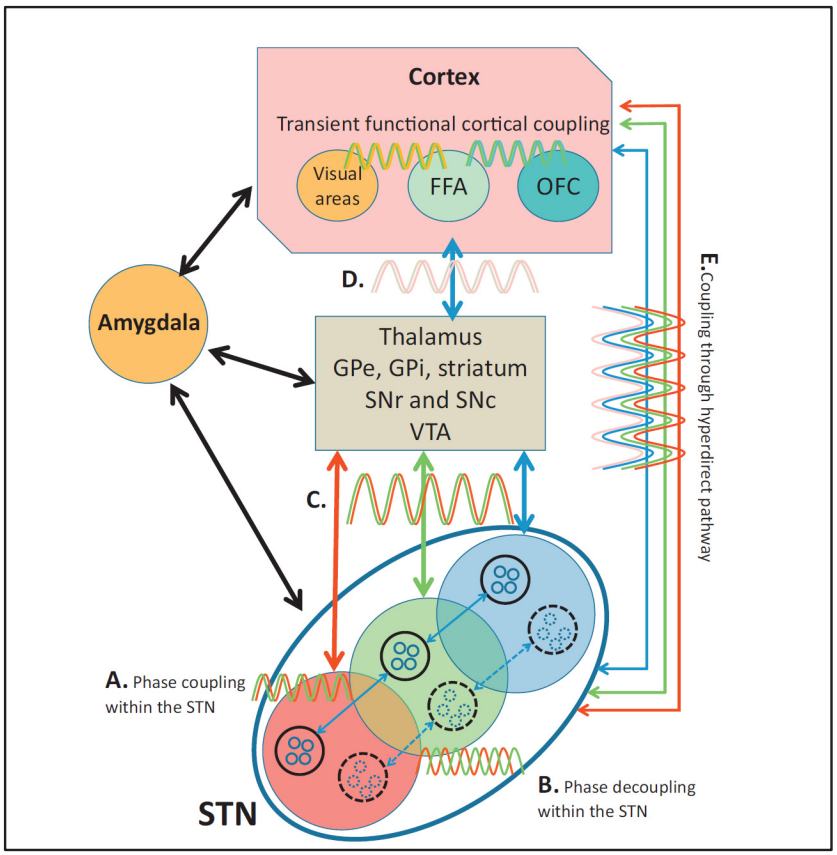

Abbildung 1: Schema zur funktionellen neuronalen Synchronisation (durch Phasenkopplung oszillierender Neurone) der Basalganglien und des Kortex am Beispiel des Nucleus subthalamicus (STN) und der Wahrnehmung emotionaler Gesichtsausdrücke. Subareale des STN repräsentiert als farbige Kreise (rot= limbisch, grün=assoziativ, blau=motorisch), innerhalb derer neuronale Cluster aktivierend (durchgezogene Kreise) oder hemmend (gestrichelte Kreise) wirken. A: Phasenkopplung limbischer und assoziativer Areale innerhalb des STN. B: Phasen-*Ent*kopplung derselben Areale aus A (bzw. Phasenkopplung mit Phasenverschiebung). C: Kopplung verschiedener STN-Areale mit anderen Basalganglienstrukturen, D: Kopplung der Basalganglien mit dem Kortex, E: Kopplung zwischen Kortex und STN-Subarealen über den *hyperdirect pathway*. Neuronale Kopplungen können innerhalb eine Frequenzbands (z.B. Beta) oder zwischen zwei Frequenzbändern (z.B. Theta-Gamma) auftreten. FFA: fusiform face area, OFC: orbitofrontaler Kortex, VTA: ventrales tegmentales Areal; aus: Péron et al., 2013.

1.2 Erkrankungen der Basalganglien

Allen Erkrankungen der Basalganglien ist gemeinsam, dass eine Dysbalance der oben beschrieben Netzwerkaktivität vorliegt. Aufgrund der, zumindest nach außen klinisch sichtbaren, Dominanz der motorischen Schleifen werden Basalganglienerkrankungen innerhalb der Neurologie im Wesentlichen als Bewegungsstörungen subsumiert. Dennoch gibt es Erkrankungen, wie beispielsweise das Tourette-Syndrom, bei denen sowohl die

motorischen, als auch emotionalen und exekutiven Aspekte der Basalganglien apparent werden. Grundsätzlich unterscheidet man *hypo*kinetische (Parkinsonsyndrome, insbesondere die Parkinson-Erkrankung) von *hyper*kinetischen Bewegungsstörungen (z.B. Dystonien und Chorea). Unter dem Begriff Parkinsonsyndrom versteht man eine Symptomkonstellation, bei der neben einer obligatorischen Bewegungsverlangsamung (Hypo-/Akinesie) mindestens eines der drei weiteren Symptome Tremor, Rigor und/oder Haltungsinstabilität auftritt (Oertel et al., 2011). Die häufigste Erkrankung, bei der ein Parkinsonsyndrom auftritt, ist die Parkinson-Erkrankung (Morbus Parkinson, MP), eine der häufigsten neurodegenerativen Erkrankungen. An ihrem Beispiel lässt sich, ausgehend vom oben beschriebenen kortiko-striato-thalamo-kortikalen Regelkreis, ein plausibles Modell zur Entstehung der Kardinalsymptome darstellen. So lässt sich Hypokinese folgendermaßen erklären: Durch den Verlust von Dopamin-produzierenden Zellen der SNc entsteht ein nigro-striatäres Dopamindefizit, das mit einer verminderten Hemmung des GPi über den *direct pathway* und einer vermehrten Aktivierung des GPi über den *indirect pathway* (Überaktivität des STN) vergesellschaftet ist. Dadurch entsteht letztlich über die Ausgangsstation (GPi/SNr) der Basalganglien eine Hemmung der motorischen Thalamusanteile, wodurch es zu einer Minderaktivierung der motokortikalen Areale mit einem entsprechend reduzierten motorischen *Output* kommt. Da aber entsprechend der oben genannten Untereinheiten der Basalganglien beim MP Verbindungen zu einer Reihe anderer kortikaler Areale (insbesondere präfrontale Areale) in Dysbalance geraten, kommt es neben den krankheitsdefinierenden Kardinalsymptomen unter anderem auch zu neuropsychologisch messbaren Störungen der Exekutivfunktionen (Oertel et al., 2011).

Spiegelbildlich zum MP lassen sich die Kardinalsymptome bei *hyper*kinetischen Störungen wie Dystonie und Chorea aus dem Basalganglienschema herleiten. Hier kommt es zu einem dopaminergen Überwiegen und zu einer verminderten Inhibition des Thalamus durch GPi/SNr und somit zu verstärkter Aktivierung des Kortex, was mit spontanen Überbewegungen wie Dystonie oder Chorea assoziiert ist. Unter Dystonie versteht man phasische bis tonische Ko-Kontraktionen agonistischer und antagonistischer Muskelgruppen. Dystonien können idiopathischer oder auch symptomatischer Ätiologie (z.B. nach Neuroleptika-Einnahme als Spätsymptom - dann genannt: Tardive Dystonie) sein und ferner fokal (z.B. zervikal) oder generalisiert auftreten. Unter Chorea versteht

man kurzzeitige, zufällig verteilte Bewegungen von Muskelgruppen. Eine Ursache für Chorea ist die Huntington-Krankheit (Huntington´s Disease, HD), eine genetisch bedingte neurodegenerative Erkrankung. Bei ihr stehen, neben den motorischen Kardinalsymptomen, kognitiver Abbau und psychiatrische Störungen im Fokus des klinischen Erscheinungsbilds. Diese lassen sich ähnlich dem MP durch Dysbalance in nicht-motorischen Untereinheiten der Basalganglien und in ihren kortikalen Verbindungen erklären (Oertel et al., 2011).

1.3 Interventionelle Neurophysiologie der Basalganglien

Unter interventioneller Neurophysiologie versteht man Verfahren, die, neben der reinen Messung elektrophysiologischer Signale, mit den neuronalen Strukturen direkt in Interaktion treten. Dies kann durch (invasive oder nicht-invasive) elektrische Stimulation geschehen oder durch invasive Ableitungen von den entsprechenden Regionen durch implantierte Elektroden. Die in dieser Habilitationsschrift beschriebenen Methoden sind einerseits das invasive Modulieren der Gehirnaktivität durch gezielte lokale elektrische Impulse im Rahmen der Tiefen Hirnstimulation, andererseits das direkte invasive Messen der Hirnaktivität über transient oder dauerhaft implantierte Elektroden.

1.3.1 Tiefe Hirnstimulation

Die Tiefe Hirnstimulation (THS) ist eine mittlerweile gut etablierte Therapie zur symptomatischen Behandlung verschiedener neuropsychiatrischer Erkrankungen mit Schwerpunkt auf der Linderung der Kardinalsymptome verschiedener Bewegungsstörungen. In Europa besteht eine CE-Zertifizierung für die Behandlung des MP, des (essentiellen) Tremors, verschiedener Formen der Dystonie (Kalia et al., 2013), der fokalen Epilepsie (Klinger and Mittal, 2016) und der Zwangserkrankung (Lipsman et al., 2013). Die häufigsten Zielpunkte der THS bei Bewegungsstörungen sind der STN, der GPi und der motorische Thalamus. Derzeit wird die THS ferner bei einer Reihe weiterer Indikationen erprobt. Technisch handelt es sich um stereotaktisch chronisch meist in

Kerngebiete der Basalganglien implantierte Elektroden, die mit einem subkutanen Impulsgenerator verbunden sind (Abbildung 2). Durch die Applikation einer hochfrequenten Stimulation (ca. 130 Hz) werden subkortikale Knotenpunkte und ihre kortikalen Projektionen in ihrer Funktion moduliert. Der genaue Mechanismus ist nicht bekannt und vermutlich komplex (Herrington et al., 2016). Man geht von lokalen und weit verzweigten Netzwerkeffekten aus, wobei es Hinweise dafür gibt, dass Zellsomata nahe der Elektrode inhibiert und Dendriten &erseits aktiviert werden, was weiteverzweigte retrograde Effekte über den *hyperdirect pathway* erklären könnte.

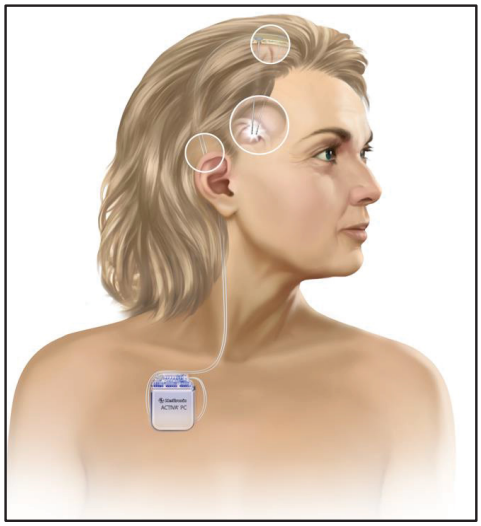

Abbildung 2: Darstellung eines implantierten THS-Systems. Subkutaner infraklavikulär gelegener Impulsgenerator, der über Extensionskabel mit THS-Elektroden verbunden ist, die nach intrakraniell und intrazerebral führen. Freundlich zur Verfügung gestellt von der Firma Medtronic.

1.3.2 Invasive Ableitung lokaler Feldpotentiale

Mittels lokaler Feldpotentiale (LFP) lassen sich auf eine invasive Art und Weise über eingeführte Elektroden direkt elektrische Signaturen neuronaler Strukturen bei verschiedenen motorischen und nicht-motorischen Funktionen erheben. Dabei entsprechen LFP der elektrischen Aktivität einige Millimeter um die Elektrode und somit einem Signal von lokalen neuronalen Clustern. Das Signal reflektiert wahrscheinlich den Input einer Zellstruktur und besteht aus den summierten synchronisierten,

postsynaptischen exzitatorischen und inhibitorischen Potentialen (Brown and Williams, 2005). Die Ableitung von LFP im Rahmen der THS kann während der Operation über Testelektroden oder postoperativ über die bereits für die chronische Stimulation vorgesehenen Elektroden erfolgen. LFP-Ableitungen können ferner mit Ableitung der Oberflächen-Elektroenzephalographie (EEG) oder mit der Magnetoenzephalographie (MEG) kombiniert werden, um subkortiko-kortikale Netzwerke zu charakterisieren. Die Datenanalyse umfasst unter anderem die Transformation des Signals in den Frequenzraum, z.B. mittels *Fast-Fourier-Transformation.* So kann oszillatorische Aktivität in spezifischen Frequenzbändern dargestellt werden: Delta (1-3 Hz), Theta (4-7 Hz), Alpha (8-12 Hz), Beta (13-30 Hz), Gamma (30-100 Hz) und Hochfrequenzoszillationen (> 100 Hz). Man geht davon aus, dass pathologische Beta-Oszillationen in den Basalganglien eine Signatur der Hypokinese bei Parkinson-Syndromen darstellen (Kühn et al., 2004). Die Analyse von LFP-Oszillationen bei kognitiven Funktionen hat sich im Zuge der weiteren Verbreitung der THS in den letzten Jahren etabliert (Marceglia et al., 2011). Grundsätzlich werden die Frequenzbänder mit spezifischen funktionellen Aufgaben in Verbindung gebracht:

- Theta: Arbeitsgedächtnis (Sauseng et al., 2005a), Fokussierte Aufmerksamkeit (Sauseng et al., 2005b)
- Alpha: Transiente Reaktivierung von Inhalten aus dem Langzeitgedächtnis (Klimesch et al., 2005), Aufmerksamkeitslenkung (Palva & Palva, 2007), Prozessierung emotionaler Stimuli (Kühn et al., 2005)
- Beta: Sensomotorische Funktionen (Pfurtscheller et al., 1996) Verschlechterung von flexiblem Verhalten und kognitiver Kontrolle (Engel & Fries, 2010)
- Gamma: *Feature binding* (Tallon-Baudry & Bertrand, 1999), Arbeitsgedächtnis (Tallon-Baudry et al., 1998), Assoziatives Lernen (Miltner et al., 1999), Aufmerksamkeit (Fries et al., 2001)

2 Eigene Arbeiten

Die Originalarbeiten, die in dieser Habilitationsschrift zusammengefasst sind, beschäftigen sich mit neurophysiologischen Untersuchungen nicht-motorischer Funktionen der Basalganglien und des Thalamus. Zu den untersuchten nicht-motorischen Funktionen gehören hier kognitive Funktionen, insbesondere Exekutivfunktionen und kognitive Kontrolle, die somatosensorische Verarbeitung und die Verarbeitung von Emotionen. Dabei wird, wie in der Einleitung dargelegt wurde, weniger davon ausgegangen, dass die Basalganglien eine spezifische inhaltliche Rolle innehaben, sondern vielmehr eine Integrationsinstanz sind, bzw. ein Tor zum Bahnen des behavioralen *Outputs* darstellen. Ein Schwerpunkt der eigenen Arbeiten ist hierbei die Untersuchung von niederfrequenten neuronalen Oszillationen als physiologisches Korrelat der integrativen Aufgabe der Basalganglien. Methodisch werden zwei wesentliche Pfeiler dargestellt, die bei THS-Patienten zum Einsatz kommen: Einerseits das Modulieren der Gehirnaktivität durch gezielte elektrische Impulse und das Untersuchen der daraus resultierenden behavioralen Folgen, andererseits das Modulieren des Verhaltens oder sensorischen Inputs mit verschiedenen Paradigmen und das Untersuchen der daraus resultierenden neuronalen (oszillatorischen) Aktivität.

2.1 Klinische und experimentelle Verhaltenseffekte der Tiefen Hirnstimulation

Die THS stellt ein therapeutisches Verfahren dar, welches lokal und sehr umschrieben in zerebrale Netzwerke eingreift und gezielt bestimmte Symptome verbessern kann. Trotzdem kann es zu unerwünschten Nebenwirkungen kommen, die teilweise durch Stimulation der angepeilten Areale selbst oder aber benachbarter Strukturen hervorgerufen werden. Durch detaillierte Untersuchungen dieser Nebenwirkungen lassen sich grundlegende Informationen über die Funktion der Zielgebiete der THS erlangen. Zudem können Stimulationsparameter systematisch moduliert und experimentelle Verhaltensparadigmen durchgeführt werden, um gezielten Fragestellungen nachzugehen. Schließlich kann die THS mit nicht-invasiven elektrophysiologischen Verfahren (EEG)

kombiniert werden. In der Folge werden zu verschiedenen nicht-motorischen Funktionen der Basalganglien entsprechende eigene Untersuchungen während aktivierter THS dargelegt.

2.1.1 Sprechen, Sprache, Exekutivfunktion, Zeitwahrnehmung und Emotion (bei M. Parkinson)

Neben den grundlegenden Effekten der THS des STN auf die motorischen Kardinalsymptome zeigen klinische Studien ebenso Auswirkungen der THS auf die Lebensqualität bei M. Parkinson. Zwei prospektive, randomisierte Studien, an denen der Autor der Habilitationsschrift beteiligt war, belegen für die THS im Vergleich zu einer medikamentösen Kontrollgruppe eine signifikante Verbesserung der Lebensqualität (Deuschl et al., 2006; Schuepbach et al., 2013). Allerdings zeigte sich insbesondere bei einem älteren Patientenkollektiv, dass sich die Kognition in der Selbsteinschätzung der Patienten nicht signifikant verbessert hatte (Deuschl et al., 2006). Eine Analyse der neuropsychologischen Testergebnisse (Witt et al., 2008) zeigte im Gesamten keine relevante Verschlechterung unter Stimulation des STN. Allerdings stellte man eine selektive Verschlechterung von frontal-exekutiven Funktionen insbesondere bei der Wortflüssigkeit fest. Die Wortflüssigkeit (*verbal fluency*; VF) quantifiziert die Anzahl genannter Wörter zu einem bestimmten Selektionskriterium während eines begrenzten Zeitraums. Als Risikofaktoren für eine Verschlechterung der VF wurde in einer weiteren Untersuchung das Alter, die tägliche L-Dopa Äquivalenzdosis und der axiale motorische Sub-Score der Unified Parkinson´s Disease Rating Scale UPDRS (Fahn et al., 1987) ausgemacht (Daniels et al., 2010). Die Auswirkung der STN-THS auf das Sprechen und die exekutive Kontrolle der Sprache stand daraufhin im Fokus folgender eigener Arbeiten.

In einer experimentellen Studie wurde der Einfluss der STN-THS im Vergleich zu L-Dopa auf die Sprechrhythmik untersucht (Skodda et al., 2012). Neben 42 MP-Patienten dienten 32 gesunde Probanden als Vergleichsgruppe. Drei verschiedene Test-Aufgaben wurden absolviert: Wiederholung von Silben in einer selbstgewählten Rhythmik, Wiederholung der gleichen Silbe mit einer durch ein Metronom vorgegebenen Geschwindigkeit und die

Wiederholung der alternierenden Silben „pa“ und ti“ mit fest vorgegebener Geschwindigkeit. Letztere Aufgabe hat durch die alternierenden zwei Silben im Vergleich zu den anderen Aufgaben den höchsten Anspruch an frontal-exekutive Funktionen (Aufgabenwechsel).

Es erfolgte eine Analyse der digital aufgezeichneten Sprechaufnahmen anhand des oszillographisch aufgezeichneten Geräuschdrucksignals. Eine Reihe von Parametern wurde untersucht, insbesondere die Stabilität des Rhythmus mittels eines relativen *coeffecient of variation (COV)*. Die Intervallänge zwischen den gesprochenen Silben der Wiederholungen 5-30 wurden hierzu ins Verhältnis zur Intervallänge der ersten vier (Rhythmus definierenden) Intervalle gesetzt. Es zeigte sich beim Vergleich der Kontrollgruppe mit der Parkinsongruppe ohne medikamentöse Therapie und mit ausgeschaltetem Schrittmacher ein *Krankheitseffekt* insofern dass die Varianz in der Parkinsongruppe deutlich erhöht war. Dieser Effekt zeigte sich in allen drei untersuchten Test-Aufgaben.

Neben diesem Anzeichen für eine irreguläre Performance der Silbenrepetition als Krankheitseffekt, zeigten sich auch verschiedene *Behandlungseffekte* durch L-Dopa, beziehungsweise die THS. In allen drei Aufgaben verursachte die THS im eingeschalteten Zustand eine Verschlechterung, d.h. eine Verstärkung der Varianz (Vergleich *Stim ON* versus *Stim OFF* signifikant für Test-Aufgabe 1 und 2, siehe auch Abbildung), während insbesondere bei dem komplexesten Test der alternierenden Silbenproduktion L-Dopa eine Verbesserung der durch die Stimulation tendenziell verschlechterten Performance nach sich zog (siehe Abbildung). Die Tatsache, dass sich die Varianz vergrößerte, hatte einerseits mit ansteigender Komplexität der Aufgabe zu tun, andererseits ist von einer stimulationsinduzierten exekutiven Dysfunktion auszugehen, welche zum Teil durch L-Dopa kompensiert werden kann (Skodda et al., 2012).

Diese experimentellen Daten zur Sprechfunktion und ihrer exekutiv-kognitiven Komponente decken sich gut mit den oben ausgeführten klinischen Studienergebnissen, welche für die STN- Stimulation negative Auswirkungen auf frontal-exekutive Funktionen zeigten.

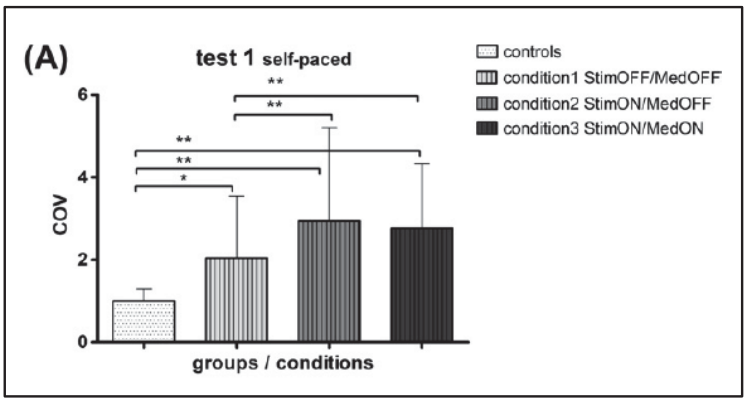

Abbildung 3: Balkendiagramm des Gruppenmittelwerts (mit Standardabweichung) der Kovarianz in Testaufgabe 1 (*self-paced* Silbenreproduktion) mit signifikanter Erhöhung im *Stim ON* versus *Stim OFF* im medikamentösen *OFF* (mittlere Balken, ** p<0.01) ; aus: Skodda […] & Wojtecki , 2012.

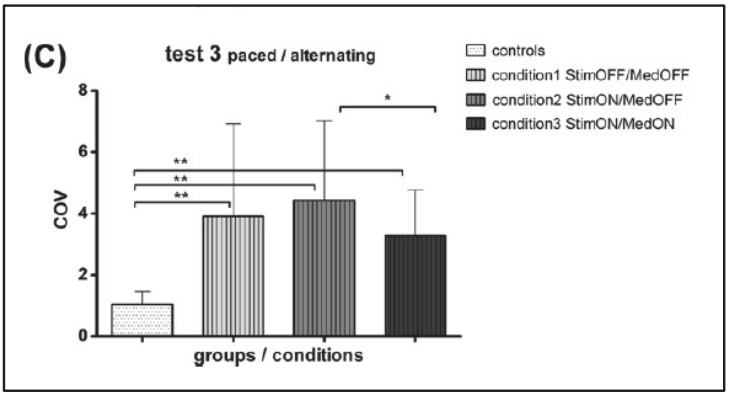

Abbildung 4:. Balkendiagramm entsprechend Abbildung 3, nun aber für die exekutiv komplexere Aufgabe der *paced/alternating* Silbenreproduktion. Es zeigt sich eine weitere Verstärkung der Kovarianz bei den Parkinsonpatienten, insbesondere unter STN-Stimulation, welche durch L-Dopa Medikation signifikant verbessert wird (rechter Balken), **p<0.01, *p<0.05; aus Skodda […] & Wojtecki 2012.

Neben dieser Studie, die einen negativen Einfluss der STN-Stimulation auf die Sprech-Exekutivfunktionen zeigte, erfolgte eine weitere Studie an 38 MP-Patienten zur akustischen Verständlichkeit des Sprechens unter STN-Stimulation (Skodda et al., 2014). Hierzu erfolgte eine Auswertung von Sprechaufnahmen einerseits durch verblindete Untersucher und andererseits mittels einer Software. Für Ersteres wurde ein Score mit vier Dimensionen (*voice, articulation, tempo/fluency, prosody*) herangezogen. Für die

Software-Analyse wurde das sogenannte PRAAT System genutzt (Boersma & Weenik, 1996). Die Ergebnisse zeigten, dass die STN-Stimulation eine höhere Lautstärke und bessere *pitch variability* bewirkte (statistische Trends). Es zeigte sich aber auch eine Untergruppe von Patienten, bei denen sich Aspekte des Sprechens verschlechterten. Die bei diesen Patienten gefundene Verschlechterung der Artikulation und der Flüssigkeit fand sich allerdings auf Boden vorbestehender Einschränkungen im Sinne von *articulatory slurring* und einer Sprechbeschleunigung während der Ausführung (Skodda et al., 2014). Es kann geschlussfolgert werden, dass die STN-Stimulation tendenziell eine Verbesserung der Sprechverständlichkeit bewirkt, wobei es eine bestimmte Risikogruppe von MP-Patienten zu geben scheint, bei denen die STN-Stimulation negative Auswirkungen hat. Die gefundenen vorbestehenden pathologischen Sprech-Parameter könnten in Zukunft als Prädiktor im präoperativen Screening ein wertvoller Zusatz sein.

Nachdem o.g. Sprech-Studien die exekutiv-kognitiven Funktionen der STN-Stimulation eher als Nebenaspekt behandelten, werden in der Folge eigene Untersuchungen zusammengefasst, die sich spezifischer auf exekutive Funktionen bezogen. Ein besonderer Schwerpunkt der eigenen Arbeiten war die Frage nach frequenzabhängiger Modulation dieser Exekutivfunktionen.

Wie in der Einleitung dargelegt wurde, geht man in den Basalganglien von unabhängigen funktionellen Schaltkreisen unterschiedlich schnell oszillierender neuronaler Populationen aus, sodass untersucht wurde, ob sich motorische und kognitive Schaltkreise entsprechend unabhängig voneinander modulieren lassen. Eine klinisch-experimentelle Arbeit, die sich auf die Motorik bei MP bezog, hatte gezeigt, dass die niederfrequente Stimulation des STN im Alpha-Frequenzbereich ein pathologisches mit 10 Hz schwingendes Motor-Netzwerk antreiben und somit die hypokinetisch-rigiden Parkinson-Symptome verstärken konnte (Timmermann et al., 2004).

Da die übliche therapeutische 130 Hz (Hochfrequenz)-Stimulation des STN entsprechend zu einer Verschlechterung von Exekutivfunktionen, insbesondere der Wortflüssigkeit, führt, lag die Hypothese nahe, dass sich die Modulation der STN-Netzwerke für Motorik und Kognition reziprok zueinander verhalten. Dies sollte eine Studie untersuchen, bei der die Wirkung der niederfrequenten (10 Hz) Stimulation auf die Wortflüssigkeit untersucht

wurde (Wojtecki et al., 2006). Die VF untersucht, wie oben erwähnt, eine Exekutivfunktion im Sinne eines Selektionsprozesses, in dem ein zu einem Kriterium passendes Wort (z.B. ein Wort beginnend mit einem bestimmten Anfangsbuchstaben; formal-lexikalische Wortflüssigkeit) aus dem Gedächtnis abgerufen und genannt wird, wohingegen unpassende Wörter nicht genannt bzw. unterdrückt werden.

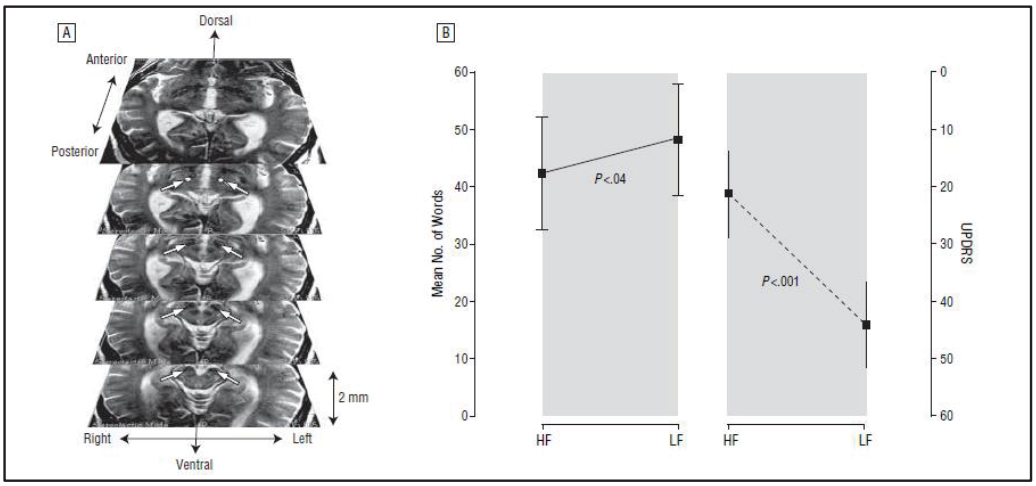

Abbildung 5: A: Stimulationsort (weiße Punkte auf transversalen MRT Schichten) im STN (weiße Pfeile). B: Mittlere Anzahl genannter Worte bei der Wortflüssigkeitsaufgabe (y-Achse links) und UPDRS Motor Score (y-Achse rechts) unter *high frequency* (HF; 130 Hz) versus *low frequeny* (LF; 10 Hz) Stimulation zeigen reziproke Ergebnisse; aus Wojtecki et al., 2006.

In einem doppelblinden, randomisierten *crossover* Design wurden die Frequenzen 10 Hz und 130 Hz hinsichtlich ihres Effekts auf die Wortflüssigkeit und die Motorik untersucht. Es zeigte sich tatsächlich, dass die niederfrequente im Vergleich zur hochfrequenten Stimulation eine Verbesserung der Wortflüssigkeit in allen Domänen (formallexikalisch und semantisch) bewirkte (siehe Abbildung 5).

Eine entsprechend Abschnitt 1.1. abzuleitende Hypothese zur Funktion des STN, der Basalganglien und des direkten, indirekten und hyperdirekten *Pathways* ist, dass der STN als eine globale *Go-No-Go*-Pforte wirkt, die je nach Aktivität Verhalten über Projektionen in funktionellen Unternetzwerken hemmen oder bahnen kann. Verhaltensaspekte beinhalten nicht nur motorischen *Output*, sondern - wie hier gezeigt - auch kognitive Operationen. Je nach Frequenz der STN-Stimulation kann es selektiv für funktionelle

Netzwerke so zur Bahnung oder zur Hemmung von entsprechenden Verhalten und somit zur Verbesserung oder Verschlechterung der im Experiment gemessenen *Performance* führen.

Jenseits der exekutiven Kontrolle der Sprache ließen sich auch noch in anderen Experimenten niederfrequente versus hochfrequente Stimulationseffekte nachweisen. Ein mutmaßlich von der Taktung neuronaler Populationen besonders abhängiger kognitiver Prozess ist die subjektive Verarbeitung von Zeit. Daher wurde eine experimentelle Studie zum Effekt verschiedener Geschwindigkeiten der STN-Stimulation auf das sogenannte *interval timing* (Zeitabschnitte im Sekundenbereich) bei 12 MP-Patienten (und 12 gesunden Kontrollprobanden) durchgeführt (Wojtecki et al., 2011a). Unter anderem wurde hier untersucht, wie Zeitintervalle von 5 und 15 Sekunden nach vorgegebenem Rhythmus reproduziert und frei produziert werden (siehe Abbildung 6).

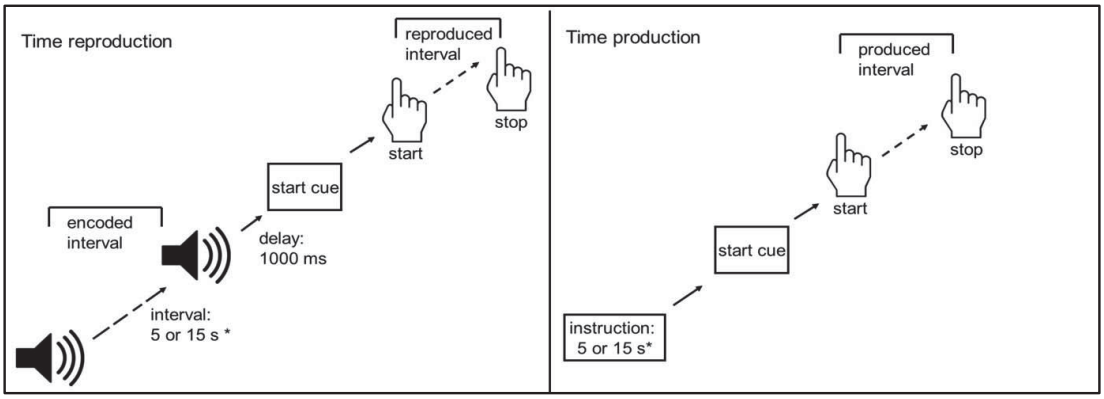

Abbildung 6: Paradigma zur Reproduktion (links) und Produktion (rechts) eines Zeitintervalls (entweder 5 oder 15 s) nach akustisch vorgegebenem Intervall; aus Wojtecki et al., 2011

Es stellte sich heraus, dass sich die niederfrequente Stimulation von der hochfrequenten Stimulation und dem Zustand mit ausgestelltem Stimulator hinsichtlich der zeitlichen Abweichung vom Zielintervall unterschied. Das lange Intervall wurde in seiner Dauer signifikant unterschätzt, wobei das kurze Intervall überschätzt wurde - bekannt als *memory migration effect* (Koch et al., 2004; Malapani & Rakitin, 2003). Die Ergebnisse sind in Abbildung 7 illustriert.

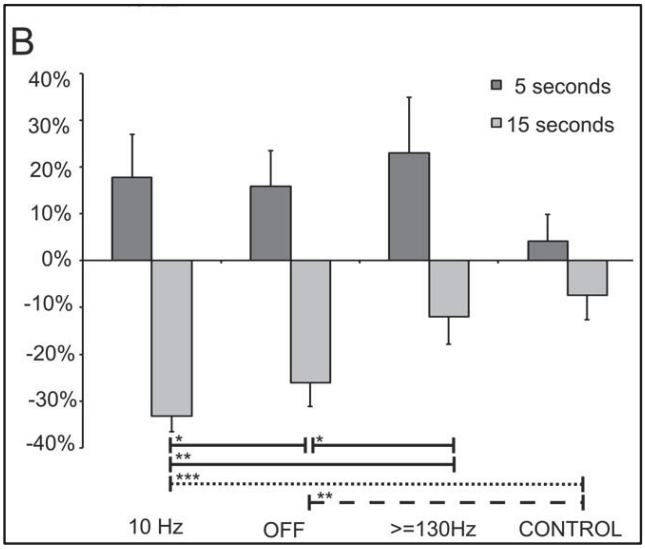

Abbildung 7: Mittlere prozentuale Abweichung (mit Standardfehler des Mittelwerts) vom Zielintervall bei der Aufgabe zur Zeitproduktion mit signifikantem Effekt der Stimulationsfrequenz auf die Produktion des 15 s Intervalls, *p<= 0.05; **p<= 0.01, ***p<= 0.001.; aus Wojtecki et al., 2011

Es zeigte sich also auch in dieser Studie, dass die STN-Stimulation frequenzabhängig kognitive Operationen moduliert. Hinsichtlich des *interval timing* scheint die Modulation eines inneren Schrittmachers (Zeitproduktion) aber auch des Arbeitsgedächtnisses (Reproduktion) eine Rolle zu spielen.

Neben direkten physiologischen Effekten der STN-Stimulation auf die Motorik und Kognition bei MP wurden ebenso Placebo- und Nocebo-Effekte betrachtet, deren vermutete Mechanismen *Erwartungshaltung* und *konditionales Lernen* beim MP und vielen anderen Erkrankungen derzeit vielfältig untersucht werden, da sie das therapeutische Ansprechen relevant beeinflussen können (Enck et al., 2013). In zwei experimentellen Studien wurde daher sowohl bei 24 hypokinetisch-rigiden (Keitel et al., 2013a), als auch bei 24 tremordominanten (Keitel et al., 2013b) MP-Patienten der Placebo- bzw. Nocebo-Effekt bei, durch verbale Suggestion erzeugter, positiver bzw. negativer Erwartung hinsichtlich einer Schein-Programmierung des STN-Schrittmachers untersucht. Zur Quantifizierung der Motorik diente der UPDRS Motor Score und die Analyse der Diadochokinese und des Finger-Tappings sowie des Tremors mittels eines 3D-Ultraschall Systems. Die exekutiv-kognitive Testung erfolgte erneut durch Testung der Wortflüssigkeit.

Im medikamentösen *OFF*-Zustand bewirkte eine positive Erwartung im Vergleich zu einer negativen Erwartung bei den hypokinetisch-rigiden Patienten eine signifikante Verbesserung der Hand-Diadochokinese, gemessen anhand der mittleren Winkelgeschwindigkeit (Grad/sek). Interessanterweise boten Placebo-Responder, deren erwartungsinduzierte motorische Verbesserung mindestens 25% betrug, einen gegenläufigen Effekt der kognitiven Leistung: die lexikalische Wortflüssigkeit verschlechterte sich (statistischer Trend) im Zuge einer positiven Erwartung hinsichtlich der Motorik (Keitel et al., 2013a). Bei den tremordominanten Patienten zeigte sich bei motorischen Nocebo-Respondern ein Generalisierungseffekt auf die Kognition: eine negative Erwartungshaltung hinsichtlich der Motorik ging auch mit einer Verschlechterung der Wortflüssigkeit einher (Keitel et al., 2013b).

An diesen Arbeiten zeigen sich exemplarisch beide Aspekte der Placebo-/Nocebo-Antwort, nämlich einerseits eine positive Erwartungshaltung, welche dopaminerg vermittelt wird und andererseits ein unbewusster, konditionaler Lernprozess, der offensichtlich für Kognition versus Motorik gegenläufig sein kann. Dies entspricht dem mehrfach genannten Modell über getrennte motorische und kognitive Netzwerke der Basalganglien, welche sich selektiv durch die THS beeinflussen lassen.

Interessanterweise konnten in eigenen Arbeiten auch klinische Effekte der STN-THS gezeigt werden, die über Motorik und Kognition hinausgehen, nämlich im Bereich der Emotion. Psychische Begleitphänomene der THS sind selten, wurden aber bereits früh beschrieben (Bejjani et al., 1999; Krack et al., 2001) und helfen, die funktionellen Verbindungen des STN und seiner Umgebung besser zu verstehen. Neben einer eigenen Kasuistik eines MP-Patienten, der abhängig von der Stimulationsamplitude gegenläufige euphorische bzw. depressive affektive Zustände erlebte (Wojtecki et al., 2011b), wurde eine Untersuchung mittels funktioneller Positronenemissionstomographie (PET) zu dem Phänomen des pathologischen Lachens und Weinens (PLC), welches durch STN-THS induziert wurde, durchgeführt (Wojtecki et al., 2007). Unter PLC versteht man das äußerlich motorische sichtbare Muster des Lachens und / oder Weinens ohne eine dabei adäquat empfundene Emotion (siehe Abbildung 8). Es konnte gezeigt werden, dass die Stimulation von im STN gelegenen Kontakten (1 und 3) zu PLC führt und mit Aktvierung (bzw. Erhöhung des regionalen zerebralen Blutflusses; rCBF) der ipsilateralen Pons, des ipsilateralen Thalamus und des kontralateralen Zerebellums einhergeht (siehe Abbildung

9). Die Ergebnisse dieser PET-Untersuchung lassen sich gut mit einem Modell zu PLC erklären (Parvizi et al., 2001). Das Modell geht davon aus, dass PLC durch eine funktionelle Unterbrechung der Kommunikation der höheren assoziativen Arealen (*induction sites*, wie z.B. ventromedialer präfrontaler Kortex, anteriores Cingulum, Amygdala, ventrales Striatum) vom Kleinhirn entsteht. Das Kleinhirn seinerseits berechnet Profile psychomotorischer Antworten und projiziert über Zwischenstationen zu *effector sites* wie Thalamus, Hypothalamus, periaquäduktalem Grau, Motorkortex und Hirnnervenkernen. Die im PET nun gefundene Aktivierung legt nahe, dass die Stimulation des STN selbst eine Aktivierung des Thalamus und eine (retrograde) ponto-zerebelläre Aktivierung verursacht, die im vorliegenden Zusammenhang eine *Über*aktiverung des PLC-modulierenden Netzwerks bedingt. Ferner ist möglich, dass o.g. Projektion zu *inductions sites* (insbesondere das ventrale Striatum) durch die Stimulation des STN, oder benachbarter Fasertrackte, beeinflusst werden. Schließlich könnte STN-THS präfrontale / parietale Assoziationskortizes aktivieren, die über pontine Kerne zum Zerebellum projizieren und eine zerebelläre Aktivierung verstärken. Auch wenn sich durch derartige Untersuchungen, die Neurostimulation und funktionelle Bildgebung kombinieren, die o.g. Zusammenhänge letztlich nicht endgültig klären lassen, liefern sie doch einen wertvollen Beitrag zum Verständnis der Netzwerkphysiologie der durch THS angesteuerten Zielareale.

Abbildung 8: Patient mit pathologischem Lachen und Weinen während STN-Stimulation; Screenshot aus Videosupplement in Wojtecki et al., 2007

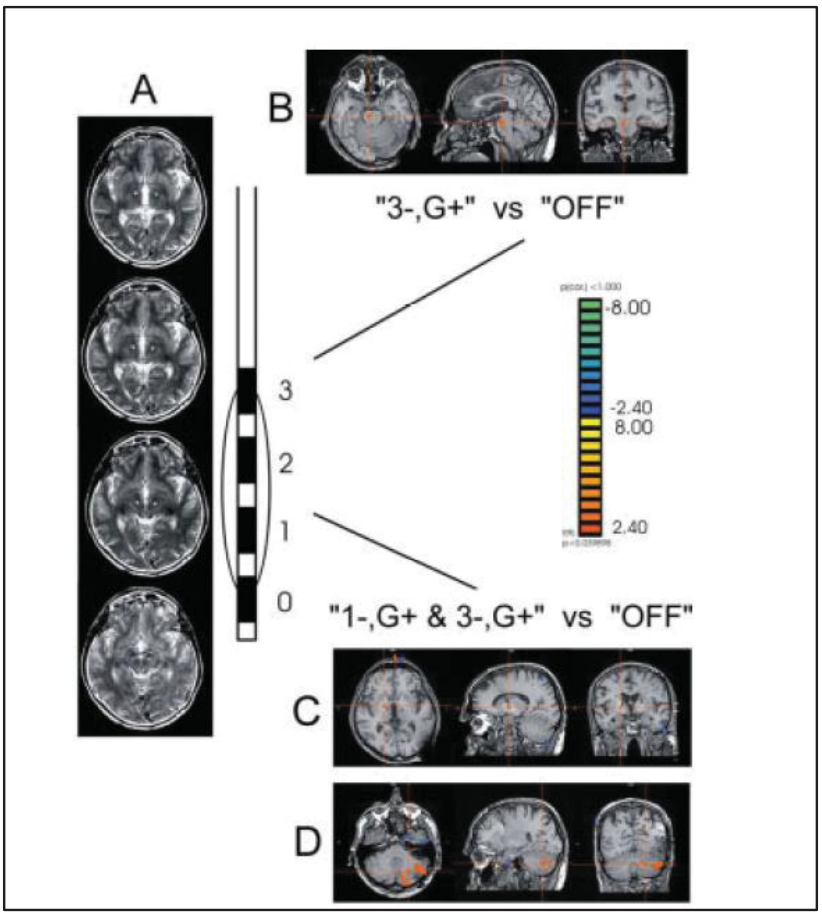

Abbildung 9: A: Schematische und anatomische Position (weisse Punkte auf transversalem T2-MRT) der Elektrodenkontakte 1-3 im STN (Ellipse). B,C,D: regionaler zerebraler Blutfluss (PET) unter Aktivierung der Kontakte (1 und 3), die PLC auslösten, im Vergleich zu *OFF* Stimulation. Es zeigen sich stimulationsinduzierte Aktivierungen in B: ipsilateraler Pons, C: ipsilateralem Thalamus, D: kontralateralem Zerebellum; aus Wojtecki et al., 2007

2.1.2 Kognitive Kontrolle (bei M. Huntington)

Neben der Stimulation des STN wurde auch die Stimulation des Pallidums in eigenen Arbeiten untersucht. Der innere Teil des Globus Pallidus (GPi) wird seit vielen Jahren bei einer Reihe von Bewegungsstörungen therapeutisch angesteuert, wobei der eigene Fokus zuletzt die Behandlung der Chorea bei der Huntington-Erkrankung war. Vor der Durchführung einer eigenen monozentrischen, prospektiv-randomisierten Pilot-Studie zur pallidalen THS bei Patienten mit Morbus Huntington (Wojtecki et al., 2015) lagen nur einige Kasuistiken und Fallserien vor, die die Wirksamkeit dieser Behandlung nahe legten (Wojtecki et al., 2016a). Tierexperimentelle Daten hatten indes dargelegt, dass hinsichtlich der Wirkung auf kognitive Kontrolle die Stimulation des *externen* Globus pallidus (GPe) von Vorteil sein könnte (Temel et al., 2006). Die eigene prospektive Pilotstudie wurde daher so konzipiert, dass beide Subareale auf ihre Wirksamkeit auf Motorik, aber auch auf basale kognitive Funktionen untersucht wurden. Zunächst zeigte sich die Chorea, gemessen am Chorea Subscore der Unified Huntington´s Disease Rating Scale UHDRS (Huntington Study Group, 1996), im Verlauf von sechs Monaten im Vergleich zur Baseline signifikant reduziert (siehe Abbildung 10). Ferner unterschied sich die GPe-THS nicht signifikant von der GPi-THS hinsichtlich ihres Effektes auf die Chorea. Die Stimulation beider Zielpunkte hatte vordergründig, gemessen an der Mattis Dementia Rating Scale (Mattis, 1988), keine signifikanten Auswirkungen auf den klinisch kognitiven Verlauf.

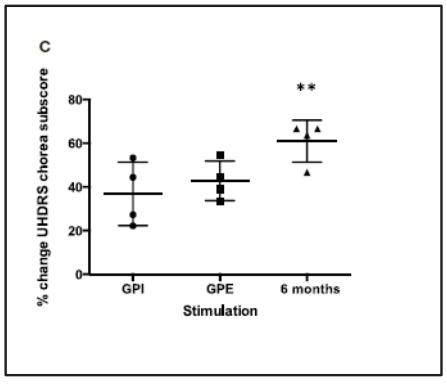

Abbildung 10: Ergebnisse der pallidalen THS angegeben in prozentualer Verbesserung (Reduktion) im UHDRS chorea subscore (Mittelwert, Standardabweichung und individuelle Werte) für randomisierte Stimulation über je sechs Wochen des GPi und GPe, sowie Stimulation des jeweils individuell besten Areals über sechs Monate. **p<0.01; aus Wojtecki et al., 2015

Aufgrund der o.g. tierexperimentellen Effekte der GPe-THS auf die Kognition wurde im Verlauf eine experimentelle Studie an Patienten mit GPe-Stimulation hinsichtlich des Effektes auf die kognitive Kontrolle ergänzt (Beste et al., 2015). Hierzu wurde ein *flanker task* verwendet (siehe Abbildung 11). Bei dieser Aufgabe umrahmen zwei nach rechts weisende Pfeilsymbole ein in der Mitte gelegenes, zum Rahmensymbol kompatibles, inkompatibles oder neutrales Stopp- oder Zielsymbol, auf das per Knopfdruck reagiert werden soll. Vier Blöcke mit je 120 Durchgängen (*trials*) wurden durchlaufen. Als Maß der kognitiven Kontrolle diente das sogenannte *post-error slowing.* Dies beschreibt das Phänomen, bei dem Probanden / Patienten nach Bemerken einer eigenen fehlerhaften Antwort beim nächsten *trial* verzögert antworten (gemessen mittels Reaktionszeit). Bei HD ist diese Verzögerung im Sinne einer pathologisch verminderten Fehlerkontrolle geringer ausgeprägt als bei gesunden Kontrollprobanden (siehe Abbildung 12). Da angenommen wird, dass das Pallidum an Prozessen der Handlungskontrolle beteiligt ist (Humphries et al., 2006), wurde mit Hilfe der eigenen Studie nun untersucht, ob die elektrische Stimulation des GPe (wie in Abbildung 11 gezeigt) im Vergleich zum ausgestellten Stimulator modulierend auf die Performanz im *flanker task* einwirken kann.

Da gleichzeitig bekannt ist, dass das entsprechende *Fehlermonitoring* mit einem elektrophysiologischen Korrelat im EEG, der *error-related negativity* (ERN), einhergeht, wurde im Vergleich GPe-Stimulation *OFF* versus *ON* ein Oberflächen-EEG abgeleitet, um das entsprechende evozierte Potential der ERN im Verglich zur *correct-related negativity* (CRN/Nc) zu bestimmen. Abbildung 12 visualisiert die Ergebnisse. Die GPe-Stimulation führte zur Normalisierung der Fehlerkontrolle bei den HD-Patienten bzw. sogar zur Optimierung des *post-error slowing* im Vergleich zu unbehandelten HD-Patienten. Die ERN, welche eine geringere Amplitude als bei Normalprobanden hatte, normalisierte sich unter GPe-Stimulation. Somit zeigen Verhaltensdaten und elektrophysiologisches Korrelat einen positiven Einfluss auf das *Fehlermonitoring* durch GPe-Stimulation. Die Tatsache, dass sich auch die Nc-Amplitude normalisierte, deutet zudem darauf hin, dass die Effekte globaler sind, im Sinne einer Verbesserung des allgemeinen *Antwortmonitorings*. Diese Ergebnisse passen sehr gut zur Funktion der Basalganglien als ein Selektions- und Kontrollschaltkreis (Humphries et al., 2006).

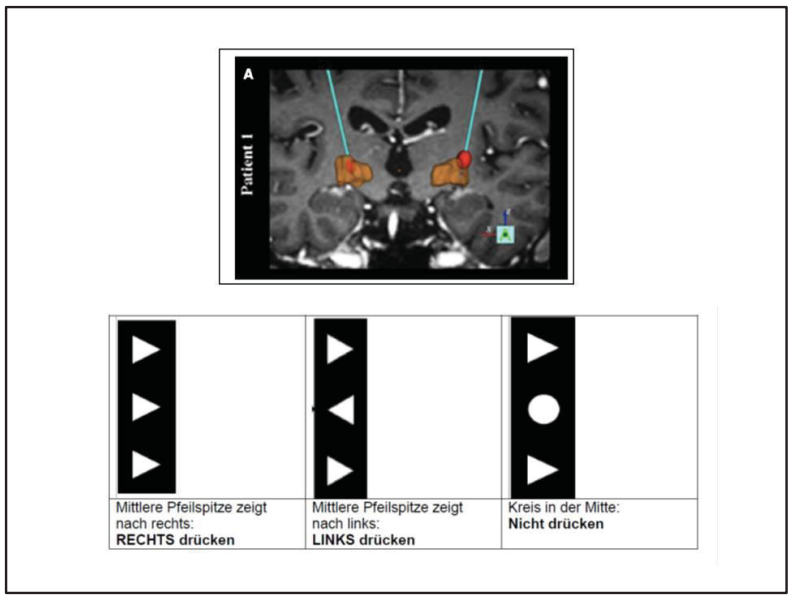

Abbildung 11: Oben: Beispiel (Patient 1) der individuellen Elektrodenlokalisation (türkis) und des berechneten *volume of tissue activated* (VTA; rot) in Bezug zum Globus pallidus (braun) in 3D Rekonstruktion mit Blick von anterior auf koronarem MRT. Sichtbar ist, dass der externe Teil (GPe) des Globus pallidus stimuliert wurde; aus Beste, […] & Wojtecki, 2015. Unten: Abbildung der Bildschirminstruktion des *flanker tasks*. Per Tastendruck soll ausschließlich auf das mittlere Symbol reagiert werden.

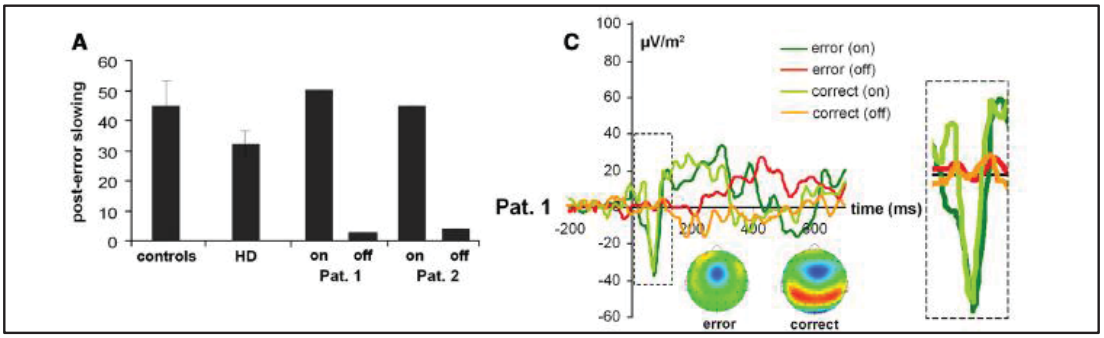

Abbildung 12: A: Grad der Verlangsamung (*post-error slowing*, in ms) für die normale Kontrollgruppe, eine HD-Kontrollgruppe ohne medikamentöse oder operative Behandlung und für zwei HD-Patienten *ON* und *OFF* GPe-Stimulation. Ohne Stimulation zeigte sich eine deutliche Verminderung des *post-error slowing*, welches sich im *ON* statistisch nicht von normalen Kontrollen unterscheidet und besser ist als bei der HD-Vergleichsgruppe ($p<.001$). C: Ereigniskorrelierte Potentiale für fehlerhafte (ERN) und korrekte Durchläufe (CRN; Nc) jeweils „ON“ und „OFF“ Stimulation bei Patient 1. Die ERN (aber auch die Nc) zeigen nur im *ON* eine deutliche Ausprägung. Zeitpunkt 0 entspricht der Antwortgabe durch Tastendruck. Der Zeitraum um 100ms ist vergrößert dargestellt. Unterhalb der Kurve: Topographie der *current source density* (CSD); Teil einer Abbildung aus Beste, […] & Wojtecki, 2015.

2.2 Lokale Feldpotentiale: Niederfrequente Oszillationen

Nach oben ausgeführten behavioralen und nicht-invasiven elektrophysiologischen Untersuchungen unter Stimulation des STN und des Pallidums wurde der Frage nachgegangen, ob sich bei direkten, also invasiven Ableitungen von den THS-Zielpunkten elektrophysiologische Korrelate von sensorischen, kognitiven und emotionalen Funktionen der Basalganglien finden lassen. Wie in Abschnitt 2.1.1 dargelegt, scheinen niederfrequente Oszillationen in den Basalganglien im Alpha- und Thetafrequenzband eine Rolle bei der Modulation von Verhalten spielen. Entsprechen erfolgten Ableitungen lokaler Feldpotentiale aus verschiedenen Zielpunkten und während der Durchführung von kognitiven, sensorischen oder emotionalen Paradigmen.

2.2.1 Exekutive Kontrolle von Sprache (bei M. Parkinson)

In Abschnitt 2.1.1 wurde dargelegt, dass vermutlich bei motorischen versus kognitiven Aufgaben in Subterritorien des STN verschiedene Oszillationen auftreten, die sich selektiv durch die THS beeinflussen lassen. Mittels bilateraler invasiver Ableitungen aus dem STN bei 16 MP-Patienten (32 STN Ableitungen) wurde die Hypothese untersucht, ob lokale niederfrequente Oszillationen im Alpha-Theta Bereich bei der exekutiven Kontrolle von Sprache eine Rolle spielen (Wojtecki et al., 2016b). Am Tag nach stereotaktischer Implantation der THS-Elektroden in den beidseitigen STN wurden LFP (Abbildung 13) in Kombination mit Oberflächen-EEG abgeleitet.

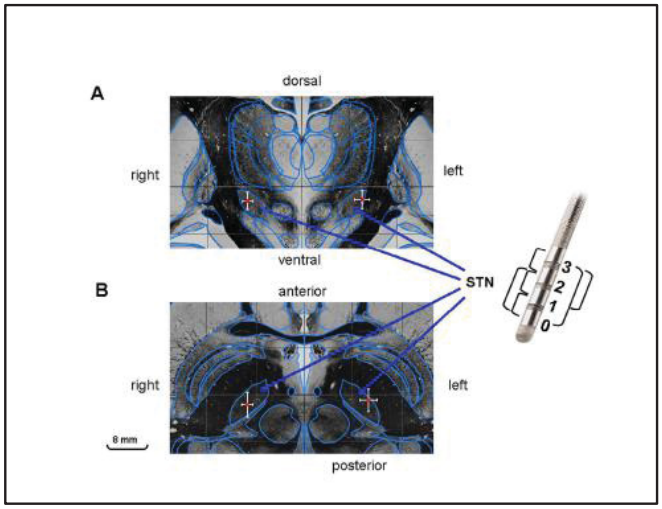

Abbildung 13: Illustration der anatomischen Lokalisation, von der bilaterale subthalamische lokale Feldpotentiale abgeleitet wurden. Der rote Punkt (weißes Kreuz: Standardabweichung) markiert die mittlere Ableitposition der bipolar referenzierten Kontakte (0-1,0-2,0-3,1-2,1-3 oder 2-3; rechts im Bild: Beispielelektrode). Koronare (A) und axiale (B) Schnitte aus dem Schaltenbrand Atlas (Schaltenbrand & Wahren, 1977) 3mm hinter dem midkommisuralen Punkt, bzw. 3,5 mm unter der Linie zwischen der anterioren und posterioren Kommissur. Blau umrandet sind relevante anatomische Strukturen, der STN ist markiert; aus: Wojtecki, et al. 2016b.

Die Aufgabe zur Exekutivfunktion für die Patienten bestand in einer formal-lexikalischen Wortgenerierungsaufgabe (siehe auch Abbildung 14). Passend zu einem dargebotenen Anfangsbuchstaben sollte in einem vorgegebenen Zeitschema ein passendes Wort zunächst in Gedanken generiert und später ausgesprochen werden. Die Aufgabe wurde in 80 Durchgängen (*trials*) durchlaufen. Ferner erfolgte eine Kontrollaufgabe mit 80 *trials*, die das stereotype Generieren des Wortes „Pause“ beinhaltete. Die elektrophysiologischen Signale wurden einer normalisierten, *baseline*-korrigierten, stimulusinduzierten Wavelet-Power-Analyse unterzogen. Die über die *trials* und alle STN gemittelten Daten (*grand averages*) sind in Abbildung 14 dargestellt. Es zeigte sich tatsächlich im Vergleich zu der Kontrollaufgabe eine Erhöhung der lokalen Alpha-Theta-Aktivität im STN. Die Stärke der Aktivierung korrelierte ferner mit der Task-Performanz. Weiterhin zeigte sich in einer Kohärenzanalyse eine verstärkte Alpha-Theta-Kopplung des STN zum Oberflächen-EEG frontal gelegener Kanäle während der Wortgenerierung (Wojtecki et al., 2016b). Die Schlussfolgerung aus dieser experimentellen neurophysiologischen Untersuchung ist, dass der STN und frontale kortikale Areale bei

der exekutiven Kontrolle von Sprache eine funktionelle Rolle spielen. Hierbei scheinen, entsprechend der Darstellung in Abschnitt 0, lokale und *long-range* Synchronisationen niederfrequent oszillierender neuronaler Cluster eine Rolle zu spielen. Die in Abschnitt 2.1.1 dargestellten klinischen Effekte von niederfrequenter Stimulation des STN auf die Wortflüssigkeit werden somit vermutlich durch Aktivierung entsprechender Alpha-Theta-Oszillationen in assoziativen STN-Subarealen vermittelt. Die Alpha-Theta-Oszillationen können als rhythmische Signatur zum *gating* des adäquaten Verhaltens über ein subthalamisch-präfrontales Netzwerk verstanden werden.

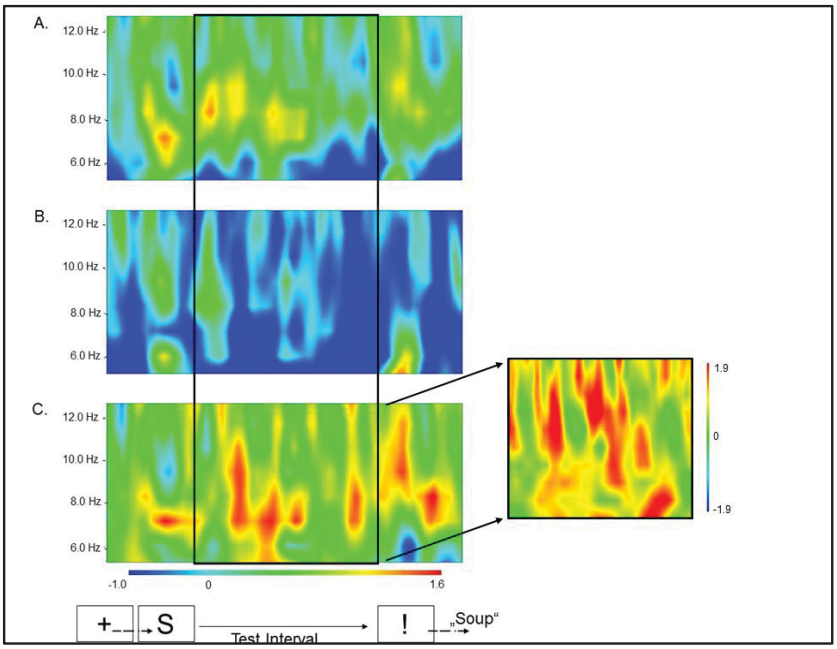

Abbildung 14: Temporäre Aktivierungsunterschiede im STN während der Durchführung einer formal- lexikalischen Wortgenerierungsaufgabe. Zeit-Frequenz-Plot mit Zeit auf der x-Achse und Frequenz in Hertz (Hz) auf der y-Achse und farbskalierter relativer *wavelet*-Power (Unit Skala) des *grand averages* aus 16 linksseitigen STN. Die Pfeile zeigen zudem t-Werte des statistischen Vergleichs der Aufgaben im Testintervall. A: Aktivierung bei der Wortgenerierungsaufgabe: Der Ablauf der Aufgabe ist unten dargestellt. Im Testintervall (schwarzer Rahmen) soll passend zu einem auf dem Monitor vorher dargestellten Anfangsbuchstaben (Beispiel: „S“) ein Wort in Gedanken generiert und nach dem dargestellten Ausrufezeichen laut ausgesprochen werden. B: Kontrollaufgabe bestehend aus stereotyper Generierung des Wortes „Pause“ mit gleichem Zeitablauf. C: Differenz aus A und B. Sichtbar wird ein aufgabenspezifischer Aktivierungsunterschied relativ zur Baseline (vor Zeitpunkt 0) mit erhöhter Power im Bereich 6-12 Hz; aus: Wojtecki, et al. 2016b.

2.2.2 Somatosensorische Verarbeitung (bei Dystonie)

Wie oben dargelegt, wird die Tiefe Hirnstimulation des Globus pallidus internus (GPi) zur Behandlung dystoner Syndrome eingesetzt.

Für verschiedene Formen der Dystonie liegen bereits zahlreiche Publikationen zu invasiven Ableitungen von LFP aus dem GPi vor. Im Zusammenhang mit den oben bei M. Parkinson ausgeführten Erkenntnissen zu niederfrequenten Oszillationen ist der Umstand interessant, dass bei der Dystonie (pathologische) pallidale Alpha-Theta-Aktivität gefunden wird, welche durch THS supprimiert wird (Barow et al., 2014). Eine eigene Arbeit untersuchte daher niederfrequente Aktivität im GPi (n=18) bei verschieden Formen der Dystonie (Trenado et al., 2016). Anders als bei der Arbeit in Abschnitt 2.2.1 wurden nicht postoperativ LFP von der THS-Elektrode abgleitet, sondern die Signale wurden bereits intraoperativ aufgezeichnet. Durch die in der Einleitung dargelegte Ableitung über die *Makrotips* von fünf konzentrisch positionierten Elektroden (Trajekten) erlaubte diese Methode Aussagen über die räumliche Verteilung der oszillatorischen Aktivität. Ferner wurde ein Vergleich der neuronalen Aktivität zwischen zwei verschieden Formen der Dystonie (zervikale versus tardive Dystonie) und zwischen Patienten in Lokalanästhesie versus Vollnarkose vorgenommen. Herauszuheben im Zusammenhang dieser Habilitationsschrift ist aber besonders der vorgenommene Vergleich der GPi-Aktivität zwischen 2 Minuten Ruheableitung und 2 Minuten sensorischer Stimulation der kontralateralen Handfläche (*sensory palmar stimulation*; SPS) mittels eines Stofftupfers. Ausgewertet wurde die *Fast Fourier transformierte* (FFT) *power spectral density* (PSD) der LFP.

Bei beiden Krankheitsentitäten zeigte sich auf allen Trajekten (mit Betonung des zentralen Trajekts) prominente Theta-Delta-Aktivität aber auch Alpha- und Beta-Aktivität. Insbesondere bei der zervikalen Dystonie zeigte sich unter SPS eine signifikante ($p<0.05$) Verlangsamung und Verringerung der Power der Theta-Delta Aktivität (Abbildung 15). Die weitere Analyse der *grand averages* über alle Trajekte zeigte, dass neben der signifikanten Modulation im Theta-Delta Band ein statistischer Trend ($p=0.88$) hinsichtlich der Alpha-Theta-Modulation zu finden war (Trenado et al., 2016). Kritisch diskutiert werden sollte die kleine Stichprobe der einzelnen Patientengruppen. Dennoch ergab die

Studie Hinweise auf die Rolle der niederfrequenten Oszillationen bei der somatosensorischen Verarbeitung im GPi. Die Veränderung der lokalen GPi-Aktivität durch SPS könnte indes ein neuronales Korrelat der sogenannten *gèste antagoniste* sein. Hierbei handelt es sich um ein, insbesondere bei der zervikalen Dystonie auftretendes, klinisches Phänomen, bei dem sich bereits durch leichte sensorische Selbst-Berührung der Haut über einem dystonen Körperareal die dystone Symptomatik verringert. Weitere Ableitungen vom GPi während dystoner Symptome und Applikation sensorischer Reize an verschiedenen Körperarealen sind zur weiteren Klärung des Kausalzusammenhangs und einer etwaigen somatotopen Gliederung in Zukunft notwendig.

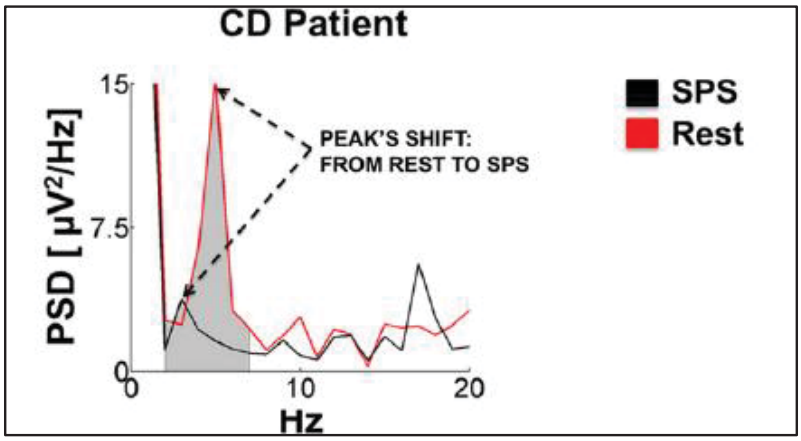

Abbildung 15: Veränderung der LFP-Aktivität (PSD: *power spectral density*) im GPi eines Patienten mit zervikaler Dystonie (CD) für das auf der x-Achse gezeigte Frequenzband bis 20 Hz. Rot: Ruheableitung, schwarz: sensorische palmare Stimulation (SPS). Sichtbar ist eine Verschiebung des Peaks im Theta-Delta-Band durch sensorische Stimulation; Teil einer Abbildung aus: Trenado, […] und Wojtecki, 2016.

2.2.2 Emotional-kognitive Sprachverarbeitung (bei chronischer Bewusstseinsstörung)

In seltenen Fällen wird die THS zur Behandlung irreversibler (Wach-)Komazustände (*chronic disorders of consciousness*, DOC) eingesetzt. Erste Daten deuten auf eine messbare Verhaltensaktivierung durch THS hin (Schiff et al., 2007). Aufgrund der multiplen Projektionen zum Kortex und seiner generellen *gating* Funktion für *arousal* und sensorischen Input dient meist der zentrale, unspezifische Thalamus (CT) als Zielpunkt der THS bei DOC. In einer eigenen Arbeit wurden LFP aus dem CT bei DOC untersucht

(Wojtecki et al., 2014). Es sollte der Frage nachgegangen werden, ob sich, trotz nach außen kaum wahrnehmbarer Interaktion eines Menschen im *minimally conscious state,* stimulusspezifische elektrophysiologische Reaktionen aus dem Thalamus ableiten lassen, die auf kognitive und oder emotionale Verarbeitung schließen lassen. Es wurden LFP bilateral aus dem Nucleus reticularis thalami und der internen medullären Lamina kombiniert mit Oberflächen-EEG abgeleitet (Abbildung 16).

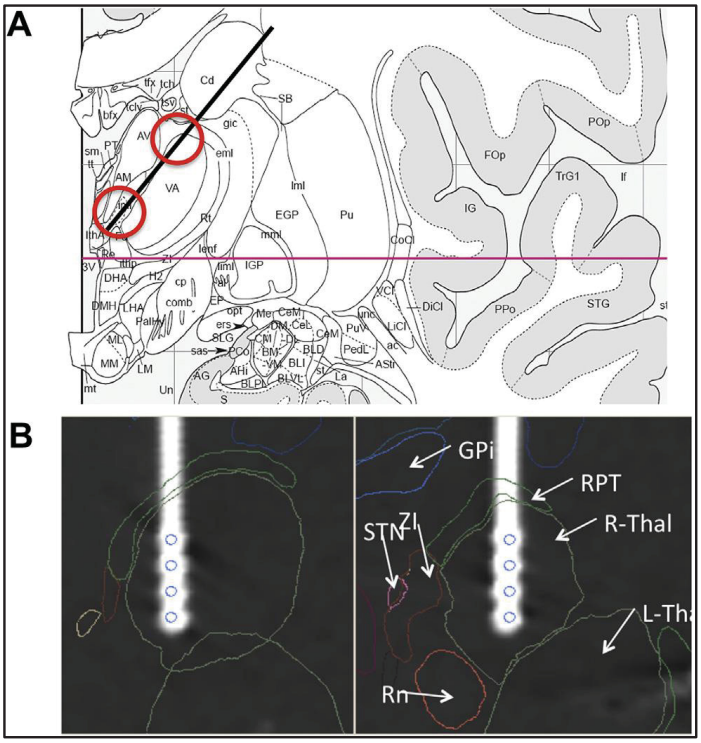

Abbildung 16: Anatomische Lokalisation der Elektroden bei Ableitung aus dem zentralen Thalamus bei *chronic disorder of consiousness* (DOC). A: Geplante Trajektorie (schwarze Linie) projiziert auf einen anatomischen Atlas (Mai et al., 2004), Sektion 30, koronar, 10,7 mm hinter der anterioren Kommissur (rote Linie verbindet anteriore und posteriore Kommissur). Rote Kreise zeigen die angestrebten Zielpunkte entlang der Elektrode. iml= interne medulläre Lamina des Thalamus, Rt= retikulärer Thalamus, VA= venteroanteriorer Thalamus, AV=anteroventraler Thalamus, AM= anteromedialer Thalamus, Fa= Nucleus fasziculosus, IthA= Adhäsio interthalamica. B: Finale Elektrode im zentralen Thalamus im 3D-Atlas (Yelnik et al., 2007). Zwei orthogonale Schichten entlang der Achse der rechten Elektrode nach Co-Registrierung des Atlas mit postoperativem CT. Die vier Kontakte der Elektrode (blaue Kreise) liegen im rechten Thalamus (R-Thal). ZI= Zona incerta, RPT= retikulärer perithalamischer Nucleus, RN= Nuclues ruber; aus: Wojtecki, et al. 2014

Bei der Patientin handelte es sich um eine 45 Jahre alte Frau, die sich sieben Jahre zuvor eine rechtshemisphärische traumatische intrazerebrale Blutung zugezogen hatte und sich

seither in einem chronischen DOC Zustand befand. Bis auf motorische Stereotypen waren weder gerichtete motorische Aktionen, noch sichtbare Reaktionen auf Stimuli aus der Außenwelt vorhanden. In einer Untersuchung mittels funktioneller Kernspintomographie (fMRT) konnte aber gezeigt werden, dass sich bei der Patientin durch auditorisches Stimulusmaterial sowohl Sprecher-spezifische (emotionale) als auch inhaltsspezifische (kognitive) reaktive Veränderungen der kortikalen (z.B. superiorer temporaler Sulcus) und subkortikalen (z.B. Amygdala) Hirnaktivität auslösen ließen (Eickhoff et al., 2008). Entsprechend wurde das Stimulusmaterial aus der fMRT–Studie angepasst, um für elektrophysiologische Ableitungen aus dem Thalamus geeignet zu sein. Konkret handelte es sich um bilateral über Kopfhörer über die Dauer von jeweils vier Sekunden blockweise in je 80 Durchgängen (*trials*) dargebotene Stimmen der Kinder der Patientin, die die Patientin direkt ansprachen. Diese wurden kontrastiert zu nicht-familiären, nicht-direkt die Patienten ansprechende Stimmen. Die während der Aufgabe aufgenommen LFP-Signale wurden einer *stimulus-locked wavelet* Zeit-Frequenzanalyse unterzogen und mit verschiedenen Mittellungs- und statistischen Verfahren (z.B. *cluster-based randomization*) zum Vergleich zwischen den beiden Bedingungen untersucht. Ferner wurde die thalamokortikale Kohärenz berechnet, um die Kopplung der lokalen Signale des Thalamus mit Regionen der Hirnoberfläche zu berechnen. Entsprechend der in der Einleitung, insbesondere in Abbildung 1 dargelegten Tatsache, dass neuronale Oszillatoren auch eine Synchronisation zwischen zwei Frequenzbändern aufbauen können, wurde zudem eine *cross-frequency* Analyse (*phase amplitude coupling*) durchgeführt. Insbesondere ist von Interesse, ob lokale Gamma-Oszillationen bei Prozessen der bewussten Verarbeitung an Theta-Oszillationen gekoppelt sind, die eine Kommunikation mit anderen neuronalen Clustern über weitere Strecken des Gehirns ermöglichen. Die Ergebnisse der lokalen Oszillationen zeigten tatsächlich, dass sich im zentralen Thalamus eine stimulusspezifische (durch emotional-adressierende Stimmen) Erhöhung der Theta-Aktivität, aber auch eine Modulation der Gamma-Aktivität fand (Abbildung 17). Die lokale thalamische Theta-Aktivität zeigte zudem eine stimulusspezifische Kopplung zum Oberflächen-EEG und es ließ sich eine signifikante *cross-frequency* Kopplung zwischen thalamischer Theta-Phase und Gamma-Amplitude darstellen (Wojtecki et al., 2014).

Die Arbeit zeigt am Beispiel der DOC die Rolle der subkortikalen, niederfrequenten

Oszillationen bei der Verarbeitung emotionaler und kognitiv relevanter Reize. Darüber hinaus ergeben sich aus der Arbeit möglicherweise neue Erkenntnisse zur klinischen Einschätzung von Koma-Fällen mittels elektrophysiologischer Zusatzdiagnostik. Eine direkte elektrophysiologische Aktivität aus dem Thalamus bei bewusstseinsgestörten Patienten als Antwort auf emotionale Reize ist bisher noch nicht aufgezeichnet worden. Der Nachweis elektrischer Signale aus dem Thalamus auf emotionale Reize könnte als klinischer Marker bei chronisch bewusstseinsgestörten Patienten dienen. Die THS kann perspektivisch zu einer differenzierteren Einschätzung des individuellen Zustands von Komapatienten und möglicherweise auch zur Entwicklung therapeutischer Ansatzpunkte beitragen.

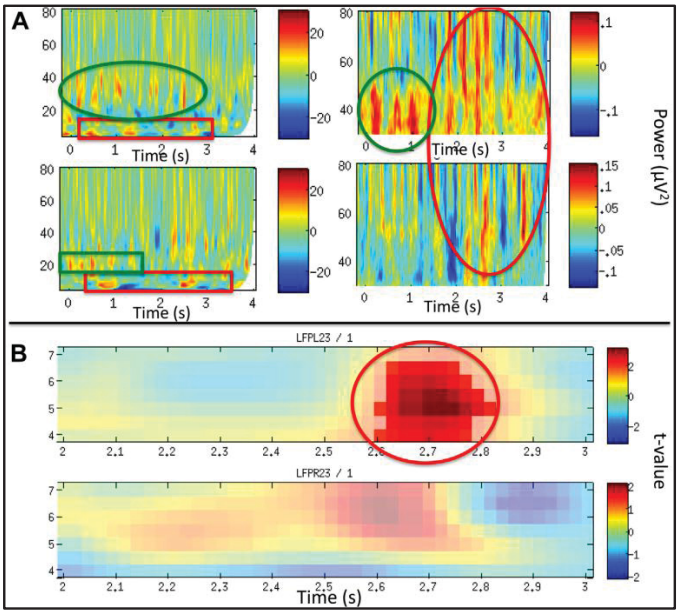

Abbildung 17: Lokale Powerveränderungen im zentralen Thalamus einer bewusstlosen Patientin während akustischer Ansprache über 4 Sekunden durch familiäre Stimmen. Obere Reihe jeweils linksseitige Elektrode, untere Reihe jeweils rechtsseitige Elektrode. A: Power Veränderungen im Vergleich zur Baseline. Zeit-Frequenz-Plot mit Zeit in Sekunden auf der x-Achse, Frequenz in Hertz (Hz) auf der y-Achse und farbskalierter Power in Mikrovolt zum Quadrat (links: breites Frequenzspektrum 5-80 Hz, rechts: nur Gamma-Band). Neben einem Anstieg der Beta-Aktivität innerhalb der ersten Sekunde (grüne Box) findet sich eine frühe und späte Theta-Modulation (rote Box). Gamma-Aktivität um 40 Hz (grüner Kreis/Ellipse) wird gefolgt von einer breiteren Gamma-Aktivität bis zu 80 Hz. B: Statistischer Kontrast zwischen der Darbietung familiärer und direkt die Patientin ansprechender Stimmen und neutraler, nicht-ansprechender Stimmen. Farbkodiert hier sind t-Werte. Auf der linken Elektrode (obere Reihe) zeigt sich bei familiär-ansprechenden Stimmen eine signifikant (p=0.048) verstärkte Theta-Aktivität um 4-6,5 Hz bei Sekunde 2,6 bis 2,8; aus: Wojtecki, et al. 2014

3 Schlussfolgerungen und Ausblick

In den vorgelegten Arbeiten wurde einerseits die Gehirnaktivität durch THS moduliert und das daraus resultierende Verhalten untersucht, andererseits wurde das Verhalten oder der sensorische *Input* mit verschiedenen Paradigmen moduliert und die daraus resultierende Veränderung lokaler neuronaler Aktivität gemessen. Diese Untersuchungen neurophysiologischer Korrelate sensorischer, kognitiver und emotionaler Funktionen der Basalganglien unterstreichen die Ansicht, dass das Netzwerk von Basalganglien, Thalamus und Kortex eine wichtige Instanz zur Modulation von Verhalten darstellt. Dabei integrieren die Basalganglien sensorische Information und justieren den behavioralen *Output.*

Als Ausblick für die Zukunft scheinen auf Grundlage der eigenen Arbeiten drei Punkte von Relevanz:

1) Therapeutische Nutzung der selektiven Modulation nicht-motorischer Netzwerke: Da gezeigt wurde, dass sich motorische und nicht-motorische Netzwerke hinsichtlich ihrer oszillatorischen Signatur unterscheiden, sollte gezielt angestrebt werden, simultan Unternetzwerke durch eigene Stimulationseinstellungen zu beeinflussen.
2) Weitere Charakterisierung der funktionellen Verbindungen der Basalganglien mit kortikalen Arealen: Methodisch lassen sich die in dieser Arbeit genutzten LFP optimieren, indem sie mit Vielkanal-EEG oder MEG kombiniert werden. Dabei sollten kluge experimentelle Paradigmen eingesetzt werden um auch die Rolle spezifischer Frequenzbänder neuronaler Oszillationen bei nicht-motorischen Funktionen zu charakterisieren.
3) Therapeutische Translation von relevanten Oszillationen in *closed-loop devices:* Das langfristige Ziel ist die Identifikation von elektrophysiologischen Korrelaten nicht-motorischer Funktionen inklusive *state marker*, auf die automatisierte Schrittmacher direkt und selektiv reagieren können.

Für die drei genannten Punkte bieten rezente technische Entwicklungen wie individualisierte Programmieroptionen, nicht-magnetische Extensionen und *sensing devices* (Vesper & Slotty, 2014) eine gute Grundlage für weitere Untersuchungen.

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Danksagung

Mein Dank gilt Prof. Dr. Volker Sturm für die Inspiration und den Einblick in die Welt der Tiefen Hirnstimulation bereits während der Promotion. Ich danke Prof. Dr. Hans-Peter Hartung für die Ausbildung in seiner Klinik und für den geschaffenen Freiraum für Forschung, verbunden mit dem hierfür ausgezeichneten und liberalen Arbeitsklima. Ganz besonderer Dank gilt Prof. Dr. Alfons Schnitzler für die langjährige Unterstützung in Klinik und Forschung, sowie für die gezielte Förderung. Er war und ist mir ein großes Vorbild darin, wissenschaftlichen Ehrgeiz und die notwendige Genauigkeit bis zum letzten Detail mit ehrlichem und tiefem Interesse für die Sache selbst zu verbinden. Prof. Dr. Jan Vesper danke ich für die Geduld im Operationssaal und für Unterstützung, Rat und Begleitung außerhalb dessen. Wissenschaft ist Teamarbeit. Daher bedanke ich mich bei allen beteiligten Kolleginnen und Kollegen, ohne die diese Arbeit nicht möglich gewesen wäre. Aus der Zusammenarbeit sind Freundschaften gewachsen. Herausheben möchte ich Herrn Professor Dr. Lars Timmermann, mit dem ich zusammen eine besondere Aufbruchsstimmung zu Beginn meiner Tätigkeit beim Aufbau des neuen THS-Teams in Düsseldorf erleben durfte, und Prof. Dr. M. Südmeyer, der mit mir Höhen und Tiefen der klinischen und wissenschaftlichen Karriere durchlebt hat. Schließlich gilt ein ganz besonderer Dank meinen Freunden und meiner Familie, vor allem meiner Frau, für die Begleitung auf dem gesamten Weg von den ersten Schritten in der Klinik bis heute. Dank ist auch angebracht für das Ertragen der häufig missglückten *work-life balance*.

The Rest is Noise.

In dieser Habilitationsschrift zusammengefasste Originalarbeiten

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ORIGINAL CONTRIBUTION

Frequency-Dependent Reciprocal Modulation of Verbal Fluency and Motor Functions in Subthalamic Deep Brain Stimulation

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Background: High-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) improves motor functions in those with Parkinson disease but may worsen frontal functions such as verbal fluency (VF). In contrast, low-frequency DBS leads to deterioration of motor functions. It is not known whether low-frequency STN DBS also has an effect on frontal functions.

Objective: To examine whether low-frequency STN DBS in contrast to high-frequency STN DBS has a positive effect on frontal functions on the basis of VF test results.

Design: A double-blind randomized crossover experiment to compare performance in 4 VF subtests and motor performance at 10 Hz, 130 Hz, and no stimulation.

Setting: University hospitals in Düsseldorf and Cologne, Germany.

Patients: Twelve patients with Parkinson disease 3 months or more after bilateral electrode implantation into the STN.

Main Outcome Measure: Mean number of words in VF at different stimulation frequencies.

Results: The VF was significantly better at 10 Hz (48.3 words) compared with 130 Hz and showed a nonsignificant trend toward worsening at 130 Hz (42.3 words) compared with no stimulation (43.8 words). These results were consistent across all subtests.

Conclusions: The study provides evidence of a beneficial effect of low-frequency (10 Hz) STN DBS on VF, which may be caused by activating neural pathways projecting to the frontal cortex. In addition, the study reproduces the negative effect of therapeutic high-frequency STN DBS on VF. The study results provide evidence for a frequency-dependent modulation of cognitive circuits involving the STN.

Arch Neurol. 2006;63:1273-1276

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HIGH-FREQUENCY (HF) DEEP brain stimulation (DBS) of the subthalamic nucleus (STN) at frequencies of about 130 Hz is a successful treatment of motor symptoms of Parkinson disease (PD).[1] However, some results from recent studies suggest that this therapeutic stimulation can have a subclinical negative effect on frontal functions such as verbal fluency (VF).[2] The involvement of the basal ganglia in nonmotor functions is supported by a model that suggests a connection to limbic and prefrontal areas.[3]

In contrast to HF STN DBS, low-frequency (LF) STN DBS of about 10 Hz can worsen motor functions.[4] Furthermore, a 10-Hz pathologic oscillatory cerebral network is associated with PD tremor.[5] This hypothesis, based on noninvasive measurements in patients with PD, is supported by intraoperative recordings in the human STN that provide evidence for pathologic synchronization at tremor frequency and around 10 Hz.[6]

There is evidence that HF STN DBS leads to improved motor functions and worsened frontal functions but that 10-Hz LF STN DBS leads to deterioration of motor functions, possibly because of enhancement of pathologic synchronization within the basal ganglia loop in patients with PD. We compared VF in patients with PD during STN stimulation at 10 Hz, at 130 Hz, and without stimulation to examine whether, in contrast to

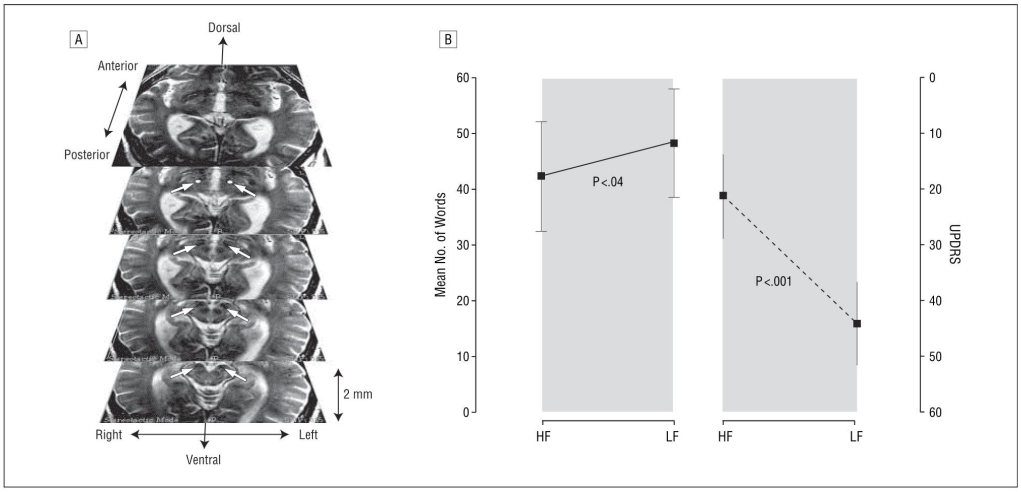

Figure. Mean stimulation position, verbal fluency, and motor performance. A, Mean position of active poles (white dots) on axial T2 magnetic resonance images in the dorsal part of the subthalamic nucleus (white arrows). B, Mean number of words and motor score of the Unified Parkinson's Disease Rating Scale (UPDRS) across all subjects and subtests; verbal fluency was significantly better during low-frequency (LF) stimulation, but motor functions deteriorated. The effects were the opposite with high-frequency (HF) stimulation.

Table 1. Patient Characteristics and Stimulation Parameters*

Patient/ Sex/Age, y	Disease Type	No. of Months Since Implant	Volts		Microseconds		Hertz		Pole	
			Left	Right	Left	Right	Left	Right	Left	Right
1/M/69	HR	36	3.5	3.3	60	60	160	130	1	1
2/M/76	HR	45	2.0	2.8	60	60	185	185	1	1
3/M/63	HR	51	3.1	3.5	60	60	130	160	1	2
4/M/64	T	3	3.2	3.2	60	60	150	150	1	1
5/F/73	HR	39	3.6	2.9	90	90	160	160	2	0
6/M/63	HR	36	3.5	3.6	60	60	185	160	3	2
7/M/61	T	28	4.5	3.5	90	120	130	130	2	2
8/M/64	HR	4	3.5	3.5	60	60	160	160	2	2
9/F/63	T	6	2.5	2.1	60	60	185	185	1	1
10/M/62	HR	14	3.2	1.6	90	60	130	130	2	2
11/M/57	HR	50	3.5	2.9	90	60	160	130	2	1 and 2
12/F/53	HR	21	4.5	2.9	60	60	150	150	1	1

Abbreviations: HR, hypokinetic-rigid; T, tremor dominant.
*Patient characteristics and stimulation parameters used for long-term stimulation and active stimulation pole (monopolar, with impulse generator used as anode) for each hemisphere.

HF STN DBS, there is a positive effect of 10-Hz LF STN DBS on frontal functions suggesting opposite functional consequences of STN stimulation on the basal ganglia cognitive and motor circuit.

METHODS

We used a double-blind randomized crossover method in 12 patients with PD who were selected from consecutive routine visits at the University hospitals in Düsseldorf and Cologne, Germany. They underwent examination at least 3 months (mean, 28 months; range 3-51 months) after bilateral stereotactic implantation of STN electrodes (model 3389; Medtronic, Minneapolis, Minn). All patients gave informed consent according to the Declaration of Helsinki.

To localize active poles used for long-term stimulation, we reimported intraoperative stereotactic radiographs or postoperative computed tomographic scans into the stereotactic planning system. Mean active pole position relative to the line between the anterior-posterior commissure was calculated, spatially normalized, and visualized at magnetic resonance imaging (**Figure**, A).

Testing was performed within 1 day after overnight withdrawal from dopaminergic medication. Stimulation was changed randomly among no stimulation (off), HF stimulation at 130 Hz or more, and LF stimulation at 10 Hz. Stimulation was kept constant with respect to the pulse width, voltage, and stimulation pole that had produced the best antiparkinsonian response during long-term stimulation (**Table 1**).

Five minutes after each change of the stimulation condition, motor functions were scored by using the motor score of

the Unified Parkinson's Disease Rating Scale under double-blinded conditions. A further 10 minutes later, 4 different VF tests were each performed for 1 minute.

In the formal lexical test, patients were asked to produce words beginning with a particular letter. In a second test, patients had to produce words of a certain semantic category, such as animals. These tests for divergent thinking emphasize the creativity of search strategies. Two other tests were categorical change subtests of each of the first 2 tests with stronger emphasis on flexibility functions. In the formal lexical category change test, patients were asked to switch between 2 different letters (eg, a word beginning with *H* and then a word beginning with *T*) and finally were given a semantic category change test in which they were asked to switch between semantic categories (eg, furniture and tools). Three parallel test versions were used for each stimulation condition to avoid learning effects.

Parallel test versions of the 4 subtests, formal lexical, semantic category, formal lexical category change, and semantic category change, were A: words with *P*, animals, words with *H*, then words with *T*, clothes and flowers; B: words with *M*, food, words with *D*, then words with *U*, furniture and tools; and C: words with *S*, first name, words with *G*, then words with R, sports and fruit. Two patients were tested in the following sequence: parallel test A at 10 Hz, parallel test B at 130 Hz, and parallel test C with no stimulation. Two patients were tested in the following sequence: A at 10 Hz, B in the off condition, C at 130 Hz, and so on.

After testing was completed in all 12 patients, every combination of stimulation frequency and test version had been randomly used twice. This randomly changed testing sequence helped to avoid potential systematic carryover effects of stimulation on fluency results. Because the raw number of words can neither interindividually nor intraindividually be compared because of different word frequencies of the parallel tests in everyday language, mean values were computed after testing all subjects and all conditions. Motor scores and VF scores were analyzed statistically by using the distribution-free Wilcoxon test for nonnormal samples.

RESULTS

The active pole was located in the STN in most cases; however, 2 left-sided poles were located in the zona incerta. The spatially normalized mean (SD) position of the active stimulation pole at the right hemisphere was as follows: 11.1 mm (1.2 mm) lateral to the anterior-posterior commissure line (x-axis), 1.0 mm (1.9 mm) behind the middle of the anterior-posterior commissure line (y-axis), and 0.7 mm (3.0 mm) below the anterior-posterior commissure line (z-axis). Coordinates for the left hemisphere correspondingly were as follows: x-axis, 11.2 mm (1.4 mm); y-axis, 0.8 mm (1.9 mm); and z-axis, 0.5 mm (2.4 mm). Altogether, the mean stimulation position was in the anterior-dorsal part of the subthalamic area (Figure, A).

All patients had mean (SD) Unified Parkinson's Disease Rating Scale motor scores in the pathologic range with no stimulation (43 [13.3]) and mean (SD) Unified Parkinson's Disease Rating Scale scores that were highly improved during HF stimulation (22.1 [7.5]); the worst scores were during LF stimulation, (44.9 [11.6]). The difference between HF and LF was highly significant ($P<.001$) (Figure, B). Reciprocally, across all subjects and subtests, mean VF (mean number of words [SD]) was significantly better ($P=.04$) during LF stimulation (48.3 [9.7]) compared with HF stimulation (42.3 [11.1]) (Figure, B). Furthermore, VF showed a nonsignificant trend to improve during LF stimulation and worsen during HF stimulation compared with no stimulation: 43.8 (9.6). Each subtest taken alone showed the same trend: VF was best during LF stimulation followed by no stimulation; HF stimulation showed the worst results in all subtests. However, these differences in the subtests were not significant (**Table 2**).

Table 2. Verbal Fluency Performance in the Subtests*

Subtest	Off	130 Hz	10 Hz
Formal lexical	10.1 (4.3)	9.1 (4.9)	10.3 (3.2)
Formal lexical category change	7.8 (3.8)	7.6 (3.8)	9.3 (3.3)
Semantic categorical	14.9 (3.8)	14.8 (3.4)	16.7 (3.9)
Semantic category change	11.1 (2.2)	10.8 (1.7)	12.1 (3.0)

*Data are given as mean (SD) number of words in verbal fluency subtests during different stimulation frequencies. All subtests showed best verbal fluency performance during stimulation with 10 Hz and worst performance during stimulation with 130 Hz.

COMMENT

Comparing therapeutic HF STN DBS with no stimulation, the present study reproduces the negative trend of HF STN DBS on VF while improving motor functions. The effect of HF STN DBS on VF has been shown in several studies, whereas some studies failed to do so.[2] Results of imaging studies suggest that HF STN DBS may worsen VF by deactivating the left inferior frontal gyrus[7] by affecting the striatothalamocortical circuits. A current basal ganglia model supports this view, showing pathways from the basal ganglia through the ventral dorsomedial thalamus to different prefrontal areas.[3] Imaging data also show that motor improvement by HF STN DBS is connected with motor-related facilitation of premotor areas.[8]

Comparing LF (10 Hz) STN DBS with no stimulation, the present study reveals the positive influence of LF stimulation on VF while worsening motor functions. Although this effect was not significant, the direct comparison of LF stimulation at 10 Hz with HF stimulation provides evidence for a reciprocal, highly significant, frequency-dependent modulation of VF and motor functions. The positive VF effect of LF STN DBS may be caused by activating neural pathways projecting to the inferior frontal cortex, whereas motor dysfunction is supposed to be caused by aggravation of pathologic synchronization in an oscillatory network,[4] which was described in a magnetoencephalography study in patients with PD tremor.[5]

Results from a recent positron emission tomography study of thalamic DBS for essential tremor[9] showed that DBS has more than a blocking effect and also allows a gradual tuning of neuronal activity within functional circuits. To our knowledge, the present study results provide the first evidence of the possibility of frequency-dependent tuning of cognitive circuits interconnected with the STN. The functional relevance of neural activity in

the 10-Hz domain for cognitive functions is supported by findings of enhancing cognitive performance by means of repetitive transcranial magnetic stimulation at α frequency.[10] Deep brain stimulation of the STN at 10 Hz obviously has an inhibitory effect on the motor circuit and a facilitatory effect on the cognitive circuit.

The exact mechanisms and structures underlying the network of frontal functions as tested by means of VF remain to be determined. For motor control in this study, the STN was not stimulated mainly in the medial-ventral cognitive part; however, more ventral stimulation might lead to a more significant VF effect and might also help to explain differential aspects of the VF subtests, which showed a homogenous trend toward improvement with LF DBS but failed to reach significance.

Besides electrode localization, other factors might influence the results. We controlled for training effects on VF by using different parallel test versions. In addition, we balanced the order of tests across subjects. From the results of this study, we cannot answer the question of how the implantation procedure per se affected VF because patients were tested only after surgery. Generally, systematic investigations on the implantation effect comparing preoperative with postoperative (within 3 months) VF with no stimulation are rare. A comparison in 3 cases was inconclusive.[11] Study results in patients undergoing subthalamotomy have demonstrated no significant decrease in VF 3 to 12 months postoperatively.[12] Thus, it is most likely that VF effects 3 or more months after STN electrode implantation are attributable to the electrical stimulation.

In summary, this study provides the first evidence of frequency-dependent differential effects of STN stimulation on frontal functions such as VF. This finding supports the hypothesis that the STN is part of a segregated cognitive network that can be modulated in a way opposite to that of the motor network.

Accepted for Publication: April 4, 2006.
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Funding/Support: This study was supported by grant J/73240 from the Volkswagen Stiftung.
Acknowledgment: We thank the patients for their excellent cooperation during the study.

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Movement Disorders
Vol. 22, No. 9, 2007, pp. 1314–1361

Brief Reports

Pathological Crying Induced by Deep Brain Stimulation

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Video 

Abstract: **Pathological crying (PLC)—an affective gesture without any or an adequate emotion—occurs with various diseases. A recent theory suggests that PLC is caused by a disruption of higher order cortical association areas from the cerebellum which computes profiles of psychomotor responses. We report a patient with Parkinson's disease who developed PLC during stimulation of the subthalamic nucleus (STN) predominantly of the right hemisphere. Positron emission tomography imaging showed thalamo-ponto-cerebellar activation during such stimulation. These findings indicate that the STN and possibly also ponto-cerebellar pathways are involved in psychomotor control and in the modulation of PLC.** © 2007 Movement Disorder Society

Key words: deep brain stimulation; Parkinson's disease; pathological crying; subthalamic nucleus; positron emission tomography

The impact of deep brain stimulation (DBS) of the subthalamic nucleus (STN) on emotional functions is poorly understood. Clinical observations showed a variety of emotional effects.[3–7] However, pathological crying (PLC) —a phenomenon of incontinence of affect without an adequate subjective feeling—induced by DBS has only once been reported.[8] PLC can occur with brain lesions and neurodegenerative disorders.[9] A theory suggests that PLC is caused by disruption of higher order cortical association areas from the cerebellum, which computes profiles of psychomotor responses.[10] We report clinical and positron emission tomography (PET) activation results of a PD patient who developed PLC during stimulation of the STN.

CASE REPORT

A 69-year-old man with advanced PD underwent bilateral STN implantation. Postoperatively, medication had been reduced from 900 mg of levodopa, 4 mg of lisuride, and 450 mg of amantadine to 300 mg of L-dopa, and 2 mg of cabergoline. The 3-year follow-up visit proved an excellent effect on motor functions (Unified Parkinson's Disease Rating Scale [UPDRS][11] Motor score: "*off*-medication/OFF-stimulation", 43; "*off*-medication/ON-stimulation", 9). Stimulation was monopolar at contact 1, 3.8 V, 90 μsec, 130 Hz (right) and 1, 2.5 V, 60 μsec, 130 Hz (left) and had been unchanged for 2 years. The patient had no symptoms of psychiatric disease, depression (Beck Depression Inventory [BDI], 4 points), cognitive deficits or dysexecutive syndromes (Behavioral Assessment of dysexecutive syndrome [BADS] total score, 13). However, he reported that short stereotypical uncontrollable episodes of crying without feeling sad had first started a few months before.

Clinical Examination

The phenomenon spontaneously took place between once a week and several times a day and more likely during emotional conversations. We systematically studied its occurrence in a double-blind randomized manner.

On medication, first we compared during a free conversation three blocks *on* and *off* stimulation using the above-mentioned stimulation parameters. Seven episodes of PLC occurred during a total of 15 minutes in the *on* but not during the *off*.

Second, for analysis of the electrode contact inducing PLC, we performed a semistandardized conversation with three "emotional" and "neutral" topics: Monopolar

This article includes supplementary video clips, available online at http://www.interscience.wiley.com/jpages/0885-3185/suppmat.

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Received 3 December 2005; Revised 24 August 2006; Accepted 24 August 2006

Published online 29 May 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21266

stimulation at every single electrode contact after another was kept constant with respect to pulse width and frequency but was increased in amplitude up to 5 volts or the threshold of side effects and applied for 5 minutes. PLC occurred most frequently using ventral contacts in the right STN and talking about emotional topics.

Structural Imaging

Magnetic resonance imaging (MRI) slices with superimposed electrode localization from computed tomography scans showed that electrodes were located in the STN. Additionally, an MRI at the 3-year follow-up visit showed T2-hyperintense signal changes in the midbrain posteroventral to the electrode artefacts.

PET Data Acquisition

Contacts in the right STN predominantly induced PLC, so we activated serially two contacts during PET scanning for stimulation effects on different parts of this STN: contact 1 for the lower and 3 for the upper part. We compared monopolar stimulation of each of the two contacts with the OFF condition using voltage and pulse width that had induced PLC most consistently before (4.2 V, 90 μsec, 150 Hz). In a pseudorandomized block design, each of the three conditions was performed four times with a 5-minute interblock interval to change stimulation settings.

PET Results

The patient did not report PLC during the scanning, however, comparison of stimulation ON with OFF condition across both contacts revealed a significantly higher regional cerebral blood flow (rCBF; $P < 0.05$) during the ON in four areas of the left cerebellum and in the right thalamus. In addition to activation of the thalamus and cerebellum, calculation of contact 3 alone showed activation of the right pons. Calculation of contact 1 alone revealed no additional information in addition to activation of the thalamus (Fig. 1).

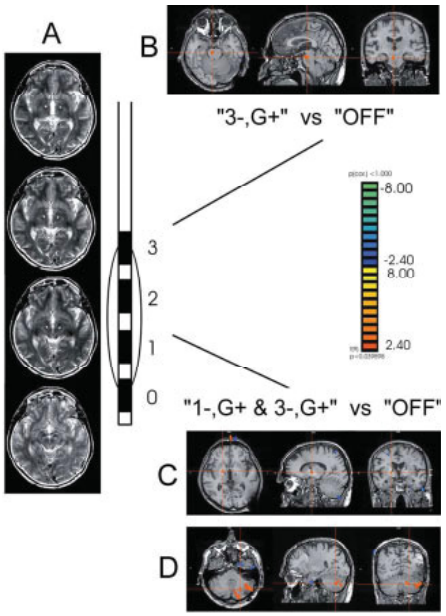

FIG. 1. Electrode localization and functional imaging data. **A:** Magnetic resonance imaging with superimposed computed tomography (contact 0 bottom) showing the right electrode located in the (predominantly lateral, sensorimotor) subthalamic nucleus (STN; hypointense). **C,D:** Calculation for monopolar stimulation of contact 1 and 3 together ("1−, G+ & 3−, G+" vs. OFF) revealed a significant higher regional cerebral blood flow (rCBF) compared to the OFF in the right thalamus (C) and in four left cerebellar areas (D). **B:** Calculation for contact 3 alone showed activation of the right pons. Color bar: *t* values for significant rCBF changes ($P < 0.05$). Talairach coordinates (*x*,*y*,*z*) of the center of gravity of the activation: C: (21, −8,1) D: (−46, −66, −56); (−23, −90, −49); (−56, −69, −46); (−27, −73, −42) B: (2, −24,−6). G, impulse generator. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

DISCUSSION

Emotional changes with STN simulation were reported so far due to two possible mechanisms: stimulation of the STN itself modulates its limbic connections or current spreads to neighboring structures such as lateral hypothalamus, ventral striatum, or nigrothalamic pathways influencing the prefrontal cortex via amygdala.[3–7]

PLC can occur by affections of the pons, thalamus, and around the third ventricle.[12] A theory[10] suggests that PLC is caused by disruption of higher association areas ("induction sites" including ventromedial prefrontal cortex, anterior cingulate, amygdala, ventral striatum) from the cerebellum, which computes profiles of psychomotor responses. Via pontine interconnections the cerebellum is proposed to project to "effector sites" (thalamus, hypothalamus, periaqueductal gray matter, motor cortex, cranial nerve nuclei).

We found stimulation-induced activation of the ipsilateral thalamus and pons and contralateral cerebellum. According to the above theory, two mechanisms could induce PLC. First, current spread of neighboring structures such as the internal capsule might functionally disrupt corticopontine pathways to the cerebellum, leading to cerebellar overactivity. That the patient had an excellent antiparkinsonian effect without clinical signs such as tonic limb contraction speaks against that mechanism. Second, stimulation of the STN itself might lead to thalamic and (retrograde) pontocerebellar activation, causing overactivation of the PLC modulatory circuit.

Furthermore, induction sites such as ventral striatum receiving projections from the STN could also be influenced by STN-DBS. STN-DBS can also activate prefrontal/parietal association cortices projecting to the cerebellum via the pontine nuclei[13] and enhance cerebellar activation.

As we used the same stimulation parameters in the scanner that had induced PLC in the conversation before, we suspect—even though the patient did not present PLC during the scan and the relation between activation pattern and PLC is not proven—that stimulation-induced activation shows the key structures in the modulatory PLC circuit. We assume if PLC took place in the scanner, activation of effector sites would occur. Discussing activation patterns, it is noteworthy that calculation was partly done for rCBF differences of two contacts together. Interpretation should be cautious concerning the STN specificity.

Electrode location supports the hypothesis that at least the behavior of PLC is due to STN stimulation itself. Because electrode localization was relatively lateral in the STN, one might speculate whether stimulation of the motor and not the limbic part induces a dissociation of motor from emotional components of a crying behavior. However, relatively high voltage was needed to induce PLC, which makes current diffusion to the limbic STN likely.

PLC is a gesture lacking the adequate feeling. It is different from hyperemotionality where the threshold of emotional response is changed but quality of emotion is adequate. Hyperemotionality induced by current flow to the neighboring substantia nigra was described before[3] and should be contrasted to the rare PLC induced by stimulating the STN itself. As we find a rare phenomenon we also find an unexpected activation pattern: Usually STN-DBS induces deactivation of the cerebellum.[13] However, this difference can also be due to different scanning conditions.

PLC could not always be elicited by stimulation. Thus we postulate that DBS lowers the threshold in a vulnerable individual, supported by our finding that an abortive suppressible crying gesture was sometimes observed without stimulation. On stimulation, the patient lost his inhibitory voluntary control. The individual vulnerability could be explained by distinct MRI intensity changes found at the 3-year visit in the brainstem, probably affecting the PLC network.

Taken together we present a case with PLC that is triggered by STN-DBS during a conversation. We provide evidence that stimulation in the subthalamic nucleus has an impact on psychomotor control involving cerebellar-ponto-thalamic pathways. We propose an individual vulnerability as an additive factor to induce this rare syndrome and the associated brain activation pattern.

Acknowledgments: We thank the patient for his cooperation and Professors Herzog and Coenen (Research Center Juelich) for providing the PET facility.

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OPEN ACCESS Freely available online

PLoS one

Modulation of Human Time Processing by Subthalamic Deep Brain Stimulation

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Abstract

Timing in the range of seconds referred to as interval timing is crucial for cognitive operations and conscious time processing. According to recent models of interval timing basal ganglia (BG) oscillatory loops are involved in time interval recognition. Parkinsons disease (PD) is a typical disease of the basal ganglia that shows distortions in interval timing. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a powerful treatment of PD which modulates motor and cognitive functions depending on stimulation frequency by affecting subcortical-cortical oscillatory loops. Thus, for the understanding of BG-involvement in interval timing it is of interest whether STN-DBS can modulate timing in a frequency dependent manner by interference with oscillatory time recognition processes. We examined production and reproduction of 5 and 15 second intervals and millisecond timing in a double blind, randomised, within-subject repeated-measures design of 12 PD-patients applying no, 10-Hz- and ≥130-Hz-STN-DBS compared to healthy controls. We found under(re-)production of the 15-second interval and a significant enhancement of this under(re-)production by 10-Hz-stimulation compared to no stimulation, ≥130-Hz-STN-DBS and controls. Milliseconds timing was not affected. We provide first evidence for a frequency-specific modulatory effect of STN-DBS on interval timing. Our results corroborate the involvement of BG in general and of the STN in particular in the cognitive representation of time intervals in the range of multiple seconds.

Citation: Wojtecki L, Elben S, Timmermann L, Reck C, Maarouf M, et al. (2011) Modulation of Human Time Processing by Subthalamic Deep Brain Stimulation. PLoS ONE 6(9): e24589. doi:10.1371/journal.pone.0024589

Editor: Warren H. Meck, Duke University, United States of America

Received March 3, 2011; **Accepted** August 15, 2011; **Published** September 12, 2011

Funding: This work was supported by a grant of the "Forschungskommission" of the medical faculty of the Heinrich-Heine University in Düsseldorf (Dr. Wojtecki). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Time is a fundamental dimension of human existence. Up to date time research is one of the fields in cognitive neuroscience with many unsolved issues and competing theories about how the human brain processes time.

In a classical concept three crucial time scales have been proposed for different aspects of life. First, circadian timing in the range of 24 hours controls the sleep-wake rhythm [1] which depends on hypothalamic structures [2]. Second, milliseconds (ms) timing is crucially involved in motor control especially of precise discontinuous repetitive automatic movements [3] and relies on the cerebellum [4]. Third, timing in the range of (multiple) seconds (s) referred to as interval timing is essential for cognitive operations such as decision processes and conscious time processing and depends on a neural system involving frontoparietal cortices and basal ganglia (BG) [5,6].

Parkinsons disease (PD) is a neurodegenerative disease characterized by akinesia, rigidity and tremor resulting from a dopaminergic cell loss in the substantia nigra. In addition to motor deficits, PD patients show distortions in interval timing that can be relieved by L-dopa [7,8,9,10]. Besides dopaminergic therapy deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a powerful treatment of PD [11,12]. DBS does not only improve motor functions but also influences cognitive and executive functions [13] by affecting non-motor loops of the STN [14,15,16,17,18]. With respect to interval timing DBS ameliorates the PD-associated impairment in memory retrieval of time intervals termed "memory migration effect" [19,20]. This effect describes a phenomenon, where representations for different time lengths migrate towards each other in memory in such a manner that long intervals are estimated shorter whereas short intervals are estimated longer during retrieval.

Classical explanations of time perception using a pacemaker-accumulator model (scalar timing theory) [21] have been supplemented by a recent proposal, alleging that interval timing relies on the detection of coincident neuronal oscillations in subcortical and cortical circuits (striatal beat frequency model (SBF) [22]). According to this model thalamo-cortico-striatal loops are involved in time interval recognition such that striatal basal

ganglia neurons detect specific oscillatory activation patterns of frontal cortical areas during time encoding into working memory. Interestingly, pathological alterations of neuronal oscillations have recently been implicated in the pathophysiology of PD symptoms [23,24,25,26,27]. Furthermore, recent studies suggest that STN-DBS differentially modulates motor and non-motor functions depending on the stimulation frequency [28,29] probably by affecting subcortical-cortical oscillatory loops.

Taking the STN-pathways as a model for SBF in human time perception we therefore investigated the influence of STN-DBS at different stimulation frequencies on time interval perception and production at various timescales in four different paradigms. A double blind, randomised, within-subject repeated-measures design was used to investigate and compare the effects of STN-DBS at ≥130 Hz, 10 Hz, and no stimulation. For interval timing 5 and 15 s time production and memory dependent reproduction tasks were performed. For millisecond timing an unpaced tapping task and a time discrimination task with deviance intervals ranging from 80 to 400 ms were used. Millisecond timing tests were performed to comprehend differential stimulation effects on BG versus other (e.g. cerebellar) timing aspects. Reaction time tasks were performed to control for potential bias of motor performance on time judgements. Motor symptoms were assessed using the Unified Parkinsons Disease Rating Scale (UPDRS) motor score [30]).

Materials and Methods

Participants

12 patients with advanced Parkinsons disease (mean age 64 years, SD 8, range: 47–72; 6 male, 6 female) with implanted deep brain stimulation devices participated in the study. 12 age and sex matched healthy subjects (mean age 66, SD: 5, range 56–74 years; 6 male, 6 female) served as a control group. Participants gave written informed consent according to the Declaration of Helsinki. The local ethics committee (Ethics committee of the Medical Faculty, Heinrich-Heine University, Düsseldorf) gave its approval for the examination of deep brain stimulated patients with Parkinsons disease using timing paradigms and using low-frequency DBS settings.

All participants had a Mattis Dementia Rating Scale (MDRS[31]) score ≥ 130 and a Beck Depression Inventory (BDI [32]) score ≤11, thereby excluding relevant cognitive decline or depression. Tables 1, 2 illustrate clinical features and scores of the PD-patients and controls.

Deep Brain Stimulation

All patients had undergone surgery for bilateral implantation of stimulation electrodes (Model 3389, Medtronic, Minneapolis, MN, USA) in the STN at least one year prior to study enrolment to prevent bias due to the micro-lesion effect. During the study the active contacts, stimulation amplitude and pulse width parameters optimized for antiparkinson therapy were used (see Table 3). Stimulation parameters were kept constant except for frequency. Frequency of stimulation was changed between ≥130 Hz, 10 Hz and no stimulation (''OFF'') (see below).

To localize active contacts used for chronic stimulation postoperative stereotactic x-rays of 10 patients were available for reimport into the stereotactic planning system. Mean active contact position relative to the middle of the line between the anterior- and posterior-commissure (mid-commissural point, MCP) was calculated and visualized on the Schaltenbrand and Wahren Atlas [33]. As Figure 1 illustrates the mean active contact localisation was at the dorsolateral border of the STN.

Design

A double blind randomised and within-subject repeated-measures design was used to investigate and compare the effects of DBS at ≥130 Hz, 10 Hz and no stimulation on time processing in PD-patients. Time processing at different time scales was

Table 1. Patient characteristics with sex, age, disease duration, daily anti-parkinson medication, months since implantation in the subthalamic nucleus, disease type, predominant side, MDRS and BDI scores.

Patient/Sex/ Age (years)	Disease Duration (years)	Medication (mg/day)	Months Since Implantation	Disease Type	Predominant Side	MDRS	BDI
1/M/46	13	8 Cabergoline, 550 L-Dopa, 600 Entacapone	42	T	L	144	4
2/F/65	12	1,5 Pramiprexole, 100 L-dopa, 400 Entacapone	19	HR	L	142	3
3/F/69	25	0,27 Pramipexole, 350 L-Dopa, 1000 Entacapone, 150 Amantadine	20	T	R	143	9
4/F/61	11	6 Cabergoline, 775 L-Dopa, 300 Tolcapone	60	T	L	140	3
5/F/73	32	0,54 Pramipexole, 700 L-Dopa, 100 Amantadine	96	HR	L	142	2
6/M/69	20	1,05 Pramipexole, 500 L-Dopa	41	T	L	138	3
7/M/66	17	6 Cabergoline, 750 L-Dopa, 1400 Entacapone, 250 Amantadine, 1 Rasagiline	73	HR	L	134	10
8/M/71	21	2,25 Ropinirole, 550 L-Dopa	70	HR	L	138	4
9/M/51	16	4 Cabergoline, 300 L-Dopa, 200 Entacapone, 1 Rasagiline	63	HR	L	142	2
10/M/72	20	15 Ropinorole, 400 L-Dopa, 400 Entacapone, 1 Rasagiline	17	HR	L	140	4
11/F/72	16	1,58 Pramipexole, 750 L-Dopa, 1000 Entacapone, 1 Rasagiline	27	HR	L	141	3
12/F/61	20	2,1 Pramipexole, 350 L-Dopa, 1 Rasagiline	25	HR	L	143	5

doi:10.1371/journal.pone.0024589.t001

Table 2. Control characteristics with sex, age, MDRS and BDI scores.

Control/Sex/ Age (years)	MDRS	BDI
1/F/56	143	0
2/M/63	144	1
3/F/66	142	5
4/M/62	144	3
5/F/69	144	3
6/F/64	136	4
7/M/74	141	6
8/F/63	138	2
9/M/65	141	7
10/F/71	140	0
111/M/70	142	3
12/M/65	135	2

Abbreviations: MDRS = Mattis Dementia Rating Scale; BDI = Beck Depression Inventory; HR = hypokinetic-rigid; T = tremor dominant; L = left; R = right.
doi:10.1371/journal.pone.0024589.t002

assessed in four different paradigms. For interval timing a memory dependent time reproduction task and a time production task for intervals of 5 and 15 s length were performed. For millisecond timing a tapping task with inter-tap intervals of 800 ms and a time discrimination task with deviance intervals ranging from 80 to 400 ms were used. Reaction time tasks were performed to rule out bias on time judgements by motor deficits. Motor symptoms were assessed using the UPDRS motor score.

Procedure

All tests were performed at the Department of Neurology of the University Hospital in Düsseldorf. Patients were tested without medication after 12 hours of dopaminergic medication withdrawal. The three deep brain stimulation conditions 10 Hz, "OFF" and ≥130 Hz were programmed directly without turning the device off between sessions in randomised order and kept constant for 15 minutes before starting the tests. In every stimulation condition all test were conducted within one block and in the same sequence. Motor examinations were performed by a blinded movement disorder specialist and videotaped. Time processing tests were initiated after careful oral and written instruction by a neuropsychologist and after a short training session. All tests were performed on a personal computer using E-Prime (Psychology Software Tools, Inc., Version 1.0 for Windows 98). For illustration of tests see Figure 2.

Interval timing

Time reproduction. A tone (700 Hz, 2000 ms duration) was presented at the beginning and end of the 5 s or 15 s intervals and subjects were instructed to encode the intervals duration. These two test intervals were presented in random order. After a delay of 1 s the subjects were instructed to reproduce the interval by two button presses, one at the beginning and one at the end. After reproduction of the interval subjects were instructed to start the next trial by pressing a button. Each interval was presented 10 times. Relative deviations from the target interval were calculated.

Time production. An instruction on the computer screen requested the subjects to produce an interval of 5 s or 15 s. The subjects were not taught how long 5 s or 15 s intervals were. After a start cue the instruction was cleared from the screen and the time interval between two button presses was measured, marking the beginning and end of the produced interval. After a delay of 3 s the subjects could start the next trail by pressing a button. 5 s and 15 s intervals were each requested 10 times in a randomised order. Relative deviations from the target interval were calculated.

Millisecond timing

Time discrimination. A tone (700 Hz, 200 ms length) was presented at the beginning and end of a standard interval of 1200 ms duration. After a delay of 3 s a comparison interval was presented in the same manner. The comparison interval had a length between 800 and 1600 ms, the length varying in steps of 80 ms (800, 880, 960, 1040, 1120, 1280, 1360, 1440, 1520, 1600 ms). Each comparison interval was randomly presented five

Table 3. Stimulation parameters used for long term stimulation and active stimulation contact (monopolar, with impulse generator used as anode) for each hemisphere.

Patient	Amplitude (V)		Pulse Width (μs)		Frequency (Hz)		Contact	
	Left	Right	Left	Right	Left	Right	Left	Right
1	3,0	3,0	60	60	150	150	2	6
2	2,2	2,4	60	60	130	130	1	5
3	2,4	2,45	60	60	130	130	3	5
4	3,1	2,5	60	60	150	150	6 and 7	00
5	1,3	3,0	60	60	130	130	1	3
6	3,8	3,8	90	120	180	180	2	4
7	4,0	1,5	60	60	130	130	4	1
8	3,4	3,4	60	60	130	130	2	5
9	3,3	2,7	60	60	130	130	2	5
10	2,6	3,6	60	60	130	130	1	5
11	3,0	3,0	60	60	130	130	3	7
12	3,2	3,9	60	60	130	130	7	3

Abbreviations: V = Volt; μs = Microseconds; Hz = Hertz.
doi:10.1371/journal.pone.0024589.t003

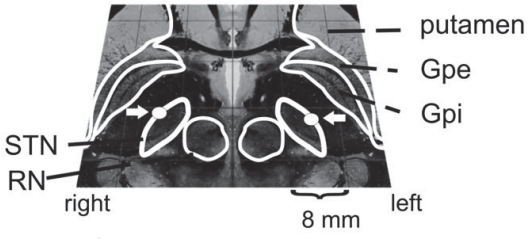

Figure 1. Stimulated area. Mean location of active contacts highlighted and marked with a white arrow at axial slice 3.5 mm under MCP of the Schaltenbrand and Wahren Atlas. Mean coordinates ± standard deviation were: right hemisphere: x-coordinate = 13.7±1.7, y-coordinate = −0.5±2.1, z-coordinate = −2.4±2.0; left hemisphere: x-coordinate = 13.0±1.3, y-coordinate = −0.3±2.3, z-coordinate = −2.8±2.8 Figure is based on the Cerefy Clinical Brain Atlas [53]. Abbreviations: STN = Nucleus subthalamicus; Gpe = Globus pallidus pars externus; Gpi = Globus pallidus pars internus; RN = Nucleus ruber; SN = substantia nigra.
doi:10.1371/journal.pone.0024589.g001

times, resulting in 10 trials per deviance (80,160,240,320, 400ms) from the standard interval, rendering a total of 50 trials. Subjects were instructed to judge if the comparison interval was longer or shorter than the standard interval by pressing respective buttons. The number of judgements "longer" and "shorter" were saved.

Tapping. The finger tapping task consisted of one run with two phases. First, subjects performed an auditory paced tapping task. Tones (700 Hz, 20 ms length) with an inter stimulus interval of 800 ms were presented and subjects were instructed to press a button with the onset of each tone. Second, after 20 auditory paced taps the tones stopped and the subjects were instructed to continue tapping at the given interval for 20 further taps without the pacer. The intertapping interval in the unpaced tapping phase was measured.

Reaction time. A tone (700 Hz, 1000 ms duration) was presented at a randomised interstimulus interval between 1 and 5 s. The participants were instructed to react to the tones as fast as possible by pressing a button. 20 trials were recorded.

Statistical analysis

Measured time intervals and relative deviation from the target intervals for reaction time, reproduction, production and tapping, correct judgements for time discrimination and results of the motor scores were analysed with SPSS for Windows (SPPS Inc., Version 12.0). Considering the small sample size and as testing with the Kolmigorov-Smirnof test failed to show normal distribution for most samples nonparametric test were used to

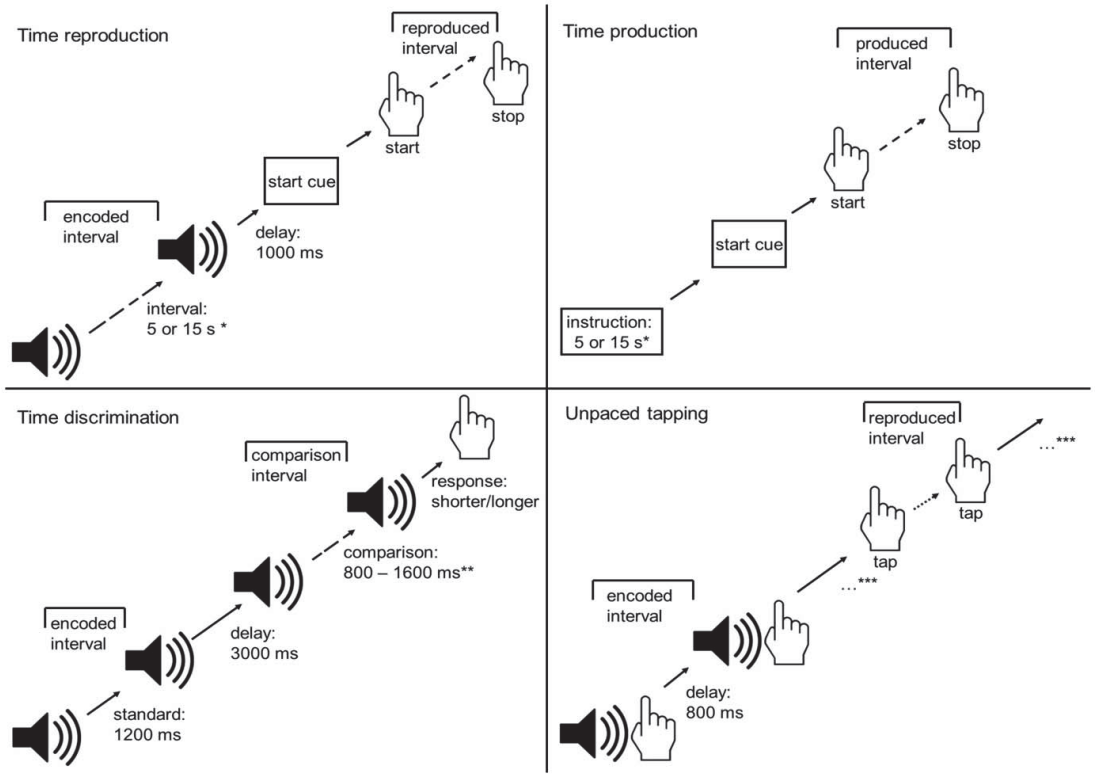

Figure 2. Paradigms. Illustration of the paradigms for time reproduction, time production, time discrimination and tapping. *10 cycles per interval, total of 20 trials; **10 steps of 80 ms, 5 cycles per interval, 10 cycles per each deviance (80, 160, 240, 320, 400 ms) from standard interval, total of 50 trials; ***total of 20 trials.
doi:10.1371/journal.pone.0024589.g002

compare results between stimulation conditions within the PD group and between the PD patients and healthy controls. Friedman tests for related samples were used to analyse the effect of the factor "stimulation setting" within the PD-group. If a significant difference between stimulation conditions was detected, sequential Bonferroni corrected Wilcoxon-tests were performed for post hoc comparisons. To compare stimulation and control groups sequential Bonferroni corrected Mann-Whitney-U-tests for unrelated samples were used.

In the discrimination tasks a measure of the comparison duration judged equal to the standard interval, the point of subjective equality (PSE), and additionally as a measure of the precision of temporal discrimination, the just noticeable difference (JND), was determined. Thus, binomial logistic regression functions were fit to the data of each patient in all stimulation conditions and for control subjects. Fitting was performed with GraphPad Prism 5 (GraphPad Software, La Jolla California, USA). Two patients and two controls were excluded from analysis of PSE and three patients and controls were excluded from analysis of JND due to ambiguous fits. The duration with 50% "longer" judgments was taken as PSE. JND was calculated by taking the duration with 75% "longer" judgements minus the duration with 25% "longer" judgements divided by two. Statistical comparison of PSE and JND was then again done within the PD group using Friedman test and between controls and patients using Whitney-U-Tests.

Results

Interval timing: Time reproduction and production

Patients and controls over-(re-)produced the 5 s interval and under-(re)produced the 15 s interval in both tasks (Figure 3 A and B).

For the 5 s interval in the production task there was no significant difference between controls and stimulation conditions or between the individual stimulation conditions after Bonferroni correction. In the 5 s reproduction task there was a trend revealing a difference between controls and patients with 10 Hz stimulation ($p = 0.06$) and without stimulation ("OFF") ($p = 0.07$)).

Comparisons of the different stimulation conditions and healthy controls in the reproduction task for the 15 s interval showed that 10 Hz stimulation significantly enhanced the 15 s underreproduction effect (10 Hz: 10.4 s± (SEM) 0.9 s; compared to OFF: 12.5±0.8 s, $p<0.05$; compared to >=130Hz: 13.5±0.6 s, $p<0.05$; compared to controls: 14.8±0.2 s, $p<0.001$). Correspondingly, in the 15 s production task underproduction was stronger with 10 Hz (10.1±0.5 s) than without stimulation (11.1±0.8 s, $p<0.05$), >=130Hz stimulation (13.2±0.9 s; $p<0.05$) and than in controls (13.9±0.7 s, $p<0.01$). Furthermore the stimulation OFF differed from >=130Hz ($p<0.05$) and normal controls ($p<0.01$).

Taken together, 10 Hz DBS significantly worsened interval timing at the 15 s interval and -discriptivly saying - controls and patients with >=130Hz DBS showed lowest impairment of time processing. Furthermore, controls and patients with >=130 Hz stimulation performed the 15 s time production significantly better compared to OFF stimulation. (Figure 3 A and B).

These differences in the production task between OFF and controls can also be interpreted as a *disease effect* (see dashed line in Figure 3 B). Correspondingly, the other differences can be named as a *stimulation effect* within the PD group, namely between 10 Hz vs. OFF and vs. 130 Hz in the reproduction task and in the production task between 10 Hz vs. OFF and vs. 130 Hz and additionally between 130 Hz vs. OFF (see continuous line in Figure 3A/B).

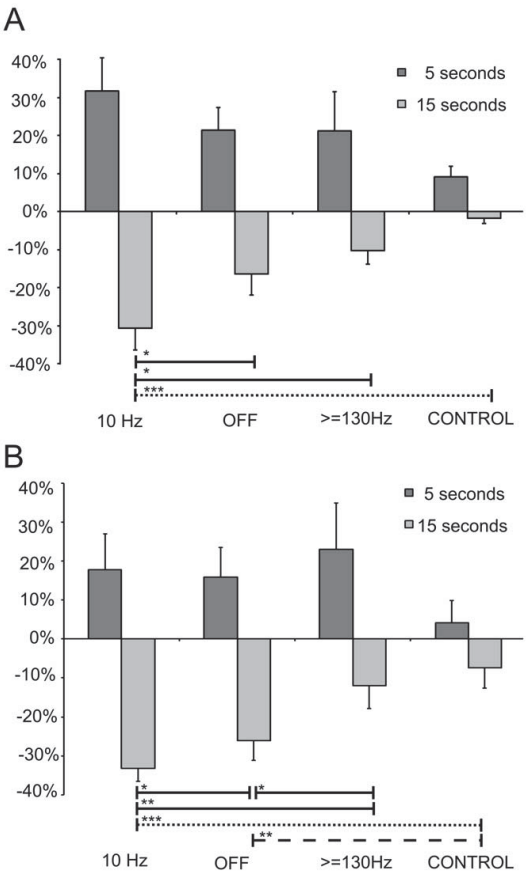

Figure 3. Mean results of interval timing. A: Mean results of time reproduction; B: Mean results of time production. Mean relative deviation (with SEM) from the target interval of 5 and 15 s for controls, PD-patients with stimulation OFF, >=130 Hz and 10 Hz. Significant differences: *p<=0.05; **p<=0.01, ***p<=0.001. Comparisons: continuous line: stimulation effect within PD group, dashed line: disease effect.
doi:10.1371/journal.pone.0024589.g003

Furthermore, as Figure 4 illustrates, these *stimulation effects* within the patient group could be found in most of the subjects, with the most pronounced under(re-)production during the 10 Hz stimulation.

Milliseconds timing: Time discrimination and tapping

In the time discrimination task number of correct judgements for comparison intervals did not significantly differ between controls (41±2) and patients or between different stimulation conditions (10 Hz: 38±1; OFF: 35±2; >=130 Hz: 35±2;). Furthermore PSE and JND did not differ significantly (PSE in ms:10 Hz: 1229 ±22; OFF: 1185 ±67; >=130 Hz: 1265 ±40; controls: 1241± 102; JND in ms: 10 Hz: 226 ±55; OFF: 259 ±181; >=130 Hz: 300 ±120; controls: 231± 118) (see Figure 5).

In the tapping task with interstimulus intervals of 800 ms the intertap interval in the unpaced phase was significantly longer ($p<0.01$) than in the paced phase in all patient conditions and in

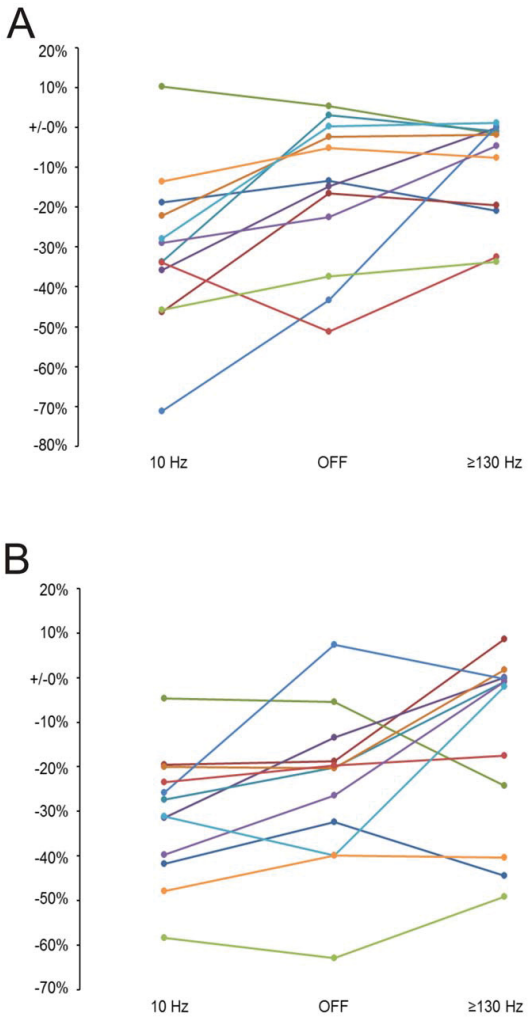

Figure 4. Individual results of interval timing. A: Indivdual time reproduction in DBS patients B: Individual time production in DBS patients. Individual relative deviation from the target interval for each PD patient and respective stimulation settings.
doi:10.1371/journal.pone.0024589.g004

normal controls. This reflects a strong anticipation in the paced phase (Figure 6). There was no significant difference of mean intervals for the paced phase between controls and patients and within stimulation conditions (mean paced intertap interval in ms: 10 Hz: 360; OFF: 315; >=130 Hz: 458; controls: 393). Finally, the main dependent variable, the mean intertap intervals in the unpaced phase, did not differ significantly between controls and patients or between different stimulation conditions (interval in ms:10 Hz: 744; OFF: 805; >=130 Hz: 819; controls: 773). Standard error of mean and standard deviation did also not differ significantly between stimulation conditions and between PD patients and controls in the paced and unpaced phase (paced SD/SEM in ms: 10 Hz: 253/63; OFF: 247/52; >=130 Hz: 220/48; control: 313/70; unpaced SD/SEM in ms: 10 Hz: 199/44; OFF: 219/49; >=130 Hz: 367/82; control: 102/23).

Taken together, performance in milliseconds timing, as measured by the time discrimination and tapping tasks, did not differ between patients and controls or between stimulation conditions.

Reaction time and motor scores

Reaction times were significantly shorter in controls (282±14 ms) than in all patients (10 Hz: 408±35 ms, $p<0.01$; OFF: 420±20 ms, $p<0.001$; >=130 Hz: 321±14 ms, $p<0.05$). Patients reacted significantly faster in the >=130Hz stimulation condition than in the OFF state ($p<0.05$) but there was no significant difference between stimulation frequencies.

Regarding the UPDRS motor score the patient's performances in all conditions was worse than that of the control group (1±0.4; $p<0.001$). Stimulation conditions differed significantly. In the 10Hz stimulation (45±2, $p<0.01$) and OFF conditions (49±3, $p<0.01$) motor performance was worse than in the >=130 Hz stimulation condition (26±3).

Thus, >=130 Hz stimulation improved motor performance whereas OFF and 10Hz stimulation did not. As a possible *disease effect* on interval timing correlation between motor score/reaction time in the stimulation OFF-state and 15 sec production and reproduction performance was calculated. However, a significant correlation between motor and interval timing performance could not be detected.

Discussion

The aim of the study was to examine the impact of 130Hz- and 10Hz STN-DBS on timing functions in PD patients. The main findings were as follows: 1) For interval timing patients and controls over(re-)produced the short intervals of 5 s and under(re-)produced the long intervals of 15 s in both the time production and the reproduction tasks. 2) There was a significantly greater underproduction of 15 s in patients in the stimulation OFF compared to controls, delineating a *disease effect*. 3) There was a significant worsening of time production and reproduction during 10 Hz STN-DBS and a mitigation of time production error during >=130 Hz STN-DBS for the interval of 15 s. 4) Timing in the milliseconds range was not significantly different between patients and controls or between the different stimulation conditions. Thus, STN-DBS modulates 5 to 15 s interval timing but not millisecond timing in a frequency-dependent manner.

Methodological consideration

Stimulated area. Stimulation contacts yielding optimal motor benefits during chronic stimulation were used. Active contacts were located in the dorso-lateral (motor) part of the STN. It is possible that if a more ventro-medial (associative/limbic) part of the STN had been stimulated impact on timing tasks could have been different. Besides stimulation of the STN per se current spread to the zona incerta or the capsula interna can also be taken into account as a possible mechanism of action.

Possible bias: Motor performance, medication influenced motivation, attention, design of the paradigm. Although interval timing tasks required motor action a general effect of motor deficits on these interval timing tasks can be ruled out, as the patients under(re-)produced the 15 s interval - by pressing the reaction button earlier - in the conditions with the worst motor scores (10 Hz and OFF) and longest reaction times. The contrary would be expected if the effects were caused by a motor deficit or by reaction time. All tasks were performed without PD-medication to test solely DBS effects.

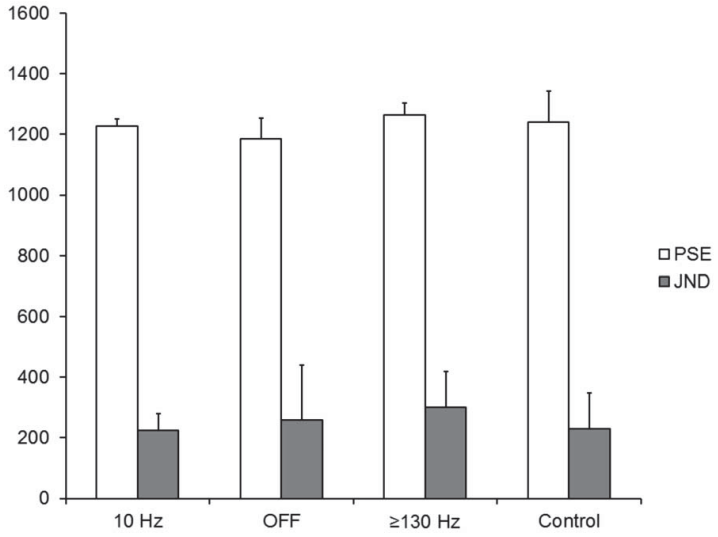

Figure 5. Mean results of time discrimination. Point of subjective equality (PSE) and just noticeable difference (JND) in ms (with SEM) for controls, PD-patients with stimulation OFF, >=130 Hz and 10 Hz.
doi:10.1371/journal.pone.0024589.g005

Long acting dopamine-agonists may have a minimal influence on results. However, 12 hours of L-Dopa withdrawal is the standard regime in clinical testing and was proven to be sufficient to obtain satisfactory results in our previous work [28,29]. Bias by motivational changes in the non-medicated state can not entirely be ruled out as it was recently shown in D2-receptor overexpressing transgenic mice that modulation of the striatal dopaminergic system can impair timing mediated by cognitive and motivational factors [34]. Another issue might have been fluctuations in the degree of attention during the paradigm. In the production or reproduction paradigm subjects might have been inattentive to the length of the present interval (5s or 15s). This could have lead to enhanced "migration" of performance in both time intervals. Thus, one might argue that e.g. 10 Hz DBS would merely enhance inattentiveness or distractibility rather than affect time processing itself. However, improved cognitive performance in a verbal fluency task during 10 Hz stimulation in our previous experiment [29] argues against this hypothesis. Finally, two issues of the paradigm design can be discussed. First, for the time discrimination task the number of correct judgements was analysed. Another approach was to calculate the difference thresholds (JND) and point of subjective equality (PSE). Such estimates, however, could be noisy due to the given number of 10 presentations per deviation

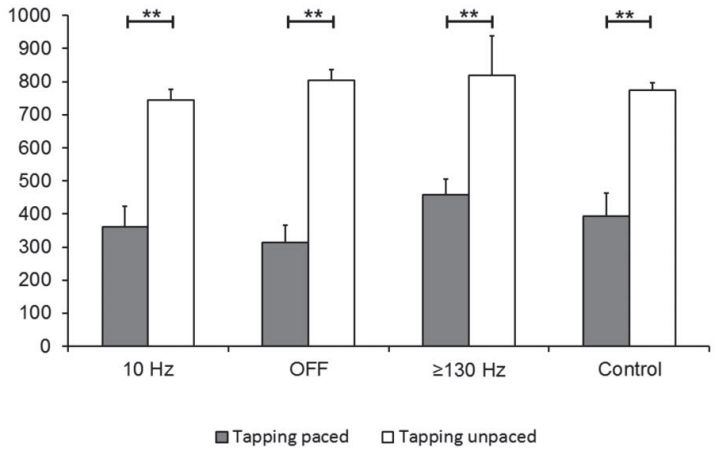

Figure 6. Mean results of tapping. Mean intertap interval in ms (with SEM) of paced and unpaced tapping for controls, PD-patients with stimulation OFF, >=130 Hz and 10 Hz. Significant difference between paced and unpaced: **p<0.01.
doi:10.1371/journal.pone.0024589.g006

from the standard interval. Nevertheless, we opted not to extend the paradigm as it would have been to demanding for patients in the unmedicated state. Secondly, we did not control for individual counting strategies during interval timing. Therefore the observed effects could be either due to influence of DBS on *timing* or on *counting*. Especially, the relatively good performance during the reproduction task makes counting seem plausible. However, it is assumed that both timing and counting involve brain areas that are influenced by DBS, such as the supplementary motor area (SMA), the inferior frontal gyrus (IFG) or the cingulum, and that counting additionally involves the primary motor cortex, the cerebellum and the putamen [35]. This important fact should be considered in the discussion of time processing effects of DBS.

Interval Timing: Memory dependent versus memory independent effects

The impact of DBS on interval timing concerning memory dependent tasks such as time *reproduction* and on the "memory migration effect" has been reported before [20]. Our results are in line with these previous findings. Moreover, we provide first evidence for a frequency dependent modulation of time intervals in the range of multiple seconds. The impact of STN-DBS on memory dependent timing functions is presumed to be due to an influence on retrieval of time representations from memory [19]. Thus, it can be concluded that STN-DBS has a frequency dependent modulatory impact on the retrieval of time representations in the range of multiple seconds. In addition, one can assume that this effect increases with higher demand on memory and with the length of the retrieved interval. Therefore this effect is more pronounced in 15 sec rather than in 5 sec. Furthermore we also found time *production* of longer intervals to be modulated in a frequency dependent manner by STN-DBS. This was not expected, as time production was not assumed to be influenced by memory. The time production paradigm was designed to examine the effect of the inner pacemaker on timing functions. It is known that a pathologically slowed internal clock in Parkinsons disease can be speeded up by L-Dopa [10] and slowed down by dopamine antagonists [36]. However, as performance for long and short time intervals lead to opposite effects our results can't be explained by modulation of an inner pacemaker alone. A confounding influence of memory functions on the production task can't be ruled out, as two different intervals were randomly requested in the task. This hypothesis is supported by recent findings illustrating that impaired interval timing in PD-patients can only be found when intervals with two different durations are tested in one session [37]. This affection of memory in the production task would reflect a stored, possibly semantic memory for intervals needed to provide the target duration. In contrast to this semantic memory for the production task, a working memory mechanism, keeping track of the target stimulus in the reproduction task hast to be considered. Thus, as proposed by the memory migration effect, the long term memory representations for the two time intervals migrated towards each other in the reproduction task rather than in the production task. The fact that patients as well as controls showed a migration of long and short time intervals towards each other indicates that this effect might be a normal working memory phenomenon rather than a pathological phenomenon in PD patients.

Multi-seconds versus milliseconds timing: Different neural systems depending on the time scale?

In contrast to interval timing in the range of several seconds, milliseconds timing was not significantly modulated by STN-DBS in our study. Therefore, one might conclude that our study supports one classic view, stating that milliseconds timing is not dependent on basal ganglia function and, thus, is not impaired in PD. According to this hypothesis, some authors report that patients with cerebellar lesions have deficits in tapping and time discrimination tasks whereas patients with PD do not have such a deficit [38]. However, this view is not generally accepted and other authors provide evidence suggesting that the basal ganglia are indeed involved in millisecond timing [39,40]. Especially the striatum seems to be involved in such tasks [41]. Our study design can neither prove nor rule out an involvement of the striatum in milliseconds timing. Nevertheless, we show that milliseconds timing is less vulnerable to electrical stimulation of the STN, presumably as this nucleus forms part of the *indirect* modulatory part of the cortico-striatal-thalamic circuit.

Impact of subthalamic deep brain stimulation on time representations

In addition to an impact on memory retrieval of time intervals in the range of multiple seconds it is also plausible that DBS affects the comparison and decision processes associated with the retrieval of time representations from memory by affection of the dorsolateral prefrontal cortex (DLPFC). It has been shown that repetitive transcranial magnetic stimulation (rTMS) of the right DLPFC can distort time reproduction of 5 and 15 s intervals [42]. Furthermore imaging studies showed that the right DLPFC is involved in timing functions [43,44,45,46]. Basal-ganglia connections with various cortical areas have been considered in timing functions in a positron emission tomography (PET) study by Jahanshahi et al. [47]. They attribute working memory for time intervals to the left premotor cortex (PMC). Interestingly activation strength of the PMC correlated with the length of the time interval. In our study the DBS effect was mainly seen in the 15 s time interval, which corresponds to the hypothesis that an influence of the PMC is more pronounced by longer intervals. Furthermore, Jahanshahi et al. discuss that the supplementary motor area (SMA) is involved in conscious time representation. An impact of DBS on cortical areas such as the DLPFC, orbital frontal cortex (OFC), SMA and PMC has been shown previously in other tasks besides timing [16,48,49]. During cognitive tasks such as verbal fluency DBS deactivates the left inferior-frontal cortex (IFC) [18]. Furthermore, a selective frequency dependent modulation of verbal fluency relying on projections between the STN and frontal cortical areas has been shown in our own previous work [29]. The present study suggests that a frequency dependent modulation of projections between the STN and the DLPFC, PMC and/or SMA might play a key role in the influence on time representations. The frequency modulatory effect on subcortical-cortical networks can be explained by the influence on oscillatory neuronal activity. As 10 Hz stimulation of the STN possibly activates [28] motor parts of a pathological tremor network [27] the current findings might be explained in a similar way. A "coincidence detection" or "striatal beat frequency model (SBF)" [22] postulates that thalamo-cortico-striatal loops are involved in time recognition: striatal neurons detect specific oscillatory activation patterns of frontal cortical areas that are involved in working memory functions. Recordings from single cells support this idea, showing that single cell macaque recordings from the striatum and prefrontal cortex display a temporal interrelation of their firing patterns during time encoding [50]. Striatal recordings in rats during a time reproduction task with a probabilistic reward show selective firing patterns for time intervals of 10 and 40 s [51] and neurons of the prefrontal cortex change their firing rate depending on the number of visually presented items [52]. Thus, the SBF model postulates that frontal cortical representations for the number of items play a role for time

recognition. In this sense the SBF model might be used to explain our finding on time processing of longer time durations on a neuronal basis. As the STN is part of the thalamo-cortico-striatal circuit STN-DBS can be interpreted as one example of frequency dependent electrical modulation within the SBF model of interval timing. However, the specific role of 10 Hz with respect to the findings and the model is not known. Nonetheless, we provide first evidence for the possibility of frequency dependent modulation of cognitive time representation in humans by DBS, during which high frequency $>=130$ Hz DBS imposes a beneficial timing signal on the basal ganglia and associated areas and 10 Hz DBS further disrupts a system which is already impaired by PD.

Acknowledgments

The authors thank all patients and control subjects for their excellent cooperation and David Petri, MSc, for statistical support.

Author Contributions

Conceived and designed the experiments: LW SE LT SJ MN AS. Performed the experiments: LW SE LT SG. Analyzed the data: LW SE LT CR SJ MP MS SG. Contributed reagents/materials/analysis tools: LW SE LT CR SJ MP MS SG VS MM. Wrote the paper: LW SE AS.

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Basal Ganglia 2 (2012) 49–54

Contents lists available at SciVerse ScienceDirect

Basal Ganglia

journal homepage: www.elsevier.com/locate/baga

Effects of levodopa and deep brain stimulation on motor speech performance in Parkinson's disease

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ARTICLE INFO

Article history:
Available online 8 February 2012

Keywords:
Parkinson's disease
Syllable repetition
Motor speech performance executive function
Subthalamic deep brain stimulation

ABSTRACT

Background: Abnormalities in motor speech performance are frequently observed in Parkinson's disease and are thought to be induced by complex dysfunction of planning, preparing and execution of speech motor sequences. The aim of our study was to test the differential influence of levodopa and bilateral deep brain stimulation of the subthalamic nucleus in Parkinsonian patients based upon a multi-level syllable repetition paradigm.
Methods: Twenty-four patients and 32 healthy subjects were tested. Patients had to perform the speech task under three different conditions: OFF-Stimulation/OFF-Medication, ON-stimulation OFF-Medication and ON-Stimulation/ON-Medication. Participants had to repeat a single syllable (/pa/) or a pair of alternating syllables (/pa-ti/) in a self chosen isochronous pace or in a given pace of 80 per minute. Percental coefficient of variance of interval length was measured for description of pace stability throughout the performance.
Results: Coefficient of variance in the patient group was elevated in the tasks consisting of a single syllable repetition and showed a further increase in the alternating syllable tasks. Deep brain stimulation led to a further deterioration whereas levodopa induced an amelioration of coefficient of variance significantly in the more complex task consisting of the repetition of alternating syllables.
Conclusions: In the patient group, pace performance was observed to be irregular in all tasks, but showed a further decline under deep brain stimulation and when two or more equal demands (steadily keeping a given pace/alternating syllables) were present as a possible hint for additional executive dysfunction which was partially compensated by levodopa.

Introduction

In Parkinson's disease (PD), the characteristic dopamine-dependent basal ganglia dysfunction leads – amongst a variety of other motor and non-motor symptoms – to instability of repetitive automated motor sequences. The instability of repetitive motor activities is characterized by deviations of amplitude and/or duration of the subsequent motor sequence from the antecedent [1]. It typically shows a tendency to further deteriorate in the course of production. There is a wealth of evidence for abnormalities of pace and rhythm in PD while executing repetitive movements within different modalities such as hand and finger tapping [2,3], diadochokinesis and gait [4], which can be partially improved by voluntary attention or the use of external cues [5,6]. Furthermore, the great majority of PD individuals develop voice and speech problems in the progression of the illness [7]. The core feature of dysarthria in PD is hypophonia. In detail, based upon the perceptual analysis of large samples of Parkinsonian speakers, first systematic research on Parkinsonian speech defined salient clusters of deviant speech dimensions in hypokinetic dysarthria including a harsh breathy voice quality, reduced variability of pitch and loudness, reduced stress, imprecise consonant articulation and short rushes of speech interrupted by inappropriate periods of silence [8,9]. Concentrating on aspects of speech rate and regularity in PD, the results of previous studies on speech rate are inconsistent, probably due to methodological differences and small sample sizes [10–12]. A recent analysis of speech rate in Parkinsonian patients revealed a significant articulatory acceleration during reading rather than an alteration of overall articulatory velocity [13]. The phenomenon of speech hastening and impaired self-paced sequencing has been confirmed by further studies based upon

Abbreviations: STN, subthalamic nucleus; DBS, deep brain stimulation; PD, Parkinson's disease; SD, standard deviation; IntDur, interval duration; avIntDur, average interval duration; COV, relative coefficient of variation; %IntDur, relative interval duration; maxSylRep, maximum syllable repetition.

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2210-5336/$ - see front matter © 2012 Elsevier GmbH. All rights reserved.
doi:10.1016/j.baga.2012.01.001

syllable repetition and oral diadochokinesis tasks, in which participants were asked to reiterate a given syllable as fast as possible in a single breath [14,15]. A recent investigation on syllable repetition capacity in PD revealed an impairment to maintain an isochronous pace with a tendency to pace acceleration throughout syllable production [16].

From the therapeutic point of view, the effect of dopaminergic stimulation on motor speech performance in PD finally remains inconclusive, whereas most of the studies found no significant changes of speech rate and rhythm after short-term levodopa administration or under long-term dopaminergic medication [17–19]. On the other hand, studies on the effect of deep brain stimulation (DBS) of the subthalamic nucleus (STN) using clinical scales have shown variable effects on different aspects of speech to stimulation [20,21]. Speech was the only function not improved following 5 years of STN stimulation [22,23]. Speech deterioration has even been reported as a common side effect of STN–DBS with a prevalence ranging from 4% to 17% [24,25]. There is some evidence for a crucial role of contact side and amplitude of stimulation on speech intelligibility, whereas in some patients, the progression of speech difficulties was not modifiable by adjusting the medication or stimulation [26–28]. However, studies on specific motor aspects of speech, like loudness of sustained phonation or tongue force have shown improvement with STN–DBS although this improvement was not reflected by an amelioration of overall speech intelligibility [29–33].

A recent investigation of the differential influence of levodopa and STN–DBS on motor speech performance based upon a simple syllable repetition paradigm showed a deterioration of the steadiness of repetition under STN–DBS whereas levodopa had no effect on motor speech performance [34]. However, these results were only preliminary due to the small sample size and the limitations of the speech paradigm. Therefore, the current study can be seen as a further development of that original investigation using a more extensive speech task with stepwise increasing complexity in order to define specific patterns of impairment and to characterize a possible differential effect of levodopa and STN–DBS on motor speech performance in PD.

Material and methods

Our study was in compliance with the Helsinki Declaration and had been approved by the local Ethics Committees (Study Nr. 3277). Written informed consent was obtained from each participant.

From 2009 to 2010, 24 patients with Parkinson's disease (PD) and chronic bilateral deep brain stimulation of the subthalamic nucleus (DBS–STN) were recruited for this study. The diagnosis of PD was based upon clinical criteria according to the UK Parkinson's Disease Society Brain Bank Criteria [35]. Patients' age ranged from 53 to 77 years (mean 67.59/median 67; 12 male, 12 female). Parkinson's disease had been diagnosed from 5 to 28 years prior to this investigation (mean 16.33/median 15.5). Each patient was tested under three conditions: stimulation OFF/medication OFF (condition1: StimOFF/MedOFF), stimulation ON/medication OFF (condition 2: StimON/MedOFF) and stimulation ON/medication ON (condition 3: StimON/MedON, testing performed 30 min after admission of 200 mg of a soluble levodopa preparation) and underwent a neurological examination, according to UPDRS Motor Scale (UPDRS III) before performing the speech task. The three conditions were chosen to quantify the stimulation effect and the additive medication effect. A fourth condition (stimulation off/medication on) was disregarded in order to avoid fatigue, to avoid too much practicing effects and thus too high demand on task randomization order and to be able to finish the "medication on" condition within one session after L-Dopa administration in a stable motor state.

Table 1
Patients' characteristics.

	Mean	Standard deviation	Range
Age (years)	67.59	7.10	53–77
Disease duration (years)	16.65	6.05	6–28
UPDRS III			
Condition 1: StimOFF/MedOFF	38.88	11.71	16–70
Condition 2: StimON/MedOFF	24.85	10.71	7–52
Condition 3: StimON/MedON	15.69	7.47	3–30
Stimulation parameter			
Amplitude (volt)			
Left STN	2.9	0.79	1.2–4.0
Right STN	3.1	0.72	1.8–4.2
Frequency (hertz)	129.6	1.38	125–130
Pulse width (microseconds)			
Left STN	62.4	8.31	60–120
Right STN	64.8	14.18	60–120

Patients' characteristics are summarized in Table 1. None of the patients experienced orofacial or abdominothoracic peak-dose dyskinesia while being tested.

As control group we tested 32 age-matched healthy persons (mean age 67.13 years/median 68 years/range 48–83 years; 19 male, 13 female).

Speech samples were digitally recorded using a commercial audio software (Steinberg WaveLab®/Steinberg Media Technologies GmbH, Hamburg, Germany) and a head-set microphone with a defined mouth to microphone distance of 3 cm. The speech task consisted of three subtests. Test 1: Repetition of the syllable /pa/ in a self chosen steady (isochronous) pace without acceleration or slowing articulatory velocity. Test 2: Repetition of the syllable /pa/ in a velocity of 80/min given by a metronome; participants had to listen to the pace first, then start with the syllable repetition; the metronome was stopped after four utterances, and participants had to keep the given pace. Test 3: Alternating repetition of the syllables /pa/ and /ti/ with the given metronome-based velocity of 80/min. Each subtest was performed twice; the average values of first and second trial were taken for the definite analyses. In each test the participants were asked to repeat the syllables at least 40 times. Only the first 30 utterances were taken for the definite analyses in order to avoid a modification of participants' articulatory velocity by the expectance of the imminent end of the task. Intervals interrupted by prolonged breathing were excluded.

The analyses were performed according to the previous reported method [16]: Based upon the oscillographic sound pressure signal of the recorded audio material, the period from onset of one vocalization until the following vocalization was defined as "interval"; interval duration (IntDur) was measured in milliseconds (ms). Stability of pace of the utterances was defined as relative coefficient of variation (COV_{5-30}) calculated for the intervals 5–30 in relation to the average interval length of the first four utterances ($avIntDur_{1-4}$) following the formula: $COV_{5-30} = SD_{5-30}/[(avIntDur_{1-4})/\sqrt{26}] \times 100$ (for abbreviations see Table 2). This procedure is based upon the hypothesis that the first utterances are necessary for the definition of the individual articulatory pace which has to be maintained throughout the ongoing speech task. As a measure for the precision of interval length reproduction, the average interval length was related to the given interval duration of 750 ms in test 2 and test 3 and defined as percental interval duration (%IntDur).

Furthermore, participants had to twice reiterate the syllables /pa/ and /pa-ti/ as fast as possible for at least 5 s. The average of all four trials was taken as a measure for the maximum syllable repetition capacity (maxSylRep in syllables per second) (The definitions are summarized in Table 2).

Table 2
Definitions and abbreviations.

Abbreviation	Definition	Formula
SD	Standard deviation	
IntDur (ms)	Interval duration	
avIntDur$_{1-4}$ (ms)	Reference interval length	Average duration of intervals 1–4
COV$_{5-30}$	Relative coefficient of variation (for the intervals 5–30 in relation to the average interval length of the first four utterances)	$COV_{5-30} = SD_{5-30}/[(avIntDur_{1-4})/\sqrt{26}] \times 100$
%IntDur	Relative interval duration (related to the given interval length of 750 ms)	Average interval length of all 30 utterances in ms/750 ms × 100
maxSylRep (syl/s)	Maximum syllable repetition in syllables per second	

Table 3
Group results and statistics.

A: Mean results and statistics between patients and controls

	Controls (n = 32)			
	Mean/SD	Condition1 (StimOFF/MedOFF) Mean/SD	Condition 2 (StimON/MedOFF) Mean/SD	Condition 3 (StimON/MedON) Mean/SD
maxSylRep (syl/s)	3.69/1.34	2.70/0.88	3.03/0.91	2.86/0.96
COV$_{test1}$	1.00/0.30	2.04/1.50*	2.94/2.27**	2.77/1.57**
COV$_{test2}$	0.98/0.34	2.43/1.77**	3.36/2.25**	2.94/1.82**
COV$_{test3}$	1.04/0.42	3.91/3.02**	4.43/2.58**	3.29/1.47**
%IntDur$_{test2}$	100.35/10.48	92.86/11.58*	98.57/12.82	94.52/15.43
%IntDur$_{test3}$	96.88/9.73	88.09/15.84*	88.66/15.95*	84.45/19.48**

B: Statistics between treatment conditions within patient group

	Condition 1 (StimOFF/MedOFF) vs. condition 2 (StimON/MedOFF)	Condition 2 (StimON/MedOFF) vs. condition 3 (StimON/MedON)	Condition 1 (StimOFF/MedOFF) vs. condition 3 (StimON/MedON)
maxSylRep (syl/s)	n.s.	n.s.	n.s.
COV$_{test1}$	$p < 0.01$	n.s.	$p < 0.01$
COV$_{test2}$	$p < 0.05$	n.s.	n.s.
COV$_{test3}$	n.s.	$p < 0.05$	n.s.
%IntDur$_{test2}$	n.s.	n.s.	n.s.
%IntDur$_{test3}$	n.s.	n.s.	n.s.

C: Statistics between speech tests within patient group/treatment condition

	COV test1 vs. test2	COV test1 vs. test3	COV test2 vs. test3	%IntDur test2 vs. test3
Condition 1 (StimOFF/MedOFF)	$p = 0.05$	$p < 0.01$	$p < 0.05$	n.s. ($p = 0.07$)
Condition 2 (StimON/MedOFF)	n.s.	$p < 0.01$	$p < 0.01$	$p < 0.01$
Condition 3 (StimON/MedON)	n.s.	n.s.	n.s.	$p < 0.01$

* $p<0.05$.
** $p<0.01$.

The examiner who conducted the analysis of the speech material (S.S.) was blinded to participants' condition.

Statistics

Winstat© (Bad Krotzingen/Germany) was used for statistical analyses. Since the data were widely normally distributed (Kolmogorov–Smirnov test), ANOVA with post hoc paired t-test was performed for conditions within the PD group and with post hoc unpaired t-test for the comparison between groups (PD vs. control group). Pearson correlation was used to test for significant correlations. The level of significance was set at $p = 0.05$.

Results

Controls as well as patients correctly performed the task in all three conditions in the sense that no wrong pronounced syllables (e.g. "ta" instead of "pa" or "pa-to" instead of "pa-ti") were found in the recordings. Thus, the main goal to produce a correct syllable was achieved in the tasks. Changes in rhythmic performance are described in the following. (For detailed results see Table 3 and Fig. 1.)

Comparison between control group and PD group condition 1 (StimOFF/MedOFF) – "disease effect"

COV$_{5-30}$ was significantly elevated in the PD group as compared to the control group as an evidence for an irregular performance of syllable repetition in the PD group in all three tests ($p < 0.01$ and $p < 0.05$ for condition 1, test1). %IntDur in test 2 and especially in test 3 were reduced in the PD group indicating an impairment to reproduce the given pace of 80/min throughout the performance with a tendency to perform in a faster pace than requested ($p < 0.05$). No significant differences were seen concerning maxSylRep between the groups.

Comparison within the PD group between the conditions – "treatment effect" (Table 3B)

In test 1 (self-paced repetition), in both StimON conditions (condition 2 and 3), COV$_{5-30}$ was elevated as compared to condition 1 (StimOFF) ($p < 0.01$). These differences were less pronounced, but still seen in test 2 (paced repetition) ($p < 0.05$). In test 3 (paced repetition of alternating syllables), the worst performance concerning syllable repetition stability was seen in condition 2 (StimON/

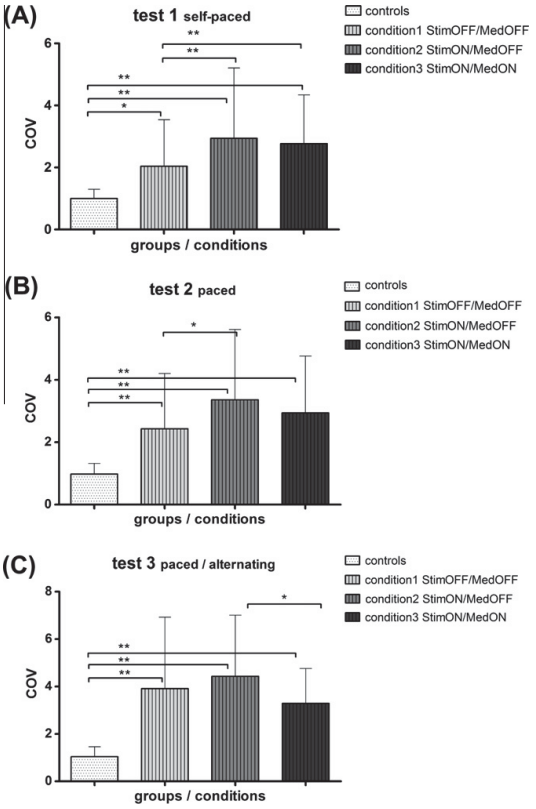

Fig. 1. Group results for coefficient of variation (COV). (A) Test 1: Self-paced syllable repetition. (B) Test 2: Paced syllable repetition. (C) Test 3: Paced alternating syllable repetition. * = $p < 0.05$/** = $p < 0.01$, error bars: standard deviation.

MedOFF), whereas additional levodopa administration (condition 3) led to a certain amelioration of COV_{5-30} ($p < 0.05$). The pattern of increasing pace velocity from test 2 to test 3 was preserved in all conditions without significant differences.

PD speakers condition 1: StimOFF/MedOFF (Table 3C)

Instability of syllable repetition as indicated by an elevated COV_{5-30} was less pronounced in test 1 (self-paced repetition) and was worst in the most complex test 3 (paced repetition of alternating syllables). Furthermore, there was a trend to shorter %IntDur in test 3 as compared to test 2 ($p = 0.07$). UPDRS III showed a significant correlation to COV_{5-30} in test 1 ($R = 0.520$, $p = 0.05$) and test 2 ($R = 0.587$, $p = 0.01$), but not in test 3. However, in test 3, there was a negative correlation between UPDRS III and %IntDur ($R = -0.435$, $p = 0.01$).

PD speakers condition 2: StimON/MedOFF (Table 3C)

Again, instability of syllable repetition was found to increase from test 1 to test 2 and was worst in test 3. In test 3, the velocity of syllable repetition was even faster than in test 2 (paced repetition) and lay significantly above the demanded velocity as indicated by a %IntDur < 100% ($p < 0.01$). No correlations were seen between UPDRS III and the speech variables.

PD speakers condition 3: StimON/MedON (Table 3C)

Although there was a tendency to higher COV_{5-30} in the more complex tests 2 and 3, the differences were not significant. In test 3, the pace acceleration as indicated by a %IntDur < 100% was even higher than in test 2 ($p < 0.01$). UPDRS III showed a positive correlation to COV_{5-30} in test 2 ($R = 0.448$, $p = 0.014$) and test 3 ($R = 0.448$, $p = 0.01$).

Discussion

In general, the current study confirms previous findings of an impairment of steady vocal pace performance in PD [16] and provides further insights into the mechanisms of syllable repetition under conditions of increasing complexity. In healthy speakers, the steadiness of syllable repetition and precision of interval reproduction were independent from the requirements of pace (self-chosen versus given) and articulation (single syllable repetition versus alternating syllables). In the PD group under untreated conditions (condition 1: StimOFF/MedOFF), the steadiness of syllable repetition showed a further deterioration in the tests that required several equal goals (test 2: steady repetition plus keeping the given pace; test 3: steady repetition plus alternating the syllables plus keeping the given pace). Furthermore, instead of keeping the given pace, patients performed in a faster velocity, with an even higher pace in the most complex test 3. Therefore, the worst performance in test 3 indicated by the highest COV_{5-30} values in all three conditions cannot be solely explained by the higher motor speech demands of the alternating pattern of syllable reproduction since one would rather expect a slowing than an acceleration of pace to compensate for the enhanced level of articulatory requirements in dysarthric speakers. These results might be interpreted as an insufficiency of Parkinsonian patients to simultaneously fulfill equal demands within the motor speech domain which actually should proceed in a highly automated mode. In condition 1, patients with higher global motor impairment showed a more pronounced instability of syllable repetition in the first two tests; however, in test 3, UPDRS III scores were not correlated to COV_{5-30} but to %IntDur indicating a dissociation of dual motor speech performance from pure motor function. Basal ganglia dysfunction in PD has been suggested to lead to an inability to perform automated movements or to difficulties in switching a learned task to the automatic phase [36]. Some of the factors related to PD patients having difficulty achieving automaticity are less efficient neural coding of movement and failure to shift execution of automatic movements more subcortically [37]. As a compensatory strategy, the performance requires more attentional resources and goes along with a stronger connectivity of networks consisting amongst others of the rostral supplementary motor area, the cingulate motor area and the left cerebellum which has been visualized by functional MRI studies [36,38]. Furthermore, there is a wealth of evidence that PD patients have difficulties performing two separate motor or cognitive tasks at the same time [39,40] maybe due to limited global processing resource or the enhanced attentional strains demanded by the impaired shift to automaticity [41,42]. Although these findings are mainly based upon investigations on pure cognitive tasks or on the effect of cognitive challenge on gait function in PD [43–46], one might assume that the same mechanisms of impaired automaticity and dual task performance are

also relevant concerning the motor speech domain leading to the phenomenon of increasing instability of syllable repetition with rising complexity of the tasks.

In condition 2 (StimON/MedOFF), the characteristic pattern of impairment already observed in condition 1 was in general found to be preserved, however, with an even worse steadiness of syllable repetition in all tests. These findings are in line with the results of a previous investigation which revealed a deterioration of syllable repetition capacity under STN–DBS [34]. Several hypotheses could explain the worsening effect of STN–DBS on the stability of syllable repetition and overall speech performance in PD. On the one hand, STN could have a different somatotopy for speech and body motor control. As a consequence, the site of STN stimulation which leads to the best effect on limb movement might provoke a worsening of dysarthria as it has been reported for contacts placed dorsomedial to the STN [47]. On the other hand, deterioration of speech under STN–DBS might be induced by the spread of current to adjacent areas such as the corticobulbar tract or pallidofugal and cerebellothalamic pathways [48,22]. Thus, speech intelligibility has been shown to be dependent from electrode localization and stimulation [49]. However, if the finding of further vocal pace deterioration under STN–DBS were caused by the spread of current e.g. to the internal capsule and the corticobulbar pathways for laryngeal motor control producing an iatrogenic spastic dysarthria, one would expect a reduction of maxSylRep which was not observed in our series. On the other hand, high-frequency DBS within the STN has been shown to worsen distinctive *cognitive* functions such as verbal fluency accompanied by a metabolic hypoactivity in frontal cortical areas as revealed by PET studies [50–53].

In condition 3, the additional levodopa administration led to a certain amelioration of pace stability especially in the most complex test 3 where participants featured a better performance than under condition 1 and 2. Therefore, levodopa seemed to compensate to some degree for the negative effects of STN–DBS on syllable repetition stability, however, without an influence on the second demand of the task, consisting of a correct reproduction of the given pace. Interestingly, in condition 3, the remaining UPDRS III scores under STN–DBS and levodopa administration were positively correlated to COV in test 2 and 3 indicating to a certain relevance of non-dopaminergic mechanisms at least for the performance of the more challenging motor speech tasks. Under the assumption that the current study deals with reliable paradigms for the investigation of single, dual and triple task performance within the motor speech domain, the results suggest a differential influence of levodopa and STN–DBS on multiple task performance. On the one hand, STN–DBS can be associated with cognitive deficits, decline in working memory and reduced information processing speed in some patients, which seems to be more pronounced under more complex cognitive challenges and with bilateral STN–DBS [54,55]. On the other hand, levodopa has been shown to enhance the functional connectivity in neuronal motor networks and to modulate task-evoked activation within frontostriatal circuits in healthy subjects [47] and in Parkinsonian patients as well [56–59]. Although there is a consensus that the extent of preoperative levodopa responsiveness predicts the efficacy of STN–DBS [60] and there is evidence that levodopa and STN–DBS exert similar influences on the dysfunctional cortico-subcortical networks in PD [61], the assumption of congruency of the both therapeutic measures has recently been scrutinized [62]. For example, levodopa and STN–DBS have been shown to differentially influence bradykinesia of arm and fingers [63]; furthermore, STN–DBS had a beneficial effect on motor perseverations that did not respond to dopaminergic stimulation [64]. On the other hand, speech intelligibility and articulation patterns can even worsen with STN–DBS plus additional levodopa [49,65].

Conclusions

According to the current data, Parkinsonian speakers feature a distinctive pattern of impairment of basic motor speech performance which might be provoked by a disturbance of automaticity, which is further unmasked under rising task complexity. Additionally, the results justify the hypothesis of a differential impact of levodopa and STN–DBS on cognitive-motor speech performance. Future studies are warranted to corroborate and further validate the introduced speech paradigms, which might serve as non-intrusive and easily applicable tools for the investigation of cognitive-motor speech function in PD.

Financial disclosure/possible conflict of interest concerning the research related to the manuscript

M.S., A.S. and L.W. have received—unrelated to the current project—honoraria in the past from Medtronic and St. Jude Medical, companies that manufacture DBS hardware.

Acknowledgements

The authors thank all patients and control subjects for cooperation. We thank Margret Schmidt and Marika Biernat for supporting the experiments.

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frontiers in NEUROLOGY

ORIGINAL RESEARCH ARTICLE
published: 13 January 2014
doi: 10.3389/fneur.2013.00218

Effect of subthalamic stimulation on voice and speech in Parkinson's disease: for the better or worse?

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Background: Deep brain stimulation of the subthalamic nucleus, although highly effective for the treatment of motor impairment in Parkinson's disease (PD), can induce speech deterioration in a subgroup of patients. The aim of the current study was to survey (1) if there are distinctive stimulation effects on the different parameters of voice and speech and (2) if there is a special pattern of preexisting speech abnormalities indicating a risk for further worsening under stimulation.

Methods: $N = 38$ patients with PD had to perform a speech test without medication with stimulation ON (StimON) and stimulation OFF (StimOFF). Speech samples were analyzed: (1) according to a four-dimensional perceptual speech score and (2) by acoustic analysis to obtain quantifiable measures of distinctive speech parameters.

Results: Quality of voice was ameliorated with StimON, and there were trends of increased loudness and better pitch variability. $N = 8$ patients featured a deterioration of speech with StimON, caused by worsening of articulation or/and fluency. These patients already had more severe overall speech impairment with characteristic features of articulatory slurring and articulatory acceleration under StimOFF condition.

Conclusion: The influence of subthalamic StimON Parkinsonian speech differs considerably between individual patients, however, there is a trend to amelioration of voice quality and prosody. Patients with stimulation-associated speech deterioration featured higher overall speech impairment and showed a distinctive pattern of articulatory abnormalities at baseline. Further investigations to confirm these preliminary findings are necessary to allow neurologists to pre-surgically estimate the individual risk of deterioration of speech under stimulation.

Keywords: deep brain stimulation of the subthalamic nucleus, Parkinson's disease, dysarthria, quality of voice, speech impairment, perceptual analysis of speech, acoustic speech analysis

INTRODUCTION

Chronic deep brain stimulation of the subthalamic nucleus (STN-DBS) has been shown to be superior over best medical treatment in patients with motor fluctuations in Parkinson's disease (PD) (1, 2). However, the effects of STN-DBS on voice and speech have been found to be variable or even adverse, at least in a subgroup of patients. According to overall perceptual evaluation based upon the speech item of the Unified Parkinson's Disease Rating Scale/Motor Score (UPDRS III), the prevalence of dysarthria under STN-DBS has been reported to vary between 1% after 6 months up to 70% at 3 years follow-up with an average of 9.3% (3–5). Furthermore, "communication" was the only item of the PD Questionnaire that showed deterioration under STN-DBS in the recently published EARLYSTIM study (6). However, there are also reports of an amelioration of distinctive parameters of voice, loudness, and non-speech vocal measures in individual PD patients under STN-DBS (7–13). As a possible explanation for these contradictory findings, it has been proposed that STN-DBS could reduce a few distinctive dysarthrophonic symptoms such as reduced loudness and glottic tremor in PD. However, these beneficial effects could be outweighed by a general dysarthrogenic impact on prosodic and articulatory functions leading to reduced overall speech intelligibility (7, 14–17). Furthermore, as a possible hint for a negative effect on basal motor speech performance, STN-DBS was found to induce abnormalities in the speed and regularity of non-speech syllable repetition (18). In respect to these conflicting results, there is still a lack of reliable predictability of speech motor outcome in the individual patient, although clinical and surgical factors (e.g., anatomic location of the electrode contact, amplitude of current in the right and left STN) seem to be critical for the speech outcome under STN-DBS (19).

The aim of the current study was to analyze the effect of STN-DBS on voice and speech in a group of PD patients based upon perceptual and acoustic analysis of distinctive speech modalities.

It had been chosen to test patients without the additional effect of dopaminergic medication to identify the exclusive impact of STN-DBS with stimulation settings previously optimized for best overall motor performance in order to test patients under their "naturalistic" stimulation situation. According to previous studies, it had been hypothesized that there would be a differential outcome of patients' speech performance under stimulation and therefore, it was further intended to better characterize the pattern of changes within the single speech modalities. In particular, attention was given to the expected subgroup of patients with a deterioration of speech performance under stimulation in order to identify patterns of preexisting speech impairment that might serve as "risk profile" for further worsening under STN-DBS.

PATIENTS AND METHODS

From 2008 to 2010, 38 patients with idiopathic PD and chronic bilateral STN-DBS were recruited for this study. The diagnosis of PD was based upon the UK Parkinson's Disease Society Brain Bank Criteria (20). After an overnight wash out period of medication, each patient was tested under two conditions OFF medication: stimulation OFF (StimOFF) and stimulation ON (StimON) and underwent a neurological examination according to UPDRS Motor Scale (UPDRS III) immediately before performing the speech task. Patients' characteristics are summarized in **Table 1**.

As control group we tested 30 age-matched healthy persons.

All participants were native German speakers, and the speech evaluation was based upon a German text. For the speech test, each participant had to read a given text composed of four phonetically balanced sentences; furthermore, participants had to produce the vowel, /a/, for as long as possible. Speech samples were digitally recorded using a commercial audio software (Steinberg WaveLab®/Steinberg Media Technologies GmbH, Hamburg, Germany) and a head-set microphone with a defined mouth to microphone distance. Speech records of the reading task were perceptually analyzed independently by two examiners (Sabine Skodda and Wenke Grönheit) who were blinded for the speakers' condition, according to a four-dimensional scoring system that is used for the description of Parkinsonian dysarthria in our clinic (**Table 2**). Inter-rater reliability was high with $w = 0.923$; in cases of divergent ratings, the higher score was chosen for the further analysis.

Additionally, acoustic analysis of speech was performed for several speech parameters for the objective description of voice, articulation, fluency, and prosody by the use of PRAAT (21) (**Table 3**). Jitter, shimmer, and noise to harmonics-ratio as measures of *voice quality* were based upon the analysis of sustained phonation (22). Mean fundamental frequency (meanF_0) of the reading task was taken as measure of *phonation. Loudness* was defined as average sound pressure level of the entire reading task. Description of *intonation variability* was based upon standard deviation (SD) of the fundamental frequency (F_0SD). Analysis of *speech rate* was performed by measuring the length of each syllable and each pause respectively based on the oscillographic sound pressure signal. Besides the conventional speech rate variables as net speech rate (NSR) and pause ratio (PR%), we additionally defined the percent ratio of pauses within polysyllabic words (Pinw%), which can be taken as a measure of precision of *stop consonant articulation* (23). *Articulatory acceleration* (AA) in the course of reading was defined as the difference of NSR between the first and last sentence with values >0 indicating acceleration (23). Description of *vowel*

Table 1 | Participants' characteristics/results of the comparison of perceptual speech analysis.

	Control group	PD group		
		StimOFF/MedOFF	StimON/MedOFF	
	Mean/SD/range	Mean/SD/range	Mean/SD/range	
Age (y)	67.14/8.03/48–80	65.69/7.85/45–77		
Age at DBS surgery		62.13/8.01/43–73		
Disease duration (y)		15.71/6.07/6–28		
Disease duration at DBS surgery		12.24/6.97/5–24		
	Median/1.–3. quartile	**Median/1.–3. quartile**	**Median/1.–3. quartile**	
UPDRS III		39/32.75–47	21.37/10.17/7–50	$p < 0.0001$
UPDRS III axial subscore (% of overall UPDRS score)		11/8.75–16 (*29.50%*)	7/5–10.25 (*37.74%*)	$p < 0.0001$
UPDRS III tremor subscore (% of overall UPDRS score)		3.5/0–8 (*11.95%*)	0/0–2.25 (*6.47%*)	$p < 0.0001$
UPDRS III akinesia subscore (% of overall UPDRS score)		25/19–29.50 (*60.72%*)	13/7–20.25 (*61.90%*)	$p < 0.0001$
UPDRS III speech item		1/0–2	1/0–2	n.s.
Perceptual speech score	1/0–2***	5/4–7	5/3–7	n.s. ($p = 0.085$)
Voice	0/0–1****	1/1–2	1/1–1.25	$p = 0.001$
Articulation	0/0–0****	2/1–2	2/1–2	n.s
Fluency	0/0–0****	1/1–2	1/1–2	n.s
Prosody	0/0–0****	1/0–1.25	1/0–1	n.s.

****$p < 0.001$.*

*****$p < 0.0001$ related to the comparison between control group and PD group with StimOFF/MedOFF.*

y, years; SD, standard deviation; n.s., not significant; UPDRS III, unified Parkinson's disease rating scale, Part III: motor part.

Table 2 | Perceptual speech score.

Speech modality		Definition
Voice	0	Normal
	1	Voice quality slightly hoarse, slightly reduced loudness, intermittently present
	2	Voice quality hoarse or tremulous, slightly reduced loudness, continuously present
	3	Voice quality hoarse or tremulous, markedly reduced loudness
	4	Marked reduction of voice quality, whispery, or scratchy voice
Articulation	0	Normal articulation
	1	Slightly reduced articulatory accuracy, intermittently present
	2	Slightly reduced articulatory accuracy, continuously present
	3	Markedly reduced articulatory accuracy, slightly reduced intelligibility
	4	Markedly reduced intelligibility
Tempo/fluency	0	Normal speech tempo and distribution of speech pauses
	1	Slightly reduced or accelerated speech tempo, intermittently present
	2	Rushes of speech and prolonged pauses, not very pronounced or only intermittently present; or slightly reduced speech tempo
	3	Rushes of speech and prolonged pauses, very pronounced or continuously present; or markedly reduced speech tempo
	4	Palilalia
Prosody	0	Normal pitch variability
	1	Slightly monotone
	2	Extremely monotone

Table 3 | Abbreviations and definitions of the speech parameters.

Speech modality	Parameter	Definition
Voice	Jitter (measure of microperturbations of frequency)	Average absolute difference between consecutive differences between consecutive periods, divided by the average period
	Shimmer (measure of microperturbations of amplitude)	Average absolute difference between consecutive differences between the amplitude of consecutive periods
	Noise to harmonics ratio (nhR)	Automatic comparison of harmonic (periodically recurring) and inharmonic sound fractions
	Loudness in dB	Average sound pressure level calculated for entire reading task
	MeanF_0	Average fundamental frequency F_0 calculated for entire reading task
Articulation	Vowel articulation index (VAI)	Comprehensive measure of the "working space" for vowels based upon the extraction of formant frequencies of defined vowels of the reading task according to the formula VAI = (F2/i/ + F1/α/)/(F1/i/ + F1/u/ + F2/u/ + F2/α/)
	Percentage of pauses within polysyllabic words (Pinw%)	Percentage of pauses within polysyllabic words of total speech pauses (periods of silence <10 ms)
Tempo/fluency	Net speech rate (NSR)	Net production of syllables per second based upon reading task
	Pause ratio (PR%)	Percentage of pause rate based upon the reading task
	Articulatory acceleration (AA)	Difference between NSR of the first and last sentence of the reading task (values >0 display acceleration)
Prosody	F_0SD	Standard deviation of fundamental frequencies calculated for the reading task as a measure of pitch variability

articulation was based upon the recently established vowel articulation index/VAI, which is a surrogate parameter of the first and second formant frequencies (F1 and F2) of the three corner vowels, /α/, /i/, and /u/ (24, 25). Since meanF_0, F_0SD, and VAI are related to the speaker's pitch of voice, the comparison of these parameters between PD patients and controls were performed separately for both genders.

Winstat© (Bad Krotzingen/Germany) was used for statistical analyses. ANOVA and paired *t*-test were performed for the comparison of patients with the control group and intra-group comparison (StimOFF vs. StimON). The variables were normally distributed (Shapiro–Wilk test). Continuous variables are presented using mean±SD. Discrete data are reported with median and quartile deviation. For the calculation of inter-rater reliability,

Kendall's coefficient of concordance was used. Spearman rank test was used to perform correlation analyses in order to account for possible outliers especially within the subgroup analyses. Due to the exploratory nature of the study, no adjustments for multiple comparisons were made, and the level of significance was set at $p < 0.05$.

Our study was in compliance with the Helsinki Declaration and had been approved by the local Ethics Committees. Written informed consent was obtained from each participant.

RESULTS

COMPARISON OF CONTROL GROUP WITH PD GROUP StimOFF

Based upon perceptual ratings, the control group featured a significantly better performance of voice, articulation, fluency, and prosody. This was reflected in the acoustic analysis by lower values for jitter, shimmer, and noise to harmonics-ratio indicating a better voice quality, by higher sound pressure levels, higher values for the measures of articulatory precision (Pinw%, VAI) and pitch variability (F_0SD), and an elevated meanF_0 in female speakers. Measures of speech rate and PR% showed no significant differences between the control and the PD group in the StimOFF condition.

This pattern of speech abnormalities was in general preserved also under StimON: there were significantly worse values for shimmer, loudness, VAI, Pinw%, and F_0SD, whereas no significant differences compared to the control group were seen concerning shimmer, meanF_0, NSR, PR%, and AA (numerical data are given in **Tables 1** and **4**).

CORRELATIONS BETWEEN PERCEPTUAL AND ACOUSTIC ANALYSIS

In the PD group in the OFF condition, there were found some significant correlations between "voice" and the jitter ($r = 0.343$, $p = 0.019$) and shimmer values ($r = 0.289$, $p = 0.041$), between "articulation" and Pinw% ($r = -0.277$, $p = 0.046$), but not with VAI, between "fluency" and NSR ($r = 0.385$, $p = 0.008$) and AA ($r = 0.478$, $p = 0.001$), but not with PR%, and between "prosody" and F_0SD ($r = -0.311$, $p = 0.028$). In general, similar correlations between perceptual and acoustic measures were also observed in the ON condition (data not shown).

In the control group, no close correlations were expected because of the low overall speech impairment with an average perceptual sum speech score of 0.88. Accordingly, there were only weak correlations between the perceptual categories "voice," "articulation," "fluency," and "prosody" on the one hand, and the accordant acoustic measures on the other ("voice"/jitter: $r = 0.417$, $p = 0.021$; no significant correlations with shimmer, nhR, and loudness; "articulation"/VAI: $r = 0.307$, $p = 0.072$, no correlation with Pinw%; "fluency"/PR%: $r = 0323$, $p = 0.062$, "fluency"/AA: $r = 0.339$, $p = 0.052$, no correlation with NSR; "prosody"/F_0SD: $r = -0.388$, $p = 0.031$).

COMPARISON WITHIN THE PD GROUP: StimOFF VS. StimON: GROUPWISE COMPARISONS

Total UPDRS III scores as well as the chosen UPDRS subscores (axial, tremor, akinesia) were significantly ameliorated under StimON condition, whereas UPDRS speech score (item 18) showed no significant difference. The more detailed perceptual speech score showed a tendency to reduced overall ratings that were mainly caused by an amelioration of voice quality in the StimON condition whereas the other speech modalities remained widely unchanged. Similar results were observed with the measures of the acoustic analysis where only sound pressure levels and meanF_0 in

Table 4 | Comparison between the PD groups with stimulation OFF and ON and comparison between the PD group/StimOFF and the control group.

	Control ($n = 30$, 15 male)	PD patients ($n = 38$, 22 male)		Comparison StimOFF/Med OFF vs. StimON/MedOFF
	Mean/SD	StimOFF/MedOFF Mean/SD	StimON/MedOFF Mean/SD	
Jitter	1.247/0.704**	2.065/1.941	1.857/2.040	n.s
Shimmer	5.613/2.722***	10.733/7.246	9.272/5.980	n.s.
nhR	0.038/0.033**	0.086/0.097	0.078/0.089	n.s.
Loudness (dB)	78.92/2.10****	70.02/7.54	71.02/8.10	n.s. ($p = 0.064$)
MeanF_0 male	118.46/13.98	117.96/19.40	121.67/18.39	n.s.
MeanF_0 female	192.83/8.51*	169.28/42.59	191.01/23.47	n.s. ($p = 0.05$)
VAI male	0.781/0.070****	0.668/0.074	0.657/0.058	n.s.
VAI female	0.914/0.050****	0.721/0.060	0.714/0.069	n.s.
Pinw%	29.77/8.53****	15.53/10.66	14.85/10.90	n.s.
NSR	5.23/0.56	5.30/1.06	5.23/1.13	n.s.
PR%	18.61/4.17	17.29/9.06	18.31/9.53	n.s.
AA	0.22/0.34	0.35/0.57	0.35/0.57	n.s.
F_0SD male	20.13/6.78**	14.58/4.29	15.42/4.45	n.s.
F_0SD female	31.86/6.11****	16.76/5.31	19.69/4.90	n.s.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$.

female PD speakers showed a (non-significant) tendency to amelioration. However, no further changes were observed between StimOFF and StimON conditions in the groupwise comparison (numerical data are given in **Tables 1** and **4**).

COMPARISONS WITHIN THE PD GROUP AND CHARACTERIZATION OF THE SUBGROUP WITH SPEECH DETERIORATION

In an evaluation of the different qualitative speech modalities in the individual patients, 12/38 patients showed no difference in the sum perceptual speech score, 18/38 showed an amelioration of the sum speech score (13 patients improved by 1 point, 4 patients by 2 points, and 1 patient by 3 points respectively), which was mainly caused by an improvement of voice ($n = 12$) and less often by amelioration of articulation ($n = 7$), prosody ($n = 4$), or fluency ($n = 1$). These improvements showed no correlation with improvement of motor symptoms as tremor, akinesia, or axial symptoms based upon the accordant UPDRS III subscores.

In 8/38 patients, there was a deterioration of speech (6 patients worsened by 1 point, 1 patient each worsened by 2 points and 3 points respectively) with worsening of articulation in 4 patients, of fluency in 3, of prosody in 3, and of voice in 1 patient. The group of patients with speech deterioration showed no significant difference concerning age and disease duration, however, UPDRS III was significantly higher in StimOFF. No differences were seen with the tremor, akinesia, or axial UPDRS subscores. The UPDRS speech item showed a tendency to higher values, however, without statistical significance. In 5/8 patients with speech deterioration, the right STN was stimulated with higher current amplitudes (compared to 11/30 in the subgroup without worsening of speech) than the left-side STN due to asymmetry of motor symptoms going along with higher total electric energy delivered/TEED (26) since pulse width, frequency, and impedances (measured in $n = 30$ patients) showed no significant differences (see **Table 5**).

Regarding the perceptual rating of speech performance in StimOFF, no significant differences were seen concerning voice, articulation, and prosody, but there was a tendency to higher impairment in the "fluency" category and the sum perceptual score as well (see **Table 6**). Based upon acoustic analysis, the speech pattern in the OFF condition in the subgroup with speech worsening under stimulation was characterized by significant reduction of Pinw% and higher grade of articulatory acceleration/AA. The other measures of speech rate (NSR and PR%) at least showed a tendency to higher average articulatory velocity/NSR and elevated ratio of speech pauses/PR%. No significant differences were found with the remaining measures of speech (see **Table 6**). Furthermore, higher UPDRS III scores in the OFF condition were correlated to more pronounced worsening of articulation ($r = -0.655$, $p = 0.039$) and overall speech performance ($r = -0.608$, $p = 0.055$) according to the perceptual speech score. Similarly, higher measures of AA showed a correlation to articulatory worsening ($r = 0.655$, $p = 0.039$) and higher values for jitter, shimmer, and nhR were correlated with an elevation of the perceptual sum speech score under stimulation ($r = 0.733$–0.764, $p = 0.014$–0.019 respectively). No such "OFF condition" pattern or similar correlations could be identified for the subgroup of patients who featured no speech worsening under stimulation.

DISCUSSION

In the groupwise comparison of speech in the StimOFF and ON conditions, only perceptual assessment of voice quality showed a significant amelioration under STN-DBS, which was mirrored by similar trends toward lower values for the accordant acoustic measures (jitter, shimmer, and nhR) as well as higher values for loudness of speech in the acoustic analysis, however, without statistical significance. These findings are in line with previous investigations reporting on a stimulation-induced improvement of voice quality and loudness, however, not necessarily accompanied by an amelioration of overall speech performance (6–12) that can in general be confirmed by our data. In the current study, perceptual and acoustic measures of articulation, fluency, and prosody showed no consistent behavior under STN-DBS, instead, there was a group of $n = 8$ patients with worsening of overall speech performance that could not be restricted to a consistent pattern but was induced by different degrees of deterioration of articulation, fluency, and prosody.

One main result of the present investigation was the identification of a subgroup with preexisting speech abnormality in the OFF condition that showed a further deterioration under stimulation. The preexisting pattern of dysarthria was found to be characterized by a high degree of articulatory slurring (as mirrored by reduced Pinw%) accompanied by an acceleration of speech in the course of the performance (indicated by significantly elevated AA). Furthermore, these patients featured not only higher overall UPDRS III scores in the OFF condition, but worse global speech performance (according to UPDRS speech item and the perceptual sum score) as well, however without statistical significance which might be due to the small sample size of $n = 8$. In this subgroup of patients with speech deterioration, there also was a correlation between higher values for UPDRS III, articulatory acceleration/AA and poor voice quality (indicated by higher values for jitter, shimmer, and nhR) in the OFF condition and the perceptually detected degree of speech worsening under stimulation.

There are only very few previous studies focused on the preexisting patients' characteristics which might be "risk factors" for stimulation-induced speech deterioration. Dromey and Bjarnason tested six PD patients with speech deterioration under STN-DBS according to perceptual ratings, however, acoustic measures of articulation and phonation deriving from analysis of speech and non-speech utterances showed mixed results with some speakers improving and others becoming worse on individual measures (27). In another investigation, negative effects on speech intelligibility were found in two out of seven PD patients and were attributed to slight stimulation-induced facial dyskinesia, which was not observed in our study (28). Pützer and coworkers obtained objective measures of phonatory and articulatory movements based upon acoustic analysis of non-speech syllable production in nine PD patients and reported mixed results under stimulation: Precision of glottal and supraglottal articulation as well as the phonatory function was reduced in some speakers, whereas for others an improvement was observed (15). In a subgroup of patients, the accuracy of stop consonant articulation was found to be impaired under stimulation, which shows some relation to our finding of increased Pinw% as a measure of overall articulatory

Table 5 | Listing and description of the stimulation parameters, impedance, and electrode settings for the entire PD group and the two subgroups with and without worsening of speech under StimON.

	Left STN					Right STN				
	Ampl. (V) Median/SD/ 1.–3. quartile	**Pulse width (μs)**	**Freq. (Hz) Median/SD/ 1.–3. quartile**	**Imp. (Ω)* Median/SD/ 1.–3. quartile**	**Elec. comb.**	**Ampl. (V) Median/SD/ 1.–3. quartile**	**Pulse width (μs)**	**Freq. (Hz)**	**Imp. (Ω)***	**Elec. comb.**
Entire PD group/$n=38$	3.19/0.74 2.8–3.7	$n=34$: 60 $n=4$: 90	$n=2$: 125 $n=31$: 130 $n=1$: 140 $n=3$: 185 $n=1$: 200	1048/94.79/71–2972	$n=5$: 0- $n=15$: 1- $n=15$: 2- $n=3$: 3-	3.25/0.67 2.8–3.8	$n=35$: 60 $n=3$: 90	$n=31$: 130 $n=2$: 125 $n=1$: 140 $n=3$: 185 $n=1$: 200	958/90.77/60–2190	$n=6$: 0- $n=10$: 1- $n=16$: 2- $n=6$: 3-
Speech worsening under StimON/$n=8$	3.53/0.70/3.0–3.7	$n=6$: 60 $n=2$: 90	$n=8$: 130		$n=2$: 0- $n=4$: 1- $n=2$: 2- $n=0$: 3-	3.66/0.51/3.3–4.2	$n=6$: 60 $n=2$: 90	$n=8$: 130		$n=2$: 0- $n=1$: 1- $n=2$: 2- $n=3$: 3-
No speech worsening/$n=30$	3.10/0.74/2.7–3.7	$n=28$: 60 $n=2$: 90	$n=2$: 125 $n=13$: 130 $n=1$: 140 $n=3$: 185 $n=1$: 200		$n=3$: 0- $n=11$: 1- $n=13$: 2- $n=3$: 3-	3.14/0.67/2.6–3.7	$n=29$: 60 $n=1$: 90	$n=2$: 125 $n=13$: 130 $n=1$: 140 $n=3$: 185 $n=1$: 200		$n=4$: 0- $n=9$: 1- $n=14$: 2- $n=3$: 3-

Ampl., amplitude; freq., frequency; imp., impedance (note that there are only measures for n= 30 patients, the missing data exclusively concern the group of "no speech worsening") elec. comb., electrode combination.*

The amplitude of the right STN stimulation was significantly higher ($p=0.047$) in the subgroup with speech worsening.

Table 6 | Comparison between the PD subgroup with worsening of speech performance with the PD subgroup with unchanged or amelioration of speech performance under stimulation.

	PD group with worse speech performance under stimulation/($n = 8$, 6 male)			PD group with unchanged or better speech performance under stimulation/($n = 30$, 16 male)	Comparison of patients with speech worsening with the group with unchanged/better speech performance, both in the OFF condition
	StimOFF condition Median/1.–3. quartile	**StimON condition Median/1.–3. quartile**	**Comparison OFF vs. ON**	**StimOFF condition Median/1.–3. quartile**	
UPDRS III	48/40.25–52.75	23.5/13.25–33	$p < 0.001$	47/31.5–46.25	$p = 0.024$
UPDRS speech item	1/1–2	1.5/1–2	n.s.	1/1–2	n.s. ($p = 0.102$)
Perceptual analysis/sum score	6/4.5–7.75	7/7–8.75	$p = 0.001$	5/3–7	n.s. ($p = 0.122$)
Voice	1.5/1–2	1.5/1–2	n.s.	1/1–2	n.s.
Articulation	2/1–2	2/2–2	$p = 0.033$	2/1–2	n.s.
Fluency	2/1–2.75	2.5/1.25–3	n.s. ($p = 0.08$)	1/1–2	n.s. ($p = 0.065$)
Prosody	1/1–2	1.5/1–2	n.s. ($p = 0.08$)	1/0–1	n.s.
Acoustic analysis	**Mean/SD**	**Mean/SD**		**Mean/SD**	
Jitter	1.535/1.244	1.560/1.304	n.s.	2.211/2.087	n.s.
Shimmer	8.551/6.256	9.062/7.097	n.s.	11.335/7.483	n.s.
nhR	0.064/0.063	0.061/0.068	n.s.	0.092/0.105	n.s.
Loudness (dB)	71.17/6.70	72.15/4.73	n.s.	69.72/7.83	n.s.
MeanF0 male	124.13/16.90	123.44/15.17	n.s.	117.75/20.09	n.s.
MeanF0 female	168.34/8.05	192.50/0.30	(n.a.)	169.41/45.69	(n.a.)
VAI male	0.681/0.075	0.648/0.065	n.s.	0.648/0.070	n.s.
VAI female	0.704/0.057	0.674/0.154	(n.a.)	0.723/0.063	(n.a.)
Pinw%	8.14/7.72	7.09/7.86	n.s.	17.50/10.56	$p = 0.025$
NSR	5.46/1.48	5.48/1.61	n.s.	5.26/0.99	n.s.
PR%	19.30/10.07	21.26/7.19	n.s.	16.75/8.87	n.s.
AA	0.95/0.73	0.61/0.63	n.s.	0.19/0.40	$p = 0.022$
F_0 SD male	15.94/2.80	14.24/3.93	n.s.	14.30/4.18	n.s.
F_0 SD female	16.16/1.58	19.60/5.99	(n.a.)	16.85/5.68	(n.a.)

(n.a.): statistical analysis not applicable because of small sample size.

slurring. However, in this previous study, the mixed response of patients' articulatory capacity had not been related to the speech performance in the StimOFF condition.

Although the present study gives some first indication for specific patient-related risk factors for speech worsening under STN-DBS, there are some undisputable limitations, especially because of the small sample size, which lessens the value of the statistic analysis. Since there was an overlap of values for AA and Pinw% in the "deteriorating" group and the group of patients with no stimulation-induced worsening of speech, positive and negative predictive values for these measures were only poor. Besides, it has to be mentioned that the speech evaluation was based upon a German text and therefore, some of the findings could be language-dependent.

Furthermore, the impact of surgical factors has not been accounted for although in previous studies, the position of the stimulation electrode within the medial and/or posterior portion of the STN was linked with poorer speech intelligibility (19, 29, 30). However, even with electrodes exactly located within the STN, a subgroup of 36% patients was found to feature a deterioration of speech under stimulation in another study (31). This might at least be explained by the explicit stimulation settings in the individual patient since high amplitude and/or high frequency stimulation was consistently found to be a risk factor for worsening of speech (19, 29–34). Furthermore, selective or predominant stimulation of the left-side STN was reported to induce profoundly negative effects on prosody, articulation, and hence, intelligibility (33, 34). In contrast, in our study, the majority of patients with speech deterioration had higher stimulation amplitudes on the right-side STN, and no clear differences were seen concerning frequencies, pulse width and/or the electrode contacts chosen for stimulation. These preliminary observations seem to underline the assumption that surgical or stimulation factors alone cannot account for overall speech performance under STN-DBS.

Another methodical weakness of our investigation is the lack of pre-surgical speech data that would be necessary to rule out a possible microlesion effect of electrode placement. Up till now, there are only very few investigations with speech testings before and at certain follow-up intervals after DBS surgery (11, 19, 28, 35). In the largest of these studies, there was a correlation between poorer speech outcome after 1 year and higher pre-surgical general motor impairment (19). Another study on seven patients found no consistent effects of DBS surgery alone (that is, no hint of the microlesion effect) and no consistent stimulation effect on speech under STN-DBS after 3 months, but a slight improvement of pitch variability and sound pressure levels under stimulation 6 months post-op (27).

Summarized, despite some methodical limitations, the current study provides first evidence for a specific patient-related "risk profile," namely high overall motor and speech impairment according to UPDRS III and preexisting articulatory slurring and articulatory hastening, which seems to be associated with further decline of speech performance under STN-DBS with stimulation settings optimized for motor function. In this subgroup of patients, a positive effect of STN-DBS on phonatory and voice parameters seems to be outweighed by a pro-dysarthrogenic stimulation effect that is correlated to the degree of AA and overall voice impairment in the OFF condition. Subsequent studies are warranted, especially with pre-surgical speech recordings, to further corroborate these preliminary findings to allow neurologists to pre-surgically estimate the individual risk of deterioration of speech under STN-DBS.

AUTHOR CONTRIBUTIONS

Dr. Sabine Skodda – study concept and design, acquisition and analysis of data, statistical analysis, and conception and writing of the manuscript; Dr. Wenke Grönheit – acquisition and analysis of data; Dr. Uwe Schlegel – critical revision of the manuscript for important intellectual content; Dr. Martin Südmeyer – analysis and interpretation of data, revision of the manuscript; Dr. Alfons Schnitzler – critical revision of the manuscript for important intellectual content; Dr. Lars Wojtecki – study concept and design, study supervision, and critical revision of the manuscript; All authors have read the manuscript, and the paper has not previously been published and is not under simultaneous consideration by another journal. There has been no ghost writing by anyone not named on the authors list.

ACKNOWLEDGMENTS

Sabine Skodda received speakers honoraria and travel grants from Desitin Arzneimittel GmbH, Orion Pharma GmBH, Teva Pharmaceutical Industries LTD., UCB Pharma LTD., and GlaxoSmithKline plc., Martin Südmeyer and Lars Wojtecki received consultant honoraria for teaching and talks/travel compensation from St. Jude Medical and "Medtronic Inc.". Alfons Schnitzler received honoraria for lectures on symposia sponsored by "Medtronic Inc.," and served as a consultant for "Medtronic Inc." Wenke Grönheit and Uwe Schlegel have no disclosures to be made.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 28 September 2013; paper pending published: 19 November 2013; accepted: 31 December 2013; published online: 13 January 2014.
*Citation: Skodda S, Grönheit W, Schlegel U, Südmeyer M, Schnitzler A and Wojtecki L (2014) Effect of subthalamic stimulation on voice and speech in Parkinson's disease: for the better or worse? Front. Neurol. **4**:218. doi: 10.3389/fneur.2013.00218*
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology.

Behavioural Brain Research 250 (2013) 199–205

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Motor and cognitive placebo-/nocebo-responses in Parkinson's disease patients with deep brain stimulation

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HIGHLIGHTS

- Positive motor expectations exert *motor placebo* responses on proximal movements.
- These motor placebo responses resemble the clinically known STN-DBS-effect.
- Shorter disease duration is correlated with a stronger motor placebo response.
- In motor responders positive motor expectations exert *cognitive nocebo* responses.
- These cognitive nocebo responses are likely due to implicit learning mechanisms.

ARTICLE INFO

Article history:
Received 26 March 2013
Received in revised form 26 April 2013
Accepted 27 April 2013
Available online xxx

Keywords:
Deep brain stimulation
Expectation
Nocebo
Parkinson's disease
Placebo
Verbal fluency

ABSTRACT

Expectation contributes to placebo and nocebo responses in Parkinson's disease (PD). Subthalamic nucleus (STN) deep brain stimulation (DBS) improves proximal more than distal movements whereas it impairs executive cognitive function such as verbal fluency (VF). We investigated how expectation modulates the pattern of motor improvement in STN-DBS and its interaction with VF.

In a within-subject-design, expectation of 24 hypokinetic-rigid PD patients regarding the impact of STN-DBS on motor symptoms was manipulated by verbal suggestions (positive [placebo], negative [nocebo], neutral [control]). Patients participated with (MedON) and without (MedOFF) antiparkinsonian medication. Motor function was assessed by Unified Parkinson's Disease Rating Scale and quantitative kinematic analysis of proximal alternating hand and distal finger tapping. VF was quantified by lexical and semantic tests.

In MedOFF, expectation significantly affected proximal but not distal movements resulting in better performance in the placebo than in the nocebo condition. Placebo responders with improvement of ≥25% were characterized by a trend for impaired lexical VF.

These results indicate that positive motor expectations exert both motor placebo and cognitive nocebo responses by further enhancing the STN-DBS-effect on proximal movements and by impairing VF. The placebo response on motor performance resembles the clinically known STN-DBS-effect with stronger improvement in proximal than distal movements. The nocebo response on VF is likely due to implicit learning mechanisms associated with an expectation-induced placebo response on motor performance.

1. Introduction

Placebo responses represent a complex psychobiological phenomenon. The counterpart of a placebo response is the so called nocebo response, comprising all negative effects such as worsening of symptoms or side effects induced by an inert substance or treatment. Cognitive factors like expectations regarding the effect of a treatment and associative learning processes like classical conditioning, have been identified as main mechanisms mediating placebo responses [for reviews see 1,2].

Abbreviations: BDI, Beck depression inventory; DBS, deep brain stimulation; MedOFF, off antiparkinsonian medication; MedON, on antiparkinsonian medication; MDRS, Mattis dementia rating scale; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; NRS, numeric rating scale; PD, Parkinson's disease; STN, subthalamic nucleus.

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http://dx.doi.org/10.1016/j.bbr.2013.04.051

In Parkinson's disease (PD), motor symptoms and physiological processes can be substantially affected by placebo treatments. For example, the administration of placebo drugs induces a significant dopamine release in the dorsal and ventral striatum [3,4] as well as alterations in neuronal firing patterns in the subthalamic nucleus [5] which are both associated with an improvement in motor function. Moreover, in a recent meta-analysis, Goetz et al. [6] conclude that clinical improvement in response to pharmacological placebo treatment is observed in 16% (range: 0–55%) of PD patients. Furthermore, placebo and nocebo responses have also been described in PD patients treated with deep brain stimulation of the subthalamic nucleus (STN-DBS). For instance, bradykinesia is not only affected by the stimulation condition per se (STN-DBS ON vs. OFF) but is additionally modulated by patients' varying expectations induced by awareness vs. non-awareness of the fact that STN-DBS is switched ON vs. OFF [7]. Likewise, motor function can be considerably modulated by means of opposite positive or negative expectations regarding STN-DBS with improved motor performance following positive expectation and impaired motor performance in consequence of negative expectation [8,9].

Dopamine replacement therapy and STN-DBS are well established and effective treatments of motor symptoms in PD [12–14]. Although both treatments generally lead to an improvement in motor function, differential therapeutic effects have been described for fine finger movements representing distal movements and arm movements reflecting proximal movements: While the dopamine precursor levodopa has a more pronounced effect on distal compared to proximal movements, STN-DBS improves proximal more than distal movements [15,16]. Additionally, a side-effect often observed in patients treated with therapeutic STN-DBS is impairment in verbal fluency [17–19].

Being part of a transregional and translational research unit investigating the role of conditioning and expectation as underlying mechanisms of placebo and nocebo responses in different physiological systems, pathophysiological conditions and therapeutic interventions, we set out to study the effect of expectation in PD patients treated with STN-DBS addressing specific issues which have not been investigated so far. Placebo and nocebo responses in PD patients treated with STN-DBS have not been studied regarding: (1) motor functions differentially affected by STN-DBS such as distal and proximal movements, (2) executive cognitive functions affected by STN-DBS, i.e. verbal fluency, (3) the manipulation of the pharmacological status, i.e. with and without antiparkinsonian medication, (4) a PD patient subgroup that is homogenous with respect to the predominant clinical symptoms, i.e. hypokinetic-rigid PD patients. Thus, the effect of expectation regarding STN-DBS should be investigated considering motor and non-motor functions that are specifically affected by therapeutic STN-DBS. Therefore, the aim of the present study was to investigate how differing expectations (positive [placebo], negative [nocebo], neutral [control]) regarding STN-DBS modulate motor function and verbal fluency in hypokinetic-rigid PD patients with and without antiparkinsonian medication. Given evidence that placebo responses mimic the response to the active treatment, we hypothesized that the effect of expectation would be more pronounced on proximal compared to distal movements. Moreover, as typical side-effects of the active treatment can also be induced by placebo treatments [20], a further aim of the study was to analyze whether expectation regarding the impact of STN-DBS on motor function would also affect verbal fluency.

2. Materials and methods

2.1. Participants

Twenty-four Parkinson's disease patients of the hypokinetic-rigid subtype (12 men and 12 women, mean age: 62.83 ± 1.9 [SEM] years, range: 39–77) with chronic bilateral STN-DBS participated in the study. Patients were recruited from the Movement Disorder Centre of the University hospital of Duesseldorf. In order to rule out possible cognitive impairment and clinically relevant depressive symptoms all patients were tested with the Mattis Dementia Rating Scale (MDRS) [21] with a cut-off score of <130 and filled in the Beck Depression Inventory (BDI) [22] with a cut-off score for clinically relevant depression of ≥18 before study participation. For patients' characteristics and stimulation parameters, see supplementary Tables 1 and 2.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbr.2013.04.051

2.2. Experimental design and procedure

Three expectation conditions (positive [placebo], negative [nocebo], neutral [control]) were applied in a counterbalanced order using a repeated-measures design. Patients were randomly assigned to one of six possible orders.

Each patient participated twice on two consecutive days, 1 day on pharmacological treatment, i.e. patients took their usual antiparkinsonian medication (MedON) and 1 day when patients had withdrawn from any antiparkinsonian medication for at least 12 h (MedOFF) prior to study participation. Whether patients were on or off medication on the first day was counterbalanced across patients, i.e. half of them were without medication on the first day and on medication on the second day and vice versa. The six orders of the expectation conditions were randomly combined between MedON and MedOFF.

The experimental sessions were performed at the Department of Neurology of the University hospital of Duesseldorf. First, at the start of the experimental session STN-DBS was turned off (Stim OFF). After a time interval of ten minutes patients were informed that STN-DBS would be turned on again. However, before STN-DBS was switched on, patients' expectations regarding the effect of the subsequent stimulation on motor symptoms were manipulated through verbal suggestions by an experienced movement disorders physician (L.W., C.H. or S.F.). The physician who induced expectations was held constant for each patient. Positive expectations were induced by informing the patient that the stimulator will be turned on with parameter settings which will strongly improve motor function (placebo condition). Negative expectations were induced by telling the patients that the stimulator will be turned on with parameter settings which will strongly impair motor function (nocebo condition). To induce a neutral expectation regarding the effect of the upcoming stimulation, patients were told that the parameter settings of the subsequent stimulation will not have any impact on motor function (control condition). Immediately after expectations were verbally induced, patients rated the extent to which they expected an improvement or impairment or no change of their current motor function by the upcoming stimulation (see Section 2.2.1). Thereafter, the stimulator was turned on (Stim ON) according to the patient's individual therapeutic settings. Note that the stimulation parameters (intensity, frequency and pulse width) were identical under all three conditions (placebo, nocebo and control). After each condition the stimulator was switched off for 10 min. STN-DBS usually improves symptoms such as rigidity and tremor in less than a minute and improvement in bradykinesia is gradually achieved within a couple of minutes [23]. Therefore, in each condition dependent variables were assessed after the stimulator had been turned on for 15 min. The experimental session lasted about 120 min per day. For an overview of the experimental procedure, see Fig. 1.

The experimenter who assessed the dependent variables was blinded regarding the expectation condition whereas patients were blinded with respect to the fact that in each condition the identical therapeutic stimulation parameters were applied. Hence, to ensure the successful manipulation of expectation it was necessary that patients were naïve concerning the exact aim of the study. Accordingly, the written patient information included a cover story regarding the aim of the study, i.e. that the study was designed to systematically investigate different settings of STN-DBS stimulation parameters and their effect on motor function. In addition, it gave note that three stimulator settings would be randomly chosen and that patients would be informed about the subsequent effect on motor function which would be induced by the chosen parameter settings. This approach was approved by the local ethics committee (see Section 2.3). Furthermore, the patient information comprised details about possible transient unpleasant but unharmful side effects resulting from changes of stimulation parameters like prickling or dizziness.

2.2.1. Expectation rating

Immediately after expectations regarding the stimulation effect of STN-DBS on motor symptoms were verbally induced, patients rated to what extent they expected an improvement, impairment or no change of their current motor state. Therefore, patients' expectation was assessed by means of a numeric rating scale (NRS) ranging from +5 indicating expectation of strong improvement to -5 indicating expectation of strong impairment of motor function while 0 represented expectation of no change of motor function.

2.2.2. Movement parameters

2.2.2.1. Distal and proximal movements: finger tapping and diadochokinesia. A finger tapping task was chosen to reflect distal movements and diadochokinesia was used to determine proximal hand movements. Finger tapping and diadochokinesia were objectively assessed by means of a 3D ultrasound motion detection system (CMS 70P

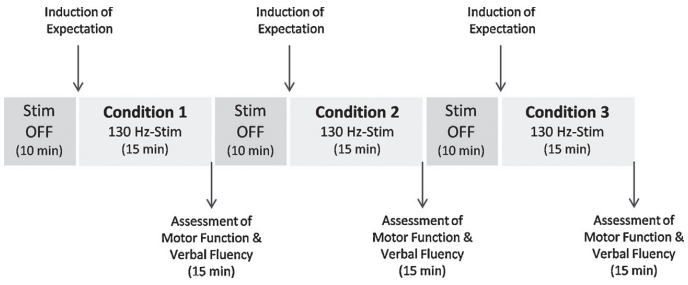

Fig. 1. Overview of the experimental procedure. Throughout the experiment, three different expectations (positive [placebo], negative [nocebo], neutral [control]) were verbally induced in a counterbalanced order. Motor function and verbal fluency were assessed three times. Parkinson's disease patients participated twice, once with ($n = 24$) and once without ($n = 23$) antiparkinsonian medication. Stim OFF denotes that deep brain stimulation of the subthalamic nucleus (STN-DBS) was switched off whereas 130 Hz-Stim indicates that STN-DBS was switched on at a frequency of 130 Hz or higher.

v 5, Zebris, Isny, Germany). This system detects the position of the ultrasound markers with a 1 mm spatial and high temporal resolution (100 Hz with two markers) by estimating transmission times and triangulation of marker position from three ultrasound microphones integrated into a mobile receiver platform. The mobile receiver platform was positioned about 1 m opposite to the side of the hand that performed finger tapping and about 1 m in front of the hand performing diadochokinesia, respectively. While assessing distal (finger tapping) and proximal (diadochokinesia) movements patients were comfortably seated in a chair with bilateral armrests. Patients performed finger tapping and diadochokinesia using the hand/arm of the clinically more affected side.

For the finger tapping the elbow was positioned on the chair's armrest and the lower arm was elevated in an angle of about 70° above the armrest. Two ultrasound transmitters were attached to the patients' hand; one to the lateral side of the index finger and one to the thumbnail. Patients were instructed to perform the finger tapping by moving the index finger and thumb as fast and as wide apart as possible. Moreover, patients were instructed to perform the movements as smoothly as possible. Three trials of 10 s of finger tapping were carried out in each condition. Between the three trials patients paused for a period of 30 s.

During diadochokinesia the elbow was positioned on the chair's armrest and the lower arm was elevated in an angle of about 70° above the armrest. Patients were asked to hold a wooden bar (diameter: 2.8 cm, length: 20 cm, weight: 104 g) with two 3D markers (ultrasound transmitters) attached to each end in the fist of the clinically more affected side. As a starting position patients were asked to keep the bar vertical and were then further instructed to turn it clockwise and anti-clockwise as fast, as smoothly and as far as possible to each side by alternating pronation–supination movements of the forearm. Furthermore, patients were asked to avoid shifts in the movement plain while performing diadochokinesia. Three trials of 10 s of diadochokinesia were performed in each condition. After each trial patients paused for a period of 30 s.

2.2.3. Clinical parameters: UPDRS

Overall motor function was assessed using the motor section of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale [24]. On 18 items, motor function is rated on a 5 point scale where 0 indicates normal function and 4 indicates severe impairment. For the motor section (MDS-UPDRS III) the ratings across all items are summed up to a total score between 0 and 132. MDS-UPDRS III was videotaped and – except for rigidity which was assessed immediately within the experimental sessions – rated by three blinded movement disorder specialists (C.H., M.S., L.W.) at a later date.

2.2.4. Cognitive function: verbal fluency

Assessment of verbal fluency was performed using four different tests, a formal lexical test, a semantic category test, a formal lexical category change test and a semantic category change test. In all tests patients were instructed to produce as many words as possible within a time period of 1 min.

In the formal lexical test patients were asked to produce words beginning with a certain letter (e.g. 'S'). In the semantic category test patients had to name words of a specific semantic category (e.g. 'animals'). In the formal lexical category change test, patients were instructed to switch between two different letters (e.g. a word beginning with the letter 'G' followed by a word beginning with the letter 'R'). In the semantic category change test patients were asked to alternate between two semantic categories (e.g. 'clothes' and 'flowers'). The aforementioned tests assess divergent thinking with focus on the creativity of search strategies in the formal lexical and semantic category test. In contrast, the formal lexical and semantic category change test put a stronger emphasis on flexibility functions.

As dependent variables were assessed six times throughout the experimental sessions (three conditions in MedON and in MedOFF, respectively), six parallel test versions of each verbal fluency test were used to avoid learning effects. The order of the parallel tests was applied randomly.

2.2.5. Questionnaires

To identify potential mediators of placebo and nocebo responses, patients' state and trait anxiety were assessed using the STAI-S and STAI-T questionnaire [25]. Moreover, patients were asked to fill in a questionnaire on beliefs about medicines [26] which assesses general views about medicines with the subscales *overuse* and *harm*. Additionally, this questionnaire focuses on specific views assessing personal beliefs about the necessity of prescribed medication to treat the disease (subscale *necessity*) and concerns about potential adverse effects of the treatment (subscale *concern*). For a more detailed description of the questionnaire see Horne et al. [26].

2.3. Ethics

All patients gave informed, written consent. The study was approved by the local ethics committee of the Medical Faculty, Heinrich-Heine-University (study no. 3403), Duesseldorf, Germany and was in accordance with the standards of the declaration of Helsinki guidelines.

2.4. Data analysis and statistics

Prior to the beginning of the experimental session in MedON, one patient dropped out because he was feeling ill on that day resulting in a sample size of $n = 23$ in MedON and of $n = 24$ in MedOFF.

Data of distal (i.e. finger tapping) and proximal (i.e. diadochokinesia) movements were stored on the recording PC's hard disk and analyzed offline. Each data set was inspected offline for artifacts. Epochs containing artifacts were excluded from further analysis. Due to considerable artifacts, one dataset of finger tapping was excluded in MedON and MedOFF, respectively. Data were analyzed using custom-made MATLAB™ 7.1 (The Mathworks Inc., Natick, MA, USA) scripts. Finger tapping was analyzed regarding mean frequency. Additionally, the product of mean amplitude and mean frequency was assessed. Therefore, we calculated the Euclidian distance between the two ultrasound transmitters and reduced noise by Savitzky–Golay filtering (order: 5, frame size: 41). Subsequently, we applied the Matlab function 'findpeaks' to the sign-inverted signal to detect local minima. A local minimum was considered to represent a touch of thumb and index finger if it was smaller than an individually adapted threshold. The tapping frequency was defined as the mean number of touches per second. In order to detect local maxima, the function 'findpeaks' was applied to the original signal. A local maximum was required to exceed 0.1 times the signal's standard deviation. Marker distance was averaged over all local maxima to obtain mean amplitude. Diadochokinesia was analyzed with respect to mean angular speed, calculated as follows: subtraction of ultrasound transmitter coordinates yielded a vector in 3-dimensional space that represented the pointing direction of the bar at each point in time. Ideally, this vector moves in one plane only. In practice, however, there is a plane containing most but not all of the movements. This plane was estimated by singular value decomposition. Subsequently, we projected the pointing direction vectors onto this plane and calculated the angle with the second singular vector to obtain angular motion. Angular motion was smoothed using a Savitzky–Golay filter (order: 10, frame size: 100). Angular velocity was computed by calculation of the first derivative of angular motion. Angular speed was defined as the absolute of angular velocity.

Of the three recorded trials for finger tapping and diadochokinesia, respectively, only the trial with the best performance was used for further analysis. This procedure was applied for each of the three conditions.

For MDS-UPDRS III, in each condition, a sumscore was calculated as well as a subscore for *bradykinesia*. Moreover, for the clinically more affected side, subscores were calculated for the MDS-UPDRS III items *finger tapping* representing distal movements and for *pronation–supination* reflecting proximal movements.

Table 1
Descriptive data of the outcome measures: mean and standard error of mean angular speed of diadochokinesia, frequency as well as frequency × amplitude of finger tapping, MDS-UPDRS III-sumscore and MDS-UPDRS III-subscores for bradykinesia, finger tapping, pronation–supination and verbal fluency tests.

	MedOFF			MedON		
	Placebo	Control	Nocebo	Placebo	Control	Nocebo
Mean angular speed of diadochokinesia (degree/s)[a]	324.57 ± 30.06	296.52 ± 24.25	279.35 ± 25.13	379.98 ± 25.21	382.09 ± 26.57	380.70 ± 22.55
Frequency of finger tapping (tap/s)[a]	2.59 ± 0.15	2.49 ± 0.16	2.56 ± 0.17	2.79 ± 0.19	2.85 ± 0.20	2.90 ± 0.20
Frequency × amplitude of finger tapping[a]	191.95 ± 20.95	182.92 ± 21.12	174.70 ± 19.08	206.69 ± 19.37	191.43 ± 12.58	193.53 ± 14.54
MDS-UPDRS III-sumscore	23.50 ± 1.90	24.46 ± 1.83	24.08 ± 1.65	19.61 ± 1.92	19.78 ± 1.73	19.26 ± 1.65
MDS-UPDRS III-bradykinesia	17.33 ± 1.40	18.17 ± 1.33	18.00 ± 1.14	13.61 ± 1.23	13.91 ± 1.22	13.34 ± 1.15
MDS-UPDRS III-finger tapping[a]	1.83 ± 0.18	1.70 ± 0.20	1.67 ± 0.17	1.43 ± 0.15	1.39 ± 0.17	1.17 ± 0.16
MDS-UPDRS III-pronation–supination[a]	1.75 ± 0.21	1.96 ± 0.21	2.04 ± 0.19	1.48 ± 0.19	1.61 ± 0.19	1.61 ± 0.20
Formal lexical (no. of words)	9.33 ± 0.94	9.96 ± 0.89	9.42 ± 0.89	9.87 ± 0.77	10.87 ± 0.97	10.43 ± 1.03
Semantic category (no. of words)	14.41 ± 0.97	15.29 ± 0.84	14.08 ± 0.96	14.57 ± 1.21	15.83 ± 1.21	14.87 ± 1.15
Formal lexical category change (no. of words)	4.04 ± 0.34	4.17 ± 0.25	4.29 ± 0.46	4.22 ± 0.33	4.26 ± 0.45	4.30 ± 0.41
Semantic category change (no. of words)	5.38 ± 0.38	5.50 ± 0.30	6.38 ± 0.62	5.78 ± 0.48	5.91 ± 0.49	6.00 ± 0.37

MedOFF, off antiparkinsonian medication; MedON, on antiparkinsonian medication; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale

[a] Clinically more affected side.

Regarding verbal fluency, correct number of words was summed up for each patient for each of the four subtests in each condition. Then mean number of words were computed across all patients and compared between conditions.

For the statistical analysis, prior to all analyses, univariate normal distribution was tested using Kolmogoroff–Smirnov goodness-of-fit test for each variable. Repeated measures analyses of variance (ANOVA) with condition (placebo vs. control vs. nocebo) as repeated measures factor were computed for MedON and MedOFF. Greenhouse–Geisser corrections were applied in case of violations of sphericity assumption. Paired *t*-tests were used for post hoc analyses. When multiple comparisons were performed, Bonferroni correction was applied. Statistical data analysis was performed using PASW statistics version 18 (SPSS, Chicago, IL). Moreover, for the complete group, a placebo-/nocebo-induced change was determined by calculating the percentage deviation from the control condition. This change was then correlated with disease associated factors (e.g. disease duration, intake of levodopa equivalent dose, duration of chronic bilateral STN-DBS) using Pearson's correlation.

In case of a significant effect of expectation on motor function we further analyzed data with respect to placebo/nocebo responders. Therefore, a placebo/nocebo response was defined as an improvement (placebo) or impairment (nocebo) in motor function of at least 25% compared to control condition (i.e. patients' individual therapeutic STN-DBS with neutral expectation reflecting the actual STN-DBS effect).

3. Results

In summary, expectation modulated proximal movements whereas no effect of expectation was observed for distal movements. Furthermore, verbal fluency was affected in patients who showed a placebo response in proximal movements. Descriptive data of results are presented in Table 1.

3.1. Effects of expectation on movement parameters

Proximal movements, i.e. mean angular speed of diadochokinesia, were significantly modulated by expectation in MedOFF ($F_{(2,46)} = 5.24$, $p < 0.01$; see Fig. 2). In the placebo condition, angular speed was significantly higher than in the nocebo condition ($t_{(23)} = 2.808$, $p = 0.005$ [one-tailed]). The comparison between placebo vs. control condition revealed increased mean angular speed in the placebo condition (+9.46%) but missed the Bonferroni adjusted significance level ($t_{(23)} = 1.962$, $p = 0.03$ [one-tailed]). For the nocebo vs. control comparison, no effect was observed with respect to mean angular speed of proximal movements ($t_{(23)} = -1.476$, $p = 0.08$ [one-tailed]). Moreover, the placebo-induced change in proximal movements in MedOFF was inversely correlated with disease duration ($r = -0.44$, $p < 0.05$) whereas it was not associated with intake of levodopa equivalent dose or duration of chronic bilateral STN-DBS (all $p > 0.58$).

The effect of expectation on proximal movements was also reflected in a trend regarding the MDS-UPDRS III subscore *pronation–supination* ($F_{(2,46)} = 2.60$, $p = 0.085$). As can be inferred from the descriptive data (see Table 1), this trend is basically due to the difference between the placebo and nocebo condition indicating that patients were less impaired on proximal movements in the placebo than in the nocebo condition. In contrast, for MedON, no effect of expectation on proximal movements observed ($F_{(2,44)} = 0.007$, $p = 0.993$). Likewise, expectation did neither affect finger tapping (frequency and frequency × amplitude) nor any other MDS-UPDRS III sub- or sumscore in MedOFF and MedON, respectively (all $p > 0.13$).

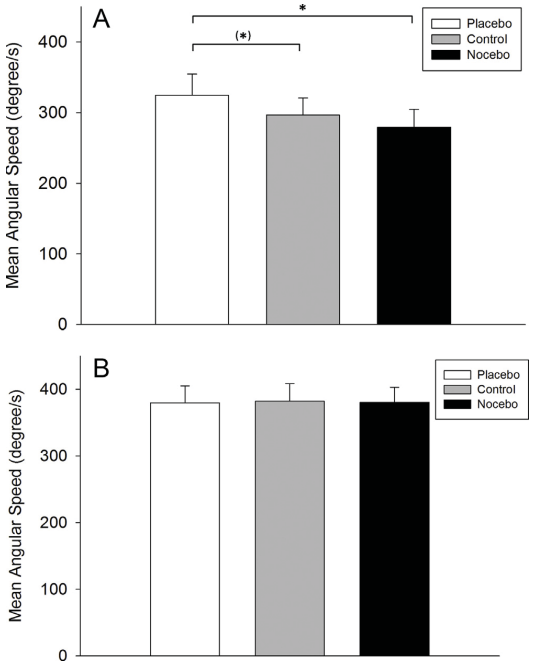

Fig. 2. Effect of expectation on proximal movements. Mean and standard error of the mean are shown for mean angular speed of proximal hand movements of the clinically more affected side under the three expectation conditions (placebo, control, nocebo) when the same Parkinson's disease patients were off ($n = 24$, A) and on antiparkinsonian medication ($n = 23$, B). * indicates that the empirical *p*-value is lower than the Bonferroni corrected significance level of $\alpha' = 0.017$ whereas (*) represents a trend ($p = 0.03$) after Bonferroni correction.

Since a significant effect of expectation was observed on proximal movements in MedOFF, these data were further analyzed with respect to responders vs. non-responders. According to the prespecified criterion of a placebo or nocebo response, 10 out of 24 (i.e. 43.67%) patients showed a placebo response with a mean improvement of 33.71 ± 3.56% in proximal movements. Only one nocebo responder was observed (with a decrease in mean angular speed of −30.71% compared to control). Responders and non-responders did not differ with respect to disease associated variables (disease duration, intake of levodopa equivalent units, duration of chronic bilateral STN-DBS), psychological variables (trait and state anxiety, beliefs about medicine) and expectation rating (all $p > 0.12$).

3.2. Effects of expectation on verbal fluency

To test for an impairment in verbal fluency in placebo responders, we compared the mean number of words between the placebo and control condition, separately for the four subtests in MedOFF. In the formal lexical test, patients produced on average fewer words in the placebo (−12.5%) than in the control condition (placebo: 9.1 ± 1.84 vs. control: 10.4 ± 1.45) which was reflected in a trend ($t_{(9)} = -1.948$, $p = 0.08$) whereas no effect of expectation was observed for any other verbal fluency subtest (all $p > 0.39$; mean number of words: semantic test: placebo: 15.4 ± 1.65 vs. control: 15.9 ± 0.78; lexical category change test: placebo: 4.2 ± 0.63 vs. control: 4.5 ± 0.48; semantic category change test: placebo: 5.0 ± 0.49 vs. control: 5.3 ± 0.65). Moreover, for the complete group, no significant effect of expectation regarding motor function was observed on any verbal fluency test in MedOFF (all $p > 0.21$) and MedON (all $p > 0.40$), respectively.

3.3. Expectation rating regarding the effect of STN-DBS on motor function

Under the three conditions, patients' expectations regarding motor function differed significantly in MedOFF ($F_{(2, 46)} = 84.98$, $p < 0.001$) and MedON ($F_{(2, 44)} = 64.29$, $p < 0.001$). Post hoc pairwise comparisons revealed a significant difference between all conditions in MedOFF and MedON with regard to patients' expectation (all $p < 0.001$) which indicates that opposite expectations as well as a control condition were induced successfully (see Fig. 3).

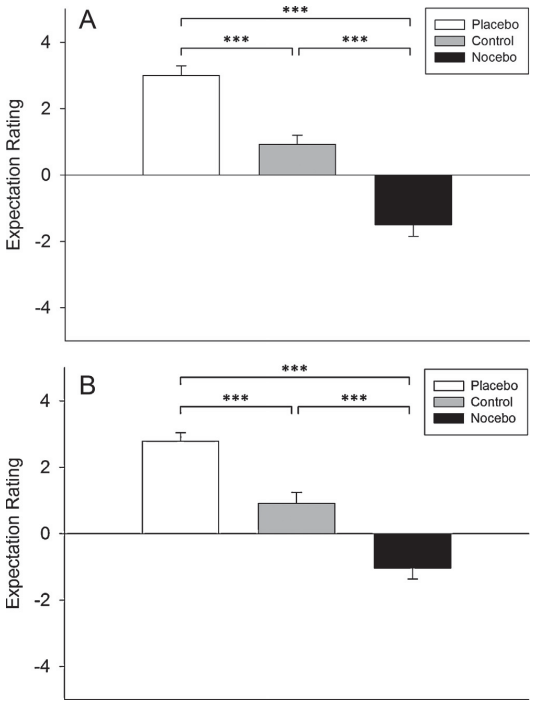

Fig. 3. Expectation rating. Mean and standard error of the mean for the expectation rating under the three conditions (placebo, nocebo, and control) when the same Parkinson's disease patients were off ($n = 24$, A) and on antiparkinsonian medication ($n = 23$, B). On a numeric rating scale patients' expectations regarding the impact of the following deep brain stimulation of the subthalamic nucleus on motor symptoms were assessed. +5 indicates expectation of strong improvement, −5 indicates expectation of strong impairment while 0 represents expectation of no change of motor function. ***$p < 0.001$.

4. Discussion

The aim of the present study was to investigate the role of expectation on motor and non-motor functions in hypokinetic-rigid PD patients chronically treated with STN-DBS.

A key finding of the present study is that performance in proximal movements was modulated by expectation when patients were off medication whereas distal movements were not affected. The further subgroup analysis of the expectation effect regarding responders vs. non-responders revealed a placebo response in 10 out of 24 patients. In these placebo responders, impairment in lexical verbal fluency was observed in MedOFF, indicating that positive expectations regarding motor function exert both motor placebo and cognitive nocebo responses.

4.1. Motor effects

Our findings regarding motor responders are in line with other studies where placebo responses were reported in PD patients [3] treated with STN-DBS [8,9] and indicates that the effect of STN-DBS on proximal movements can be further enhanced by means of verbally induced positive expectations. The occurrence and extent of placebo responses usually vary considerably across individuals and studies. While some individuals are prone to respond to placebo treatments and subsequently show substantial placebo responses, others do not respond to placebo treatments at all [27]. Thus, in placebo research, the identification of possible psychological, neuroendocrine and genetic factors that might play a role in placebo responsiveness and responses, respectively, is matter of current debate and investigation [for a review see 28]. In an attempt to identify factors that potentially mediate placebo responses, we analyzed whether placebo responders and non-responders differed with respect to disease associated variables, psychological variables and expectation rating. However, as responders and non-responders did not differ significantly regarding the aforementioned factors there are apparently other factors involved that are related to placebo responses in PD which need to be elucidated in future studies.

As regards the underlying mechanism of placebo responses in PD, there is evidence for an expectation-induced dopamine release in the ventral and dorsal striatum [3,4,29] in which the dopamine release in the latter is related to improvement in motor function [3]. Such an endogenous dopamine release subsequently to positive expectation might have occurred and mediated placebo responses in the patients of the present study. This hypothesis is supported by the observed inverse correlation between the placebo-induced change in proximal hand movements and disease duration. This correlation might thus be interpreted as proneness of earlier stages of PD – due to a lower dopaminergic deficit – to placebo responses. However, the exact role of dopamine release in the present placebo

responses remains speculative as dopamine release was not measured.

On the other hand, it is of interest that in MedOFF expectation did not have an effect on distal movements. Given that STN-DBS compared to levodopa has a more pronounced impact on proximal than on distal movements and vice versa [15,16], our data suggest that the effect of expectation is particularly prominent on symptoms primarily suppressed by the actual treatment – independent of the role of dopamine.

4.2. Cognitive effects

We showed that positive expectations regarding motor function exerted cognitive nocebo responses besides motor placebo responses. Deterioration of verbal fluency is a side-effect often described in PD patients treated with STN-DBS [17–19]. Although the exact neurophysiological mechanisms underlying this STN-DBS associated impairment are still not precisely understood, there is evidence from imaging studies suggesting a decreased activation in a left-hemispheric frontotemporal network during high-frequency stimulation of the STN which is related to impairment in verbal fluency [30,31]. This indicates that a stimulation-induced interference with basal ganglia thalamocortical circuits may underlie impairment in verbal fluency. The observed impairment in verbal fluency in placebo responders of the present study is in line with a previous study which showed that typical side-effects can also be triggered by a placebo treatment [20] and suggests the occurrence of implicit learning between the therapeutic effect, i.e. improved motor function and side effects, i.e. impaired verbal fluency.

For the complete group, expectation regarding the impact of STN-DBS on motor function had no effect on verbal fluency in MedOFF. This indicates that expectation of improvement or impairment in a specific domain does not exert a global (placebo/nocebo) effect. More precisely, expectation of improvement or worsening in (e.g. motor function) does not readily generalize to other domains (e.g. cognitive function), emphasizing that the effect of expectation is restricted to the domain as to which it is elicited.

4.3. Placebo- versus nocebo-response

In contrast to previous findings, we did not observe relevant nocebo responses regarding motor performance in consequence of verbally induced negative expectations as reported by others [8,9]. A possible explanation might be based on the fact that patients generally have positive experiences and thus strong positive expectations regarding the effect of STN-DBS on motor symptoms whereas the majority of patients usually have not experienced impairment of motor symptoms due to STN-DBS. Thus, in the absence of a previously experienced impairment induced by STN-DBS, it obviously might be more difficult to induce negative expectations regarding STN-DBS than it is to evoke positive expectations. This notion is also supported by the patients' expectation ratings regarding the impact of STN-DBS on motor function: the degree to which patients expected a worsening of motor function by STN-DBS is considerably lower than to which patients expected an improvement (see Fig. 3). Therefore, it is likely that patients' expectations regarding the effect of STN-DBS on motor function were biased by their previous good experience in each condition. The importance of prior experience in the context of placebo and nocebo responses is also pointed out by studies in the field of experimentally induced pain [32,33].

4.4. Medication 'on' versus medication 'off'

Regarding proximal and distal movements, MDS-UPDRS III scores as well as verbal fluency, no effect of expectation was observed when patients were taking their usual prescribed antiparkinsonian medication (MedON). Moreover, in contrast to MedOFF, no placebo responders were observed with respect to proximal movements. A possible explanation for this might be the presence of a ceiling effect: the best possible performance is already obtained in combined therapy (i.e. combination of pharmacological treatment and STN-DBS) and thus cannot be further enhanced by placebo interventions. This interpretation is also corroborated by the fact that across all conditions the best performance in distal and in proximal movements as well as in MDS-UPDRS III scores was observed when patients were on combined therapy (see Fig. 2 and Table 1). Correspondingly, Timmermann et al. [15] showed that performance in proximal movements did not differ between PD patients under combined therapy and healthy matched controls.

5. Conclusion

Taken together, the results of the present study suggest that the effect of expectation regarding STN-DBS closely resembles the actual STN-DBS effect with stronger improvement in proximal than in distal movements and impairment in formal lexical verbal fluency. This indicates that the STN-DBS effect on proximal movements can be further enhanced by positive expectations suggesting that even in very effective treatments as in STN-DBS, the effect of the actual treatment can be boosted by placebo interventions. Moreover, the occurrence of a cognitive nocebo response reflected in impaired verbal fluency in motor placebo responders implies that nocebo responses cannot only be induced by nocebo interventions but may – putatively due to implicit learning between improvement of symptoms and side effects – also be triggered by placebo interventions. Altogether, the findings of the present study underscore the potency and clinical relevance of patients' expectations regarding therapeutic interventions and their outcomes.

Acknowledgments

The authors thank the patients for their contribution. This study was funded by the German Research Foundation (DFG) within the Research Unit 'Expectation and Conditioning as Basic Processes of the Placebo and Nocebo Response. From Neurobiology to Clinical Application' (FOR 1328), Subproject 7 (A. Schnitzler/L. Wojtecki).

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PLOS ONE

Expectation Modulates the Effect of Deep Brain Stimulation on Motor and Cognitive Function in Tremor-Dominant Parkinson's Disease

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Abstract

Expectation contributes to placebo and nocebo responses in Parkinson's disease (PD). While there is evidence for expectation-induced modulations of bradykinesia, little is known about the impact of expectation on resting tremor. Subthalamic nucleus (STN) deep brain stimulation (DBS) improves cardinal PD motor symptoms including tremor whereas impairment of verbal fluency (VF) has been observed as a potential side-effect. Here we investigated how expectation modulates the effect of STN-DBS on resting tremor and its interaction with VF. In a within-subject-design, expectation of 24 tremor-dominant PD patients regarding the impact of STN-DBS on motor symptoms was manipulated by verbal suggestions (positive [placebo], negative [nocebo], neutral [control]). Patients participated with (MedON) and without (MedOFF) antiparkinsonian medication. Resting tremor was recorded by accelerometry and bradykinesia of finger tapping and diadochokinesia were assessed by a 3D ultrasound motion detection system. VF was quantified by lexical and semantic tests. In a subgroup of patients, the effect of STN-DBS on tremor was modulated by expectation, i.e. tremor decreased (placebo response) or increased (nocebo response) by at least 10% as compared to the control condition while no significant effect was observed for the overall group. Interestingly, nocebo responders in MedON were additionally characterized by significant impairment in semantic verbal fluency. In contrast, bradykinesia was not affected by expectation. These results indicate that the therapeutic effect of STN-DBS on tremor can be modulated by expectation in a subgroup of patients and suggests that tremor is also among the parkinsonian symptoms responsive to placebo and nocebo interventions. While positive expectations enhanced the effect of STN-DBS by further decreasing the magnitude of tremor, negative expectations counteracted the therapeutic effect and at the same time exacerbated a side-effect often associated with STN-DBS. The present findings underscore the potency of patients' expectation and its relevance for therapeutic outcomes.

Citation: Keitel A, Ferrea S, Südmeyer M, Schnitzler A, Wojtecki L (2013) Expectation Modulates the Effect of Deep Brain Stimulation on Motor and Cognitive Function in Tremor-Dominant Parkinson's Disease. PLoS ONE 8(12): e81878. doi:10.1371/journal.pone.0081878

Editor: Oscar Arias-Carrion, Hospital General Dr. Manuel Gea González, Mexico

Received July 2, 2013; **Accepted** October 17, 2013; **Published** December 2, 2013

Funding: This study was funded by the German Research Foundation (DFG) within the Research Unit 'Expectation and Conditioning as Basic Processes of the Placebo and Nocebo Response – from Neurobiology to Clinical Application' (FOR 1328), Subproject 7 (A. Schnitzler/L. Wojtecki). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

In Parkinson's disease (PD), dopamine replacement therapy and deep brain stimulation (DBS) of the subthalamic nucleus (STN) are well established and effective treatments for the cardinal symptoms resting tremor, bradykinesia and rigidity [1–3]. Although both treatments generally lead to improvement in motor symptoms, tremor is usually more effectively supressed by STN-DBS as compared to dopamine replacement therapy (for a review see [4]). Moreover, while STN-DBS does not affect overall cognitive function [5,6], adverse effects of therapeutic STN-DBS have been reported for verbal fluency [7–9].

There is considerable evidence that PD is among the disorders in which placebo and nocebo responses play a significant role and can thus contribute to the outcome of treatments. The occurrence of placebo and nocebo responses in PD has been observed in pharmacological placebo-controlled clinical trials [10–12] and in studies experimentally investigating the role of expectation as one of the main mechanisms mediating those responses (for reviews see [13,14]). For example, the administration of placebo drugs which PD patients expect to be a potent antiparkinsonian medication induces a substantial dopamine release in the striatum and alterations in the firing rate of single neurons in the STN associated with improvement in rigidity [15–17]. Furthermore, the therapeutic effect of STN-DBS on bradykinesia can be modulated by verbally induced opposite expectations regarding the effect of STN-DBS with improvement following positive expectation and impairment in consequence of negative expectation [18–21]. Interestingly, a modulation of verbal fluency has been described in relation to expectation-induced placebo responses in bradykinesia in PD patients treated with STN-DBS [21].

While it has been repeatedly shown that bradykinesia and rigidity are responsive to verbally induced expectation [15,18–21], research regarding its effect on resting tremor in PD patients treated with STN-DBS is scarce. Given evidence of a worsening of resting tremor in PD patients performing cognitive tasks or during

mental stress [22], it is of clinical relevance to investigate whether the therapeutic effect of STN-DBS on tremor can also be modulated by patients' expectations. Furthermore, while there is strong evidence for expectation-induced placebo responses, much less is known about nocebo responses in PD which have only been described for bradykinesia in two studies so far [18,20]. Thus, the primary aim of the present study was to systematically investigate how differing expectations induced by verbal suggestions (positive [placebo], negative [nocebo], neutral [control]) modulate the therapeutic effect of STN-DBS on resting tremor and its interaction with verbal fluency in tremor-dominant PD patients. The secondary aim was to study the effect of expectation regarding STN-DBS on proximal and distal movements.

The present study was part of a transregional and translational research unit investigating the role of conditioning and expectation as underlying mechanisms of placebo and nocebo responses in different physiological systems, pathophysiological conditions and therapeutic interventions, where we set out to examine the effect of expectation on motor and cognitive functions in PD patients treated with STN-DBS.

Materials and Methods

Participants

Twenty-four Parkinson's disease patients of the tremor-dominant subtype (19 men and 5 women, mean age: 64.17 ± 1.6 [SEM] years, range: 45–75) with chronic bilateral STN-DBS participated in the study. Patients were recruited from the Movement Disorder Centre of the University Hospital Duesseldorf. In order to rule out a possible cognitive impairment and clinically relevant depressive symptoms all patients were tested with the Mattis Dementia Rating Scale (MDRS [23]) with a cut-off score of ≤ 130 and filled in the Beck Depression Inventory [24] with a cut-off score for clinically relevant depression of ≥ 18 before study participation. For patients' characteristics and stimulation parameters see Table S1 and Table S2.

Experimental Design and Procedure

Using a repeated-measures design, three expectation conditions (positive [placebo], negative [nocebo], neutral [control], see below) were applied in a counterbalanced order and patients were randomly assigned to one of six possible orders. Patients participated twice on two consecutive days, one day on (MedON) and one day off (MedOFF) antiparkinsonian medication, i.e, after withdrawal from any antiparkinsonian medication for at least twelve hours prior to study participation.

The experimental sessions were performed at the Department of Neurology of the University Hospital Duesseldorf. Different expectations (positive, negative, neutral) were induced using verbal suggestions. Prior to each verbal suggestion, STN-DBS was switched off for ten minutes. Before STN-DBS was turned on again patients' expectations regarding the effect of STN-DBS on motor symptoms were verbally manipulated by an experienced movement disorders physician (L.W., M.S., S.F.). In the positive expectation condition, patients were informed that parameter settings of the upcoming stimulation would be adjusted in order to strongly improve tremor and motor function in general (placebo condition). That is, in the aforementioned condition patients were told the following: 'The upcoming stimulation will be turned on with parameter settings which will effectively improve tremor and motor function and thus will considerably improve your current motor state'. In contrast, in the negative expectation condition patients were told that the subsequent stimulation would strongly worsen tremor and motor function (nocebo condition). In the neutral expectation condition, patients were informed that the upcoming stimulation would not have any impact on tremor and motor function (control condition). Thus, the neutral expectation condition in which no specific expectation was induced served as a control condition considered to reflect the genuine STN-DBS effect. The text used for verbal suggestions was standardized and the physician who induced expectations was held constant for each patient. After expectations were verbally induced, STN-DBS was turned on (Stim ON) according to the patient's individual therapeutic settings in each condition. This means that stimulation parameters (intensity, frequency and pulse width) were identical in all three conditions, a fact patients were blinded to. In between the conditions, the stimulator was switched off for ten minutes. STN-DBS usually improves symptoms such as rigidity and tremor in less than a minute and improvement in bradykinesia is gradually achieved within a couple of minutes [25]. Consequently, in each condition assessment of dependent variables was undertaken after STN-DBS had been turned on for 15 minutes. The experimental session lasted about 120 minutes per day. For more details of the procedure see Keitel et al. [21].

Expectation Rating. Directly after expectations were verbally induced, patients rated to what degree they expected improvement, impairment or no change of their current motor state on a numeric rating scale. The numeric rating scale ranged from +5 indicating expectation of strong improvement to -5 indicating expectation of strong impairment of motor function while 0 represented expectation of no change of motor function.

Motor Function: Resting Tremor, Distal and Proximal Movements. Resting tremor was objectively determined by means of an accelerometer whose signal was recorded using an analogue channel of a 3D ultrasound motion detection system (CMS 70P v 5, Zebris, Isny, Germany). In order to assess resting tremor, the accelerometer was attached to the patient's hand of the clinically more affected body side. Tremor was then recorded during 30 seconds of rest in each condition. For recording, patients were seated in a chair with bilateral armrests, placed the hand of the clinically more affected side as comfortable as possible on the armrest and were asked to avoid any voluntary movements.

Moreover, the ultrasound motion detection system was used to assess performance in proximal (diadochokinesia) and distal (finger tapping) movements. For the assessment of diadochokinesia, patients were asked to rotate using a wooden bar with two 3D markers (ultrasound transmitters) attached to each end. To record finger tapping, two ultrasound transmitters were attached to the patients' hand; one to the lateral side of the index finger tip and one to the thumbnail. Patients performed three trials of 10 seconds of finger tapping as well as of diadochokinesia using the hand/arm of the clinically more affected side in each condition. Between the trials, patients paused for a period of 30 seconds. Details regarding the assessment of diadochokinesia and finger tapping can be found elsewhere [21].

Cognitive Function: Verbal Fluency. Verbal fluency was assessed using four different tests: a formal lexical test, a semantic category test, a formal lexical category change test and a semantic category change test. In each test, patients were asked to produce as many words as possible within a time period of one minute. In the formal lexical test patients were instructed to produce words beginning with a specific letter (e.g. 'S'). In the semantic category test they had to name words of a certain semantic category (e.g. 'animals'). In the formal lexical category change test, patients were asked to switch between two different letters (e.g. a word beginning with the letter 'G' followed by a word beginning with the letter 'R'). In the semantic category change test patients had to alternate between two semantic categories (e.g. 'clothes' and 'flowers').

As dependent variables were assessed six times throughout the experimental sessions (three conditions in MedON and in MedOFF, respectively), six parallel test versions of each verbal fluency test were employed in a randomized order to avoid learning effects.

Questionnaires. To identify potential mediators of placebo and nocebo responses, patients' state and trait anxiety were assessed using the STAI-S and STAI-T questionnaire [26]. Moreover, patients were asked to fill in a questionnaire on beliefs about medicines [27] which assesses general and specific views about medicines.

Ethics

According to the cognitive screening (MDRS-scores, see Materials and Methods as well as Table S1) none of the patients who participated in the present study was cognitively impaired and had thus no compromised capacity to consent. All patients gave informed, written consent themselves. The study was approved by the local ethics committee of the Medical Faculty, Heinrich-Heine-University (study no. 3403), Duesseldorf, Germany and was in accordance with the standards of the declaration of Helsinki guidelines.

Data Analysis and Statistics

Data of tremor as well as of distal (i.e. finger tapping) and proximal (i.e. diadochokinesia) movements were stored on the recording PC's hard disk and analyzed offline. Each data set was inspected offline for artifacts. Epochs containing artifacts were excluded from further analysis. Data were analyzed using custom-made MATLAB^{TM} 7.1 (The Mathworks Inc., Natick, MA, USA) scripts. Tremor was analyzed regarding power at tremor frequency. For each patient, the tremor frequency was determined when STN-DBS was switched off and when patients were off antiparkinsonian medication and power at tremor frequency was assessed. Input to spectral analysis was the signal of the accelerometer. Spectral power at individual tremor frequency ± 1 Hz was computed using Welch's method with half-overlapping segments. The segment length equaled twice the sampling rate, i.e. frequency resolution was 0.5 Hz. Additionally, using an exploratory approach, tremor data were further explored with respect to placebo/nocebo responders. Therefore, a placebo/nocebo response was defined as an improvement (placebo) or worsening (nocebo) in resting tremor of at least 10% compared to the control condition (i.e. patients' individual therapeutic STN-DBS with neutral expectation reflecting the actual STN-DBS effect).

Finger tapping was analyzed with respect to mean frequency and additionally regarding the product of mean amplitude and mean frequency. Therefore, the Euclidian distance between the two ultrasound transmitters attached to index finger and thumb was calculated and noise was reduced using Savitzky-Golay filtering (order: 5, frame size: 41). A tap was defined as a local distance minimum and tap amplitudes were determined by the detection of local maxima. The Matlab function 'findpeaks'was applied to the sign-inverted signal in order to detect local minima. A local minimum was considered to represent a touch of thumb and index finger if it was smaller than an individually adapted threshold. The tapping frequency was defined as the mean number of taps per second. For detection of local maxima the function 'findpeaks' was applied to the original signal. A local maximum was required to exceed 0.1 times the signal's standard deviation. Distance traces were checked visually to ensure that individual taps and tap amplitudes were identified correctly.

Diadochokinesia was analyzed with respect to mean angular speed which was calculated as follows: Subtraction of ultrasound transmitter coordinates yielded a vector in 3-dimensional space that represented the pointing direction of the bar at each point in time. Ideally, this vector moves in one plane only. In practice, however, there is usually a plane which contains most but not all of the movements. This plane was estimated by singular value decomposition. Afterwards, we projected the pointing direction vectors onto this plane and calculated the angle with the second singular vector to obtain angular motion. Using a Savitzky-Golay filter (order: 10, frame size: 100), angular motion was smoothed. Angular velocity was computed by calculation of the first derivative of angular motion and angular speed was defined as the absolute of angular velocity. In each condition, only the trial with the best performance in finger tapping and diadochokinesia, respectively, was used for further analysis.

In order to analyze verbal fluency, for each patient the correct number of words was summed up for each subtest in each condition. Then the mean number of words was computed across all patients and compared between conditions.

Prior to all statistical analyses, univariate normal distribution was tested using Kolmogoroff-Smirnov goodness-of-fit test for each variable. Repeated measures analyses of variance (ANOVA) with condition (placebo vs. control vs. nocebo) as repeated measures factor were computed for MedON and MedOFF. Paired *t*-tests were utilized for post-hoc analyses. In case of violation of sphericity, Greenhouse-Geisser corrections were applied. The non-parametric Friedman test was used instead of ANOVA in case of violation of normal distribution, which was the case for tremor data. When multiple comparisons were performed, Bonferroni correction was applied. Comparison of placebo/nocebo responders vs. non-responders was carried out using the non-parametric Mann-Whitney U test. Statistical data analysis was performed using PASW statistics version 18 (SPSS, Chicago, IL). Regarding tremor data, four outliers were excluded prior to further statistical analysis as the values deviated from the respective group mean by more than three standard deviations.

Results

In brief, expectation did not significantly affect resting tremor on group level but modulated the effect of STN-DBS on resting tremor in a subgroup of patients. Furthermore, verbal fluency was adversely affected in patients showing a nocebo response in resting tremor. On the other hand, bradykinesia of proximal and distal movements was not significantly modulated by expectation. Descriptive data of the results are presented in Table 1.

Effect of Expectation on Tremor

In an exploratory approach, tremor data were inspected individually for the analysis of responders and non-responders. According to the prespecified criterion (i.e. improvement [placebo] or worsening [nocebo] in resting tremor of at least 10% compared to the control condition), eight out of twenty patients showed a placebo response with a mean tremor reduction of $-22.84\pm5.20\%$ (see Fig. 1A) and five patients displayed a nocebo response with a mean tremor increase of $39.00\pm13.80\%$ (see Fig. 1B) in MedON. In MedOFF, seven patients were characterized by a placebo response with a mean tremor reduction of $-38.30\pm6.77\%$ (see Fig. 1C) and two patients showed a nocebo response with a mean tremor increase of $95.03\pm72.41\%$ (see Fig. 1D). Yet on group level, expectation did not have a significant effect on resting tremor in MedON and MedOFF (all $p>0.59$).

Table 1. Descriptive data of the outcome measures: Mean and standard error of power at tremor frequency, mean angular speed of diadochokinesia, frequency as well as frequency x amplitude of finger tapping and verbal fluency tests.

		MedOFF			MedON	
	Placebo	Control	Nocebo	Placebo	Control	Nocebo
Power at Tremor Frequency (a.u.)	1.47±0.40	1.88±0.74	1.60±0.51	1.03±0.20	1.12±0.22	1.39±0.38
Mean Angular Speed of Diadochokinesia (degree/s)#	432.31±33.70	436.38±34.99	425.96±39.09	428.90±28.95	421.47±29.38	441.82±27.76
Frequency of Finger Tapping (tap/s)#	2.26±0.13	2.25±0.10	2.32±0.13	2.39±0.16	2.44±0.16	2.41±0.18
Frequency x Amplitude of Finger Tapping#	179.00±17.70	182.43±20.98	179.70±17.53	186.60±19.80	187.25±20.42	178.71±21.01
Formal Lexical (no. of words)	9.04±0.89	8.13±0.98	8.39±0.86	8.74±0.98	7.61±0.68	7.26±0.81
Semantic Category (no. of words)	13.87±0.98	13.48±1.47	13.91±1.01	13.48±1.02	13.26±0.86	12.78±0.74
Formal Lexical Category Change (no. of words)	3.30±0.40	3.56±0.48	3.13±0.46	3.57±0.46	3.57±0.30	3.65±0.38
Semantic Category Change (no. of words)	5.61±0.59	5.04±0.54	5.39±0.38	5.78±0.59	6.00±0.62	4.70±0.35

MedOFF = off antiparkinsonian medication; MedON = on antiparkinsonian medication; # refers to the clinically more affected side; a.u. = arbitrary units.
doi:10.1371/journal.pone.0081878.t001

Moreover, responders and non-responders did not differ significantly with respect to disease-associated variables (disease duration, intake of levodopa equivalent units, duration of chronic bilateral STN-DBS), psychological variables (trait and state anxiety, beliefs about medicine) and expectation rating (placebo responders vs. placebo non-responders: all $p>0.14$; nocebo responders vs. nocebo non-responders: all $p>0.10$).

Effect of Expectation on Verbal Fluency

To assess the impact of expectation regarding STN-DBS on verbal fluency, we tested whether it was affected in the subgroups of patients showing a placebo or nocebo response in resting tremor. Therefore, for placebo responders, the mean number of words was compared between the placebo and control condition, separately for the four subtests. For nocebo responders, this comparison was undertaken for the nocebo and control condition. Due to the small sample size of responders, these analyses were performed using the non-parametric Wilcoxon signed-rank test. These analyses revealed that verbal fluency in the semantic category change test was reduced in nocebo responders, i.e., they produced significantly fewer words in the nocebo compared to the control condition ($p<0.05$; see also Fig. 2) whereas no significant effect of expectation was observed for any other verbal fluency subtest (all $p>0.19$). In contrast, no significant effect of expectation on verbal fluency was observed for placebo responders (all $p>0.28$). Moreover, on group level, the three conditions did not differ significantly regarding lexical and semantic verbal fluency in MedOFF and MedON (all $p>0.12$).

Effect of Expectation on Bradykinesia

Expectation did not significantly affect bradykinesia of distal and proximal movements in MedOFF and MedON, respectively (all $p>0.39$).

Expectation Rating regarding the Effect of STN-DBS on Motor Function

Patients' expectations regarding the effect of STN-DBS on motor function differed significantly in MedON ($F_{(2,\ 46)} = 30.87$, $p<0.001$) and MedOFF ($F_{(2,\ 46)} = 21.30$, $p<0.001$), respectively. Post-hoc pairwise comparisons using paired *t*-tests revealed a significant difference between all conditions in MedON (all $p<0.01$; see Fig. 3A). In MedOFF, expectations between the placebo and nocebo condition as well as between the placebo and control condition differed significantly ($p<0.001$) whereas no significant difference was observed for the comparison between the nocebo and control condition ($t_{(23)} = -0.90$, $p = 0.38$; see Fig. 3B).

Discussion

The main findings of the present study are that the therapeutic effect of STN-DBS on resting tremor was modulated by verbally induced expectation in a subgroup of PD patients and that negative expectation regarding the STN-DBS effect on motor function also adversely affected verbal fluency in patients showing a nocebo response in resting tremor.

Effect of Expectation on Tremor

A nocebo increase of tremor subsequently to negative verbal suggestions was observed in some patients when they were *on* and in others when they were *off* antiparkinsonian medication, indicating that the effect of a dopaminergic treatment as well as STN-DBS can be undermined by negative expectations in a subgroup of patients. Given the known phenomenon that tremor often worsens in PD patients experiencing mental stress or performing cognitive tasks [22], the observed increase of tremor in the nocebo condition suggests that expectation of symptom worsening is apparently also a factor which can contribute to tremor aggravation. Regarding expectation-induced placebo responses, subsets of patients *on* as well as *off* antiparkinsonian medication were characterized by a reduction in resting tremor suggesting that expectation of benefit can increase the therapeutic effect of STN-DBS on tremor. Thus, these findings provide evidence that the therapeutic effect of STN-DBS on resting tremor can be modulated by patients' positive and negative expectations and indicate that tremor is also among the parkinsonian symptoms responsive to placebo and nocebo interventions. This view is supported by a study which evaluated the placebo arm of a randomized placebo-controlled pharmacological trial in PD patients assessing the response of motor symptoms to placebo medication. In essence, cardinal motor symptoms such as bradykinesia, rigidity and tremor responded to placebo treatment. Yet tremor was the symptom where the magnitude and occurrence of placebo responses was lowest [10]. Hence, it seems generally possible to modulate tremor by placebo and nocebo treatments although compared to other parkinsonian symptoms

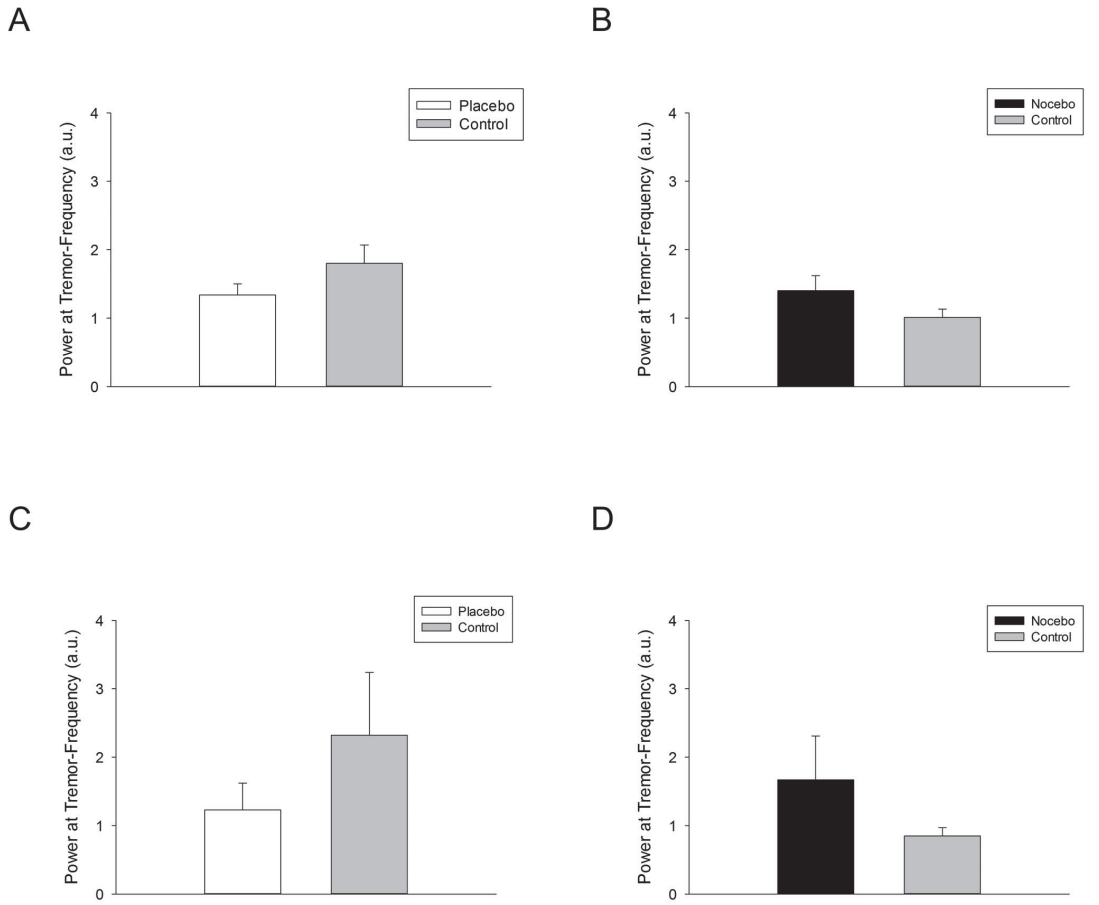

Figure 1. Impact of expectation on resting tremor. Power at tremor frequency (mean and standard error of the mean) in tremor-dominant Parkinson's disease patients treated with deep brain stimulation (DBS) of the subthalamic nucleus (STN). Upper row: Power of tremor in placebo responders in the placebo (open bars) and control condition ([grey bars] n = 8, Fig. 1A) and in nocebo responders in the nocebo (black bars) and control condition (n = 5; Fig. 1B) *on* antiparkinsonian medication. Lower row: Power of tremor in placebo responders (n = 7, Fig. 1C) in the placebo and control condition and in nocebo responders in the nocebo and control condition (n = 2, Fig. 1D) *off* antiparkinsonian medication.
doi:10.1371/journal.pone.0081878.g001

such as bradykinesia and rigidity it appears to be the symptom least responsive to those interventions. Interestingly, concordance in patients who showed a placebo as well as a nocebo response was rather low indicating that being responsive to placebo interventions is not necessarily accompanied by proneness to respond to nocebo treatments.

On group level, expectation did not significantly affect resting tremor in the patients of the present study. This finding is in agreement with a study by Mercado et al. [19] who did not observe a modulation of tremor using a different paradigm to manipulate patients' expectation regarding STN-DBS. However, given the relatively small number of placebo and nocebo responders in the present study, the lack of statistical significance on group level is not surprising. In general, the occurrence and extent of placebo and nocebo responses vary considerably across individuals and studies [28]. Thus, the identification of potential psychological, neuroendocrine and genetic factors that might play a role in mediating responsiveness and responses, respectively, is a matter of current debate and investigation in placebo and nocebo research (for a review see [14]). In an attempt to identify factors potentially mediating placebo and nocebo responses in PD, responders and non-responders were compared regarding disease-associated variables, psychological variables and expectation ratings but did not differ significantly with respect to those factors. Consequently, this may indicate involvement of other factors that are related to placebo and nocebo responses in PD which were not assessed in the present study and need to be elucidated in future studies. Moreover, as the subgroup of responders was considerably small, statistical power might not have been sufficient in order to detect significant differences between responders and non-responders.

Another possible explanation for the absence of an effect of negative verbal suggestions on resting tremor in the overall group of the present study might be related to the fact that it is obviously

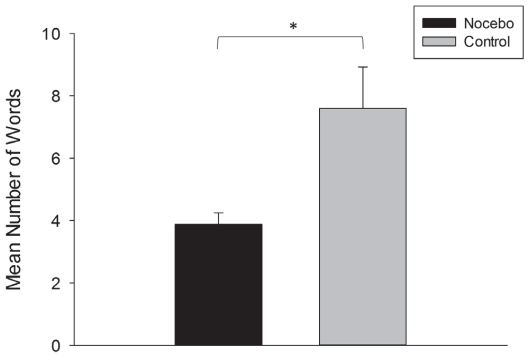

Figure 2. Impact of expectation on verbal fluency in nocebo responders. Performance in verbal fluency of tremor-dominant Parkinson's disease patients showing a nocebo response in tremor: Number of words (mean and standard error of the mean) produced in the semantic category change test in the nocebo condition (black bars) and the control condition (grey bars) in 5 patients on deep brain stimulation of the subthalamic nucleus and on antiparkinsonian medication. * $p<0.05$.
doi:10.1371/journal.pone.0081878.g002

more difficult to induce negative expectations regarding STN-DBS. This interpretation is corroborated by the patients'expectation ratings (see Fig. 3) indicating that on average patients did not expect strong impairment of motor symptoms by STN-DBS in the nocebo condition. Generally, the majority of patients had long-standing beneficial experience with effective suppression of tremor by STN-DBS whereas they usually had not experienced worsening of tremor induced by this treatment and consequently did not establish strong expectations of impairment in the nocebo condition. Indeed, the importance of prior experience with effectiveness or ineffectiveness of a treatment in order to form pronounced expectations regarding its (in-)efficacy, thus providing the basis for the occurrence of placebo and nocebo responses, is also pointed out by studies on placebo analgesia and hyperalgesia [29,30]. Furthermore, the absence of an expectation-induced effect on resting tremor in the placebo condition on group level might be explained by a floor-effect: As resting tremor was assessed when STN-DBS was switched on, power at tremor frequency was rather low in most patients and barely detectable in some patients in the control condition. Thus, positive expectation could not further substantially decrease resting tremor in the placebo condition. In future studies it would be of interest to assess the impact of expectation on tremor when STN-DBS is - unbeknownst to the patients - switched off to avoid potential floor effects.

There is one limitation regarding the assessment of resting tremor that we would like to address. Given that the amplitude of resting tremor in Parkinson's disease can show considerable variability over time, a longer period of tremor recording would have been useful. However, for practicability reasons - mainly to keep time and effort for the patients on a reasonable level - tremor was only measured for 30 seconds keeping in mind that the study lasted approximately 120 minutes each on two consecutive days. Although we do not have any reason to assume that spontaneous fluctuations in the amplitude of resting tremor varied substantially between conditions, a measurement for a longer period should be considered in future studies to control for potential variability in tremor that might occur over time.

Effect of Expectation on Verbal Fluency

Those patients who showed an aggravation of resting tremor in the nocebo condition were also characterized by impairment in semantic verbal fluency. Thus, negative expectation regarding the effect of STN-DBS on motor function did not only modulate the magnitude of resting tremor but additionally had an adverse effect on a cognitive function often affected in PD patients treated with STN-DBS [6–9]. This suggests an expectation-induced generalization of a nocebo response manifesting on motor as well as on cognitive functions. Yet this finding has to be substantiated in future studies using larger sample sizes in order to increase the likelihood of a greater number of potential responders. In contrast to patients in the subgroup who showed a nocebo response in tremor, no significant effect of expectation on verbal fluency was observed on group level.

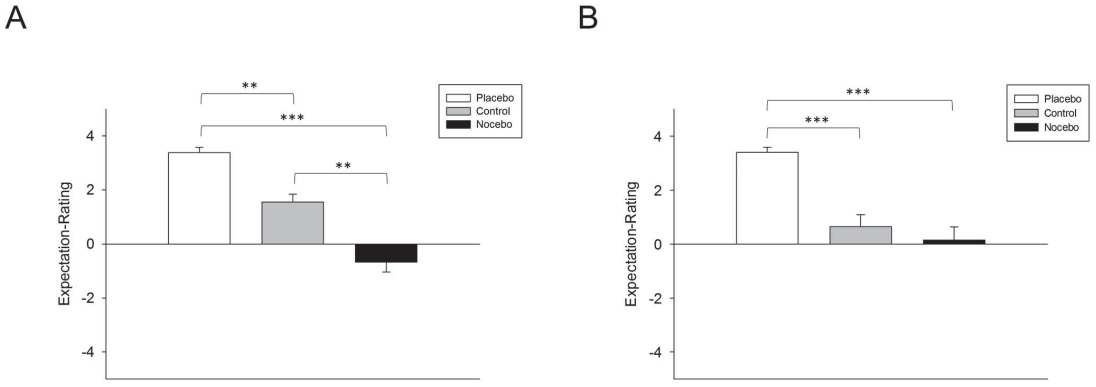

Figure 3. Expectation Rating. Mean and standard error of the mean for the expectation rating under the three conditions (placebo, nocebo, control) when the same Parkinson's disease patients were *on* (n = 24 [Fig. 3A]) and *off* antiparkinsonian medication (n = 24 [Fig. 3B]). On a numeric rating scale patients' expectations regarding the effect of deep brain stimulation of the subthalamic nucleus on motor symptoms were assessed. +5 indicates expectation of strong improvement, −5 indicates expectation of strong impairment while 0 represents expectation of no change of motor function. ** $p<0.01$; *** $p<0.001$
doi:10.1371/journal.pone.0081878.g003

In a previous study using the same paradigm as employed in the present study [21], hypokinetic-rigid PD patients who showed a placebo response in bradykinesia were also characterized by a tendency for impairment in lexical verbal fluency. Thus, in contrast to the present study, expectation of beneficial STN-DBS modulated motor and cognitive functions in opposite directions. The discrepant results of an expectation-induced modulation of the STN-DBS effect on motor and cognitive functions in tremor-dominant and hypokinetic-rigid PD patients, indicates that these two PD subtypes do not only differ regarding the clinical phenotype and related underlying pathophysiological patterns such as neuronal oscillations [31,32], neuroimaging patterns of dopaminergic degeneration [33] and cortical Lewy bodies [34], but diverge also with respect to expectation-induced placebo and nocebo responses and their interaction with verbal fluency.

Effect of Expectation on Bradykinesia

Expectation did not affect bradykinesia of distal or proximal movements in the patients of the present study. This result differs from the findings of previous studies where a modulation of bradykinesia by expectation was reported [18–21]; yet in those studies either exclusively hypokinetic-rigid or a mixture of hypokinetic-rigid and tremor-dominant PD patients were analyzed suggesting that placebo and nocebo responses mainly manifest on symptoms of predominant relevance to the patients, that is, tremor in the patients of the present study. Moreover, although expectations regarding the effect of STN-DBS were not exclusively induced with respect to tremor but also regarding motor symptoms in general, patients may have specifically focused their expectation on tremor rather than on other symptoms such as bradykinesia.

Conclusion

Taken together, the results of the present study provide evidence that the therapeutic effect of STN-DBS on resting tremor can be modulated by expectation in a subgroup of patients. Moreover, the present findings indicate that tremor is among the parkinsonian symptoms responsive to placebo and nocebo interventions - although less so than other cardinal symptoms. While positive expectations enhanced the effect of STN-DBS by further decreasing the magnitude of resting tremor, negative expectations did not only counteract the therapeutic effect of STN-DBS by increasing the amplitude of tremor, but additionally exacerbated impairment in verbal fluency, a side-effect often associated with therapeutic STN-DBS. This suggests that – at least in a subgroup of patients - negative expectations can undermine the therapeutic effect even of very efficacious treatments such as STN-DBS while at the same time exacerbating side-effects. However, given the relatively small size of responders and the exploratory descriptive approach, future studies are needed to substantiate the findings of the present study and to elucidate the prerequisites and patient-associated factors which contribute to responsiveness to placebo and nocebo interventions in PD. Nevertheless, the present results underscore the potency of patients' expectation and thus its relevance for therapeutic outcomes and should consequently be considered in the context of patient-physician interaction.

Supporting Information

Table S1 Patient characteristics including sex, age, MDRS- and BDI-scores, disease duration, clinically more affected side, daily antiparkinsonian medication, months since implantation of DBS-electrodes and MDS-UPDRS-scores.
(DOC)

Table S2 Stimulation parameters used for chronic bilateral deep brain stimulation of the subthalamic nucleus.
(DOC)

Acknowledgments

The authors thank the patients for their contribution. Furthermore, we thank Dr. C. J. Hartmann for support in manipulating patients' expectations and M. Sc. J. Hirschmann for support and advise in data analysis.

Author Contributions

Conceived and designed the experiments: LW AS AK. Performed the experiments: AK SF MS LW. Analyzed the data: AK LW AS. Wrote the paper: AK LW AS SF MS.

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CORTEX 60 (2014) 94–102

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Special issue: Research report

Modulation of central thalamic oscillations during emotional-cognitive processing in chronic disorder of consciousness

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ARTICLE INFO

Article history:
Received 7 June 2013
Reviewed 1 November 2013
Revised 16 June 2014
Accepted 10 September 2014
Published online 26 September 2014

Keywords:
Disorder of consciousness
Coma
Central thalamus
Emotional-cognitive processing
Local field potentials
Oscillations

ABSTRACT

We report on thalamic recordings in a patient with chronic disorder of consciousness (DOC). Implantation of central thalamic deep brain stimulation (CT-DBS) electrodes was chosen, as this treatment has been reported to display beneficial effects with respect to behavioural responsiveness in DOC. Local field potential (LFP) oscillations were recorded from central thalamic electrodes and their changes elicited by speech stimuli consisting either of familiar voices addressing the patient or unfamiliar non-addressing phrases were studied. In response to familiar-addressing speech we observed modulation of oscillatory activity in the beta and theta band within the central thalamus accompanied by an increase in thalamocortical coherence in the theta band. Furthermore, the theta phase was coupled to the amplitude of gamma locally in the thalamus. These findings indicate a local and long-range cross-frequency response which is not only indicative of the principle involvement of the central thalamus in processing emotional and cognitive information, but also point towards intact physiological functions that may serve as a marker in diagnosing DOC patients and determining novel targets and parameters concerning therapeutic efforts.

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http://dx.doi.org/10.1016/j.cortex.2014.09.007

1. Introduction

Assessment of consciousness is still a major issue in the field of clinical neuroscience, both concerning basic research, as well as clinically relevant applications. Recently, it has been suggested to extend established clinical routines in the evaluation of patients displaying diverse disorders of consciousness (DOC) by determining changes in brain activity towards externally applied stimuli (Menon et al., 1998; Monti et al., 2010; Owen et al., 2006). In this context, a differential response in electrophysiological (Cruse et al., 2011) and/or neuroimaging (Eickhoff et al., 2008) derived signals may indicate distinct residual functions of processing emotional and cognitive information and could, thereby, contribute to a more appropriate and sophisticated estimation of a patient's individual state of consciousness, regardless of individual (clinically determined) responsiveness (Fins & Schiff, 2010). Identifying neurophysiological correlates of such residual capacities may, moreover, reveal new and promising targets for novel therapeutic interventions. There is evidence that invasive neuromodulation by means of electrical deep brain stimulation (DBS) of the central thalamus is associated with improvements in behavioural responsiveness after traumatic brain injury (Schiff et al., 2007; Yamamoto & Katayama, 2005; Yamamoto et al., 2005). This is thought to reflect the principle involvement of the thalamus in providing excitatory projections to wide-spread cortical areas and, in turn, facilitating sensory processing. In this context, emphasizing patterns of activity elicited by sensory stimulation via DBS may promote information processing and, thereby, help to re-establish functional integrity in DOC patients.

We examined in a case of chronic DOC distinguishable patterns of central thalamic activity in response to emotionally and cognitively relevant sensory stimulation, i.e., the addressing voices of her children, as compared to unfamiliar voices. The patient was shown before to exhibit specific patterns of cortical and subcortical activity towards these stimuli as revealed by functional magnetic resonance imaging (MRI) (Eickhoff et al., 2008). With respect to these findings, we subsequently assessed electrophysiological measures by means of combined surface EEG recordings and local field potentials (LFPs) from the central thalamus (Ncl. reticularis thalami and internal medullary lamina) to determine modulations in oscillatory activity within these areas.

There are recent publications of LFP recordings from various thalamic regions in different diseases in humans and animals. They report theta, alpha and beta thalamocortical coherence. Especially reports about theta-coherence (Sarnthein & Jeanmonod, 2007, 2008), beta–gamma cross-frequency coupling in memory retrieval (Staudigl et al., 2012) and alpha–gamma coupling based on attention demands (Saalmann, Pinsk, Wang, Li, & Kastner, 2012) supported our hypothesis that (though recorded from a different thalamic site) stimulus-elicited coupling and maybe also local changes in lower frequency power (theta, alpha and/or beta) might occur. We proposed that theta coupling might be a signature of long-range thalamocortical communication and theta might show local entrainment with gamma activity by means of cross-frequency coupling.

2. Methods

2.1. Patient and procedure

A 45-year-old woman sustained a closed head injury at the age of 38 resulting in a massive subarachnoid haemorrhage and right-hemispheric, space occupying parenchymal haematoma associated with a chronic DOC. Except for stereotypic movements of the left arm she never showed any spontaneous motor activity nor did she respond to environmental stimuli. In the initial assessment following the trauma she was diagnosed with a Glasgow coma scale (GCS) of 4 in the beginning and failed to respond to pharmacotherapeutical intervention (for details of the clinical status see Eickhoff et al., 2008). Since there is evidence for beneficial effects of central thalamic DBS in patients with DOC on behavioural parameters (Schiff et al., 2007; Yamamoto & Katayama, 2005; Yamamoto et al., 2005), after obtaining an ethical vote of the local ethic committee the patient was designated to undergo implantation of bilateral DBS electrodes in the internal medullary lamina and the Ncl. reticularis thalami (Fig. 1A). Target localisation was defined based on atlas coordinates using the atlas by Mai and colleges (Mai, Assheuer, & Paxinos, 2004). Targeting was achieved with neuroimaging by fusion of stereotactic cranial computed tomography (CT) and high-resolution MRI. Furthermore, intraoperative microelectrode recordings using the INOMED MER system (INOMED Corp., Emmendingen, Germany) were performed to obtain some information about the occurrence of bursting activity e.g., of the reticular thalamus. During the operation final macroelectrodes (model 3387 quadripolar DBS lead, Medtronic Inc., Minneapolis, MN, USA) were connected to sterile percutaneous extension wires (model 3550-05, Medtronic), which were led out through the scalp and could be connected postoperatively to EEG amplifiers (BrainAmp, Brain Products GmbH, Gilching, Germany) via external cable connectors (twist lock cable model 3550-03, Medtronic and custom made connector to DIN 428092 touch proof connectors). Thus, postoperative recordings of LFPs from the central thalamus were achieved. Postoperative electrode localisation was visualized on a 3D atlas (Yelnik et al., 2007) by fusion of preoperative MRI and postoperative CT scans with the atlas (Bardinet et al., 2009).

2.2. Recordings

Recordings of intrathalamic LFPs were conducted two days after initial implantation of the DBS electrodes and prior to internalization of the corresponding leads and impulse generator. Electrodes provided four distinct contacts along the dorsoventral axis, which provided post-hoc bipolar referencing of adjacent contacts to ensure the local origin of the recorded potentials. Electrical activity of the cortex was measured applying surface EEG-electrodes that were mounted according to the 10-20-System and consisted of the fronto-central (Fz), centro-central (Cz), parieto-central (Pz), occipito-central (Oz) temporal 4 (T4) and temporal 3 (T3) site with a frontopolar reference (Fpz). Signals were recorded with a sampling-frequency of 5 kHz, amplified, low-pass filtered (1000 Hz) and

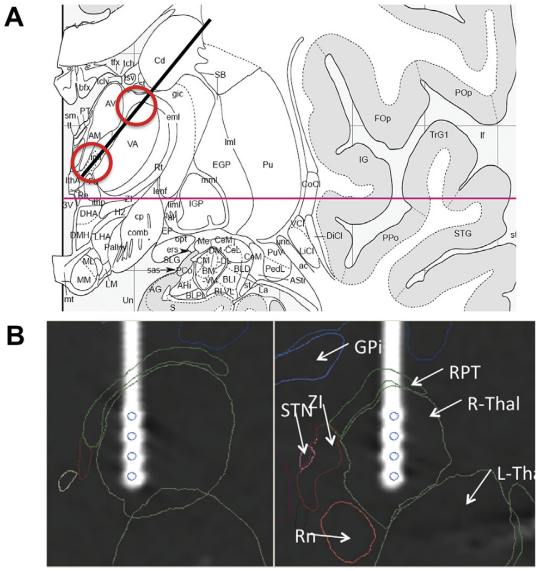

Fig. 1 – Anatomical localisation on different atlases. A: Planned trajectory (black line) projected on an anatomic atlas (Mai et al., 2004), section 30, coronary, 10.7 mm behind AC (red line: AC-PC plane). Red circles mark targeted areas of the lowermost 15 mm (atlas grid size: 10 mm) with iml = internal medullary lamina thalami and Rt = reticular thalamic nucleus. VA = ventroanterior thalamic nucleus, AV = anteroventral thalamic nucleus, AM = anteromedial thalamic nucleus, Fa = fasciculosus nucleus, IthA = interthalamic adhesion B. Final electrode in the central thalamus visualized on a 3D atlas (Yelnik et al., 2007). Two orthogonal planes of section along the axis of the electrode in the right hemisphere after registration of the 3D atlas with the CT scan. The four contacts of the electrode (blue circles) are located in the right thalamus (R-Thal). GPi = internal globus pallidus, STN = subthalamic nucleus, ZI = zona incerta, RPT = reticular perithalamic nucleus, RN = red nucleus.

stored to hard disk for later off-line analysis (BrainVision Recorder, Brain Products GmbH, Gilching, Germany).

2.3. *Paradigm*

The patient was presented with auditory stimuli that apparently differed in the magnitude of emotional connotation and cognitive demand. These consisted of voices of her children (both girls, aged 6 and 8) addressing the patient in short sentences (10 short words) or voices of a non-familiar female speaker enumerating a list of neutral words (longer nouns, cumulatively eight syllables) without addressing the patient. Each stimulus lasted 4 sec and was equal with respect to loudness. Speech stimuli were applied binaurally via headphones. Stimuli were chosen from and according to findings observed in previous fMRI experiments showing that these were capable of causing a speaker-specific (emotionally) plus content specific (cognitively) brain responses in distinct cortical and subcortical areas (Eickhoff et al., 2008). The patient was presented consecutively with the unfamiliar non-addressing and familiar-addressing speech stimuli, starting with the latter ones in a block design. The stimulus duration was 4 sec (+jittered 4–5 sec inter-stimulus-interval) for each particular stimulus, resulting in a total of 80 trials per condition, which were averaged in the subsequent analysis in order to improve the signal-to-noise-ratio and to assess stimulus-specific evoked plus induced power changes in oscillatory activity.

2.4. *Data analysis*

All off-line analysis was performed applying algorithms from the software suite BrainVision Analyzer (Brain Products GmbH, Germany) and by the use of MATLAB scripts (MathWorks, Natick, Massachusetts, USA) and the FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011). Recordings were visually inspected for high amplitude technical artefacts resulting in an elimination of one trial in the neutral and three trials in the familiar-addressing condition. Signals were downsampled to a sampling-frequency of 512 Hz and filtered applying a high-pass filter of 1 Hz (48 dB/oct) and a low-pass filter of 80 Hz (48 dB/oct). Also a notch-filter with a given centre-frequency of 50 Hz was applied to attenuate power-supply-associated artefacts. Virtual bipolar re-referencing of the four contacts of the DBS-electrode was performed using combinations of adjacent contacts, i.e., left contact 0 (most ventral; LFPL0) versus left contact 1 (LFPL1), LFPL1 versus LFPL2, and LFPL2 versus LFPL3 (most dorsal) resulting in three bipolar channels per hemisphere. Surface signals were also referenced bipolarly considering neighbourhood relations resulting in a virtual montage of Cz/Fz, Pz/Cz, Oz/Pz, T3/Cz and T4/Cz channels.

2.4.1. *Local oscillatory activity*

Power was analysed using stimulus-locked wavelet time frequency analysis. The initial transformations applied here were of the Morlet Wavelet type (width = 5). On each hemisphere the bipolar channel with highest theta power across conditions over the whole length of the trial was used for further analysis. The choice of the theta band was driven by the aforementioned hypotheses and due to a distinct peak in the power spectrum. Thus, contact LFPL23 and LFPR23 was selected. In the first step, driven by hypotheses and to obtain statistical power, analysis was focused on the frequency range from 4 to 25 Hz within the first second of the trial. The pre-stimulus time from −1000 to −1 msec was considered as baseline. Frequency wise mean baseline power was subtracted from each time frequency plot bin for baseline correction. A cluster-based (for dimensions time and frequency) randomization approach (Maris & Oostenveld, 2007) was used for statistical analysis between conditions considering a p-level of .05 in a two-sided test. Thus, modulations elicited specifically by the degree of the speaker's familiarity and cognitive demand (emotional-addressing) were revealed. Due to the finding of theta thalamocortical coherence and theta-gamma cross-frequency coupling (see below), in second step of analysis we took a closer look on theta and gamma throughout the whole duration of the trial (0–4 sec). Gamma

was then visualized between 30 and 80 Hz, with a window length of seven cycles, moved in steps of 25 msec and three tapers from a multitaper sequence resulting in smoothing of .3*frequency. Based on descriptive findings of late theta increase, theta (4–7 Hz) was additionally statistically tested with the cluster-based randomisation approach between conditions for the 2–3 sec time period of the trial.

2.4.2. *Thalamocortical coherence*

Frequency coupling revealed by coherence analysis (defined as a measure of the linear relationship in the frequency domain of two signal time series displaying a constant ratio of amplitudes; Halliday et al., 1995) between the thalamic and cortical activity during the auditory stimulation (0–4 sec) was determined. LFP-EEG coherence was calculated for the same bipolar contact (LFP23 left and right) that had been used for power calculations. Coherence was calculated to all bipolarly referenced surface EEG channels (Cz/Fz, Pz/Cz, Oz/Pz, T3/Cz and T4/Cz). The epoch from to 0–4 sec in each trial was cut into segments (segment duration: 1 sec, overlap: 50%). Coherence was computed up to 25 Hz over all segments for each condition. For statistics a cluster-based (for dimensions time and frequency) randomization approach for within-subject analysis of coherence was used considering a p-level of .05 in a two-sided test (Maris, Schoffelen, & Fries, 2007). Furthermore, the imaginary part of coherence was computed (Nolte et al., 2004).

2.4.3. *Cross-frequency phase amplitude coupling (PAC)*

For cross-frequency analysis, the entire, continuous recording was used and PAC was calculated. A methodology called normalized direct PAC (ndPAC) was used (for details see: Özkurt, 2012). In essence, it is a normalized version of the Modulation Index as used by Canolty et al (Canaolty, et al. 2006). ndPAC shows if a given coupling is significant or not. All spurious couplings were set to 0 (p-level: .01) without a further test for differences between conditions. Applied phase frequency range was 3–22 Hz and amplitude frequencies range was 35–80 Hz. The selected channels were LFPR23 and EEGFzPz because of coherence changes there.

3. Results

3.1. *Electrode localisation*

Final coordinates (x; y; z) of the lowermost electrode contact zero relative to the midcommissural point (MCP) was 4.3; 0.2; 4.1 mm for the right and 5.7; 3.4; 2.6 mm for the left hemisphere. AC-PC length was 24.3 mm. Preoperative MRI and postoperative CT corregistration was successful, however MRI-atlas coregistration was complicated by the distorted anatomy of the patient due to the head trauma. Thus, final electrode visualisation was assumed to be in central thalamus with some uncertainty (Fig. 1B).

3.2. *Local oscillatory activity*

Analysis of the stimulus-locked modulation of oscillatory activity within central thalamus revealed a right-sided significant ($p = .044$) increase of beta power (12–25 Hz) within the first second (.45–.55 sec, Fig. 2) when contrasting both experimental conditions (unfamiliar-neutral *vs* familiar-addressing voices).

Furthermore, over the period of 3 sec theta power was modulated. Statistical contrast between conditions revealed significant ($p = .048$) theta increase in the familiar-addressing condition at 4–6.5 Hz, at second 2.6–2.8 on LFPL23 and increase (trend) on LFPR23 (Fig. 5). Stimulus-elicited gamma activity around 40 Hz from the beginning of the trial was followed by broader and higher gamma activity up to 80 Hz beginning about 2 sec after stimulus onset (Fig. 5).

3.3. *Thalamocortical coherence*

Coherence analysis of channel LFPR23 (right hemisphere) yielded significant differences between conditions in the theta band for coupling with surface EEG channel PzCz. Imaginary part of coherence showed deviation from zero meaning a phase delay between LFP and EEG. Thus, the effect was not due to volume conduction (Fig. 3).

3.4. *Cross-frequency PAC*

Local analysis revealed significant ($p = .01$) theta-gamma PAC (with max. at 5-to-75 Hz) of right local LFP channel LFPR23-LFPR23 in the familiar-addressing condition (Fig. 4).

4. Discussion

The present case study not only provides electrophysiological evidence for the involvement of the central thalamus in processing emotionally-cognitively relevant speech stimuli in terms of increased oscillatory activity and thalamocortical

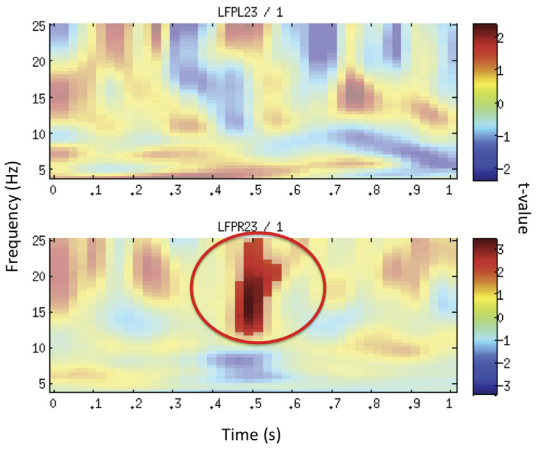

Fig. 2 – Time frequency plot of local oscillatory power contrasting neutral versus familiar-addressing condition for the first second. Colour coded are t-values. Top: left channel LFPL23, bottom: right channel LFPR23. Significant beta increase 12–25 Hz, .45–.55 sec, $p = .044$ (red circle).

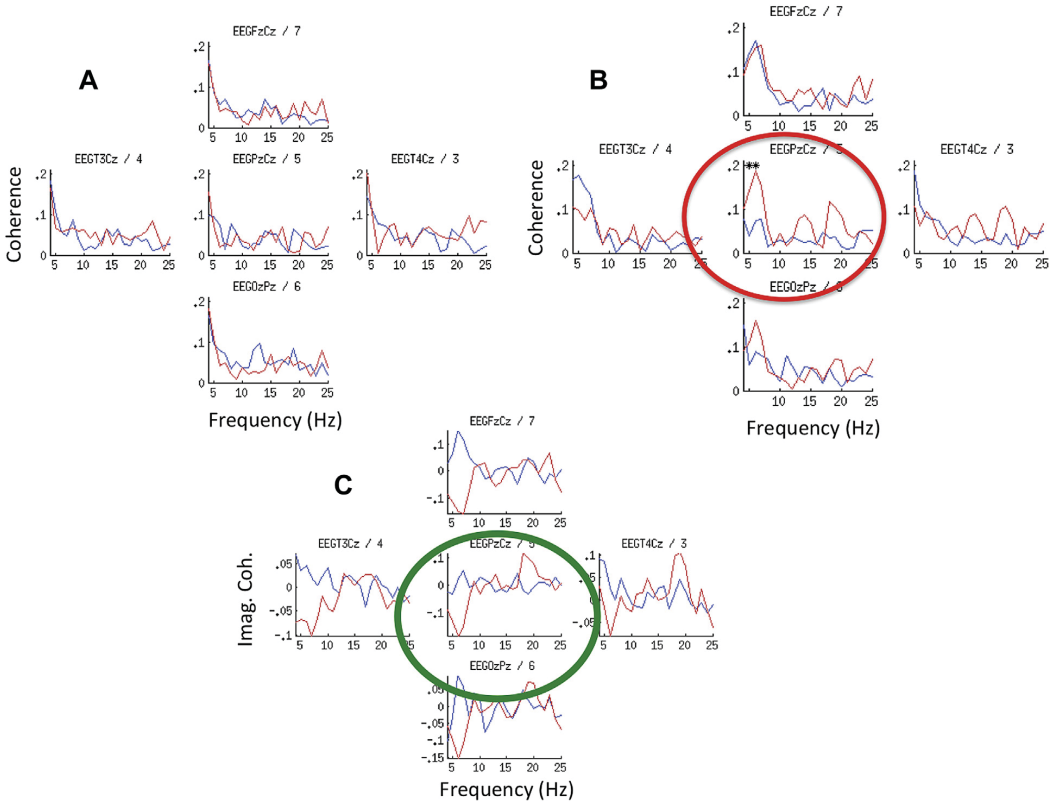

Fig. 3 – EEG-LFP coherence. Familiar-addressing condition (red line) and neutral condition (blue line). Epoch of 0–4 sec cut into segments of 1 sec duration and average over segments. A: Coherence with channel LFPL23 left hemisphere, B: Coherence with channel LFPR23 right hemisphere. Red circle/stars showing significant difference between conditions for coherence with channel PzCz, 5–6 Hz, $p = .044$. C: Imaginary part of coherence of LFPR23 right hemisphere (in green circle coherence with channel Cz) shows deviation from zero meaning a phase delay between LFP and EEG (thus effect not due to volume conduction).

coherence in different frequency bands, but also demonstrates remarkable 'higher-order' residual functions in patient with chronic DOC that may serve as a clinical marker of awareness and may, further, help refining parameters of potentially relevant therapeutic applications.

Some limitations of the study should be mentioned: Due to the block design of the paradigm habituation to the stimuli might have biased the contrast between conditions. However, analysis of mean LFP power over the trials in the frequency band that showed significant differences between conditions did not show a continuous reduction over time but rather a stepwise reduction with the first neutral trial, which speaks against a major bias by habituation. Furthermore, to make the paradigm suitable for post-op recordings we shortened the initial fMRI paradigm (Eickhoff et al., 2008) contrasting now only two conditions.

Thus, it cannot be distinguished whether effects are due to emotional or cognitive processing alone or combined or just by addressing vs. non-addressing speech. When it comes to interpretation of cognitive processing semantic content differences between conditions have to be taken into account. Finally, the fact that stimuli did not match exactly in terms of speech rhythm and speed, acoustical differences has also been regarded as limitation concerning the specificity of the findings.

Although the subject presented here lacks of any signs of behaviourally relevant consciousness, we observed a differential response in brain activity that was elicited specifically by the addressing voices of her children. Unlike processing simple auditory stimulation, evaluating the emotional and addressing content of speech represents an elaborated higher brain function. The findings reported by Eickhoff et al. (2008) are also in line with this observation being a specific emotional response, since it was shown that another subcortical structure associated with limbic circuitry, namely the amygdala, was also activated by the stimuli applied in this particular patient. A further activation of the superior temporal sulcus reflected cognitive language processing of the

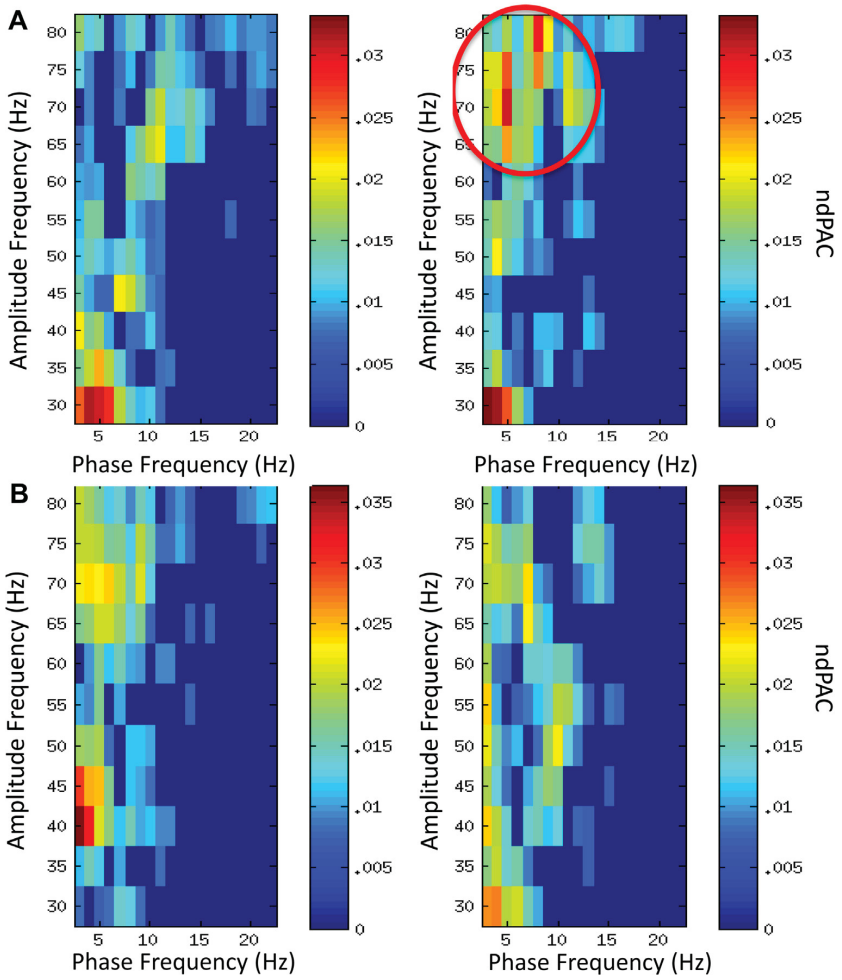

Fig. 4 – Phase amplitude coupling (PAC) for phase frequencies 3–22 Hz and amplitude frequencies 35–80 Hz. Colour coded is normalized direct phase-amplitude coupling (ndPAC). Spurious coupling is set to 0 ($p = .01$). Conditions: left: neutral, right: familiar-addressing. A: PAC of right local LFP channel LFPR23-LFPR23 showing PAC in familiar-addressing condition with max. at 5-to-75 Hz (red circle). B: PAC of right LFP-EEG combination with LFPR23-EEGPzCz.

direct addressing speech (Eickhoff et al., 2008). Since bipolar referencing of the thalamic LFPs was carried out in the present study, it is unlikely that the observed activity patterns reflect mere far field potentials of the activity of the amygdala. The 'higher-order' character of the findings is also reflected by the latency of the stimulus-elicited modulations of oscillatory activity (~200 msec). Whereas event-related potentials of simple auditory stimulation should be expected already 50 msec after stimulus onset (Onitsuka, Ninomiya, Sato, Yamamoto, & Tashiro, 2000), the present findings reflect rather elaborated processing.

Stimulus induced oscillatory activity has been shown to be specifically modulated in the high gamma range (45–75 Hz) by speech stimuli as compared to non-speech sounds (Palva et al., 2002), which fits to our findings within the later time period of the trials. Such alterations are discussed to encode for complex Gestalt or cognitive properties of the stimulus, such as coherence or meaningfulness. A potential link to the functional meaning of the effects in this context may arise when taking into account the relationship between gamma and theta oscillations (as displayed by the patient). Cross-frequency coupling, defined as the linear relationship between either the amplitudes, the phases or the phase-to-amplitude-correlation of two oscillating signals (Jensen & Colgin, 2007), is thought to reflect a fundamental principal within functionally specialized networks of neuronal ensembles, providing exact spatial and temporal mechanisms of communication and processing. With respect to this assumption, it was demonstrated, that the amplitude of stimulus-elicited gamma oscillations is modulated by theta rhythms in terms of phase-

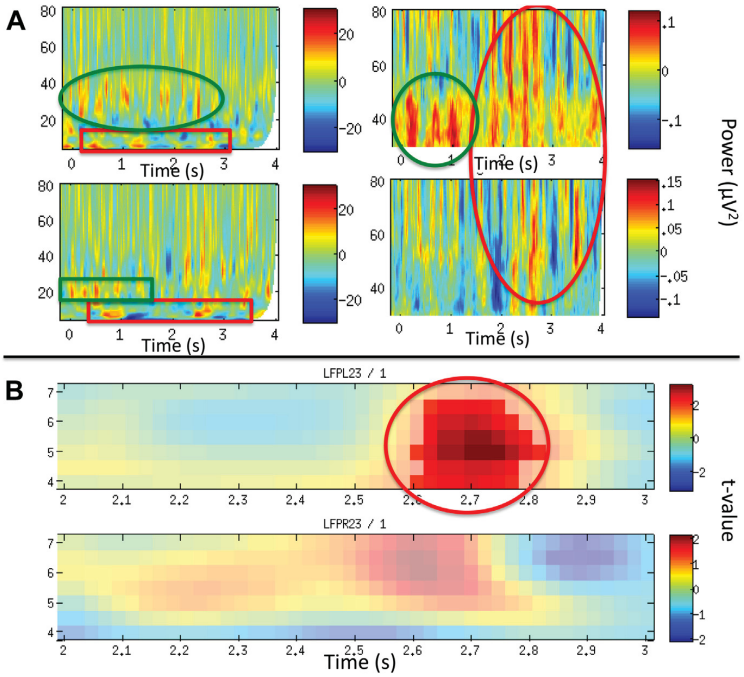

Fig. 5 – Time frequency plots of local power changes at LFP23. A: Power difference from baseline in the familiar-addressing condition over the period of the trial (0–4 sec). Left: broad frequency band 5–80 Hz, right: gamma band. Top row: left hemisphere (LFPL23), bottom row: right hemisphere (LFPR23). Note: beside beta increase within the first second (green box) there is early and late theta modulation (red box). Gamma around 40 Hz (green circle/ellipse) is followed by broader and higher gamma up to 80 Hz. B: Statistical contrast between conditions illustrating significant theta increase in the familiar-addressing condition at 4–6.5 Hz, at second 2.6–2.8 (red circle), $p = .048$ on LFPL23 and increase (trend) on LFPR23. Colour coded are t-values. Top: left hemisphere (LFPL23), bottom: right hemisphere (LFPR23).

locking. This has been shown to apply for various areas of the brain, including hippocampal formation and entorhinal cortex (Mormann et al., 2005), as well as the auditory cortex (Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008).

As mentioned in the introduction, for the thalamus cross-frequency coupling has been recently reported in different frequency bands (Fitzgerald, Valentin, Selway, & Richardson, 2013; Saalmann et al., 2012; Staudigl et al., 2012). Our finding of beta increase around 500 msec (though without prominent beta–gamma cross-frequency) might reflect memory retrieval, as beta–gamma coupling with a similar timing was observed between the thalamus and cortex in such processing (Staudigl et al., 2012).

The stimulus-elicited modulation of oscillatory activity within the central thalamus and the associated increase in thalamocortical coherence in the theta band observed in the present study further suggests a thalamic involvement of the theta rhythm that accounts for cortical cross-frequency coupling. This is also in line with assumptions attributing the central thalamus a key role in maintaining global excitability of various brain areas (including cortical, thalamic and striatal targets) underlying behaviourally relevant sensory processing (Schiff, 2012). The functional significance of theta driven activity has also been discussed to promote large-scale integration across a variety of functionally distinct and spatially separated brain areas (von Stein and Sarthein, 2000). Due to their 'slower' nature and associated conduction delays, theta oscillations have been discussed to be quite suitable for temporo-spatial conduction, coordination and integration of particular neural activity across the brain (Jensen & Colgin, 2007). In this context, the prominent role of (theta entrained) gamma activity in feature binding should also be highlighted (Singer, 1999). The findings reported here, contribute to the comprehension of the central thalamic role in these oscillatory phenomena. Standing to reason, a potential application of these results would be to intervene in the central thalamus, enhancing theta rhythms by means of central thalamic DBS (CT-DBS) and, thereby, improving sensory processing that may, in turn, increase behavioural responsiveness. As demonstrated by Schiff et al. (2007), CT-DBS is capable of reducing unresponsiveness in DOC patients. According to the protocol reported, this study applied CT-DBS within a frequency range of 70–250 Hz. Potential effects of stimulation utilizing lower frequencies (i.e., theta or beta rhythms) would be highly interesting with respect to stimulus-elicited brain activity, as well as behavioural outcome.

The obvious question if, despite her behavioural unresponsiveness, the patient consciously perceives her children's voices should be handled with care. It should be noted that a consistent concept of human consciousness is lacking in neuroscience, psychology and philosophy. One can think of consciousness on different levels from responsiveness and alertness to self-awareness. From the neuroscientific view consciousness can be defined as an emergent property of many interacting modules of perception and cognition (Owen, 2012 in Cyranoski, 2012). In this context, the findings reported here may not be interpreted as evidence for a conscious state of the patient, but as a measure of functional integrity of a severely damaged system.

Competing interest

None.

Acknowledgements

We thank Volker Sturm, MD, PhD and Harald Treuer, PhD for intraoperative support for target planning.

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frontiers in Neurology

ORIGINAL RESEARCH
published: 18 August 2015
doi: 10.3389/fneur.2015.00177

A prospective pilot trial for pallidal deep brain stimulation in Huntington's disease

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OPEN ACCESS

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 18 June 2015
Accepted: 27 July 2015
Published: 18 August 2015

Citation:
Wojtecki L, Groiss SJ, Ferrea S, Elben S, Hartmann CJ, Dunnett SB, Rosser A, Saft C, Südmeyer M, Ohmann C, Schnitzler A and Vesper J for the Surgical Approaches Working Group of the European Huntington's Disease Network (EHDN) (2015) A prospective pilot trial for pallidal deep brain stimulation in Huntington's disease. Front. Neurol. 6:177. doi: 10.3389/fneur.2015.00177

Background: Movement disorders in Huntington's disease are often medically refractive. The aim of the trial was assessment of procedure safety of deep brain stimulation, equality of internal- and external-pallidal stimulation and efficacy followed-up for 6 months in a prospective pilot trial.

Methods: In a controlled double-blind phase six patients (four chorea-dominant, two Westphal-variant) with predominant movement disorder were randomly assigned to either the sequence of 6-week internal- or 6-week external-pallidal stimulation, or vice versa, followed by further 3 months chronic pallidal stimulation at the target with best effect-side-effect ratio. Primary endpoints were changes in the Unified Huntington's Disease Rating Scale motor-score, chorea subscore, and total motor-score 4 (blinded-video ratings), comparing internal- versus external-pallidal stimulation, and 6 months versus baseline. Secondary endpoints assessed scores on dystonia, hypokinesia, cognition, mood, functionality/disability, and quality-of-life.

Results: Intention-to-treat analysis of all patients ($n = 3$ in each treatment sequence): Both targets were equal in terms of efficacy. Chorea subscores decreased significantly over 6 months (−5.3 (60.2%), $p = 0.037$). Effects on dystonia were not significant over the group due to it consisting of three responders (>50% improvement) and three non-responders. Westphal patients did not improve. Cognition was stable. Mood and some functionality/disability and quality-of-life scores improved significantly. Eight adverse events and two additional serious adverse events – mostly internal-pallidal stimulation-related – resolved without sequalae. No procedure-related complications occurred.

Conclusion: Pallidal deep brain stimulation was demonstrated to be a safe treatment option for the reduction of chorea in Huntington's disease. Their effects on chorea and dystonia and on quality-of-life should be examined in larger controlled trials.

Keywords: Huntington's disease, deep brain stimulation, chorea, pallidum

Introduction

Huntington's disease (HD) is a progressive, motor, cognitive, and psychiatric neurodegenerative disorder caused by an expanded CAG repeat in the Huntingtin gene. To date, there is no causal or disease modifying treatment for HD. The typical motor symptom in HD is chorea, but other movement abnormalities, such as dystonia and hypokinesia, can occur – especially in juvenile onset HD (Westphal variant). Although dopamine antagonists and dopamine-depleting drugs have demonstrated some symptomatic efficacy in patients in whom chorea is the dominant feature, they often do not produce significant functional improvement. The rationale for using deep brain stimulation (DBS) of the internal pallidum (GPI) for HD is based on evidence that GPI–DBS is effective in suppressing non-HD choreiform dyskinesias, such as levodopa-induced dyskinesia (1) in Parkinson's disease and the dystonic movements of primary dystonia (2). Case reports have shown that GPI–DBS has been effective in various other neurological disorders presenting with choreiform symptoms [for review, see Ref. (3)]. For the treatment of HD-chorea itself, several reports provide preliminary evidence for the feasibility of pallidal DBS, with reports up to 5 years (4–6). There might be a better response on chorea rather than on dystonic symptoms (7). The experience with for Westphal patients is sparse (8). Some case reports on HD-chorea used blinded assessments (9, 10) but the only prospective two clinical trials evaluating DBS for choreatic movements (besides levodopa-induced dyskinesias in Parkinson's disease) was performed for dystonia–choreoathetosis in cerebral palsy (11) and recently for HD (12) with the latter however lacking a destinct pre-defined protocol, a control-group, blindend assessments, and systematic evaluation of adverse events.

It is not known whether high frequency internal pallidal stimulation affects cognitive abilities in HD. Most reports do not identify any changes, however, some decline was noted in two patients (13). In contrast, motor *and* cognitive improvements were reported with stimulation of the external pallidum (GPE) in animal experiments (14). Further evidence for the usefulness of GPE stimulation comes from preliminary PET imaging data (15) of a series of HD patients undergoing GPE–DBS, which showed decreasing activity and modulation of connectivity within the basal ganglia-thalamocortical circuit and sensorimotor cortical areas.

Given this scientific background, it is legitimate to assess pallidal DBS as a treatment option in HD, starting with a prospective clinical trial assessing its safety and efficacy. About efficacy, in this prospective 6-months pilot trial, we tested the hypothesis that randomized GPI and GPE stimulation would be equivalent in terms of their effects on motor function. We also tested the hypothesis that chronic stimulation of the pallidum would be a safe and effective treatment first in motor function as chorea, hypokinesia and dystonia and, second on non-motor aspects as cognition, emotion, functional disability and quality of life.

Abbreviations: BDI, Beck depression inventory; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; DBS, deep brain stimulation; GPE, globus pallidus externus, external pallidum; GPI, globus pallidus internus, internal pallidum; HADS, Hospital Anxiety and Depression Scale; HD-ADL, Huntington's Disease Activities of Daily Living scale; HD, Huntington's disease; MADRS, Montgomery-Åsberg Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale; MDRS, Mattis Dementia Rating Scale; MDS-UPDRS, Movement Disorder Society's Unified Parkinson's Disease Rating Scale; SF-36, Short Form Health Survey; TEED, total electrical energy delivered; UHDRS, Unified Huntington's Disease Rating Scale; VTA, volume of tissue activated.

Patients and Methods

The trial was designed as a prospective pilot trial focusing on the safety and efficacy of pallidal DBS in HD. The protocol consisted of a randomized, controlled crossover design to examine the hypothesis of the equivalence of GPI and GPE stimulation, and an uncontrolled 6-month follow-up to assess chronic treatment effects on movement, cognition, emotion, functional disability, and quality of life. Timepoints for assessments were based on the hypothesis that delayed effects were expected.

The trial was monocentric and performed at the Center for Movement Disorders and Neuromodulation of the Heinrich-Heine-University Düsseldorf in Germany. The trial was performed according good clinicial practice, fullfiled the CONSORT criteria, was registered with ClinicalTrials.gov (NCT00902889) and approved by the local authorities according to the German Medical Devices Act (MPG), as well as by the ethics committee of the Medical Faculty of the Heinrich-Heine University Düsseldorf (3100). The study was monitored and adverse events were formally reported and evaluated by an independend data and safety monitoring board (DSMB).

Patients

Six patients with genetically confirmed HD and predominant motor symptoms were included in the study. All patients gave written informed consent. Inclusion criteria were: symptomatic and genetically confirmed HD (CAG repeats >36) for at least 3 years, at least moderate-stage motor symptoms as measured by ≥ 30 points on the motor component of the Unified Huntington's Disease Rating Scale (UHDRS) (16) and failure as measured by lack of effect or side effects with at least two medical treatments (tiapride and tetrabenazine mandatory for chorea patients) at the maximal tolerable dose. Exclusion criteria were: cognitive decline as measured by fewer than 120 points on the Mattis Dementia Rating Scale (17) or <80% of motoric performable tasks, major depression or dominant psychiatric symptoms, previous stereotactic interventions, severe brain atrophy as revealed by MRI scans (defined as cortical atrophy or atrophy of the pallidum which rendered planning of a stereotactic trajectory impossible), coagulopathy, immunosuppression, history of cerebrovascular disease, or cerebral micro- or macroangiopathy, or general medical contraindication to surgery. Inclusion and exclusion criteria were assessed twice within 3–6 months, prior to final inclusion, to ensure that included patients had a stable motoric and cognitive baseline.

Procedure

After assessment of inclusion and exclusion criteria with a stable clinical baseline of at least 3 months (week W–1), patients underwent presurgical clinical examination. The basic examination (week W0) comprised videotaped motor functions assessed

according to the UHDRS motor, chorea, and TMS-4 subscores (16), the motor scores of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) (18) and the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS–UPDRS III) (19). For cognitive and mood assessment the basic test program contained the Mattis Dementia Rating Scale (MDRS) (17), the Beck Depression Inventory (BDI) (20), the Montgomery-Åsberg Depression Rating Scale (MADRS) (21), the Brief Psychiatric Rating Scale (BPRS) (22) and the Hospital Anxiety and Depression Scale (HADS) (23). An extended, detailed test program contained: the UHDRS functional/behavioral assessment, the BFMDRS disability scale, the Huntington's Disease Activities of Daily Living (HD-ADL) (24) scale, and the Short Form Health Survey (SF-36) (25).

Surgery was performed in week 0 after baseline assesments under general anesthesia (propofol, remifentanil). Stereotactic planning was done by fusion of stereotactic CT with preoperative MRI (essentially MPRAGE, FLAIR, T2 Space). The trajectory was planned in such a way that the lowermost contact of the final electrode would be located in the upper part of the GPI, while the higher contacts would be positioned in the GPE. For intraoperative targeting, resting activity of up to five concentric oriented microelectrodes was recorded. Stimulation of the macro tip of the recording electrode above and below the target was done intraoperatively to assess possible major side effects such as stimulation of the internal capsule.

Medtronic 3387 electrodes (Medtronic Inc., Minneapolis, MN, USA) were implanted bilaterally and final electrode placement was verified by a postoperative stereotactic CT. An individualized visualization of the volume of tissue activated (VTA) was performed with a customized version of Cicerone (26), as previously described (27).

The electrodes were connected to a subcutaneous implanted Kinetra® impulse generator (Medtronic Inc., Minneapolis, MN, USA). Five to seven days after surgery (week W0/1) all contacts were tested for their therapeutic range, using 120 µs pulse width and 130 Hz frequency as default settings. Stimulation was applied up to the threshold for side effects, or to the maximum of 5 V. After first testing, patients were randomized into their treatment intervention sequence: either stimulation of the two adjacent lowermost contacts (GPI) for 6 weeks, followed by stimulation of the two adjacent uppermost contacts (GPE) for 6 weeks, or vice versa. Thus three of the patients underwent the sequence GPI–GPE and three underwent the sequence GPE–GPI, during the first 12 weeks of stimulation. Stimulation was set just below the threshold for side effects but was intended to cover a broad anatomic distance of the target area and was thus chosen double monopolar. On the basis of the clinical best effect-side effect ratio, the treating physician selected either GPE or GPI stimulation for further chronic stimulation during the 6-month follow-up.

At preoperative baseline (W0) and 6-month follow-up, the detailed test battery was performed; for 6- and 12-week GPI/GPE visits, the basic test program was performed. At all timepoints tests were performed in the same order. The primary endpoints were UHDRS motor, chorea and TMS-4 scores for GPI versus GPE stimulation, and for 6 months versus baseline. Secondary endpoints were BFMDRS and UPDRS motor scores, cognition and mood scores, for GPI versus GPE and for 6 months versus baseline, as well as quality of life and functional assessments for 6 months versus baseline.

Randomization and Blinding

Patients were randomly allocated to the treatment sequence by the Coordinating Center for Clinical Trials (KKS) Düsseldorf on the basis of faxed forms filled in by the investigators. The treating physician performed the treatment, and clinical assessments of scores were performed double-blind by a scoring physician (directly for rigidity items, video rating for other motor score items) and a neuropsychologist.

Statistical Analysis

The results were analyzed by intention to treat. Data are reported as mean (SD) and compared by two-tailed paired Student's *t*-tests. Kolmogorov–Smirnov test showed normal distribution of samples. Probability values of 0.05 or less were considered statistically significant. Comparisons were calculated for scores GPI versus GPE and baseline versus 6 months' stimulation for primary and secondary endpoints. Additional subgroup analysis was performed excluding the Westphal variant disease subgroup. Effect size (Cohen's *d*) was calculated for significant differences.

Results

Six patients were included in the trial. All patients were randomly assigned, resulting in three patients receiving the intended treatment in the sequence GPE-GPI and three patients receiving the intended treatment in the sequence GPI–GPE. All patients were analyzed for the primary and secondary endpoint. For a flowchart of the study see **Figure 1**. Mean baseline UHDRS motor score was 54.3 with a high SD of 17.6. Two of the patients suffered from the hypokinetic-rigid Westphal variant of HD. For patient details and stimulation settings see **Table 1**. All patients subjectively reported improvement in daily life with GPI and GPE stimulation and at 6-month follow-up. The specific group results are reported in **Tables 2**–**4** and illustrated in **Figures 2** and **3**.

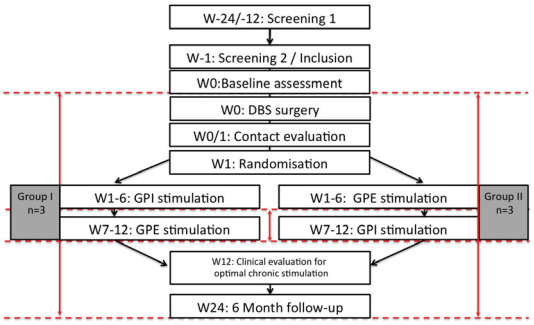

FIGURE 1 | Flow chart of the study. $n = 6$, W: week, M: month, dashed red lines illustrate timepoints of study assessments, red arrows illustrate calculated comparisons.

TABLE 1 | A: patient characteristics and B: stimulation parameters with 120 µs and 130 Hz, two contacts "monopolar" with IPG + except Pat. #2 bipolar due to limiting side effects.

A

	Pat. 1	Pat. 2	Pat. 3	Pat. 4 Westphal variant	Pat. 5 Westphal variant	Pat. 6
Age (years)	52	71	38	25	23	29
Sex	M	F	M	M	M	F
Symptom duration (years)	3	21	10	11	8	4
CAG repeats	17/43	19/41	17/52	19/68	17/70	9/53
Medication (mg)	Amitriptyline (100), Trospiumchloride (60)	Sulpiride (200), Ramipril (5), HCT (25), L-Thyroxine 75 µg	Tetrabenazine (50), Tiapride (300)	Quetiapine (37.5), L-Dopa (300), Pramipexole (0.54)	Rotigotine (10), Topiramate (200), Amantadine (200), Pantoprazole (40), Domperidone (30)	Tetrabenazine (25), Tiapride (300), Citalopram (40), Quetiapine (25)

B

		Active electrodes		Voltage (V)		TEED (µJ)	
		Left	Right	Left	Right	Left	Right
Pat. 1	GPI	0−, 1−	4−, 5−	2.5	1.8	225	108
	GPE	2−, 3−	6−, 7−	2.5	2.0	241	119
	6 Month	2−, 3−	6−, 7−	2.5	2.2	148	131
Pat. 2	GPI	0−, 1−	4−, 5+	1.5	1.7	44	50
	GPE	2−, 3−	6+ , 7−	3.0	2.7	267	79
	6 Month	0−, 1−	4−, 5+	1.5	1.7	44	51
Pat. 3	GPI	0−, 1−	4−, 5−	2.0	2.0	119	119
	GPE	2−, 3−	6−, 7−	3.6	3.6	355	521
	6 Month	0−, 1−	4−, 5−	2.0	1.5	119	90
Pat. 4	GPI	0−, 1−	4−, 5−	1.4	1.0	42	30
	GPE	2−, 3−	6−, 7−	1.7	1.7	102	51
	6 Month	0−, 1−	4−, 5−	2.4	2.4	173	173
Pat. 5	GPI	0−, 1−	4−, 5−	1.5	1.5	44	44
	GPE	2−, 3−	6−, 7−	2.0	2.0	101	101
	6 Month	2−, 3−	6−, 7−	2.0	2.0	120	92
Pat. 6	GPI	0−, 1−	4−, 5−	1.4	1.2	42	36
	GPE	2−, 3−	6−, 7−	1.5	1.3	44	39
	6 Month	2−, 3−	6−, 7−	1.5	1.3	44	39

TEED, Total electrical energy delivered in Microjoule (µJ) per second calculated using the formula: Amplitude in Volt (V^2) × frequency in Hertz (Hz) × pulse width in microseconds (µs) / impedance in Ohm (Ω). Mean stimulation amplitude: GPI: 1.6 V, GPE: 2.3 V, 6 months: 1.9 V.

Primary Endpoints: UHDRS Motor Score, UHDRS Chorea Subscore, TMS-4

GPI Versus GPE

Although GPE stimulation scored slightly better, there was no significant difference between GPI and GPE stimulation in terms of motor effects on the UHDRS.

Six Months Versus Baseline

Based on clinical judgment, three patients (#2, 3, 4) were selected for chronic GPI stimulation and three (#1, 5, 6) for chronic GPE stimulation. Analysis of the primary endpoint at 6-month stimulation versus baseline showed a mean difference of 6.1 points on the UHDRS. Due to a high SD this was not significant (for individual scores see **Figure 3A**). However, the UHDRS chorea subscore decreased significantly over the course of 6 months from 8.8 to 3.5 points (−5.3 (60.2%), $p = 0.037$). The effect on TMS-4 was not significant.

Secondary Endpoints

GPI Versus GPE

There was no significant difference between GPI and GPE stimulation in UPDRS and BFMDRS scores. Cognition and mood did not differ significantly either.

Six Months Versus Baseline

Effects on dystonia were not significant over the group, however half the patients (#1, 2, 3) showed marked improvement of more than 50% on the BFMDRS, with patient #2 showing a decrease from 19.5 to 3 points (−16.5 (84.7%), see **Figure 3B**). Further assessment of mood, cognition, functionality and quality of life

TABLE 2 | Motor results.

	Baseline		GPI		GPE		6 months		*p*-Value GPI vs. GPE	*p*-Value 6 months vs. baseline
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
A										
UHDRS	54.3	17.6	54.0	18.1	50.8	22.2	48.2	24.4	0.181	0.160
UHDRS chorea	8.8	7.5	5.7	3.8	5.2	4.7	3.5	3.2	0.611	0.037[#]
TMS-4	37.0	12.0	35.5	13.5	35.0	15.6	32.3	15.8	0.611	0.135
UPDRS	41.3	23.3	45.5	26.1	48.7	27.9	45.8	28.3	0.066	0.117
BFMDRS	21.8	17.4	24.8	18.7	22.7	21.7	20.3	27.0	0.205	0.802
B										
UHDRS	46.5	15.4	44.5	12.9	39.5	17.0	35.0	15.4	0.155	0.016[##]
UHDRS chorea	13.2	4.0	8.0	1.4	7.7	3.2	5.2	2.2	0.500	0.009[###]
TMS-4	32.5	11.6	29.0	11.0	27.7	13.2	24.0	10.7	0.368	0.012[####]
UPDRS	27.2	8.8	30.5	13.8	32.5	14.0	29.0	13.6	0.343	0.523
BFMDRS	15.0	10.8	15.2	8.2	12.0	10.6	5.9	4.5	0.150	0.111

A: complete group (n = 6), B: chorea subgroup, Westphal patients excluded (n = 4).
Effect size (Cohen's d): [#]0.919, [##]0.747, [###]2.478, [####]0.762.

TABLE 3 | Results for cognition and mood: Mattis Dementia Rating Scale and subscores (in percent of performable points), BDI, MADRS, BPRS, HADS-D.

	Baseline		GPI		GPE		6 months		*p*-Value GPI vs. GPE	*p*-Value 6 months vs. baseline
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
A										
Mattis Total score	88.2	7.1	86.7	8.0	86.5	9.0	86.9	7.4	0.849	0.213
Mattis Attention	88.7	6.7	89.6	6.3	89.6	7.1	86.9	7.3	1.000	0.328
Mattis Concentration	76.0	14.4	70.0	17.0	72.1	18.2	71.4	15.8	0.493	0.027[#]
Mattis Visuoconstruction	100.0[a]	0.0[a]	100.0[b]	0.0[b]	100.0[b]	0.0[b]	100.0[b]	0.0[b]	*	*
Mattis combinatoric	97.4	2.8	97.4	2.8	96.1	4.5	97.4	2.8	0.203	*
Mattis memory	89.3	7.4	87.3	13.5	85.3	11.2	90.7	7.9	0.456	0.530
BDI	6.60[c]	7.63[c]	3.00	5.02	3.83	6.15	2.60	2.70	0.402	0.230
MADRS	7.50	7.97	3.83	5.08	3.17	2.40	2.83	3.49	0.684	0.081
BPRS	26.17	8.56	21.67	4.50	21.00	2.10	21.00	3.52	0.586	0.063
HADS-D	7.60	8.08	3.50	5.82	3.50	4.59	3.60	5.68	1.000	0.04[##]
B										
Mattis total score	91.4	6.6	90.4	6.2	91.3	5.2	90.8	5.4	0.342	0.693
Mattis attention	91.9	5.8	91.9	6.6	93.2	4.7	91.2	4.0	0.664	0.789
Mattis concentration	82.2	13.8	77.0	15.7	82.4	10.2	79.0	13.5	0.161	0.168
Mattis visuoconstruction	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	*	*
Mattis combinatoric	98.7	2.6	98.7	2.6	98.1	3.8	98.7	2.6	0.391	*
Mattis memory	91.0	7.6	93.0	8.9	89.0	11.5	93.0	3.8	0.182	0.495
BDI	7.50	8.50	3.75	6.18	5.50	7.19	3.00	2.94	0.102	0.299
MADRS	9.00	9.76	5.00	6.00	3.25	2.99	4.25	3.50	0.432	0.249
BPRS	29.00	9.42	22.75	5.25	21.50	2.38	22.25	3.77	0.516	0.104
HADS-D	8.75	8.85	5.25	6.65	5.00	5.10	4.50	6.14	0.824	0.093

A: complete group (n = 6), B: chorea subgroup, Westphal patients excluded (n = 4).
*[a,b,c]Data from 3, 4, or 5 patients; *cannot be calculated.*
Effect size (Cohen's d): [#]0.304, [##]0.573.

revealed the following change from baseline at 6-month follow-up: cognition was stable as measured by Mattis, although a slight but significant deterioration was noted in tests of concentration, from 76.0 to 71.4% ($p = 0.027$). In accordance with the exclusion criteria, patients showed normal mood and psychiatric scores at baseline, however HADS-D (depression) improved significantly ($p = 0.044$), and MADRS and BPRS showed a statistical trend toward improvement. Several items in the quality of life and functional assessments showed significant improvement, such as the SF-36 vitality and mental health scores, while others showed a statistical trend toward improvement (SF-36 social role functioning score, UHDRS behavioral assessment).

Subgroup Analysis

Post hoc analysis of the choreatic subgroup of patients (non-Westphal, $n = 4$) for the primary endpoints showed no significant difference between GPI and GPE stimulation. At 6-month follow-up the primary endpoints showed significant results: the UHDRS showed a significant decrease: from 46.5 to 35.0 points (−11.5 (24.7%), $p = 0.016$). For the chorea subscore the difference

TABLE 4 | Results for activity of daily living and quality of life.

	Baseline		6 months		*p*-Value 6 months vs. baseline
	Mean	SD	Mean	SD	
A					
UHDRS functional capacity	12.0	8.7	12.7	9.7	0.465
UHDRS functional assessment	5.2	3.9	6.7	5.5	0.237
UHDRS behavioral assessment	8.0	4.6	4.2	5.3	0.057
HD-ADL	28.6[a]	11.0[a]	21.2[a]	16.6[a]	0.227
BFMDRS disability scale	14.2	7.8	13.0	8.9	0.302
SF-36 physical functioning	30.83	29.9	38.3	40.6	0.620
SF-36 physical role function	54.2	40.1	58.3	51.6	0.793
SF-36 bodily pain	66.7	51.6	81.7	40.2	0.648
SF-36 general health perception	63.0	21.5	79.2	12.7	0.169
SF-36 vitality	48.3	12.1	70.8	23.1	0.030[#]
SF-36 social role functioning	52.2	25.5	77.3	30.8	0.090
SF-36 emotional role functioning	72.2	44.4	77.8	40.4	0.788
SF-36 mental health	69.3	13.3	90.7	13.3	0.022[##]
B					
UHDRS functional capacity	16.0	7.4	17.5	7.8	0.215
UHDRS functional assessment	6.5	4.0	9.2	4.9	0.102
UHDRS behavioral assessment	8.5	4.8	5.5	6.1	0.245
HD-ADL	25.3	6.7	10.7	7.0	0.080
BFMDRS disability scale	10.2	4.7	7.7	3.9	0.030[#]
SF-36 physical functioning	42.5	30.1	57.5	35.7	0.525
SF-36 physical role function	56.2	51.5	75.0	54.0	0.319
SF-36 bodily pain	50.0	57.7	75.0	50.0	0.638
SF-36 general health perception	68.5	7.0	76.5	15.4	0.380
SF-36 vitality	47.5	13.2	66.2	28.1	0.141
SF-36 social role functioning	56.2	31.4	66.0	32.7	0.430
SF-36 emotional role functioning	58.2	50.0	75.0	50.0	0.602
SF-36 mental health	61.0	3.8	87.0	15.4	0.063

[a]*Data from five patients.*
A: complete group (n = 6), B: chorea subgroup, Westphal patients excluded (n = 4).
SF-36, UHDRS functional capacity, functional assessment: increase = improvement.
BFMDRS disability scale, HD-ADL, UHDRS behavioral assessment, care giver rating: decrease = improvement.
Effect size (Cohen's d): [#]1.22, [##]1.609.

between baseline and 6 months was highly significant: 13.5 compared to 5.2 points (−8 (60.6%), $p = 0.009$). The TMS-4 also showed a significant decrease, from 32.5 to 24.0 points (−8.5 (26.2%), $p = 0.012$). Concerning secondary endpoints in the non-Westphal subgroup the BFMDRS disability score improved significantly and the HD-ADL and SF-36 mental health score showed a trend toward improvement.

In the secondary motor endpoints the Westphal patients (#4, 5) showed no improvement in dystonia (BFMDRS) or hypokinetic-rigid symptoms (UPDRS) with GP stimulation.

Medication

Medication for motor treatment was kept stable throughout the trial in most patients. In one patient (#2), sulpiride was reduced from 200mg to 100mg after the operation, while in another (#3), tetrabenazine (50mg) and tiapride (300mg) were completely withdrawn after the operation.

Electrode Localization and Volume of Tissue Activated

Mean electrode localization is provided in **Figure 4**. Furthermore, images of individual electrodes with volume of tissue activated (VTA) are shown in **Figure 5**. Mean coordinates with reference to the midcommissural point [*x*, *y*, *z* (SD)] were: 21.8 (2.1), 3.8 (1.0), −3.6 (2.4) for GPI; 22.9 (2.0), 5.9 (1.2), 2.4 (3.2) for GPE; and 22.4 (2.0), 4.8 (1.8), 0.2 (5.6) for stimulation at 6-month follow-up. In summary, the mean stimulated area at 6 months was located in projection to the laminal border zone between the internal and external pallidum.

Adverse Events

No procedure-related complication such as bleeding occurred. Eight adverse events were recorded: possibly related to treatment: bradykinesia (GPI), hyperthermia possibly related to stimulation due to stable medication (GPI, Westphal), gait impairment and fall (GPI 6 month), increased chorea after reprograming due to bradykinesia (GPI 6 month); possibly related to stimulation system: deactivation of impulse generator (GPE); unrelated to stimulation but possibly due to hospitalization: thrombophlebitis (W0 postop), MRSA nose infection (W0 postop), superficial nose abrasion (GPE). In addition, two serious adverse events were reported: gait impairment and hyperkinesia after reprograming (GPI 6 month, Serious Adverse Event (SAE) criterion: leading to hospital admission and requiring reprograming) and postoperative (W0 postop) malignant hyperthermia possibly related to stimulation due to stable medication (SAE criterion: life-threatening and leading to prolonged hospital stay). All stimulation-related adverse events occurred under GPI stimulation. All adverse events resolved without sequalae.

Individual Patient Discription

For individual motorscores please see **Figure 3**. For individual electrode localization please see **Figure 5**.

Patient 1 is a patient with predominant choreatic and dystonic trunk-movements that impacted his quality of life. Although the chorea sum-score was below 10 points he had benefit from DBS. Dystonic movements also improved. GPE stimulation

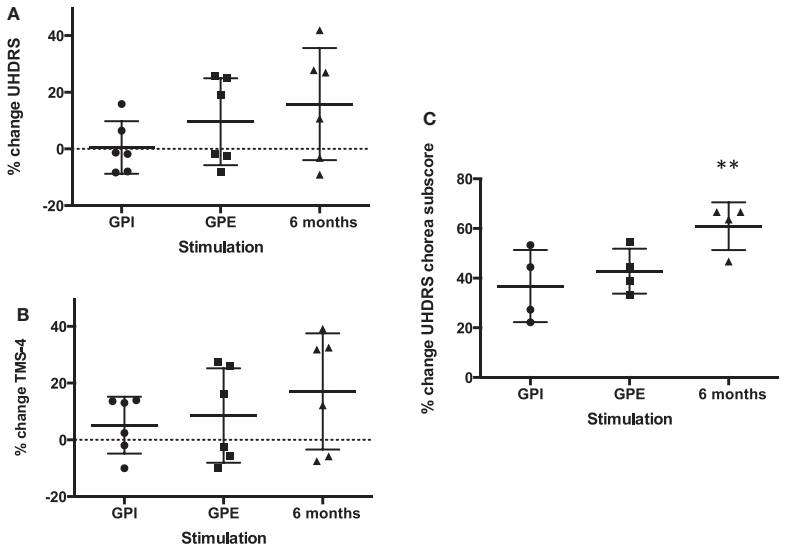

FIGURE 2 | Percent change improvement from baseline of primary endpoints. Mean with SD (error bars) and individual results **(A)**: UHDRS, **(B)**: TMS-4, **(C)**: UHDRS chorea subscore, note: chorea subscore could only be calculated for four patients (non-Westphal). **Significant change from baseline, $p < 0.01$.

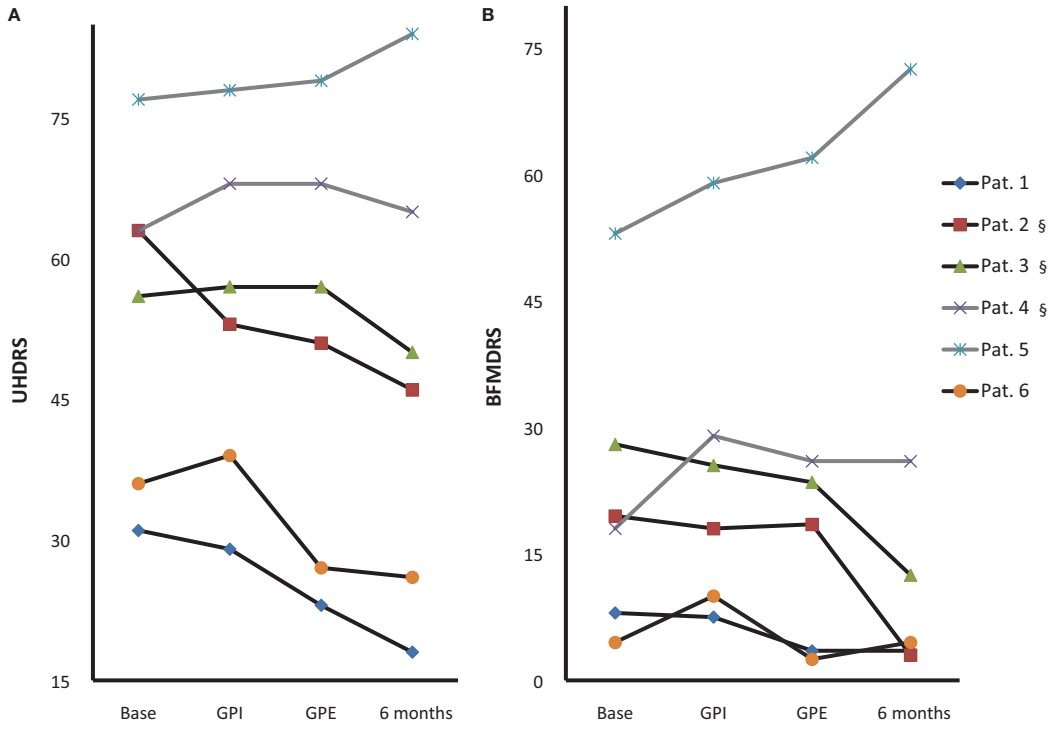

FIGURE 3 | Individual motor score changes. Individual UHDRS **(A)** and BFMDRS **(B)** at baseline, with GPI, GPE and chronic 6-month stimulation [Pat. #1, 5, 6 GPE; Pat. #2, 3, 4 GPI (§)]; Westphal patients: gray lines, #4, 5. Note: GPI/GPE sequence was randomized with GPI first in Pat. #1, 4, 5 and GPE first in Pat. #2, 3, 6.

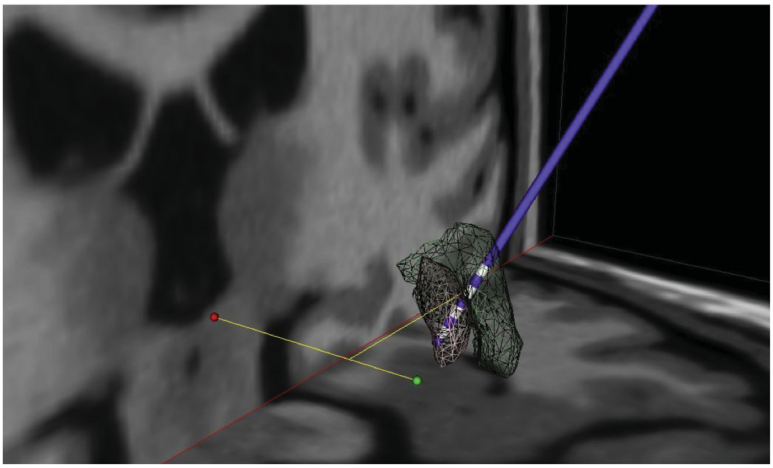

FIGURE 4 | Mean electrode localization. Visualization of mean coordinates of left and right hemisphere mirrored to the left; 3D space relative to AC-PC line (green dot: AC, red dot: PC), gray mash: GPI, green mash: GPE; lowermost contacts comprise GPI and uppermost contacts comprise GPE stimulation. Thus, mean chronic stimulation at 6-month follow-up projects mid-electrode to the border zone between GPE and GPI. For visualization the following atlas software was used: Medtronic DBS Neurosurgical Simulator, licensed 2008, Version 1.2.3, Medtronic Inc., Minneapolis, MN, USA.

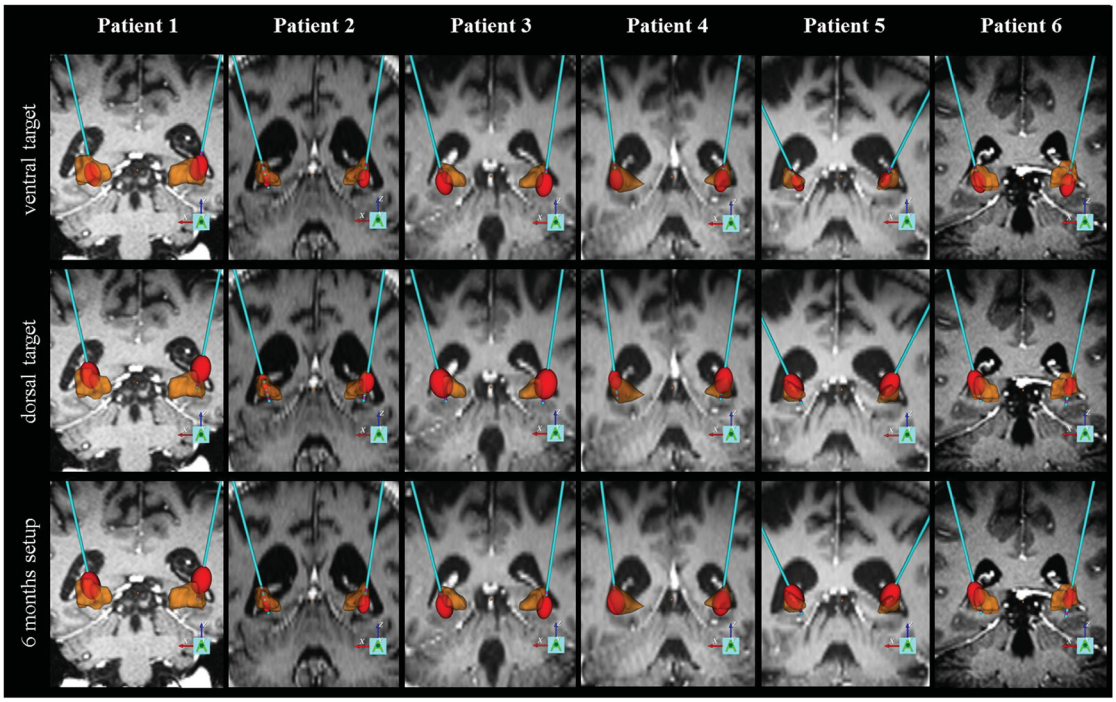

FIGURE 5 | Individual electrode localization. Visualization on 3D coronary MRI-view of individual electrodes and volume of tissue activated (VTA, in red) in relation to the pallidum (in brown) for the ventral target (GPI), the dorsal target (GPE) and the target at 6-month follow-up.

was slightly more effective than GPI stimulation. *Patient 2* had generalized chorea. She suffered from postural instability due to anti-chorea drug treatment before surgery. With DBS chorea suppression was possible with minor impairment of balance. GPI and GPE stimulation was similar in terms of chorea reduction. GPI stimulation was better tolerated and chosen for chronic stimulation. The narrow therapeutic window between brady- and hyperkinesia remained a difficult issue resulting in two adverse events of reprograming (bradykinesia, increased chorea). Dystonia also markedly improved in this patient at 6 month follow-up. *Patient 3* showed improved chorea and dystonia, however this effect was seen mainly at 6 month follow-up. GPI stimulation was chosen for chronic stimulation. Stimulation-induced gait impairment led to a SAE in this patient. *Patients 4 and 5* suffered from the Westphal variant with strong bradykinesia and dystonia. Although objectively no improvement could be observed in the scores, the caregiver reported improved dystonia of the neck. Both Westphal patients had issues with (S)AE (pneumonia and hyperthermia). *Patient 6* had marked improvement of her generalized chorea especially with GPE stimulation. Before surgery, she had frequent falls with bone fractures due to drug treatment that could be stopped after surgery.

Discussion

This is the first prospective trial for DBS in Huntington's disease according to the CONSORT criteria following a predefined protocol using a controlled phase and blinded assessments of primary endpoints and with full reporting of adverse events under monitoring of a DSMB. The data provide preliminary evidence that DBS electrode implantation can be performed in a safe procedure with no procedure-related side effects. Moreover, primary endpoint analysis showed that: (1) external pallidal stimulation was equivalent to internal pallidal stimulation; and (2) chronic stimulation of the pallidum was effective in terms of significant reduction of chorea over 6 months in patients comprising large effect sizes. Secondary endpoint analysis showed that effects on dystonic symptoms varied inter-individually from no response to a strong response. Hypokinetic-rigid symptoms and Westphal patients did not improve. Cognition was generally stable over 6 months. Several measures of quality of life and functionality improved significantly, as did measures of mood. Electrode localization revealed that mean chronic stimulation at 6-month follow-up was applied in the GPI/GPE border zone.

The strengths of the current study are: the prospective design, the double-blinded assessment of the GPI- versus GPE-phase, and the examination of the effects and side-effects of chronic stimulation on non-motor aspects of HD, as well as on quality of life. On the basis of these preliminary results, it can be concluded that pallidal DBS is a potential treatment option for chorea in HD, and should be further examined in larger, multicentric, placebo-controlled trials.

Limitations of the current study should be noted. Due to the pilot, monocentric nature of the trial, sample size was limited, meaning that the finding of equivalent efficacy for GPI and GPE, in particular, could be underpowered. Furthermore, one has to be aware of the limits of statistical validity with a small sample size. Despite the small sample size for the open label comparison between baseline and GP stimulation at 6 months, we still observed remarkable reduction of chorea (60.2%), statistically however with a p-value ($p = 0.037$) just below the threshold of significance.

Although both the patients and the scoring physician were blinded according to the destinct stimulation site, the prospective design did not include a placebo control group, which means blinding concerning active treatment in general. At the current state, we can not rule out a bias by placebo responses and emotional state especially on chorea and quality of life. Both these limitations – the small sample size and the lack of a placebo control group – should be examined further in a larger trial. Given the authors' experience with trials on other hyperkinetic disorders such as dystonia (2), a placebo sham stimulation controlled trial will be the next reasonable step rather than arguing in favor of an ON–OFF (crossover) design of a trial. Thus, a multi-center trial that randomizes patients directly after surgery blinded either into the stimulation ON or OFF group and assesses clinical effects after 3 months has just started. This design can control for lesion and placebo effects directly after the surgical intervention, which would not be the case for a crossover ON vs. OFF phase during the trial.

Some technical aspects of the design could have further biased the results. For safety reasons, we chose to implant only one electrode per hemisphere. Thus, more ventral "internal" and more dorsal "external" pallidal stimulation was achieved by contact programing. Although electrode targeting was adjusted accordingly, for anatomical reasons it is not possible to stimulate both the most ventral GPI and the most dorsal part of the GPE with one electrode. As we did not find it justified to implant four electrodes and in order to make the electrode position suitable for a crossover design of GPI versus GPE stimulation, we implanted the electrodes slightly more dorsal than the usual GPI target point. One has to be aware that this approach might have biased the results. Furthermore, the fact that we used double-monopolar stimulation might have biased the spatial discrimination of effects between GPI and GPE target areas.

We calculated the mean contact position of the chronic stimulation at 6 months virtually, and visualized it on an atlas in the border zone between the GPI and GPE. Brain atrophy makes it hard to judge the exact electrode position with respect to the pallidum in HD patients. However, we furthermore provide individual electrode scans together with calculation of volume of tissue activated (VTA) of the patients.

To standardize stimulation parameters as much as possible, we worked with fixed frequencies and pulse widths. Thus, we are not able to answer questions concerning frequency effects with this study. Besides worsening of hypokinesia with high frequency stimulation of more than 130 Hz, some reports have noted improvement of chorea with minor worsening of hypokinesia at 40 Hz, suggesting that frequency settings might play a major role (10). This fits with our long-term clinical experience (28). However, there have been other reports of more heterogeneous outcomes with 40Hz (13), and even worsening of chorea (29). Besides stimulation frequency, the period of chronic application of stimulation can be of importance. We chose a period of 6 weeks of chronic stimulation to compare GPI with GPE. Although some effects on chorea could be observed within minutes, we cannot

rule out that some treatment effects were missed due to the short period of stimulation. Note that several patients showed greater improvement on the UHDRS at 6 months than at any of the 6-week assessments. This observation speaks in favor of a chronic (neuroplasticity) effect of stimulation that outweighs clinical disease progression, and against a strong placebo effect. Increased treatment effect over time seems not be caused by stimulation strength as amplitudes at 6 months were similar to the mean of GPI and GPE stimulation at 12 weeks.

Concerning the generalizability of our findings, we think it is appropriate to conclude that chronic pallidal DBS should be considered as a treatment option for choreatic forms of HD. Patients without significant chorea seem not to benefit from pallidal DBS. It is, however, questionable whether our negative findings in Westphal patients can be generalized. Not only was the Westphal group too small to generate results of any significance, but the two Westphal patients suffered from the highest number of CAG repeats and the highest UHDRS scores. It is possible that the lack of effect we observed in the Westphal subgroup was due to the stage of the disease rather than to the motor phenotype (dystonia and mainly bradykinssia) itself. On the other hand, the bradykinetic phenotype might have profited more from subthalamic or posterior-ventral pallidal stimulation rather than from the chosen dorsal GPI/ventral GPE stimulation. Correlations of treatment effect with CAG repeats, UHDRS scores at baseline and burden of disease scores should be calculated in future larger trials. In the current study, the sample size was too small to allow calculation of proper correlations. A larger sample size will probably also shed light on predictors of non-response with respect to dystonic symptoms. Although the effects were not significant over the group, the current study shows that effects can be large, thus corroborating earlier findings for DBS in HD (10).

The final interpretation of our results must include a discussion of the harm-benefit ratio of this invasive treatment. It is important to note that the implantation procedure itself was safe. Adverse events were mainly related to stimulation. In line with previous findings and expected under high frequency stimulation [e.g., see Ref. (9)], we found that internal, as opposed to external, pallidal DBS can incur side effects such as gait problems and bradykinesia. Although the beneficial treatment effects did not differ significantly between GPI and GPE stimulation, the slightly larger improvement in motor scores, combined with the lower risk of side effects and higher tolerated stimulation amplitudes and TEED, seen with GPE stimulation, speak in its favor. Overall, cognition was stable across the group, however the cognitive subscore "concentration" deteriorated slightly, and no cognitive improvement was seen. In addition, due to the effect-side effect ratio, it might be reasonable to choose GPE stimulation for a larger trial, in order to try to achieve the improvement in cognition that has been reported in animal experiments (14). The results of the current trial suggest that it could also be reasonable to expect effects on quality of life in a larger trial, because even in this small sample, subscores showed significant improvement. However, as some of significant non-motor effects got lost in the non-Westphal group despite motor improvement a considerable higher number of patients will be needed to show stable results on quality of life.

In summary, it might be promising to further examine pallidal DBS concerning the question if it is an effective and safe treatment option for HD patients with severe chorea. Its effects on other outcome measures such as dystonia and non-motor aspects of the disease should also be examined in a larger trial.

Author Contributions

LW, SG, AS, CO, SD, AR, CS, JV: study design and/or clinical management; LW, SG, SF, SE, SR, CH, MS: data acquisition of videos and clinical scores; SG: blinded video rating; LW, SF: clinical data analysis; LW, CH, JV: data analysis of electrode contacts; LW, AS, JV: drafting of the manuscript. All authors: revision and approval of the manuscript.

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Acknowledgments

We thank the following persons for organisational and statistical support: M. Biernat, M. Blicke, S. Rödel (Department of Neurology and Institute of Clinical Neuroscience and Medical Psychology Düsseldorf); G. Felder, Q. Yang, M. Partowinia-Peters (Coordinating Centre for Clinical Trials (KKS) Düsseldorf); C. Schade-Brittinger (Coordinating Centre for Clinical Trials (KKS) Marburg). We thank Cameron C. McIntyre for giving us the opportunity to calculate VTA with his tools. We thank the medical writer Laura Spinney for lecturing the manuscript. We thank the patients for their participation. *Trial Registration*: The trial was registered in ClinicalTrials.gov (NCT00902889). *Funding*: The study was sponsored by a seed fund from the European Huntington's Disease Network (EHDN). The funding source of the EHDN itself, represented by the Scientific and Bioethics Advisory Committee (SBAC), had no role in the study design, data collection, data analysis, data interpretation or writing of the report. EHDN sponsored the medical writer for lecturing the manuscript. The surgical approaches working group of the EHDN contributed to the study design. The corresponding and senior authors had full access to all the data and final responsibility for the decision to submit the paper for publication.

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Conflict of Interest Statement: Lars Wojtecki, Jan Vesper, Alfons Schnitzler, and Martin Südmeyer received consultant honoraria and travel grants from Medtronic. The remaining authors have no conflict of interest to declare.

Brain Struct Funct
DOI 10.1007/s00429-014-0805-x

ORIGINAL ARTICLE

Behavioral and neurophysiological evidence for the enhancement of cognitive control under dorsal pallidal deep brain stimulation in Huntington's disease

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Received: 14 February 2014 / Accepted: 19 May 2014

Abstract Deep brain stimulation of the dorsal pallidum (globus pallidus, GP) is increasingly considered as a surgical therapeutic option in Huntington's disease (HD), but there is need to identify outcome measures useful for clinical trials. Computational models consider the GP to be part of a basal ganglia network involved in cognitive processes related to the control of actions. We examined behavioural and event-related potential (ERP) correlates of action control (i.e., error monitoring) and evaluated the effects of deep brain stimulation (DBS). We did this using a standard flanker paradigm and evaluated error-related ERPs. Patients were recruited from a prospective pilot trial for pallidal DBS in HD (trial number NCT00902889). From the initial four patients with Huntington's chorea, two patients with chronic external dorsal pallidum stimulation were available for follow-up and able to perform the task. The results suggest that the external GP constitutes an important basal ganglia element not only for error processing and behavioural adaptation but for general response monitoring processes as well. Response monitoring functions were fully controllable by switching pallidal DBS stimulation on and off. When stimulation was switched off, no neurophysiological and behavioural signs of error and general performance monitoring, as reflected by the error-related negativity and post-error slowing in reaction times were evident. The modulation of response monitoring processes by GP-DBS reflects a side effect of efforts to alleviate motor symptoms in HD. From a clinical neurological perspective, the results suggest that DBS in the external GP segment can be regarded as a potentially beneficial treatment with respect to cognitive functions.

Keywords Deep brain stimulation · Cognitive enhancement · Huntington · Response monitoring · EEG · Globus pallidus

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Introduction

Deep brain stimulation is increasingly considered as a surgical therapeutic option in HD where GP is targeted (Huys et al. 2013; Demeestere and Vandenberghe 2011; Moro et al. 2004). Only a few cases have been reported so far (e.g. Spielberger et al. 2012; Kang et al. 2011; Fasano et al. 2008; Biolsi et al. 2008; Groiss et al. 2011). Besides

Published online: 31 May 2014

preliminary findings reporting more beneficial cognitive effects for external pallidal stimulation (globus pallidus externus, GPe) (Temel et al. 2006) than for globus pallidus internus (GPi) stimulation, the outcomes of pallidal DBS in HD are widely unknown. However, computational models consider the GP to be part of a basal ganglia network involved in cognitive processes related to the control of actions (Humphries et al. 2006). Action control processes are an important instance of executive control functions and are especially important when response errors occur. Error monitoring processes are of special relevance in HD because it has been suggested that the major phenotype of HD (i.e., movement disturbances) may begin as a dysfunction in error feedback control (Smith et al. 2000). It is therefore possible that, as far as motor symptoms are alleviated by GP-DBS, error monitoring functions may also be modulated.

These error monitoring processes are assumed to be mediated via a basal ganglia anterior cingulate network (Holroyd and Coles 2002) and have already been shown to be altered in HD (e.g. Beste et al. 2006, 2007, 2008). In particular it has been shown that the error-related negativity (ERN) (Gehring et al. 1993; Falkenstein et al. 1991), which has been shown to drive behavioural adaptation processes after an error has occurred (Debener et al. 2005), is smaller in HD. Post-error slowing is also less pronounced.

It is possible that during stimulation of the GP, error processing functions are intact even in strongly affected HD patients. Hence, if the GP is no longer stimulated, a critical element in the basal ganglia circuitry for response control processes becomes dysfunctional. It is therefore possible that error monitoring as well as general response monitoring functions unrelated to error processing are diminished or even absent when the GP is transiently not stimulated. In the current study we examine this question in a case–control study where we report two cases with GP-DBS and investigate error monitoring processes in these cases with deep brain stimulation switched on and switched off. To objectify error monitoring processes, we record event-related potentials (ERPs) along with behavioural data. Response monitoring processes are a relevant outcome measure since these processes have repeatedly been reported to be dysfunctional in HD (Beste et al. 2006, 2007, 2008; for review: Nguyen et al. 2010). We expect that error monitoring is dysfunctional in HD when DBS is turned off, which can be quantified by a reduced error-related negativity (ERN) amplitude and reduced post-error slowing effects. We also compare the effects of DBS (on/off) against a group of un-medicated manifest HD patients to control for the effects of electrode placement in GP. We expect that manifest HD patients show better performance than un-medicated manifest HD patients (i.e., a larger ERN and stronger post-error slowing) only when DBS stimulation is turned on.

Materials and methods

Patients and controls

Patients were recruited from a prospective pilot trial for pallidal DBS in HD (ClinicalTrials.gov NCT00902889). This pilot trial is–to our knowledge–the biggest DBS cohort so far available with HD-DBS. In this trial clinical, effects of internal versus external dorsal pallidal stimulation were assessed in patients with predominant movement disorder and without severe psychiatric or cognitive disabilities. From the initial four patients with HD, three patients were available for long-term follow-up and two patients (one male and one female) under chronic external dorsal pallidum stimulation were able to perform the paradigm with respect to their hand motor abilities and thus were included in this Flanker task study. Clinically they had stable motor effects with DBS. The patients were examined twice, with DBS turned on and off. The stimulation condition was kept constant for 5 min before start of the paradigm. The patients were not aware of the stimulation parameter settings. Clinical data are provided in Table 1. The electrode positioning in the brain of the two patients are shown in Fig. 1.

To visualize the electrodes' position in an individualized manner in relation to the pallidum, whole brain segmentation of the patients' MRI was initially performed employing the recon-all pipeline of the Freesurfer toolbox (Fischl et al. 2002). Next, the resulting anatomical labels of the pallidum and other structrues were converted into three-dimensional models using Slicer (Fedorov et al. 2012, retrieved from http://www.slicer.org). These models were implemented into Cicerone (Miocinovic et al. 2007), which was used to reconstruct the electrodes position based on the coordinates of the stereotactic target and the characteristic artifact in the postoperative CT scan (Hemm et al. 2009). Using the individual stimulation settings and the closest applicable impedance value (either 500 or 1,000 Ohms), Cicerone was utilized to approximate the local volume of tissue activated.

The study was conducted in accordance with the Declaration of Helsinki. All patients gave informed consent.

A sample of 20 subjects (10 females and 10 males) between 30 and 60 years of age was recruited as a control group. The mean age was 48.5 ($\pm$12.9) years and controls had received 15.1 ($\pm$4.2) years of education. The controls had normal or corrected-to-normal vision and no history of psychiatric and neurological diseases. Furthermore, a group of $N = 13$ manifest HD gene mutation carriers

Table 1 Clinical data of the patients including DBS settings

	Age (years)	Sex	CAG repeats	Medication	UHDRS motor score (Stim ON)	Mattis score	Years since DBS implant	DBS settings (Kinetra©) left/right	*x*, *y*, *z* coordinates of stimulated contacts in mm with reference to AC-PC line Left/right[a]
Patient 1	57	M	42	Trospiumchloride, Olanzapine, Mirtazapine Tiapride, Lorazepam, Duloxetine	37	126/144	4	2-C+, 2.5 V, 60 µs, 140 Hz, 650 Ω/6-C+, 1.7 V, 120 µs, 140 Hz, 890 Ω	27.7, 4.8, 5.4/20.8, 5.7, 2.1
Patient 2	32	F	53	Tiapride, Sulpiride, Citalopram, Pirenzepine	46	137/144	3	2-3-C+, 1.3 V, 120 µs, 130 Hz, 680 Ω/6-7-C+, 1.3 V, 120 µs, 130 Hz, 680 Ω	20.0, 4.9, 1.7/20.1, 5.0, 2.6

Note that especially *z* coordinates suggest localization above AC-PC line in external parts of the pallidum

UHDRS unified Huntington's disease rating scale, *C* case, *V* volt, *µs* microseconds, *Hz* hertz, *Ω* ohm

[a] If more than one contact was activated mean coordinates of activated contacts were calculated

(5 females/8 males) between 35 and 57 years was included in the study with a mean age of 40.52 (±9.1) years. This group was without any medication and was included to control for possible prolonged lesion effects of electrode placement in the GP. The mean CAG-repeat length of this group was 44.1 (±4.5), the mean UHDRS motor score was 22.25 (±6.6).

Task

The Flanker Task applied is identical to previous studies in Huntington's disease (e.g. Beste et al. 2006). The task examines the ability to adapt behaviour in response to the commitment of response errors. Stimuli (arrowheads) were presented vertically arranged. The target stimulus (arrowhead) was presented in the center with the arrowhead pointing to the left or right. The central stimuli were flanked by two adjacent arrowheads (above or below the target) which either pointed in the same (compatible) or opposite direction (incompatible condition). In case of target stimuli (arrowheads pointing to the left or right) participants had to press a response button with their left or right thumb. The flankers preceded the target by 100 ms. The target was displayed for 300 ms. The response-stimulus interval was 2,000 ms to avoid a large number of missed trials in the motor disabled patients. Flankers and target were switched off simultaneously. Time pressure was administered by asking the subjects to respond within 600 ms. Four blocks of 105 stimuli each were presented in this task. Compatible (70 %) and incompatible stimuli (30 %) were presented randomly (cf. Beste et al. 2010).

EEG recording and analysis

During the task, EEG was recorded from 64 Ag–AgCl electrodes against a reference electrode located at Fz at a sampling rate of 5 kHz. Data were amplified and band-pass filtered from 0.5 to 1,000 Hz using a portable amplifier (BrainVision Recorder, BrainAmp MR plus, Brain Products GmbH, Munich, Germany, Version 1.03). Electrode impedances were kept below 5 kΩ. First the EEG data were filtered (0.3–20 Hz), also to eliminate the noise produced by the DBS generator. After that a raw data inspection was conducted and technically occurring artifacts were discarded by manual inspection of the data. Afterwards, independent component analysis (ICA, Infomax algorithm) was applied and independent components reflecting blinks, saccades and pulse were rejected. The data were segmented into correct and error trials. The response was set to time point 0 (i.e., the time point of button press). A baseline correction was applied −200 ms until button press. An automated artifact rejection procedure was applied within the segments applying an amplitude threshold of ±80 µV. After this data, were re-referenced using the CSD-transformation, which eliminates the reference potential (Nunez and Pilgreen 1991). Error-related negativity (ERN) and correct-related negativity (CRN/Nc) were defined as the most negative peak within 50–120 ms after response. The ERN occurs after the commitment of a response error, while the Nc is a negative going potential that is evident after correct responses (Falkenstein et al. 1991). The ERN and Nc were quantified at electrode FCz, which revealed the centre of the topography in controls and the two HD patients. The ERN and

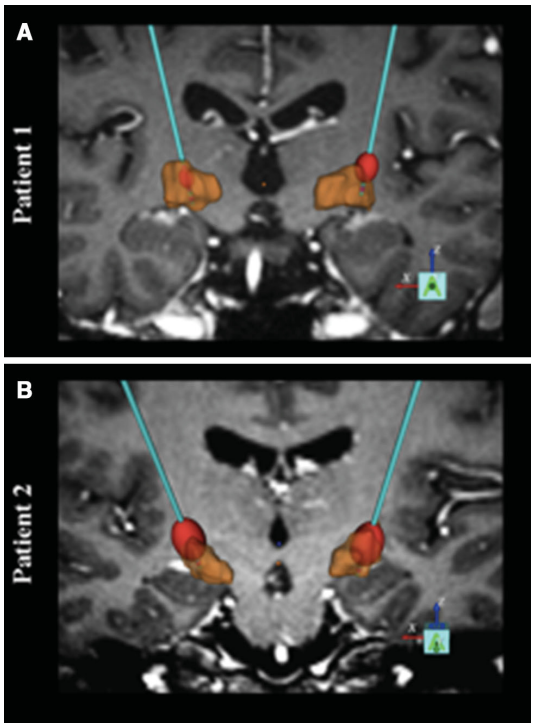

Fig. 1 Individualized visualization of the DBS electrodes. For both patients, the electrodes (*turquoise*) are shown with respect to the dorsal pallidum (*brown*) on both hemispheres. The stimulation settings were utilized to approximate the volume of tissue activated (*red*). Details for patient 1 are visualized in a coronal view from anterior (**a**) and for patient 2, in an angled view from anterodorsal (**b**). Despite the heterogeneity of the volumes of tissue activated, a common target for all four scenarios (*left and right* stimulation for both patients) was the external part of the dorsal pallidum

Nc are quantified as maximum negative peaks for error and correct trials, respectively. To obtain an estimate about the reliability of the neurophysiological data, we calculated the signal-to-noise ratio (SNR) in the HD cases and controls as implemented in the Brain Vision Analyzer II software package (BrainProducts Inc.).

Statistical analysis

To compare the performance and electrophysiological data of the HD cases on and off stimulation with the control group and the un-medicated manifest HD group, we used the Crawford Howell method (for review: Crawford and Garthwaite 2012). This method offers the best way to compare single cases with groups of control subjects (for review: Crawford and Garthwaite 2012). For comparisons within the control group, *t* tests were used and Bonferroni-corrected wherever necessary.

Results

Behavioural data

The behavioural data are shown in Fig. 2a.

For the controls, reaction times (RTs) were faster on error (289 ± 18 ms) than on correct trials (398 ± 19 ms) ($t_{19} = 19.28$; $p < .001$). The controls revealed a substantial post-error slowing (44 ± 5 ms) significantly different from 0 (denoting no post-error slowing) ($t_{19} = 22.67$; $p < .001$). The un-medicated manifest HD group also revealed post-error slowing (31 ± 5 ms), which was lower than in controls ($t_{31} = 4.52$; $p < .001$), but significantly different from 0 ($t_{12} = 17.84$; $p < .001$). RTs were also faster on error (270 ± 9 ms) than on correct trials (450 ± 23 ms) ($t_{12} = 11.35$; $p < .001$). Reaction times on correct trials were also slower compared to the healthy controls ($t_{12} = 11.35$; $p < .001$).

In patient 1 reaction times on error and correct trials were slower compared to controls, regardless of whether DBS was switched on (correct 708 ms; error 592 ms) or off (correct 751 ms; error 633 ms) ($t = 3.78$; $p < .001$; 95 % CI 2.57 to 5.16). The degree of post-error slowing in patient 1 was 50 ms in DBS-on state and 3 ms in the DBS-off state. Post-error slowing in the DBS-off state was significantly lower than in controls ($t = -8.02$; $p < .001$; 95 % CI −10.81 to −5.57); in the DBS-on state there was no difference ($p > .4$). Compared to the un-medicated manifest HD group, the degree of post-error slowing was lower in the DBS-off state ($t = -8.67$; $p < .001$; 95 % CI −12.58 to −5.40) and higher in the DBS-on state ($t = 6.42$; $p < .001$; 95 % CI 3.97 to 9.34).

In patient 2 similar results were obtained. Here, the degree of post-error slowing was also different from controls in the DBS-off state (5 ms) ($t = -7.81$; $p < .001$; 95 % CI −10.55 to −5.43), but not in the DBS-on state where slowing was at 45 ms. However, opposed to patient 2, the RTs on correct and error trials were no different from controls in the DBS-on (correct 385 ms; error 354 ms) and the DBS-off state (correct 354 ms; error 241 ms) ($p > .3$). Also in this patient the degree of post-error slowing was lower in the DBS-off state ($t = -8.03$; $p < .001$; 95 % CI −11.66 to −4.99) and higher in the DBS-on state ($t = 4.81$; $p < .001$; 95 % CI 2.94 to 7.04), when compared to the un-medicated manifest HD group. The behavioural data, therefore, suggest that post-error slowing becomes comparable to controls under GP-DBS and is better than in un-medicated manifest HD patients.

Neurophysiological data

The neurophysiological data in controls are shown in Fig. 1b together with the un-medicated manifest HD group,

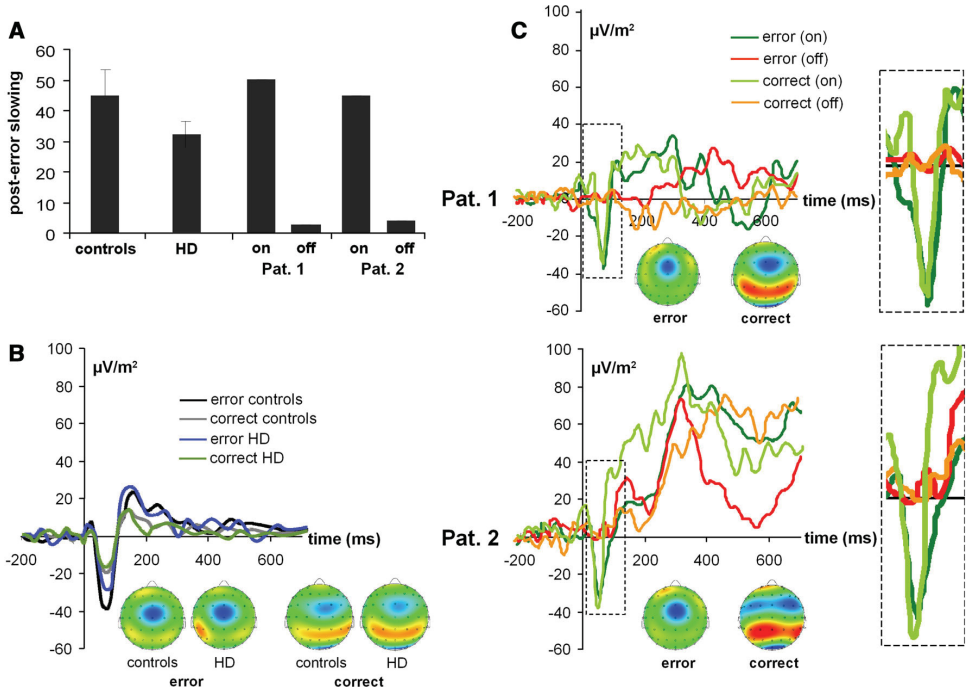

Fig. 2 **a** The degree of post-error slowing (ms) for the control group and the two HD cases in the DBS-on state and the DBS-off state. Note that in the DBS-on state, the degree of slowing was not different from controls. **b** The event-related potentials (ERPs) in the control group. Time point 0 denotes the time point of response execution. The *black* ERP traces denote the potential on error trials (i.e., ERN), the *grey* ERP traces denote the potential on correct trials (i.e., Nc). For the un-medicated manifest HD group the potential on error trials is denoted in *blue*, for correct trials in *green*. **c** Response-locked ERPs in error and correct trials for the two DBS-HD cases. *Dark green traces* denote the ERPs on errors trials in the DBS-on state, *light green traces* denote the ERPs on correct trials in the DBS-on state. *Red traces* denote the ERPs on error trials in the DBS-off state, *orange traces* denote the ERPs on correct trials in the DBS-off state. Time point 0 denotes the time point of response execution. Along with the ERPs the CSD-scalp topography plots for error and correct trials are given. In these plots the peak of the ERP component averaged across subjects in controls and the un-medicated manifest HD group and for the single HD patients undergoing DBS is given

the two cases are shown in Fig. 1c. For the controls there was a difference in the amplitude between the ERN (-40.48 ± 2.82 µV/m^2) and the Nc (-20.90 ± 2.12 µV/m^2) ($t_{19} = -13.26$; $p < .001$). The latencies were not different between correct and error trials ($p > .15$). As to the un-medicated manifest HD group, the results show that the ERN amplitude was smaller in the group of un-medicated manifest HD (-30.56 ± 3.11 µV/m^2), compared to controls ($t_{31} = -6.44$; $p <$. 001). The Nc (-17.89 ± 3.02 µV/m^2) was not different to controls ($t = -1.91$; $p > .12$).

In patient 1 the ERN was not different from controls in the DBS-on state ($p > .4$). However, in the DBS-off state, the ERN was -1.23 µV/m^2 and hence significantly smaller than in controls ($t = 15.22$; $p < .001$; 95 % CI 15.60 to 20.53). In the DBS-off state the Nc (-1.02 µV/m^2) was also smaller compared to controls ($t = 3.09$; $p = .001$; 95 % CI 2.06 to 4.25). Yet, in the DBS-on state, the Nc was significantly larger (-34.12 µV/m^2) than in controls ($t = 2.11$; $p = .02$; 95 % CI 1.34 to 2.97) and not different from the amplitude of the ERN in controls ($p > .4$). Compared to the un-medicated manifest HD group, the ERN was larger in the DBS-on state ($t = 3.06$; $p = .004$; 95 % CI 1.89 to 4.42) and lower in the DBS-off state ($t = 15.22$; $p < .001$; 95 % CI 15.60 to 20.53). Compared to the un-medicated manifest HD group, the Nc was larger in the DBS-on state ($t = 6.65$; $p < .001$; 95 % CI 4.3 to 9.43) and smaller in the DBS-off state ($t = -5.44$; $p < .001$; 95 % CI -7.73 to -3.49).

In patient 2 the results are similar. Here, the ERN was also not different from controls in the DBS-on state ($p > .4$). In the DBS-off state, the ERN had an amplitude of -2.13 µV/m^2 and was thus significantly smaller than in controls ($t = 63.83$; $p < .001$; 95 % CI -9.24 to -4.76). For the Nc the results show that in the DBS-off state, the Nc was smaller than the Nc in controls ($t = -3.56$;

$p = .001$; 95 % CI −4.89 to −2.42). As with patient 1, the Nc in patient 2 was also significantly larger in the DBS-on state compared to controls ($t = 2.27$; $p = .01$; 95 % CI 1.46 to 3.18). As with patient 1 the ERN was larger in the DBS-on state ($t = 3.04$; $p = .004$; 95 % CI 1.87 to 4.39) and lower in the DBS-off state ($t = -9.34$; $p < .001$; 95 % CI −13.21 to −6.07) when compared to the un-medicated manifest HD group. Also, the Nc was larger in the DBS-on state ($t = 7.11$; $p < .001$; 95 % CI 4.4 to 9.66) and smaller in the DBS-off state ($t = -8.56$; $p < .001$; 95 % CI −12.77 to −5.87) compared the to the un-medicated manifest HD group.

Calculation of the SNR, as implemented in the Brain Vision Analyzer II software package, revealed that for correct trials the SNR was 0.18 (±0.04) in controls, and for error trials the SNR was 0.39 (±0.07) in controls. In the un-medicated manifest HD group the SNR was 0.19 (±0.06) for correct trials and 0.34 (±0.09) for error trials.

In patient 1 the SNR was 0.15 for correct trials and 0.34 for error trials; in patient 2 the SNR was 0.13 for correct trials and 0.33 for error trials. The SNRs did not differ between controls and un-medicated manifest HD patients as well as the DBS-HD cases on correct and error trials ($p > .7$) showing that the EEG signals compared are similarly reliable in the groups and the DBS-HD cases.

Discusssion

In the current study we analyzed response monitoring processes in manifest HD patients with DBS of the external GP. The behavioural and the electrophysiological data show that error monitoring processes and general response monitoring processes were intact and comparable to healthy controls and un-medicated manifest HD in a state where the GP was stimulated. For error-related behavioural adaptation, the degree of post-error slowing and the amplitude of the ERN were not different from controls. Opposed to this, error monitoring processes were absent when DBS was switched off; i.e., no ERN or post-error slowing was evident. This concurs with increased error rates suggesting that general response monitoring was also deficient, which is further corroborated by the reduction in Nc amplitude. The results suggest that error monitoring processes are normalized in HD undergoing DBS in pallidal structures. In comparison to the un-medicated manifest HD group, the ERN was larger in the DBS-on state and also post-error slowing was stronger. This underlines the effectiveness of DBS treatment and the beneficial effects on cognitive functions also in comparison to a non-DBS HD group. These results fit well into the literature of DBS effects in HD and the role of the globus pallidus for the modulation of cognitive functions in HD. In a transgenic animal study, Temel et al. (2006) showed that DBS in the GPe lead to better response control in a continuous reaction task. In an imaging study, Politis et al. (2011) provided compelling evidence for the relevance of the GP for cognitive functions in HD. Similar findings are also reported by Jürgens et al. (2008). However, manipulating the DBS parameter (on/off DBS) has an effect on motor performance, as can be seen in the reaction time data in the patients when DBS was turned off, compared to the "on-state", though differences in reaction times were not large (∼60 ms). Importantly, this does not affect the post-error slowing parameter. This parameter gives the prolongation of responses after the commitment of a response error and is calculated separately for the "on-state" and "off-state" in the DBS patients. Therefore, this parameter is not affected by a general slowing of response times, because the parameter is a "ratio" between two types of responses that are equally affected by general effects of motor slowing.

Interestingly, the Nc in the patients under GP-DBS was as large as the ERN and furthermore did not differ from the ERN of the controls; the Nc was also larger than in the un-medicated manifest HD group. Usually, the Nc is smaller than the ERN (e.g. Falkenstein et al. 1991). The Nc has previously been shown to reflect general response monitoring functions related to the motor aspects of a response (e.g. Beste et al. 2010; Yordanova et al. 2004). As such the results suggest that GP stimulation does not exert differential effects on error monitoring and general response monitoring processes. The results suggest that the GP reflects a basal ganglia element important not only for error processing and behavioural adaptation, but for general response monitoring processes as well. These results are well in line with computational assumptions of the basal ganglia, indicating for a 'selection pathway' and 'control pathway' (Humphries et al. 2006). These two functional entities of the basal ganglia are mediated via distinct neurobiochemical and neuroanatomical substrates. Here the GP has been suggested to be part of the control pathway (Humphries et al. 2006). Control and monitoring processes are evident on correct and error trials. Therefore it seems plausible that no differential effects of GP-DBS are evident. However, other targets within the basal ganglia may show similar effects. The model by Humphries et al. (2006) does not distinguish between the GPe and the GPi. It can therefore not be ruled out that similar effects may be obtained using GPi stimulation. Furthermore, electrode localization in our study does not rule out stimulation effects of the GPi. Moreover, the STN is involved in the control pathway and may therefore also show similar effects. Yet, as the STN is also part of the selection pathway effects may also differ from the pattern observed in the current study. Indeed it has been shown that the effects of

STN-DBS on error monitoring depend on dopaminergic medication profile and disease onset (Siegert et al. 2014).

The results are also of interest in the ongoing debate whether the ERN and Nc reflect different functional processes. It has been suggested that the ERN simply reflects an intensification of processes also occurring during general response monitoring, reflected by the Nc (Hoffmann and Falkenstein 2010; Vidal et al. 2000; Coles et al. 2001). The current results suggest that as far as the GP is concerned, this may be possible since both the ERN and Nc show similar modulations as an effect of switching GP-stimulation on and off.

GP-DBS is currently investigated to treat motor symptoms in manifest HD. From a clinical neurological perspective the results suggest that GP(e)-DBS reflects a safe treatment in HD with respect to cognitive functions, when response monitoring processes are considered. A reason for this may be that the emergence of motor symptoms in HD and cognitive dysfunctions related to response monitoring and error processing reflect interrelated phenomena (Smith et al. 2000). As such, the modulation of response monitoring processes by GP-DBS reflects a side-effect of efforts to alleviate motor symptoms in HD. However, it needs to be noted that due to the limited sample size the results are preliminary, but provide information useful in future multicenter clinical studies investigating the effectiveness of pallidal DBS in HD.

Acknowledgments This work was supported by a Grant from the Deutsche Forschungsgemeinschaft (DFG) BE4045/10-1. The initial clinical trial was supported with a seed funding by the European Huntingtońs Disease Network (EHDN). We thank the patients for their cooperation.

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Journal of the Neurological Sciences 366 (2016) 68–73

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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Local field potential oscillations of the globus pallidus in cervical and tardive dystonia

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ARTICLE INFO

Article history:
Received 16 December 2015
Received in revised form 16 March 2016
Accepted 16 April 2016
Available online 19 April 2016

Keywords:
Cervical and tardive dystonia
Local field potentials
Oscillations
Globus pallidus
Intraoperative recordings

ABSTRACT

Background: Reports about neural oscillatory activity in the globus pallidus internus (GPi) have targeted general (GD) and cervical dystonia (CD), however to our knowledge they are nonexistent for tardive dystonia (TD).
Methods: Local field potentials (LFPs) from seven CD and five TD patients were recorded intraoperatively. We compared LFP power in thetadelta, alpha and beta band during rest and sensory palmar stimulation (SPS) in patients with general anesthesia and local/analgo sedation.
Results: We found prominent LFP power activity in thetadelta for both CD and TD. Unlike TD, a significant difference between rest and SPS was revealed for CD.
Conclusions: Our data support the presence of LFP oscillatory activity in CD and TD. Thetadelta power modulation in the GPi is suggested as a signature for sensory processing in CD.

1. Introduction

Dystonia is a movement disorder characterized by persistent muscle contractions and abnormal postures that may be idiopathic as in the case of segmental or focal dystonia which includes cervical dystonia (CD) [1]. Tardive dystonia (TD) is a secondary dystonia, occurring as side effect of prescribed drugs. To date, the pathophysiology of CD and TD remain poorly understood [2]. Nevertheless, several studies point towards neural dysfunction of multiple brain regions [3] and particularly the basal ganglia which are targeted by deep brain stimulation (DBS). This therapy aims to modulate changes in oscillatory activity mostly in the globus pallidus internus (GPi) of dystonia and myoclonus dystonia patients [4,5,6,7,8,9,10]. In particular, some authors reported that neuronal synchronization indexed by LFP oscillations in the globus pallidus is correlated with movement parameters and signals such as dystonic muscle activity by focusing on theta, alpha, low beta and gamma bands [11,12,13]. It was also shown that such oscillations in the 8–12 Hz frequency range synchronize with local neuronal discharges (microelectrode activity) in the GPi and possess higher amplitude than in the globus pallidus externus [14]. LFP oscillatory activity in the GPi has also been reported from Huntington's [15] and Parkinson's disease [16], while the spatial pattern of spectral power corresponding to intraoperative trajectories has been studied by our group [15,17,18,19,20]. In this report, we address the spatial oscillatory pattern of intraoperative trajectories targeting GPi (frequency range up to 100 Hz) by focusing on the mentioned dystonic groups and also comparing LFP power between conditions: CD vs. TD, with vs. without general anesthesia, and rest vs. sensory palmar stimulation (SPS) at specified frequency bands. Based on our findings, we suggest thetadelta modulatory activity in the GPi as a correlate of sensory processing in CD rather than TD.

2. Materials and methods

2.1. Participants

A total of 18 GPis (eleven CD and seven TD) in seven CD and five TD patients who underwent deep brain stimulation (DBS) surgery of the GPi, were recorded (Table 1). The study was in compliance with the Helsinki Declaration and had been approved by the local Ethics Committee at the University Hospital Düsseldorf (Study Nr. 2459). Informed consent was obtained from each patient.

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http://dx.doi.org/10.1016/j.jns.2016.04.033
0022-510X/

Table 1
Patient's characteristics. (CD: cervical dystonia, TD: tardive dystonia).

Patient #	Gender	Disease	Years since disease onset	Age in years at surgery	Anesthesia during surgery
1	Male	CD	12	59	General
2	Male	CD	15	68	Local/analgo sedation
3	Female	CD	26	66	Local/analgo sedation
4	Male	CD	17	45	General
5	Female	CD	25	66	General
6	Female	CD	16	56	Local/analgo sedation
7	Female	CD	36	45	General
8	Female	TD	21	44	General
9	Male	TD	11	48	Local/analgo sedation
10	Female	TD	28	57	General
11	Female	TD	24	72	General
12	Female	TD	13	66	General

2.2. Micro- and LFP macrorecordings

DBS target was determined by fusion of stereotactic CT and preoperative 3 Tesla MRI. Intraoperative multiunit activity (MUA) and LFPs were recorded simultaneously with up to 5 combined micro-macroelectrodes (microelectrode and macroelectrode tip 1.5 mm apart) (M: medial, C: central, L: lateral, A: anterior and P: posterior or alternatively AM: anteriormedial, AL: anteriorlateral, PM, posteriormedial, PL: posteriorlateral) (Fig. 1A) in steps of 0.5 to 1 mm, starting 10 mm above the target point by using the INOMED ISIS microelectrode recording system (Inomed Medizintechnik GmbH, Emmendingen, Germany).

It was not possible to measure the impedance of the macroelectrodes, although the manufacturer of the INOMED system reports a generic value of 1 kΩ. LFP-signals were amplified by a factor of 2000 and sampled at 2.5 KHz. Patients were awake or sedated during surgery by taking into consideration their particular symptoms and physical condition. The protocol for patients in general anesthesia included propofol (mean dosage 6.088 ± 1.730 mg/min) and remifentanil (mean dosage 15.110 ± 5.984 μg/min). Patients without general anesthesia underwent analgosedation with the above mentioned drugs that were paused before recordings.

Determined by optimal microelectrode activity around the calculated target point (±1 mm) two conditions were recorded with LFP: 1) twice 1 min of rest before and after (to avoid order effects) 2) two minutes of SPS of the contralateral hand (palm) with cotton swabs. We applied the same stimulation protocol for all the patients (CD and TD).

2.3. Off-line analysis

Postoperative (offline) analysis of macroelectrode trajectories around the target point (±1 mm) was carried out by using BrainVision Analyzer software (version 2, Brain Products GmbH, Munich, Germany). Data were down-sampled to 512 Hz, band-passed between 0.5 and 160 Hz, and notch-filtered at 50 Hz. The fast Fourier transform (FFT) was applied over each recorded segment of 120 s, with a Hanning window of 0.5 s and 50% overlap, leading to a spectral resolution of 1.2 Hz. By using the FFT, power spectral density (PSD) was subsequently calculated as implemented in the mentioned software. PSD was used to study the strength of LFP's spectral power variation as a function of frequency. Throughout the text "PSD of LFP" is just referred to as PSD for brevity.

2.3.1. Peak analysis

For each GPi, the trajectory with the highest PSD peak amplitude in the frequency range 1–30 Hz during rest condition was selected for further statistical comparison. Analysis of LFP oscillatory activity was performed by comparing amplitude and frequency of selected PSD peaks between the considered conditions: CD vs. TD, rest vs. SPS and with vs. without general anesthesia. The analysis focused on the frequency bands (thetadelta (θ-δ): 1–7 Hz, alpha: 8–12 Hz, beta: 13–30 Hz).

For the comparison of PSD peaks between conditions, we took the peak with maximum amplitude (within a specified frequency band) in the rest condition and compared it with the one in the SPS condition by allowing a variance of ±1 Hz.

2.3.2. Grand average of PSD/mean PSD analysis

Grand average (GAV) of PSD was calculated for CD and TD across all trajectories regarding the condition rest vs. SPS. For each PSD spectra used in the calculation of these GAVs, mean PSD in the frequency ranges thetadelta (θ-δ) (1–7 Hz) and theta-alpha (θ-α) (5–12 Hz) were calculated.

In addition, GAV of PSD was calculated for each trajectory across all patients regarding the condition rest vs. SPS. For each PSD spectra used in the calculation of these GAVs, mean PSD in the frequency range thetadelta (θ-δ) (1–7 Hz) was calculated.

SEM bar graphs were calculated for mean PSD values (rest and SPS) in the case of CD for the frequency bands θ-δ and θ-α.

2.4. Statistical analysis

For selected trajectories in the peak analysis, we compared peak amplitudes and their corresponding frequencies for the considered conditions. Because the assumption of normality in the distribution of most variables was violated (Shapiro–Will test), we made use of the Mann–Whitney and the Kruskal–Wallis tests for comparisons between independent groups, and the Wilcoxon signed rank test (alternatively the sign test for non-symmetrical distributions) for intra-individual differences.

For variables meeting the assumption of equality of variations a mixed design ANOVA was additionally performed to study a possible effect of anesthesia between groups, although with caution considering the limitation of a small sample-size for both dystonic groups.

For the comparison of mean PSD values between rest and SPS for CD, TD and each trajectory, the Wilcoxon signed rank test (alternatively the sign test) was applied.

Statistical analysis was performed through SPSS software (IBM SPSS Statistics, IBM Corp). The level of significance for all statistical tests was fixed at $p < 0.05$.

3. Results

We obtained the oscillatory pattern of trajectories targeting the GPi in CD and TD by focusing on the selected frequency bands.

With regard to CD (rest), we found prominent LFP oscillatory activity in thetadelta (all GPis), alpha (5 GPis) and beta (4 GPis) as reflected by the presence of PSD peaks with maximum amplitude within each considered frequency band. With regard to TD (rest), oscillatory activity was found in thetadelta (all GPis), alpha (6 GPis) and beta (1 GPi).

Based on the number of recordings with a peak within a specified frequency band for each trajectory (Table 2(A, B)), we found that each considered frequency band was represented in each trajectory and that the highest number of recordings with PSD peak occurrences corresponded to the central trajectory. Note that Table 2 summarizes the number of recordings over the whole group of patients/recordings.

The comparison between recording conditions revealed the following details.

3.1. CD vs. TD

We found no significant difference between CD and TD by considering PSD peak frequency and PSD peak amplitude in the frequency bands thetadelta, alpha and beta, which suggests a similar oscillatory pattern for both dystonia groups.

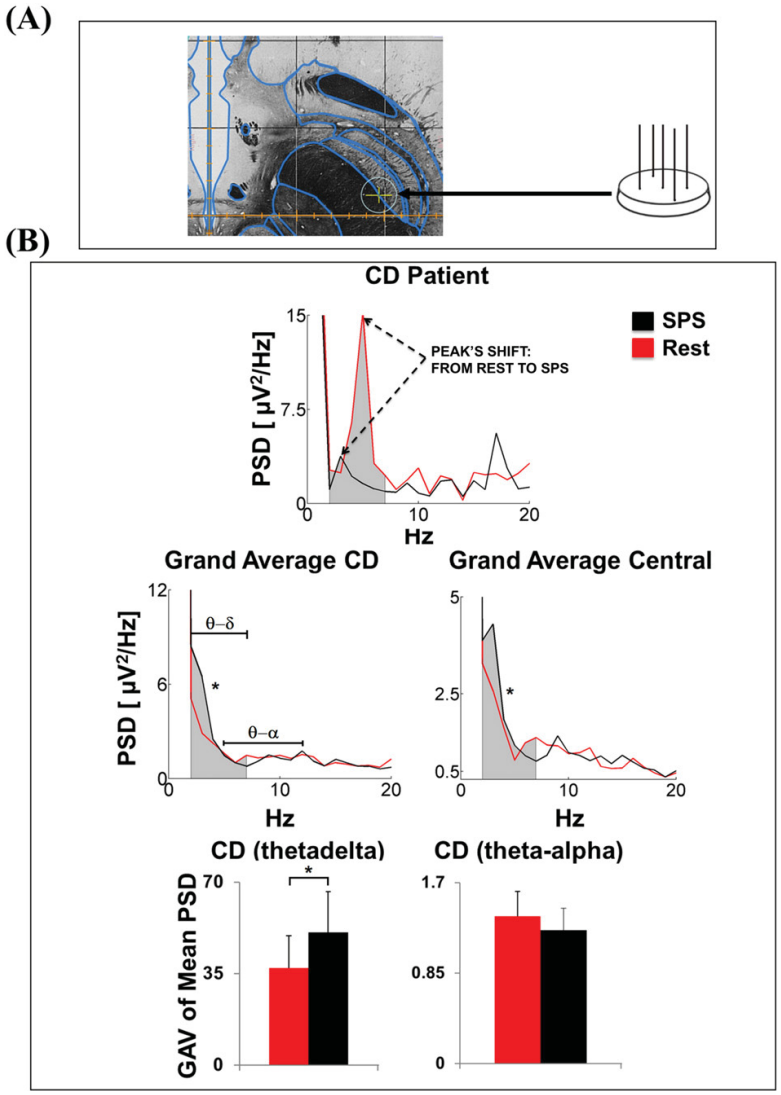

Fig. 1. (A) Mean recording location in posterolateral GPi (center of the cross) mirrored on left axial slice of Schaltenbrand atlas. Error bars denote standard deviation; circle defines spatial range of microelectrodes; (B, top) Example of LFP-PSD corresponding to a CD patient, rest (red) and sensory palmar stimulation (SPS) (black). This graph illustrates a frequency shift in the thetadelta range. Note: change in beta power seen in this example was not significant over the group. The LFP recording was performed 1 mm below target and the patient was awake; (B, middle (left)) Grand average of LFP PSD for CD across all trajectories, a significant difference in mean PSD between rest and SPS in θ-δ ($Z = -2.328$, $p = 0.020$) and a non-significant trend (rest > SPS) ($Z = -0.144$, $p = 0.88$) in θ-α were revealed; (B, middle (right)) Grand average of LFP-PSD for the central trajectory across all patients, a significant difference in mean PSD between rest and SPS in Θ-δ was revealed (sign test, $p = 0.049$); (B, bottom) standard error of mean (SEM) bar graphs depicting grand average of mean PSD values for CD across all trajectories in θ-δ (left) and θ-α (right). In the graphs, *denotes statistical significant difference and shaded (gray) areas correspond to the frequency band θ-δ.

3.2. Rest vs. SPS

3.2.1. Peak analysis

We found a significant difference between rest and SPS in peak frequency (thetadelta) for the whole group (CD and TD) ($Z = -2.498$, $p = 0.013$, Wilcoxon). In the case of CD, we found a significant difference between rest and SPS in peak frequency (thetadelta) ($Z = -2.197$, $p = 0.028$, Wilcoxon) and in peak amplitude ($Z = -2.090$, $p = 0.037$, Wilcoxon) e.g. a significant shift in peak frequency from high (during rest) to a low (during SPS), which was accompanied by a corresponding decrease in amplitude (see example Fig. 1(B, top)). No significant difference was found between rest and SPS for TD.

3.2.2. Mean PSD analysis

A significant difference ($Z = -2.328$, $p = 0.020$, Wilcoxon) in mean PSD values between rest and SPS in θ-δ for CD across all trajectories was revealed (Fig. 1(B, middle (left)) (B, bottom (left))). Also, a significant difference ($p = 0.049$, sign test) in mean PSD values between rest and SPS in θ-δ for the central trajectory across all patients was revealed (Fig. 1(B, middle (right))). Notably the significant difference in CD was

Table 2
Number of target point-recordings with a PSD peak within a specified frequency band (thetadelta, alpha, beta) for each trajectory (M: medial, C: central, L: lateral, A: anterior and P: posterior, AM: anteriomedial, AL: anteriolateral, PM, posteriomedial, PL: posteriolateral). Note that due to anatomical constraints in some patients, a rotation of the electrode system by 45° took place giving place to trajectories (AM, AL, PM, PL).

Macroelectrode	Total recordings	Thetadelta	Alpha	Beta
(A) Rest				
A	11	11	10	11
M	13	10	9	9
C	18	17	17	18
L	12	12	11	12
P	11	7	7	7
AM	2	1	2	2
AL	2	1	2	2
PM	2	2	2	2
PL	2	2	2	2
(B) Sensory stimulation				
A	11	11	11	11
M	13	10	10	10
C	18	17	18	18
L	12	12	12	12
P	11	7	7	7
AM	2	2	2	2
AL	2	1	2	2
PM	2	2	2	2
PL	2	2	2	2

accompanied by a non-significant trend (rest > SPS) in θ-α Fig. 1(B, middle (left), (B, bottom (right))).

3.3. Anesthesia

By focusing on PSD-peaks on a descriptive level for the comparison of rest with SPS in CD, we found that 2/4 patients under general anesthesia exhibited a difference above average (with one of them showing only a minor difference). 3/3 patients under local/analgo sedation exhibited a difference above average.

This descriptive comparison in TD, showed that 2/4 patients under general anesthesia and 1/1 patient under local/analgo sedation exhibited a difference above average between rest and SPS.

Statistically, we found no significant difference between with (8 patients) and without (4 patients) general anesthesia groups by focusing on peak frequency and peak amplitude in all of the considered frequency bands and dystonia groups. However, only in patients without general anesthesia, a significant difference between rest and SPS in peak frequency (thetadelta) ($Z = -2.460$, $p = 0.014$, Wilcoxon) and peak amplitude ($Z = -1.960$, $p = 0.05$, Wilcoxon) was revealed.

Furthermore, by using a mixed design ANOVA, we found no significant effect of anesthesia between rest and SPS regarding peak amplitude in the alpha band ($F = 0.009$, $p = 0.926$), peak frequency in the beta band ($F = 1.011$, $p = 0.330$), or peak amplitude in the thetadelta band ($F = 0.030$, $p = 0.866$). In case of peak frequency in the alpha band and thetadelta band and peak amplitdue in the beta band the assumption of equality of variances was violated.

With regard to SPS, no significant difference between with and without anesthesia groups concerning peak amplitude and peak frequency in any of the considered frequency bands was revealed by the Kruskal–Wallis test.

4. Discussion

To our knowledge this is the first study reporting on intraoperative oscillatory activity in the GPi for TD, while our results supported previous studies addressing LFP oscillatory activity in the GPi for CD patients [11,21].

Focusing on CD patients, we reported a significant peak frequency shift from high (during rest) to low (during SPS) in thetadelta band, which was often accompanied by a corresponding decrease in peak amplitude. Such a power modulation during sensory stimulation in contrast to the rest condition was observed in several of the CD patients pointing to distinctive thetadelta oscillatory activity in the pallidum.

We did not find a significant difference between with and without general anesthesia groups nor an effect of anesthesia on the comparison between rest and SPS, in contrast to studies reporting that GPi theta power was significantly higher in patients without than in patients with general anesthesia for CD [8]. However, in our data a significant difference between rest and SPS was revealed only in patients without general anesthesia.

Taken together, the results of our statistical analyses support only minor effects of anesthesia on the contrast between rest and SPS in thetadelta. Consequently, the significant thetadelta modulation of PSD in CD that was found is suggested as a putative signature of sensory processing for this group.

Nevertheless, it should be mentioned that it is problematic to distinguish between with and without general anesthesia strictly as both groups were exposed to sedative drugs. The clinical difference between general anesthesia and analgosedation represents thus more two ends of a continuum rather than two distinct approaches.

Previous studies reported that antagonistic gestures, such as touching the face with fingertips, has the potential to relieve dystonic symptoms in up to 70% of patients with idiopathic CD [22]. Moreover, evidence was recently provided that release of dystonic contraction under sensory tricks in CD patients, is mediated by changes of motor cortex excitability putatively linked to inhibition of abnormal muscle contraction [23]. In the present study, we provide evidence for the involvement of the GPi in sensory motor processing as we showed that the applied sensory stimulus on the contralateral hand of CD patients led to significant LFP power modulation in the thetadelta band. Interestingly, such an effect was not observed in TD patients, which might emphasize differential neural processing in the GPi of both disorders. Nevertheless, we found similar oscillatory signatures in both dystonia types. Further studies will be required to better understand the influence of different sensory stimuli on CD and TD patients, which may lead to the development of novel therapeutic approaches based on sensorimotor stimulation.

Our results and others favor the hypothesis that sensory stimulation facilitates sensorimotor integration and regulates excitability of the sensorimotor system, which appears to be altered in dystonia patients [23,24]. In fact, a very recent study provides evidence for the normalization of sensorimotor integration in dystonia patients by applying 1 Hz repetitive transcranial magnetic stimulation over primary sensory and motor cortices [25].

Some limitations of the present study include a small sample of dystonia patients, which is due to the rarity of the disease and prevents us from performing statistical corrections for multiple analyses. Due to variability in the anesthesia protocol (constituent dosage and administration throughout the surgery procedure) and stimulation related factors such as density and orientation of tactile mechanoreceptors in the palm of each patient, it is likely that neuronal oscillatory activity in the GPi was influenced differently in some of the patients. As such, this could be a contributing factor why some patients did not show the pattern of decreased LFP power amplitude during sensory stimulation in the thetadelta band. Although the sensory trick was not directly administered in the dystonic limb or the patient's face due to constraints in the surgery setting, it is tempting to speculate that SPS provided activation of the GPi via the sensory motor pathway thus stressing a potential role of the GPi in sensory motor processing.

5. Conclusion

In conclusion, we provide support for the presence of LFP oscillatory activity in CD and TD with emphasis on the thetadelta bandwidth. Thetadelta power modulation in the GPi is suggested as a signature for sensory processing in CD. We also hypothesize that the reported thetadelta modulation in the GPi-LFP power may also be a signature of sensory tricks. Further studies should clarify the role of such LFP power modulation by considering different sensory stimuli and stimulation locations in a controlled setting.

Author roles

1. Research project: A. Conception, B. Organization, C. Execution.
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique.
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

Carlos Trenado: 1C; 2A, B, C; 3A.
Christian Hartmann: 1C; 2A, B; 3B.
Saskia Elben: 1C; 2B, 3B.
Amande Pauls: 1C; 2B; 3B.
Lena Friggemann: 1C; 2B; 3B.
Stefan Jun Groiss: 1C; 2B; 3B.
Lars Timmermann: 1A; 2C; 3B.
Jan Vesper: 1C; 2C; 3B.
Alfons Schnitzler: 1A; 2C; 3B.
Lars Wojtecki: 1A, B, C; 2A, B, C; 3A, B.

Full financial disclosure of the last year of all authors

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Carlos Trenado: Stock Ownership in medically-related fields, Consultancies and Partnerships, Intellectual Property Rights, Expert Testimony, Employment, Contracts and Royalties: none Honoraria: none
Grants: none

Christian Hartmann: Stock Ownership in medically-related fields, Consultancies and Partnerships, Intellectual Property Rights, Expert Testimony, Employment, Contracts and Royalties: none
Honoraria: none
Grants: the German Academic Exchange Service and the "Forschungskommission", Heinrich-Heine-University, Düsseldorf (Germany).

Saskia Elben: Stock Ownership in medically-related fields, Consultancies and Partnerships, Intellectual Property Rights, Expert Testimony, Employment, Contracts and Royalties: none. Honoraria: Biogen Idec.
Grants: none.

K. Amande M. Pauls: Stock Ownership in medically-related fields, Consultancies and Partnerships, Intellectual Property Rights, Expert Testimony, Employment, Contracts and Royalties: none. Honoraria: none
Grants: none.

Lena Friggemann: Stock Ownership in medically-related fields, Consultancies and Partnerships, Intellectual Property Rights, Expert Testimony, Employment, Contracts and Royalties: none
Honoraria: none
Grants: none.

Stefan Jun Groiss: Stock Ownership in medically-related fields, Consultancies and Partnerships, Intellectual Property Rights, Expert Testimony, Employment, Contracts and Royalties: none.
Honoraria: Medtronic, Boston Scientific, Actelion
Grants: none.

Lars Timmermann: Stock Ownership in medically-related fields, Consultancies and Partnerships, Intellectual Property Rights, Expert Testimony, Employment, Contracts and Royalties: L.T. has been a consultant for Medtronic Inc., Boston Scientific, SAPIENS, GE Medical, UCB Schwarz Pharma, Archimedes Pharma. Neither L.T. nor any member of his family holds stocks, stock options, patents or financial interests in any of the mentioned companies or their competitors
Honoraria: Zambon Pharma, TEVA Pharma, Medas Pharma, UCB Schwarz Pharma, Desitin Pharma, GlaxoSmithKline, Orion Pharma, Medtronic, Boston Scientific, Abbvie, GE Medical, Archimedes, Bayer, ProsStrakan Pharma
Grants: The institution of L.T., not L.T. personally, received funding by the German Research Foundation, the German Ministry of Education and Research, Hoffnungsbaum e. V., NBIA DISORDERS SOCIETY USA, Köln Fortune, Medtronic, Deutsche Parkinson Vereinigung, Archimedes Pharma, Abott, Bayer, UCB, zur Rose Pharma, TEVA.

Jan Vesper: Stock Ownership in medically-related fields, Consultancies and Partnerships, Intellectual Property Rights, Expert Testimony, Employment, Contracts and Royalties: J.V. has been a consultant for St. Jude Medical and Boston Scientific
Honoraria: St. Jude Medical and Boston Scientific
Grants: none.

Alfons Schnitzler: Stock Ownership in medically-related fields, Consultancies and Partnerships, Intellectual Property Rights, Expert Testimony, Employment, Contracts and Royalties: A.S. has been serving as a consultant for Medtronic Inc., Boston Scientific, St. Jude Medical
Honoraria: A.S. has received lecture fees from Abbvie Boston Scientific, St. Jude Medical, Medtronic Inc., UCB, MEDA Pharma, Teva Pharma, and GlaxoSmithKline
Grants: As Government employee, A.S. has received through his institution research funding from German Research Council and German Ministry of Education and Health.

Lars Wojtecki: Stock Ownership in medically-related fields, Consultancies and Partnerships, Intellectual Property Rights, Expert Testimony, Employment, Contracts and Royalties: none
Honoraria: St. Jude Medical, Medtronic, Deutsche Parkinson Vereinigung
Grants: DFG, Deutsche Parkinson Vereinigung, ParkinsonFonds, ERA-NET NEURON (BMBF).

Acknowledgments

The authors gratefully acknowledge all the patients who participated in this research.

This work was supported by ERA-NET NEURON/BMBF Germany (TYMON/01EW1411) to LW.

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EJN European Journal of Neuroscience

FENS Federation of European Neuroscience Societies

European Journal of Neuroscience, pp. 1–12, 2016 doi:10.1111/ejn.13429

The rhythm of the executive gate of speech: subthalamic low-frequency oscillations increase during verbal generation

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Keywords: executive function, local field potentials, subthalamic nucleus, verbal fluency

Edited by John Foxe

Received 13 March 2012, revised 6 September 2016, accepted 5 October 2016

Abstract

We investigated neurophysiological mechanisms of subthalamic nucleus involvement in verbal fluency through of a verbal generation task. The subthalamic nucleus is thought to act as a behavioural go/no-go instance by means of oscillatory communication in the theta band with the prefrontal cortex. Because subthalamic alpha-theta frequency stimulation has been shown to exert beneficial effects on verbal fluency in Parkinson′s disease, we hypothesized that an alpha-theta oscillatory network involving the subthalamic nucleus underlies verbal generation task performance as a gating instance for speech execution. Postoperative subthalamic local field potential recordings were performed during a verbal generation compared to a control task. Time-frequency analysis revealed a significant alpha-theta power increase and enhanced alpha-theta coherence between the subthalamic nucleus and the frontal surface EEG during the verbal generation task. Beta and gamma oscillations were not significantly modulated by the task. Power increase significantly correlated with verbal generation performance. Our results provide experimental evidence for local alpha-theta oscillatory activity in the subthalamic nucleus and coherence to frontal associative areas as a neurophysiological mechanism underlying a verbal generation task. Thus, verbal fluency improvement during subthalamic alpha-theta stimulation in Parkinson′s disease is likely due to an enhancement of alpha-theta oscillatory network activity. Alpha-theta oscillations can be interpreted as the rhythmic gating signature in a speech executing subthalamic-prefrontal network.

Introduction

The subthalamic nucleus (STN) is involved in an associative basal-ganglia-thalamocortical network (Temel *et al.*, 2005) and acts as input area through which the cerebral cortex controls motor and behavioural aspects (Benarroch, 2008). Its ventromedial part corresponds to the associative territory and has connections with the prefrontal and anterior-cingulate cortices, critical structures in cognition (Alexander *et al.*, 1990; Benarroch, 2008). The clinical relevance of this network is highlighted by cognitive side effects of high-frequency deep brain stimulation (HFS). STN-HFS is an established treatment in Parkinson's disease (PD; Deuschl *et al.*, 2006; Weaver *et al.*, 2009; Williams *et al.*, 2010). However, studies report decline in verbal fluency (VF) during HFS (Witt *et al.*, 2008; Weaver *et al.*, 2009). VF demands a complex performance, including working memory and word retrieval, executive aspects as a retrieval strategy, selection from competing lexical alternatives, subcategory shifting and vocabulary access. STN-HFS impairs VF-associated activation in a left-sided frontotemporal network (Schroeder *et al.*, 2003). Furthermore, VF decline correlates with reduction in perfusion (Cilia *et al.*, 2007) and metabolism (Kalbe *et al.*, 2009) in left dorsolateral-prefrontal, inferior-frontal and anterior-cingulate areas. Although STN stimulation below 100 Hz can be beneficial to some motor aspects (di Biase & Fasano, 2016), in contrast to HFS, low-frequency alpha-theta-stimulation (LFS) of the STN of about 10 Hz worsens limb motor symptoms in PD, possibly due to enhancement of a 10 Hz pathologic oscillatory network (Timmermann *et al.*, 2003, 2004). On the

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other hand, alpha-theta-LFS at 10 Hz improves VF (Wojtecki *et al.*, 2006), possibly by activation of oscillatory connections with frontal areas. Generally, oscillatory synchronization is a feature for information processing of neuronal networks (Singer, 1999; Varela *et al.*, 2001; Schnitzler & Gross, 2005). 10 Hz oscillatory activity may represent various cognitive operations in cortico-thalamic-circuits, such as theta-oscillations (4–7 Hz) reflect working memory and alpha-oscillations (8–12 or 13 Hz, individually variable) play a role in transient reactivation of long-term memory codes during short-term storage (Klimesch *et al.*, 2005).

A method to find evidence for the involvement of a neuronal structure in a given task is to directly record local field potentials (LFPs) from it. LFPs presumably reflect input signals of the target structure and contain electrical activity of a millimetre range from an electrode, consisting of the summated synchronized postsynaptic excitatory and inhibitory potentials (Brown & Williams, 2005; Kuhn *et al.*, 2005b). Analysis of LFP-basal-ganglia-oscillations for the cognitive domain has progressed substantially due surgery for deep brain stimulation (Munte *et al.*, 2008; Marceglia *et al.*, 2011). Up to date STN-LFP recordings suggest local involvement of theta-, alpha- and beta-modulations (13–30 Hz) during cognitive tasks (Rektor *et al.*, 2009, 2010; Fumagalli *et al.*, 2011).

Although VF is the most often affected cognitive function in STN–HFS it has not extensively been investigated with LFPs so far. There is first evidence for local gamma (30–100 Hz) STN modulation during VF (Anzak *et al.*, 2011) and beta desynchronization during speech (Hebb *et al.*, 2012). However, oscillatory activity in the theta-band seems to be crucial for communication of the subthalamic nucleus with the prefrontal cortex (Cavanagh *et al.*, 2011) to act as a behavioural go/no-go behaviour-gating instance (Frank, 2006). Thus, using a verbal generation (VG) paradigm comprising all aspects of a formal-lexical phonemic VF task we aimed to investigate more elaborately if there is evidence for the involvement of the STN in a VF-network, by means of increased low-frequency (alpha-theta) oscillatory LFP-activity and coherence to surface electroencephalography (EEG). This would provide an explanation for the beneficial effects of STN-LFS on VF and disentangle the rhythmic signature in a speech-gating network as representative example of the integrative function of the STN.

Materials and methods

Patients and surgery

Sixteen patients with Parkinson's disease (eight female, eight male; age 62 ± 6.6 years) who underwent bilateral implantation of deep brain electrodes in the STN were enrolled in the study. In all patients, cognitive impairment was excluded during routine presurgical evaluation [Mattis Dementia Rating Scale (MDRS) score 138.7 ± 5.4 points]. Mean disease duration at the time of implantation was 14.1 years (±4.9 years). All patients showed motor symptoms, consisting of akinesia, resting tremor and/or rigidity that responded positively to pharmacological treatment with levodopa, with the exception of tremors. The presurgical Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987) ON and OFF medication was assessed. Due to insufficient control of motor fluctuations and/or tremor by medication, our centre's guidelines suggested to proceed with the implantation of deep brain stimulation (DBS) electrodes to further reduce the patients' symptoms in accordance with the German recommendations for DBS in Parkinson's disease (Hilker *et al.*, 2009; Voges *et al.*, 2009).

All anti-parkinson medication was withdrawn at least 12 h before surgery (dopamine agonists 2–3 days before). The clinical details are summarized in Table 1. All patients were implanted bilaterally in the STN. The location of the STN was determined based on Schaltenbrand–Wahren-Atlas (SWA; Schaltenbrand & Wahren, 1977) coordinates, stereotactic cranial computed tomography (CT) and high-resolution magnetic resonance imaging (T1 weighted MPRAGE and T2 SPACE MRI). To determine the STN borders and the optimal implantation area, we performed intraoperative microelectrode recordings (MER), using the INOMED MER system (INOMED, Emmendingen, Germany) with up to five electrodes (central, anterior, posterior, lateral, medial) that were concentrically configured with a distance of 2 mm from the central electrode. The final placement of the DBS electrode (electrode model 3389, Medtronic Corporation, Minneapolis, MN, USA) was based on multiunit cell activity, a profile of stimulation effects, and side effects. DBS surgery based on intraoperative multiple trajectories MER and test stimulation can be beneficial to optimal placement of DBS electrodes in the dorsolateral (motor) STN and clinical outcome

TABLE 1. Clinical characteristics of PD patients

Patient	Gender	Age (years)	Disease Duration (years)	PD Medication (LED mg/day)	Disease Type (AR: akinetic-rigid T: tremor)	Predominant Side	MDRS	Motor UPDRS	
								OFF	ON
1	Male	62	16	750	AR	Left	142	36	11
2	Female	71	24	900	AR	Right	142	25	16
3	Female	68	22	1150	AR	Left	131	72	37
4	Male	55	14	950	AR	Right	144	48	18
5	Female	62	10	200	AR	Left	141	35	13
6	Female	66	14	900	AR	Left	139	24	11
7	Male	57	8	400	T	Left	139	31	15
8	Female	74	15	400	T	Right	139	23	7
9	Female	67	14	625	AR	Right	142	38	19
10	Female	55	15	1001	AR	Left	133	45	21
11	Male	64	11	1300	AR	Right	141	35	19
12	Male	68	8	700	AR	Left	139	28	10
13	Male	60	15	300	AR	Right	143	35	4
14	Male	51	10	1480	AR	Right	138	35	26
15	Female	64	21	200	T	Left	138	32	12
16	Male	55	9	600	T	Left	140	45	38

LED, Levodopa equivalent dose of PD-medication at the day of the recording; MDRS, Mattis Dementia Rating Scale; UPDRS, Unified Parkinson´s disease-rating scale with and without medication at the preoperative screening.

(Reck *et al.*, 2012). During the operation, final macroelectrodes were connected to sterile percutaneous extension wires (model 3550-05, Medtronic), which were externalized through the scalp and could be connected postoperatively to EEG amplifiers via external cable connectors (twist lock cable model 3550-03, Medtronic and custom made connector to DIN 428092 touch proof connectors). Postoperative stereotactic computed tomography (CT) scans were performed in all patients to ensure correct electrode placement.

Paradigm

The experiment consisted of two parts (Fig. 1). The first task was a VG task, comprising all aspects of a formal-lexical (phonemic) VF task. The task consisted of the presentation of the 10 most frequent initial letters of the German language (S, A, M, K, B, G, R, H, E, D), each presented for eight times successively (total of 80 trials). Each trial began with the presentation of a letter in the centre of the screen for 1 s. Onset of the letter was time point zero. Subjects were instructed to think of a word beginning with that letter without speaking aloud. Furthermore, patients were asked to avoid repetitions, words with the same word stem and names. After a test period of 3 s, rendering speech preparation and movement artefact-free segments, an exclamation mark appeared on the screen for 1 s representing a 'go' cue and indicating to the subjects to speak the thought of word out loud during the presentation of the exclamation mark and the following second. Between trials there was a variable interstimulus interval of 1–3 s during which a fixation cross was provided at the centre of the screen. The last 1 s before time point zero was used as baseline. The principle and timing of the task was derived from electrophysiological studies examining word processing and generation (Snyder *et al.*, 1995; Rowan *et al.*, 2004; Dalal *et al.*, 2009). The control task consisted of a word retrieval task lacking only the executive component of a VF task. Instead of different initial letters only the letter 'P' was presented. Subjects were instructed to always think of and verbalize the German version of the word 'pause' during the total of 80 trials. To ensure efficient performance, patients were trained with the task 1 day before operation.

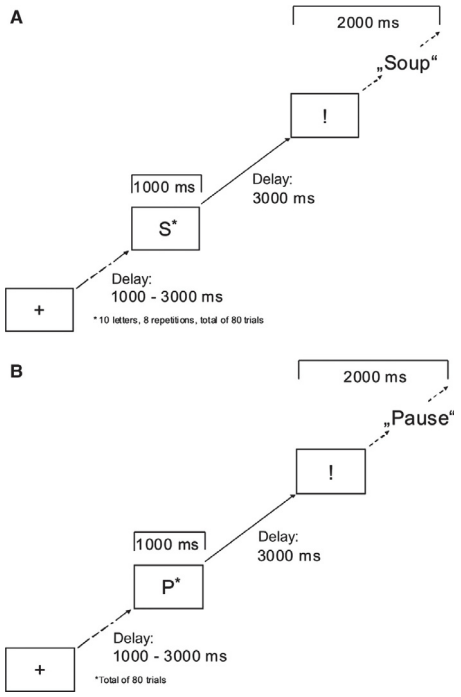

FIG. 1. Paradigm. (A) Verbal generation task. (B) Control task. After a jittered interval of 1–3 s with a fixation cross on the screen patients were presented a certain letter in the VG task or the letter 'P' in the control task for 1 s. After letter offset, the movement artefact-free test period of 3 s for LFP analysis began. After that an exclamation mark appeared on the screen for 1 s representing a 'go' cue and indicating to the subjects to verbalize the thought-of word.

Recordings

All patients gave written informed consent and the study was approved by the ethics committee of the Medical Faculty of the Heinrich-Heine-University Duesseldorf in accordance to the Declaration of Helsinki. The whole postoperative recording session took place 1 day after electrode implantation. All patients were examined with their respective anti-parkinson medication without any change to the preoperative dose. The medication ON state was chosen as we wished to determine whether the subthalamic nucleus is involved in the execution of a VG task in a state as physiological as possible. None of the patients showed tremor or levodopa-induced dyskinesia during the experimental session. During the experiment, patients were comfortably seated in their bed about 80 cm from a personal computer screen (10.6″ screen diagonal, screen refresh rate 60 Hz) displaying the task stimuli, using E-PRIME software (Psychology Software Tools, Inc., USA).

As the operation was performed bilaterally in all patients, recordings were carried out from 32 subthalamic nuclei. LFP activity was monopolarly recorded during task performance from the four platinum-iridium cylindrical contacts of the DBS-electrode numbered 0, 1, 2, 3 from the tip of the electrode (1.27 mm diameter and 1.5 mm length and a contact to contact separation of 0.5 mm) against a surface midline frontopolar reference. Signals were amplified and band-pass filtered from 0.5 to 1000 Hz, using a portable amplifier (BrainVision Recorder, BrainAmp MR plus, Brain Products GmbH, Munich, Germany, Version: 1.03). Signals were sampled at 5 kHz and monitored online. The responses to the stimuli were monitored, tagging wrong or no responses to obtain a measure for task performance for later correlation with electrophysiological findings. Additionally, in five patients, surface electrodes were placed at scalp sites Fz, F3/4, F7/8, Cz, C3/4, Pz, Oz, and O1/2 to record a simultaneous scalp electroencephalogram (EEG).

Analysis

The aim of the analysis was to compare the focal maximum-induced oscillatory activity changes from baseline – predominantly in the alpha-theta band – during the test interval in a correct performed VG task with the respective maximum activity changes during the test interval in the control task. An additional aim was to compare maximal STN-to-surface-EEG-coherence in the respective time period and frequency band and at the same recording location between the tasks. Thus, the first analysis step was to select only data with correct behavioural performance in the test interval.

Furthermore, bipolar STN references for each hemisphere with the strongest averaged power changes during the test interval of the considered task were selected for the alpha-theta band. For the power analysis, the maximum activity was derived from 1-s during the strongest activation in each task for each STN and an additional *t*-test was applied. For coherence analysis, the EEG channel with the strongest coherence in the alpha-theta band to the selected STN reference was chosen and this coherence was compared between tasks. In a further step, individual data were averaged for group statistics between tasks. Details for each analysis step are provided below.

All data were analysed offline, using the BRAINVISION ANALYSER software (Brain Products GmbH, Munich, Germany, Version: 1.05). Individual traces were visually inspected and trials containing noise, movement or eye blink artefacts and trials with wrong or no behavioural responses were discarded from further analysis. The four DBS-electrode contacts were re-referenced against each other, resulting in six bipolar derivations for each STN (0–1, 0–2, 0–3, 1–2, 1–3, 2–3). The bipolar activity was filtered with a low pass filter of 160 Hz and down-sampled to 512 Hz. Trials were segmented starting 1 s prior to stimulus onset to 2 s after exclamation mark onset, resulting in segments of 7 s duration.

Definition of frequency bands

We focused our analysis on the theta, alpha, beta and gamma frequency bands known from literature and stated in the introduction. However, to exclude low frequency noise common in LFP recordings, we only included activity in the high theta range and defined theta as 5–7 Hz. Regarding alpha activity, it should be mentioned that individual alpha frequency (IAF) varies to a large extent as a function of age, neurological diseases, memory performance, brain volume and task demands from 8 to 13 Hz and 'upper alpha' can be defined as 2 Hz above IAF and thus up to 15 Hz (Klimesch *et al.*, 2005). Therefore, we defined for our analysis alpha as 8–15 Hz and alpha-theta as 5–15 Hz, Beta was defined as 13–30 Hz and gamma as 30–100 Hz.

Local field potential activity analysis

LFP segments further underwent normalized baseline corrected time-frequency analysis for induced activity with a continuous Morlet Complex Wavelet transformation with Morlet c = 8 and 10 linear frequency steps (layers) from 5 to 15 Hz for the alpha-theta band and 10 linear steps from 13 to 30 Hz for the beta band. For the gamma band Morlet c = 15 was used with 10 linear steps from 30 to 100 Hz. Time-frequency plots were averaged across trials and power modulations were defined as power change over the trials during the 3 s test interval compared to individual baseline, consisting of 1 s before stimulus presentation. The contact pair used for further analysis was chosen according to the strongest activation during the test interval in the VG tasks. For statistical comparison, the mean activity of the 1-s and the respective frequency layer displaying the strongest activation during the test interval was exported for both tasks from each STN recording (for layer definition please refer to the first sentence of this paragraph). As beta and gamma bands represent a wide frequency range, a wide-band layer (13–30 Hz for beta and 30–100 Hz for gamma) was exported for statistical analysis of higher frequencies. Mean activation over the group was then compared between both conditions, using a Wilcoxon Test (SPSS 18, Chicago, IL, USA). Differences were considered significant at $P < 0.05$.

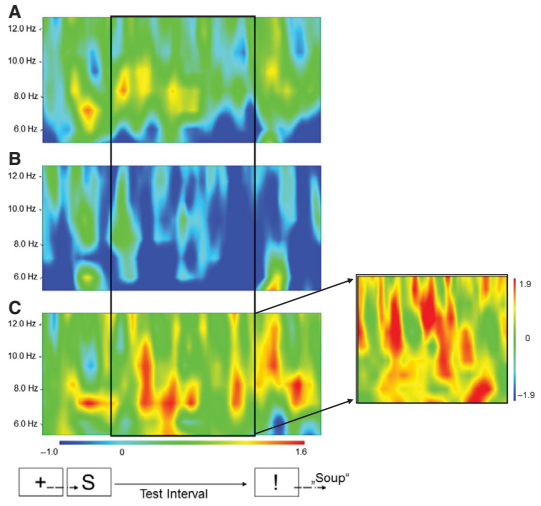

FIG. 2. Time frequency plot of temporal activation changes from baseline during the course of the task period. (A) Verbal generation. (B) Control tasks. (C) Difference between both tasks. The temporal changes depict the modulation of activation during the course of the task as indicated by the paradigm schema at the bottom, starting from letter onset until exclamation mark offset. The black frame highlights the task interval used for analysis. Strongest activation relative to baseline in the difference plot between both tasks takes place around 6–12 Hz. Mean relative wavelet power (Unit Scale) changes are shown color coded (grand average of left bipolar contact pairs, $n = 16$ subjects, 16 subthalamic nuclei of the left hemisphere). Arrows furthermore highlight color coded *t*-values of *t*-test of the task interval.

Furthermore, grand averages for left and right STN-LFP time frequency plots were visualized for the lower frequency band and an additional *t*-test between conditions was applied.

For surface EEG recordings, activation changes were calculated and statistically analysed in the same way as for deep brain recordings. For this analysis, the bipolar surface EEG channels of both hemispheres were chosen that showed the strongest coherence to the ipsilateral bipolar STN recording with maximum activity increase.

Coherence analysis

Coherence analysis between the bipolar derivations of the left and the right macroelectrode and respective ipsilateral and frontal scalp electrodes (F3/7, F4/8 to Fz) was calculated for 10 STN recordings to determine whether there was coupled activity between the recorded low frequency LFPs and cortical activity changes during VG and control tasks. Coherence is calculated in the range of 0–1, with 1 representing an ideal linear correlation and 0 an independence of the two signals (Halliday *et al.*, 1995). After bipolar referencing of the respective ipsilateral scalp electrodes against Fz and bipolar re-referencing of the DBS-electrode contacts, raw data was processed as mentioned above. From the 7 s epoch, the period of 3 s only including the test interval, starting at stimulus offset to exclamation mark onset was selected. This segment was further divided into equal sized segments of 1 s, with an overlap of 0.5 s. Using the fast-Fourier transformation (FFT) power spectra of this time window was obtained. To calculate the coherence, FFT transformed data was analysed using the formula (abbreviations: c: channel, f: frequency, CS: cross spectrum, i: index number of segment):

$$\mathrm{Coh}(c1,c2)(f) = \frac{|\mathrm{CS}(c1,c2)(f)|^2}{(|\mathrm{CS}(c1,c1)(f)||\mathrm{CS}(c2,c2)(f)|)}$$

with

$$\mathrm{CS}(c1,c2)(f) = \sum c1,i\,(f)\,c2,i\,(f).$$

To analyse the confidence level for the coherence, the methodology implemented by Halliday *et al.* (1995) was used. Only peaks of LFP-EEG coherence were accepted as significant if they reached a 95% confidence level in the main frequency band of interest (alpha-theta). The ipsilateral bipolar frontal electrode with strongest significant coherence to the bipolar STN-LFPs during the VG task was chosen for further analysis for each STN. The largest peak in the alpha-theta band was determined for both conditions and statistically compared over the group for the right and the left STNs separately with using a Wilcoxon-Test (SPSS 18, Chicago, IL, USA), considering differences as significant at $P < 0.05$. As an additional step, we analysed the coherence between the STN and frontal regions during the overt speech. We used the same procedure as stated above but only included the active speech component of the trial (5000–6000 ms).

Recording location

For the inspection of the anatomical location of the contacts used for analysis, the location of the electrodes was derived by fusion of the postoperative stereotactic CT onto the individual preoperative stereotactic planning software. This was available for 28 STNs (Table 2). Contact coordinates with reference to the middle of anterior-posterior-commissural line (mid-commissural point, MCP) were normalized and visualized on the stereotactic Schaltenbrand Atlas (Nowinski & Thirunavuukarasuu, 2004).

Results

Task-induced power changes

In the VG task, alpha-theta activity increase on the STN electrodes could be detected during the task period mainly between 6 and 12 Hz. On the same bipolar electrode contacts, for the control task power decrease in the alpha-theta band during the task period could be observed over the group, with some individual recordings showing a slight increase, decrease, or no change (see Table 3). Figure 2 displays the time-frequency representation during the VG and control task for all left nuclei. The activity in the alpha-theta band (mean peak frequency around 8 Hz, see Table 3) was significantly stronger for the VG task compared to the control task for the same left and right bipolar derivations during the task period, as revealed by the Wilcoxon test [relative modulation from baseline: during VG task for all left nuclei = 1.4 (standard error of mean (SEM) 0.2), during control task for all left nuclei = −0.6 (SEM 0.3), $P < 0.001$; mean during VG task for all right nuclei = 1.4 (SEM 0.4), during control task for all right nuclei = −0.8 (SEM 0.4), $P < 0.001$; Fig. 3]. Even when comparing the bipolar contact derivations with the maximum activity during the VG task with the bipolar derivation that showed maximum activity increase in the control task [mean (SEM): left −0.1 (0.2), right 0.1 (0.2)], the difference between both tasks remained highly significant for both hemispheres ($P < 0.01$). Peak activity change latencies were around 2000 ms.

On the most coherent surface EEG channels no local significant (compared to the control task) VG-task related increase in low frequency activity could be detected over the group altough modulation of activity was seen at the same mean peak frequency around 8 Hz with increased activity in some patients (see Table 3C).

Beta activity showed no task-induced modulation from baseline that differed significantly between the two tasks [STN activity change (SEM) left VG 0.07 (0.07), control −0.08 (0.1) right VG −0.19 (0.1) control −0.29 (0.17), $P > 0.05$, n.s.].

Gamma activity showed minimal task-induced modulation, and the comparison between the two tasks failed to reach significance level [STN activity change in (SEM) left VG 0.00 (0.04), control −0.04 (0.03), right VG −0.06 (0.06) control −0.1 (0.5), $P > 0.05$, n.s.].

As a further control beta and gamma activity during baseline (−1000–0 ms) was compared with the active speech component (5000–6000 ms) of the trial. For beta a minimal desynchronization during the active speech component could be observed, but as revealed by the Wilcoxon test failed to reach significance ($P > 0.05$). Gamma activity was also minimally modulated during the active speech component, but not in a significant manner ($P > 0.05$).

Coherence

Coherence analysis showed coupling of LFP- and (inferior)-frontotemporal EEG-electrodes. We identified significant coherence between LFPs and surface electrodes in the alpha-theta frequency band (mean peak frequency around 7 Hz) in all 10 STN recordings in the VG condition and in six recordings in the control condition. Maximum coherence to STN-LFPs found for (inferior)-frontotemporal location was: four times F3/F4 respectively, six times F7/F8 respectively. Comparison between the largest peaks in the alpha-theta band of the two tasks revealed a significant difference of LFP-EEG coherence during the VG task for both hemispheres (coherence left hemisphere $P = 0.036$, coherence right hemisphere $P = 0.016$, Fig. 4).

During overt speech, coherence analysis between the STN and (inferior)-frontotemporal EEG electrodes failed to reveal significant coupling of activity in the alpha-theta frequency band.

TABLE 2. Bipolar contact combinations used for final analysis and their coordinates

Patient	Contact left	*x*	*y*	*z*	Contact right	*x*	*y*	*z*
1	1–2	−11.3	−2.1	−4.3	0–1	11.8	−3.5	−4.3
2	1–2	−12	−1	−0.9	2–3	11	−1.9	−1.6
3	0–2	–	–	–	0–2	–	–	–
4	0–2	−12.2	−2.8	−1.2	0–2	11.3	−2.8	−5.2
5	0–3	−12.3	−2.2	−2.7	0–3	12.6	−1.4	−1.9
6	1–2	−14.1	−1.1	−0.4	0–1	11.3	−3.6	−1.8
7	0–1	−12.3	3.4	−3.4	0–2	12	−1.8	−2.2
8	0–1	−12.7	−2.8	−5.4	0–2	11.6	−1.9	−4.8
9	1–2	−15.1	4.1	1.1	0–2	13.8	5.7	0.3
10	1–3	–	–	–	0–2	–	–	–
11	0–3	−11.2	−4.4	−3.9	0–2	11.4	−4.8	−6.9
12	1–2	−12.4	−0.1	−1.9	0–2	11.7	−4	−3.8
13	0–2	−12	−1.2	−4.6	1–2	8.8	−2.4	−2.4
14	0–2	−11.9	−1.8	−5.1	1–3	10.2	−1	−3.7
15	0–3	−13.5	1.2	−0.7	1–3	11.4	−1.8	−0.1
16	1–2	−13.1	−2	−5.2	1–2	12.7	−0.7	−4.1

Coordinates in mm with reference to the mid-commissural point (MCP) derived from individual postoperative imaging.

TABLE 3. Individual task-related alpha-theta power changes and coherence. (A) STN power changes. (B) STN-Surface-EEG coherence. (C) Surface-EEG power changes

A

	Power left STN				Power right STN			
Patient	VG	Control	Peak Frequency (Hz)	Peak Latency (ms)	VG	Control	Peak Frequency (Hz)	Peak Latency (ms)
1	1.9	0.3	8	2400	0.4	−0.8	9	2300
2	1.8	−1.1	8	1600	0.1	−2.1	8	1900
3	1.1	0.8	6	2500	2.9	2.3	9	2000
4	1.6	−1.6	8	1600	3.2	−2.6	6	1700
5	0.5	−2.1	10	2000	3.3	−0.2	8	2200
6	0.8	0.5	11	1700	0.9	0.4	10	2000
7	0.9	0.6	8	1900	0.9	−0.1	8	2500
8	2.3	−0.4	8	3200	3.1	0.3	7	1300
9	0.2	−1.3	10	2500	0.4	−2.2	10	1100
10	1.6	−0.9	7	1500	3.2	−4.5	8	1500
11	1.5	0.6	9	1200	2.5	−0.9	9	1700
12	1.0	0.6	8	2600	0.5	0.1	8	3100
13	2.0	−2.1	9	1600	1.1	−1.5	11	1500
14	2.3	−0.9	8	2500	1.5	−1.5	8	2700
15	0.6	−1.4	9	2800	0.3	0.3	9	3000
16	1.5	−0.3	8	2200	1.1	0.3	10	1300
Mean	1.4***	−0.6***	8.4	2113	1.4***	−0.8***	8.6	1988
SEM	0.2	0.3	0.3	139	0.4	0.4	0.3	152
SD	0.6	0.9	1.2	540	1.4	1.5	1.2	589

B

	Coherence left STN to surface EEG			Coherence right STN to surface EEG		
Patient	VG	Control	Peak Frequency (Hz)	VG	Control	Peak Frequency (Hz)
1	0.04	0.03	8	0.04	0.00	6
5	0.06	0.01	6	0.08	0.00	8
11	0.03	0.00	7	0.01	0.00	7
14	0.03	0.03	6	0.05	0.01	6
16	0.05	0.02	7	0.06	0.02	6
Mean	0.04*	0.02*	6.8	0.05*	0.01*	6.6
SEM	0.01	0.01	0.4	0.01	0.01	0.4

C

	Power left surface EEG			Power right surface EEG		
Patient	VG	Control	Peak Frequency (Hz)	VG	Control	Peak Frequency (Hz)
1	−4.6	−3.4	7	−3.4	−0.3	6
5	−0.6	−1.9	9	−1.3	−3.5	12
11	0.4	−0.2	9	0.4	−0.2	9
14	1.5	0.6	7	1.0	0.8	6
16	1.3	−0.1	8	1.1	−0.2	8
Mean	−0.4†	−1.0†	8	−0.4†	−0.7†	8.2
SEM	1.1	0.7	0.4	0.8	0.7	1.1

(A) Rounded numbers for relative power changes from baseline at peak frequency and peak latency for the left and right STN in the VG and control task for contact combination with strongest VG activation changes. ***$P < 0.001$ significant differences for the comparison between tasks. (B) Rounded numbers for STN-surface-EEG coherence at peak frequency for the individual most coherent surface-EEG contact for both conditions. 0.00 indicates no significant coherence peak. *$P < 0.05$ significant differences for the comparison between tasks. (C) Rounded numbers for power changes of surface recordings for EEG channels with highest coherence to STN channels. †No significant differences for the comparison between tasks.

Recording location

All 32 bipolar contact pairs that showed the strongest task-dependent low frequency modulation and thus were used for further analysis are listed in Table 2. The majority (28/32) of bipolar derivations were recording a field below or around contact 1 (0–1, 0–2, 0–3, 1–2), which refers to the lower part of the electrode. Accordingly, the most frequent contact combination was 0–2 ($n = 12$). Additionally, as Fig. 5 illustrates, the mean recording coordinates with reference to the mid-commissural point (MCP) of both the right and left hemispheres corresponded well with a location within the STN rather than the outer dorsolateral border to adjacent fibre tracts and thus reflect a recording location involving non-motor parts of the nucleus (coordinates in mm with standard deviation: right hemisphere $x = 11.5 \pm 1.6$, $y = -1.9 \pm 2.5$, $z = -3.0 \pm 2.0$ mm; left hemisphere $x = -12.6 \pm 1.1$ mm, $y = -0.9 \pm 2.4$ mm, $z = -2.8 \pm 2.1$ mm; Fig. 5).

Correlation of task-dependent activity changes with performance

As a measure of performance in the VG task and the control task the number of correctly performed words was counted. Discarding

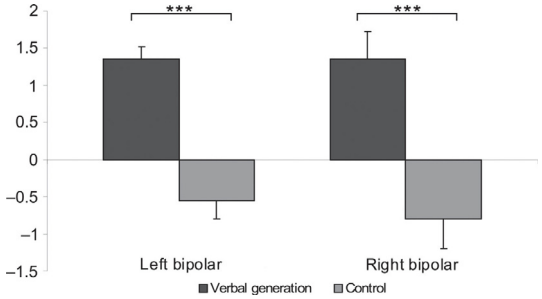

FIG. 3. Mean wavelet power (Unit Scale) relative to baseline during the VG and control tasks. VG task is shown in dark grey and control task in light grey from the left (left plot, $n = 16$) and the right (right plot, $n = 16$) bipolar macroelectrode pairs in the alpha-theta band. ***$P < 0.001$. Errors bars showing standard error of mean.

trials with no responses (in the control and VG task) or with wrong responses (repetitions, words with the same word stem and proper names for the VG task) resulted in a mean performance of 71.3 (SEM 1.0) words in the VG task and 72.2 (SEM 0.8) words in the control task. Furthermore, discarding trials containing noise, movement or eye blink artefacts from further electrophysiological analysis left on average 65.8 (SEM 1.6) trials for the VG task and 70.4 (SEM 0.8) for the control task. Pearson r was used to determine correlation between performance and activity changes. Correct performance of words correlated significantly with activity increase in the left ($r = 0.58$, $P < 0.05$) and right ($r = 0.82$, $P < 0.001$) STN in the VG task. This correlation was not significant in the control task, additionally as Fig. 6 illustrates performance and activation showed a restricted range in this task.

Discussion

We investigated the role of the STN in a VG task by means of postoperative recordings of oscillatory activity. We show a dynamic modulation of STN-LFP alpha-theta activity in response to and correlated with the performance of a VG task as opposed to a control task. This finding renders electrophysiological proof for the involvement of the STN in the processing of executive functions such as VF and further supports the hypothesis that the STN processes these functions by specifically modulating low-frequency oscillations. Alpha-theta oscillations can be interpreted as the rhythmic gating signature in a speech executing subthalamic-prefrontal network. A direct modulation or interruption of this process through high frequency stimulation may explain behavioural sequelea seen in patients with STN-HFS. Furthermore, the improvement in VF during LFS (Wojtecki *et al.*, 2006) may thus be due to power increase in this particular frequency. In the following, some particular aspects of the work will be discussed.

Origin of recorded activation and the STN – cortical cognitive network

The STN is part of the cortico-basalganglia-thalamo-cortical network and is subdivided into different territories. Its ventromedial part corresponds to the associative territory with connections to pallidal and nigral behavioural-cognitive circuits and input from the dorsolateral-prefrontal and lateral-orbitofrontal cortex. This associative circuit also involves cortical areas of the VF-mediating network, including inferior frontal gyrus, anterior cingulate cortex and superior temporal regions (Alexander *et al.*, 1990; Benarroch, 2008).

In our analysis, contacts showing the strongest task-dependent activation were located within the STN according to postoperative imaging. Furthermore, placement of the electrode in the STN was supported by intraoperative microelectrode recordings and test stimulation. Finally, the use of bipolar re-referencing, analysing activity as focal as possible, makes volume conduction from another neuronal source unlikely. Our finding that the oscillatory activity was modulated during an executive task therefore most likely represents neuronal oscillatory activity of the STN or from the cortex projecting into the STN. The observation, that particularly recordings of the lower contacts, with locations involving central rather than

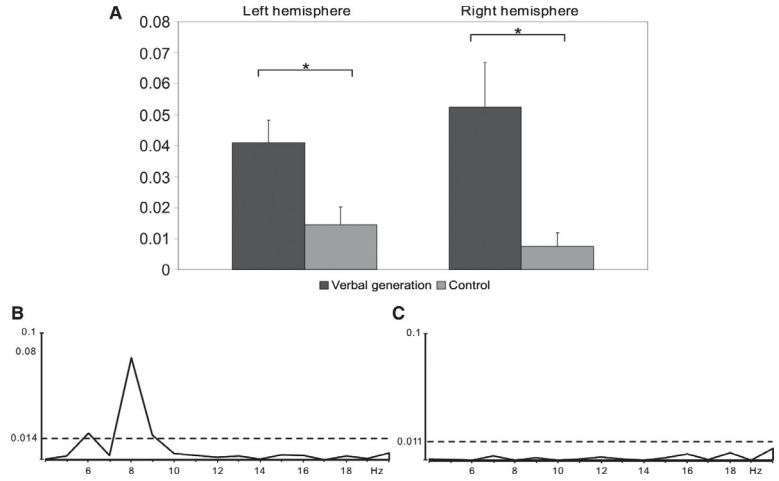

FIG. 4. Coherence at peak frequency. Mean over the group coherence (A) and example of coherence spectra during the VG (B) and the control task (C). Mean coherence (with errors bars showing standard error of mean) between STN contacts and respective ipsilateral frontal surface electrodes for the VG (dark grey) and control (light grey) tasks from the left hemisphere (left plot, $n = 5$) and the right hemisphere (right plot, $n = 5$). *$P < 0.05$. Example for coherence between contact pair 1–2 of one right macroelectrode and the respective bipolar surface electrodes (F8 against Fz). Dotted line indicates the 95% confidence level. Coherence is normalized between 0 and 1. Main peak in alpha but also small significant peak in theta frequency during the VG task.

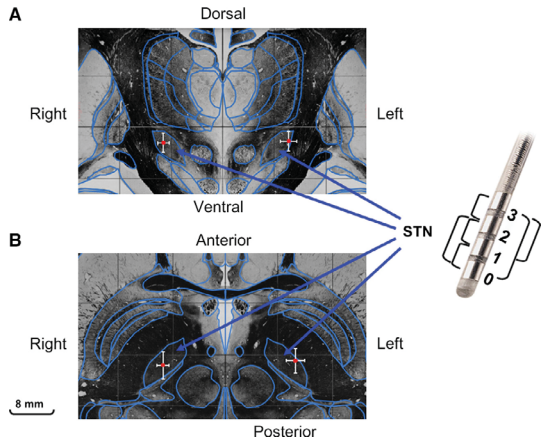

FIG. 5. Recording location visualized on anatomical atlas. (A) Coronary slice, (B) Axial slice. Mean recording sites with standard deviation of analysed bipolar referenced contacts of (0–1, 0–2, 0–3, 1–2, 1–3 or 2–3) for both the right and left STN visualized on the Schaltenbrand atlas. Coronary slice 3 mm postmid-commissural point (MCP), axial slice 3.5 mm below anterior-posterior commissure line (AC-PC line). STN, subthalamic nucleus.

dorsolateral parts of the STN, displayed activation during this cognitive task corresponds to neuroanatomic evidence that especially the ventromedial STN has connections with inferior-frontal associative areas. Additionally, coherence analysis revealed significant coupling between the STN LFPs and the (inferior-)frontotemporal surface electrodes. This finding further supports a functional relevant connection between the ventromedial STN and the frontal cortex. No significant coherence was found for overt speech production. Failing to do so might be due to the fact that the exact time point of overt speech production for the analysis was not available to us. Due to technical reasons, measured speech onset with EMG and a microphone did not provide an exact time point for overt speech production and we discarded this recording. Furthermore, the limited number of available patients with surface EEGs has to be taken into account pertaining to interpretation of the chorence statistics.

Verbal generation paradigm

VF has been shown to be affected by STN DBS on a behavioural basis (Wojtecki *et al.*, 2006) as well in functional imaging (Schroeder *et al.*, 2003). For methodological reasons, we used a verb*al generation* task rather a verbal fluency task, however, still comprising all aspects of a formal-lexical phonemic VF task. We chose a phonemic task as it mainly involves frontal and subcortical regions, compared to an involvement of temporal and parietal regions during a semantic fluency task (Troyer *et al.*, 1998; Baldo *et al.*, 2006). In order to be able to analyse averaged time-locked-induced activity changes from baseline, we developed a paradigm in which a single word was produced in each trial. Thus, we also had the possibility to delineate the time point when the subthalamic nucleus was engaged in the task (around 2000 ms). It has to be noted that this might differ from a verbal fluency paradigm in which the production of as many words as possible in 1 min is demanded. Therefore, we termed the used paradigm as verbal generation. However, the usefulness of a VG paradigm to assess frontal networks involved in

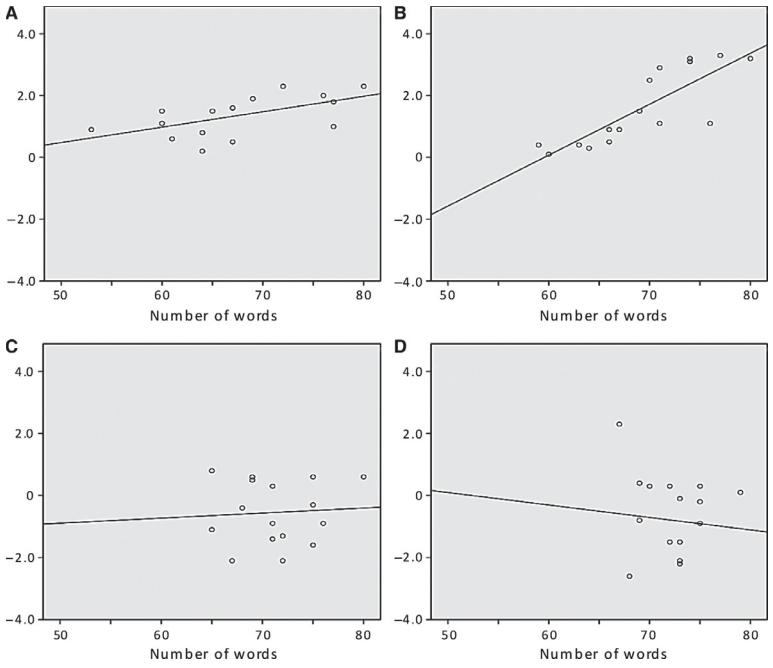

FIG. 6. Correlation of task-dependent relative wavelet power changes with number of correctly performed words. (A) Verbal generation task left STN, (B) Verbal generation right STN. (C) Control task left STN, (D) control task right STN. Coefficients: VG task: left: $r = 0.58$, $P < 0.05$/right $r = 0.82$, $P < 0.001$. Control task: left: $r = 0.07$, n.s./right $r = -0.08$, n.s.

executive function was derived from several publications outlined in the following.

Invasive and non-invasive electrophysiological recording showed processing of written words within the first second (Snyder *et al.*, 1995; Dalal *et al.*, 2009). For VG event-related potential (ERP) changes in surface EEG starting about 1 s after a cue and lasting 3-s until a 'speak'-cue can be found on frontocentral and inferior-frontal electrodes in contrast to passive listening, non-word repetition and word repetition. Furthermore, frontal EEG modulation is in agreement with functional MRI data showing left inferior-frontal activation during this VG paradigm (Rowan *et al.*, 2004). In terms of timing, other imaging studies assessing a VF network ranged from real fluency task with covert production of several words over a period up to a minute, to overt production of a few words in a short block or overt production of a single word during a 2–4 s period (Yetkin *et al.*, 1995; Pujol *et al.*, 1996; Phelps *et al.*, 1997; Schlosser *et al.*, 1998; Abrahams *et al.*, 2003; Schroeder *et al.*, 2003; Weiss *et al.*, 2003, 2004; Amunts *et al.*, 2004; Schaufelberger *et al.*, 2005). Whatever paradigm was chosen, the results revealed activation of a fronto-temporal network including the middle frontal, anterior-cingulate, inferior-frontal gyrus and superior temporal regions. We aimed to investigate oscillatory communication of the STN with this proposed network. In the light of functional imaging and EEG studies it is plausible to use the paradigm with the timing as presented. In order to have control over the performance and to exclude movement artefacts, we chose an overt speech paradigm and short trials with analysis of the signals before the onset of speech of a single word. However, one should be aware of limitations of the task, such as that in the seconds after the letter presentation there is no clear evidence as to what the patients are doing (e.g. maintain a word repeating it continuously vs. searching for a new word). Furthermore, a similar limitation should be noted for the control condition. Patients were carefully instructed to covertly think of the word 'pause' during the covert phase of the task. However, there is no absolute control over the adherence of the patients to the instructions.

Frequency range of oscillatory activity changes

We focused the analysis on alpha-theta range between 5 and 15 Hz as our previous work revealed improvement of VF with 10-Hz-STN-LFS (Wojtecki *et al.*, 2006). Our main finding was a significant task-related modulation of local alpha-theta activity increase focused between 6 and 12 Hz with a peak around 8 Hz. Our definitions of the theta (5–7 Hz) and alpha bands (8–15 Hz) thus included the relevant oscillations, regardless of defined boarders. There is further evidence that oscillations in this frequency might be involved in non-motor tasks such as motor imagination (Kuhn *et al.*, 2006), action observation (Marceglia *et al.*, 2009) and emotional processing (Kuhn *et al.*, 2005a; Brucke *et al.*, 2007; Huebl *et al.*, 2011). A modified oddball paradigm with increased demand on executive function revealed an evoked potential in the STN which was modulated by repetitive transcranial magnetic stimulation (TMS) of the inferior-frontal cortex (Balaz *et al.*, 2008). Respective STN oscillatory activity showed alpha-beta desynchronization (8–20 Hz) in the oddball tasks with increased demand on executive function (Rektor *et al.*, 2010). In a complex visuomotor-cognitive task including planning, inhibition of automatic responses and mental inversion 7–14 and 16–30 Hz modulation of alpha-beta was observed in the STN (Rektor *et al.*, 2009). During conflict decision, low frequency alpha-theta (5–13 Hz) STN-modulation was reported (Fumagalli *et al.*, 2011). When it comes to language processing, recordings from the thalamus showed ERP changes, reflecting the processing of syntactic and semantic language violations (Wahl *et al.*, 2008) and first STN-LFP recordings suggest gamma changes associated with verbal fluency (Anzak *et al.*, 2011). However, there is lack of evidence for the lower frequency range and its presumed network. In this study, our main finding was a task-dependent significant local alpha-theta activity increase between 6 and 12 Hz (peak around 8 Hz) and coherence increase to surface EEG between 6 and 7 Hz. We also found activity in higher frequencies up to the gamma range, but it has to be noted that this activity revealed no significant time locked task-specific modulation, as it was the case for alpha-theta. Irrespective of the used task gamma activity was expected, especially due to the used dopaminergic ON-state (Alegre *et al.*, 2010; Lopez-Azcarate *et al.*, 2010). Minimal gamma and beta-modulation during active speech phase was also not significant in our data although this was reported before (Anzak *et al.*,2011; Hebb *et al.*, 2012). It should be taken into consideration that a lack of power changes in the beta frequency may be due to a selection of bipolar pairs that are representative of alpha-theta modulation and not beta modulation. Our results reveal mild changes in beta activity that did not differ significantly between both tasks. It should be noted, that our main analysis focused on the test interval, during the cognitive epoch of the task. As cited in our introduction and found in previous studies, mainly theta and alpha oscillations are revealed during such cognitive processes. Additionally, as a further control, beta activity during baseline was compared to the active speech component of the trial. For beta, a minimal desynchronization during the active speech component could be observed, but failed to reach significance. This might be due to an analysis not timed precisely to the time epoch of speech onset and termination. It should also be noted, that for beta modulation, the window for the analysis of beta changes for a single word might have been too wide.

Previous studies focusing on limb motor control have manly revealed basal ganglia oscillations in the beta and gamma range (Brittain & Brown, 2014). Theta and alpha oscillations have been associated with ongoing cognitive processes such as verbal generation, as cited in our introduction.

As we aimed at studying a cognitive process underlying a verbal generation task, we specifically employed a paradigm rendering LFP recordings free from speech and movement artifacts. This paradigm has already been used in previous electrophysiological studies examining word processing and generation (Snyder *et al.*, 1995; Rowan *et al.*, 2004; Dalal *et al.*, 2009). The analysis of the test interval free of movement revealed results in line with previous studies, depicting a role of theta and alpha oscillations during verbal control. Additionally, analysis of the overt speech production epoch revealed beta desynchronization, as expected by previous findings in literature.

Generally, theta oscillations found dominantly in our data reflect working memory functions and alpha oscillations play a role in long-term memory and transient reactivation of long-term memory codes during short-term storage (Klimesch *et al.*, 2005). Additionally, theta oscillations can particularly be observed at frontal sites when subjects maintain focussed attention by concentrating on a task during an extended period of time (Klimesch *et al.*, 2005).

All these components are crucial in our VG task and thus alpha-theta activation is consistently found in our recording. Furthermore, we found mean coherence to surface recording in the theta range, which reflects the idea, that long-range synchronization is a functional role of theta oscillations. On the other hand, local LFP power increase was more prominent in the alpha range. Alpha oscillations have been thought to reflect idling inhibition of task irrelevant areas, but recent models propose that alpha rhythmicity plays an active role in attention and consciousness (Palva & Palva, 2007). In

contrast, beta-band oscillations might reflect a deterioration of flexible behavioural and cognitive control (Engel & Fries, 2010). The idea of theta communication of the STN with cortical areas would correspond well with the 'systems oscillators theory' proposed for the role of the basal ganglia for speech and language: articulation and phoneme are represented by a higher frequency than words and sentences which are organized as packets over a slower frequency. The frequency of oscillations in the basal-ganglia-thalamo-cortical loop is given by the number of connection nodes, represented in anatomical structures. In this model the STN is in a side loop with a specific go/no-go gating function of the indirect and hyperdirect pathway (Montgomery, 2008). As an experimental base for that model STN microelectrode recording showed a modulation of bursting activity during the generation of meaningful speech utterances in sentence repetition compared to meaningless syllable repetitions (Watson & Montgomery, 2006). Current findings further support this model of a go/no-go gating instance of the STN by revealing oscillatory theta activity in decision processes (Cavanagh *et al.*, 2011). These findings correspond well with our recordings suggesting that the STN has oscillatory alpha-theta signature in gating speech execution.

Clinical relevance of STN-stimulation for speech

This study provides evidence for regions in the STN relevant for executive speech functions. We found a significant correlation of VG performance with low-frequency oscillation increase in the STN, thus improvement in VF during LFS might be explained by enhancement of this predominant frequency. However, LFS can lead to detoriation of motor functions (Timmermann *et al.*, 2004). The findings can be relevant for future stimulation patterns to improve cognitive-motor outcome. New approaches of modelling volume of tissue activated showed – congruent with our recordings – that ventral contacts result in more tissue activation associated with affection on VF performance (Mikos *et al.*, 2011). This should be regarded especially for the programming of the lower contacts. Modelling stimulation parameters can lead to improved cognitive-motor outcome (Frankemolle *et al.*, 2010). Taking into account information about frequency domains in executive functions derived by the current study, one can anticipate that advanced frequency programming (e.g. with special local low frequency interleaving modes on lower electrodes) might further help to improve clinical outcome.

Disclosure

LW, JV and AS have received – unrelated to the current project – honoraria in the past from Medtronic and St. Jude Medical and Boston Scientific, companies that manufacture DBS hardware. The authors thank the patients for their excellent cooperation.

Acknowledgements

This work was supported by the Research Commission (′Forschungskommission′) of the Medical Faculty of the Heinrich-Heine University Duesseldorf and by BMBF/ERANET Neuron Grant 'TYMON' (01EW1411) to LW.

Abbreviations

c, channel; CS, cross spectrum; CT, computed tomography; DBS, deep brain stimulation; EEG, electroencephalography; ERP, event-related potential; f, frequency; FFT, Fast-Fourier Transformation; HFS, high-frequency deep brain stimulation; Hz, Hertz; i, index number of segment; LFP, local field potentials; LFS, low-frequency alpha-theta-stimulation; MCP, mid-commissural point; MDRS, Mattis Dementia Rating Scale; MER, microelectrode recordings; mm, millimetre; MRI, magnetic resonance imaging; PD, Parkinson's disease; STN, subthalamic nucleus; SWA, Schaltenbrand-Wahren-Atlas; TMS, transcranial magnetic stimulation; UPDRS, Unified Parkinson's Disease Rating Scale; VF, verbal fluency; VG, verbal generation.

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