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Význam elektroencefalografie ve funkčním mapování kortikální a subkortikální aktivity lidského mozku

Habilitační práce (komentovaný soubor prací)

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Souhrn

Elektroencefalografie (EEG) je významná a klinicky zavedená vyšetřovací metoda především u epilepsie, poruch spánku a vědomí, kde hraje zásadní úlohu v diagnostickém procesu a dlouhodobém sledování klinického stavu. Zdánlivě bezvýznamné se EEG dříve jevilo v souvislosti s neurodegenerativními onemocněními jako je Parkinsonova nemoc (PN). Nicméně už i u těchto onemocnění začíná mít své klinické využití, kdy pomocí kvantitativního hodnocení EEG lze rozlišit mezi časnými stádii několika typů demencí. Zejména s použitím moderních analytických metod a matematických přístupů výrazně přispívá ke znalosti patofyziologických procesů, které jsou podkladem onemocnění. Detailní poznání elektrofyziologických změn, které souvisejí s jednotlivými motorickými a nemotorickými příznaky v časných i pokročilých stádiích PN je nezbytné především z pohledu neuromodulační léčby.

Hluboká mozková stimulace (DBS) je moderní chirurgická léčba různých vnějších příznaků neurologických a některých psychiatrických onemocnění. Nejčastější indikací k této léčbě jsou pozdní hybné komplikace Parkinsonovy nemoci. Přesto, že se jedná o celkově velmi úspěšnou terapii a pravděpodobně největší léčebný pokrok po zavedení léčby levodopou a dopaminergními agonisty, má hluboká mozková stimulace své limitace. V klinické praxi se bohužel občas setkáváme s nedostatečným léčebným efektem nebo s nežádoucími účinky, které komplikují léčbu hlavních příznaků. Nežádoucí účinky se objevují nejčastěji právě u pacientů s PN se zavedenou DBS subthalamického jádra (STN) a to především v podobě různých kognitivních a neuropsychiatrických obtíží. Mechanismus vzniku nežádoucích účinků stále není zcela objasněn. K minimalizaci těchto rizik byla stanovena přísná klinická indikační kritéria. Hlavním směrem současného výzkumu na poli neuromodulace je hledání nových strategií, které by vedly ke zvýšení efektivity DBS a k redukci výskytu nežádoucích účinků.

Byla publikována celá řada elektrofyziologických prací, které popisují patologickou EEG aktivitu související s jednotlivými klinickými symptomy PN a to jak na úrovni subkortikálních struktur jako je STN nebo GPi, tak na úrovni kortikální, nebo na úrovni porušených kortiko- subkortikálních vztahů. Určitě nejvýznamnějším objevem je nález zvýšené synchronie ve frekvenčním pásmu beta v oblasti bazálních ganglií a v kortiko-subkortikálních motorických okruzích, která koreluje s tíží hlavních hybných příznaků tj. s rigiditou a hypokinezou a která je potlačována po užití medikamentózní terapie i při DBS. Na základě této znalosti byl učiněn terapeutický pokrok v podobě zavedení adaptivní hluboké mozkové stimulace (aDBS). Tyto „chytré“ stimulátory jsou založeny na detekci patologické beta aktivity z oblasti STN, stimulují pouze intermitentně a reflektují tím současný klinický stav a potřeby pacienta. Takto cílená stimulace založená na zpětné vazbě je proto klinicky i ekonomicky efektivnější a pravděpodobně může znamenat i redukci nežádoucích účinků. K optimalizaci DBS jsou hledány i jiné stimulační cíle a přístupy např. přímá stimulace motorického kortexu pomocí epidurálních elektrod. Z tohoto pohledu je důkladná znalost elektrofyziologických fenoménů spojených s PN nezbytná.

Předkládaná habilitační práce je komentovaným souborem autorských a spoluautorských prací, které se vztahují k danému tématu. Hlavním zaměřením je mapování elektrofyziologických změn, které souvisejí s nemotorickými (především kognitivními) funkcemi a s jejich poruchami u PN. Autorka se zaměřila na tuto tématiku proto, že kognitivní a neuropsychiatrické obtíže jsou nejčastějšími nežádoucími účinky DBS.

Summary

Electroencephalography (EEG) is a well known and clinically established method mainly in the case of epilepsia, sleep and consciousness disorders, where significantly helps in the diagnostic process and long-term patient monitorings. It could seem to be useless in relation to neurodegenerative disorders such as Parkinson´s disease (PD). However, currently EEG starts to have a clinical impact also in neurodegenerative disordes. It has been shown that quantitative EEG abnormalities can discriminate between three types of dementia. EEG analysis contributes to detailed knowledge of pathophysiological processes that underlie the disease, mainly by using modern analythical approaches and advanced mathematical methods. Detailed knowledge of electrophysiological phenomena linked to the motor and non-motor signs in early and advanced PD stages is necessary mainly in relation to neuromodulation therapy.

Deep brain stimulation (DBS) is a modern surgical therapy of symptoms that accompany some of neurological and psychiatric disorders. The most common indication for this treatment are the late motor complications in advanced PD. Although DBS is generally a successful therapy and perhaps the second most important therapeutic advance in Parkinson´s disease (PD) after the introduction of L-dopa and dopamine agonists, it is not without limitations. Unfortunately, in the clinical practise we sometimes face some adverse side effects that complicate the therapy of main symptoms. These side effects occur mainly in PD patients with DBS of the subthalamic nucleus (STN) and represent particularly various cognitive and neuropsychiatric disorders. The mechanism underlying these side effects is not yet fully understood. Strict indication criteria were established to reduce the risk of neuropsychiatric side effects. Searching for novel strategies that would help to increase the effectivity and minimise the side effects is the main focus of the current research on the neuromodulation field.

Many electrophysiological studies describing pathological EEG activity related to PD clinical symptoms on the subcortical, subcortico- cortical and cortico- cortical levels were published. Certainly the most important finding was the increased synchrony in beta frequency range in the basal ganglia as well as in the cortico- subcortical motor circuits, which correlates with the main motor PD symptoms i.e. bradykinesia and rigidity and is known to be suppressed by levodopa therapy as well by DBS. A therapeutic progress has been made based on this knowledge- the introducing of adaptive DBS (aDBS). These 'smart' stimulators provide targeted stimulation based on real-time readouts of neural signals reflecting the patient's actual clinical state. This feedback-dependent intermittent stimulation can be more efficient and clinically superior to the current standard continuous DBS and probably might also reduce the ocuurence of side effects. New stimulation targets and approaches are explored to optimise the DBS treatment, for example the direct stimulation of the motor cortex via epidural electrodes. For this reason, the detailed knowledge of electrophysiological phenomena related to PD is necessary.

This habilitation thesis represents a collection of the author´s previously published research (as the main author or as a co-author) relevant to the topic. Mapping of the electrophysiological changes linked with non-motor (mainly cognitive) functions and disorders in PD is the main focus of this work as the cognitive and neuropsychiatric side effects represent the most common DBS complications.

Poděkování

Mé hlavní poděkování patří vedoucímu našeho výzkumného týmu prof. I. Rektorovi. Bez jeho podpory, rad a pomoci bych se jistě nedostala do okamžiku odevzdání této habilitační práce. Ráda bych poděkovala i dalším členům z centra pro abnormní pohyby a parkinsonismus l. neurologické kliniky tj. prof. I. Rektorové a doc. M. Balážovi za spolupráci a vedení pro stránce klinické. Za velmi hodnotnou dlouhodobou spolupráci pří zpracovávání dat děkuji Ing. P. Jurákovi, J. Halámkovi, J. Chládkovi, M. Lamošovi, P. Klimešovi a Evě Výtvarové. Děkuji i kolegům z neurochirurgie tj. prof. Z. Novákovi a prof. J. Chrastinovi, bez kterých by nebylo možno realizovat výzkum na poli intracerebrálního snímání. V neposlední řadě děkuji svému muži a celé rodině za pochopení a poskytnutí prostoru k pokračování ve vědecké činnosti, především v období dvou mateřských dovolených.

Obsah:

Seznam použitých zkratek

AAL anatomical automatic labelling (atlas)

aDBS adaptivní hluboká mozková stimulace

EEG elektroencefalografie

fMRI funkční magnetická rezonance

DBS hluboká mozková stimulace

HD-EEG high density EEG (EEG s vysokou hustotou kanálů)

l- dopa levodopa

MEG magnetoelektroencefalografie

PN Parkinsonova nemoc

rTMS repetetivní transkraniální magnetická stimulace

SMA supplementární motorická area

STN **s**ubthalamické jádro

TFA time frequency analysis (časově frekvenční analýza)

UPDRS unified parkinson´s diasease rating scale

1. Úvod

Elektroencefalografie (EEG) je významná vyšetřovací metoda s hojným využitím v klinické praxi. Krom toho patří EEG vedle MEG (magnetoelektroencefalografie) a fMRI (funkční magnetická rezonance) mezi hlavní metody, které lze využít pro funkční mapování mozkových činností. Oproti fMRI má EEG výhodu přesnějšího časového rozlišení, je snadno dostupné a bez významnější zátěže pacienta. S využitím nových technik tj. EEG s vysokou hustotou kontaktů s 256 elektrodami (HD-EEG) a moderních matematických metod, které umožňují rekonstrukci dat do objemu, lze hodnotit signál i z hlouběji uložených mozkových struktur jako je např. thalamus. Tím je eliminována dřívější hlavní nevýhoda EEG na poli funkčního mapování oproti fMRI, tj. prostorové omezení pouze na kortikální struktury. Navíc, vedle běžného skalpového snímání, které zaznamenává elektrickou aktivitu mozku z povrchu hlavy, máme v určitých případech možnost snímat elektrickou aktivitu některých struktur přímo pomocí hlubokých mozkových elektrod implantovaných do mozkové tkáně. Tyto intracerebrální elektrody jsou zaváděny buď z diagnostických důvodů např. u pacientů s epilepsií k přesné lokalizaci epileptogenního ložiska před plánovaným operačním řešením, nebo z terapeutických důvodů v rámci DBS programu. U pacientů po zavedení DBS elektrod je možné v krátkém pooperačním období, kdy stimulační elektrody ještě nejsou tzv. internalizovány (tedy napojeny na stimulátor), snímat EEG přímo z v hloubce uložených jader šedé hmoty jako je např. subthalamické jádro (STN) a další struktury. Takto získaný signál představuje velmi cenné informace, které nám pomáhají pochopit nejen fyziologické funkce těchto struktur, ale i jejích zapojení do patofyziologických procesů konkrétního onemocnění, pro které je DBS zaváděna. Při kombinaci intracerebrálního snímání a skalpového EEG lze studovat vztahy mezi subkortikálními a kortikálními strukturami a jejich poruchy v souvislosti s danou diagnózou. V EEG lze krom základní aktivity hodnotit fázové změny, které jsou vázány na určitý děj, tzv. evokované potenciály (EP). Lze je získat po zprůměrnění záznamu a

mají své typické charakteristiky v souvislosti s různými mozkovými funkcemi. Patří sem vizuální, motorické, somatosenzitivní, sluchové a kognitivní EP. I tyto fenomény se dají využít ke studiu funkčních vztahů mezi jednotlivými strukturami. Dále lze hodnotit změny, která jsou vázány na určitý podnět časově, ale ne fázově, tj. oscilační rytmické aktivity v jednotlivých frekvenčních pásmech. K jejich hodnocení je nutné použit složitější metody než je pouhé zprůměrnění, tj. např. časově frekvenční analýzu (TFA) nebo Fourrierovu transformaci (FFT). Výsledkem je buď pokles výkonu v určité frekvenci tzv. event -related desynchronizace (ERD) nebo nárůst výkonu v určité frekvenci tzv. event-related synchronizace (ERS) (Pfurtscheller a Aranibar, 1977). Oproti EP má ERD/S výhodu v tom, že dokáže rozlišit mezi aktivací nebo inhibicí (popř. aktivní inhibicí) dané oblasti. ERD v alfa a beta frekvenčním pásmu je považována za korelát aktivace, naopak ERS za korelát inhibice dané oblasti (Pfirtscheller 2001). Ve vyšších gamma pásmech je naopak ERS považována za znamení aktivace s různými funkčními koreláty (Schürmann et al. 1997)- viz. příloha 1. Moderní pokročilé matematické metody analýzy EEG signálu jsou popsány v kapitole 3.4.

EEG má krom výzkumného potenciálu rovněž klinické využití už i u neurogenerativních onemocnění. Pomocí kvantitativního hodnocení EEG (QEEG) lze rozlišit mezi časnými stádii několika typů demencí na základě charakteristických frekvenčních peaků– tj. mezi demencí s Lewyho tělísky, demencí u Alzheimerovy choroby a Parkinsonovy nemoci (Bonanni et al. 2008). QEEG bylo nedávno dokonce zařazeno mezi guidelines jako podpůrný ukazatel při diagnostice demence s Lewyho tělísky, která je také spojena s obrazem parkinsonismu (Ferreira et al. 2016).

Čím dál více se ukazuje, že důkladná znalost elektrofyziologických procesů je nezbytná také z pohledu neuromodulační léčby, která se stále dynamicky vyvíjí. Stran hluboké mozkové stimulace je nejlépe elektrofyziologicky probádanou diagnózou Parkinsonova nemoc. Na

základě znalosti EEG korelátů hlavních hybných příznaků PN byl učiněn terapeutický pokrok v podobě nových adaptivních DBS systémů (aDBS).

Tato habilitační práce shrnuje hlavní elektrofyziologické poznatky u PN a dále obsahuje komentovaný soubor autorských a spoluautorských prací, které se vztahují k tomuto tématu.

Příloha 1

2. Parkinsonova nemoc a hluboká mozková stimulace

Parkinsonova nemoc je chronické progresivní neurodegenerativní onemocnění především centrálního nervového systému. PN je charakterizována čtveřicí hlavních hybných příznaků, kterými jsou třes, rigidita, hypokineza a posturální instabilita (Aarsland et al. 2011). Je doprovázena také četnými nemotorickými symptomy, které nelze opomíjet. Jedná se o různé neuropsychiatrické příznaky (deprese, anxieta, kognitivní deteriorace, poruchy impulsivity, psychóza), poruchy spánku (nadměrná denní spavost, insomnie, poruchy REM spánku), autonomní dysfunkce (ortostatická hypotenze, nadměrné pocení a slinění, gastrointestinální obtíže, močové a sexuální dysfunkce) (Seppi et al. 2019). Fenotyp a klinické projevy jsou velmi variabilní mezi jednotlivými pacienty, stejně jako rychlost progrese, zastoupení a tíže jednotlivých motorických a nemotorických příznaků (Eggers et al. 2012). Kognitivní obtíže a demence jsou časté v pokročilejší fázi onemocnění a výrazně zhoršují invaliditu a úmrtnost. V současnosti neexistuje kauzální léčba, pouze symptomatická terapie. Medikamentózní léčba značně zlepšuje kvalitu života v prvních letech onemocnění. Po určité době onemocnění jsou možnosti medikamentózní léčby vyčerpány s nástupem pozdních hybných komplikací jako jsou choreatické dyskinézy a výkyvy klinického stavu (on/off fluktuace). V současnosti existustují tři druhy invazivní léčby pozdních stádií PN- subkutánní apomorfinové pumpy, kontinuální intestinální pumpy Duodopa a hluboká mozková stimulace (DBS). Každá z těchto

metod má své výhody a indikace. Nicméně právě DBS je některými autory považována za druhý největší terapeutický pokrok po zavedení léčby levodopou (Weaver et al. 2009, Witt et al. 2012). Přestože se jedná pouze o léčbu symptomatickou, která nedokáže zabrátit další progresi neurodegenerativního procesu, zlepšuje DBS kvalitu života pacientů- viz. příloha 2. I přes úspěšnost léčby DBS stran hlavních hybných příznaků PN se v klinické praci občas setkáváme s nedostatečným klinickým efektem nebo i s určitými komplikacemi této terapie. Jedná se především o nežádoucí účinky, které u některých pacientů ztěžují léčbu. Mezi nejčastější nežádoucí účinky patří poruchy řeči (hlavně dysartrie), přibývání na váze, kognitivní obtíže (poruchy paměti a exekutivních funkcí) a další neuropsychiatrické komplikace (deprese, manie, anxieta, změny osobnosti, hypersexualita) (Saint-Cyr et al. 2000, Romito et al. 2002, Temel et al. 2006, Witt et al. 2008, Balestrino et al. 2017). Přísná klinická indikační a vylučovací kriteria byla stanovena s cílem minimalizovat riziko vzniku těchto nežádoucích účinků (Benabid et al. 2009). Mechanismus, jakým DBS ovlivňuje jednotlivé přínaky PN, stale není zcela objasněn. Stejně tak není znám ani přesný mechanismus vzniku nežádoucích účinků. Studium patofyziologických změn, které jsou podkladem jednotlivých symptomů PN a vlivu DBS je proto nezbytné.

Příloha 2

3. Elektrofyziologie u Parkinsonovy nemoci

Hlavní směry výzkumu v oblasti Parkinsonovy nemoci jsou zaměřeny na neurozobrazování, genetiku, metabolické a imunologické faktory. Elektrofyziologii je v tomto ohledu věnováno daleko méně pozornosti. Přitom zejména elektrofyziologie a již výše zmíněné moderní technické a analytické metody mohou přínést informace, které by byly využitelné v dalším vývoji neuromodulační terapie s cílem optimatilizovat klinický efekt a minimalizovat výskyt nežádoucích účinků. EEG je jednoduchá a pacienta nezatěžující metoda, která má navíc potenciál přinést prospektivní biomarkery, které by mohly pomoci předvídat vývoj onemocnění a jednotlivých klinických příznaků, stejně jako odpovídavost na léčbu DBS.

Parkinsonova nemoc je spojena s celou řadou EEG změn od poruch základní aktivity až po komplexní postižení funkční konektivity na kortikální a kortiko-subkortikální úrovni. Zde je přehled nejvýznamnějších recentních poznatků týkajících se EEG korelátů u Parkinsonovy nemoci, viz. také příloha 3.

Příloha 3

Skalpové EEG

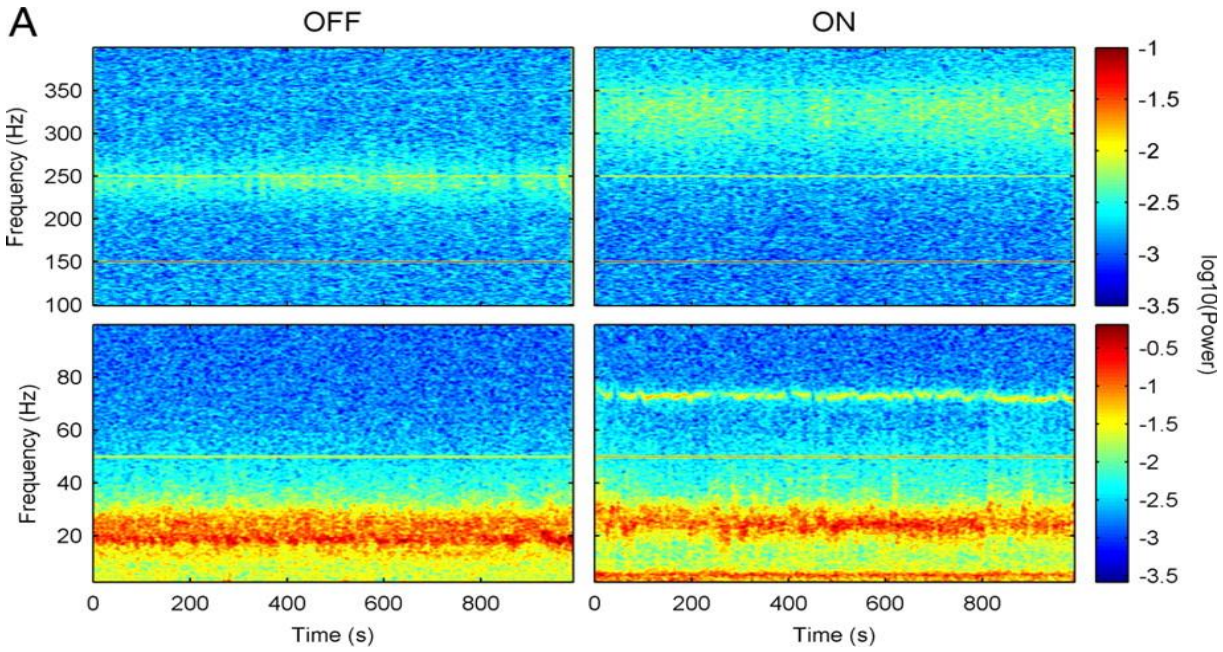
Hlavní změnou, které je detekovatelná při běžném skalpovém EEG, je celkové zpomalení základní aktivity (Neufeld et al. 1988; Soikkeli et al. 1991; Neufeld et al. 1994; Kotini et al. 2005; Sinanovic et al. 2005; Bosboom et al. 2006; Stoffers et al. 2007). Toto zpomalení je pak dále prohloubeno u pacientů s demencí. V časném stádiu u PN v porovnání se zdravými dobrovolníky lze pozorovat nárůst theta a nízké alfa aktivity a současně pokles v beta a gamma pásmech (Stoffers et al. 2007). Užití dopaminergní léčby moduluje EEG aktivitu především v pásmech alfa a beta (Melgari et al. 2014). Stejně jako je zpomalena základní aktivita, tak je prodloužena latence a snížena amplituda motorických a kognitivních evokovaných potenciálů (Tanaka et al. 2000, Georgiev et al. 2016). Hodnocení kognitivních

evokovných potenciálů by mohlo složit jako pomocný prediktor pro rozvoj demence u pacientů s PD (Tanaka et al. 2000), nicméně se v klinické praxi neukázalo jako dostatečně spolehlivé.

Intrakraniální EEG

Intrakraniální studie jsou velmi cenné, neboť přinášejí unikátní informace z v hloubce mozku uložených struktur, které jsou jinak nedostupné při běžném skalpovém snímání. Jedná se o specifický typ výzkumu na poměrně malých souborech pacientů. Počty pacientů jsou limitovány klinickými účely. V případě Parkinsonovy nemoci je možné intrakraniální snímání z DBS elektrod pouze v těsném pooperačním období, kdy jsou elektrody externalizovány ještě před napojením na neurostimulátor. Navíc, ne všichni pacienti jsou schopni takové měření absolovovat pro běžné přechodné pooperační komplikace jako je např. pneumocefalus a s tím související kognitivní obtíže a pod. Nicméně právě tyto analýzy lokálního EEG, tedy tzv. lokálních potenciálů (local field potentials- LFP), zásadním způsobem přispěly k největšímu současnému pokroku v DBS- tj. k zavedení adaptivních stimulátorů (aDBS) (Little et al. 2013). Nejvíce probádanou oblastí v tomto ohledu je STN, které je nejčastějším DBS cílem v léčbě PN. Hypersynchronie v pásmu beta 13-35 Hz je oscilační aktivitou, která koreluje s některými hlavními motorickými příznaky PN tj. s hypokinezou a rigiditou a jejich tíží. Beta hypersynchronie je potlačitelná po užití dopaminerní terapie stejně jako v rámci vysokofrekvenční DBS, což následně koreluje se zlepšením těchto klinických příznaků (Brown 2003 and 2006; Kühn et al. 2006; Androulidakis et al. 2007; Giannicola et al. 2010, 2013; Chen et al. 2010). Oscilace v beta a gamma frekvenčních pásmech jsou zásadní pro řízení pohybu v oblasti bazálních ganglií (BG) a v BG-thalamo-kortikálních okruzích (Brown 2003 and 2006). Beta aktivita je desynchronizována před a v průběhu pohybu a tato desynchronizace (tzv. ERD- event related desynchronization) také koreluje se silou prováděného pohybu (Williams et al. 2003; Alegre et al. 2005; Androulidakis et al. 2008;

Oswal et al. 2012, 2013; Tan et al. 2013). Beta ERD je rovněž modulována kognitivními faktory nejen v oblasti STN, ale také v dalších podkorových i korových strukturách (Oswal et al. 2013; Bočková et al. 2007, 2015, 2017)- viz. příloha 4, 5 a 6. Oscilace v nižších frekvečních pásmech, tedy v alfa a theta pásmu v oblasti BG korelují s mimovolními pohyby jako je chorea (i poléková u PD) a dystonie (Silberstein et al. 2003; Priori et al. 2004; Foffani et al. 2005; Marceglia et al. 2007; Barow et al. 2014). Různé nemotorické funkce (např. pozornost a rozhodování) a nemotorické příznaky Parkinsonovy nemoci (deprese a poruchy impulzivity) se rovněž projevují reaktivitou v těchto nižších pásmech. Nárůst výkonu (tzv. event- related synchronizace, ERS) v nižším alfa pásmu byl popsán v STN (a rovněž v theta pásmu v oblasti prefrontálního kortexu viz. příloha 8) v souvislosti s nechtěnou orientací pozornosti na vzácné neterčové podněty tzv. distraktory (Bočková et al. 2011, 2012)- viz. příloha 7, stejně jako při konfliktním rozhodování (Fumagalli et al. 2011) a poruchách impulzivity a patologickém hráčství (Rodriguez-Oroz et al. 2011; Rosa et al. 2013). V oblasti STN byly detekovány i vysokofrekvenční oscilace (high frequency oscillations, HFOs) kolem 300 Hz (Foffani et al. 2003; López-Azcárate et al. 2010). Oscilace v jednom frekvenčním pásmu mohou být spojeny nebo přímo ovlivňují změny v jiném frekvenčním pásmu (tzv. cross-frequency coupling). Ukázalo se, že fázové změny v nízkých frekvencích korelují se změnami v amplitudě ve vyšších pásmech (tzv. phase-amplitude coupling). Tyto vzájemné dynamické vazby představují fyziologické mechanismy a jejich porušení je součástí patofyziologických změn u Parkinsonovy nemoci. Zejména vztahy mezi nízkou beta aktivitou a HFOs a jejich poruchy jsou podkladem hlavních hybných příznaků PN (Obrázek 1).



Obrázek 1: Časově frekvenční analýza znázorňující oscilační aktivitu v off a on stavu (před a po medikaci levodopou). Patologická beta hypersynchronie je v on stavu potlačena a současně je obnovena fyziologická gamma aktivita (60-80 Hz). Je vidět i potlačení patologického spojení beta hypersynchronie s HFOs a obnovení více fyziologického vzorce ve vysokofrekvenčních oscilacích (López-Azcárate et al. 2010).

Příloha 4

Příloha 5

Příloha 6

Příloha 7

Příloha 8

Kortiko-subkortikální vztahy

Dynamické vztahy mezi jednotlivými mozkovými oblastmi jsou označovány jako tzv. funkční konektivita. Funkční konektivita se může lišit od anatomické konektivity a lze ji studovat pomocí různých metod. Jedná se o statisticky významné vazby neurální aktivity mezi určitými mozkovými oblastmi. PN je spojena s poruchou oscilační reaktivity na úrovni kortiko-subkortikálních interakcí (Schnitzler and Gross 2005). Jednou z metod, jak studovat tyto

vzájemné vztahy mezi oscilacemi v jednotlivých frekvenčních pásmech a jejich poruchy, je studium tzv. koherencí. Koherence hodnotí úroveň vzájemných asociací (tzv. coupling) ve frekvenčním spektru ve dvou nebo více mozkových oblastech. Bylo zjištěno, že třes u PN je spojen se zvýšenou koherencí mezi STN, GPi, thalamem a kortikálními oblastmi ve frekvenčním pásmu 3-10 Hz (Volkmann J et al. 1996, Brown et al. 2001, Williams et al. 2002). Oscilace v beta a gamma frekvenčních pásmech jsou rozhodnující pro řízení hybnosti na úrovni BG-thalamo-kortikální. Je známo, že zvýšená koherence v beta pásmu 11-30 Hz mezi STN, GPi a z kortikálních motorických oblastí především se supplementární motorickou areou (SMA), je spojena s hlavními hybnými příznaky PN tj. s hypokinezou a rigiditou (Marsden et al. 2001, Williams et al. 2002, Brown 2003). Tato zvýšená beta synchronie je potlačitelná po užití dopaminergní medikace stejně jako v rámci DBS. Současně dochází k nárůstu synchronie v pásmu gamma nad 60 Hz, což je aktivita, která má prokinetický charakter. Zřejmě i proto vysokofrekvenční DBS STN i GPi zmírňuje hlavní hybné příznaky PN.

Jsou popsány dvě hlavní funkční sítě mezi STN a kortexem. Motorické a premotorické oblasti jsou funkčně propojeny s STN na úrovni beta oscilací, temporo-parietální oblasti zase především v pásmu alfa (Litvak et al. 2010; Litvak et al. 2011; Hirschmann et al. 2011). Koherence v theta pásmu mezi STN a prefrontálním kortexem je nezbytná pro některé kognitivní funkce jako je konfliktní rozhodování a vyhodnocování chyb (Zavala et al. 2014, 2016). Potlačení patologické nadměrné beta synchronie v motorických okruzích je pokladem úspěšné léčby pomocí DBS. Nicméně DBS může ovlivňovat i oscilační aktivitu v ostatních frekvenčních pásmech v různých kortikálních a subkortikálních oblastech, což není žádoucí a je to zřejmě podkladem vzniku nežádoucích účinků, které mohou komplikovat léčbu. Proto jsou vyvíjeny nové moderní stimulátory s cílem zajistit co nejlepší klinický efekt na hybné funkce a minimalizovat riziko vzniku nežádoucích účinků. Současným největším pokrokem,

který vychází z výše zmíněných elektrofyziologických poznatků, je zavedení “chytrých” tzv. adaptivních stimulátorů (aDBS). Tyto stimulátory detekují EEG aktivitu z oblasti STN a stimulují pouze intermitentně v případě detekce nárůstu beta synchronie. Proto jsou efektivnější než klasické stimulátory jak klinicky, tak i ekonomicky, a navíc je sníženo riziko vzniku nežádoucích účinků (Little et al. 2013).

Další možností, jak studovat dynamické funkční vazby mezi jednotlivými mozkovými oblastmi jsou již výše zmíněné cross- frequency a phase-amplitude coupling metody, které lze použít i na interregionální úrovni. V případě Parkinsonovy nemoci jsme prokázali lateralizované vazby mezi theta fází v STN a beta oscilacemi v různých kortikálních oblastech- viz. příloha 9.

Příloha 9

Poruchy funkční konektivity na kortiko-kortikální úrovni

Změny, které PN a léčba DBS mohou způsobovat na úrovni složitých kortiko-kortikálních funkčních interakcí, stále nejsou zcela objasněny. Nicméně právě tyto znalosti by mohly pomoci objasnit mechanismus vzniku jednotlivých nežádoucích účinků DBS a také nedostatečného klinického efektu této léčby, který občas vídáme u některých pacientů. Nové moderní akviziční systémy a metodické přístupy jako jsou HD-EEG (high density EEG, tj. EEG s vysokou hustotou 256 kanálů), objemová rekonstrukce dat, síťová analýza pomocí teorie grafů a další, přinášejí nové cenné informace, které mohou sloužit jako prediktivní biomarkery pro úspěšnost DBS terapie a vývoje PN a také jsou pokladem pro vznik nových neuromodulačních technik. Jednou z těchto nových metod, které by mohly představovat další generaci neurostimulátorů, je přímá kortikální stimulace motorického kortexu pomocí epidurálních elektrod, která je založena na detekci neuronální aktivity (Beuter et al. 2014). Mapování elektrofyziologických fenoménů na kortikální úrovni může také pomoci při

zavádění neinvazivních stimulačních technik jako je např. rTMS (repetetivní transkraniální magnetická stimulace) do klinické praxe.

Jedním z prvních nálezů je nárůst klidové globální funkční konektivity v alfa pásmu jako korelátu počínající Parkinsonovy nemoci. S progresí onemocnění se tato funkční porucha rozšiřuje na frekvenční pásma 4-30 Hz, tedy theta i beta (Stoffers et al. 2007, 2008). Kognitivní obtíže jsou spojeny s nárůstem interhemisferické alfa konektivity. Kortiko-kortikální alfa a beta koherence korelují s tíží hlavních hybných parkinsoniských symptomů jako je rigidita a hypokineza, a jsou potlačitelné jak po užití l- dopa, tak i v rámci léčby DBS (Silberstein et al. 2005). Studium kortikální funkční konektivity může být také užitečné jako prediktivní ukazatel pro rozvoj demence u PN, kdy je popisován celkový pokles globální konektivity a vícečetné snížení interregiálních funkčních vztahů (Ponsen et al. 2012). Poruchy impulzivity jsou zase spojeny s poruchou modulace theta aktivity ve frontocentrální oblasti (Carriere et al. 2016). Analýza kortikální oscilační aktivity objemově rekonstruovaného skalpového HDEEG by mohla pomoci při detekci pacientů s nedostatečnou odpovědí na léčbu DBS nebo pacientů se zvýšeným rizikem vzniku nežádoucích účinků této léčby. V naší práci jsme detekovali podskupinu subjektů s opačnou elektrofyziologickou reaktivitou v podobě snížení desynchronizace v pásmech alfa a beta při zapnuté stimulaci. Tito pacienti měli současně horší reakční časy při provádění kognitivně motorické úlohy v průběhu stimulace, horší klinické výsledky hodnocené pomocí UPDRS škály a horší výsledky v testech na sémantickou paměť- viz. příloha 10.

Šíťová analýza pomocí tzv. teorie grafů je další moderní metodický přístup umožňující hodnotit funkční vztahy a jejich patologické poruchy na úrovni jak regionální, tak na úrovni mozku jako celku. Teorie grafů popisuje síť a funkční vztahy mezi jejími jednotlivými oblastmi (uzly) pomocí měření síly uzlů, která je definována počty spojů mezi sousedními

uzly a jejich významností, dále podle klastrovacího koeficientu, který určuje míru funkční segregace a podle délky cesty, která je znamením funkční intergrace. Klastrovací koeficient hodnotí jakým způsobem jsou vzájemně pospojovány sousední uzly. Prodloužená delká cesty je znamením ztráty funkčních spojů mezi vzdálenými uzly. K zachycení významných bodů v síti existují různé způsoby hodnocení jejich centrality (review viz. Bullmore and Sporns 2009). Jako první změny v souvislosti s PN jsou popsány poruchy lokálního shlukování v delta pásmu. V pozdějších stádiích onemocnění dochází k postižení i ostatních frekvenčních pásem a k prodlužení délky cesty (Olde Dubbelink et al. 2014). Byly zkoumány i změny funkční konektivity v souvislosti s DBS léčbou. Mezi hlavní nálezy patří především pokles interhemisferické koherence v beta pásmu mezi motorickými kortikálními oblastmi během stimulace (Weiss et al. 2015), na základě které je možno předvídat klinický efekt léčby. Na souboru našich STN-DBS pacientů jsme nepozorovali změny globální konektivity při zapnuté oproti vypnuté stimulaci. Při hodnocení regionálních změn došlo k nárůstu významnosti (zvýšená síla uzlu nebo eigenvector centralita) především oblasti levé a pravé SMA v průběhu stimulace, což zřejmě souvisí s obnovením fyziologické funkce této oblasti, která je známá svým funkčním propojení s STN a důležitostí v regulaci hybnosti. U podskupinu subjektů se suboptimální odpovědí na DBS (horší klinická odpovídavost, reakční časy a výsledky paměťových testů) byl naopak pozorován pokles globální konektivity (ve frekvenčním pásmu 1-8 Hz) v on stimulačním stavu, chyběla regionální změna v oblasti SMA a navíc byl pozorován pokles lokální konektivity v celé řadě především frontálních struktur při zapnuté stimulaci. Tito pacienti zřejmě mohou být z tohoto důvodu rizikovější pro rozvoj kognitivních a jiných neuropsychiatrických nežádoucích účinků DBS- viz. příloha 11.

Příloha 10

Příloha 11

4. Závěr a shrnutí výsledků vědeckých prací autorky

Společným prvkem níže uvedeného souboru publikací je matematická analýza EEG signálu jako nástroje pro mapování mozkových funkcí a poruch. Podstatná část prací se zabývá hodnocením intracerebrálně snímaného EEG, získaného jednak z kortikálních struktur u pacientů s implantovanými exploračními elektrodami v rámci epileptochirurgického programu, a dále pak ze subkortikálních struktur u DBS pacientů s Parkinsonovou nemocí a také s dystonií. Hlavním cílem těchto intrakraniálních studií bylo mapování oscilačních změn v souvislosti s kognitivními funkcemi v těchto v hloubce mozku uložených strukturách. Metodou hodnocení EEG signálu byla tzv. event related de/synchronizace (ERD/S), která je podrobně vysvětlena v přiloženém sourhnném článku. Zjistili jsme, že zvýraznění desynchronizace v alfa a beta pásmu souvisí s vyšší kognitivní zátěží, především se zapojením exekutivních funkcí. Tento fenomém byl detekovatelný z kortikálních struktur překvapivě především v oblasti temporálního neokortexu, a ze subkortikálních struktur pak v oblasti STN, GPi i v AN thalamu. Prokázali jsme tak zapojení těchto subkortikálních oblastí do kognitivních okruhů a popsali elektrofyziologické koreláty odpovídající kognitivní činnosti. Pozdější publikace se zabývají hodnocením EEG změn u pacientů s Parkinsonovou nemocí léčených DBS. Jedná se o pokročilé metody snímání (pomocí tzv. HD-EEG systému) a hodnocení skalpového EEG. Pomocí tzv. rekonstrukce dat do objemu lze i takto získat signál z v hloubce mozku uložených struktur. Poslední dvě přiložené publikace popisují změny oscilační aktivity, globální a regionální konektivity u pacientů se suboptimální odpovědí na DBS. U těchto subjektů jsme pozorovali zhoršení ERD po DBS v alfa a beta pásmu, snížení globální konektivity v pásmu 1-8 Hz a žadnou změnu regionální konektivity oblasti SMA, která je v rámci DBS očekávaná. Naopak jsme pozorovali sníženou konektivitu v celé řadě především frontálních struktur. Tyto změny mohou být podkladem nedostatečné klinické odpovědi na DBS a mohou znamenat vyšší riziko vzniku nežádoucích účinků této léčby.

V návaznosti na tyto výsledky se ve své další vědecké činnosti plánujeme zabývat studiem prospektivních biomarkerů, které by mohly do budoucna pomoci předvídat klinické výsledky léčby DBS u jednotlivých pacientů. Výzkumný a klinický potenciál EEG u Parkinsonovy nemoci z pohledu DBS je popsán v přiložené souhrnné publikaci na toto téma.

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6. Přílohy – komentovaný soubor prací autorky

6.1. Příloha 1 - Desynchronizace a synchronizace EEG rytmů

Bočková M a Rektor I. Desynchronizace a synchronizace EEG rytmů. Neurologie pro praxi 2009; 10(4): 242–245.

V tomto přehledovém článku je popsána metoda hodnocení EEG signálů pomocí tzv. event-related desynchronizace a synchronizace (ERD/S). Jedná se o kvantitativního hodnocení oscilačních změn v jednotlivých frekvenčních pásmech, které jsou vázány na určité podněty. Typickým příkladem takové oscilační změny je dobře známá alfa atenuační reakce nad okcipitálním kortexem, kde při aktivaci této oblasti po otevření očí dochází k rozpadu alfa rytmu, tedy k ERD. Obdobné reakce lze hodnotit i v jiných oblastech v souvislosti s různými dalšími funkcemi. Tento druh hodnocení EEG má význam především v neurovědním výzkumu, kdy je na základě této analýzy možné rozlišení mezi aktivací a inhibicí určité oblasti.

Desynchronizace a synchronizace EEG rytmů

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Event-related synchronizace a desynchronizace (tzv. ERD/S) představuje kvantitativní nelineární metodu analýzy EEG signálu umožňující hodnocení změn základní EEG aktivity v libovolných frekvenčních pásmech. Tyto změny jsou vázány na zevní či vnitřní podnět a jsou spojeny s určitou mozkovou aktivací. Metoda je široce využívána v neurovědním výzkumu jako forma funkčního mapování. Velký význam má pak především rozbor dat získaných pomocí hlubokých mozkových elektrod.

Klíčová slova: oscilace, synchronizace, desynchronizace, EEG.

Desynchronization and synchronization of EEG rhythms

Event-related synchronization and desynchronization (ERD/S) represents a quantitative non-linear EEG signal analysis method, that enables to evaluate the changes of the background activity in any frequency ranges. These changes are related to an external or internal stimulus and are linked to the brain activation. It is widely used in the neuroscience research as a form of functional brain mapping. Especially the intracerebral recording data analysis have a big importance.

Key words: oscillations, synchronization, desynchronization, EEG.

Neurol. prax 2009; 10 (4): 226–229

Seznam zkratek

EEG – elektroencefalografie
ERD – event-related desynchronizace
ERS – event-related synchronizace
IF – individuální frekvence
TFA – time frequency analysis (frekvenční analýza)
EcoG – elektrokortikografie
GTS – gyrus temporalis superior
DBS – deep brain stimulation (hluboká mozková stimulace)
STN – subtalamické jádro
SEEG – stereoelektroencefalografie
GPi – vnitřní pallidum
fMRI – funkční magnetická rezonance
rTMS – repetitivní transkraniální magnetická stimulace
BCI – brain computer interface

Úvod

Hlavní úlohou centrální nervové soustavy jako řídícího a integračního systému je přenos a zpracování informací. Tyto funkce jsou umožňovány na základě elektrochemických procesů na synaptických spojích mezi jednotlivými neurony, které jsou navzájem propojeny v rozsáhlé funkční okruhy neboli neuronální sítě. Vlastní informace je kódována do podoby bioelektrických potenciálů. Z pohledu neurofyziologie je jednou ze základních vlastností mozkové tkáně schopnost generovat elektrickou rytmickou oscilační aktivitu o různých frekvencích, která vzniká synchronní činností jednotlivých neuronů zapojených do různých neuronálních sítí (Pfurtscheller, 2006). Těmito mechanizmy vzniká i základní rytmická elektrická aktivita mozku, která je běžně snímána a hodnocena v rutinní klinické diagnostice a praxi prostřednictvím elektroencefalografie (EEG) a která podléhá při prakticky jakékoli neuronální činnosti a aktivaci dynamickým změnám ve všech svých frekvenčních pásmech (delta 0–3 Hz, theta 4–7 Hz, alfa (MU) 8–13 Hz, beta 14–30 Hz a gamma nad 30 Hz). Dobře známým příkladem takovéto změny mozkových elektrických oscilací v alfa frekvenčním pásmu je před mnoha lety Bergerem (Berger, 1929) popsaná alfa atenuační reakce nad okcipitálním kortexem, která se objevuje při jeho aktivaci v návaznosti na otevření očí v podobě rozpadu alfa rytmu. O mnoho let později byla Pfurtschellerem (Pfurtscheller a Aranibar, 1977) popsána metoda kvantitativní analýzy těchto na určitý podnět vázaných dějů. Jedná se o hodnocení změn amplitudy a frekvence základní EEG aktivity, které jsou vázány na vnitřní či zevní podněty, které doprovázejí určitou mozkovou činnost (např. motorickou či kognitivní) a které jsou dány sumací dendritických potenciálů určité populace kortikálních neuronů (Crone et al., 2001). Potlačení rytmické oscilační aktivity v podobě snížení její amplitudy je označováno jako event-related desynchronizace (ERD), naopak nárůst rytmicity oproti výchozímu intervalu je nazýván jako event-related synchronizace (ERS).

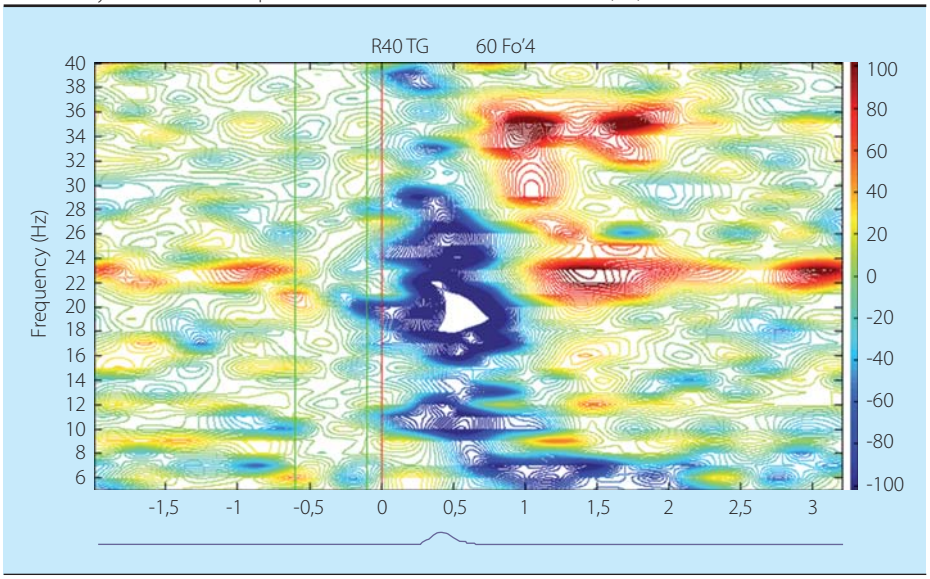
Z hlediska fyziologického významu je ERD v alfa a beta pásmu interpretována jako korelát aktivace určité oblasti, zatímco ERS v nižších frekvenčních pásmech nejspíše odpovídá deaktivaci (Lopes da Silva a Pfurtscheller, 1999) nebo tzv. aktivní inhibici (Pfurtscheller, 2001). Diskutována je otázka vyššího beta frekvenčního pásma (20–30 Hz), ve kterém je rovněž ERD považována za korelát aktivace, ale za určitých okolností to může být i ERS (Cassim et al., 2001). Odlišná situace je pak v gamma (nad 30 Hz) pásmu (na rozdíl od alfa a beta pásem), ve kterém právě synchronizace je chápána jako ukazatel aktivace s mnoha funkčními koreláty (Schürmann et al., 1997) a vyskytuje se současně s alfa a beta ERD jako tzv. vložená (embedded) a multifokální aktivita. Předpokládá se, že je generována intrakortikálně (Szurhaj et al., 2005). Prostorové hodnocení rytmických elektrických oscilací je v posledních desetiletích široce používanou metodou studia motorických, senzorických i kognitivních mozkových funkcí. V současnosti je důležitá především pro základní neurovědní výzkum jako forma funkčního mapování (Neuper et al., 2006).

Kvantitativní hodnocení ERD/S

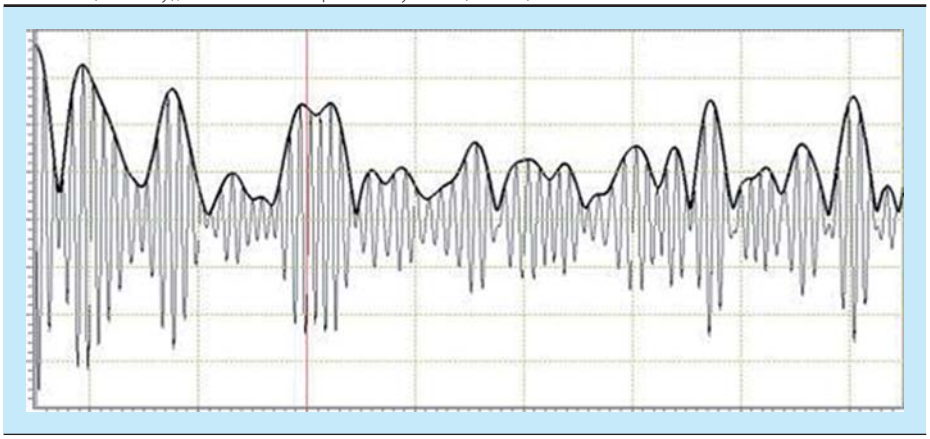
ERD/ERS jsou na určitý podnět vázány časově, ale na rozdíl od evokovaných dějů ne fázově, proto nestačí k jejich hodnocení použít pouhé zprůměrnění opakujících se EEG úseků, ale je nutné použít lineární metody, jako je např. Fourrierova transformace nebo časově frekvenční analýza.

Dělení na jednotlivá frekvenční pásma je umělé, neboť v různých kortikálních okrscích a při provádění odlišných úkolů může docházet k oscilačním změnám v jiné spektrální úrovni. Taková úroveň je pak označována pojmem individuální frekvence (IF) a jedná se o frekvenční úsek s maximálním nárůstem nebo poklesem výkonu, může jich být i více v rámci jedné kortikální oblasti. IF stanovíme přesně pomocí tzv. časově frekvenční analýzy (TFA, time frequency analysis).

Graf 1. Ukázka časově frekvenční analýzy SEEG (stereoencefalografie) v průběhu motorické úlohy (stisknutí tlačítka v návaznosti na detekci terčového podnětu) z jednoho z kontaktů hluboké mozkové elektrody, implantované do oblasti levého primárního motorického kortexu. Modrá barva: ERD s maximem v IF pásmu 16–30 Hz, červená barva: ERS po ukončení pohybu v individuálních frekvencích (IF) 20–24 Hz a 32–36 Hz. Po neterčových podnětech, které nebyly spojeny s motorickou odpovědí, byla TFA bez významných změn. Mezi zelenými liniemi je vyznačen referenční interval. Vodorovná osa – čas (sekundy), bod 0 – okamžik prezentace stimulu, motorická odpověď zaznamenána pomocí zvláštního kanálu – vyznačeno modře pod obrázkem. Svislá osa – frekvence (Hz)



Graf 2. Výkon (hodnota amplitudy na druhou): světlejší křivka, obálka výkonu: tmavší křivka. Vodorovná osa – čas (sekundy), svislá osa – amplituda výkonu (uV^2/Hz)



Definitivní křivku, kterou hodnotíme, získáme zprůměrněním EEG signálu, filtrací IF, dále umocněním amplitudy na druhou, čímž získáme tzv. výkon. Nakonec z výkonu pomocí Fourrierovy transformace vypočítáme tzv. obálku výkonu viz. graf 2.

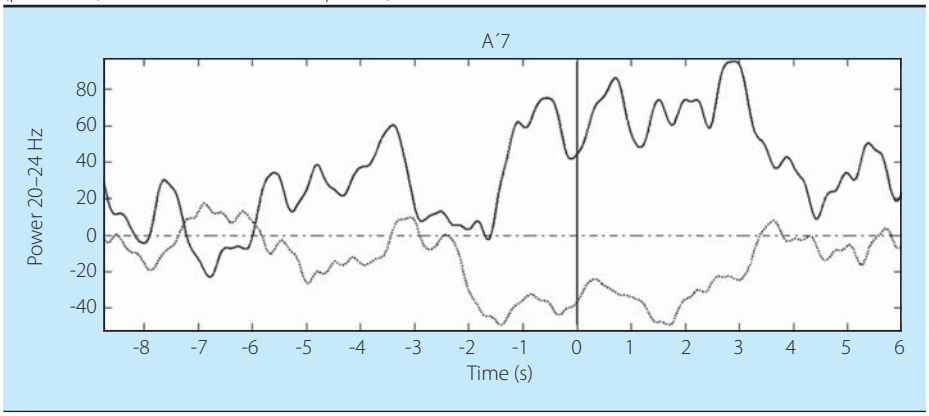
ERD/S, motorika a senzitivita

Snad nejlépe prozkoumanou oblastí pomocí metody ERD/S je motorika a s ní spojená senzitivita. Je tedy dobře známo, že příprava, provádění, ale také i pouhé představování si pohybu způsobuje ERD v alfa (MU) pásmu nad motorickými oblastmi. MU ERD je nejvíce vyjádřena kontralaterálně k pohybu v průběhu přípravy motorického úkolu (pre-movement ERD) a při započetí pohybu se šíří oboustranně. ERD v průběhu motorické imaginace se velmi podobá právě pre-movement ERD. Obecně lze říci, že i beta oscilace jsou desynchronizovány v průběhu přípravy, provádění a imaginace motorického úkolu. Po skončení pohybu se beta obnovuje velmi rychle, tj. do 1 sekundy, a následně se objevují krátkodobé tzv. beta bursts neboli post-movement beta ERS (také nazýváno beta rebound), které se vyznačují vysokým stupněm somatotopické specificity. Pomocí transkraniální magnetické stimulace bylo dokázáno, že tato 20 Hz ERS odpovídá intervalu přechodně snížené excitability primárního motorického kortexu (Hummel et al., 2002). Původní práce byly prováděny ze skalpového EEG. Registrací z intracerebrálních elektrod byla v motorickém kortexu popsána gamma ERS mezi 40–60 Hz v distribuci, která byla konzistentní s funkční mapou stanovenou na základě elektrické stimulace (Szurhaj et al., 2005). Rovněž senzitivní podněty způsobují změny rytmických mozkových aktivit. V návaznosti na senzitivní stimulaci byla detekována ERD v alfa a beta pásmu (10–20 Hz) především v oblasti primárního somatosenzitivního kortexu oboustranně, přičemž kontralaterální ERD byla výraznější. Desynchronizace je pak následována tzv. post-stimulus synchronizací okolo 20 Hz, která se vyskytuje v kontralaterálním somatosenzitivním kortexu a SMA (supplementární motorická area). Přesnou somatotopickou organizaci, jako v oblasti motorického kortexu, se v případě senzitivních kortikálních oblastí nepodařilo prokázat. Bolestivé laserové stimuly, stejně jako chladové a tepelné, byly spojeny s 10 a 20 Hz ERD, po které však nenásledovala 20 Hz ERS. Předpokládá se proto, že post-stimulus ERS je spojena s neuronální transmisí v lemniskálním systému. Oscilační změny tedy modulují přípravu jednotlivých drah ke zpracování přicházejících senzitivních informací (Stančák, 2006).

ERD/S a smyslové vnímání

Okcipitální alfa ERD v podobě atenuační reakce po otevření očí, která je známkou aktivace zrakového kortexu, byla zmíněna již dříve (Berger, 1929) jako nejznámější příklad oscilační změny vůbec. Další smyslovou modalitou, která byla zkoumána, je sluch. Zajímavým a překvapivým nálezem byla detekce nárůstu výkonu, namísto očekávaného poklesu v alfa pásmu (8–13 Hz) při percepci tónů a samohlásek nad sluchovým kortexem, což vedlo k závěru, že percepce v této oblasti není spojena s alfa ERD. Tyto výsledky nakonec nebyly potvrzeny pomocí elektrokortikografické (ECoG) studie levého gyrus temporalis superior (GTS), ve kterém byla jasně přítomna alfa suprese při sluchové stimulaci. Tento rozdíl je pravděpodobně dán tím, že běžné rozložení skalpových elektrod zřejmě nestačí k záchytu alfa ERD v temporálním laloku. Elektrokortikografickou explorací byla současně s alfa aktivitou zkoumána i nižší (40–80 Hz) a vyšší (80–100 Hz) gamma aktivita při prezentaci jednoduchých tónů a slabik. U všech subjektů byla prokázána gamma synchronizace v levém GTS, a to především v souvislosti s vnímáním slabik ve Wernickeově oblasti (Crone et al., 2001). Nárůst výkonu v tomto pásmu byl přítomen na více kontaktech a s větší amplitudou při vnímání slabik než v průběhu percepce jednoduchých tónů, což je pravděpodobně dáno tím,

Graf 3. Ukázka ERS (černá barva, úkol 1) a ERD (šedá barva, úkol 2) v IF pásmu 20–24 Hz v oblasti temporálního neokortexu v průběhu dvou kognitivně motorických úkolů spojených se psaním jednoduchých písmen. Úkol 1 – kopírování písmen, úkol 2 – psaní jiných písmen. ERD v tomto případě souvisí se zvýšenou kognitivní zátěží v průběhu úkolu 2, u kterého předpokládáme vyšší zapojení exekutivních funkcí (plánování, inhibice automatické odpovědi)



že obecně percepce řeči je vázána na levou hemisféru a vyžaduje vyšší stupeň kognitivní integrace mezi neuronálními populacemi. Lokalizace této gamma aktivace byla v korelaci s výsledky kortikální stimulace v oblasti sluchové kůry. Výskyt gamma ERS byl podobně jako u motorických studií mnohem více diskrétní než přítomnost alfa ERD.

ERD/S a kognitivní funkce

Analýzy ERD/ERS jsou široce užívány i v kognitivním neurovědním výzkumu. Tyto operace vyžadují přechodnou integraci celé řady různých a mnohdy vzdálených oblastí mozku. Jedním z pravděpodobných mechanizmů této integrace je formování dynamických spojek zprostředkovaných neuronálními oscilačními systémy, které jsou důležité pro komunikaci funkčních sítí paměti a kognice. Na základě celé řady prací bylo zjištěno, že změny rytmických aktivit v souvislosti s kognitivními funkcemi jsou velmi specifické pro určitý úkol nebo proces (tzv. task-specific) a závisí značně na modalitě stimulu. Například pro vizuální stimulaci je charakteristická alfa ERD s okcipito-parietálním maximem. Při zapojení kognice po sluchovém stimulu, je proces kódování spojený s difuzní rozsáhlou alfa ERS. Rozpoznávání a vybavování potom s alfa ERD, jejíž lokalizace závisí na typu úlohy. Je tedy zřejmé, že pojem inhibice pro alfa ERS není absolutní. Důležité je, spíše než se snažit přiřadit určité mentální funkci specifické frekvenční pásmo nebo mozkovou areu, chápat lidskou kognitivní kapacitu jako oscilační síť konstantně interagujících kortikálních oblastí (Krause, 2006). Zvyšující se exekutivní zátěž způsobuje rozdíly v aktivaci mezi jednoduchými a složitějšími úkoly v řadě především frontálních a temporálních neokortikálních stuktur. Pomocí hlubokých mozkových elektrod byla při provádění jednodušší operace detekována ERS, nevýznamné změny nebo nižší ERD v alfa a beta frekvenčních pásmech, zatímco v průběhu složitějšího úkolu byla nalezena významná ERD ve stejných pásmech. Také gamma ERS se zdá být elementární změnou signálu, která je spojena s kognitivními funkcemi a pamětí a hraje důležitou roli při multimodální a multiregionální integraci kortikálního zpracování (Bočková et al., 2007). Bylo rovněž prokázáno, že oscilační změny v souvislosti s kognitivními procesy (jako je paměť, pozornost a odhad času) v průběhu motorických úloh jsou více vyjádřeny než evokované děje a byly detekovány v primárním motorickém a somatosenzitivním kortexu, dále v SMA, cingulu, premotorickém, orbitofrontálním a dorzolaterálním prefrontálním kortexu a také v oblasti temporálního a parietálního laloku (Rektor et al., 2006; Sochůrková et al., 2006a, b).

ERD/S a patologické stavy

Specifické změny mozkových elektrických oscilací byly popsány v souvislosti s celou řadou neurologických a psychiatrických poruch. U Parkinsonovy nemoci je nejvýraznější známou abnormitou zpoždění začátku ERD v kontralaterální senzorimotorické oblasti v průběhu volního pohybu. Další změny charakteristik MU a beta ERD v souvislosti s volním pohybem, např. dřívější začátek nebo zvýšená exprese v ipsilaterálním senzorimotorickém kortexu nebo meziálních frontálních strukturách, byly nalezeny ve vazbě na celou řadu patologických situací, jakými jsou např. Parkinsonova nemoc, Alzheimerova nemoc, frontální epilepsie, kapsulární mozkový infarkt, roztroušená skleróza. Tyto změny jsou pak interpretovány jako kompenzace pro zjevnou nebo subklinickou motorickou poruchu nebo jako nedostatek kortikální aktivace oblastí, které by za normálních okolností měly být při provádění daného úkolu aktivně zapojeny. Rovněž oslabená nebo méně fokální post-movement beta ERS, která byla prokázána u Parkinsonovy nemoci, demence, obsedantně kompulzivní poruchy a roztroušené sklerózy, je často interpretována jako indikátor neefektivních kortikálních inhibičních mechanizmů na konci motorického aktu (Leocani a Comi, 2006).

Intrakraniální ERD/S

Nezastupitelnou roli ve studiu oscilací mají analýzy EEG signálu, který je získán intrakraniální registrací z hlubokých mozkových (SEEG – stereoelektroencefalografie) a subdurálních elektrod (ECoG – elektrokortikografie), které jsou v indikovaných případech zaváděny k vyšetření pacientů s farmakorezistentní epilepsií před plánovaným operačním řešením. Gamma aktivita je mnohdy zachytitelná pouze v jednom z kontaktů hluboké mozkové elektrody, které jsou od sebe vzdáleny 1,5 mm, což potvrzuje teorii, že gamma je generována malými neuronálnímu populacemi. To je také důvod, proč je tak obtížné ji zaznamenat při povrchovém snímání EEG (Szurhaj et al., 2005). Invazivní techniky typu hluboké mozkové stimulace (DBS – deep brain stimulation) rovněž umožnily získat cenné informace z oblasti v hloubce uložených subkortikálních struktur, především ze subtalamického jádra (STN) u pacientů s pozdními hybnými komplikacemi Parkinsonovy nemoci, a napomohly pochopení patofyziologických procesů v bazálních gangliích. Bylo zjištěno, že Parkinsonova nemoc je spojena se zvýšenou synchronií ve frekvencích 8–35 Hz v oblasti STN i GPi (vnitřní pallidum). Tato ERS působí akineticky a je suprimována po podání dopaminergní terapie (Kühn et al., 2009). Gamma ERS, která v off stavu narůstá při započetí pohybu v STN symetricky oboustranně, se pak v průběhu on stavu při L-dopa terapii zvýrazňuje a je signifikantně více vyjádřena na straně kontralaterální k pohybu. Z toho vyplývá, že dopaminergní terapie v podstatě obnovuje fyziologický vzorec aktivity v subtalamickém jádře u pacientů s Parkinsonovou nemocí (Androulidakis et al., 2007). ERD/S v alfa a beta oblasti byly studovány i v oblasti putamen u neparkinsonských pacientů (Sochůrková a Rektor, 2003).

Závěr

Analýza ERD/S změn především prostřednictvím intracerebrálních elektrod má velký význam z hlediska neurovědního výzkumu a v kombinaci s dalšími neurofyziologickými metodami jako je fMRI a rTMS je velmi přínosná pro funkční mapování mozkových oblastí. Zatím minimálně prozkoumanou oblastí jsou vysoká frekvenční pásma.

Objev ERD/S umožnil rozvoj odvětví zvaného brain computer interface (BCI), kdy oscilační změny mozku jsou zaznamenávány pomocí počítače, protřednictvím kterého je pak možno myslí ovládat externí zařízení např. protetickou končetinu. BCI je prakticky využíván u pacientů trpících amyotrofickou laterální sklerózou nebo u locked-in syndromu (Birmbauer, 2006).

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6.2. Příloha 2 - DBS amplitude setting can improve aspects of quality of life in patients with Parkinson's disease

Baláž M, Bočková M, Rektor I. DBS amplitude setting can improve aspects of quality of life in patients with Parkinson's disease. J Neural Transm 2013;120(4):643-8.

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Hluboká mozková stimulace je efektivní léčba hybných příznaků Parkinsonovy nemoci. Tato práce se zabývá studiem vlivu DBS také na nemotorické příznaky a celkovou kvalitu života pacientů. Za tímto účelem byl použit dotazník hodnotící kvalitu života PDQ-39, který byl pacienty vyplňován před a 36 měsíců po operaci. Testovány byly dvě podskupiny subjektů. Skupina A zahrnovala 12 pacientů, kteří požadovali další navyšování stimulace (i přes objektivně uspokojivý hybný stav) a skupina B rovněž 12 pacientů, kteří byli spokojeni se svým současným klinickým stavem. Nejdříve došlo u obou skupin k falešnému navýšení stimulace (sham stimulace) na dobu dvou měsíců k vyloučení placebo efektu. Dále pak byla u skupiny A skutečně navýšena stimulace o 0,3-0,5 V. Po navýšení parametrů stimulace jsme pozorovali zlepšení v PDQ-39 o 22,9% u pacientů ze skupiny A, především v položkách emoce, komunikace a sociální stigmatizace. Přitom současně nedošlo ke změně hybného stavu dle UPDRS skóre. V průběhu sham stimulace nedošlo ke statisticky signifikantní změně v PDQ-39 ani u jedné ze skupin. Úprava stimulačních parametrů tedy může u některých pacientů vést ke zlepšení nemotorických příznaků a aspektů kvality života. Kteří z pacientů mohou takto těžit z dalšího navyšování stimulace nad hodnoty, které vedou k uspokojivému motorickému efektu, je nutné ověřit v rozsáhlejších studiích.

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DBS amplitude setting can improve aspects of quality of life in patients with Parkinson's disease

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Abstract The DBS STN is a non-curative treatment; its effect on the patient's quality of life (QoL) determines the therapeutic success of this procedure. We aimed to assess whether stimulation parameters setting may influence also some of the non-motor aspects of QoL. The QoL was assessed by PDQ-39 questionnaire. The questionnaire was administered to patients before and after the DBS surgery. A sham change of stimulation amplitude was performed before the actual increase. After the further amplitude increase in subgroup of patients (mean increase of amplitude of 0.35 V), there was a statistically significant additional improvement of total PDQ-39 score by another 22.9 %. In this group the emotions, stigma and communication subscales improved after the stimulation increase, without further change of UPDRS III. We were able to demonstrate that the increase of stimulation parameters (amplitude) has a potential to improve some non-motor functions and aspects of QoL and thus has an additional effect on quality of life in certain subset of PD patients. The meticulous observation of QoL should be a routine part of assessments before and after the DBS STN surgery, and can even aid during the parameter setting.

Keywords Deep brain stimulation (DBS) · Subthalamic nucleus (STN) · Non-motor symptoms · Quality of life

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Introduction

High-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a preferred surgical treatment for motor symptoms of advanced Parkinson's disease (PD). As the DBS STN is a non-curative treatment, its effect on the patient's quality of life (QoL) determines its therapeutic success. Several studies have shown that this procedure indeed improves QoL in PD patients (Deuschl et al. 2006); (Weaver et al. 2009).

The non-motor symptoms are prevalent in PD. In many patients the QoL appears to be impaired more by the non-motor symptoms of PD than the motor ones (Schrag et al. 2003; Volkmann et al. 2009).

Non-motor factors may reasonably be included in the selection of surgical target for deep-brain stimulation (Follett et al. 2010).

Quality of life in PD patients is influenced by motor and several non-motor aspects of the disease. The most prominent non-motor symptoms are depression, sleep problems and pain (Schrag et al. 2003; Schrag et al. 2000). Social aspects such as communication, social support and disease burden impair the QoL as well. Progression of PD and disease severity is associated with a decline in QoL, but the exact longitudinal course and the contributing factors are not well established.

Sufficient voltage is required to achieve desired clinical effects of the stimulation, however the likelihood of side effects increases (Kuncel and Grill 2004). The change of stimulation parameters is usually reflected by the improvement of motor symptoms of the PD.

We have noticed that a certain sub-group of patients requests further increase of stimulation parameters, despite the significant improvement of their motor functions after the DBS STN.

We decided to comply with patients wishes, increase the stimulation and observe whether it has any effect on the

QoL. We decided to use sham stimulation increase as a suitable way that would enable us to assess whether the real stimulation increase was not related to possible placebo effect. We believe that without using this approach we would be unable to compare the benefits gained from the stimulation increase in selected group of patients.

We specifically aimed to assess whether stimulation parameters setting may also influence some of the non-motor aspects of QoL.

Methods

We compared stimulation amplitude and its relation to QoL measured by PDQ-39 scale and NMS-Q, non-motor symptoms questionnaire (Chaudhuri et al. 2006). In our study, we included two groups of patients with PD, 36 months after the DBS STN surgery.

Patients

Each group consisted of 12 patients with similar clinical profile (duration of disease, timing of DBS surgery in course of PD, L DOPA dose, age, and stimulation amplitude). Group A consisted of 12 patients (8 men, 4 women). These patients requested further increase of stimulation parameters, despite clinically significant improvement of their motor functions after the DBS as judged by experienced clinician (by rating of UPDRS III subscale). Average duration of the disease at the time of the operation was 11.4 ± 3.5 years. Average age was 59.6 ± 7.8 years.

Group B consisted of 12 matched patients (7 men, 5 women) who were satisfied with their overall clinical condition 3 years after the surgery. The characteristics of both patients groups are presented in Table 1.

There were no neuropsychological disturbances, including the impulsivity change in either group A or B

Procedure

The initial coordinates for the STN (dorsolateral part) were determined in reference to AC–PC line (defined on the primary registration series) using indirect technique, typically 11–12 mm lateral to and 3 mm posterior to and 5 mm ventral to intercommissural point. The final target coordinates and electrode position were then modified with respect to direct visualisation of STN on T2 fat sat scans and relationship of the STN to red nucleus anterior margin, and largest red nucleus cross-sectional area. The intraoperational microrecording and stimulation were used. There was no difference in final electrode position between the groups of patients reported in this paper.

Assessments

The QoL was assessed by PDQ-39 questionnaire (Jenkinson et al. 1997). The questionnaire was administered to patients before the DBS surgery and at 36 months after the surgery. In both the groups, the assessment of QoL was repeated again 2 months after the change of stimulation parameter settings (performed in group A only).

The NMS-Q was filled in by the patients in Group A before the stimulation parameters were increased and then again after 2 months. The effect of stimulation increase on individual items of NMS-Q was recorded. The NMS-Q assessment was based on patient response with "yes" and "no". An item was considered to be improved, as long as there was a change in answer from "yes" to "no" in statistically significant number of patients.

Stimulation settings change

The stimulation parameters change in this preliminary study was an increase of stimulation amplitude by 0.3–0.5 V. Average amplitude increase was 0.35 V (± 0.1). The frequency (130 Hz) and pulse width (90 μs) were not

Table 1 Patient groups data before and 36 months after the DBS average values (± SD) of UPDRS II and III scores and PDQ-39 score

	Before DBS (medication off)		36 months after DBS (medication off/ stimulation on)		Average p value of both groups (difference 36 months vs. before DBS)
	Group A	Group B	Group A	Group B	Group A/B
UPDRS II	21 ± 4	20 ± 5	18 ± 3	17 ± 3	0.032/0.034
UPDRS III	43 ± 8	42 ± 7	26 ± 5	24 ± 5	<0.0001 both
LEDD (mg)	1002 ± 305	1012 ± 274	600 ± 280	580 ± 240	<0.0001 both
Stimulation amplitude[a] (V)	–	–	2.8 ± 0.4 V	2.7 ± 0.4 V	–
PDQ-39 (overall score)	74 ± 12	71 ± 10	48 ± 10	40 ± 12	0.00123/0.00142

L DOPA equivalent daily dose equivalent (LEDD) is shown in milligram of the average daily dose. There were no statistically significant differences in the overall improvement between the two groups. Group A—patient with subsequent stimulation increase, B—control group

[a] The frequency and pulse width were 130 Hz and 90 μs in all these cases

adjusted. The stimulation increase did not lead to dyskinesia or any other side effects in these selected patients.

A sham change of stimulation amplitude was performed before the actual increase. During the sham stimulation change the patients were informed about the parameter increase, which, in fact, did not occur. After 2 months of sham stimulation change, the actual stimulation increase described below was performed. The sham stimulation increase was performed in both group, A and B. After the real change of stimulation amplitude settings (performed in group A only) the assessment of QoL was performed again.

The stimulation increase did not lead either to dyskinesia or any other side effects in these selected patients. The UPDRS III did not change either.

Statistical analysis

The ANOVA and Tukey test were used to evaluate differences between respective subscales and the groups of patients.

Results

The QoL significantly improved after the DBS in both groups of patients as shown by the improvement in UPDRS III score. However, group A (patients demanding the stimulation increase) showed less pronounced improvement of QoL (especially in emotions subscale) compared to group B (Table 2, 3). After the further amplitude increase in group A (mean increase of amplitude of 0.35 V), there was statistically significant additional improvement of total PDQ-39 score by another 22.9 %. In group A the emotions, stigma and communication subscales improved after the stimulation increase. The UPDRS III did not improve further, however.

After the sham stimulation increase in group B, there was no further improvement of either motor or non-motor functions (Table 3).

A sham stimulation increase did not cause any change in PDQ-39 scale or NMS-Q.

The motor improvement observed in our study (UPDRS III improvement of 40 or 43 % in our groups) is in line

Table 2 QoL subscale changes in both groups

PDQ–39	Before DBS		36 months after DBS		*p* values, 36 months vs. before the DBS	
	Group A	Group B	Group A	Group B	Group A	Group B
Mobility	64	66	27	32	<0.0001	<0.0001
Activity of daily living	35	37	26	28	0.11	0.27
Emotions	40	42	25	26	0.017	0.015
Stigma	50	48	27	21	0.0007	0.0002
Social support	30	28	16	17	0.014	0.021
Cognition	33	32	30	31	0.24	0.23
Communication	39	42	21	22	0.001	0.001
Body discomfort	25	24	17	16	0.1120	0.1230

The statistically significant improvements in emotions, stigma, social support and communication subscales

Table 3 Significantly improved subscales in individual patients of Group A (after the actual stimulation parameter increase compared to sham stimulation change)

	Group A			Group B	
	At 36 months	After the actual increase	After the sham increase	At 36 months	After the sham increase
PDQ–39 Overall score	48 ± 12	37 ± 10	47 ± 13	38 ± 10	39 ± 10
Mobility	30 ± 11	26 ± 9	31 ± 10	32 ± 12	33 ± 12
Emotions	25 ± 8	19 ± 10	25 ± 8	26 ± 9	25 ± 9
Stigma	19 ± 6	16 ± 8	19 ± 7	21 ± 10	21 ± 10
Communication	22 ± 7	18 ± 6	21 ± 6	22 ± 10	24 ± 10
UPDRS III (med off/stim on)	24 ± 5	23 ± 4	24 ± 5	26 ± 5	25 ± 5

No change in non-motor scales were present in group B after the sham stimulation change

with outcomes reported in several studies (Rodriguez-Oroz et al. 2005; Simuni et al. 2002).

Discussion

We report improvement in PDQ-39 score of approximately 32 % after 3 years of DBS STN. This result is in line with the previous observation. As noted in recently published metaanalysis (Martinez-Martin and Kurtis 2012), considering four class I studies on bilateral STN published to date (Deuschl et al. 2006; Esselink et al. 2004; Follett et al. 2010; Williams et al. 2010) with a total of 855 patients (mean: 214; 34–366) and mean follow-up of 12 months, the average improvement in HrQoL using the PDQ-39 was 15.4 %. These results are lower than those reported in reviews dating 4 or 5 years ago, where published trials on bilateral subthalamic DBS showed a HRQoL improvement of 60.5 % in generic measures (Martinez-Martin and Deuschl 2007) and 33.8–34.5 % in disease-specific scales (Kleiner-Fisman et al. 2006; Martinez-Martin and Deuschl 2007).

Our observations suggest that the DBS may have a certain beneficial effect on non-motor features and social aspects of the disease and also on patient's evaluation of the disease stigma, at least in some patients.

In our study the emotions, stigma and communication as evaluated by the PDQ-39 improved after the stimulation increase.

The overall NMS-Q score showed no further improvement after 2 months of stimulation increase. However, there was a significant improvement, i.e. significant number of patients reported improvement in questions 13 (loss of interest), 22 and 23 (daytime sleepiness, difficulty getting to sleep).

Both PDQ-39 scale and NMS-Q showed a partial amelioration of non-motor signs and non-motor aspects of QoL.

The selection of stimulation parameters for these patients may be insufficient if based only on the purely motor assessment.

Several open studies found marked improvements in physical and psychosocial aspects of HrQoL after STN stimulation using generic or PD-specific scales (Spottke et al. 2002).

In general, non-motor symptoms of PD, such as mood disturbances, drive problems, pain and sleep disorders have an impact on HrQoL, which may equal or exceed the influence of motor impairment (Volkmann et al. 2009). Well-known motor problems after STN-DBS, such as poor gait, balance, or speech had surprisingly little impact on HrQoL in this study.

A recent large short-term randomized controlled multicenter study compared HrQoL in a group of 156 patients with severe motor symptoms of Parkinson's disease, who were randomly assigned in pairs to receive either bilateral DBS of the STN in combination with medical treatment or best medical therapy alone (Deuschl et al. 2006).

At 6 months, an improvement of HrQoL (PDQ-39 score) by about 25 % was found only in the surgically treated group, indicating that the symptomatic benefits of STN-DBS outlast the inherent surgical risks and lead to more effective reduction of the burden of disease than optimal drug therapy. An extended observational period, however, is necessary to assess the stability of these results along the chronic course of PD.

The prospective study of Volkmann et al. (2009) found out sustained improvements in HrQoL at 3 to 4 years in a relatively large proportion of Parkinsonian patients those suffered from substantial disability at baseline despite best medical treatment.

On the other hand, the work of Drapier et al.(2005) using patient's self-assessment scales showed the clinical benefit of STN-DBS on non-motor signs was quite subtle; physical items of QoL significantly improved, whereas mental items such as emotional well-being, social support, cognition and communication showed no improvement. The authors suggest a dissociation of motor and non-motor symptoms control after bilateral STN-DBS in PD patients.

In a study by Witjas et al. 2007, patients implanted with bilateral STN-DBS experienced significant benefits with sensory/painful fluctuations, dysautonomia (excessive sweating), and cognitive fluctuations. In another study by Zibetti et al. (2007), sleep and constipation were the only symptoms that improved following bilateral STN-DBS surgery in 36 PD patients.

Quality of life scales such as the PDQ-39 (Jenkinson et al. 1997) and questionnaires [NMS-Q—(Chaudhuri and Martinez–Martin 2008)] should become an integral part of the clinical protocol for patients admitted to a Parkinson's disease surgical program. This may help to identify factors that affect the patient's QoL other than the motor activity.

Conclusions

We have been able to demonstrate that the increase of stimulation parameters (amplitude) has a potential to improve some non-motor functions and aspects of QoL and thus has an additional effect on QoL in certain subset of PD patients. The meticulous observation of QoL should be a routine part of assessments before and after the DBS STN surgery, and can even aid during the parameter setting. Certain effect of DBS STN on non-motor functions and social aspects of QoL (such as stigma, emotion, and communications) can explain the further improvement of overall QoL after the stimulation amplitude increase.

Possible explanations for benefit of stimulation increase could be one or more of the following:

1. Influence of non-motor symptoms of PD that are difficult to ascertain during regular visits on QoL.
2. Psychological aspect related to stimulation change.
3. Improvement of apathy, which is sometimes observed after the DBS STN.

Further study with random design and larger number of subjects is warranted.

Especially important will be to describe the subjects who may benefit from an increase of the stimulation parameters beyond the values that improve the usual motor symptoms of PD.

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Conflict of interest The authors declare that they have no conflict of interest.

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6.3. Příloha 3 - Impairment of brain functions in Parkinson's disease reflected by alterations in neural connectivity in EEG studies: a viewpoint

Bočková M, Rektor I. Impairment of brain functions in Parkinson's disease reflected by alterations in neural connectivity in EEG studies: a viewpoint. Clin Neurophysiol. 2019;130(2):239-247.

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Tato práce je souhrnným článkem a pojednává o nejvýznamnějších elektrofyziologických poznatcích u Parkinsonovy nemoci. Byla hodnocena recentní literatura tj. od roku 2000 a pozdější, celkem 85 publikací. Hlavní důraz byl kladen na oscilační fenomény a konektivitu mezi jednotlivých kortikálními a subkortikálními oblastmi hodnocenou pomocí moderních technik a matematických metod. Popsán je také význam těchto poznatků pro vývoj nových metod DBS- tzv. adaptivních systémů. Článek dále obsahuje vlastní úhel pohledu autorů a perspektivy pro další elektrofyziologický výzkum na poli DBS, který má za cíl optimalizovat léčbu DBS a minimalizovat riziko nežádoucích účinků této léčby.

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Review

Impairment of brain functions in Parkinson's disease reflected by alterations in neural connectivity in EEG studies: A viewpoint

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HIGHLIGHTS

- EEG studies in PD were reviewed, with the focus on oscillatory activities and DBS.
- Knowledge of EEG patterns in PD enables progress particularly in DBS therapy.
- Progress was reported recently using advanced analytical methods.

ABSTRACT

Clinical symptoms of Parkinson's disease (PD) are accompanied by pathological phenomena detected locally in the basal ganglia (BG) as changes in local field potentials (LFPs) and also in cortical regions by electroencephalography (EEG). The literature published mainly between 2000 and 2017 was reviewed with an emphasis on approaches emerging after 2000, in particular on oscillatory dynamics, connectivity studies, and deep brain stimulation. Eighty-five articles were reviewed. The main observations were a general slowing of background activity, excessive synchronization of beta activity, and disturbed movement-related gamma oscillations in the BG and in the cortico-subcortical and cortico-cortical motor loops, suppressible by dopaminergic medication as well as by high-frequency deep brain stimulation (DBS). Non-motor symptoms are related mainly to changes in the alpha frequency range. EEG parameters can be useful in defining the risk of dementia in PD. Further progress was reported recently using advanced analytical technologies and high-performance computing (graph theory). Detailed knowledge of LFPs in PD enabled progress particularly in DBS therapy, which requires optimizing the clinical effect and minimizing adverse side effects. The neurocognitive networks and their dysfunction in PD and DBS therapy are promising targets for future research.

Contents

Abbreviations: AD, Alzheimer's disease; aDBS, adaptive deep brain stimulation; BCI, brain–computer interface; BP, Bereitschaftspotential; BG, basal ganglia; CNV, contingent negative variation; DBS, deep brain stimulation; DLB, dementia with lewy bodies; EEG, electroencephalography; EP, evoked potentials; ERD/S, event-related de/synchronization; GPi, globus pallidum; HD-EEG, high-density EEG; HDP, hyperdirect pathway; HFOs, high-frequency oscillations; ICD, impulse control disorders; LFPs, local field potentials; MEG, magnetoencephalography; MRI, magnetic resonance imaging; P3, cognitive evoked potential; PFC, prefrontal cortex; PD, Parkinson's disease; PDD, Parkinson's disease with dementia; PPN, pedunculopontine nucleus; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area; STN, subthalamic nucleus; tCDS, transcranial direct current stimulation; UPDRS, unified Parkinson's disease rating scale.

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1. Introduction

Parkinson's disease (PD) is characterized mainly by motor symptoms of tremor, rigidity, bradykinesia, and postural instability (Aarsland et al., 2011) and is accompanied by several non-motor symptoms. The phenotype of the disease varies among patients. The speed progression is very individual, as is the representation of motor and non-motor symptoms (Eggers et al., 2012). Cognitive impairment and dementia are common in advanced PD. Severe cognitive impairment increases disability and mortality in advanced PD.

Research on brain functions in PD has been focused mainly on metabolic, genetic, imaging, and clinical studies. Much less attention has been paid to electrophysiological studies. Electroencephalography (EEG) and magnetoencephalography (MEG) have several advantages over functional imaging methods, mainly the best time resolution. The fine analysis of the frequency spectrum ranging from very slow (subdelta) to very high frequency oscillations (over 300 Hz) enables precise connectivity studies. The bioelectric activity within the brain tissue may be recorded directly via surgically inserted intracerebral electrodes, even in very small structures like the subthalamic nucleus (STN). The deep brain stimulation (DBS) electrode may be used for recording of the LFPs during the interval between the intracranial implantation and connection to the extracranial current generator.

PD is linked with various electrophysiological signs, from changes of EEG-detected background activity to complex disturbances in functional connectivity on the cortico-subcortical and cortico-cortical levels. The potential for electrophysiological studies in PD has not yet been fully explored. For this reason, we decided to review the recent literature with the aims of identifying the recent electrophysiological findings related to PD, exploring their clinical relevance, and inspiring future research. Detailed knowledge of physiological and pathophysiological phenomena related to PD may help to develop novel approaches in PD treatment, for example in the domains of invasive and non-invasive neuromodulatory treatment.

2. Methods

The recent literature concerning PD-related EEG changes was summarized to provide a viewpoint about the potential of measuring brain bioelectrical activity for clinical use. A large amount of data about EEG in PD has been published; We focused mainly on recent articles concerning oscillatory phenomena and DBS as they may have a clinical impact. The search was performed in the PubMed database. A total of 85 articles, mainly published between 2000 and 2017, were selected and reviewed for this report. Seminal articles published earlier were included only exceptionally.

3. Results

3.1. Surface (scalp) EEG/MEG

Several scalp EEG and MEG studies have shown a general slowing of resting state background activity in PD (Neufeld et al., 1988; Soikkeli et al., 1991; Neufeld et al., 1994; Kotini et al., 2005; Sinanovic et al., 2005; Bosboom et al., 2006; Stoffers et al., 2007). Changes were described in de novo PD patients compared to healthy controls, including a widespread increase of power in the theta and low alpha bands, as well as a decrease of beta and gamma power (Stoffers et al., 2007); see Table 1. Levodopa intake modulates scalp EEG activity in PD patients and is associated mainly with power increases in the alpha and beta rhythms in centro-parietal areas (Melgari et al., 2014). The amplitude of movement-related slow potentials (CNV- contingent negative variation and BP- Bereitschaftspotential) is decreased in PD (for review, see Georgiev et al., 2016). Patients with dementia (PDD) have slower background EEG than patients without dementia. An increase of delta activity and a diffuse decrease in alpha power was found in PDD patients compared to PD patients without dementia (Bosboom et al., 2006). Worse cognitive performance was also linked to increases in the central and parietal low alpha activity. This could be a sign of a pathological level of attention, as alpha oscillations have an important role in attentional processes. The higher level of attention might produce increased perseveration (Stoffers et al., 2007). The suppression of alpha activity due to eye opening is reduced in PDD (Soikkeli et al., 1991; Bosboom et al., 2006). The evaluations of cognitive evoked potentials (P3) in PD patients without dementia can serve as predictors of dementia (Tanaka et al., 2000). With increasing dementia in PDD patients, the amplitude and power of P3 potential is decreased, and the P3 latency is increased; see Table 1. Apathy in PD patients is associated with decreased amplitude of novelty P3 potential in a three-stimulus oddball paradigm (Kaufman et al., 2016). Visual reading of EEG should be performed with caution, as the parkinsonian tremor can diffusely influence the scalp signal, mainly in the theta band power through movement artefacts (Timmermann et al., 2003).

3.2. Local field potentials (LFP) in the basal ganglia

Intracranial studies enable direct recordings from the subcortical structures that are not within reach of scalp measurements. The analysis of LFPs has provided accurate knowledge about physiological and pathophysiological phenomena in the BG, mainly in the STN, which is the most frequent DBS target for treatment of motor symptoms in advanced PD. Phase and time locked event-related potentials (evoked potentials) are detected by averaging the EEG signal. Movement-related slow potentials (BP and CNV) as well as cognitive event-related potentials were detected in the STN (Purzner et al., 2007; Baláž et al., 2008). These findings indicate that STN plays an important role not only in self-paced and cued movements but also in cognition. Oscillatory changes in ongoing EEG signals can be evaluated as event-related de/synchronization (ERD/S) of some frequency component. ERD/S are time locked but not phase locked phenomena and are analysed as power changes (squared amplitude values). ERD represents a power decrease, ERS means a power increase (Lopes da Silva, 2006). Oscillations in the beta and gamma frequencies play a major role in motor control in the BG (Brown, 2003; 2006); see Table 2. STN beta activity is desynchronized before self-paced voluntary movement as well as before cued movements and also correlates with the force of motor effort (Williams et al., 2003; Alegre et al., 2005; Androulidakis et al., 2008; Oswal et al., 2012, 2013; Tan et al., 2013). An increase in

Table 1
Surface studies.

	Background activity	EP	Delta	Theta	Alpha	Beta	gamma
PD motor symptoms	General slowing (Neufeld et al. 1988; Soikkeli et al. 1991; Kotini et al. 2005; Sinanovic et al. 2005)	CNV and BP ↓ amplitude (Georgiev et al. 2016)		↑ (Stoffers et al. 2007) tremor ↑ ↑ (Timmermann et al. 2003)	↑(Stoffers et al. 2007)	↓(Stoffers et al. 2007)	↓(Stoffers et al. 2007)
PDD	↑ ↑ general slowing (Bosboom et al. 2006)	P3 ↓ amplitude ↑ latency (Tanaka et al. 2000)	↑ (Bosboom et al. 2006)		↓ (Bosboom et al. 2006)		
Levodopa					↑ CP (Melgari et al. 2014)	↑ CP (Melgari et al. 2014)	

Legend: Summary of the main surface EEG and MEG findings. ↑: Increase, ↓: Decrease. CP: Centroparietal, CNV: Contingent negative variation, BP: Bereitschaftspotential. The summary is based on the comparisons of PD versus healthy controls, PDD versus PD without dementia, and PD on versus off levodopa.

Table 2
STN local field potentials.

	Off state	On state	Nonmotor
Theta-alpha		↑ dyskinesias, dystonia (Foffani et al. 2005; Barow et al. 2014)	ERS ↑ with attention and ICD (Bočková et al. 2011; Rodriguez-Oroz et al. 2011) ↓ - emotions (Huebl et al. 2014)
Beta	↑↑ Bradykinesia, rigidity (Brown 2003; Kühn et al. 2006; Androulidakis et al. 2007; Giannicola et al. 2013; Chen et al. 2010)	↓ Motor improvement (Brown 2003, Kühn et al. 2006; Androulidakis et al. 2007; Giannicola et al. 2013; Chen et al. 2010) ↑ stop signal (Ray et al. 2012; Wessel et al. 2016)	↓ cognitive complexity ↓ reward (Oswal et al. 2013; Bočková et al. 2017)
Gamma	↓ Bradykinesia, rigidity (Brown 2003; Androulidakis et al. 2007)	↑ Motor improvement (Brown 2003; Androulidakis et al. 2007)	
HFOs	↑ Coupled to low beta (López-Azcárate et al. 2010)	Decoupling, perimovement ↑ (López-Azcárate et al. 2010)	

Legend: Summary of the known functional significance of the oscillations in each frequency band in the STN, during motor off and on states and related to nonmotor functions. ↑: Power increase (ERS), ↓: Power decrease (ERD), ICD: Impulse control disorders

beta power is linked to successful stopping of a motor action (Ray et al., 2012; Wessel et al., 2016). Changes in beta reactivity are also influenced by contextual factors like reward or cognitive complexity (Oswal et al., 2013; Bočková et al., 2017). Beta event-related desynchronization (ERD) was observed during saccadic eye movement; moreover, this beta ERD was increased during antisaccades that required inhibition of reflexive responses (Yugeta et al., 2013) and could therefore reflect the involvement of executive functions. Hypersynchrony in the 13–35 Hz frequency range correlates to clinical motor symptoms in PD and is suppressed by dopaminergic medication and high-frequency DBS, and the degree of suppression is linked with clinical improvement (Brown, 2003; 2006; Kühn et al., 2006; Androulidakis et al., 2007; Giannicola et al., 2010, 2013; Chen et al., 2010); see Table 2.

Increased low-frequency oscillations (5–13 Hz) in PD were detected after dopaminergic medication in the STN as well as in the GPi and are related to chorea and dystonic movements (Silberstein et al., 2003; Priori et al., 2004; Foffani et al., 2005; Marceglia et al., 2007; Barow et al., 2014).

High-frequency oscillations (HFOs) around 300 Hz have also been reported in the STN in PD patients (Foffani et al., 2003; López-Azcárate et al., 2010).

Alterations in LFPs are also related to non-motor functions (attention and decision making), clinical symptoms (depression), and complications in PD (ICD), mainly in lower frequencies (5–13 Hz). Event-related synchronization (ERS) in the low alpha frequency range was detected in the STN as a response to distractor stimuli in a three-stimulus paradigm, reflecting an attentional orienting response (Bočková et al., 2011). An increase in the 5–13 Hz frequency range is related to the conflictual decision-making condition (Fumagalli et al., 2011). A local decrease in alpha power was found for emotionally arousing but not for neutral pictures. This alpha power decrease was reduced for pleasant stimuli and increased for unpleasant stimuli in depressive patients compared with patients without depression (Huebl et al., 2014). This probably reflects the depressive mood disturbances in PD patients with STN-DBS. Increased theta-alpha activity is associated with impulse control disorders (ICD) and pathological gambling in PD (Rodriguez-Oroz et al., 2011; Rosa et al., 2013); see Table 2. Oscillations in one frequency range can be accompanied and influenced by changes in another frequency range. Moreover, it has been shown that the phase of low frequency activity can drive the amplitude of gamma oscillations. These dynamic interactions can be studied as cross-frequency coupling or phase-amplitude coupling and represent both a physiological mechanism and part of the pathophysiology of symptoms in PD. Pathological low-beta and HFOs coupling was observed during the PD off state in the STN, and there was no change during movement performance. In the on state, low-beta activity was suppressed, pathological coupling disappeared, and the HFOs displayed movement-related modulation (López-Azcárate et al., 2010); see Table 2 and Fig. 1.

New DBS targets are being examined and introduced in PD. Pedunculopontine nucleus (PPN) has been recently introduced as

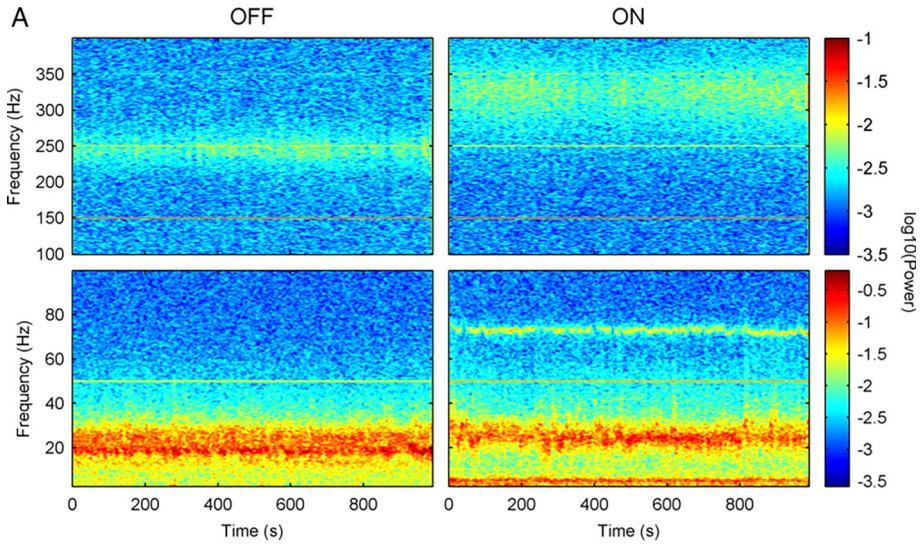

Fig. 1. Time-frequency analysis showing oscillatory dynamics during off and on states in the STN. Pathological beta hypersynchrony linked to the main motor symptoms in the PD off state is reduced while gamma activity (60–80 Hz) is restored during the on state after dopaminergic medication intake. Changes in HFOs are also displayed. Pathological phase-amplitude coupling between low-beta and HFOs was demonstrated. These beta-coupled HFOs show little or no change during voluntary movements, depending on the level of bradykinesia and rigidity. In the on state, the beta hypersynchrony disappears, leading to functional decoupling with clear movement-related modulation in HFOs (used from López-Azcárate et al. 2010, with permission).

Table 3
STN functional connectivity (FC).

Symptoms	STN FC to				Prefrontal cortex
	GPi	Thalamus	Motor cortex (SMA)	Temporo- parietal cortex	
Tremor	3–10 Hz coherence spreading from STN to GPi, from GPi to thalamus and then from thalamus to motor cortex(Volkmann et al., 1996; Brown et al. 2001; Williams et al. 2002)				
Bradykinesia, rigidity	11–30 Hz hypersynchrony (Marsden et al 2001; Williams et al. 2002; Brown 2003)		11–30 Hz hypersynchrony (Marsden et al 2001; Williams et al. 2002; Brown 2003)		
Prokinetic effect/ clinical improvement	synchronous gamma oscillations (over 60 Hz) (Brown et al. 2001; Williams et al. 2002; Cassidy et al. 2002)		synchronous gamma oscillations (over 60 Hz) (Brown et al. 2001; Williams et al. 2002; Cassidy et al. 2002)		
Non-motor functions				7–12 Hz oscillations cognitive functions (Litvak et al. 2010; Litvak et al. 2011; Hirschmann et al. 2011)	4–8 Hz coherence conflict conditions and error monitoring (Zavala et al. 2014, 2016).

Legend: summary of the functional coupling (connectivity) of the STN to the subcortical and cortical structures in relation to motor and nonmotor PD symptoms.

a promising target mainly in patients with severe gait disorders. Direct LFP recordings have detected mainly alpha oscillations that are enhanced after levodopa intake (Androulidakis et al., 2008). Another interesting finding is a different beta band reactivity of PPN LFPs in comparison to STN and GPi. Movement-related beta ERD was observed during the off state and surprisingly premovement beta ERS occurred in the on state. Beta oscillations probably have a prokinetic nature in the area of PPN (Tsang et al., 2010). Somatosensory evoked potentials were recorded from PNN, suggesting probably direct somatosensory connections of the PPN (Yeh et al., 2010; Insola et al., 2014).

3.3. Functional connectivity disturbances in Parkinson's disease on the cortico-subcortical level

Integration of activity within various brain areas is necessary for normal brain functioning. Dynamic relationships called coupling between different brain regions can be studied as functional connectivity using several methods. Functional connectivity is defined as a statistical relation between the neural activity of regions of interest. Neurological disorders such as PD are associated with changes in the functional connectivity of oscillatory reactivity (Schnitzler and Gross, 2005).

Coherence evaluation is one of the analytical methods for testing if different brain regions have similar oscillatory activity. It measures the level of association of frequency spectra of two or more areas. Coherence coupling between STN and GPi LFPs and between their thalamic projections and the cortex in the 3–10 Hz oscillation range are related to tremor in untreated parkinsonian states. STN activity precedes that of GPi, and activity in the GPi's thalamic projection precedes cortical activity. This finding is consistent with the net driving of the motor cortex at tremor frequencies through the GPi-thalamo-cortical pathway (Volkmann et al., 1996; Brown et al., 2001; Williams et al., 2002; for review see Brown, 2003); see Table 3. Beta and gamma range oscillations are crucial in motor control in cortico-basal ganglia loops (Brown 2006). Beta band coherence (11–30 Hz) between the STN, GPi, and cortical structures (mainly the supplementary motor area - SMA) has a strong antikinetic character. It is greater in the hypodopaminergic condition and decreased before and during voluntary movement (Marsden et al., 2001; Williams et al., 2002; Brown 2003); see Table 3. Gamma synchrony (over 60 Hz) was

found in the STN, GPi, and SMA after levodopa medication. These oscillations are considered to be prokinetic in nature. A prokinetic effect in PD patients is observed during stimulation of the STN and GPi using frequencies higher than 60 Hz (Brown et al., 2001; Williams et al., 2002; Cassidy et al., 2002; Brown, 2003); see Table 3. Reduction in the cortico-subthalamic gamma activity was observed to be related to response inhibition and was disturbed in patients with impulse-control disorders (ICD) (Alegre et al., 2013).

Two different functional networks with frequency-specific couplings have been described between the STN and cortical structures in PD (Litvak et al., 2010; 2011; Hirschmann et al., 2011); see Table 3. The temporo-parietal areas are coupled to STN at alpha band (7–12 Hz). The motor and premotor regions are coupled to the STN at beta frequencies (13–30 Hz). A recent combined simultaneous surface MEG and intracranial LFP recording study during ongoing DBS showed that clinically effective STN-DBS suppresses local low beta activity in the STN and furthermore that the level of this suppression correlates with improvement of motor symptoms. DBS also suppressed synchronization between the STN and mesial premotor regions, mainly the SMA. Coupling between these structures is predominantly in the high beta band. Beta coupling between the STN and primary (lateral) motor cortex was surprisingly not influenced by DBS. High and low beta band connectivity between the cortex and the STN may reflect coupling via the hyperdirect pathway (HDP) and indirect pathways (Oswal et al., 2016). Beta-band resynchronization was found in the STN in conflict situations (Stroop effect) and stops the motor system until the conflict is resolved. This is considered to be the correlate of the hyperdirect inhibitory activity from the cortex to the STN (Brittain et al., 2012). Subdural cortical (strip) recordings were used to obtain direct signal from the motor cortex corresponding to the HDP during STN-DBS. STN local beta power was decreased dependent on the voltage used during high-frequency DBS. Beta power reduction in the motor cortex was most likely propagated antidromically or orthodromically through cortico-basal ganglionic pathways, which supports the hypothesis that DBS improves the motor clinical symptoms by reducing excessive synchrony in the sensorimotor network (Whitmer et al., 2012). However, this reduction is fixed and depends on the ongoing DBS. This stimulation condition leads to the absence of an ideal balance in network functioning (excessive reduction of beta synchrony and disturbed cross-frequency coupling) and can impair other behaviour performance (Brittain et al., 2014). For example, theta band coherence between the prefrontal cortex and STN is important in conflict conditions and error monitoring. It has been hypothesized that this theta coupling could be disturbed via DBS, leading to impulse control disorders (Zavala et al., 2014, 2016). Moreover, it has been shown that DBS does not supress beta hypersynchrony in all subjects, in contrast to levodopa. The diverse responsiveness to DBS in some patients remains to be clarified. There is no additional effect of DBS when beta oscillations are already suppressed by levodopa (Giannicola et al., 2010). These findings have contributed to the development of 'smart' stimulators that provide spatially targeted stimulation based on real-time readouts of neural signals reflecting the patient's actual clinical state that is displayed in LFPs. In adaptive DBS (aDBS) a brain–computer interface (BCI) system is used to detect and subsequently suppress excessive beta activity that is recorded directly from the STN. This feedback-dependent intermittent stimulation can be more efficient and clinically superior to current standard continuous DBS (Little et al., 2013).

Concerning the PPN area, LFP alpha activity is coupled to similar cortical activity after levodopa before self-paced movement performance. These interactions are probably related to attentional processes that are necessary for correct movement performance (Androulidakis et al., 2008). A direct connection between PPN and STN was confirmed using direct recordings of PPN-evoked potentials during STN stimulation (Neagu et al., 2013).

3.4. Functional connectivity disturbances in Parkinson's disease on the cortical level

Growing interest has been focused on DBS-induced connectivity modifications on the cortical level. DBS-induced changes of PD-related EEG phenomena might be important and are still largely unknown. Here we summarise some studies with heterogeneous and partly contradictory results. Disease stage-specific markers are also documented. New methodological approaches, such as high-density EEG, source reconstruction, and graph theory might be helpful in this field.

In earlier studies, an increased resting-state cortico-cortical functional connectivity in the alpha frequency band was found to be a sign of early PD. A 4–30 Hz range functional connectivity disturbance increases with disease progression (Stoffers et al., 2007, 2008). Interregional functional connectivity between different brain areas is increased in theta (4–8 Hz), alpha (8–13 Hz), and beta (13–30 Hz) bands in PD patients without dementia compared to healthy individuals (Bosboom et al., 2009). Cortico-cortical alpha-beta coherence (10–35 Hz) is linked to the severity of clinical symptoms, mainly bradykinesia, and is reduced after both levodopa and DBS (Silberstein et al., 2005).

Cognitive dysfunctions are associated with increased interhemispheric functional connectivity in the alpha range (Stoffers et al., 2008).

Current studies report specific movement-related coupling from the prefrontal cortex (PFC) to the SMA in the gamma band in healthy controls. PD patients in the off state did not express any frequency-specific coupling between these areas and the physiological pattern was reinstated after levodopa (Herz et al., 2013).

EEG connectivity patterns are a promising tool for detecting cognitive impairment risks in PD. In PD patients with dementia (PDD), reduced functional coupling in the delta (0.5–4 Hz), theta, and alpha rhythms was found, and it was most pronounced in the inter-temporal and fronto-temporal functional connections (Bosboom et al., 2009). Slowing in neuronal activity and a reduction in functional connectivity in PDD patients was described in comparison to PD patients without dementia (Ponsen et al., 2012). Compared to PD patients, PDD patients had more delta and theta power in the parieto-occipital and fronto-parietal areas. The PDD patients had less alpha and beta power in the parieto-temporo-occipital and frontal areas. In addition, connectivity in PDD patients between pairs of regions was stronger in the theta band and weaker in the delta, alpha, and beta bands. EEG parameters can be useful in defining the risk of dementia in PD. Both a lower-than-median background rhythm frequency and a higher-than-median EEG power in the theta band are associated with a higher risk of dementia in this population (Klassen et al., 2011). Impulse control disorders (ICDs) in PD are associated with deficient modulation of frontocentral theta activity (Carriere et al., 2016).

A network science called graph theory is a new methodological approach. It enables a macroscopic perspective of brain connections on the regional and whole brain network level and has therefore become a popular tool for distinguishing between health and disease since it can capture whole brain changes. Graph theory characterizes a network and the relationships between its nodes (different brain areas) by measuring the node degree as the number of connections with neighbouring nodes, the node strength by taking node weights into account, the clustering coefficient as a measure of segregation, and the shortest path length as a measure of integration. The clustering coefficient defines how neighbouring nodes are interconnected. The shortest path length is the

length of the shortest path between any two nodes. Longer path lengths suggest a loss of links between functionally distant nodes. To capture nodes with important positions in network topology, there are numerous measures of centrality. A more regular character of the network suggests decreased efficiency in transferring information between distant regions of the brain (for review, see Bullmore and Sporns, 2009). In a recent graph theory study in PD, resting-state brain networks in early stage patients showed decreases in local clustering with preserved path length in the delta range in comparison to controls. A long-term analysis over a four-year period showed progressive impairment in local clustering in multiple frequency bands and also a decrease in path length in the alpha range. The longitudinal network changes were linked to the deterioration of motor and cognitive functions (Olde Dubbelink et al., 2014). According to a recent MEG study using graph analysis, a reversal of the physiological posterior-to-anterior information flow might play an important role in PD-related cognitive impairment (Boon et al., 2017).

The effect of DBS on cortical connectivity was also studied. Movement-related power decreases in the upper alpha and beta ranges were more facilitated with stimulation 'on' than with stimulation 'off' in many areas: the bilateral sensorimotor, premotor, SMA, parietal and prefrontal cortex. During the 'on' state, interhemispheric cortico-cortical coherence in the beta band was significantly reduced between the bilateral sensorimotor areas. The clinical effect on motor symptoms could be predicted from this cortical decoupling (Weiss et al., 2015).

4. Discussion, viewpoint and perspectives:

Electrophysiological phenomena related to motor dysfunctions in PD, mainly bradykinesia, tremor, and dyskinesias, have been widely studied and precisely described. Beta hypersynchrony in motor circuits is currently the most important finding enabling therapeutic progress: the development of adaptive neurostimulators (Little et al., 2013). However, these stimulators reflect beta oscillations only; changes in other frequency bands are not considered. It has been reported that non-motor symptoms in PD are associated with oscillatory activity in all frequency ranges – theta (impulse control disorders), alpha (depression), beta (cognitive impairment), and gamma (cognitive inflexibility). Moreover, there are dynamic relationships between lower and higher frequency ranges like phase-amplitude coupling with physiological and pathological significance. Pathological low-beta/HFO coupling is described in relation to PD motor symptoms. In general, phase-amplitude coupling is known to play an important role in cognitive functioning in large-scale brain networks. However, there is a lack of information about such interactions linked to non-motor symptoms in PD. Frequency-specific interregional couplings related to different actions and conditions is rather complex and remain to be fully elucidated by further research. For example, while pathologically increased power in the low beta range was observed in the STN, interregional pathological coupling between the STN and motor cortex occurs in the upper beta band. In the cognitive STN/temporo-parietal network, the connectivity in the alpha range plays a major role; for a review, see Oswal et al. (2013).

Current DBS with constant settings suppresses beta hypersynchrony and improves movement-related gamma reactivity resulting in improvements of bradykinesia and rigidity. Beta suppression may result in behavioural disturbance, for example in situations requiring the stop signal where rapid synchronization is necessary. The optimal level of beta ERD/S is not fully constant; it is task dependent. Moreover, the fine cross-frequency and phase-amplitude coupling relationships on local, subcortico-cortical, or cortico-cortical levels can be modified by DBS, resulting in diminished flexibility during cognitive and complex motor cognitive performance. To focus exclusively on beta suppression is helpful, but closed-loop neurostimulation based on the analysis of broader frequency bands and possibly also more flexible interfaces could increase effectivity and decrease the adverse effects of DBS.

These DBS related phenomena have yet to be fully clarified as the cognitive impairment and non-motor neuropsychiatric side effects of DBS therapy are poorly understood. Detailed knowledge of cross-frequency interactions in large-scale networks under different conditions could be helpful for further progress in aDBS in making the brain-computer interface more flexible. New potential structural targets and parameter settings could be defined.

The individual oscillatory reactivity related to DBS represents another interesting issue. It has been shown that there is variability in oscillatory reactivity to DBS even in such well-known responses as beta hypersynchrony reduction, which was absent in some patients (Giannicola et al., 2010). Frequency peaks in the STN vary among subjects. Different frequency reactivity in motor and cognitive tasks could underlie diverse effects of DBS and the occurrence of neuropsychiatric side effects. In some predisposed patients, DBS could influence both the beta band and the alpha range, resulting in cognitive dysfunctions. Biomarkers for identifying these subjects remain to be elucidated. Short-term DBS at individualized gamma frequencies did not differ from commonly used high-frequency stimulation in a clinical evaluation using UPDRS. Surprisingly, beta peak DBS did not lead to worsening of the clinical state (Tsang et al., 2012). Individualized stimulation frequencies should be also tested in long-term studies.

Closed-loop cortical stimulation of the motor cortex via epidurally implanted electrodes is another possible development direction in neuromodulatory therapy in PD. This line of research may help to provide next generation of neurostimulators using computational models of brain activity (Beuter et al., 2014). Mapping PD-related electrophysiological phenomena on the cortical level might also help to introduce non-invasive cortical stimulation techniques (rTMS, tCDS, etc.) into clinical practice.

High-density EEG (HD-EEG) and HD-EEG combined with direct local field recordings can reveal large-scale cortical and cortico-subcortical networks involved in PD pathophysiology, including non-motor circuits and the influence of DBS treatment. Advanced analytical technologies and high-performance computing methods, such as source reconstruction analysis and graph theory could help to define biomarkers indicating various disturbances in PD. Modelling of a system network is often a simplification, but it makes it possible to describe global organization and interactions between brain areas and helps to capture processes happening in the whole brain. For this reason, the network analysis approach could provide additional information to the local field and interregional coupling studies.

Parkinsonian state marker was described recently as an increased phase-amplitude coupling between the beta and gamma frequencies over the sensorimotor cortex using scalp EEG (Swann et al., 2015). This finding has the potential to help in differential diagnoses. Studies using novel computational electrophysiological methodologies should be more focused on cognitive and behavioural symptoms in PD itself and in DBS-related disturbances. It has been shown that EEG abnormalities can discriminate between dementia with Lewy bodies (DLB), Alzheimer's disease (AD), and PDD in the early stages of dementia (Bonanni et al., 2008). Quantitative EEG was recently introduced in the guidelines as a supportive biomarker for diagnosing DLB (Ferreira et al., 2016). As EEG is an easily accessible method, its use as a predictor of cognitive decline and possibly other types of non-motor dysfunction in PD might help to individualize the decision of whether DBS or another therapy for advanced PD (intestinal levodopa, apomorphine pumps) is indicated. Longitudinal EEG studies in DBS patients

could reveal biomarkers related to the adverse effects of DBS and in consequence could help to identify subjects at increased risk.

Concerning data acquisition during the DBS ON state, the possibility of synchronizing the clock with the DBS stimulator would be very beneficial. It could make it possible to sample the DBS artefacts (contained in the data during the DBS ON state) very precisely in the same phase in each repetition. In combination with a very high sampling frequency and proper artefact suppression techniques (Erez et al., 2010), it could reduce artefact residues to a minimum and enable the analysis of data in frequencies higher than high gamma (Özkurt et al., 2011). The combination of EEG with other brain mapping methods has been largely unexplored. For example, it was demonstrated recently that combined EEG and MRI indices could assist in the differential diagnosis of AD and DLB (Colloby et al., 2016).

It is evident that the potential of the electrophysiological recording techniques is large and many questions still remain.

5. Conclusions:

The main EEG correlates of PD are:

1. General slowing of scalp EEG-detected resting state background activity (increase in theta and low alpha power, loss of beta and gamma power); this is further increased in PDD.
2. In the BG, an excessive synchronization of 13–35 Hz activity is associated with motor impairment. It is suppressed by dopaminergic medication as well as by high-frequency stimulation of the STN. Non-motor symptoms are related mainly to changes in the alpha frequency range.
3. A characteristic sign in dopamine-depleted motor circuitries in PD is an abnormal cortico-subcortical coupling at beta frequencies (13–30 Hz). Coherence at 11 to 30 Hz between the STN, GPi, and SMA has a strong antikinetic nature. Synchronous oscillations in frequencies over 60 Hz within these structures have been found after levodopa intake and are considered to be prokinetic.
4. Cortico-cortical beta band coupling is related to the severity of parkinsonism, mainly bradykinesia, and is reduced with both levodopa and STN stimulation. STN-DBS facilitates movement-related beta desynchronization. Moreover, movement-induced gamma band coupling from the PFC to the SMA is absent in PD and reinstated after levodopa. Tremor and ICDs are associated with increased coupling in the theta band, cognitive disturbances are associated with increased interhemispheric functional connectivity in the alpha band. The clinical improvement after STN-DBS can be predicted by interhemispheric cortico-cortical decoupling in the beta band.
5. EEG parameters can be useful in defining the risk of dementia in PD. Both a lower-than-median background rhythm frequency and a higher-than-median EEG power in the theta band are associated with a higher risk of dementia in this population. Changes in P3 response and increased functional connectivity in the alpha band are described in relation to PDD.
6. Improved knowledge of cortical large-scale networks involved in PD dysfunctions and DBS therapy could help to individualize the choice of therapy in advanced PD and introduce new neurostimulation techniques. Graph theory has potential to be helpful in evaluating the dynamic consequences in large cortical networks.
7. Future research focused on DBS-related electrophysiological correlates of neuropsychiatric and cognitive side effects could be helpful for clinical practice in defining some biomarkers of DBS-related cognitive decline. Individual frequency reactivity among patients could be one of the clues.
8. Functional coupling in the cognitive networks between the STN and temporo-parietal associative areas is mediated via the alpha band. Alpha reactivity plays a major role in cognitive and non-motor dysfunctions in PD. Beta coupling related to motor activity is also modulated by cognitive factors. These interactions are probably influenced by STN-DBS in some subjects, resulting in neuropsychiatric and cognitive side effects. This remains to be elucidated in future research studies.

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Conflict of Interest

There is no conflict of interest.

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6.4. Příloha 4 - Oscillatory reactivity to effortful cognitive processing in the subthalamic nucleus and internal pallidum: a depth electrode EEG study

Bočková M, Chládek J, Jurák P, Halámek J, Rapcsak SZ, Baláž M, Chrastina J, Rektor I. Oscillatory reactivity to effortful cognitive processing in the subthalamic nucleus and internal pallidum: a depth electrode EEG study. J Neural Transm. 2017;124(7):841-852.

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Hluboká mozková stimulace je moderní a účinná chirurgická léčba pozdních hybných příznaků u Parkinsonovy nemoci. Nicméně krom vlivu na motorické okruhy a funkce může ovlivňovat i celou řadu dalších struktur a způsobovat různé nežádoucí účinky např. neuropsychiatrické komplikace. Cílem této práce proto bylo zjistit, jakým způsobem se v STN a GPi, což jsou hlavní stimulační cíle v případě Parkinsonovy nemoci, projevují kognitivní funkce v průběhu kognitivně motorické úlohy. Jedná se o intracerebrální studii, kdy v těsném pooperačním bylo snímáno EEG přímo z externalizovaných DBS elektrod v průběhu provádění experimentálního paradigmatu, který se skládal ze dvou úloh s odlišnou kognitivní zátěží: 1) opisování písmen a 2) psaní jiných písmen. Úkol 2 je po kognitivní stránce komplikovanější a vyžaduje vyšší zapojení exekutivních funkcí (především plánování a inhibici automatických odpovědí). Zvýšená kognitivní zátěž se projevila zvýšenou desynchronizací v beta pásmu, tj. výraznějším poklesem výkonu v tomto pásmu, s lateralizací na levou stranu v obou strukturách, především ale v GPi. Změny v ostatních frekvenčních pásmech nebyly tak konzistentní. Nicméně v oblasti STN byl v souvislosti s úkolem 2 pozorován i nárůst synchronizace, tj. zvýšení výkonu, i v oblasti gamma frekvenčního pásma. Beta aktivita se zdá být rozhodující v souvislosti s kognitivně motorickými procesy. Rozdíly v oscilační aktivitě mezi oběma strukturami jsou pravděpodobně dány jejich odlišnou funkční konektivitou a mohou být podkladem rozdílu ve výskytu kognitivních nežádoucích účinků při DBS, které jsou méně časté v případě GPi.

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Oscillatory reactivity to effortful cognitive processing in the subthalamic nucleus and internal pallidum: a depth electrode EEG study

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Abstract This study investigates how complex motor-cognitive activities are processed in the subthalamic nucleus (STN) and internal globus pallidum (GPi), as adverse neuropsychiatric effects may accompany deep brain stimulation (DBS), mainly in Parkinson's disease (PD) and STN-DBS. Dystonia patients with GPi-DBS electrodes ($n = 5$) and PD subjects ($n = 5$) with STN-DBS electrodes performed two tasks: (1) copying letters; and (2) writing any letter other than that appearing on the monitor. The cognitive load of the second task was greater than that of the first. Intracranial local field potentials (LFPs) were analysed. A beta power decrease was the main correlate of the enhanced cognitive load during the second task in both structures, with a lateralization to the left side, mainly in the GPi. A gamma power increase linked with the increased cognitive activity was observed only in the STN. Differences were also observed in the theta and alpha bandpasses. Beta ERD reactivity seems to be essential during the processing of complex motor-cognitive tasks, increases with enhanced cognitive effort, and was observed in both the STN and GPi. Oscillatory reactivity to effortful cognitive processing in other frequency bands was less consistent, with differences between the studied nuclei. Lateralization of activity related to cognitive factors was observed mainly in the GPi.

Keywords Subthalamic nucleus · Internal globus pallidum · Complex cognitive functions · Lateralization · Deep brain stimulation · ERD/S

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Introduction

The subthalamic nucleus (STN) and internal globus pallidum (GPi) are common targets for deep brain stimulation (DBS) which is an effective long-term treatment for neurological patients with a variety of movement disorders. For some patients, the generally successful DBS may be accompanied by cognitive impairment and neuropsychiatric disorders, especially in the case of the STN in Parkinson's disease (PD) patients (Saint-Cyr et al. 2000; Temel et al. 2006; Voon et al. 2006; Witt et al. 2008). GPi is used as DBS target in dystonia patients (Jankovic 2006; Kupsch et al. 2006; Vidailhet et al. 2013). In PD patients, similar motor improvements were observed with both STN and GPi DBS. There are some studies suggesting fewer adverse cognitive, behavioural, or neuropsychiatric events in GPi-DBS than in STN-DBS (Anderson et al. 2005; Videnovic and Metman 2008; Follett et al. 2010; Rouaud et al. 2010; Fasano and Deuschl 2012; Emre et al. 2014). A long-term multicentre study on bilateral STN and GPi-DBS reported the occurrence of cognitive decline in 23% of the STN patients and in 12% of the GPi patients 5–6 years after surgery (Moro et al. 2010). By contrast, other studies

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have not observed a significant difference in mood or cognition (Okun et al. 2009) except for depression that was significantly less frequent in patients with GPi DBS (Sako et al. 2014).

Intracranial recordings via DBS electrodes provide direct access to the deep brain nuclei and local field potentials (LFPs) analysis has contributed significantly to knowledge about the physiology of the basal ganglia and the pathophysiological changes associated with movement disorders, in particular PD. Synchronized oscillations in the beta and gamma frequencies have a key role in motor control in cortico-basal ganglia loops (Brown 2006). STN LFP activity in the beta bandpass is suppressed before self-paced voluntary movement as well as before cued movements (Williams et al. 2003; Alegre et al. 2005; Androulidakis et al. 2008; Oswal et al. 2012, 2013). Changes in beta activity are not linked only to the movement, but they are modulated by contextual factors like reward or cognitive complexity (Oswal et al. 2013). Synchronized low-frequency oscillations (5–13 Hz) in Parkinson's disease increase after dopaminergic medication both in the STN and the GPi and are related to PD dyskinesias as well as to dystonic movements (Silberstein et al. 2003; Priori et al. 2004; Foffani et al. 2005; Marceglia et al. 2007; Barow et al. 2014). Their possible role in non-motor functions has been also documented (Fumagalli et al. 2011; Rosa et al. 2013).

The aim of our work was to study processing of cognitive activity in the basal ganglia and to compare neurophysiological changes during complex motor-cognitive processing in the STN and GPi.

Methods and materials

Subjects

Five dystonia patients implanted with GPi electrodes and five PD patients with STN targets participated in the study (see Table 1). UPDRS (Unified Parkinson's Disease Rating Scale) and dystonia rating scales (Comella et al. 2003) were used for the evaluation of the current clinical condition. The recordings were performed in the postoperative period before the stimulator implantation and the system internalisation. All patients were considered appropriate candidates for DBS by the Commission for Neuromodulation Surgery in Brno. All subjects were informed about the nature of this study and gave their informed consent. The study received the approval of the local ethics committee. Before the operation, all subjects underwent a detailed neuropsychological examination that revealed no evidence of dementia.

Surgical procedure

The stereotaxic frame used during the surgical procedure (electrode implantation) was the Leibinger open frame with the Praezis Plus software and the Talairach diagram. The STN coordinates used were in respect to the AC-PC (anterior commissure–posterior commissure) line: 12.0 mm laterally, 5.0 mm below, and 3.0 mm behind the midpoint of the AC-PC line. The GPi coordinates were: 20.0 mm laterally, 4.0 mm below, and 3.0 mm in front of the midpoint of the AC-PC line. The stimulation electrodes (Medtronic, Inc.) were implanted bilaterally into the targeted structure by stereotaxic MRI-guided technique under local anaesthesia (general anaesthesia in the GPi cases because of dystonia). The definitive electrode placement was confirmed by four microelectrode recordings. The motor part of the STN was identified by recording the specific patterns of neuronal activity and background activity, and by following motor responsiveness to intraoperative stimulation. Once the final target coordinates were determined, a permanent quadripolar DBS electrode (model 3389, with 1.5 mm contact length and 0.5 mm intercontact distance) was implanted. The electrode position was verified by the intraoperative use of fluoroscopy comparing the position of the microrecording electrodes trajectories with the definitive quadripolar macroelectrode trajectory. After surgery completion, CT scans under stereotactic conditions covering the entire length of the implanted electrodes were added. The series of images were reimported to the planning workstation and subsequently the coordinates were correlated with the real position of implanted electrodes. The change of electrode position is evident in the planning datasets so that the final electrode position can be evaluated without being burdened by artefacts caused by electrode material both in CT and MRI scans. Exact final electrode positions for each subject are presented in Fig. 1. In the immediate post-implantation period, the electrodes remained externalized. A special externalized cable enabled the intracranial EEG recording. The internalisation and the stimulator implantation were performed within a week after the positioning of the DBS electrodes.

Experimental protocol and recordings

We used a visuomotor paradigm that we had employed in a previous study that investigated the neurophysiological correlates of increased task complexity and cognitive load on cortical structures and anterior nucleus of the thalamus in epilepsy surgery patients (Bočková et al. 2007, 2015). The visual stimuli were the letters of the alphabet presented in a random order on a monitor; there were 50 visual

Table 1 Patient characteristics

Subject	Sex	Age	Diagnosis, clinical state	Target	Medication	HD
1	M	26	MD, right side torticollis + other symptoms, BFMDRS 48	GPi	Clo, Tia	Right
2	M	69	OFD, BFMDRS 20	GPi	Clo	Right
3	M	65	GD, left side torticollis + other symptoms, BFMDRS 40	GPi	Tez	Right
4	F	42	CD, right side torticollis, BFMDRS 8	GPi	None	Right
5	M	68	CD, left side torticollis, BFMDRS 8	GPi	None	Right
6	M	69	PD, UPDRS 36	STN	Rop, L-dopa, Ent	Right
7	M	46	PD, UPDRS 44	STN	Rop, L-dopa, Tol	Right
8	F	51	PD, UPDRS 30	STN	L-Dopa	Right
9	M	65	PD, UPDRS 49	STN	Rop, L-dopa, Ent	Right
10	F	63	PD, UPDRS 15	STN	Rop, L-dopa, Ama	Right

HD hand dominance, *PD* Parkinson's disease, *GD* generalized dystonia, *MD* multifocal dystonia, *OFD* orofacial dystonia, *CD* cervical dystonia, *ET* essential tremor, *STN* subthalamic nucleus, *GPi* globus pallidus internus, *BFMDRS* Burke–Fahn–Marsden dystonia rating scale, *UPDRS* Unified Parkinson's disease rating scale, *Clo* clonazepam, *Tia* tiapride, *Tez* tetrazepam, *Rop* ropinirole, *Ent* entacapone, *Tol* tolcapone, *Ama* amantadine

stimuli. Subjects performed two different visuomotor cognitive tasks. The first task was a simple cognitive task (Task 1)—copying letters from the monitor. The second task was a more complex cognitive task (Task 2)—writing a letter other than that which appeared on the monitor. The patients were instructed to write any letter other than the one on the monitor but not a letter that would immediately precede or follow that letter alphabetically. Patients received clear instructions and practised the task briefly before the recordings. They were asked to react immediately to the letter displayed on the monitor rather than engage in prolonged preparation and response planning.

The duration of the stimulus exposure was 200 ms; the interstimulus interval was 16 s.

Subjects reclined comfortably in the monitoring bed, in a quiet room, with a constant temperature. They were instructed to remain calm to keep their eyes fixed on the monitor, and to avoid unnecessary movements. The monitor was situated in the same place for all the subjects, 1.5 m in front of their eyes, at the end of the monitoring bed. Subjects wrote letters using an electrically connected pen. The paper the subjects wrote on was placed on a desk situated near their lower abdomen. The testing was visually supervised by the examiners and was also videotaped.

The intracerebral EEG signal was recorded by the EEG system TruScan 32 channel (Deymed Diagnostic, Alien Technic) and in subjects 4, 5 and 10 using the M&I EEG system because of EEG unit renovation. The recordings were monopolar, with a linked earlobe reference. The sampling rate was 1024 Hz with standard anti-aliasing filters before digitalization. In the trigger channel, the stimuli and motor reactions (pen-to-paper contact) were recorded, so that response onset time (RT) and duration of motor response could be monitored.

Data analysis

The data were processed and analysed off-line using ScopeWin and ScopeMat software. The data were segmented according to the stimulation trigger onset as we were mainly interested in the cognitive aspects of the task performance. The segments were visually inspected, and segments containing artificial signals or incorrect responses were removed. Between 20 and 50 segments were used for the final analysis. In each segment, the linear trend was eliminated. Bipolar montage evaluation was used to exclude the volume conduction from other structures, namely from the cortex or transsynaptic propagation along cortical-subcortical pathways (Wennberg and Lozano 2003, 2006) and confirm the local origin of the potentials. The bipolar power envelopes from two neighbouring contacts (contacts are presented in Fig. 1 for each subject) located within the targeted structure with eliminated phase-lock signals (subtraction of averaged trial) were computed in the determined frequency windows: theta 3–7 Hz, alpha 7–13 Hz, beta 13–35 Hz, and gamma (lower 35–80 Hz), using the Hilbert transform demodulation. The power envelopes were then averaged in single subject and in the GPi and STN subgroups of subjects to obtain grand averages (GA, see Figs. 3, 4). The statistical significance of ERS (event-related synchronization, power increase)/ERD (event-related desynchronization, power decrease) was analysed from the differences over trials between the mean power at baseline (1.6–0.1 s before stimuli) and the mean power in the 500 ms lasting segments. First segment starts at the 0 ms (stimuli position), second at 500 ms and last segment at 9500 ms position in trial. We used the non-parametric Wilcoxon rank sum (signed-rank) test for paired samples in each trial (Purcell et al. 2013) corrected for

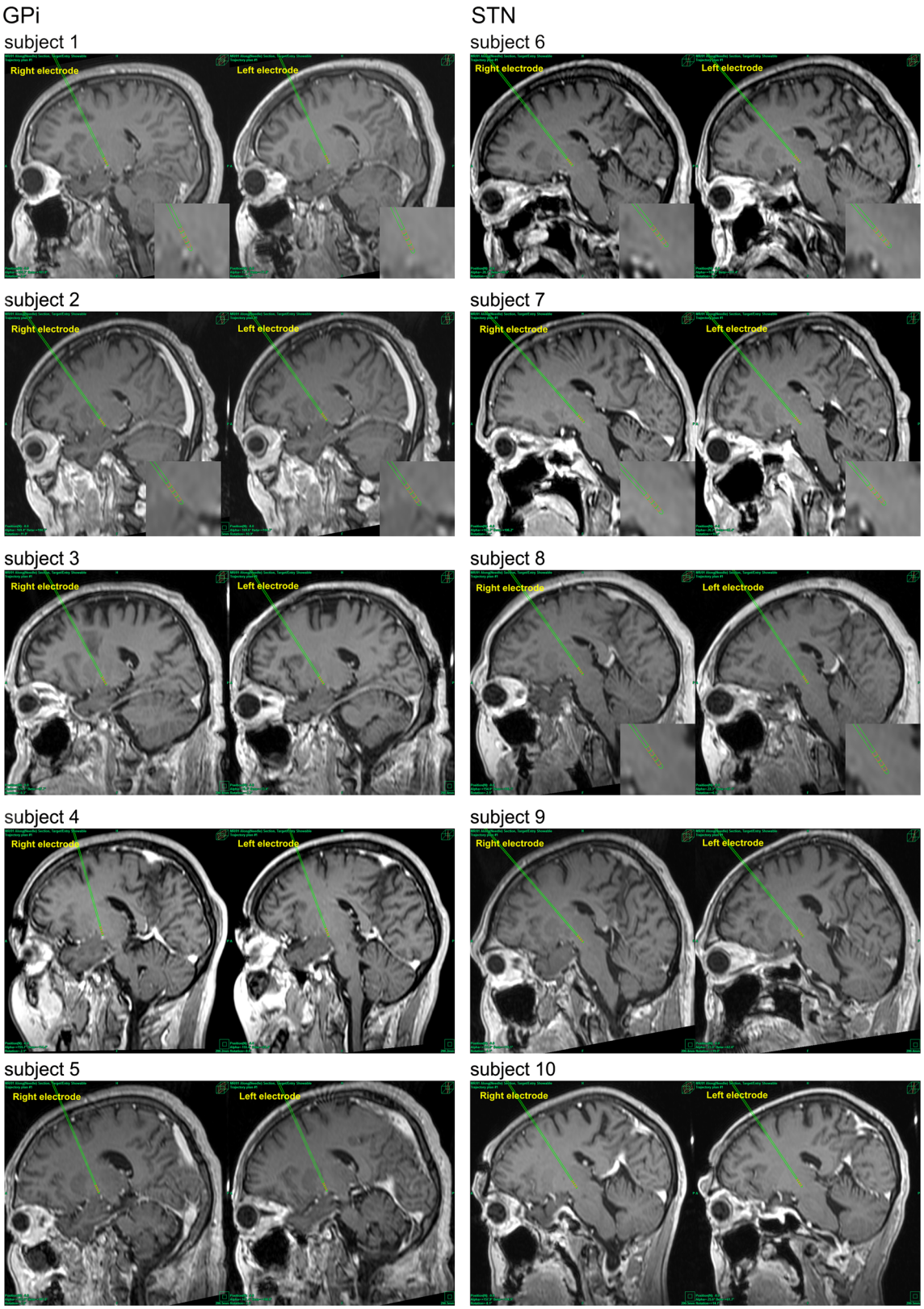

Fig. 1 Electrodes and contacts positions. *Left column* GPi, subject 1–5, *right column* STN, subject 6–10

Contact pairs used for the GA analysis:

	Subject	LEFT	RIGHT
GPI	1	L1-L2,L2-L3	R1-R2,R2-R3
	2	L1-L2,L2-L3	R1-R2,R2-R3
	3	L2-L3,L1-L3	R2-R3, R3-R4
	4	L1-L2,L2-L3	R1-R2,R2-R3
	5	L1-L2,L2-L3	R1-R2,R2-R3
STN	6	L1-L2,L2-L3	R1-R2,R2-R3
	7	L2-L3,L1-L3	R1-R3
	8	L1-L2,L2-L3	R1-R2,R2-R3
	9	L1-L2,L2-L3	R1-R2,R2-R3
	10	L1-L2,L2-L3	R1-R2,R2-R3

Fig. 1 continued

multiple comparisons across 20 moving segments. The differences between Task 1 and Task 2 were analysed with an unpaired *t* test; they are presented in Figs. 3, 4, and 6 (Kiebel et al. 2005) (see Fig. 2). Reaction times (RT) and motor response durations (defined from first pen touch to last pen liftoff) were also computed and correlated to the EEG changes; see Table 2, Figs. 5 and 6.

Results

We analysed oscillatory changes within the 3–80 Hz frequency ranges in five subjects with GPi electrodes and five subjects with STN electrodes. Figures 3 and 4 show GPi and STN grand averages in theta, alpha, beta, and gamma frequency ranges. In the theta bandpass, there were no significant differences between Task 1 and Task 2 observed in the two structures, except of higher activation (theta ERS) in Task 2 in the left STN. Alpha power ERD was observed on a comparable level in the STN during both tasks, in the GPi, a power decrease in the alpha frequency range was related only to Task 2. The most prominent oscillatory pattern related to the higher cognitive load was beta ERD in both structures. Beta ERD was higher and longer on both sides in the GPi. In the STN, the beta ERD was higher during Task 1 early after the stimulation, but lasted significantly longer during Task 2. Stronger gamma power ERS was found in the STN during Task 2; the opposite situation was found in the GPi. The increased beta ERD represents a pattern modification related to the increased cognitive complexity during Task 2, consistent with our previous recording studies from other brain structures (Bočková et al. 2007, 2015) and also described in a recent intracranial recording study in the subthalamic nucleus (Oswal et al. 2013).

Reaction times (RT) and motor response durations in each subject were computed and related to the beta ERD occurrence; see Table 2, Figs. 5 and 6 upper panel. Reaction times were markedly longer in Task 2 in all participants. This was not the case for the motor response duration, which was sometimes longer during Task 1 and sometimes during Task 2. The Task 2 related beta ERD was significantly longer in almost all cases. This prolonged activation was therefore not related to the longer motor performance, but to the cognitive processes. Figure 6 shows the differences between the two tasks in all subjects and grand averages. The differences between the tasks are presented in theta, alpha, beta, and gamma frequency ranges. There was a lateralization to the left side, mainly in the GPi in the beta frequency range, which was linked in this case with the enhanced cognitive load during Task 2.

Analysis with data segmented to the reaction onset (pen-to-paper contact)—see Figs. 7 and 8 was also performed to differentiate changes related only to movement performance from changes related to cognitive activity. The movement related activity starts immediately before and continue during motor reaction. Mean reaction time was significantly shorter than beta ERD duration—Table 2. Consequently, the higher beta power decrease can be observed not only immediately before the motor reaction onset, but significantly longer, i.e. 3–2 s before movement onset. This activity is therefore linked to increased cognitive load in Task 2 and demonstrates a true cognitive difference between Task 1 and Task 2.

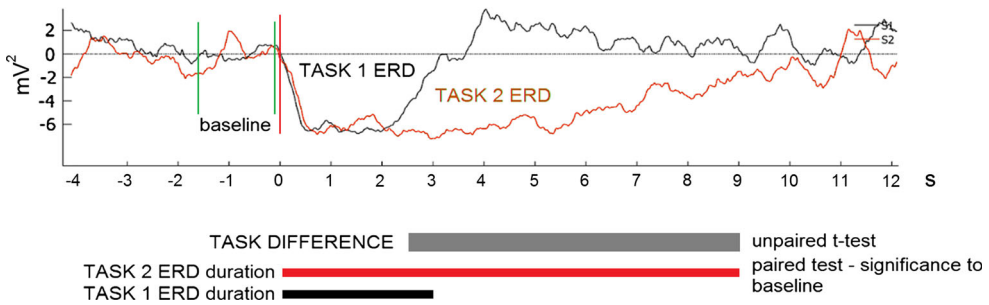

Fig. 2 Example of beta ERD durations in one STN subject. *Black curve* Task 1, *red curve* Task 2. *Red and black horizontal bars* the ERS/ERD duration—statistical significance of differences between the mean power at the baseline region and the mean power in the window moving over the segment. *Thick grey horizontal line* the significant difference between Task 1 and Task 2

Table 2 Reaction times (RT), motor responses and beta ERD durations

Subj. no.	Mean reaction time (ms)		BetaERD duration left side (ms)		betaERD duration right side (ms)		Mean duration of motor response (ms)		
	Task 1	Task 2	Left Task 1	Left Task 2	Right Task 1	Right Task 2	Task 1	Task 2	
1	1884	3426	4500	6000	4500	7000	1899	1617	GPI
2	2032	5517		5500			2483	1998	
3	2930	3822		5500		9000	3708	2647	
4	2351	3504	3500	5000	4000	5500	1547	1109	
5	1634	2438		7500	8000	7500	3075	4166	
6	1763	5436	4000	9500		8500	2497	3533	STN
7	2492	4773		5500			681	1118	
8 off state	2742	3827	5500	6500	4000	5500	1089	1958	
8 on state	2440	3968	3500	7500	6000		1081	1759	
9 off state	2178	2684	3500	5500			1001	1384	
9 on state	2262	3206					1507	666	
10 off state	1715	2701	3000	7000	3650	7000	1055	3927	
10 on state	1552	2700	6000	7500	6750	8000	2979	2890	

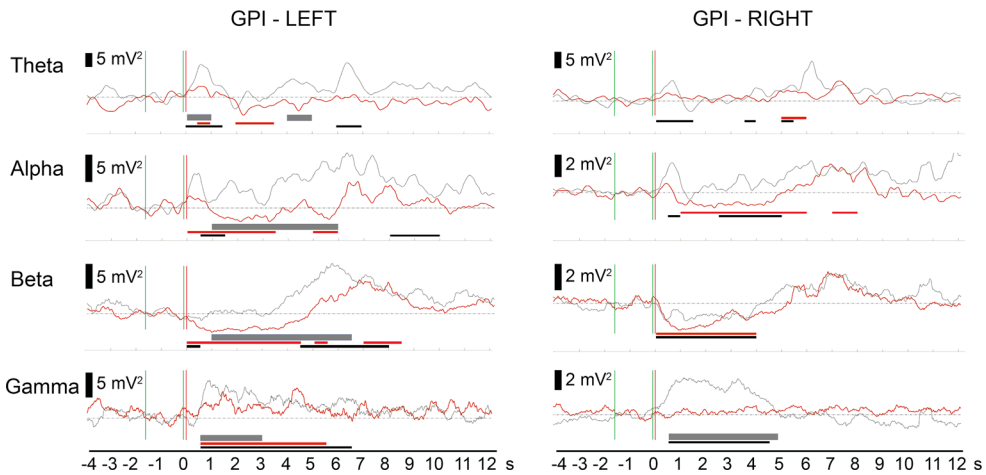

Fig. 3 Grand averages in GPi. *Black curve* Task 1, *red curve* Task 2. *Thin black horizontal line* statistical significance of the ERS/ERD, Task 1. *Thin red horizontal line* statistical significance of the ERS/ERD, Task 2. *Thick grey horizontal line* significant differences between Task 1 and Task 2

In three of our PD patients, the recordings were performed in off as well as in on states. After levodopa intake, the beta power was slightly higher and prolongated, but without a statistical significance.

Discussion

In this study, we examined non-phase-locked event-related changes in oscillatory activities during a visuomotor task with two different levels of complexity. The power of oscillations may decrease (desynchronize) or increase (synchronize) during cognitive task performance. The main advantage of the event-related desynchronization/synchronization (ERD/S) methodology is the ability to distinguish between cortical inhibition and activation. We analysed power changes in the 2–80 Hz frequency range, i.e. within the theta, alpha, beta and gamma frequencies. The ERD of the alpha and beta rhythms has been interpreted as a correlate of activation, i.e. increased excitability of the cortex. The ERS in the alpha and lower beta bands has been interpreted as a correlate of a deactivation, i.e. cortical idling or active inhibition (Pfurtscheller 2001). Gamma band ERS is considered to be an elementary signal change with multiple functional correlates related to the information spread across brain networks (Basar-Eroglu et al.

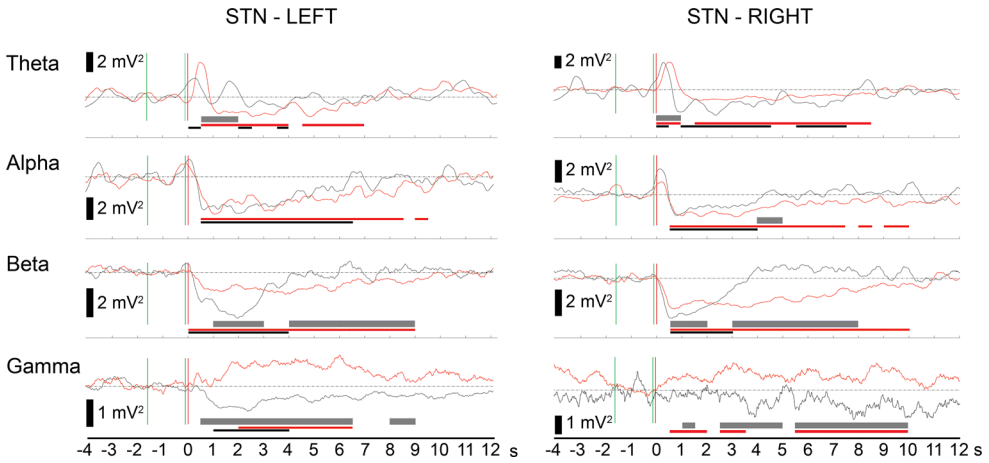

Fig. 4 Grand averages in STN. *Black curve* Task 1, *red curve* Task 2. *Thin black horizontal line* statistical significance of the ERS/ERD, Task 1. *Thin red horizontal line* statistical significance of the ERS/ERD, Task 2. *Thick grey horizontal line* significant differences between Task 1 and Task 2

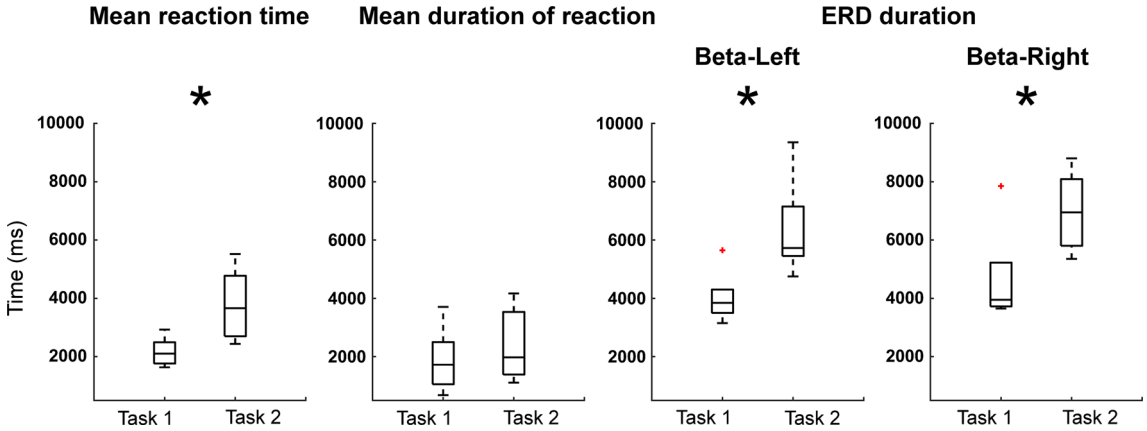

Fig. 5 Reaction times, motor responses, and beta ERD correlation. Boxplots of reaction times in ms from the left to the right: Mean reaction time, mean duration of reaction, duration of ERD for beta band power individually for left and right side. Significant difference (Wilcoxon, $p \leq 0.05$) between Task 1 and Task 2 are marked by an *asterisk*

1996; Schürmann et al. 1997; Crone et al. 1998; De Pascalis and Ray 1998; Pfurtscheller et al. 2003; Szurhaj et al. 2005; Ihara and Kakigi 2006).

We evaluated the human event-related EEG signal recorded via intracerebral depth electrodes.

Each electrode contained four 1.5 mm contacts with 0.5 mm intercontact distance. According to the postoperative CT scans and preoperative MRI scans fusion in the planning workstation, the real contacts positions were displayed. Contact pairs located directly in the targeted structures and the bipolar montages from these were used for the grand average analysis.

Our experimental protocol contained two tasks involving writing of single letters. The first task consisted of copying a letter from the screen; the second task required writing a different letter than that appearing on the screen. These two tasks are characterized by several shared cognitive components related to the writing of single letters. Specifically, the two tasks had in common the visual detection and reading of the letter on the screen and the preparation and execution of the writing movements. We supposed that attention and working memory were engaged to a comparable level in both experimental tasks, as the stimuli were the same in both conditions and the letters of the alphabet had to be maintained in working memory before and during motor execution. However, the second task was more complex and involved a higher cognitive load attributable to the additional requirement to perform several mental operations that are covered by the common term of executive function: the inhibition of an automatic (habitual) response (i.e. simply copying the letter shown on the screen) and the selection, planning, and execution of the alternative non-routine motor response based on a strategic memory search to retrieve a letter different from the one presented (Bočková et al. 2007). We therefore assumed that the most prominent difference between the

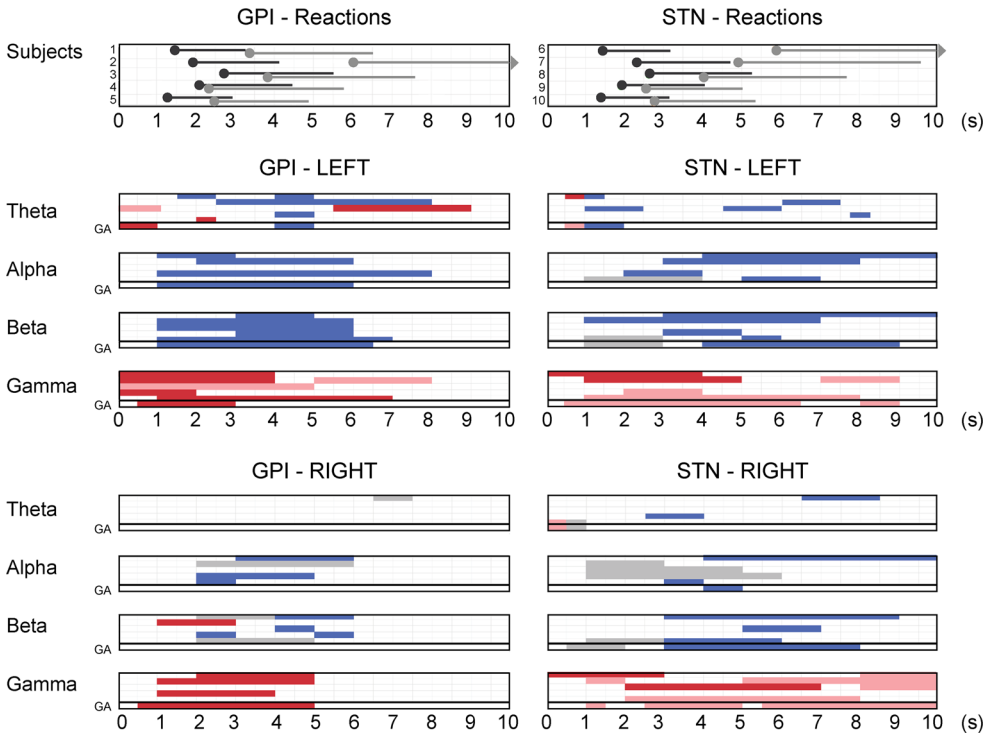

Fig. 6 Task differences. The table introduces the temporal distribution of differences between tasks in GPi (*left panel*) and STN (*right panel*), and theta, alpha, beta, and gamma ranges in the 10-s interval after stimulation. *Upper panel* shows mean reaction time (*point*) and mean reaction duration (*horizontal bar*) for each of five GPI and five STN subjects. *Black colour* represents Task 1 and grey represents Task 2. *Middle* and *bottom panels* show Task 1 and Task 2 differences. Each *horizontal bar* represents a significant task difference in one subject. Grand averages (GA) are shown below each 5-patient block. *Blue, grey, dark red,* and *light red horizontal bars* represent durations of significant differences between Task 1 and Task 2: *blue* higher ERD during Task 2, *grey* higher ERD during Task 1, *dark red* higher ERS during Task 1, *light red* higher ERS during Task 2

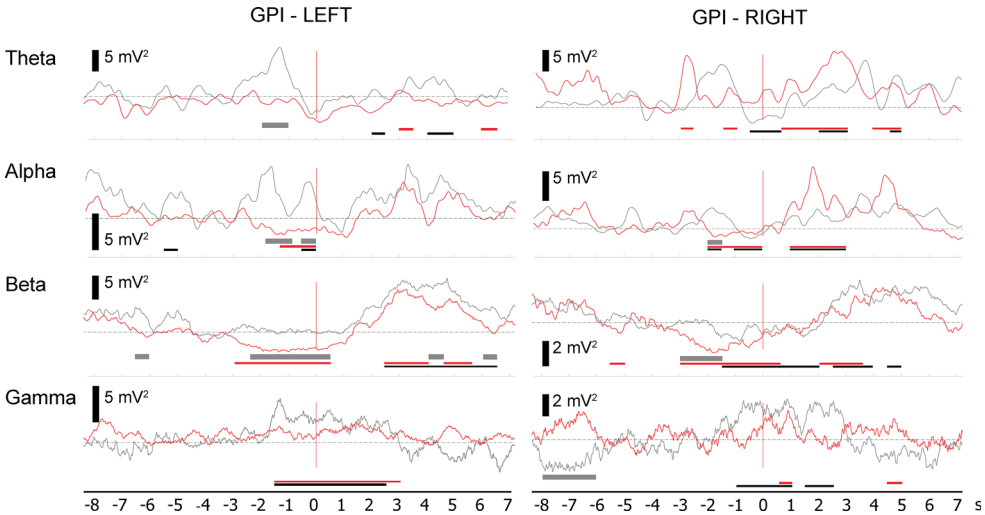

Fig. 7 Grand averages in GPi, movement onset cued analysis. *Black curve* Task 1, *red curve* Task 2. *Thin black horizontal line* statistical significance of the ERS/ERD, Task 1, *thin red horizontal line* statistical significance of the ERS/ERD, Task 2. *Thick grey horizontal line* significant differences between Task 1 and Task 2

two writing tasks is the higher cognitive effort and executive demand associated with the second task condition. The same experimental protocol was tested in studies with intracerebral recordings from the frontal, parietal and temporal cortices as well as from the anterior nucleus of the thalamus in patients with epilepsy. Consistent with the results reported here, the complex task elicited larger alpha and beta ERD than the simple task in several brain areas (Bočková et al. 2007, 2015).

Cognitive processes like decision making were reported to be linked with low-frequency (5–12 Hz) ERS in the STN (Marceglia et al. 2011). In this study, we did not observe

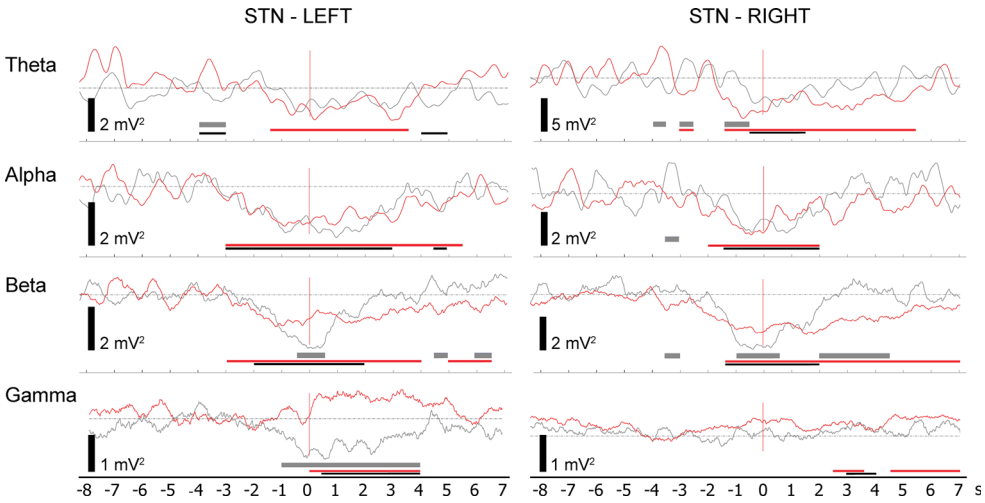

Fig. 8 Grand averages in STN, movement onset cued analysis. *Black curve* Task 1, *red curve* Task 2. *Thin black horizontal line* statistical significance of the ERS/ERD, Task 1. *Thin red horizontal line* statistical significance of the ERS/ERD, Task 2. *Thick grey horizontal line* significant differences between Task 1 and Task 2

any important changes within the low frequencies, except of higher theta ERS (which is known to be a correlate of activation) in Task 2 in the left STN. Activations in the alpha range (ERD) were present only during Task 2 in the GPi bilaterally. In contrast, there were similar activations during both tasks in the STN in the alpha frequency range. Higher gamma ERS was observed only in the STN bilaterally during Task 2. The increased cognitive demand produced mainly enhanced or prolonged local beta desynchronization in both structures; a lateralization to the left language-dominant hemisphere was observed mainly in the GPI; see Fig. 5.

Similar to the findings presented here are the results reported in another study from the STN. Perimovement activity was modified by cognitive factors; the beta power decreased while gamma power increased reciprocally (Oswal et al. 2013). The cognitive-motor integration required for successful execution of complex action sequences is mediated by basal ganglia-thalamocortical neural circuitry. In particular, the beta ERD appears to be a ubiquitous pattern reflecting complex cognitive activation in the brain. Consistent with this notion, the same oscillatory patterns were observed in frontal and temporal cortical structures and the anterior nucleus of the thalamus during performance of the cognitive-motor task used in this study (Bočková et al. 2007, 2015).

Differences between the STN and GPi, mainly the stronger lateralization in the GPi, and differences in the theta, alpha, and gamma oscillatory responses could be explained by different functional and anatomical connectivity of both structures (Manes et al. 2014). The STN is a basal ganglia input nucleus; the GPi is a major output nucleus of the BG-thalamocortical circuitry. The GPi, besides the excitatory inputs from the indirect pathway via the STN, receives inhibitory inputs from direct pathway striatal neurons, the thalamus, and brain stem nuclei (for review, see Nelson and Kreitzer 2014). The STN receives input in the circuitry from the indirect pathway as well as direct (hyperdirect) cortical input from the pericentral and prefrontal cortices (Haynes and Haber 2013). The cognitive role of the STN differs from the role of other structures within the BG circuitry; this difference is probably related to the function of the hyperdirect pathway. Based on direct depth electrode recordings, we suggested two ways that the STN may participate in cognitive activities. First, the STN is a relay nucleus that participates in processing cognitive and behavioural activities within the cortico-BG-thalamocortical loop. In addition to this known function, we suggested that the STN may (under the direct cortical control conveyed by the hyperdirect pathway) exert modulatory control over the output part of the cortico-BG-thalamocortical loop (Rektor et al. 2015). Difference in gamma reactivity between STN and GPi, i.e. higher gamma ERS linked with cognitive activity observed only in the STN might be related also to pedunculopontine nucleus (PPN) activity. This structure is connected with the STN and not with the GPI. PPN region has been studied as a novel target for DBS in PD. Improvement of levodopa-resistant motor symptoms like gait disorders, falls, freezing and postural imbalance was documented (Hamani et al. 2016; Mazzone et al. 2016; Fytagoridis et al. 2016). Individual PPN-DBS planning is required because of variability in the brainstem anatomy (Mazzone et al. 2013). The activation of PPN was linked with an increment in gamma band activity (Garcia-Rill 2015, Garcia-Rill et al. 2015, Urbano et al. 2016) and is proposed to participate in the process of preconscious awareness. Arousing stimuli simultaneously activate ascending projections of the PPN (Garcia-Rill et al. 2016).

Dopaminergic medication modifies the local field potentials in PD patients (Kühn et al. 2006; Androulidakis et al. 2007; Giannicola et al. 2010, 2013; Rodriguez-Oroz et al. 2011; Huebl et al. 2014). In three of our PD patients, we recorded the LFPs in both off and on states. Unfortunately, in the other two patients we could not record the on state because of time restrictions, and in one subject the

quality of recording was not optimal. In general, oscillatory activity in the 8–35 Hz range is known to be suppressed after levodopa intake (Kühn et al. 2006; Giannicola et al. 2010). In this study, the beta power ERD slightly increased and was prolongated after levodopa intake in both the tasks, but without a statistical significance. Unfortunately, we could analyse ON state medication condition only in two subjects. Therefore, more data are needed to confirm our observation.

The main limitation of this study is that we recorded data from the STN in PD and from GPi in patients with dystonia. Differences in medication and disease pathophysiology may influence oscillatory patterns. Unfortunately, we did not have a sufficient number of GPi PD patients, as the STN is used as the primary target of choice for PD treatment at our centre. However, the main physiological oscillatory pattern related to the increased cognitive load, beta ERD enhancement, was observed in both structures regardless of the clinical diagnosis and treatment. Mainly, theta ERS is linked to abnormal involuntary movements, so we assume that dystonia should not greatly influence the beta frequency reactivity.

Conclusion

Beta ERD reactivity seems to be essential in processing complex motor-cognitive tasks. Beta increase with enhanced cognitive effort was observed in both the STN and GPi. Oscillatory reactivity to effortful cognitive processing in other frequency bands was less consistent with differences between the studied nuclei. The lateralization of activity related to cognitive factors was observed primarily in the GPi. It may be hypothesized that the differences in oscillatory patterns related to complex cognitive tasks in the GPi and in the STN is related to different anatomical and functional connectivity.

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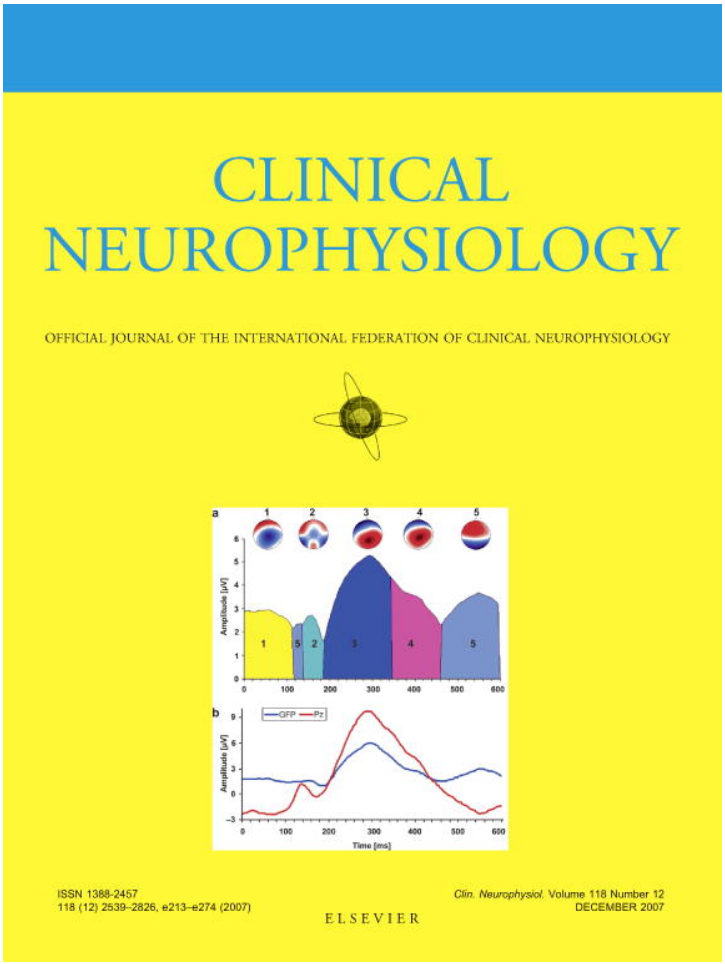
6.5. Příloha 5 - Executive functions processed in the frontal and lateral temporal cortices: intracerebral study

Bočková M, Chládek J, Jurák P, Halámek J, Rektor I. Executive functions processed in the frontal and lateral temporal cortices: intracerebral study. Clinical neurophysiology 2007;118:2625-2636

IF: 2,5

Cílem této práce bylo zkoumání oscilační aktivity v kortikálních neurokognitivních okruzích v souvislosti s exekutivními funkcemi. Jedná se o kortikální intracerebrální studii na souboru osmi epileptochirurgických pacientů, kterým byla snímána EEG aktivita přímo z hlubokých mozkových elektrod implantovaných v rámci epileptochirurgického programu. V průběhu snímání byl použit stejný experimentální protokol jako v případě práce popsané v příloze 4. Zvýšená exekutivní zátěž v průběhu druhého úkolu se projevila zvýšenou aktivací v podobě zvýrazněné desynchronizace v alfa a beta frekvenčních pásmech (což je považováno za korelát aktivace dané oblasti) především v oblastech prefrontálního a orbitofrontálního kortexu a překvapivě také v oblasti temporálního neokortexu. Temporální neokortex tak pravděpodobně společně s frontálními oblastmi tvoří kognitivní kortikální síť, která je zapojena do zpracovávání exekutivních úloh.



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Executive functions processed in the frontal and lateral temporal cortices: Intracerebral study

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Abstract

Objective: The study was designed to investigate the neurocognitive network in the frontal and lateral temporal cortices that is activated by the complex cognitive visuomotor tasks of letter writing.
Methods: Eight epilepsy surgery candidates with implanted intracerebral depth electrodes performed two tasks involving the writing of single letters. The first task consisted of copying letters. In the second task, the patients were requested to write any other letter. The cognitive load of the second task was increased mainly by larger involvement of the executive functions. The task-related ERD/ERS of the alpha, beta and gamma rhythms was studied.
Results: The alpha and beta ERD as the activational correlate of writing of single letters was found in the sensorimotor cortex, anterior cingulate, premotor, parietal cortices, SMA and the temporal pole. The alpha and beta ERD linked to the increased cognitive load was present moreover in the dorsolateral and ventrolateral prefrontal cortex, orbitofrontal cortex and surprisingly also the temporal neocortex. Gamma ERS was detected mostly in the left motor cortex.
Conclusions: Particularly the temporal neocortex was activated by the increased cognitive load.
Significance: The lateral temporal cortex together with frontal areas forms a cognitive network processing executive functions.

Keywords: SEEG; Executive functions; ERD/S; Temporal neocortex

1. Introduction

The aim of this study was to answer two main questions. First we were interested in which cortical areas are activated during the writing of single letters. In a previous fMRI study Rektor et al. (in press) confirmed that despite the fact that the writing of single letters is an overlearned, near-automatic activity, it activates widespread cerebral areas – bilateral premotor and inferior/superior parietal cortices, SMA and the thalamus with left predominance. The second question concerned which parts of the human brain will be additionally engaged during task performance with elevated cognitive load with the accent on the executive functions.

Cognitive models typically describe executive functions as higher-level processes that exert control over elementary mental operations. Willed and automatic actions are controlled at different levels depending on the degree of task difficulty and complexity (Norman and Shalice, 1986; Luu and Tucker, 2002). Neuroimaging studies have identified a number of cortical areas involved in the executive control of conscious actions. The areas most frequently implicated are the prefrontal and cingulate cortices (Badgaiyan, 2002), but there are a lot of studies which have documented the diversity of executive functions and related anatomy and pointed out that the executive processes involve links between different parts of the brain and are not exclusively associated with a frontal location (Godefroy, 2003; Andrés, 2003). In this study we particularly focused on the temporal neocortex.

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Event-related decreases and increases in the band power of intracerebrally recorded EEG (SEEG) rhythms were evaluated. A decrease in band power indicates induced (non-phase-locked, non-coherent) event-related desynchronization (ERD) and an increase in band power indicates event-related synchronization (ERS) (Pfurtscheller and Aranibar, 1977). Spatial mapping of ERD/ERS can be used to study the dynamics of cortical activation patterns (Pfurtscheller, 2001). We analysed power changes within the alpha, beta and gamma frequency. The ERD of the alpha and beta rhythms is interpreted as a correlate of an activated cortical area with increased excitability. The ERS in the alpha and lower beta bands can be interpreted as a correlate of a deactivated cortical area, i.e. cortical idling or active inhibition (Pfurtscheller, 2001). Post-movement beta ERS might reflect movement-related somatosensory processing (Cassim et al., 2001; Szurhaj et al., 2001). The lower (40–60 Hz) and higher (more than 60 Hz) gamma band ERS seems to be an elementary signal change with multiple functional correlates (Schürmann et al., 1997), and is related to the movement initiation and execution (Crone et al., 1998b; Pfurtscheller et al., 2003; Szurhaj et al., 2005), cognitive functions and memory (Basar-Eroglu et al., 1996; De Pascalis and Ray, 1998) and various sensory functions; for example a transient ERS in the gamma band around 70 Hz was observed between the bilateral occipitotemporal areas during the visual perception of letters (Ihara and Kakigi, 2006).

2. Methods and materials

2.1. Subjects

Eight pharmacoresistant epilepsy patients participated in the study. All patients were referred for pre-operative intracranial exploration by a special epilepsy surgery commission in order to precisely localize their seizure onset zone. Each patient received 6–13 orthogonal platinum electrodes in the investigated brain structures using the methodology of Talairach et al. (1967). Standard Micro Deep semi-flexible 5–15 contact electrodes (DIXI), 0.8 mm diameter, 2 mm contact lengths, and 1.5 mm intercontact intervals, were used for invasive EEG monitoring. Contacts at the electrode were numbered from the medial to the lateral side. The exact positions of the electrodes and their contacts in the brain were verified using post-placement magnetic resonance imaging with electrodes in situ. The recordings from lesional anatomical structures and epileptogenic zones were not included in the analysis. All the subjects were informed about the character of this study and gave their informed consent. The study received the approval of the local Ethics Committee.

2.2. Procedure and recordings

The visual stimuli were the letters of the alphabet presented in a random order on a monitor. Subjects performed two different visuomotor cognitive tasks. The first task was a simple cognitive task (task I) – copying letters from the monitor. The second task was a more complex cognitive task (task II) – writing a letter other than that which appeared on the monitor. The patients were instructed to write any letter other than the one on the monitor but not a letter that would immediately precede or follow that letter alphabetically. Patients received clear instructions and practiced the task briefly before the recordings. They were asked to react immediately to the letter displayed on the monitor, and not to pre-prepare their responses. The task II was more complex, the cognitive load was increased, the long-term memory (recall of the alphabetical order) and the executive functions were expected to be more engaged, especially the inhibition of automatic habitual responses and the planning.

The duration of the stimulus exposure was 200 ms. The interstimulus interval was 16 s. The number of trials was min/max 50/70. In the trigger channel, the stimuli and reactions (pen-to-paper contact) were recorded. The mean reaction times in task I and II and its SD are shown in Table 1 for each subject.

Subjects reclined comfortably in the monitoring bed, in a quiet room, with a constant temperature. They were instructed to remain calm, to keep their eyes fixed on the monitor, and to avoid unnecessary movements. The monitor was situated in the same place for all the subjects, 1.5 m in front of their eyes, at the end of the monitoring bed. Subjects wrote letters using an electrically connected pen. The paper the subjects wrote on was on a desk situated near their lower abdomen. The testing was visually supervised by the examiners and was also videotaped. Failed trials were removed.

The EEG signal was recorded from the frontal, lateral temporal, and parietal cortices using the intracerebral electrodes. The EMG (m. flexor carpi radialis) and EOG were recorded simultaneously. For the first two patients, the 96 channel BrainScope EEG system (M&I) was used. The other patients were recorded by the EEG system TruScan 128 channel (Deymed diagnostic, Alien Technic) system because of EEG unit renovation. The recordings were monopolar, with a linked earlobe reference. The sampling rate was 256 Hz. Standard anti-aliasing filters were used.

2.3. Data analysis

Data were processed and analysed off-line using ScopeWin and ScopeMat software. Recordings were made with respect to a reference, with a ground lead placed on the earlobes. The possible negative effects of the reference electrode (unipolar reference) were tested and were considered insignificant.

2.3.1. Data segmentation and individual frequency band estimation

Data were first segmented according to the stimulation trigger onset, and the trials were visually inspected to

Table 1
Patient characteristics

Subject no.	1	2	3	4	5	6	7	8
Sex	male	male	male	male	male	male	female	female
Age	22	30	33	48	25	31	41	16
Hand dominance	right	left	right	right	right	right	right	right
MRI:	smaller LT lobe	normal	normal	normal	normal	FCD L sup. T sulcus	RP calcif. in falx	cystis in LT pole
SOZ	left mesio-T	left mesio-T	right mesio-T	left mesio-T	left insulo-opercular	left mesio-T	undetected, extra-T	left T
Therapy	LTG, CBZ	TOP	LVT, CBZ	LVT, CBZ	LVT, PNT, CLO	LVT, LTG	LTG, CBZ	LTG, LVT, TOP
Rec. structures	LT, LF	LT, LF, RT	LT, LF, RT, RF, RP	LT, LF, RT, RF	LF, LT	LT	LF, LT, RF, RP, RT	LT, RT
Rec. sites	65	84	106	115	51	42	110	81
Latency task I [s]	1.44 ± 0.22	1.27 ± 0.17	1.67 ± 0.36	1.33 ± 0.23	1.60 ± 0.38	1.31 ± 0.24	1.77 ± 0.31	2.80 ± 0.73
Latency task II [s]	2.14 ± 0.71	2.93 ± 1.17	3.2 ± 0.77	1.84 ± 0.49	2.10 ± 0.48	1.69 ± 0.28	2.62 ± 0.90	4.17 ± 1.11
Wada test-language dominance	left	bilat.independence, slightly stronger left side	left	left	NA	left	NA	left

T, temporal; F, frontal; P, parietal; R, right; L, left.
LTG, Lamotrigine; CBZ, Carbamazepin; TOP, Topiramate; LVT, Levetiracetam; PNT, Phenytoin; CLO, Clonazepam.
FCD, focal cortical dysplasia; calcif, calcification.
SOZ, seizure onset zone; rec, recording.
Latency is the time between stimulus and pen-to-paper contact.
NA, not available; bilat., bilateral.

eliminate EEG segments containing any artefact activity or mistaken response. The mean number of remaining analysed trials was 45 (min/max 25/67). The averaged trials were then subtracted from each trial to eliminate phase-coherent components (Kalcher and Pfurtscheller, 1995). After this subtraction, the trials were resegmented according to the reaction trigger onset (pen-to-paper contact) and the individual frequency (IF) windows were determined in the alpha 7–14 Hz, beta 16–30 Hz and gamma (lower 30–60 Hz, higher 60–90 Hz) bands using Time Frequency Analysis (TFA) (Akay, 2000) for each contact and subject separately (example on Fig. 1). TFA produces a matrix in which each row represents the averaged signal power in a 2 Hz frequency band width (x-axis represents time; y-axis represents frequency). The frequency step between two rows is 0.5 Hz. Rows of matrix are normalized according to the baseline by $\frac{\mathrm{Pw}(t)-\mathrm{Pw}_{ref}}{\mathrm{Pw}_{ref}}100\%$, where $\mathrm{Pw}_{\mathrm{ref}}$ is the baseline parameter computed as the mean from a time region 2–0.5 s before stimulation onset and $\mathrm{Pw}(t)$ is the power value in time. IF was determined as a frequency area with the maximal power decrease/increase. There could be several contacts of an electrode in a given structure. In such cases, the contact with the most prominent ERD/S change was chosen for further evaluation.

2.3.2. ERD/ERS evaluation

To study the ERD/ERS related to the reaction preparation, onset and performance, we used the averaged power envelope in the IF range segmented according to the reaction. The ERD/ERS is determined as a decrease/increase of power in the IF band related to the baseline (Pfurtscheller and Aranibar, 1977). In normalized TFA matrix ERS is represented by positive values and ERD by negative values. The numerical analysis of ERD/ERS level and its significance were based on mean levels of relative power for IF bandpasses in three intervals: interval A, 0–1 s, immediately after the reaction onset (pen-to-paper contact); intervals B, −0.5–0 s, and C, −1–0 s, immediately before the reaction (Fig. 1). The latency between the stimulus and the pen-to-paper contact were significantly subject dependent (Table 1). The occurrence of the neurocognitive processes before reaction may depend on their latency. The neurocognitive processes may have an evolution in time before the pen-to-paper contact. That is why we chose two overlapped intervals: B and C. The interval C length respects the shortest reaction time in task I and creates compromise between maximal length and possible elimination of residual evoked potentials. The results in B and C intervals were nearly the same; any differences were insignificant.

Generally the ERD/ERS registered from the contacts of one electrode within one area were similar, and the results from the most reactive contact of each electrode were selected for further analysis. The number of electrodes in a given area varied among the subjects.

2.3.3. Statistical analysis

The statistical significance of the differences between the mean power observed during the baseline and those measured inside the evaluated intervals A, B, and C was expressed as a probability value (p) using a

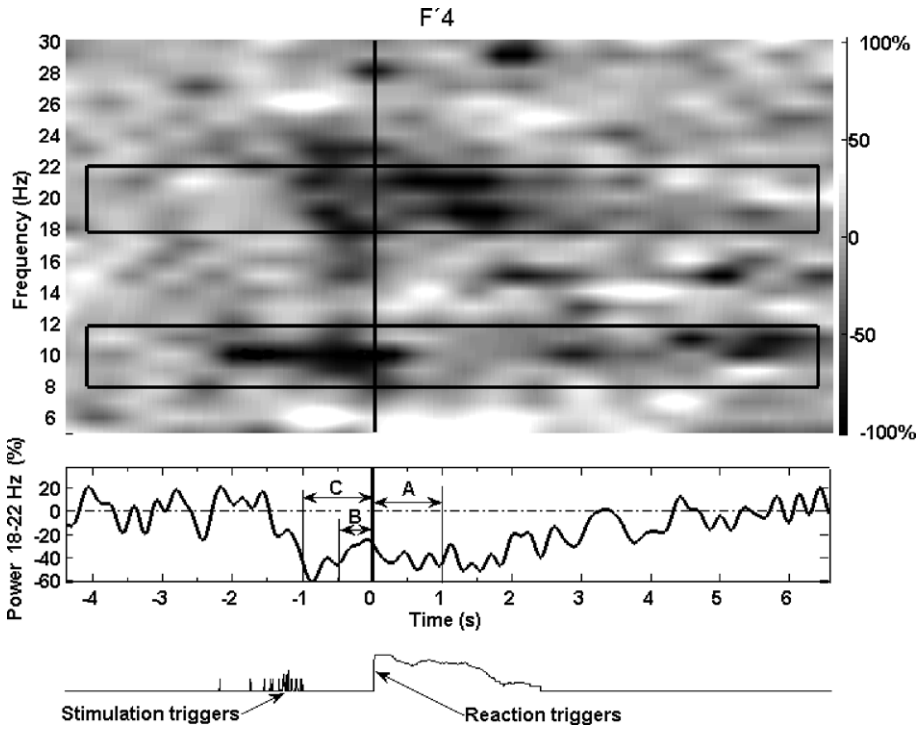

Fig. 1. Patient No. 4., task I, F′4 EEG contact (the record from BA 6 – left supplementary motor area). Normalized power segmented according to the reaction and averaged. Events coherent with stimulation were eliminated (paragraph 2.3.1). In the trigger channel, the stimuli and reactions (pen-to-paper contact) were recorded and are seen below. Upper panel: time frequency analysis, the black rectangles represent selected individual frequency bands in the alpha and beta regions. Bottom panel: an example of relative power envelope in individual frequency range 18–22 Hz. In intervals A and B an induced response is expected primarily.

non-parametric Wilcoxon Rank Sum (Signed rank) test for paired samples. Two vectors m_r and m_{ref} of mean values computed from intervals A, B, and C (m_r vector) and a baseline interval (m_{ref} vector) were collected from all segments. The power changes were considered as significant when $p < 0.05$.

3. Results

We evaluated the signal recorded from the contacts placed in the lateral and mesial frontal cortices and lateral temporal neocortex and from some contacts localized in the parietal lobe. Tables demonstrating the results from the temporal neocortex in alpha and beta frequency range (Table 2) and the most important changes in the gamma bandpass (Table 3) are shown (Figs. 2–5).

3.1. Alpha and beta

Alpha and beta were analysed together, ERD in both these frequency bandpasses is known to be a correlate of a cortical activation. For each subject and electrode the IF band was determined. Generally, widespread cortical activations were present during execution of the two visuomotor cognitive tasks. Moreover the activation of some areas was induced only by the second more complex cognitive task.

3.1.1. Temporal neocortex (BA 21, 22)

The bilateral temporal neocortex was the most extensively explored cerebral area. Here the most prominent differences between the two tasks were observed i.e. a higher activation connected with the raised cognitive engagement. Nineteen electrodes were implanted to the left middle temporal gyrus (BA 21). In the majority of the electrodes (12) we detected a significant ERD during performance of the second task at variance with the first task where we observed ERS and no or smaller ERD. In the right gyrus temporalis medius (BA 21) a significantly higher activation (larger alpha and beta ERD) during the executive second task was found in 7 of the total number of 13 electrodes localized in this area.

Six electrodes were placed in the left gyrus temporalis superior (BA 22), in four of these electrodes the ERD was more expressed with higher cognitive load while in the other two electrodes no significant difference between the two tasks was detected. Finally the right gyrus temporalis superior (BA 22) was explored by 3 electrodes. The results obtained from this area are in correlation with the results received from the majority of the contacts placed in the temporal neocortex, only SEEG from one electrode was without any oscillatory changes.

3.1.2. Temporal pole (BA 38)

In one electrode implanted in this area on the left side the ERD in alpha frequency bandpass was recorded in

Table 2
The alpha–beta relative ERD/ERS (in percent, mean value) in the temporal neocortical structures (BA21, 22), where the difference between the two tasks was present

	BA	Su	Co	S	IF	A	A	B	B	C	C
						I	II	I	II	I	II
1	21	1	A′8	L	9–13	**−15**[a]	−33	**−31**[a]	**−56**[a]	−18	**−52**[a]
2		1	B′12	L	9–13	**−30**[a]	**−42**[a]	**−34**[a]	**−65**[a]	**−30**[a]	**−59**[a]
3		1	C′9	L	8–12	**−39**[a]	**−36**[a]	**−53**[a]	**−67**[a]	**−47**[a]	**−67**[a]
4		8	A10	R	8–14	**−37**[a]	**7**[a]	**−5**[a]	**−57**[a]	**−38**[a]	**−60**[a]
5		8	B9	R	8–14	**−21**[a]	**−52**[a]	**−16**[a]	**−28**[a]	**−31**[a]	**−58**[a]
6		2	B10	R	10–14	0	−41	−14	−54	−15	**−39**[a]
7		5	P′10	L	14–18	**60**[a]	**−40**[a]	**70**[a]	**−46**[a]	**70**[a]	**−46**[a]
8		7	C′10	L	14–18	**−54**[a]	**−48**[a]	**−25**[a]	−35	**−25**[a]	−40
9		2	A′7	L	18–22	**−24**[a]	**−30**[a]	**−16**[a]	**−35**[a]	−13	−33
10		2	B′15	L	18–22	**−20**[a]	**−36**[a]	**−17**[a]	**−33**[a]	−8	**−29**[a]
11		2	C′11	L	18–22	1	**−46**[a]	**−6**[a]	**−54**[a]	−10	**−47**[a]
12		3	A10	R	18–22	**58**[a]	−41	**30**[a]	−58	29	−55
13		3	B′8	L	19–23	53	**−26**[a]	39	−22	**60**[a]	**−18**[a]
14		3	B10	R	20–24	**45**[a]	**−45**[a]	33	**−37**[a]	−12	**−36**[a]
15		3	C10	R	20–24	**−7**[a]	**−47**[a]	−2	**−51**[a]	**63**[a]	**−50**[a]
16		3	A′7	L	20–24	**86**[a]	−33	**51**[a]	**−48**[a]	**63**[a]	**−44**[a]
17		3	C′10	L	20–24	**83**[a]	**−35**[a]	**50**[a]	−32	**82**[a]	**−35**[a]
18		8	P′8	L	24–26	**−2**[a]	−56	**28**[a]	−7	**−11**[a]	**47**[a]
19		8	C10	R	24–30	**134**[a]	**−30**[a]	**103**[a]	**8**[a]	**103**[a]	**−25**[a]
20	22	1	T′3	L	8–12	**−43**[a]	**−48**[a]	**−50**[a]	**−73**[a]	**−48**[a]	**−75**[a]
21		2	T′2	L	10–14	2	**−39**[a]	1	**−46**[a]	23	−37
22		2	T5	R	10–14	−1	−27	9	**−36**[a]	8	**−23**[a]
23		8	T4	R	14–18	**46**[a]	−29	**−19**[a]	−20	−41	−31
24		4	T′4	L	16–20	4	−9	−3	**−44**[a]	−21	**−48**[a]
25		6	T′4	L	16–22	**−48**[a]	**−57**[a]	**−33**[a]	**−50**[a]	**−46**[a]	**−54**[a]

Su, subject number; Co, contact; S, side (L, left side; R, right side); A, B, C, analysed intervals; I, task I; II, task II.
[a] Mark ∗ and bold number represent statistically significant ERD/ERS with $p < 0.05$. BA, Brodmann's area.

Table 3
Gamma oscillations (in percent, mean value)

BA	Su	Co	S	IF	A	A	B	B	C	C
					I	II	I	II	I	II
BA 4	5	M′1	L	60–90	**740**[a]	**660**[a]	**400**[a]	**514**[a]	**330**[a]	**550**[a]
BA 4	7	L9	R	40–60	**−82**[a]	**−74**[a]	**−83**[a]	**−61**[a]	**−83**[a]	**−65**[a]
SMA, BA 6	4	M1	R	54–70	**−35**[a]	**−61**[a]	−16	**−63**[a]	**−25**[a]	**−63**[a]
BA 6	5	F′6	L	32–40	**−76**[a]	**−70**[a]	**−70**[a]	**−77**[a]	**−77**[a]	**−75**[a]
BA 6	7	G8	R	32–50	**−62**[a]	**−59**[a]	**−67**[a]	**−57**[a]	**−67**[a]	**−58**[a]
BA 11	7	O8	R	26–42	**45**[a]	**48**[a]	**35**[a]	**51**[a]	**42**[a]	**51**[a]
BA 21	8	P′10	L	78–82	−46	**−25**[a]	**−4**[a]	**64**[a]	**20**[a]	**166**[a]
BA 22	5	5/I′10	L	60–90	**79**[a]	**270**[a]	**94**[a]	**370**[a]	**115**[a]	**500**[a]

Su, subject; Co, contact; S, side; L, left side; R, right side; BA, Brodmann's area; IF, individual frequency; A, B, C, analysed intervals; I, task I; II, task II.
[a] Bold number represents a significant value with $p < 0.05$.

the simple as well as in the more complex tasks (subject No. 1 both the tasks −40%).

3.1.3. Dorsolateral prefrontal cortex (BA 9, 46)

Three electrodes were implanted on the left side and three on the right side. In one of the electrodes implanted in the left DLPFC there were no significant power changes in the alpha and beta frequency bandpasses detected during performance of the first simple task, but in contrast there was about −50% ERD in higher beta (subject No. 2 task I 0 task II −50%) during the second more complex task. From the other two left electrodes we recorded a larger ERD during the more complex task (subject No. 7 two electrodes task I: −30%, task II: −70%). Another situation was on the right side; activation was similar for the simple as well for the more complex task (subject No. 4 two electrodes −40% and −50%, and subject No. 7 −40%).

3.1.4. Ventrolateral prefrontal cortex (BA 45)

Two electrodes were located in this area, one on the left side and one on the right side. No significant changes during performance of the first simple task and about −30%

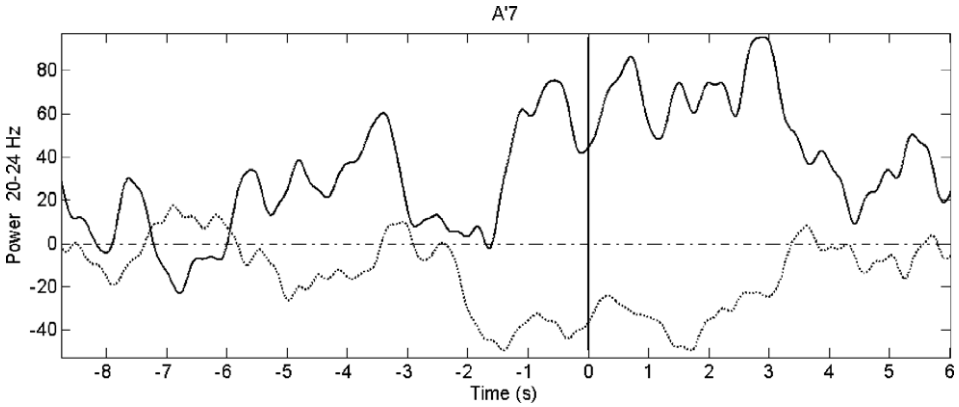

Fig. 2. Example of the power envelopes in the individual frequency range (subject No. 3, contact A′7, BA 21, left side). Point 0 = reaction onset time (pen-to-paper contact). Task I – thick line and task II – thin line.

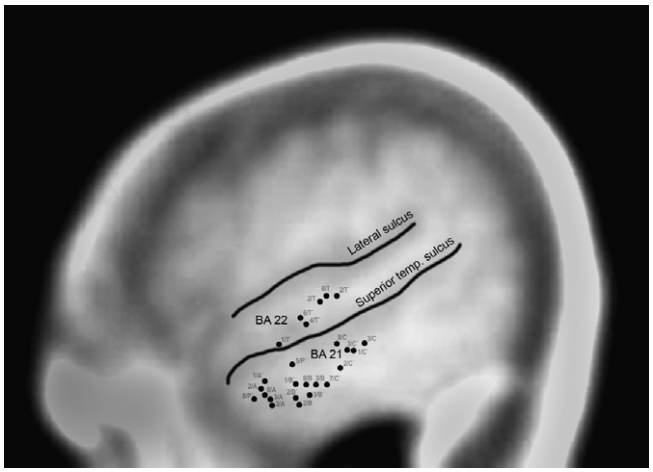

Fig. 3. Exact position of the contacts placed in the temporal neocortex where the specific higher executive activation was present. A MR scan averaged through the group of patients.

ERD during the second more complicated one were registered in the alpha frequency range in the left ventrolateral prefrontal cortex in subject No. 2. In the beta frequency bandpass in the right ventrolateral prefrontal cortex there was a significant difference between the two tasks (subject No. 3 task I −20%, task II −40%).

3.1.5. Orbitofrontal cortex (BA 10, 11)

In three of the four electrodes implanted in the left orbitofrontal cortex we detected significant differences between the two tasks. In the beta frequency range the ERD was more expressed during the second more complex task (subject No. 1 task I +10% task II −30%, subject No. 3 task I +20% task II −30%, subject No. 7 task I −20% task II −60%). In one of the left side electrodes an ERD similar for both the tasks was found (subject No. 4 −40%). The SEEG registered from one electrode in the right orbitofrontal cortex displayed a difference between the two tasks in beta bandpass (subject No. 3 task I −20% task II −50%) and from the second one there was a corresponding activation found for both the tasks in the alpha range (subject No. 7 close to −100%).

3.1.6. Primary motor cortex (BA 4)

The primary motor cortex was explored in two subjects (subject No. 5 on the left side and subject No. 7 on the right side). In both left and right primary motor cortex an extensive ERD (close to −100%) was found before the movement onset and during movement execution in the alpha and beta frequency bandpasses during performance of the two tasks.

3.1.7. Primary somatosensory cortex (BA 1, 3)

In this area one electrode was implanted on the left side (subject No. 5) and one electrode on the right side (subject No. 7). Here also a wide ERD (close to −100% in alpha and beta range) was detected for both the tasks.

3.1.8. Premotor cortex (lateral BA 6 and BA 8)

Three electrodes were localized in the left premotor cortex and three in the right premotor cortex. Significant ERD in beta frequency were recorded similarly in the task I and task II (left side: subject No. 2 −40%, subject No. 4 −60%, subject No. 5 −70%, right side: subject No. 4 −50%, subject No. 7 two electrodes −80 and close to −100%).

3.1.9. Supplementary motor area (SMA, BA 6) and medial BA 8

This area was explored by two left and four right electrodes. ERD in both alpha and beta frequency bandpasses was registered for both the tasks of our experimental protocol (left side: subject No. 4 −40%, subject No. 5 −70%, right side: subject No. 4 two electrodes −50%, subject No. 7 two electrodes −80%).

3.1.10. Cingulate (BA 24, 32, 31)

Three electrodes were placed in the left anterior cingulate (BA 24, 32), three electrodes in the right anterior cingulate and one electrode in the right posterior cingulate (BA 31).

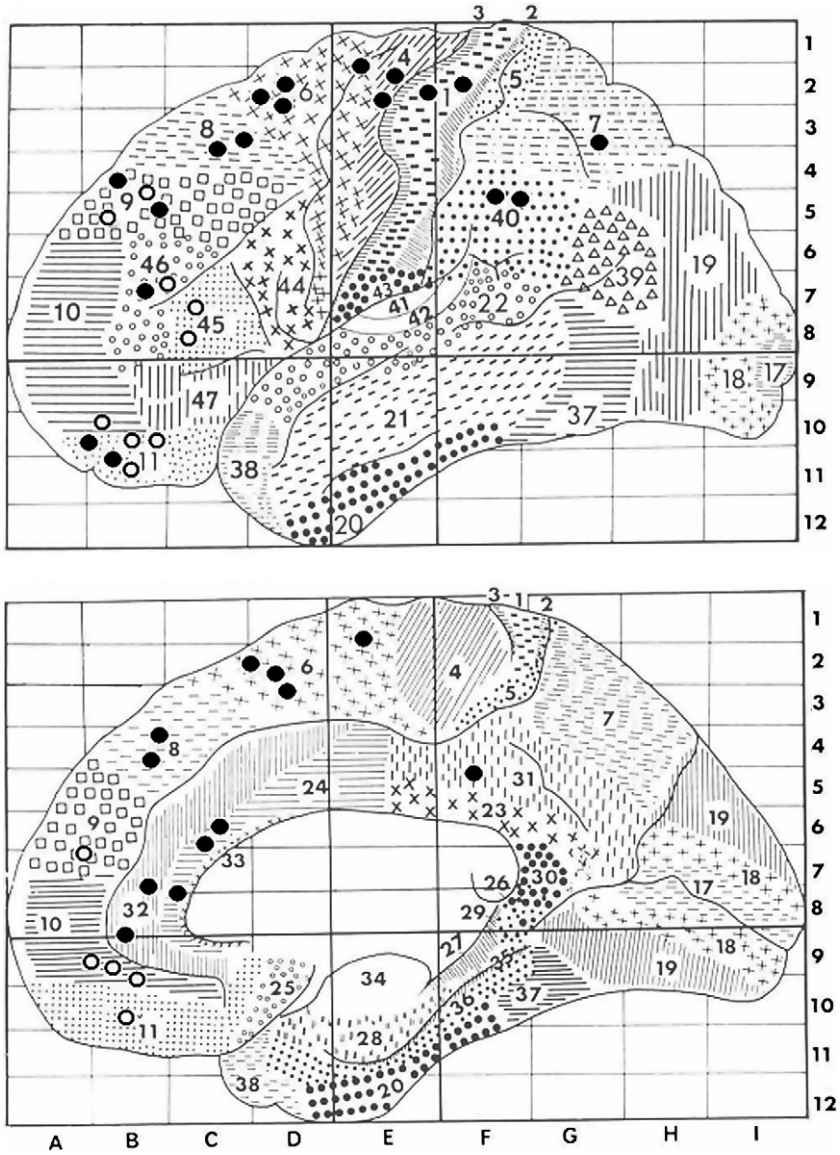

Fig. 4. Schematic presentation of the distribution of ERD in the alpha and beta frequency ranges in the frontal and parietal cortices. The black circles indicate the ERD during both tasks. The empty circles indicate contacts where ERD was present only during task II (complex cognitive task). The coplanar stereotactic atlas (Talairach and Tournoux, 1988) was used for reconstruction of the intracerebral electrodes position.

No significant changes were detected in one subject on the left side (subject No. 2), but in the other contacts the changes were similar to the results obtained from the SMA and premotor cortex i.e. activation in the two tasks. The ERD was less expressive than in the SMA and premotor cortex (left side: subject No. 4 −50%, subject No. 7 −30%, right side: subject No. 3 −30%, subject No. 4 −30%, subject No. 7 anterior cingulate −80%, posterior cingulate close to −100%).

3.1.11. Parietal cortex (BA 7,40)

Three electrodes were localized in the right parietal cortex (subject Nos. 3 and 7). Here also a large ERD (subject No. 3 around −50% and subject No.7 two electrodes close to −100%) was detected during performance of both tasks.

3.2. Gamma

The strongest results in lower and higher gamma frequency range were located in the left primary sensorimotor cortex, which was explored by several electrodes in subject No. 5 (right hand dominance). In the left BA 1,3,4 we found ERS in the lower and also higher gamma frequency range starting before movement onset (pen-to-paper contact) and continuing for about one second during performance of both the tasks of our experimental protocol.

A different situation was found in one electrode placed in the right primary motor cortex (subject No. 7, right hand dominance) where there was no ERS, but ERD in lower gamma was found for both tasks. This might be explained by the fact that the electrode was not situated contralaterally to the movement.

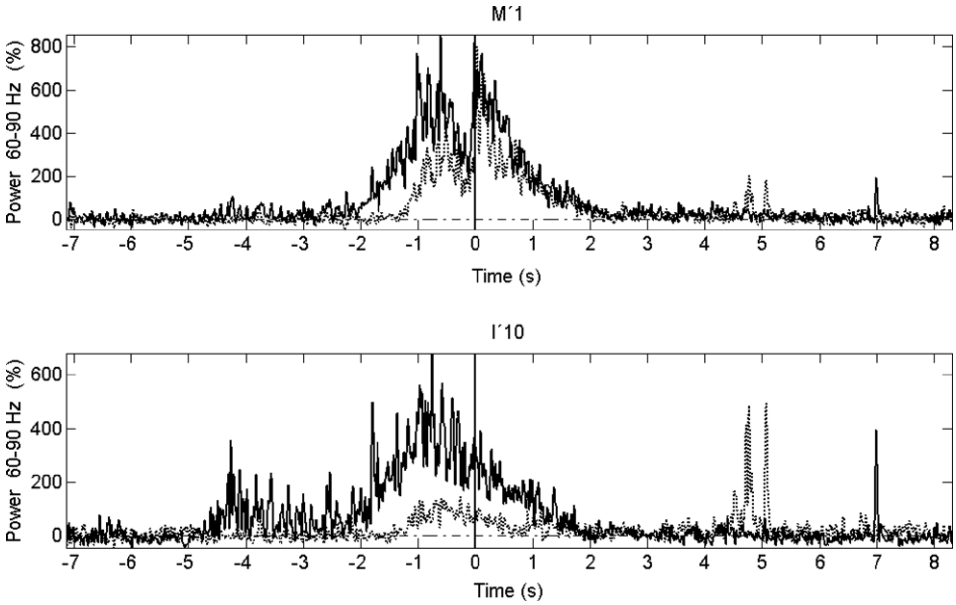

Fig. 5. Normalized power in frequency range 60–90 Hz, segmented according to the reaction and averaged. Events coherent with stimulation were eliminated. Thin line – task I, thick line – task II. Upper panel – contact placed in the left primary motor cortex (BA 4, subject No. 5); no significant difference was present between task I and task II. Bottom panel – contact situated in the left gyrus temporalis superior (BA 22, subject No. 5), significant difference was present between task I and task II.

Interesting gamma oscillatory changes which were similar in three subjects were detected in the left and right SMA and the premotor cortex (BA 6): ERD in the lower gamma range for the two tasks.

Higher activation connected with the complex task was present only in a few contacts. Surprisingly, no relevant changes were observed in the dorsolateral prefrontal and ventrolateral prefrontal cortex. In one electrode placed in the right orbitofrontal cortex (BA 11) the ERS in the lower gamma band was larger during the second task.

A significant difference between the two task was present in the left gyrus temporalis medius (BA 21) and left gyrus temporalis superior (BA 22); the ERS was higher for the more complex task in the higher and lower gamma in two subjects.

4. Discussion

Our experimental protocol contained two tasks with the writing of single letters. The first task consisted of copying a letter from the screen; the second task required writing a different letter than that appearing on the screen. First, we investigated which parts of the frontal and temporal cortices were activated or deactivated during the performance of the two tasks. Next, we searched for the differences between the two tasks. These two tasks are characterized by several common aspects linked with the writing of single letters. The two tasks had in common: visual detection and reading of the letter on the screen, the preparation and the execution of writing. As the second task was more complex and less automated, a larger demand on the attention can be expected. Bastiaansen and Brunia (2001) found that the anticipatory attention produced a 10 Hz ERD over the sensory cortex, corresponding to the modality of the stimulus. In their study, occipital ERD occurred before visual stimuli. We did not have the opportunity to explore the occipital cortex and we did not find ERD preceding the stimuli in the other cortical areas. Alpha ERD is also increased by an increased working memory load (Schack et al., 2005; Gomarus et al., 2006). We supposed the working memory load to be engaged on a comparable level in both of the tasks in our experimental protocol as the stimuli were same for both tasks – the letters of the alphabet had to be kept in working memory before and during the task performance. The second task moreover demanded a higher cognitive load which was comprised of several components; a higher demand on long-term memory (retrieval of the letters of the alphabet) and several acts that are covered by the common term of executive function: the inhibition of the automatic (habitual) responses, the choice and planning and executing of the chosen response. We assumed that the most prominent difference between the tasks is the higher involvement of the executive functions in the second task.

We observed widespread cortical activation during the preparation and execution of the two visuomotor cognitive tasks. Similar activational patterns – the alpha and beta ERD – during both tasks were present in the frontal structures, specifically in the left and right primary motor cortex (BA 4), bilateral anterior cingulate (BA 24, BA 32), left and right premotor cortex and SMA (BA 6), but also in the left temporal pole (BA 38, the

right temporal pole was not explored), right parietal cortex (BA 7,40, the left parietal cortex was not explored) and bilateral primary somatosensory cortex (BA 1,3). This activation is probably associated with common components of the two tasks, mainly the writing of single letters, which is a complex but overlearned and near-automatic movement. The motor activity linked with execution of writing in the two tasks can explain the activity of several brain areas (BA 4,24,32,6,8,40,1,3). The anterior cingulate, premotor cortex, and supplementary motor area are involved in the preparation and execution of movement (Rektor et al., 1998; for review see Rektor et al., 2003). In intracranial recording studies, movement related ERD/ERS in the alpha and beta bands have been observed in the primary sensorimotor cortices and in the SMA (Ohara et al., 2000; Crone et al., 1998a; Pfurtscheller et al., 2003; Szurhaj et al., 2003; Sochůrková et al., 2006) as well as in the basal ganglia (Sochůrková and Rektor, 2003). Area 40 is a territory strongly linked with associative functions, and is connected to the temporal pole and the frontal lobe (Talairach and Tournoux, 1988). This might explain the synchronous activation of the inferior parietal lobe, the temporal pole and the frontal movement-responsible structures.

The increased cognitive load task produced differences between the simple and more complex tasks in several frontal and temporal neocortical structures, where we found no significant power changes, ERS or lower ERD during the simple task in contrast with a larger activation (alpha and beta ERD) during the complex task. It was in the left DLPFC (BA 9,46), left and right ventrolateral prefrontal cortex (BA 45), bilateral orbitofrontal cortex (BA 10,11) and surprisingly also the left and right temporal neocortex (BA 21,22). ERS was observed in some subjects during task I, mostly in the beta frequency range. A generalized statement regarding the correspondence between beta EEG activity and the activity state of the underlying cortical neuron populations, without further specification, is not in general adequate (Lopes da Silva, 2006). The ERD/ERS pattern is interpreted as a thalamo-cortical mechanism to facilitate focal activation and information processing (focal ERD) by simultaneous deactivation or inhibition of other cortical areas (surround ERS) with the goal to optimize the energy demand in task-related cortical areas (Pfurtscheller, 2006). In the context of our experimental protocol, we assume this beta ERS during the simple task to be a correlate of an inactive state of a given area.

The temporal cortex was the region with the highest number of recording sites and the different responses in the two tasks were here the most prominent. That indicates a prominent involvement of the temporal neocortex in the cognitive activities specific for the second task, i.e. mostly with the executive functions.

Stuss and Benson (1986) suggesting that the centre of the executive functions is situated in the prefrontal cortex was critically reviewed by Parkin (1998), who demonstrated extensive heterogeneity, with different executive tasks associated with different neural substrates. Executive dysfunctions arise not only from damage to the frontal lobes and frontal lobe damage does not necessarily lead to executive deficits (Baddeley and Della Sala, 1996). The activation of various neocortical regions and the engagement of the temporal neocortex in processing executive and cognitive functions have been suggested by Berman's (Berman et al., 1995), Ragland's (Ragland et al., 1997), Nagahama's (Nagahama et al., 1996) and Ojemann's studies (Ojemann, 2005). Several studies were devoted to the relationship between ERD/ERS and cognitive processes (Babiloni et al., 2004), memory functions (Krause et al., 1996) or working memory (Sauseng et al., 2004). Their results support the theory that cognitive processing is associated with the prefrontal–temporal networks.

The temporal neocortex is traditionally connected with auditory and visual functions. A lot of studies describing the important role of the temporal neocortex in cognitive processing were performed; the function of the temporal neocortex is fundamental for learning, memory storage, retrieval, and consolidation and semantic cognition (Jones-Gotman et al., 1997; Cheung and Chan, 2003; Wiltgen et al., 2004; McClelland and Rogers, 2003; De Zubicaray et al., 2006). Zatorre (Zatorre et al., 2004) demonstrated a functional network between the inferior frontal areas and the superior temporal sulcus. In our study we explored the bilateral superior and middle temporal neocortex. The activity specific for the executive functions was detected in the central and anterior parts of the middle temporal gyrus (BA 21) and in the central part of the superior temporal gyrus (BA 22). There were no electrodes either in the primary auditory cortex, or in the Wernicke speech area. The great involvement of the temporal neocortex in the cognitive functions and memory is evident from previous studies. We document the importance linked to the executive functions producing widespread temporal neocortical activation. We suppose the cooperation between the temporal neocortical and prefrontal areas. These interconnections seem to be fundamental for executive functioning in the studied cognitive task.

In this study we also analysed the gamma frequency range. It has been shown that neuronal activity in the gamma band is associated with cortical activation and may play a role in the multi-regional and multi-modal integration of cortical processing (Crone et al., 1998b). Gamma band activity is of particular interest in neuroscience research and it has been linked to a variety of perceptual and cognitive functions (Bertrand and Tallon-Baudry, 2000; Engel and Singer, 2001; Fell et al., 2003; Keil et al., 2001; Tiitinen et al., 1993; Varela et al., 2001; Brovelli et al., 2005). We found ERS, starting about one second before movement onset and continuing during movement performance, in the left (contralateral to the movement) primary sensorimotor

cortex (BA 4, 1, 3) in one subject (this region was explored only in two subjects; in the second one only the ipsilateral side). Similarly, Szurhaj et al. (2005) described ERS related to the movement onset in the sensorimotor cortex. In two patients gamma ERS was recorded in the left temporal neocortex (BA 21, 22) and it was significantly more marked during performance of the second more complex task. These results correlate with the results analysed in the alpha and beta bandpasses. A corresponding situation was obtained from one electrode placed in the right orbitofrontal cortex. Gamma ERD was located in the SMA and premotor cortex (BA 6, 8) in three subjects. It is evident that more data are needed before discussing the heterogeneous gamma band recordings.

We evaluated the human event-related EEG signal recorded via intracerebral depth electrodes. The electrode positioning is determined by clinical intention – not all structures can be fully explored. The intracerebral recordings are performed in epileptic patients and we cannot fully exclude pathological process influence on the recorded electrical activity. In order to minimise the risk of such bias we excluded recordings from brain tissue with pathological activity – the contacts inserted into the epileptogenic zones and lesions are not implicated in the analysis. On the other side the depth electrodes are submerged in the brain tissue and record from their immediate vicinity, the data are obtained directly from cortical structures; some of them almost inaccessible by scalp or subdural measurement. The quite limited spatial resolution that is typical for intracerebral recordings could be compensated for by a large number of recording sites (in this study 654). In our group, most patients suffered from left mesiotemporal epilepsy. We did not analyse the SEEG obtained from mesiotemporal structures. There was also one patient with right mesiotemporal epilepsy, one with insulo-opercular epilepsy, and one with undetected extra-temporal epilepsy. We obtained nearly identical results from both the right and left temporal neocortical structures in all subjects, and so we do not believe that our results were influenced by the fact that the majority of our subjects have left mesiotemporal epilepsy.

5. Conclusion

We detected an activation connected with executive functions during higher cognitive stress in the dorsolateral prefrontal, ventrolateral prefrontal, and orbitofrontal cortices and – more surprisingly – also in the superior and middle temporal neocortices. Our results support the theory of a widespread and complex neurocognitive network of the executive functions, and underline the importance of the temporal neocortex in higher cognitive processing. More studies are needed to answer the question of whether the participation of the temporal neocortex in executive processing is related to specific cognitive activity or is a general feature of executive brain network.

Abbreviations:

ANOVA	Analysis of Variance
BA	Brodmann's area
C	contact
Calcif	calcification
CBZ	carbamazepin
CD	complex demodulation
CLO	clonazepam
DLPFC	dorsolateral prefrontal cortex
EEG	electroencephalography
EMG	electromyography
EOG	electrooculography
ERD/ERS	event-related desynchronization/ synchronization
F	frontal
FCD	focal cortical dysplasia
fMRI	functional magnetic resonance imaging
IF	individual frequency
L	left
LTG	Lamotrigine
LVT	Levetiracetam
NA	not available
p	probability
P	parietal
PET	positron emission tomography
PNT	phenytoin
R	right
rec	recording
S	side
SD	standard deviation
SEEG	stereoelectroencephalography
s	second
SMA	supplementary motor area
SOZ	seizure onset zone, rec – recording
Subj	subject
Sup	superior
T	temporal
TFA	Time Frequency Analysis
TOP	Topiramate

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6.6. Příloha 6 - Complex Motor-Cognitive Factors Processed in the Anterior Nucleus of the Thalamus: An Intracerebral Recording Study

Bočková M, Chládek J, Jurák P, Halámek J, Stillová K, Baláž M, Chrastina J, Rektor I. Complex Motor-Cognitive Factors Processed in the Anterior Nucleus of the Thalamus: An Intracerebral Recording Study. Brain Topogr. 2015;28(2):269-78.

IF: 3,7

Hluboká mozková stimulace předního jádra thalamu (AN) se stala nadějnou léčbou farmakorezistentní epilepsie od doby, kdy byla v roce 2010 publikována studie SANTE. Nicméně byly publikovány i studie na zvířatech a lidských subjektech, které dokumentují výskyt potíží s pamětí v průběhu AN-DBS. Toto pravděpodobně souvisí s tím, že AN je součástí Papezova okruhu. Cílem této práce bylo zkoumání možného zapojení AN do dalších kognitivních funkcí, které by AN-DBS případně mohla ovlivňovat. Opět byl použit výše zmíněný experimentální protokol se psaním jednoduchých písmen, který je zaměřen především na exekutivní funkce. I v oblasti AN thalamu byla pozorována obdobná zvýrazněná alfa a beta ERD, jakožto korelát zvýšené kognitivní zátěže v průběhu druhého úkolu, který vyžadoval vyšší zapojení exekutivních funkcí. AN se tak pravděpodobně také podílí na zpracování kognitivně motorických úloh. U pacientů s AN-DBS je tedy třeba dbát pozornosti na event. exekutivní dysfunkce, který by mohly komplikovat léčbu.

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ORIGINAL PAPER

Complex Motor–Cognitive Factors Processed in the Anterior Nucleus of the Thalamus: An Intracerebral Recording Study

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Abstract Cognitive adverse effects were reported after the deep brain stimulation (DBS) of the anterior nucleus of the thalamus (AN) in epilepsy. As the AN may have an influence on widespread neocortical networks, we hypothesized that the AN, in addition to its participation in memory processing, may also participate in cognitive activities linked with the frontal neocortical structures. The aim of this study was to investigate whether the AN might participate in complex motor–cognitive activities. Three pharmacoresistant epilepsy patients implanted with AN–DBS electrodes performed two tasks involving the writing of single letters: (1) copying letters from a monitor; and (2) writing of any letter other than that appearing on the monitor. The cognitive load of the second task was increased. The task-related oscillatory changes and evoked potentials were assessed. Local event-related alpha and beta desynchronization were more expressed during the second task while the lower gamma synchronization decreased. The local field event-related potentials were elicited by the two tasks without any specific differences. The AN participates in cognitive networks processing complex motor–cognitive tasks. Attention should be paid to executive functions in subjects undergoing AN–DBS.

Keywords Anterior nucleus of the thalamus · Complex cognitive functions · Deep brain stimulation · ERD/S · ERP

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Introduction

Deep brain stimulation (DBS) of different brain targets has been successfully used to treat various neurological and psychiatric disorders. Since the SANTE Study (Fisher et al. 2010) was published, DBS of the anterior nucleus of the thalamus (AN) has become a promising method of treating refractory epilepsy. For some patients, especially those with advanced Parkinson's disease (PD), generally successful DBS may be accompanied by cognitive impairment and neuropsychiatric disorders (Saint-Cyr et al. 2000; Herzog et al. 2003; Anderson et al. 2005; Temel et al. 2005, 2006; Voon et al. 2006; Witt et al. 2008; Ballanger et al. 2009; Okun et al. 2009). That is because the basal ganglia, particularly the subthalamic nucleus, which is the most common stimulation target, participate in the cognitive neuronal circuits (Parent and Hazrati 1995; Baunez and Robbins 1999; Graybiel 1997; Aron et al. 2007; Benarroch 2008; Baláž et al. 2008, 2010, Bočková et al. 2011). Little is known about the involvement of AN in cognitive activities in human subjects. It is probable that AN–DBS produces memory changes. A recent experimental study in rats (Hamani et al. 2010) as well as studies in human subjects (Fisher et al 2010) showed that high frequency electrical stimulation of AN could decrease performance in memory paradigms. This may be explained

by the position of the AN within the Papez circuit. The AN may also have an influence on widespread neocortical networks, particularly in the frontal lobe. The AN projects to the cingulate gyrus, which has well-documented roles in self-regulation and executive cognition (Jones et al. 2006), with further projections to wide regions of the neocortex (Zhong et al. 2011). The AN is also a key structure in the intrathalamic pathways. We hypothesized that the AN, in addition to its participation in memory processing, may also participate in other cognitive activities, namely in those that are processed in networks comprising the frontal neocortical structures. For these reasons, we focused on complex motor–cognitive tasks as it is known that willed and automatic actions are controlled at different levels depending on the degree of task difficulty and complexity (Norman and Shalice 1986; Luu and Tucker 2002).

We recorded electrical activity linked with cognitive functions via DBS electrodes implanted in the AN. Intracranial recording studies provide direct access to the subcortical structures. The aim of this study was to investigate whether the AN might participate in processing higher order cognitive activities. If so, AN–DBS might lead to adverse effects in the studied domains, and attention should be paid to these functions in human subjects undergoing AN–DBS. We have not seen any published data regarding the higher order cognitive functions related to the AN or in patients with AN–DBS.

Materials and Methods

Subjects

Three pharmacoresistant epilepsy patients with DBS macroelectrodes implanted in the AN target participated in the study (see Table 1). The recordings were performed in the postoperative period before the stimulator implantation and the system internalisation. Two patients had a previous surgical intervention and all patients had undergone unsuccessful vagal nerve stimulation treatment; the device was finally explanted. All patients were indicated for the DBS surgery by the Commission for Neuromodulation Surgery of the Brno Epilepsy Centre. All the subjects were informed about the character of this study and gave their informed consent. The study received the approval of the local ethics committee. Before the operation, all subjects underwent a detailed neuropsychological examination (Wechsler adult intelligence scale, Wechsler memory scale III, Stroop test, Rey-osterrieth complex figure test, Verbal fluency test, Boston naming test, Hamilton anxiety scale, Montgomery-asberg depression rating scale). The examination showed no signs of dementia. Patients intellect ranged from the population average to borderline deficiency. All patients had a slight to moderate impairment of executive functions, diminished quality of performance was particularly in psychomotor speed and attentional functions. Basic symbolic functions were without specific disorders. Mnestic abilities varied from average to mild impairment.

Table 1 Patient characteristics

Subject no.	1	2	3
Sex	Female	Male	Female
Age	47	29	44
Hand dominance	Right	Right	Right
MRI	Normal	Left temporal postoperative defect	Defect after callosotomy
SOZ	Multifocal	Left lateral temporal	Frontal, laterality unclear
Therapy	LTG, CLO	TOP	LTG, CBZ, LVT, CLOB

LTG lamotrigine, *CBZ* carbamazepine, *TOP* topiramate, *LVT* levetiracetam, *CLO* clonazepam, *CLOB* clobazam

Surgical Procedure

The stereotactic frame used during the surgical procedure was the Leibinger ceramic open frame with the Praezis Plus software and the Talairach and Schaltenbrand Bailey atlases. The initial coordinates for the anterior thalamic nucleus as related to the AC–PC (anterior commissure–posterior commissure) line centre were 0–2 mm anterior to the midpoint, 5.5 mm laterally, and 10–12 mm above AC–PC line. The entry point for the electrode was planned at the proximity of coronal suture. The final target was modified according to local anatomy, and particular attention was paid to the safe distance of the trajectory from thalamostriate vein and choroid plexus. All four electrode contacts were planned to be inside thalamic structures. The stimulation leads (Medtronic, Inc.) were implanted bilaterally into the targeted structure by stereotactic MRI-guided technique under local anaesthesia. Intraoperative micro recordings to guide lead placement were employed. Intraoperative stimulation was used to test possible adverse effects. Once the final target coordinates were defined, a permanent quadripolar DBS electrode (model 3389, with 1.5 mm contact length and 0.5 mm intercontact distance) was implanted. The electrode position was verified by the intraoperative use of fluoroscopy comparing the position of the micro recording electrodes trajectories with the definitive quadripolar macro electrode trajectory. After surgery completion, CT scans under stereotactic conditions covering the entire length of the

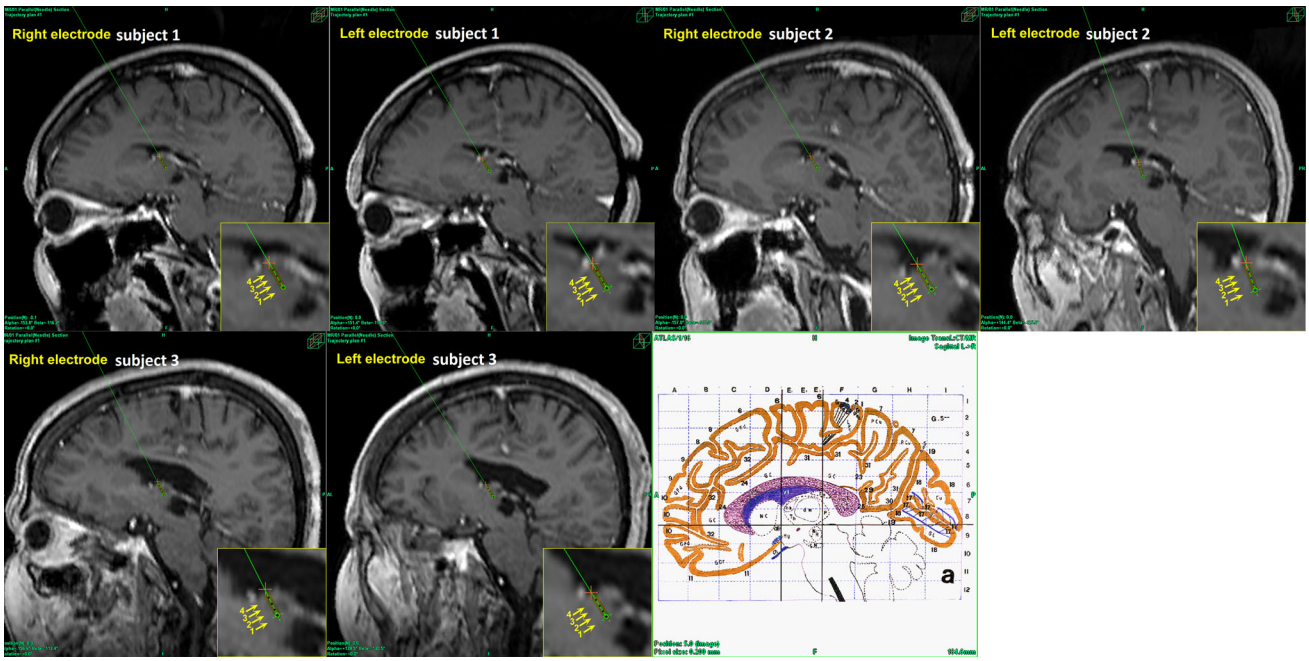

Fig. 1 The real electrode and all contacts positions are shown for both sides as defined by the fusion of postoperative CT with preoperative MRI scans in the planning workstation. MRI projections are along the electrode trajectory. An image from the Talairach atlas (Talairach et al. 1967) in approximately same position is shown. Contacts 4 are placed in the borderline between the AN and the lateral ventricle. Contacts 3 are all placed in the AN. Contacts 2 are localized in the AN or on the border between the AN and the DMN of the thalamus. Contacts 1 are all located in the DMN of the thalamus

implanted electrodes were added. The series of images were reimported to the planning workstation and subsequently the coordinates were correlated with the real position of implanted electrodes (as shown in Fig. 1). The change of electrode position is evident in the planning data sets so that the final electrode position can be evaluated without being burdened by artefacts caused by electrode material both in CT and MRI scans. The positions of the electrodes and their contacts in the brain were also later verified using post-placement magnetic resonance imaging with electrodes in situ.

Experimental Protocol and Recordings

We used a complex visuomotor paradigm with an increased load of complex cognitive functions that we had used in an earlier work for studying the frontal, parietal, and temporal cortices (Bočková et al. 2007). The visual stimuli were the letters of the alphabet presented in a random order on a monitor. Subjects performed two different visuomotor cognitive tasks. The first task was a simple cognitive task (task 1)—copying letters from the monitor. The second task was a more complex cognitive task (task 2)—writing a letter other than that which appeared on the monitor. The patients were instructed to write any letter other than the one on the monitor but not a letter that would immediately precede or follow that letter alphabetically. Patients received clear instructions and practised the task briefly before the recordings. They were asked to react immediately to the letter displayed on the monitor, and not to pre-prepare their responses.

The duration of the stimulus exposure was 200 ms; the interstimulus interval was 16 s.

Subjects reclined comfortably in the monitoring bed, in a quiet room, with a constant temperature. They were instructed to remain calm, to keep their eyes fixed on the monitor, and to avoid unnecessary movements. The monitor was situated in the same place for all the subjects, 1.5 m in front of their eyes, at the end of the monitoring bed. Subjects wrote letters using an electrically connected pen. The paper the subjects wrote on was on a desk situated near their lower abdomen. The testing was visually supervised by the examiners and was also videotaped.

The intracerebral EEG signal was recorded by the M&I EEG system. The recordings were monopolar, with a linked earlobe reference. The sampling rate was 20 kHz with standard anti-aliasing filters before digitalization. The signal was thereafter off-line filtered in the band pass up to 300 Hz and downsampled to 1 kHz. The filter was based on Fourier transformation. In the trigger channel, the stimuli and reactions (pen-to-paper contact) were recorded, so the response onset time could be monitored.

Data Analysis

The data were processed and analysed off-line using ScopeWin and ScopeMat software. The data were first segmented according to the stimulation trigger onset. The segments were visually inspected, and segments containing artificial signals or mistaken responses were removed. In each segment the linear trend was eliminated.

Time frequency analysis (TFA) (Akay 2000) with eliminated phase-lock signals (subtraction of averaged trial) was used to determine the event related desynchronization/synchronization (ERD/S) in 2–80 Hz frequency ranges (see Fig. 3). TFA produces a matrix in which each row represents the over trials averaged signal power envelopes in a 4 Hz frequency band width (x-axis represents time; y-axis represents frequency). The frequency step between two rows was 1 Hz. The signal power envelope within rows was evaluated by Hilbert transform demodulation. One matrix thus contains, in the vertical axis, power envelopes for the frequencies 2–6, 3–7, and up to 76–80 Hz, with 75 rows in total. The horizontal axis of the matrix represents the time intervals from 4 s before stimulation to 12 s after simulation. In the baseline-normalized TFA matrix, ERS is represented by positive values (red) and ERD by negative values (blue). Normalization with a baseline was done according the equation:

$$\mathrm{ERS} = 100 \times (\mathrm{PW(t)/PWbaseline} - 1), \text{ when } \mathrm{PW(t)/PWbaseline} \leq 1.$$

$$\mathrm{ERD} = 100 \times (1/(\mathrm{PW(t)/PWbaseline}) - 1), \text{ when } \mathrm{PW(t)/PWbaseline} < 1.$$

PWbaseline—mean power from baseline, PW(t)—instantaneous power. The limitation of ±100 of normalized values is used. The scale in the TFA matrix in the figures is +100, −100. The +100 value (red) means a doubling of instantaneous power with respect to the baseline region; the −100 value (blue) means a drop by half. This procedure provides a comparable colour interpretation of ERS and ERD.

The statistical significance of ERS/ERD was analysed from the differences over trials between the mean power at baseline and the mean power in the window moving over segment. Statistical significance is presented in a matrix where the significant changes to baseline are dark red, light red, dark blue, and light blue. Dark red identifies a power increase when $P < 0.01$, light red a power increase when $P < 0.05$, dark blue a power decrease when $P < 0.01$, and light blue a power decrease when $P < 0.05$. White regions of this matrix identify non-significant changes to baseline.

To identify differences between stimuli in time–frequency interpretation, we computed an inter-stimulus statistical significance matrix—Fig. 2, right panel. Each point of the matrix represents the significance of differences between tasks in the corresponding time and frequency position. In each time–frequency position, we tested the differences of two vectors that represent the power envelope value in the appropriate frequency range and time position over trials from task1 and task2. We used a non-paired *t* test to determine significance. In Fig. 2, dark grey represents $P < 0.01$ and light grey $P < 0.05$. The significance is after correction, as the same data are used two times.

Event-related potentials (ERPs) were given in averaged segments filtered in 0.1–40 Hz bandwidths. The baseline interval was determined as 1,600–100 ms prior to stimuli. The statistical significance of ERPs to baseline was analysed in a similar way as for ERS/ERD, analysing the differences over trials between the mean computed during the baseline and the mean computed inside the moving interval with a length of one-third of baseline. Non-parametric Wilcoxon rank sum (signed rank) test for paired samples was used. The ERP were considered as significant when $P < 0.05$, indicated by black rectangles in Fig. 3.

Bipolar montage evaluation was used to exclude the volume conduction from other structures, namely from the cortex or transsynaptic propagation along cortical-subcortical pathways (Wennberg and Lozano 2003, 2006) and confirm the local origin of the potentials. Contacts in the thalamus were placed very close together. Any EEG signal from the common reference was eliminated by a bipolar montage. Even minor bipolar montage activity displays the origins of detected activity in the AN.

Results

As the first step, we analysed oscillatory changes. Figure 2 shows TFA with statistical significance where a local AN alpha and beta ERD was more expressed during task 2 and comprised a wider frequency range on the left side in subject 1 and 2, and on both sides in subject 3. This represents a pattern modification related to the increased complexity during task 2, which is known from our previous study (Bocková et al. 2007) and was described in a recent intracranial recording study in the subthalamic nucleus (STN) (Oswal et al. 2013). This ERD started around 500 ms in subjects 1 and 3. It started after 2 s in subject 2. Because the reaction times started after 1,500 ms, we assume the later ERD in subject 2 also related to the task performance (see Table 2). We observed these oscillatory changes in the left sided electrodes in all patients, and in patient 3 also in the right sided electrode. Whether this lateralization has a physiological significance, e.g. a relation to the lateralization of the reading and

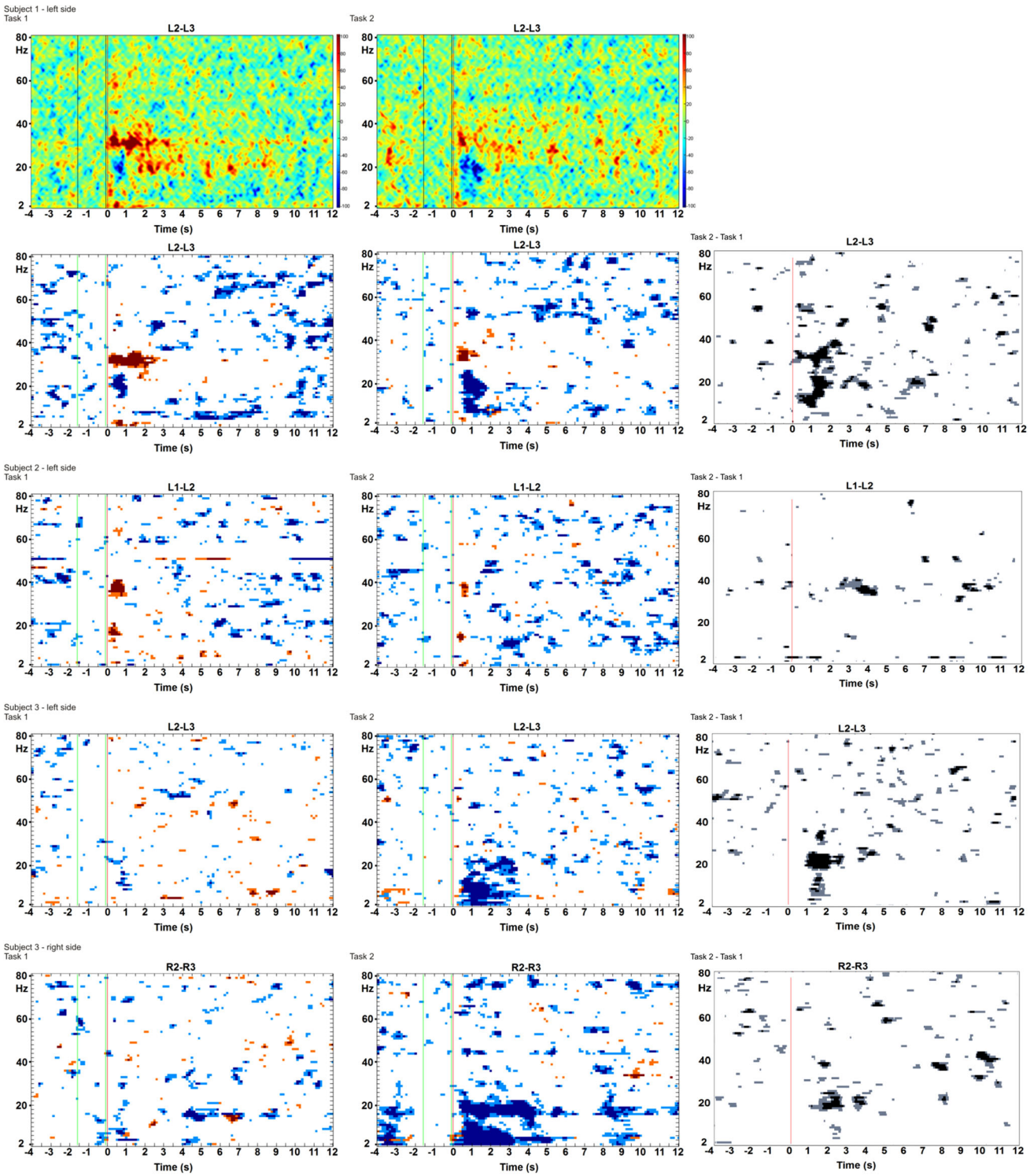

Fig. 2 ERD/ERS in 2–80 Hz frequency range and intervals −4 and 12 s before and after stimuli expressed by TFA, in bipolar montage analysis. The TFA with statistical significance to baseline region (baseline region is determined by *green vertical lines*) is shown. *Red* identifies a power increase (synchronization), *blue* a power decrease (desynchronization). On the *top* both TFA power and TFA with statistical significance in subject 1 are presented. Local field lower gamma ERS can be observed during both tasks with writing single letters in subjects 1 and 2, weaker during task 2. Specific higher activation—alpha and beta ERD—related to increased complexity appeared during task 2 in all subjects: in subjects 1 and 2 on the left side and in subject 3 on both sides. *Left panel* task 1, *middle panel* task 2, *right panel* task 2–task 1 difference (Color figure online)

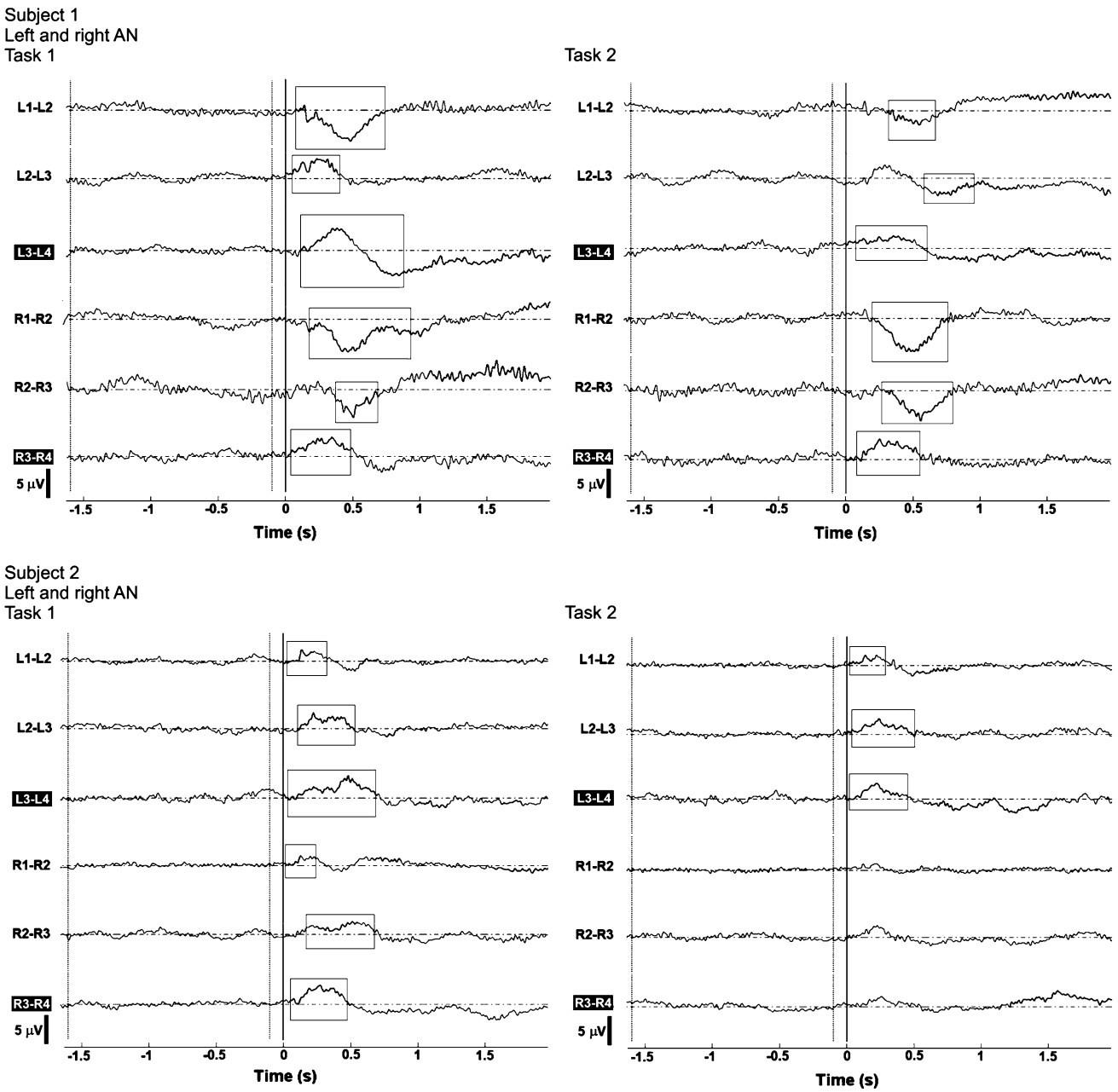

Fig. 3 ERPs in bipolar montage analysis. The *black rectangle* defines the area up to 1 s after stimulus, in which statistically significant differences to baseline can be observed. In subject 1, local phase reversals (generated in contacts L3 and R4—highlighted in *black* fields) are shown; in subject 2, local amplitude gradients are shown (with the maximum in contacts L4 and R4—highlighted in *black* fields, except on the right side during task 2, where no significant changes were found)

Table 2 Reaction times

Subject no.	1		2		3	
	Task 1	Task 2	Task 1	Task 2	Task 1	Task 2
Mean reaction times	0.93 ± 0.36	1.80 ± 0.68	1.59 ± 0.14	1.53 ± 0.34	3.06 ± 1.04	3.61 ± 1.53

Results are in seconds ± STD (standard deviation). Subject 1 has the largest difference between reaction times in the two tasks. In subject 2, there is no difference in reaction times between the two tasks, and the task 2 reaction time is the shortest within the group. Subject 3 has the longest reaction times

writing to the left hemisphere, remains to be examined on a larger population of tested subjects.

In addition, we found significant lower gamma (around 30–40 Hz) ERS during both tasks in subjects 1 and 2. The gamma power reciprocally also slightly decreased while the alpha and beta power decreased with the higher complexity during the task 2.

As the second step we analysed ERPs. Figure 3 displays ERPs in bipolar montage analysis where we observed AN area local field evoked potentials on both the left and right sides in two subjects during both visual cognitive motor tasks with writing single letters, without any specific differences between the tasks. An early peak around 100–200 ms, probably corresponding to the N_2 component known from scalp recordings, was followed by a slow wave ERP lasting between 300 and 750 ms, peaking at 300–500 ms. As the slow wave formed a plateau, the exact latency of the peak could only be estimated approximately. In the bipolar montage, subject 1 displayed phase reversal (generated in contacts L3 and R4) and subject 2 an amplitude gradient (with the maximum in contacts L4 and R4) in the AN area with both tasks. This indicates the involvement of the AN area in cognitive processes that are common to both tasks, i.e. the detection and reading of the letter on the screen and the preparation and the execution of writing. ERPs in subject 3 were not analysable because of prominent slow spontaneous activity of unknown origin with a frequency around 2 Hz that disturbed the evoked potentials (on the other hand, oscillations on frequencies higher than 2 Hz remained analysable).

Discussion

We studied the non-phase-locked event-related changes in the oscillatory activities, as well as phase-locked cognitive event-related electrical activity, i.e. ERPs. In the first case, the power of oscillations may decrease (desynchronize) or increase (synchronize). The main advantage of the ERD/S methodology in comparison to ERPs is the ability to distinguish between cortical inhibition and activation. We analysed power changes in the 2–80 Hz frequency range, i.e. within the theta, alpha, beta, and low and high gamma frequencies. The ERD of the alpha and beta rhythms has been interpreted as a correlate of activation, i.e. increased excitability of the cortex. The ERS in the alpha and lower beta bands has been interpreted as a correlate of a deactivation, i.e. cortical idling or active inhibition (Pfurtscheller 2001). Gamma band ERS seems to be an elementary signal change with multiple functional correlates related to the information spread across brain networks (Basar-Eroglu et al. 1996; Schürmann et al. 1997; Crone et al. 1998; De Pascalis and Ray 1998; Pfurtscheller et al. 2003; Szurhaj et al. 2005; Ihara and Kakigi 2006).

Our experimental protocol contained two tasks with writing single letters. The first task consisted of copying a letter from the screen; the second task required writing a different letter than that appearing on the screen. These two tasks are characterized by several common aspects linked with the writing of single letters. The two tasks had in common: visual detection and reading of the letter on the screen and the preparation and execution of writing. We supposed the attention and working memory load to be engaged on a comparable level in both of the tasks in our experimental protocol as the stimuli were same for both tasks—the letters of the alphabet had to be kept in working memory before and during the task performance. The second task was more complex and less automated and demanded a higher cognitive load which comprised several components, including a higher demand on long-term memory (retrieval of the letters of the alphabet) and several acts that are covered by the common term of executive function: the inhibition of automatic (habitual) responses and the selection, planning, and execution of the chosen response. We assumed that the most prominent difference between the tasks is the higher complexity in the second task. The same experimental protocol was tested in a study with intracerebral recordings from the frontal, parietal and temporal cortices. In several frontal and temporal neocortical areas, the complex task elicited larger alpha and beta ERD than the simple task (Bočková et al. 2007).

As AN–DBS may affect frontal lobe as well as temporal lobe epilepsy, we assumed that cortical regions that had been activated by our tasks could be in functional relation with the AN. AN stimulation produces EEG changes in the frontal and temporal cortex (Kerrigan et al. 2004) and inhibits frontal and temporal lobe seizures.

In this study, the enhanced cognitive demand in task 2 led to an enhanced desynchronization of the oscillations in the AN area in all tested subjects. A large alpha and beta ERD appeared during the complex task in contrast with no significant changes or weak ERD during the simple task. A reciprocal lower gamma ERS decreased with the enhanced complexity. Similar findings were reported in a study from the subthalamic nucleus in PD patients. Peri movement activity was modified by cognitive factors; the beta power decreased while gamma power increased reciprocally (Oswal et al. 2013). We observed gamma power reduction during task 2. Both structures displayed the same desynchronization in the lower frequencies, which is probably a correlate of a mental effort. While the degree of difference between the oscillatory changes elicited by the two tasks varied across the subjects, the general pattern could be detected in all subjects (see Fig. 2). Subject 1 had the largest difference between reaction times in the two tasks.

That is probably because in this subject, the increased mental effort in the more complex task was clearly apparent and was reflected by the alpha and beta ERD enhancement. In subject 2, there was no difference in reaction times during the two tasks and the task 2 reaction time was the shortest within the group. We believe that in this case the mental effort increase was the lowest and was reflected by a weak ERD. This subject was the youngest and had the highest score in the presurgical IQ test. Brighter individuals might be characterized by lower and topographically more differentiated brain activation (alpha band ERD) than less intelligent individuals (Neubauer et al. 2006). The later latency of the ERD onset for subject 2 might be explained by the fact that this ERD is just a fragment of the ERD generally observed in the other subjects, probably active stimulus–response remapping (Oswal et al. 2013). Each subject can have an individual strategy for processing complex cognitive tasks. In this case, the ERD started after the movement onset, while in the other two subjects it started before the movement. The ERD in subject 2 was also related to the complex cognitive task performance, as the general pattern of gamma ERS reduction/alpha and beta ERD increase was also present in this subject. Subject 3 had the longest reaction times, and there was a clear difference in reaction times between the tasks with appropriate ERD changes linked to high mental effort.

We also observed cognitive activity related evoked potentials in two subjects (in subject 3 the ERPs were not analysable due to strong slow external activity that disturbed the phase-locked changes in the thalamus). Steep amplitude gradients and phase reversals were observed between neighbouring contacts L3–L4 and R3–R4 (the ERPs are shown in Fig. 3). These evoked potentials and the low gamma ERS were observed during both tasks of our experimental protocol and probably reflect common processes, e.g. attention, working memory, and reading and writing letters. It confirms that the AN participates in processing complex cognitive visuomotor tasks.

The ERD/ERS pattern is interpreted in general as a thalamocortical mechanism to facilitate focal activation and information processing (focal ERD) by simultaneous deactivation or inhibition of other cortical areas (surround ERS) with the goal of optimizing the energy demand in task-related cortical areas (Pfurtscheller 2006). There is no reason to speculate that the ERD/ERS in the AN should represent another function than it does in the cortex. The second task related occurrence of alpha–beta ERD indicates that the AN participates actively in the cortico-subcortical network processing cognitive functions. The AN stimulation might influence complex cognitive functions via pathways connecting the AN with the prefrontal cortex.

We evaluated the human event-related EEG signal recorded via intracerebral depth electrodes.

Each electrode contained four 1.5 mm contacts with 0.5 mm intercontact distance. Not all contacts were inserted directly to the anterior thalamus; some were placed in its proximity. According to the postoperative CT scans and post-placement MRI, mainly L3 and R3 contacts were placed in the area that anatomically corresponds to the anterior thalamus. The local ERD sources were observed in L2–L3 and R2–R3 montages, i.e. directly in the AN. In subject 2, we observed the local generation of ERD during task 2 on the left side in more distal contacts between L1–2. Contact L1 was located in the dorsal medial nucleus (DMN) so this activity could have been generated in the AN as well as in the DMN. As we observed the origin of this LFP in the AN in the other subjects, we suggest that the ERD in subject 2 more probably also originated in the AN. A possible bias might be due to the small size of the AN from which we could record activity produced in the neighbouring structures. In another study, the verification of DBS electrode placement indicated that structures other than the AN were also stimulated, namely the thalamic nuclei latero-polaris, reticulatus polaris, ventro-oralis internus, and campus Forelii (Osorio et al. 2007). We assume that we recorded mainly from the AN area but some influence of neighbouring thalamic structures cannot be excluded.

Intracerebral recordings are performed on epileptic patients, and we cannot fully exclude the influence of the pathological process and of drugs on the recorded electrical activity. The depth electrodes are submerged in the brain tissue and record from their immediate vicinity. The data are thus obtained directly from subcortical structures, which are inaccessible by scalp measurement. It is not possible to record from the deep brain structures other than in patients with diseases affecting the brain. On the other hand, no interictal epileptiform activity has been recorded in the human AN. We should be careful in interpreting our data in the light of these limitations.

More clinical and experimental studies focused on the possible impact of the high frequency stimulation of the AN on cognitive functions are needed in order to find optimal stimulation parameters with clinical effect and minimalise possible cognitive adverse effects.

Conclusion

The anterior thalamus and frontal and temporal areas participate in cognitive networks processing complex visuomotor tasks. Therefore AN stimulation could influence performance of higher mental cognitive operations. More

attention should be paid to complex cognitive functions in subjects undergoing AN–DBS.

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6.7. Příloha 7 - Involvement of the subthalamic nucleus and globus pallidus internus in orientation and attention

Bočková M, Chládek J, Jurák P, Halámek J, Baláž M, Rektor I. Involvement of the subthalamic nucleus and globus pallidus internus in orientation and attention. J Neural Transm. 2011;118:1235-45

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Cílem této další intracerebrální studie bylo rovněž zkoumání elektrofyziologických fenoménů spojených s kognitivními funkcemi v oblasti bazální ganglií, tj. STN a GPi. Tato práce byla zaměřena na orientaci pozornosti. Intrakraniální EEG bylo snímáno u sedmi pacientů s Parkinsonovou nemocí z oblasti STN a u jednoho pacienta s generalizovanou dystonií z oblasti GPi. Jako experimentální protokol bylo použito tří- stimulové paradigma s frekventními, terčovými a vzácnými neterčovými podněty. Terčové podněty jsou následovány motorickou odpovědí typu „go“, kdežto vzácné neterčové podněty tzv. distraktory mají být ignorovány. Nicméně tyto podněty svojí odlišností a vzácností způsobují nechtěnou orientaci pozornosti a tendenci k odpovědi typu „no-go“. Byly hodnoceny kognitivní evokované i indukované děje. V návaznosti na distraktory byla pozorována specifická pozitivní odpověď v evokovaných potenciálech a dále nízkofrekvenční synchronizace (ERS) v nižším alfa pásmu. Alfa ERS je považována za korelát aktivní inhibice a v tomto případě je tedy korelátem inhibice nechtěné motorické odpovědi na vzácné, ale neterčové podněty. Tento typ reakce byl pozorován u šesti ze sedmi parkinsonských pacientů v STN a i u pacienta s dystonií v oblasti GPi. Je tedy pravděpodobné, že tyto dvě struktury jsou součástí neurokognitivních okruhů, které se podílejí na zpracování a řízení pozornosti.

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MOVEMENT DISORDERS - ORIGINAL ARTICLE

Involvement of the subthalamic nucleus and globus pallidus internus in attention

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Abstract We studied the appearance of cognitive event-related potentials (ERPs) and event-related de/synchronizations (ERD/S) in the subthalamic nucleus (STN) and globus pallidus internus (GPi). We particularly focused on the rare non-target (distractor) stimuli processing. ERPs and ERD/S in the alpha and beta frequency range were analyzed in seven Parkinson's disease patients and one primary dystonia patient with implanted deep brain stimulation (DBS) electrodes. A visual three-stimulus protocol was used (frequent stimulus, target stimulus, and distractor). The non-target and distractor-related waveforms manifested similar shapes. A specific positive ERP peak around 200 ms and a low alpha frequency ERS were detected from the STN as a response to the distractor stimuli in six of the patients with Parkinson's disease and also in the primary dystonia patient's GPi. This positivity probably reflects an attentional orienting response to the distractor stimuli. The STN and GPi are probably involved in attentional cerebral networks.

Keywords Basal ganglia · ERP · ERD/S · Attention · DBS

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Introduction

Deep brain stimulation (DBS) has become a routine functional neurosurgery operation. It is an effective long-term treatment for motor symptoms in advanced Parkinson's disease (PD) (Krack et al. 2003). The most frequently used DBS target is the subthalamic nucleus (STN). The STN plays a major role in motor control and receives projections from the pallidum and from the motor cortical areas (Nambu et al. 2002; Hamani et al. 2004; Aron et al. 2007). In addition, the STN receives projections accounting for involvement in emotional and cognitive activities from the anterior cingulate, and inferior frontal cortex, as well as the medial and dorsolateral prefrontal cortices (Aron et al. 2007; Benarroch 2008). An integrative function in both motor and cognitive operations (Parent and Hazrati 1995; Baunez and Robbins 1999b; Graybiel 1997) has been suggested. The STN has a central position within the basal ganglia-thalamocortical motor, associative, and limbic circuits and might serve as a potent regulator of these pathways. STN–DBS may modulate cognitive and affective functions (Temel et al. 2005). That is probably why, for some patients, the beneficial effects of STN–DBS on motor functions may be accompanied by cognitive impairment and other neuropsychiatric disturbances (Saint-Cyr et al. 2000; Herzog et al. 2003; Anderson et al. 2005; Ballanger et al. 2009). While the impact of STN on non-motor functions appears to be accepted by most authors, its clinical significance is still controversial (Voon et al. 2006). Up to 41% of PD patients treated by STN–DBS face cognitive problems (Temel et al. 2006). However, randomized multicentre studies showed that STN–DBS does not impair overall cognition or affectivity, although there was a selective decrease in frontal cognitive functions after the treatment (Witt et al. 2008). DBS causes only minor

changes in most cases, possibly related to the effect of surgery (Okun et al. 2009). However, at least in some patients the change in cognitive functions after STN–DBS may have a clinical importance.

Intracranial recording studies provide direct access to the deep brain nuclei. Although the electrical event-related activities (evoked as well as induced activities) in the cortical structures during cognitive processing have been quite widely studied, identifying the role of the human subcortical structures has been delayed because of their inaccessibility for scalp measurements. Stereoelectroencephalography (SEEG) recordings in epilepsy surgery patients have enabled the study of electrophysiological phenomena in the basal ganglia. Generators of cognitive event-related potentials were detected in the putamen, pallidum, caudate, and cortex (Rektor et al. 2003, 2005). Recent functional neurosurgery has provided the opportunity to record directly from the STN and globus pallidus internus (GPi), most commonly in patients with PD and primary dystonia undergoing implantation of DBS electrodes (Brown and Williams 2005). In studies based on direct recordings from the STN, it has been suggested that the STN takes part in executive functions processing (Baláž et al. 2008, 2010). The role of the frontal cortex in executive functions is well known. We wondered whether the STN might also play a role in other cognitive functions that implicate the frontal cortices. Experiments in animals have shown an involvement of the basal ganglia nuclei in attentional and motivational functions (Baunez and Robbins 1997, 1999a, b; Christakou et al. 2001; Rogers et al. 2001; Baunez et al. 2002, 2005). Bilateral high-frequency stimulation of the STN in both intact and parkinsonian rats transiently decreased accuracy in performing a visual attentional task, suggesting impaired attention (Baunez et al. 2007). The aim of this work was to study the involvement of the STN in attentional and orienting processes that are linked to the rare distractor stimuli (Squires et al. 1975; Desmedt 1981; Halgren et al. 1995a).

Methods and materials

Subjects

Seven Parkinson's disease patients suffering from late L-DOPA-induced motor complications and one primary generalized dystonia patient (suffering predominantly from trunk lateroflexion) with externalized DBS electrodes implanted in the STN or GPi participated in the study (Tables 1, 2). We had to exclude three other dystonic patients from the data analysis because their severe abnormal movements produced too many artefacts. All patients were indicated for the DBS surgery by the Commission for Neuromodulation Surgery of the Brno Movement Disorders Centre. All the subjects were informed about the character of this study and gave their informed consent. The study received the approval of the local ethics committee. The measurements were performed during the patient's "on" state in PD, approximately 1 h after morning dopaminergic medication dose. The medication was stable in all subjects.

Before the operation, all subjects underwent a detailed neuropsychological examination; the examination showed no signs of dementia (Table 3).

Surgical procedure

The stereotaxic frame used during the surgical procedure (electrode implantation) was the Leibinger open frame with the Praezis Plus software and the Talairach diagram. The STN coordinates used were in respect to the AC–PC (anterior commissure–posterior commissure) line: 12.0 mm laterally, 5.0 mm below, and 3.0 mm behind the midpoint of the AC–PC line. The GPi coordinates were: 20.0 mm laterally, 4.0 mm below, and 3.0 mm in front of the midpoint of the AC–PC line. The stimulation electrodes (Medtronic, Inc.) were implanted bilaterally into the targeted structure by stereotaxic MRI-guided technique

Table 1 Patient characteristics

Su. No.	Sex	Age (years)	Dg.	Target	Medication	LEDD (mg)	HD	DD (years)
1	M	65	PD	STN	L-DOPA, entacapone, pramipexol, amantadine	1150	Right	13
2	M	55	PD	STN	L-DOPA, entacapone, ropinirole, amantadine	1800	Right	11
3	F	66	PD	STN	L-DOPA, entacapone, ropinirole	1150	Right	6
4	F	69	PD	STN	L-DOPA, entacapone	600	Right	7
5	M	56	PD	STN	L-DOPA, entacapone, rotigotine	1100	Left	7
6	F	68	PD	STN	L-DOPA, entacapone, pramipexol	1450	Right	14
7	F	55	PD	STN	L-DOPA, entacapone, pramipexol	800	Right	12
8	M	50	GD	Gpi	None	0	Right	30

Su. subject, *No.* number, *Dg.* diagnosis, *HD* hand dominance, *DD* disease duration, *LEDD* levodopa equivalent daily dose, *PD* Parkinson's disease, *GD* generalized dystonia, *STN* subthalamic nucleus, *GPi* globus pallidus internus

Table 2 DBS clinical effectiveness in PD patients—UPDRS III scores

Subject no.	(1) UPDRS III—preoperative	(2) UPDRS III—postoperative
1	61	20
2	54	40
3	24	6
4	28	11
5	44	NA
6	64	NA
7	39	14

(1) Off medication preoperative, (2) on stimulation/off medication 12 months after operation

under local anaesthesia (general anaesthesia in the GPi case because of generalized dystonia). The definitive electrode placement was confirmed by four microelectrode recordings. The motor part of the STN was identified by recording the specific patterns of neuronal activity and background activity, and by following motor responsiveness to intraoperative stimulation. Once the final target coordinates were determined, a permanent quadripolar DBS electrode (model 3389, with 1.5 mm contact length and 0.5 mm intercontact distance) was implanted. The electrode position was verified by the intraoperative use of fluoroscopy comparing the position of the microrecording electrodes trajectories with the definitive quadripolar macroelectrode trajectory and also by a post-operative CT scan. In the immediate post-implantation period, the electrodes remained externalized. A special externalized cable enabled the intracranial EEG recording. The internalization and the stimulator implantation were performed within a week after the positioning of the DBS electrodes.

Experimental protocol and recordings

The EEG signal was recorded in the post-operative period during which the electrodes were externalized. For cognitive testing, a visual three-stimulus protocol was used (Conroy and Polich 2007; Polich 2007) (see Table 2). The frequent (non-target, standard) stimuli, which were 70% of all the stimuli, were small blue circles. These were not to be followed by a reaction. The target stimuli, which were 15% of all the stimuli, were larger blue circles. The subjects were asked to press an electrically connected button at the time of the target detection. The distractors (rare non-target stimuli), which were presented 15% of the time, were black and white checkerboards; no response was required (Table 4).

The interstimulus interval was 4 s. The duration of the stimulus exposure was 200 ms.

The visual stimuli were presented in a random order on a monitor 1.5 m in front of patients. Subjects received clear instructions and practiced the task briefly before the recordings. Subjects reclined comfortably in the monitoring bed, in a quiet room with a constant temperature. They were instructed to remain calm, to keep their eyes fixed on the monitor, and to avoid unnecessary movements. Subjects received clear instructions and practiced the task briefly before the recordings.

The EEG system TruScan 32 channel (Deymed Diagnostic, Alien Technic) was used for the recording. The recordings were monopolar, with a linked earlobe reference. The sampling rate was 1024 Hz. Standard anti-aliasing filters were used.

Data analysis

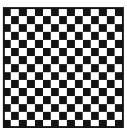
The EEG signal was processed and analyzed off-line using ScopeWin and ScopeMat software. The data were first

Table 3 Neuropsychological examination (preoperative)

su	WAIS	Mattis	roI	roL	roR	stI	stW	stC	stWC	TL	MADRS	BDI
1	91	144	51	60	39	54	20	33	34	29	2	3
2	106	144	60	44	47	53	45	44	45	32	10	18
3	90	136	51	51	60	49	38	40	37	NA	17	10
4	116	144	51	51	54	66	48	59	70	32	6	12
5	97	144	51	50	43	60	47	42	31	33	7	9
6	120	140	54	55	55	64	49	55	67	30	6	7
7	100	140	64	64	64	57	36	38	47	31	14	17
8	95	130	NA	NA	NA	NA	NA	NA	NA	28	0	NA

su subject number, *WAIS* Wechsler Adult Intelligence Scale—IQ score, *Mattis* Mattis Dementia Rating Scale—raw score, *roI* Rey-Osterrieth Complex Figure Test, immediate reproduction—*T* score, *roL* Rey-Osterrieth Complex Figure Test, later reproduction—*T* score, *roR* Rey-Osterrieth Complex Figure Test, recognition—*T* score, *stI* Stroop Test-interference—*T* score, *stW* Stroop Test words—*T* score, *stC* Stroop Test colours—*T* score, *stWC* Stroop Test words/colours—*T* score, *TL* Tower of London Test—raw score, *MADRS* Montgomery-Asberg Depression Rating Scale—raw score, *BDI* Beck depression inventory—raw score; *NA* not available

Table 4 Experimental paradigm

Category	Description	Image	Dimension	Duration (ms)	Response	Trials	Proportion (%)
Target P3b	Large blue circle		Diameter = 3.5 cm	200	Press a button	30	15
Non-target	Small blue circle		Diameter = 3.0 cm	200	No response	140	70
DistractorP3a	Large black and white checkerboard		Side = 14.0 cm	200	No response	30	15

segmented according to the visual stimuli trigger onset (vertical line marks in the EEG trace indicating the time of visual stimuli presentation to the subjects). The segments of 4 s length were visually inspected, and segments containing artificial signals or mistaken responses were removed. After trend elimination in each segment, data were filtered with 0.2–40 Hz bandwidths and averaged to obtain evoked responses: event-related potentials (ERPs). The baseline interval was determined 600–100 ms before stimuli presentation. The mean values from the baseline intervals were subtracted within each trial. The unipolar reference (Fig. 1) analysis was followed by a bipolar montage (Fig. 2) evaluation to exclude the volume conduction from surface neocortical discharges or transsynaptic propagation along cortical–subcortical pathways and confirm the local generation of the potentials (Wennberg and Lozano 2003). Contacts in the STN are placed very close together. Any EEG signal on the common reference is eliminated by a bipolar montage. Even a small bipolar montage activity corresponding with the common reference activity can display the origin of detected activity in the STN.

Time frequency analysis (TFA, Fig. 3) (Akay 2000) was used to determine the event-related de/synchronizations (ERD/S) in the alpha and beta frequency ranges. A decrease in band power indicates induced event-related desynchronization (ERD), an increase in band power indicates event-related synchronization (ERS) (Pfurtscheller and Aranibar 1977). The ERD of the alpha and beta rhythms is interpreted as a correlate of an activated cortical area with increased excitability. The ERS in the alpha and lower beta bands can be interpreted as a correlate of a deactivated cortical area, i.e., cortical idling or active inhibition (Pfurtscheller 2001). TFA produces a matrix in which each row represents the over trials averaged signal power envelopes in a 2 Hz frequency band width (x-axis represents time; y-axis represents frequency). The frequency step between two lines was 1 Hz. In the baseline-normalized TFA matrix, ERS is represented by positive values (yellow, red) and ERD by negative values (green, blue).

Statistical analysis

Two types of statistical significances were tested:

(1) The statistical significance of the differences between the mean amplitude observed during the baseline region and the mean value computed as a mean from the neighbourhood of each point (150 ms length) after stimuli was expressed as a probability value (p) using a non-parametric Wilcoxon Rank Sum (Signed Rank) test for paired samples. The amplitude changes were considered as significant when $p < 0.05$; see Fig. 1 significance to baseline.
(2) The differences between stimuli were analyzed by the post hoc Scheffe test for multiple comparisons. The level of significance was set at $p < 0.01$; see Fig. 1 inter-stimuli significance.

Results

We evaluated the signal recorded from four contacts placed in the STN and GPi bilaterally in each subject. The ERP shape was individual; latencies and amplitudes varied according to the stimulus type and among the subjects, and did not fully correspond to the P300 potentials commonly observed from scalp recordings. In six subjects (in subjects 4 and 7 only on the right side) we found a late positivity in

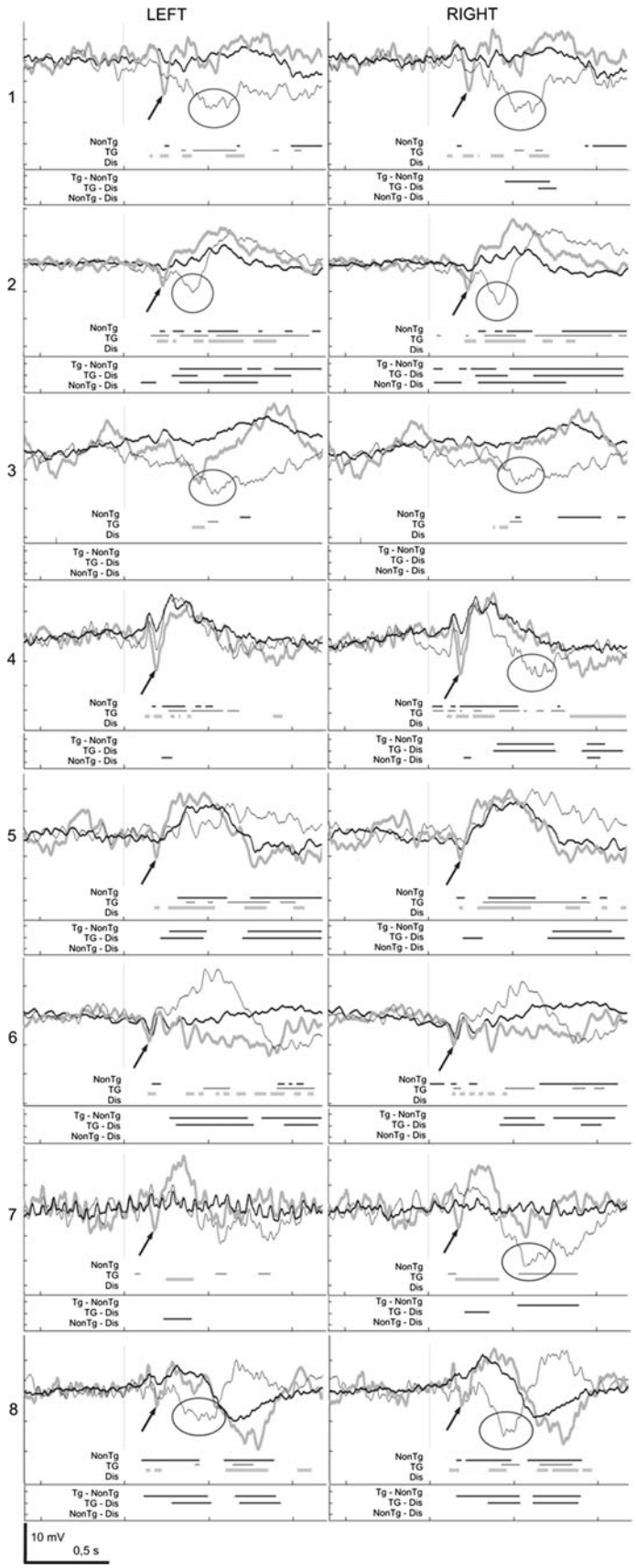


Fig. 1 ERPs recorded in the STN and Gpi. Of the four DBS electrode contacts, the most reactive contact (i.e., the contact with the highest amplitude event-related potential) from the four contacts of the DBS electrodes is shown for each subject. In the majority, the most reactive contact corresponds to the contact located within the STN (or Gpi) as defined by the intraoperative microrecording and the postoperative CT scan. It is usually also the contact with the best clinical effect on motor symptoms during DBS stimulation. Subject no. *1–7* Parkinson′s disease STN, subject no. *8* generalized dystonia Gpi. *Thick grey line*—distractor, *medium black line*—non-target, *thin line*—target. The distractor-related early positive peaks with latency around 200 ms are marked by *arrows*. The target-related late positive waves with latency around 400–600 ms are marked by *circles*. *Horizontal bars* below curves indicate significance. *Upper horizontal bars* determine significance to baseline: *thick grey bar*—distractor, *medium black bar*—non-target, *thin bar*—target. *Bottom horizontal bars* determine inter-stimuli significance—pairs are marked on the left

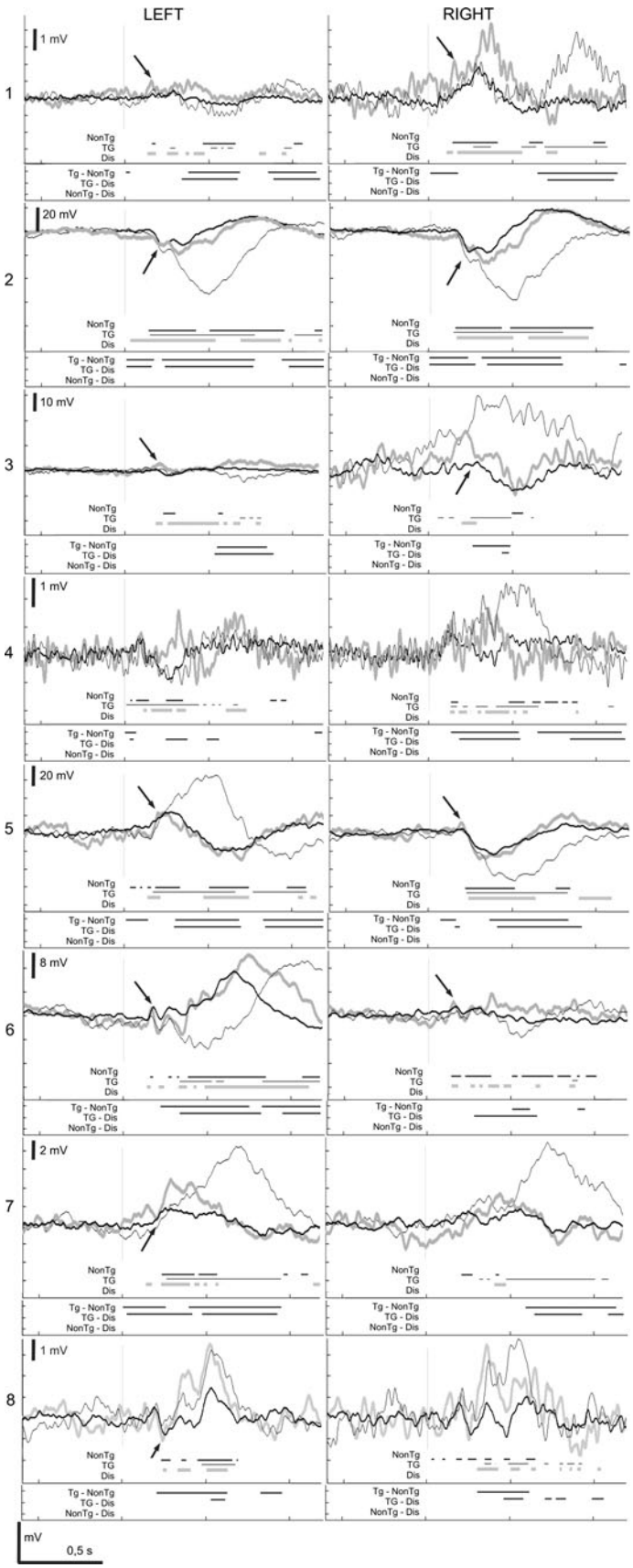


Fig. 2 The most reactive (with the highest amplitude) bipolar montage (montage between the contacts within the DBS electrode). Next description is the same as in Fig. 1. For most subjects, the distractor activity can be observed and is marked with an *arrow*. This activity corresponds to the marked activity in Fig. 1. This finding confirms the assumption that the detected STN activity is not artificial and that this early positive peak originated in the STN (and Gpi). The volume conduction from surface neocortical discharges or transsynaptic propagation along cortical–subcortical pathways are excluded

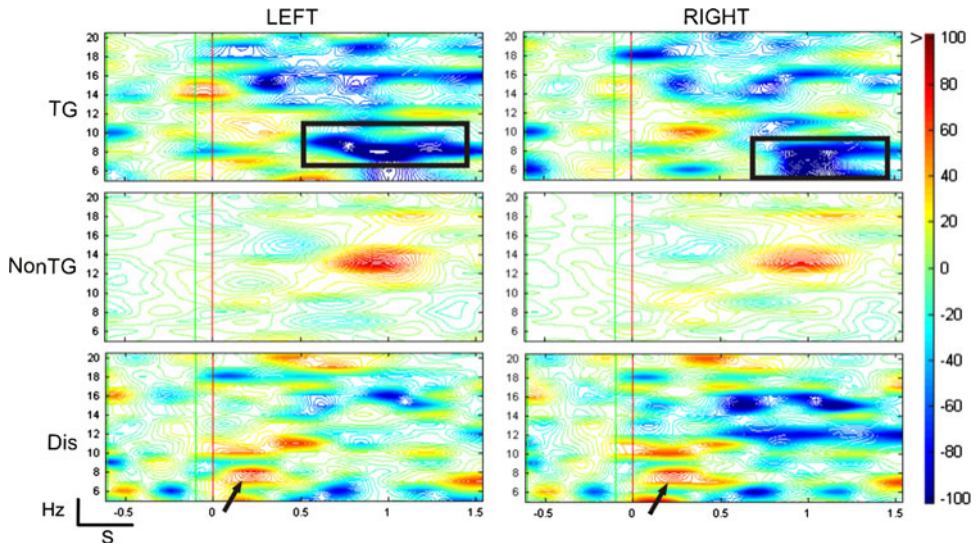


Fig. 3 Time frequency analysis (TFA) in the alpha and low beta frequency range. The *horizontal axis* represents time, *vertical axis* represents frequency. Subject No. 1, contacts in the STN on the left and right side. *Red* indicates ERS—event-related synchronization, increase in band power. *Blue* indicates ERD—event-related desynchronization, decrease in band power. TFA values are normalized to baseline region (*green vertical lines*) 600–100 ms prior stimulus (*red vertical line*). A positive value 100 (ERS) means two times power increase, and a negative value (ERD) −100 means two times power decrease to the mean from the baseline region. ERS values higher then 100 are cut away. The specific distractor-related early ERS is marked by *arrows*, the target-related late ERD by *rectangles*

the latency range 400–600 ms related to the target stimuli in the STN as well in the Gpi. The majority of the subjects were right-handed and the motor task was performed using the right hand. For this reason, we think that the potentials are not potentials associated with movement (they were present bilaterally or only in the right STN), but that they are related to the cognitive activity processed by target stimuli response performance. The non-target and distractor-related waveforms manifested similar shapes. The amplitude of the distractor ERPs was slightly higher. The most prominent difference between the ERPs was in the appearance of an early positive peak around 200 ms evoked by the distractor that was not displayed after the target and non-target stimuli. This positivity probably reflects the attentional orienting response to the distractor stimuli. This potential was detected in all subjects except subject 3. In subject 7, the EEG signal in the domain of frequent stimuli appeared to be contaminated by artefacts (probably tremor-related) on the left side, however, even in this subject the distractor-evoked 200 ms potential could be recorded.

The bipolar montage analysis was also performed, and the local generation of the potentials was confirmed. Local field sources of the distractor-evoked early positive peak were found in six STN PD patients and in the primary dystonia Gpi (Fig. 2).

The induced oscillatory activities (ERD/S) in the alpha and low beta frequency range were analyzed using the TFA. We observed a constant early increase (ERS) in the low alpha band power in all subjects (except subject 3), which corresponds to the specific distractor-related early peak in ERPs, more pronounced on the right side. In addition, there was a late higher alpha power decrease (ERD) related to the target stimuli (also except in subject 3), which temporally followed the P3b-like wave in the ERPs.

The different results in subject 3 in comparison to the whole group could have been caused by a worse cognitive performance of the paradigm. The percentage of this patient's correct responses was the lowest (86% subject 3, 98–100% other subjects). The preoperative neuropsychological examination did not show any significant deficits in comparison to the other subjects, only Montgomery-Asberg Depression Rating Scale (MADRS) score was the highest in this subject. We may hypothesise only that depression or a microlesional effect in the STN after the electrode implantation could have caused an attentional deficit during the performance of the experimental paradigm.

Discussion

We studied the electrical phenomena accompanying the cognitive processing recorded in the STN in seven Parkinson's disease patients and in the GPi in one primary dystonia patient.

A three-stimulus visual experimental paradigm was used. This paradigm is similar to the classical oddball task consisting of frequent (non-target) stimuli and rare (target)

stimuli that evoke cognitive event-related potential called P300 (or P3). In a three-stimulus paradigm a third, non-frequent stimulus appears without any required response (Polich 2007). This distractor stimulus evokes a response called P3a on the scalp (Courchesne et al. 1975; Grunwald et al. 1998; Knight 1984, 1997). This response is task-irrelevant, but insufficiently ignored, and precedes the task-relevant target stimulus evoked potential (called P3b) (Squires et al. 1975; Schröger and Wolff 1998; Kaipio et al. 2000). The distractor-evoked ERP had a frontocentral maximum on the scalp (latency around 375 ms), whereas the target-related ERP had a parietal maximum (latency range 450–475 ms) in a study using the same protocol that was used in this study (Conroy and Polich 2007; Polich 2007). The distractor-related evoked potential is interpreted as an orienting response, an involuntary rapid shift of attention to new (never previously experienced), unexpected (out of context), or unpredictable stimuli. The ERP occurrence indicates that the distractor stimulus has involuntarily captured the attention and is most likely within the focus of attention (Friedman et al. 2001). It was suggested that the distractor-related response represents the cortical component of the early attentional system, while target processing reflects a higher cognitive closure, perhaps including memory processes (Halgren et al. 1995a).

Intracerebral recording in epilepsy surgery patients displayed multiple cortical and subcortical generators of various cognitive ERPs (Rektor et al. 2007). The shape of intracerebral potentials frequently varies, and it is often difficult to identify the equivalents of individual components recorded on the scalp. The generators (steep amplitude gradients or phase reversals indicating a local origin of the potential) of distractor-related ERP were found in several frontal areas, and they were also recorded in more posterior cortical areas, namely the parietal, temporal, and limbic cortices. The latencies in the frontal lobe were shorter than that of P3a recorded on the scalp. The latency of the distractor-evoked ERP in the prefrontal cortex was also shorter than the latency of ERP recorded in the parietal or temporal lobes. A temporal hierarchy within the network for directed attention was suggested, with a key role played by the prefrontal cortex (Halgren et al. 1995a, b; Baudena et al. 1995). The central role of the prefrontal cortex in directing attention to novel events was also confirmed by other studies (Daffner et al. 2000; Bledowski et al. 2004; Kiehl et al. 2005; Strobel et al. 2008). The prefrontal cortex can have both an excitatory and inhibitory influence on the neural generators of early ERP components and is involved in early attentional processing stages (Herrmann and Knight 2001).

In our study, as the first step in the analysis, we analyzed the ERPs from the STN and Gpi. We observed a late positive potential in the latency range around 500 ms linked to the target stimuli processing. The distractor stimuli were accompanied by a specific short positive peak in the latency range around 200 ms. ERP latency depends on the classification speed, which is proportional to the time required to detect and evaluate the stimulus (Kutas et al. 1997; Magliero et al. 1984; Polich 2007). The latency of this early distractor-specific potential might indicate a fast evaluation and categorization of the distractor stimuli in the basal ganglia. The nearly simultaneous appearance of the early distractor-specific potentials in the two structures forming consecutive parts of the cortico-basal ganglia-thalamocortical circuitry, i.e., GPi and STN, may be interpreted as a sign of the specific involvement of the basal ganglia in orienting and attentional processes. Local field generation of this early distractor-related activity was confirmed using the bipolar montage analysis. The only patient with GPi electrodes also displayed a short latency distractor-evoked potential. Unfortunately, we had to exclude other dystonia Gpi patients because of severe abnormal movement-related artefacts. We decided to present the data from the only analyzable subject because the results were interesting in the context of the STN recordings and because technically correct recordings from Gpi in dystonia are rare. We are aware that data obtained from only one subject must be further verified by recordings in more subjects.

Event-related cerebral activity may be evoked or induced. Evoked potentials (ERP) are time and phase locked to the stimuli. Induced changes (ERD/S) are time locked, but not phase locked to the stimuli. As the second step, we were interested in the relationship of the ERP to the ERD/S, especially in the lower and higher alpha frequency range, as it is known that alpha band spectral power co-varies with P300. Other frequency ranges demonstrate similar associations, but slow alpha activity yields the strongest correlation (Intriligator and Polich 1995; Polich 1997). Alpha ERD occurs during cognitive processing; target-related P3 potential is clearly related to the desynchronization of late alpha frequency EEG (Boiten et al. 1992; Pfurtscheller and Klimesch 1991, 1992; Klimesch 1997; Polich 2007; Sergeant et al. 1987; Yordanova et al. 2001). We have observed ERD in higher alpha frequencies following the late positive response in the ERP (latency 500–1500 ms) induced by the target stimuli. This probably represents the performance of the target-related cognitive–motor response. An early lower alpha frequency band ERS was observed exclusively after the distractor stimuli. There was a temporal overlap of the distractor-specific ERS and ERP. As the ERS in the alpha band is considered as a correlate of an active inhibition, this reaction probably represents suppression of an involuntary shift of attention and then inhibition of further cognitive processing of the distractor stimuli. Both early distractor-related ERS and

ERP may share common mechanism with the N200 response in the scalp recordings. The amplitude of N200 is higher in stop trials than in go trials in go/no and stop-signal tasks (Enriquez-Geppert et al. 2010). The inferior frontal cortex (IFC) plays an inhibitory role in motor control. It was demonstrated that the IFC may modulate various cognitive functions of the basal ganglia and specifically of the STN via a direct functional projection between the IFC and the STN (a "hyperdirect" pathway) (Aron and Poldrack 2006; Aron et al. 2007; Baláž et al. 2010). Apart from the striatum, the STN is the only structure in the basal ganglia that receives a direct cortical projection (Albin et al. 1989; Parent and Hazrati). For this reason, we would expect a later latency of the attentional phenomena in the Gpi. An early positive peak was present in the Gpi at around 200 ms after the distractor stimuli. In the Gpi, a slow wave with a latency around 800 ms following the distractors was also observed. The early activation of the STN may lead to response suppression (in our case, inhibition of further cognitive processing of the distractor stimuli and suppression of the motor response). The co-activation of the Gpi (Mink 1996) may lead to subsequent inhibition of the thalamo-cortical motor program (Coxon et al. 2006; Aron et al. 2007).

We evaluated the human event-related EEG signal recorded via intracerebral depth electrodes. The main disadvantage of all intracerebral recordings is that they are performed in structures that could be modified by pathological processes (in this case by Parkinson's disease and generalized dystonia) and that the results could be influenced by medication. The other limitation of this study is the absence of simultaneous scalp recordings (Fz, Cz, Pz), which could not be placed because of the sterile bandaging over the parietally localized electrode extensions as we respected the patients safety and the prevention from infectious complications. On the other hand, as the depth electrodes are submerged directly into the brain tissues and record from their immediate vicinity, the results are obtained directly from cerebral structures. Some of them are almost inaccessible by scalp measurements, so the data measured by the depth recordings provide important information about the function of the subcortical structures. We performed simultaneous scalp recordings (Fz, Cz, Pz—in this case they could be placed because of other electrode trajectory) using the same experimental paradigm in an epilepsy surgery group of patients with implanted deep brain electrodes. We did not observe the distractor-related early short positive peak on the scalp.

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6.8. Příloha 8 - Oscillatory changes in cognitive networks activated during a three-stimulus visual paradigm: an intracerebral study

Bočková M, Chládek J, Šímová L, Jurák P, Halámek J, Rektor I. Oscillatory changes in cognitive networks activated during a three-stimulus visual paradigm: an intracerebral study. Clin Neurophysiol. 2013;124:283-91

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Třístimulové kognitivní paradigma bylo použito i ke studiu kognitivních oscilací v oblasti kortikálních struktur na souboru pěti epileptochirurgických pacientů s intracerebrálními elektrodami, které byly implantovány k exploraci epileptogenního ložiska před plánovaným operačním řešením. Byl hodnocen intrakraniální EEG signál z celkem 404 kontaktů. Hlavním zaměřením této práce byla odpověď na vzácné neterčové podněty tzv. distraktory a její porovnání s výsledky z předchozí práce z oblasti bazálních ganglií na souboru DBS subjektů. Byla pozorována časná ERS v oblasti theta frekvenčního pásma jako korelát inhibice nechtěné odpovědi a orientace pozornosti, a to především v oblasti prefrontálního kortexu. Prefrontální kortex a STN se tak pravděpodobně spolupodílí na orientaci pozornosti a inhibici odpovědí typu „no-go“, což je pravděpodobně podkladem i tzv. hyperpřímé dráhy.

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Oscillatory changes in cognitive networks activated during a three-stimulus visual paradigm: An intracerebral study

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HIGHLIGHTS

- We studied oscillatory changes in cognitive networks activated during a three-stimulus paradigm.
- The SEEG signals were analysed using event-related de/synchronization methodology.
- Prefrontal structures seem to be essential in attention orienting response and generating the "no-go" signal.

ABSTRACT

Objective: The aim of this work was to study the oscillatory changes during target and distractor stimuli processing. We focused mainly on responses after distractor stimuli in the prefrontal cortex and their possible relation to our previous results from the basal ganglia.
Methods: Five epilepsy surgery candidates with implanted depth electrodes performed a three-stimulus paradigm. The frequent stimulus (70%; without required response) was a small blue circle, the target stimulus (15%; with motor response) was a larger blue circle, and the distractor stimulus (15%; without required response) was a checkerboard. The SEEG signals from 404 electrode contacts were analysed using event-related de/synchronization (ERD/S) methodology.
Results: The main response to the target stimuli was ERD in the alpha and low beta bands, predominantly in the motor control areas, parietal cortex and hippocampus. The distractor stimuli were generally accompanied by an early theta frequency band power increase most markedly in the prefrontal cortex.
Conclusions: Different ERD/S patterns underline attentional shifting to rare target ("go") and distractor ("no-go") stimuli.
Significance: As an increase in lower frequency band power is considered to be a correlate of active inhibition, the prefrontal structures seem to be essential for inhibition of non-required movements.

1. Introduction

A previous intracerebral study of the basal ganglia, i.e. the subthalamic nucleus (STN) and internal globus pallidum (Gpi), was performed on a group of Parkinson's disease and dystonia patients who underwent deep brain stimulation electrodes (DBS) implantation (Bočková et al., 2011). The results of that study led us to undertake this study. A visual three-stimulus protocol (frequent stimulus, target stimulus, and distractor) was used in both studies to investigate cognitive patterns related to rare target and distractor stimuli. Target stimulus is associated with the cognitive processes of context updating, context closure, and event categorization. Distractor stimulus is mainly connected with an attentional orienting response (Friedman et al., 2001; Bledowski et al., 2004) and possibly also with the inhibition of an involuntary response. We focused mainly on the non-phase locked (induced) EEG changes. Different patterns related to targets and distractors were observed in the STN and Gpi. Target stimuli were followed by a decrease in higher alpha frequencies, while distractors elicited an early lower alpha frequency band power increase. The distractor-related response occurred very early, around 200–250 ms, and had a rather inhibitory character. As the distractor-related response is generally connected to the prefrontal cortex, we hypothesized that this signal could originate from the frontal cortex and be conducted to the STN via a "hyperdirect pathway" (Nambu et al., 2002; Aron and Poldrack, 2006; Aron et al., 2007; Baláž

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et al., 2010). For this reason, we decided to explore EEG changes using the same experimental paradigm on a group of epilepsy surgery patients via electrodes implanted to the cortical structures in order to compare the results from the prefrontal cortex and the basal ganglia and to map cognitive networks activated by target and distractor stimuli in general using the ERD/ERS methodology, that has not yet been performed for this reason in intracerebral recordings to our knowledge.

Time and phase-locked (evoked) EEG changes, called event-related potentials (ERPs), and time but non-phase locked (induced) EEG changes can be studied. We did not further analyse the cognitive event-related potentials because they have been widely studied using scalp EEG recordings as well as stereoencephalography (SEEG). P300 (P3) is a long – latency positive waveform known to be a correlate of cognitive processing, generated by the voluntary detection of a task – relevant stimulus (Sutton et al., 1965; Squires et al., 1975; Knight, 1997). P3 has a widespread topography and has been subdivided into P3a with dominant fronto-central distribution and later parieto-temporal P3b. A P3a potential is elicited by the distractor stimuli in a three-stimulus novelty protocol (Comerchero and Polich, 1999; Polich, 2007). P3b is enhanced by the certainty of target detection elicited by rare stimuli requiring a response; P3a is linked to the rare non-target (distractor) or novel stimuli not requiring a response (Squires et al., 1975; Desmedt, 1981; Halgren et al., 1995a,b). Intracranial SEEG studies in epilepsy surgery patients display multiple cortical generators of both P3a and P3b components. A network processing P3b composed of the lateral prefrontal and temporal cortices, the amygdalo-hippocampal complex, the cingulate, and possibly the superior parietal cortex was described (Rektor et al., 2007). The generators of P3a were found in several frontal areas, mostly in the dorsolateral prefrontal cortex, the anterior cingulate, and the orbitofrontal cortex. P3a waves were also recorded in more posterior cortical areas, namely the parietal, temporal, and limbic cortices. Intracerebrally recorded frontal P3a latency occurred earlier than in scalp recordings, but also had a shorter latency than P3a recorded in the parietal or temporal lobes. According to these findings, a temporal hierarchy within the network for directed attention was suggested, with a key role played by the prefrontal cortex (Halgren et al., 1995a,b; Baudena et al., 1995). The central role of the prefrontal cortex in directing attention to novel events was confirmed by a study in patients with frontal lobe damage who exhibited a markedly reduced amplitude of the novelty P3 response (Daffner et al., 2000) and by fMRI studies devoted to cerebral hemodynamic changes related to novelty and target stimuli (Bledowski et al., 2004; Kiehl et al., 2005; Strobel et al., 2008).

In this study, we focused on non-phase locked (induced) EEG changes using event-related synchronization (ERS) and desynchronization (ERD) methodology. Task-related modifications of the brain rhythms may reveal other aspects of brain functions beyond the electrical activity in the ERP (P3) protocols. The cerebral distribution of non-phase-locked changes of brain rhythms elicited by a given task may be wider than that of ERPs (Sochůrková et al., 2006) and may reveal the participation of a brain structure in the functional task-related networks in the brain. Spatial mapping of ERD/ERS is widely used to study the dynamics of cortical activation patterns (Pfurtscheller, 2001). The main advantage of this methodology in comparison to ERPs is the possibility to distinguish between cortical inhibition and activation, thus providing another dimension to the analysis. A decrease in frequency power indicates ERD; an increase in frequency power indicates ERS (Pfurtscheller and Aranibar, 1977). We analysed power changes within the theta, alpha, beta, and low gamma frequencies. The ERD of the alpha and beta rhythms has been interpreted as a correlate of activation, i.e. increased excitability of the cortex. The ERS in the alpha and lower beta bands has been mostly interpreted as a correlate of a deactivation, i.e. cortical idling or active inhibition (Pfurtscheller, 2001). Gamma band ERS seems to be an elementary signal change with multiple functional correlates (Basar-Eroglu et al., 1996; Schürmann et al., 1997; Crone et al., 1998; de Pascalis and Ray, 1998; Pfurtscheller et al., 2003; Szurhaj et al., 2005; Ihara and Kakigi, 2006).

2. Materials and methods

2.1. Subjects

Five pharmacoresistent epilepsy patients participated in the study. The patient characteristics are shown in Table 1. All patients were referred for pre-operative intracranial exploration by a special epilepsy surgery commission in order to precisely localize the seizure onset zone. Each patient received 6–13 orthogonal platinum electrodes in the investigated brain structures using the methodology of Talairach. Standard Micro Deep semi-flexible five to fifteen contact electrodes (DIXI), 0.8 mm diameter, 2 mm contact lengths, and 1.5 mm inter-contact intervals were used for invasive EEG monitoring. Contacts at the electrode were numbered from the medial to the lateral side. The exact positions of the electrodes and their contacts in the brain were verified using post-placement magnetic resonance imaging with electrodes in situ. The recordings from lesional anatomical structures and epileptogenic zones were not included in the analysis. All the subjects were informed about the character of this study and gave their informed consent. The study received the approval of the local ethics committee.

2.2. Experimental protocol and recordings

Subjects reclined comfortably in the monitoring bed, in a quiet room, with a constant temperature. They were instructed to

Table 1
Patient characteristics.

Subject No	1	2	3	4	5
Sex	Male	Female	Female	Female	Female
Age	25	41	16	29	40
Hand dominance	Right	Right	right	Right	Right
MRI	Normal	RP calcif. in falx	Cystis in LT pole	LT FCD	Right mesio- T sclerosis
SOZ	Left insulo-opercular	Undetected, extra-T	Left T	Left T	Right mesio- T
Therapy	LVT, PNT, CLO	LTG, CBZ	LTG, LVT, TOP	LTG, CBZ	TOP, GAB
Rec. structures	LF, LT	LF, LT, RF, RP, RT	LT, RT	LT, RT	LF, LT, RF, RT
Rec. sites	51	110	81	57	105

T – temporal; F – frontal; P – parietal; R – right; L – left; LTG – lamotrigine; CBZ – carbamazepine; TOP – topiramate; LVT – levetiracetam; PNT – phenytoin; CLO – clonazepam; GAB – gabapentin; FCD – focal cortical dysplasia; calcif – calcification; SOZ – seizure onset zone; Rec – recording; Rec. sites – number of intracerebral electrode contacts.

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Table 2
Experimental paradigm.

Category	Description	Image	Dimension	Duration (ms)	Response	Trials	Proportion (%)
Target	Large blue circle		Diameter = 3.5 cm	200	Press a button	30	15
Non-target	Small blue circle		Diameter = 3.0 cm	200	No response	140	70
Distractor	Large black and white checkerboard		Side = 14.0 cm	200	No response	30	15

remain calm, to keep their eyes fixed on the monitor, and to avoid unnecessary movements. The monitor was situated in the same place for all the subjects, 1.5 m in front of their eyes, at the end of the monitoring bed.

The EEG signal was recorded from the frontal, temporal, and parietal cortices using the intracerebral electrodes. The EMG (m. flexor carpi radialis) and EOG were recorded. The recordings were performed using the EEG system TruScan 128 channel (Deymed Diagnostic, Alien Technic). The recordings were monopolar, with a linked earlobe reference. The sampling rate was 256 Hz, standard anti-aliasing filters were used – the upper and lower frequencies of EEG recording were 0.05–100 Hz.

For cognitive testing, a visual three-stimulus protocol was used (Conroy and Polich, 2007; Polich, 2007) (see Table 2). The frequent (non-target, standard) stimuli, which were 70% of all the stimuli, were small blue circles. These were not to be followed by a

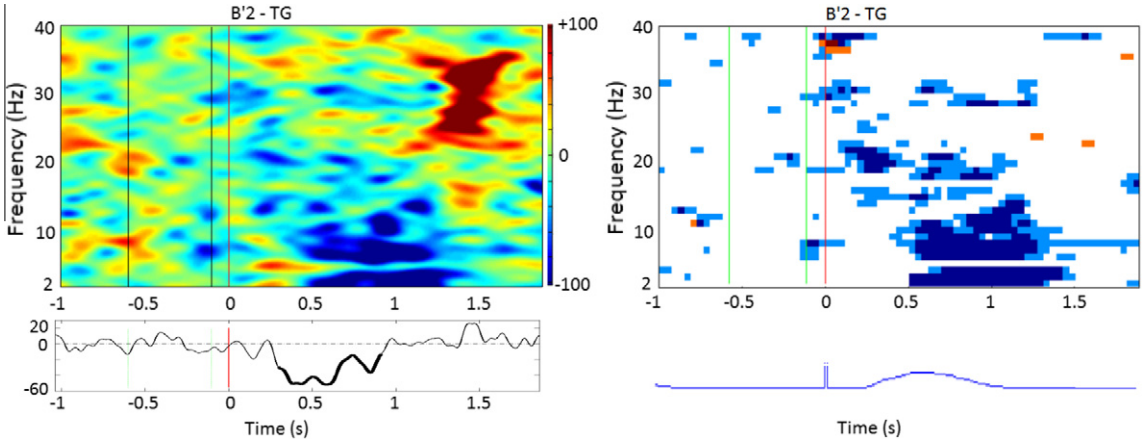

Fig. 1. Upper panel left: TFA. Upper panel right: TFA with significance. The statistical significance was evaluated using Wilcoxon rank sum (signed rank) test for paired samples. Example of a significant power decrease 2–16 Hz, 500 ms after stimuli in subject 4 from the left hippocampus followed by a non-significant power increase in beta frequency range 24–30 Hz appearing 1500 ms after target stimuli. We suppose the 2–16 Hz ERD to be a correlate of activation during target detection and performance of the motor response. The later beta ERS could represent "beta rebound", but statistical analysis showed it to be insignificant. Lower panel left: a P3b-like response in ERP from the same contact in bandpass 0.1–16 Hz. The thick part of the line indicates significance $p < 0.05$. Lower panel right: the line planes indicates stimulation trigger and following reactions.

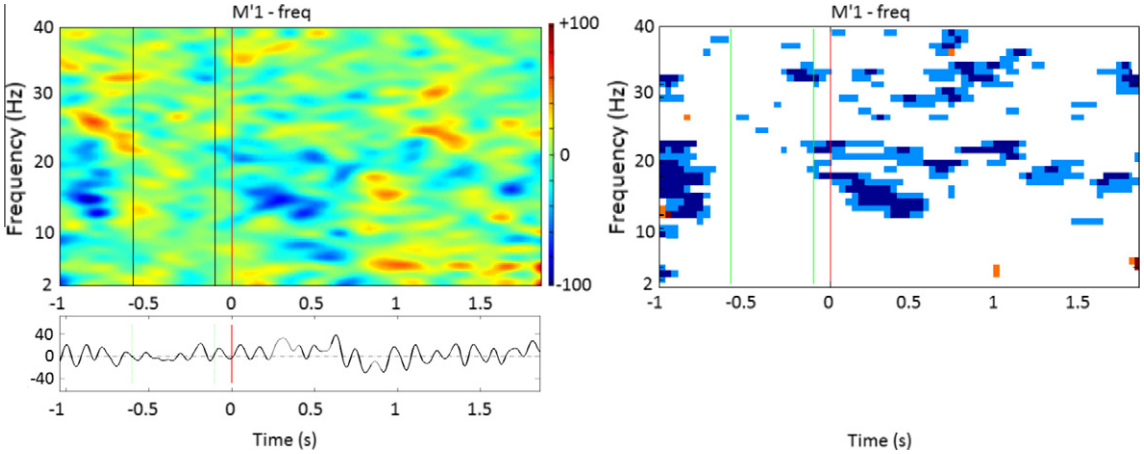

Fig. 2. See Fig. 1 for further details. Example of weak power changes after frequent (non-target) stimuli from left primary motor cortex in subject 1. Lower panel left: no significant changes in ERP from the same contact.

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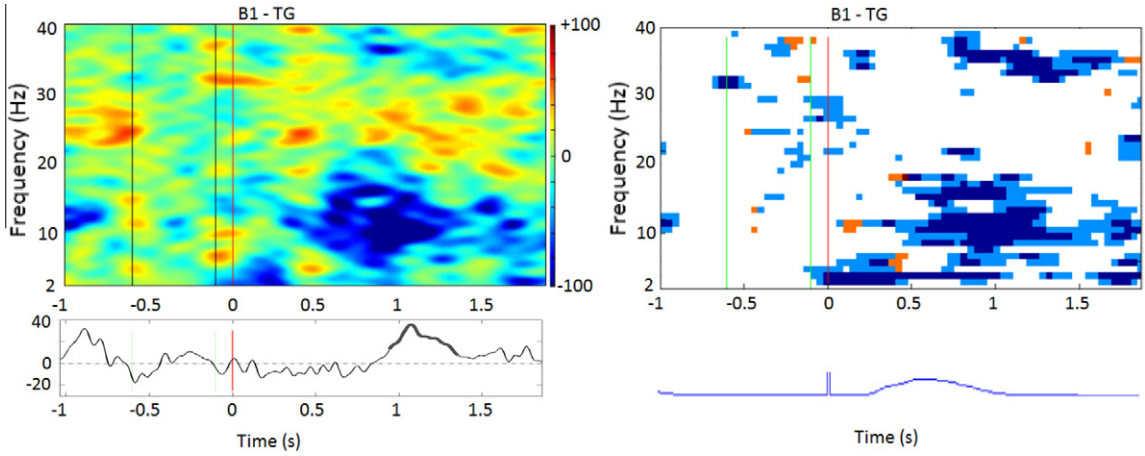

Fig. 3. See Fig. 1 for further details. Target-related response recorded from the right hippocampus in subject 5: a significant alpha and beta ERD lasting approximately 1 s starting around 500 ms after stimuli presentation. Lower panel left: no P3-like response was present in this case in ERP from the same contact. We observed only a late slow positive wave with a latency around 1000 ms; probably "movement accompanying slow potential" (Rektor et al., 1998). The thick part of the line indicates significance $p < 0.05$. Lower panel right: the line planes indicates stimulation trigger and following reactions.

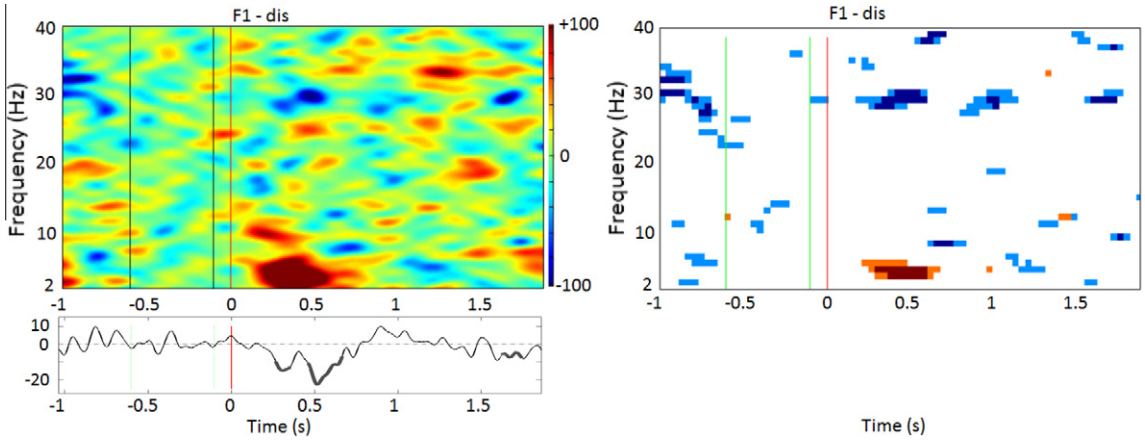

Fig. 4. See Fig. 1 for further details. A typical distractor-related significant early theta band power increase (duration from 200–700 ms after stimuli presentation) from the mesial prefrontal cortex (BA9) in subject 2. Lower panel left: a P3a-like response in ERP from the same contact. The thick part of the line indicates significance $p < 0.05$.

reaction. The target stimuli, which were 15% of all the stimuli, were larger blue circles. The subjects were asked to press an electrically connected button at the time of the target detection. The distractor (rare non-target) stimuli, which were presented 15% of the time, were black and white checkerboards; no response was required. The interstimulus interval was 4 s. The duration of the stimulus exposure was 200 ms. The visual stimuli were presented in a random order. Subjects received clear instructions and practised the task briefly before the recordings.

2.3. Data analysis

The data were processed and analysed off-line using ScopeWin and ScopeMat software. The data were first segmented according to the stimulation trigger onset. The segments were visually inspected, and segments containing artificial signals or mistaken responses were removed. In each segment the linear trend was eliminated, and then ERPs and Time Frequency Analysis (TFA) were analysed.

ERP were given by averaged segments filtered in 0.1–40 Hz bandwidths. The baseline interval was determined 600–100 ms prior to stimuli. The statistical significance of the ERP was analysed from the differences over trials between the mean computed during the baseline and the mean computed inside the moving interval with the length of one third of baseline. A non-parametric Wilcoxon rank sum (signed rank) test for paired samples was used. The ERP were considered as significant when $p < 0.05$, indicated by a thick line (Figs. 1–4).

Time Frequency Analysis (TFA) (Akay, 2000) with elimination of phase-locked signals was used to determine the event-related de/synchronizations (ERD/S) in 2–40 Hz frequency ranges. TFA produces a matrix in which each row represents the over trials averaged signal power envelopes in a 4 Hz frequency band width (*x*-axis represents time; *y*-axis represents frequency). The frequency step between two rows was 1 Hz. In the baseline-normalized TFA matrix, ERS is represented by positive values (red) and ERD by negative values (blue). Normalization with a baseline was done according the equation:

$$\mathrm{ERS} = 100 \times (\mathrm{PW}(t)/\mathrm{PWbaseline} - 1), \quad \text{when } \mathrm{PW}(t)/\mathrm{PWbaseline} \geqslant 1$$

$$\mathrm{ERD} = 100 \times (1/(\mathrm{PW}(t)/\mathrm{PWbaseline}) - 1), \quad \text{when } \mathrm{PW}(t)/\mathrm{PWbaseline} \leqslant 1$$

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PWbaseline = mean power from baseline, PW(t) = instantaneous power. The limitation ±100 of normalized values is used. The scale in the TFA matrix in figures is +100, −100. Red value +100 means doubling of instantaneous power with respect to baseline region, blue value −100 means drop by half. This procedure provides a comparable color interpretation of ERS and ERD.

The statistical significance of ERS/ERD was analysed as in ERPs, analysing the differences over trials between the mean power at baseline and the mean power in a window moving over a segment. Statistical significance is presented in a matrix, where the significant changes to baseline are dark red, light red, dark blue, and light blue. Dark red identifies a power increase when $p < 0.01$, light red a power increase when $p < 0.05$, dark blue a power decrease when $p < 0.01$, and light blue a power decrease when $p < 0.05$. White regions of this matrix identify non-significant changes to baseline.

Each figure shows the TFA matrix in the left panel and the TFA with significance in the right panel. The right panel shows the importance of considering TFA and TFA with significance together. TFA can include a power increase (see Fig. 1) which is not significant, rather sporadic, irregular, or artificial. On the other hand, a general decrease in power (ERD) was regular and statistically significant. Reduced significance was most often observed for ERS in the frequency bands higher than theta and latencies longer than 500 ms from stimuli.

Generally the ERD/ERS registered from the contacts of one electrode within one area were similar, and the results from the most reactive contact of each electrode were selected for further analysis. The number of electrodes in a given area varied among the subjects.

3. Results

We evaluated the signals recorded from 404 electrode contacts placed in the lateral and mesial frontal and temporal cortices and a few leads in the parietal lobe. Theta, alpha, beta, and lower gamma ranges were analysed. The range of interest in the evaluated post-stimulus interval results from the mean reaction times after target stimuli, presented in Table 3, i.e. 0–1500 ms. Generally, widespread cortical activations (desynchronizations) were present during target stimuli detection and performance of the motor response, which started around 500 ms after stimuli presentation.

Table 3
Reaction times.

Subject	Mean ms	Median ms	std ms	Maximal latency s
1	771	789	249	1,38
2	443	449	120	1,09
3	639	625	83	1,15
4	586	586	98	1,05
5	592	570	158	1,35

Target related motor responses times, std-standard deviation.

Typical examples are shown in Figs. 1 and 3. Different inhibitory patterns were present in reaction to distractor stimuli: early power increase in the theta (200–700 ms after stimulus presentation) and sometimes also in the lower gamma band (35–40 Hz), shown in Fig. 4. Non-targets were mainly accompanied by non-significant changes or weaker reactions resembling target-related responses, as shown in Fig. 2, so these results are not further discussed. The target and distractor-related results from all investigated areas are summarized in Table 4. ERPs from the same contacts are shown in each figure in comparison to TFA. ERPs are produced by a neuronal response which is additive to an independent ongoing activity, but the power changes can contribute to ERP generation (Min et al., 2007).

3.1. Temporal lobe

The bilateral temporal cortex was the most extensively explored cerebral area.

3.1.1. Hippocampus

Thirteen electrodes were implanted in the hippocampal area: 7 on the right and 6 on the left. In 9 electrodes, we detected a significant ERD during target detection and motor response. An example is shown in Fig. 3. In reaction to the distractor stimuli, we found no significant changes in 5 electrodes, early increase in the theta band power in 5 electrodes, and low gamma ERS in 2 electrodes.

3.1.2. Amygdala

Four electrodes were placed in the amygdala: 1 on the left and 3 on the right. Almost no significant changes were observed. ERD

Table 4
Results summary.

Area	Target ERD		Distractor ERS	
	Left side	Right side	Left side	Right side
Mesial prefrontal cortex (BA24,31,32,9,10,11)	0/5	2/5	5/5	4/5
Left + right side	2/10		9/10	
Lateral prefrontal cortex (BA10,11,44,45,9,46)	2/3	2/5	2/3	5/5
Left + right side	4/8		7/8	
Mesial motor control areas (BA 6- SMA)	1/1	1/1	1/1	1/1
Left + right side	2/2		2/2	
Lateral motor control areas (BA 1,3,4,6)	3/3	3/3	3/3	1/3
Left + right side	6/6		4/6	
Lateral parietal cortex (BA 7,40)	1/1	2/2	1/1	1/2
Left + right side	3/3		2/3	
Hippocampus and amygdala	4/7	6/10	1/7	4/10
Left + right side	10/17		5/17	
Lateral temporal cortex (BA 21,22)	6/10	2/11	1/10	3/11
Left + right side	8/21		4/21	

X/Y – appearance of ERD or ERS/total number of implanted contacts in the area.
There was not considerable lateralization in the occurrence of ERD/ERS changes. When the recordings in the 2 hemispheres were pooled, evident differences in the location of target-related ERDs and distractor-related ERS appeared. The distractor-related ERS occurred more frequently in the lateral and mesial prefrontal cortices. The statistical significance was not counted because of relatively small numbers in the table.
From all 404 electrode contacts, the results from only 67 contacts are presented in the table. There could be several contacts of an electrode in a given structure. In such cases, the contact with the most prominent ERD/S change was chosen for further evaluation.

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related to the target stimuli was present only in 1 electrode and distractor stimuli theta increase and low gamma ERS were also found in 1 electrode, all on the right side.

3.1.3. Temporal neocortex-gyrus temporalis medius (BA21) and superior (BA22)

We analysed the SEEG signal from 21 electrodes placed in these areas. In 8 electrodes, target-related alpha and beta ERD was present; 4 electrodes showed distractor-related early theta increase, and 1 electrode showed low gamma ERS. The temporal neocortex was not very reactive during the three-stimulus paradigm.

3.2. Parietal lobe: lobus parietalis superior and inferior (BA7, BA40)

Two electrodes were implanted in the right and 1 in the left parietal cortex. In all contacts, a typical target-related reaction was present; in 2 contacts a typical distractor-related theta reaction was found. We also detected alpha ERD after the distractor stimuli in 1 electrode.

3.3. Frontal lobe

3.3.1. Cingulate (BA24, BA31, BA32)

Two electrodes were placed in the left cingulate and 2 in the right cingulate. In all electrodes, a distractor-related theta increase was observed. Target ERD was present only in 1 electrode and was accompanied by a theta band power increase.

3.3.2. Orbitofrontal cortex (BA10, BA11)

Three electrodes were placed in the orbitofrontal cortex. On the mesial side, we detected ERD in the beta frequency band after target stimuli that were accompanied by alpha ERS 1 time. In 2 electrodes on both sides there was a theta power increase linked to distractor stimuli, and in 1 electrode also alpha ERS. No significant changes were found on the left side of the lateral cortex. There was distractor-related theta and alpha ERS in 2 electrodes on the right side.

3.3.3. Prefrontal cortex: dorsolateral prefrontal cortex (BA9, BA46) and ventrolateral prefrontal cortex (BA44, BA45)

Five electrodes were placed in the prefrontal cortex: 2 on the left and 3 on the right. Target-related beta ERD was present in 4 electrodes and distractor-related theta increases in all electrodes. The mesial part of BA9 was mapped with 1 left and 1 right mapped. No significant target-related changes were found. On the left, there was a weak distractor-related theta response; on the right a very prominent theta increase was observed. This early theta reaction was the strongest from all the contacts (Fig. 4).

3.3.4. Primary motor (BA4) and somatosensory cortex (BA1, BA3)

Two electrodes were located on the left and 2 on the right. Movement-related prominent alpha and beta ERD followed target stimuli in all electrodes. Distractor-related theta increase was present on the left.

3.3.5. Supplementary motor area (SMA, mesial BA6) and premotor cortex (lateral BA6)

Two electrodes were located on the left and 2 on the right. In the left SMA, a specific frequency diverse response to the target stimuli was found: an early theta/alpha ERS and beta ERD (before 500 ms) were followed by alpha ERD and beta ERS (after 500 ms). On the right, targets were followed by early theta increase and later prominent alpha and beta ERD. After distractor stimuli, no significant changes were found on the right; theta increase was present on the left. In the premotor cortex, target stimuli were accompanied by alpha and beta ERD on both sides and distractors by early theta response only on the left.

4. Discussion

A three-stimulus visual experimental paradigm was used in this work. This paradigm is similar to the classical oddball task consisting of frequent (non-target) stimuli and rare (target) stimuli. In a three-stimulus paradigm, a third, non-frequent stimulus, the distractor stimulus, appears without any required response (Polich, 2007). The distractor stimulus is task-irrelevant, but insufficiently ignored. Distractor-related activity is interpreted as an orienting response, an involuntary rapid shift of attention to new (never previously experienced), unexpected (out of context), or unpredictable stimuli. Distractor stimulus involuntarily captures the attention and is most likely within the focus of attention (Friedman et al., 2001). It was suggested that the distractor-related response represents the cortical component of the early attentional system, while target processing reflects a higher cognitive closure, perhaps including memory processes (Halgren et al., 1995a). As the distractors are rare stimuli like the targets and their character completely differs from the target and non – target blue circles, they disturb the subject's attention and the subjects tend to have mistaken and unwanted reactions. For this reason, we suggest that distractors-related responses also contain an inhibition of involuntary motor responses – a "no-go" signal.

Exactly the same experimental paradigm was used in our previous study of the BG, i.e. the subthalamic nucleus and internal globus pallidum on a group of DBS (deep brain stimulation) patients (Bočková et al., 2011). We observed target-related ERD in higher alpha frequencies. An early lower alpha frequency band ERS was observed exclusively after the distractor stimuli. As the ERD in these frequencies is considered in most cases to be a correlate of activation and ERS a correlate of active inhibition, target stimuli were accompanied mainly by "go" signal reactions and distractor stimuli by "no-go" signal responses. Alpha ERD occurs during cognitive processing; target-related P3 potential is clearly related to the desynchronization of late alpha frequency EEG (Sergeant et al., 1987; Pfurtscheller and Klimesch, 1991, 1992; Boiten and Sergeant, 1992; Klimesch, 1997; Yordanova et al., 2001; Polich, 2007). ERS in lower frequency bands is mostly, but not always, interpreted as an inhibition. The 2 Hz rhythm was described as an induced rhythm during signal detection and decision making (Basar, 1999; Schürmann and Basar, 2001). Theta oscillations were observed after inadequate stimulation (Basar, 1999; Basar et al., 2001), and theta ERS was connected with memory retrieval (Bastiaansen and Hagoort, 2006). Alpha ERS was also described as an activity important for functional coupling between prefrontal cortical areas and more posterior sites in a working memory task (Sauseng et al., 2005), internally directed attention and increased task demands (Cooper et al., 2003) and active task-relevant processing (von Stein et al., 2000; Palva and Palva, 2007, 2011; Mo et al., 2011). Induced alpha rhythm changes following a stimulus or event may have a multitude of specific functional meanings and correlations with ERP wave components (Ergenoglu et al., 2004). Post-movement beta ERS (called beta rebound) might reflect movement-related somatosensory processing (Cassim et al., 2001; Szurhaj et al., 2001); it also occured in a no-go condition as a sign of withholding a motor task (Zhang et al., 2008; Solis-Escalante et al., 2012), and is associated with unification operations (Bastiaansen and Hagoort, 2006). Despite these different findings from the literature, in the three-stimulus paradigm we used, we consider ERD in lower frequency bands to be a correlate of activation and ERS of active inhibition, according to the nature of the expected cognitive responses after target and distractor stimuli.

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In this study, we observed cortical oscillatory changes that were similar to those observed in the basal ganglia in the previous study. Cortical areas participating in processing the target and distractor stimuli overlapped partially. Target-related alpha and beta ERD was present predominantly in the motor control areas, i.e. the primary motor and somatosensory cortex and the premotor cortex, than in the parietal cortex and hippocampus. The involvement of motor areas is probably due to the motor response following target detection and represents a "go" signal. Activation of the parietal cortex and hippocampus might be related to cognitive processes connected with target stimuli processing that can also promote memory operations (Knight, 1996; Squire and Kandel, 1999; Brázdil et al., 2001, 2003; Polich, 2007). The cortical distribution of the oscillatory responses to target stimuli mainly in the temporal and parietal lobes corresponds with the cortical distribution of the target-related activation in ERP (P3b) and fMRI studies (Brázdil et al., 2005; Bledowski et al., 2004; Rektor et al., 2007).

Early theta and sometimes also low gamma distractor-related power increase were observed mainly in frontal areas: cingulate, orbitofrontal cortex and prefrontal cortex. This observation might indicate a fast evaluation and categorization of the distractor stimuli. The prefrontal cortex can have both an excitatory and inhibitory influence and is involved in early attentional processing stages (Herrmann and Knight, 2001). Scalp recordings show that ERD/ERS involves the coactivation of a large number of neurons and the process is time-dependent related to the frequency range (Hari et al., 1998, Kemp, 1983). For example, theta activity was synchronized in a working memory task in a MEG study with a duration approximately around 600 ms (Tesche and Karhu, 2000). Out theta band power increase lasted about 200–700 ms, i.e. in most cases the duration was around 500 ms or shorter. The shorter duration of this theta increase could be caused by the fact that intracranial recordings provide direct access to the explored structures and can detect the activity of a smaller number of neurons. Shapes, latencies, amplitudes, and durations of intracerebrally recorded phenomena often vary from that known from scalp measurements. For this reason, we suggest that our early and brief theta increases to correspond to ERS. This reaction is probably linked with suppressing an involuntary shift of attention and then inhibiting further cognitive processing of the distractor stimuli and involuntary motor reaction, i.e. "no-go" signal. Inhibitory control and error detection are among the highest evolved human self-monitoring functions. The inferior prefrontal cortex (IFC) is believed to mediate response inhibition; the mesial prefrontal cortex should be responsible for error detection (Rubia et al., 2003). In our study, we observed the inhibitory response signal predominantly in the prefrontal cortex. The appearance of the distractor-related ERS was evidently higher than that of the target-related ERD in both the mesial and lateral prefrontal cortices. Our study indicates that the brain network processing of the early attentional and inhibitory reactions is more distributed than the network elaborating response to target stimuli in the frontal cortex. The widespread distribution of the distractor-related ERS may be interpreted as a sign of the active inhibition of an involuntary response elicited by a rare distractor stimulus.

We observed early ERS after distractor stimuli both in the prefrontal cortices in this study and in the BG, namely in the STN and the GPi, in an earlier study (Bočková et al., 2011). It was demonstrated that the prefrontal cortex may modulate various cognitive functions of the BG and specifically of the STN via a direct functional projection between several frontal lobe areas including the IFC and the STN (a "hyperdirect" pathway) (Nambu et al., 2002; Aron and Poldrack, 2006; Aron et al., 2007; Baláž et al., 2010). An early lower alpha frequency band ERS was observed exclusively after the distractor stimuli in the subthalamic nucleus and internal globus pallidum in our previous study (Bočková et al., 2011). This finding could be in correlation with the theory of a hyperdirect connection between the prefrontal cortex and STN which probably serves the inhibitory control mechanisms. The prefrontal cortex and BG are candidate agents of response inhibition (Band and van Boxtel, 1999). The right IFC, or some other frontal regions, may block the execution of the "go" response via the BG (Eagle and Robbins, 2003; Rieger et al., 2003; Aron et al., 2007). The role of the subthalamic nucleus (STN) in response inhibition has been revealed by deep brain stimulation in human patients (van den Wildenberg et al., 2006), local field potential changes (Kuhn et al., 2004), and high-resolution fMRI (Aron and Poldrack, 2006). Activation of the STN leads to co-activation of the Gpi (Mink, 1996; Bočková et al., 2011) and to subsequent inhibition of the thalamo-cortical motor program (Coxon et al., 2006; Aron et al., 2007). Inhibitory oscillatory signals, i.e. early theta band power increases, directed from prefrontal cortex to subcortical structures could probably underline physiological significance of the "hyperdirect pathway". Dysfunction of these inhibitory cortico-subcortical mechanisms may play a role in symptoms such as motor freezing and hesitation in Parkinson's disease. The mechanism might be insufficient inhibition of distracting motor programmes.

In this study, the patient age varied from 16 to 41 years. This variance could influence the results. On the other hand, we were interested mainly in the function of the prefrontal cortex, which was not explored in the 16 year old subject. All the other subjects were adults, in a comparable age range. We evaluated the human event-related EEG signal recorded via intracerebral depth electrodes. The electrode positioning is determined by clinical intention; not all structures can be fully explored. Intracerebral recordings are performed on epileptic patients, and we cannot fully exclude the influence of the pathological process on the recorded electrical activity. In order to minimise the risk of such bias, we excluded recordings from brain tissue with pathological activity. The depth electrodes are submerged in the brain tissue and record from their immediate vicinity. The data are thus obtained directly from cortical structures; some of which are almost inaccessible by scalp or subdural measurement. The quite limited spatial resolution that is typical for intracerebral recordings could be compensated for by a large number of recording sites. The comparison of the activities in the BG and in the cortex might be biased also by the fact that explored patients suffered from movement disorders in the BG recordings and epilepsy in the cortical recordings. There is no reason to believe that this resulted in bias, as the results are consistent across the study, but this cannot be fully excluded. On the other hand, there is no possibility to record from the cortex other than in patients with diseases affecting the brain. We should be careful in interpreting our data in the light of these limitations.

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6.9. Příloha 9 - Phase amplitude coupling between subthalamic nucleus theta and cortical beta oscillations in the resting human brain

Alena Damborská, Denis Brunet, Serge Vulliemoz, Martin Lamoš, Martina Bočková, Barbora Deutschová, Marek Baláž, Ivan Rektor. Phase amplitude coupling between subthalamic nucleus theta and cortical beta oscillations in the resting human brain.

Submitováno

Tato práce se zabývá fyziologickými a patofyziologickými vazbami mezi oscilacemi v různých frekvenčních pásmech mezi STN a kortikálními oblastmi, konkrétně hodnotí vztahy mezi theta aktivitou v oblasti STN a beta oscilacemi v oblasti kortexu. Cílem této práce bylo také studium lateralizace těchto funkčních vazeb. Je známo, že STN je spojeno prostřednictvím theta couplingu s mediálním prefrontálním kortexem a touto cestou se podílí na řízení chování, ale není jasné, zda tato theta aktivita ovlivňuje kortikální beta oscilace, které jsou zásadní pro řízení hybnosti. Za tímto účelem byla použita metoda tzv. phase-amplitude coupling, pomocí které byly hodnoceny záznamy ze simultánního snímání z intracerebrálních DBS elektrod (v těsném pooperačním období) a skalpového HDEEG na souboru 11 DBS pacientů s PN. Jedná se první práci, která potvrdila existenci vazby STN theta fáze a amplitudy kortikální beta aktivity. Byla pozorovány i lateralizace těchto vazeb, které se lišily v různých kortikálních oblastech. Naše výsledky přispívají k lepšímu pochopení funkční organizace v kortiko-subkortikálních okruzích.

Phase amplitude coupling between subthalamic nucleus theta and cortical beta oscillations in the resting human brain

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Keywords: subthalamic nucleus; cortico-subcortical interactions; phase-amplitude coupling; cross-structural coupling; simultaneous intracranial and scalp EEG

Abstract

The presumed physiological role of beta oscillations and coupling within the cortico-subcortical networks is the maintenance of the current sensorimotor or cognitive state. Recently, theta oscillations in the subthalamic nucleus (STN) were suggested to reflect inputs from the medial prefrontal cortex, thus implementing behaviour control. It is unclear whether the STN theta oscillations are related to cortical beta activity in the resting human brain. To investigate these interactions, we recorded simultaneous scalp electroencephalographic activity and local field potentials in the STN in eleven patients with Parkinson's disease in the on-medication state during rest. We assessed the cross-structural phase-amplitude coupling (PAC) between the STN theta (4-7 Hz) and cortical beta 2 (20-40 Hz) levels. The STN theta - cortical beta PAC was observed in all subjects and showed a left-right asymmetry. In some cortical regions, the PAC was significantly higher with the left STN (maximum *t*-values 3.82, $p \leq 0.05$, paired *t*-test); in others with the right STN (maximum *t*-values -3.74, $p \leq 0.05$, paired *t*-

test). A cross-frequency functional linkage between the STN and the cortex during resting conditions is suggested, with specific patterns related to the laterality of the STN. Our results contribute to a better understanding of functional organization within the cortico-subcortical circuitries.

Introduction

The subthalamic nucleus (STN) is known to have a central position in basal ganglia-thalamocortical circuits. Excessive beta band (15–35 Hz) oscillations at multiple nodes throughout the basal ganglia-thalamo-cortical motor network is the most commonly reported electrophysiological abnormality of Parkinson's disease (PD) patients[1-6].

Several studies have shown that beta is not the only frequency band that is associated with PD, suggesting that an integral view of activities throughout the entire frequency spectrum could help better understand parkinsonian pathophysiology[7]. Theta and beta oscillations were observed in the STN during resting conditions in PD patients in the off-medication state, and the existence of two different specific local functional organizations of oscillating neuronal populations in the STN was suggested[8]. Several functional sub-loops defined in terms of coherence at distinct frequency bands between the STN and cortical motor regions were identified in untreated PD[9]. Increased resting-state cortico-cortical functional connectivity in the alpha range (8–10 Hz) was suggested as a feature of PD from the earliest clinical stages onward[10].

Another important aspect of functional organization within the cortico-subcortical circuits is the involvement of multiple frequencies during the on-medication state of PD. Modulations induced by dopaminergic medication have been observed within the cortico-subcortical networks in the theta-alpha range[11, 12], as well as in the beta and gamma frequency bands[13-17]. A bidirectional pattern of cortico-basal ganglia communication was reported that is differentially patterned across frequency bands and changes with movement and dopaminergic input[15]. Such cortico-subcortical coupling patterns observed under on-medication conditions make it possible to speculate whether this communication at different frequency bands is physiological or related to the pathophysiology of PD. The results of nonhuman studies and of pharmacological studies in patients suggest that the coherence between the STN and EEG in the sub-beta and beta bands represents, at the very least, a pathological exaggeration of physiological activity (for review, see[3, 18, 19]).

A "communication-through-coherence" hypothesis was formulated more than ten years ago that suggested that communication between two neuronal groups depends on coherence

within specific frequency bands[20]. The cross-frequency interactions within neuronal circuits are less understood. Studies involving hierarchical cross-frequency interactions between the phase of slow activities and the amplitude of fast activities have suggested a physiological role of these interactions in facilitating the transient coordination of cortical areas[21-23]. Whether hierarchical cross-frequency interactions occur also between the STN and the cortex is unclear.

Bilateral deep brain stimulation of subthalamic nucleus (STN-DBS) improves dopamine-resistant motor symptoms. Interestingly, it has been shown that similar improvements can be achieved with unilateral STN-DBS in some patients[24, 25]; it has been suggested that these patients presenting such a "dominant-STN" might not need bilateral STN-DBS surgery[26]. Since the neural substrate of functional asymmetry of the STN is largely unknown, the analysis of cross-frequency interactions of the left and right STN with the cortex could yield great insight into the dynamics of the subcortical-cortical circuitry.

For the present study, we investigated the cortico-subcortical interactions in the resting electrophysiological activity of PD patients under their usual anti-parkinsonian medication. We chose the on-medication state because we wanted to study the physiological cross-frequency cross-structural interactions in the cortico-subcortical circuits. Bearing in mind a possible role of theta and beta oscillations in communication between the STN and cortical neuronal groups[3, 18, 27], we focused on the STN theta and cortical beta activities. We performed local field potential (LFP) recordings from the STN in combination with simultaneous electroencephalography (EEG). The study character was explorative. To examine whether specific cross-frequency and cross-structure phase-amplitude coupling (PAC) patterns occur in the cortico-subcortical circuits, we investigated coupling between the STN theta phase and cortical beta amplitude. Using a relatively high-density EEG of 53 channels and a bilateral LFP recording in the STN on a representative sample of 11 subjects enabled us to assess the spatial characteristics of the cortico-subcortical relations. Given the presumed functional asymmetry in the STN-cortical interactions, we compared the subcortico-cortical PAC for the left versus right STN.

Results

In all subjects, significant correlations were observed between the STN theta phase and beta 2 amplitude on scalp recordings (Figure 1). Different patterns of the PAC were observed amongst subjects with respect to the scalp topography and laterality of the STN. For example, in subject 10, highly significant correlations with the left STN but not with the right STN

were observed in many regions. In subject 5, highly significant correlations with the right STN were observed in most regions of the right but not left hemisphere, and highly significant correlations with the left STN were observed in the left but not right frontal regions. In most regions, the PAC values varied greatly across subjects (see the scalp distribution of high values of standard deviations in Figure 2). No general pattern of PAC was observed with respect to the laterality of the first manifestation of the PD. For example, in both subject 5 and subject 10, both right-handed subjects with evidently different PAC patterns, the PD was first manifested on the left side (Table 1).

The results of the paired *t*-test on the group level across all subjects showed left/right asymmetry in the STN-cortical PAC (see Figure 3) that varied across scalp recording sites and frequencies. In some regions, the PAC was significantly higher with the left STN (maximum *t*-values 3.82, $p \leq 0.05$, paired *t*-test); in other regions, the PAC was significantly higher with the right STN (maximum *t*-values -3.74, $p \leq 0.05$, paired *t*-test). The STN-cortical PAC was significantly higher for the right STN than the left STN, mainly in the temporo-parieto-occipital region of both hemispheres in the 20–30 Hz frequency range and in the left parieto-occipital and right frontal regions in the 30–40 Hz frequency range. The STN-cortical PAC correlations were significantly higher for the left STN than the right STN, mainly in the right frontal and temporal regions in the 20–30 Hz frequency band and in the left frontal, temporal, and parietal regions in the 30–40 Hz frequency band. The results of the PAC differences between the left and right STNs were thus further subdivided into the 20–30 Hz and 30–40 Hz frequency bands. The topography maps of the mean *t*-values are presented in Figure 4. In the lower frequency band, the left STN-cortical PAC dominated in the anterior cortical regions; the right STN-cortical PAC prevailed in the posterior cortical regions. In the higher frequency band, the pattern with significantly higher left STN-cortical PAC than right STN-cortical PAC dominated in most cortical regions.

Discussion

The main results of the study include the evidence of the STN theta phase and cortical beta 2 amplitude coupling of electrophysiological brain activity. This finding suggests the existence of cross-frequency functional connectivity within the cortico-subcortical networks during resting conditions. The observed left-right asymmetry in the STN-cortical PAC pattern was another important finding that opens interesting directions for further research in this field and might contribute to ongoing discussions on unilateral versus bilateral deep brain stimulation treatments of PD.

On theoretical grounds, the coupling between the STN phase and cortical amplitude of neuronal activity represents a serious candidate for physiological functional interactions between these brain structures during resting conditions. The neuronal oscillations in the neocortex tend to couple hierarchically, with the phase of lower-frequency oscillations modulating the higher frequency amplitudes[21]. The lower-frequency phase determines momentary power in higher frequency activity. The observed PAC between the STN and cortex could thus be considered as a manifestation of fluctuations of excitability in local neuronal assemblies in the cortex with rhythmic activity in the STN. This interpretation is in agreement with previously reported evidence of driving from the STN to the cortex in resting conditions. It has been suggested that in the presence of dopaminergic activity, the STN may produce a high frequency 70–85 Hz drive to the cerebral cortex during resting conditions[14], thus demonstrating that STN should not be viewed simply as a passive servant to the cortical inputs.

Increasing evidence indicates a physiological role of STN theta oscillations during conflict monitoring[28], suggesting that STN theta oscillations entrain STN neuronal firing[29]. An important role of theta oscillations has also been reported in the cortico-subcortical interactions. The STN and medial frontal cortex theta coherence was shown to be involved in conflict and error monitoring[30, 31]. It has also been suggested that the STN theta oscillations may reflect inputs from cortical structures such as the medial prefrontal cortex[27, 30] that projects into the STN through the hyperdirect pathway[32]. Our results rely on cross-frequency cross-structural coupling rather than on the previously reported coherence within the theta band. Thus, our findings do not allow for more detailed discussion on their relation to these studies. The demonstrated STN theta-cortical beta linkage presents, however, an interesting perspective for further research focused on cortico-subcortical functional interactions.

Our results have also shown differing involvement of the left and right STNs in the cortico-subcortical interaction that was typically specific for each individual subject, scalp recording site, and cortical frequency. Such dependency suggests the presence of specific factors that might characterize interregional relationships of the neuronal network and specific individual features of resting state brain activity. Although a recent study reported that alpha/beta band oscillations and PAC within the STN were greater in the more affected hemisphere in PD patients[33], our data suggest otherwise. The observed left-right asymmetry in the STN-cortical PAC in our data did not show any relation to the laterality of the clinical manifestation of the disease, although it was not tested statistically due to the small sample size. In contrast to the study by Shreve et al.[33], our patients were recorded during the on-medication state, where a

reduced influence of PD on brain activity could be expected due to the exogenous dopaminergic input that is supposed to reverse the core deficit in PD. The fact that we observed significant differences between the left and right STNs in PAC may represent electrophysiological evidence of asymmetry in the cortico-subcortical functional linkage. In the 20–30 Hz cortical frequency band, the theta left STN coupling dominated in the anterior cortical regions while the theta right STN coupling prevailed in the posterior cortical regions. In the 30–40 Hz cortical frequency band, the theta left STN coupling dominated in most cortical regions. It is not known, which activities of which cortical regions reflect the clinical improvements of PD as a consequence of DBS treatment. Our findings thus cannot favor in general any of the possible treatment approaches, i.e. right-sided vs left-sided vs bilateral DBS. On the other hand, the observed high interindividual variability in the STN-PAC in many cortical regions, both for the left and right STNs (see Figure 2), does not exclude the possibility that in some PD patients the cortical regions critical for DBS efficacy are targeted with stimulation of only a single STN. It has been shown that a non-negligible part of PD patients might not need bilateral STN surgery[26]. In these patients, the stimulation of the "dominant STN" is able to improve motor function to an extent similar to the bilateral stimulation. We might speculate that this could happen due to the dominance of one STN in terms of its functional connectivity with relevant cortical areas.

The main limitation of our study is the employment of a patient population to investigate physiological processes. We studied functional connectivity on unique data that cannot be obtained from healthy humans due to ethical constraints. This approach proved to be fruitful in previous studies that investigated electrophysiological activity of large-brain networks using intracranial data from epileptic[34-38] and PD[14, 28-31] patients. Nevertheless, the inferences with regard to the normal functioning of the brain should be made with caution in our study. We also admit that source imaging would have been better than correlation with electrode signals. This was, however, technically impossible given the missing signals close to the vertex.

In summary, the results of the present study represent the first report on STN-cortical functional interaction in the cross-frequency domain from simultaneous intracranial and scalp recording that provides evidence for coupling of theta phase STN and beta 2 cortical amplitude in humans. This finding contributes to a better understanding of integrative processes reflecting fundamental self-organization within the brain. The demonstrated cross-structural and cross-frequency linkage in the cortico-subcortical circuits presents an interesting perspective for further research. If the cross-structural cross-frequency approach is

applied both during the on- and off-medication states, both before and after the DBS stimulation, the relation to the clinical outcome could be evaluated, which could lead to new findings for a better understanding of the pathophysiology of PD.

Methods

Subjects. Eleven right-handed PD patients having enrolled in deep brain stimulation of subthalamic nucleus (DBS-STN) program participated in the study. All participants were recruited between 2012 and 2018 at the First Department of Neurology, St. Anne's Faculty Hospital, Masaryk University in Brno. They were implanted with STN-DBS quadricontact electrodes bilaterally. Stereotactic coordinates, direct visualization of the lead location on postoperative MRI scan, and the antiparkinsonian effects of high-frequency stimulation confirmed the lead placement within the desired target region. Intervals of four to five days between the implantation and final internalization of DBS electrodes served for clinical assessment and testing of DBS efficacy. We used this period for simultaneous scalp and intracranial EEG recording. Patients were recorded on their usual anti-parkinsonian medication. The patients' characteristics are given in Table 1.

Procedure. Subjects were lying in a light and sound attenuated room. They were instructed to move as little as possible and to refrain from extensive eye movements. One session of 15 minutes in the off-stimulation and on-medication state in resting conditions was recorded with eyes open.

Recording. Recording sessions were conducted 2 to 3 days after the surgery, having ensured that the patients' general state was satisfactory and they could collaborate appropriately. The electrophysiological activity was recorded simultaneously intracranially and from the scalp using Brain Scope EEG system. The LFP data were obtained from quadricontact DBS electrodes implanted bilaterally into the STN. The EEG data were collected in each patient using up to 62 Ag-AgCl electrodes (see Table 1) placed on the scalp according the International 10/10 System. The central scalp region was covered by postoperative bandages and thus not explored. The size and shape of this unexplored scalp region slightly differed amongst patients. All intracranial and scalp recordings were monopolar on-line referred to an average reference of all scalp electrodes, except for the most peripheral ones with a higher risk of possible muscle artifacts (F9, F10, FT9, FT10, T9, T10, TP9, TP10, P9, P10, Nz, Iz). Eye movements were recorded with electrodes placed above right and below left lateral canthi. The sampling rate was 5 kHz. Recordings were visually inspected and 1-5 minute

almost artifact-free simultaneous intracranial and scalp recordings in each subject were selected for further analysis.

Analyses. Intracranial data were band-pass filtered from 0.1 to 20 Hz and then down-sampled to 500 Hz. Three bipolar montages from two neighboring contacts of the quadricontact DBS electrode were calculated for each STN. Recording from one bipolar contact closest to each STN was used for further analysis. Individual theta frequency was identified as a maximal mean power of 1–5 minute period within the 4–7 Hz frequency range (see Supplementary Fig. S1 online). Recordings from scalp EEG data were band-pass filtered from 0.1 to 200 Hz and notch filtered at 50 Hz. Subsequently, in order to remove ballistocardiogram and oculo-motor artifacts, infomax-based Independent Component Analysis (ICA)[39] was applied on all but one or two channels rejected due to abundant artifacts. In most subjects, two (five subjects) or three (four subjects) ICA components were removed. Four components were removed in patient 9 and four components were removed in patient 10. Only artifacts related to ballistocardiogram, saccadic eye movements, and eye blinking were removed, based on the waveform, topography, and time course of the component. Every scalp electrode with a recording available for at least eight subjects was included in further analysis. Previously identified noisy channels and recordings from the electrodes that were missing at most in three subjects were interpolated using a 3-D spherical spline[40]. Thus, for each subject, a set of the same 53 channels was obtained that covered all scalp regions except for the central area (see Supplementary Fig. S1 online). The number of channels interpolated in each subject is given in Table 1. The scalp data were then down-sampled to 500 Hz. The instantaneous phase was computed in each STN for the subject's individual theta frequency. The instantaneous amplitude (power) was computed for all scalp recordings between 20 and 40 Hz (0.5 Hz resolution). Correlation between the phase of the intracranial recordings and the amplitude of the scalp recordings were computed over a time window of 1–5 minutes of the artifact-free EEG. Randomization was done as 5000 random shuffles in the time of intracranial and scalp data. Mean and standard deviation of the correlations of all shuffled repetition was computed. The significance level of real correlation values was set as a value higher than two standard deviations of correlations in the randomized data. A paired *t*-test was used to assess the differences between the left and right STNs in cortico-subcortical PAC. The significance level was set to 5%. FDR correction adjusting p-values to q-values was performed to correct for multiple testing. The procedure was implemented using CARTOOL software by Denis Brunet (https://sites.google.com/site/fbmlab/home).

Data availability. The datasets generated and analyzed during the current study are available at the CEITEC MU repository.

Ethics statement. All participants gave their written informed consent prior to the experiment and the study received the approval of the Ethics Committee of St. Anne's Hospital in Brno. All experiments of this study were performed in accordance with relevant guidelines and regulations.

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Author Contributions

A.D. designed the analysis, collected and analyzed the data, and wrote the manuscript. D.B., M.L., and S.V. critically reviewed the analysis. B.D., M.Ba, and M.Bo collected the data. I.R. developed the initial idea. All authors reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Table 1. Patients' characteristics

Subject No.	Age (years)	Sex	Duration of PD (years)	Medication	First manifestation	Rec. (Int.)
1	59	F	8	L-dopa	right H-R	51(11)
2	49	M	14	L-dopa	right H-R, left T	57(3)
3	56	F	7	L-dopa, Ent, Pra	left T	58(2)
4	51	M	9	L-dopa, Ent, Pra	right T	60(0)
5	63	F	12	L-dopa, Ent, Rop, Ama	left H-R	52(10)
6	63	M	16	L-dopa, Ent, Pra	left T	53(2)
7	60	M	6	L-dopa, Ent, Rop	left H-R	47(10)
8	70	M	8	L-dopa	right H-R, right T	60(0)
9	63	M	9	L-dopa, Rop	right T	61(5)
10	61	M	9	L-dopa, Ent, Rot	left T	62(1)
11	54	M	6	L-dopa, Pra	right H-R, right T	60(4)

L-dopa – levodopa, Ent – entacapone, Rop – ropinirole, Pra – pramipexole, Rot – rotigotine, Ama – amantadine; Rec.(Int.) – number of recording (interpolated) scalp electrodes; H-R – hypokinesia and rigidity; T – tremor

Figure legends

Supplementary Figure S1. (A) Example of individual theta power identification (subject 1). Maximal individual theta frequency was identified at 5.5 Hz in bipolar contacts from the left (L1L2) and in the right (R0R1) subthalamic nuclei; (B) Localization of 53 scalp recording sites used for analysis. Each scalp electrode was available in at least eight subjects.

Figure 1. Significant correlations between the theta phase in the left and right subthalamic nuclei and beta 2 amplitude on scalp recordings. Note different patterns of the phase-amplitude coupling correlations across subjects with respect to the scalp topography, laterality of the STN, and frequency on the scalp. (LF – left frontal, LT – left temporal, LP – left parietal, RF – right frontal, RT – right temporal, RP – right parietal scalp regions)

Figure 2. Mean correlation values and standard deviations (SD) of the subthalamic nucleus theta phase – cortical beta amplitude coupling across 11 subjects. Note that high SD values were observed in most scalp regions and frequencies for both STNs. Results are given for 53 scalp recording sites and different frequencies within the 20–40 Hz band. (LF – left frontal, LT – left temporal, LP – left parietal, RF – right frontal, RT – right temporal, RP – right parietal scalp regions)

Figure 3. The left/right subthalamic nucleus (STN) significant differences in the STN theta phase and cortical beta 2 amplitude coupling in 11 subjects ($p \leq 0.05$, paired *t*-test). Note that the left/right STN asymmetry in the STN-cortical PAC varied across scalp recording sites and frequencies. Positive *t*-values indicate that the phase-amplitude coupling was significantly higher with the left STN than with the right STN; negative *t*-values indicate that the phase-amplitude coupling was significantly higher with the right STN than with the left STN. Results are given for 53 scalp recording sites and different frequencies within the 20–40 Hz band.

Figure 4. The scalp topography maps of the mean *t*-values ($p \leq 0.05$, paired *t*-test) of the left/right subthalamic nucleus (STN) differences in the STN theta phase and cortical beta 2 amplitude coupling across 11 subjects for the 20–30 Hz and 30–40 Hz frequency bands. Note that in the higher frequency bands, the positive mean *t*-values dominated; in the lower frequency bands, the negative mean *t*-values dominated. The mean *t*-values were calculated from the data presented in Figure 3, where positive values indicate that the phase-amplitude coupling was significantly higher with the left STN than with the right STN, and negative values indicate that the phase-amplitude coupling was significantly higher with the right STN than with the left STN.

Figure 1

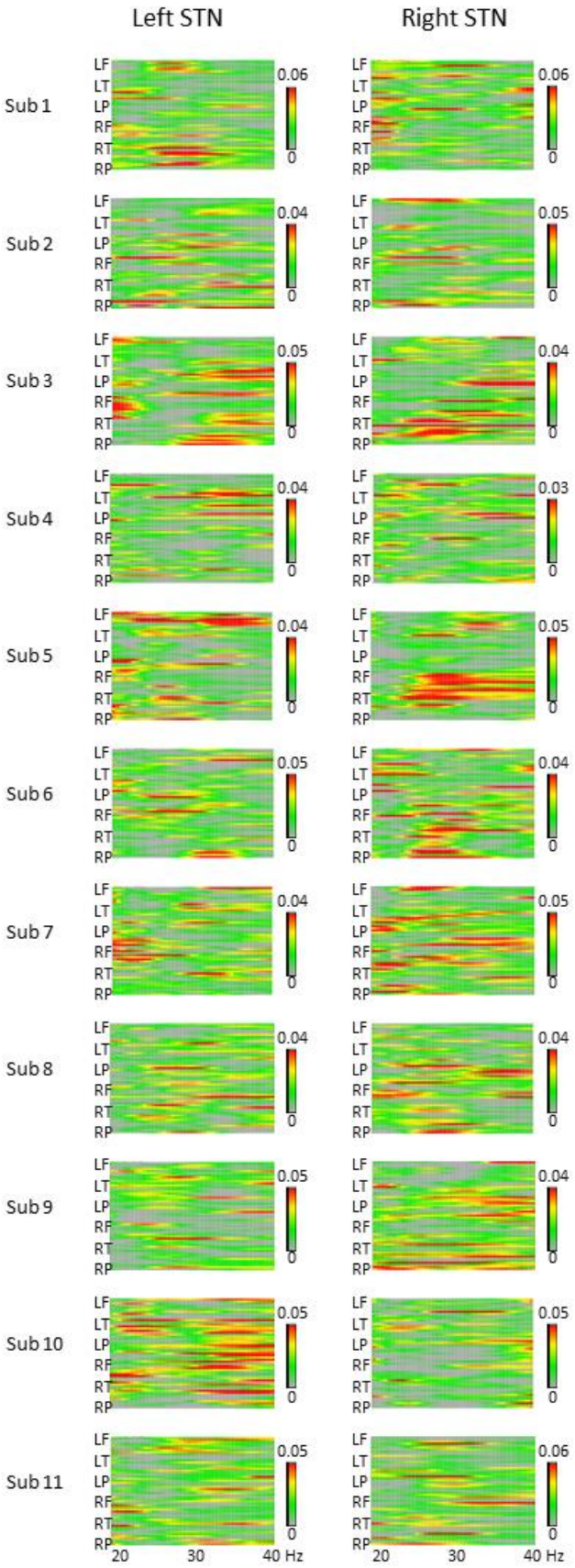

Left STN
Right STN
Sub 1
Sub 2
Sub 3
Sub 4
Sub 5
Sub 6
Sub 7
Sub 8
Sub 9
Sub 10
Sub 11
LF
LT
LP
RF
RT
RP
0.06
0.04
0.05
0.03
0
20
30
40 Hz

Figure 2

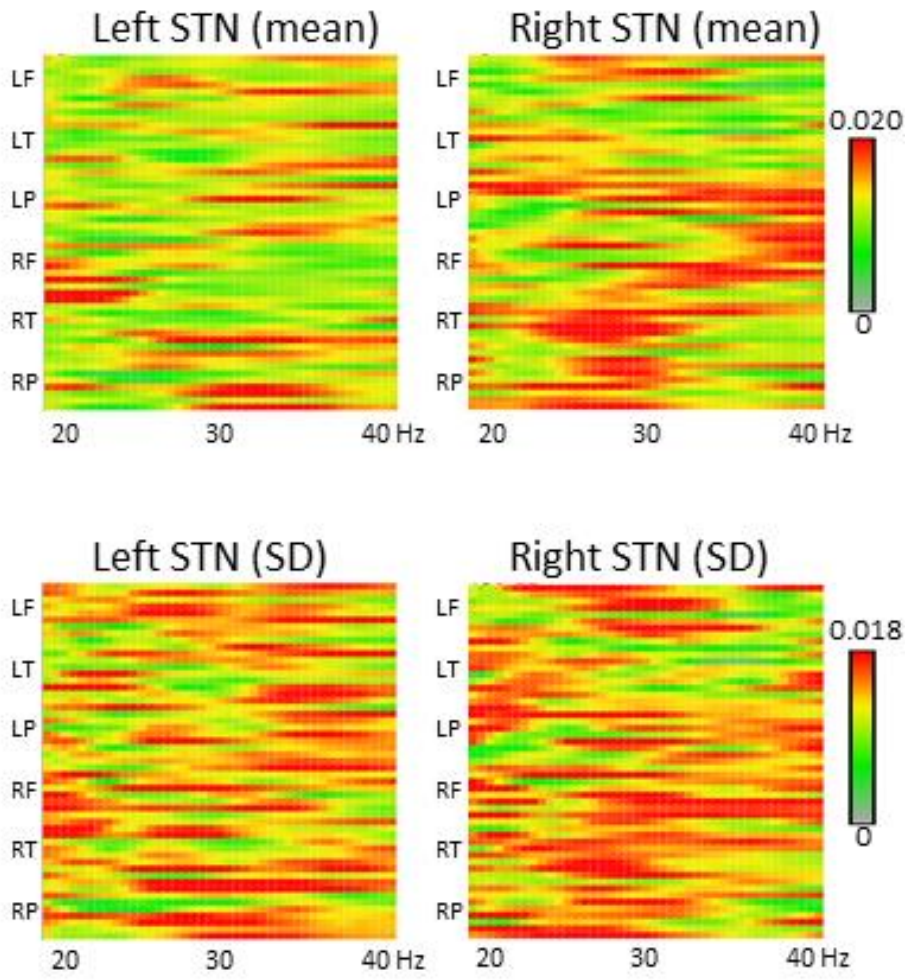
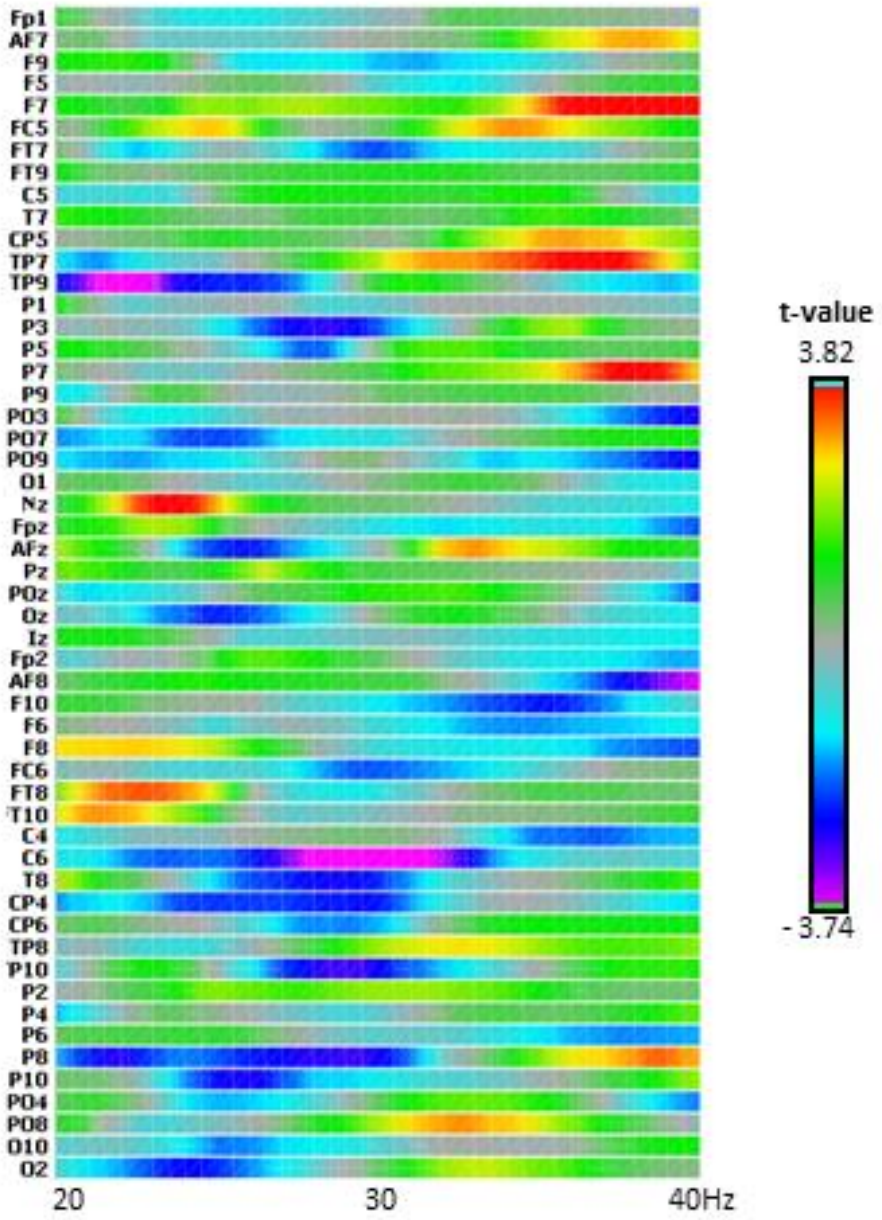

Left STN (mean)
Right STN (mean)
LF
LT
LP
RF
RT
RP
20
30
40 Hz
0.020
0
Left STN (SD)
Right STN (SD)
0.018
0

Figure 3


Fp1
AF7
F9
F5
F7
FC5
FT7
FT9
C5
T7
CP5
TP7
TP9
P1
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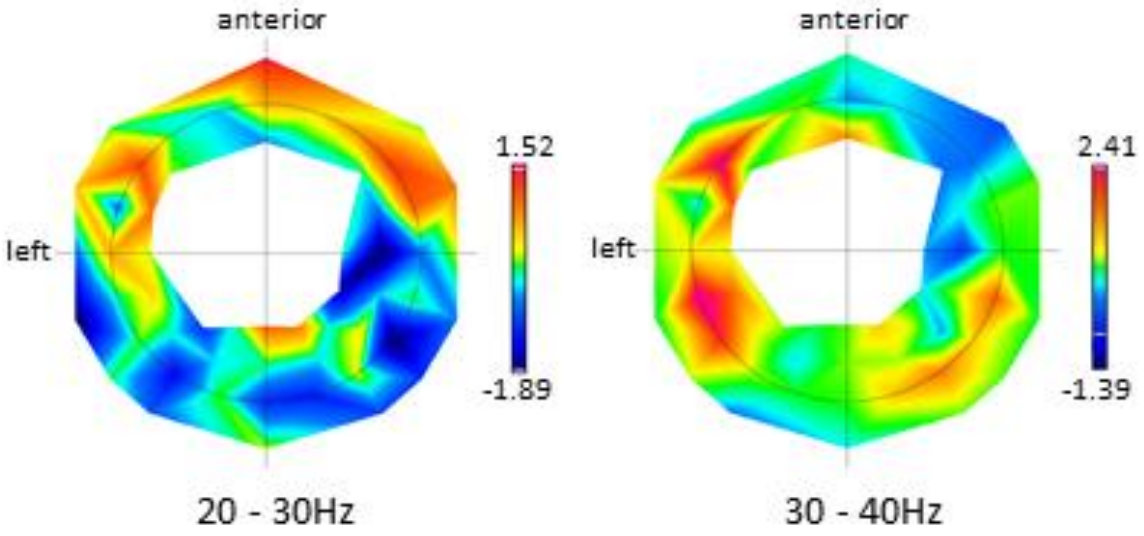
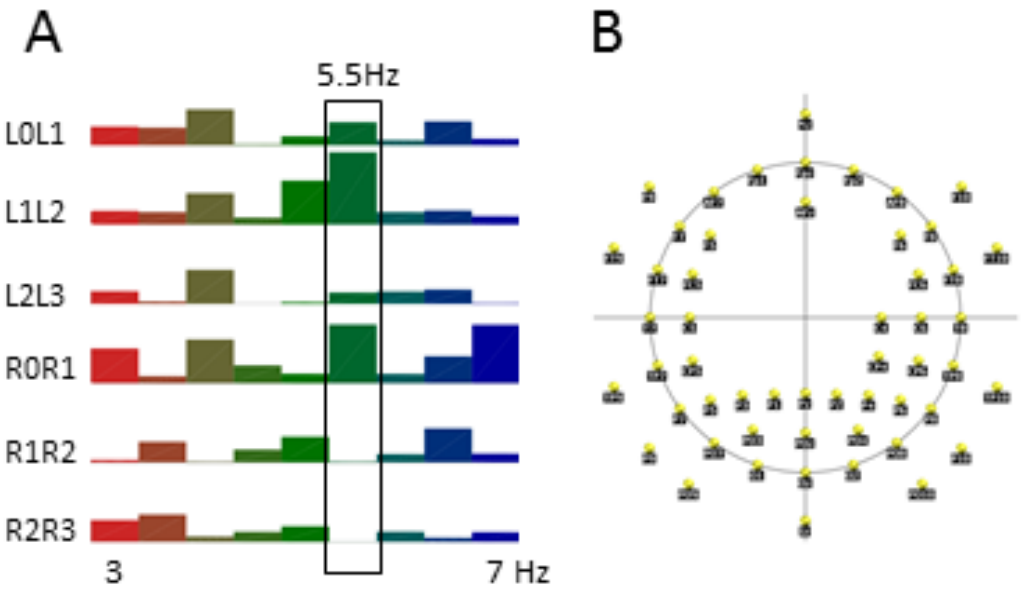
P5
P7
P9
PO3
PO7
PO9
O1
Nz
Fpz
AFz
Pz
POz
Oz
Iz
Fp2
AF8
F10
F6
F8
FC6
FT8
T10
C4
C6
T8
CP4
CP6
TP8
P10
P2
P4
P6
P8
P10
PO4
PO8
O10
O2
20
30
40Hz
t-value
3.82
- 3.74

Figure 4



Supplementary Figure S1



6.10. Příloha 10 - Cortical oscillatory activity can identify a subgroup of Parkinson's disease patients with suboptimal responses to deep brain stimulation of the subthalamic nucleus

Martina Bočková, Martin Lamoš, Petr Klimeš, Pavel Jurák, Josef Halámek, Sabina Goldemundová , Marek Baláž, Ivan Rektor. Cortical oscillatory activity can identify a subgroup of Parkinson's disease patients with suboptimal responses to deep brain stimulation of the subthalamic nucleus.

Submitováno

Cílem této práce bylo hodnocení oscilačních změn v souvislosti s léčbou STN-DBS u PN pacientů v průběhu provádění kognitivně- motorické úlohy. Kognitivní a neuropsychiatrické obtíže občas mohou komplikovat jinak úspěšnou DBS, proto jsme se zaměřili i na kognitivní funkce. U 32 pacientů se zavedenou STN-DBS jsme snímali HD-EED v průběhu třístimulového paradigmatu s neterčovými, terčovými a distrakčními podněty. Data byla rekonstruována do objemu dle AAL atlasu. Oscilační změny ve vybraných oblastech byly analyzovány pomocí TFA (časově frekvenční analýza) a korelovány s klinickým hodnocením (UPDRS škála a neuropsychologické vyšetření). Hlavní změnou při zapnuté stimulaci bylo zvýšení desynchronizace s pásmech alfa a beta, což je považováno za korelát aktivace a pravděpodobně to souvisí se zlepšením kognitivně motorického výkonu v DBS on stavu. Mezi pacienty jsme překvapivě identifikovali podskupinu šesti subjektů s horšími reakčními časy při zapnuté stimulaci. Tito pacienti měli současně horší klinickou odpověď na DBS v podobě menšího rozdílu v off/on UPDRS skórech a také nejvyšší UPDRS skóre v on stimulačním stavu. V souboru nebyli pacienti s jasnou demencí, nicméně pacienti z této podskupiny měli signifikantně horší výsledky v testech na sématickou pamět. Jejich elektrofyziologická reaktivita byla rovněž odlišná- v on stavu došlo se snížení desynchronizace především v alfa a méně i v beta pásmu. Zdá se tedy, že analýza oscilačních

změn v HD-EEG by mohla být do budoucna užitečná při hledání prospektivních biomarkerů předpovídajících odpověď na léčbu DBS a při individualizaci léčebných strategií.

Cortical oscillatory activity can identify a subgroup of Parkinson's disease patients with suboptimal responses to deep brain stimulation of the subthalamic nucleus

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Abstract

Introduction: Although deep brain stimulation of the subthalamic nucleus (STN-DBS) in Parkinson's disease (PD) is generally a successful therapy, it is not without limitations. Adverse events, mainly neuropsychiatric and/or insufficient clinical effects, can occur in some patients. Biomarkers identifying suboptimal responders to STN-DBS would be beneficial for clinical practice.

Objective: We studied cortical oscillations related to STN-DBS in a cognitive-motor task. We hypothesized that the impact of stimulation on oscillations related to cognitive and motor functions might help to identify patients with suboptimal responses to STN-DBS.

Methods: High-density EEG was recorded during a visual three-stimuli paradigm in DBS "off" and "on" conditions in 32 PD patients with STN-DBS. Pre-processed scalp data were reconstructed into the source space, the time-frequency analysis was evaluated and correlated to the behavioral parameters.

Results: Alpha and beta event-related desynchronizations (ERD) were observed as the main activation correlate during target processing. The ERD area was larger in the majority of subjects in the "on" condition, and it was related to faster or unchanged reaction times during the "on" stimulation. We identified a subgroup of six patients with longer reaction times and smaller ERD areas in the "on" state, mainly in the alpha range. These subjects had lower motor responsiveness to DBS and decreased memory test results.

Conclusions: A subgroup of PD patients with a suboptimal response to STN-DBS could be identified. The level of alpha ERD connected with cognitive performance should be studied prospectively as a potential biomarker for suboptimal responses to STN-DBS.

Key words: HD-EEG, deep brain stimulation, time frequency analysis, biomarkers

1. Introduction:

Deep brain stimulation (DBS) is an established treatment for late motor symptoms in Parkinson's disease (PD). Although DBS is generally a successful therapy and perhaps the second-most important therapeutic advance in PD after the introduction of L-dopa and dopamine agonists, it is not without limitations (Habets et al., 2018 [9]). We sometimes encounter insufficient clinical effects on motor symptoms and adverse side effects such as dysarthria, weight gain, cognitive difficulties, and other neuropsychiatric complications in clinical practice (Saint-Cyr et al., 2000 [27]; Temel et al., 2006 [28]; Witt et al., 2008 [32]; Balestrino et al., 2017 [2]). Therefore, strict indication and exclusion criteria have been

recommended to achieve sufficient clinical benefits and reduce the risk of side effects during DBS therapy in PD (Benabid et al., 2009 [3]). However, there is still a need to optimize the treatment according to the individual patient needs. Defining predictive biomarkers for DBS clinical outcomes and the risk of side effects would be very useful in clinical practice. Based on the literature data, we presumed that advanced analysis of the HD EEG signal could provide this information (for review see Bočková and Rektor, 2019 [5]). Electrophysiological studies are crucial in combination with neuromodulation therapy.

In this study, we focused on cognitive and motor functions in PD influenced by STN-DBS. Analysis of task-related modifications of surface EEG signals is a generally accessible diagnostic method. Surface EEG slowing was introduced as a marker for diagnosis of Lewy Body Disease (Bonanni et al., 2008 [6]). We explored whether EEG analysis could help to distinguish between optimal and suboptimal responders to STN-DBS in PD. We hypothesized that the impact of STN-DBS on brain oscillations related to cognitive and motor functions might help to identify patients with suboptimal responses to therapy.

2. Methods

2.1. Subjects

STN-DBS patients (n=32) with implanted Activa PC (Medtronic) or Libra XP (St. Jude Medical) devices participated in the study. All subjects were informed about the nature of this study and gave their informed consent. The study received the approval of the local ethics committee. The Unified Parkinson's Disease Rating Scale (UPDRS) and a neuropsychological examination were used to evaluate each patient's current clinical condition. The neuropsychological tests performed were: Digit Span (Wechsler Adult Intelligence Scale-III), Word List (Wechsler Memory Scale-III), Stroop Test, Mattis Dementia Rating Scale, Verbal Fluency Test, and Montgomery-Åsberg Depression Rating

Scale. Patients did not express signs of dementia and did not have any other important neuropsychological disorders. The therapeutic parameters were used for recording during the STN-DBS “on” condition; see Supplementary material.

Supplementary material- Patient characteristics

2.2. Experimental protocol and recordings

Subjects reclined comfortably in the monitoring seat, in a Faraday shielded room, with a constant temperature. They were instructed to remain calm, to keep their eyes fixed on the monitor, and to avoid unnecessary movements. A high-density EEG (HD-EEG) system with 256 channels from Electrical Geodesics, Inc. (EGI) was used for the scalp EEG recording. The sampling rate was 1 kHz. For cognitive testing, a visual three-stimuli protocol was used (Conroy and Polich, 2007 [12]; Polich, 2007 [24]); see Table 1. The frequent (non-target, standard) stimuli, which were 70% of all the stimuli, were small blue circles. These were not to be followed by any reaction. The target stimuli, which were 15% of all the stimuli, were larger blue circles. The subjects were asked to press a response button at the time of the target detection. The distractors (rare non-target stimuli), which were 15% of the stimuli, were black and white checkerboards; no response was required. The interstimulus interval was 4 seconds. The duration of the stimulus exposure was 200 ms. The visual stimuli were presented in random order on a monitor. Subjects were in the “off” medication condition (12-hour medication withdrawal) and repeated the experimental paradigm in both STN-DBS “on” and “off” states.

Table 1

2.3. Data analysis

2.3.1. Reaction times

Reaction times (RT) during target stimulation were determined for each patient in stimulation "off" and "on" states separately. RT was measured as the delay between target stimulus and the patient's reaction (button press) recorded by the acquisition system. Subsequently, the statistical difference between RT-DBS-"on" and RT-DBS-"off" was tested using the Wilcoxon rank-sum test. Based on this calculation, three group of patients were distinguished: RT faster in DBS "on" (Group 1), RT faster in DBS "off" (Group -1), and no significant RT difference between DBS "on" and DBS "off" (Group 0). Response accuracy was measured as the percentage of correct responses, however no significant difference between groups was found. Mean accuracy was 96%.

2.3.2. Pre-processing and artifact suppression

The EEG data were processed off-line using SignalPlant software (Plesinger et al., 2016 [23]) and EEGLAB toolbox (Delorme and Makeig, 2004 [13]) complemented by an in-house solution running under MATLAB 2014b (The MathWorks, Inc, Natick, USA). We reduced the number of channels to 204, discarding facial and neck-line electrodes. Data were filtered to 0.1-100 Hz bandwidth. Residues of DBS-related artifacts under 100 Hz were visually detected in the frequency domain in each subject and suppressed by a fast Fourier transform (FFT) filter. Data were visually inspected in SignalPlant software and bad trials were marked to be discarded from further analysis. Independent component analysis (ICA) was used to eliminate common artificial signals from blinking and ECG.

2.3.3. Source reconstruction

Electrical source imaging (ESI) was performed in Cartool software complemented by an in-house solution running under MATLAB 2014b. The Montreal Neurological Institute (MNI) template was used for forward Locally Spherical Model with Anatomical Constraints (LSMAC) model construction and Low-Resolution Electromagnetic Tomography (LORETA) was used for inversion. Reconstructed signals were parcellated based on the anatomical automatic labelling (AAL) atlas, and only centroid area signals were selected. Electrical dipoles from each area were projected to the refined average dipole orientation based on the approach by Coito et al., (2016 [11]).

2.3.4. Time-frequency analysis

Time-frequency analysis (TFA) was calculated for averaged target, frequent, and distractor stimuli, DBS "off" and DBS "on", starting 1 second before stimulation and ending 2 seconds after. TFA was calculated by FFT for the frequency range 0-100 Hz; FFT window width was 500 ms with a 10 ms step. Subsequently, event-related significant power increases (event-related synchronization; ERS) and event-related significant power decreases (event-related desynchronization; ERD) were calculated for averaged target, frequent, and distractor stimuli, using the non-parametric Wilcoxon rank-sum (Signed Rank) test for paired samples in each trial, $p < 0.01$ (Pfurtscheller, 2001 [22]). ERS/ERD was computed for each subject separately as an average ERS/ERD from the areas that are known to be involved in target response processing and are functionally coupled to the STN (Polich, 2007 [24]; Litvak et al., 2010 [20]; Litvak et al., 2011 [21]; Hirschmann et al., 2011 [16]), namely, the temporal and parietal cortex (temporal lateral cortex, superior and inferior parietal cortex, angular and

supramarginal areas), premotor regions (SMA and paracentral lobule), and the thalamus. Finally, the average size of the ERD/S was calculated in a grand average analysis (GA) for patient groups sorted by reaction times. The size of ERD/S was determined by the size of blue/red areas (statistically significant ERD/ERS change after stimuli, $p<0.01$), as shown in Figure 1 and calculated as a percentage of square area 100-1500 ms after stimulation and selected frequency range.

3. Results

Alpha and beta ERDs were observed in GA analysis and in individual subjects' data as an activation response to target stimuli that requires both motor and cognitive processing. In a majority of subjects (Groups +1 and 0), we observed enlarged ERD, mainly in the alpha range, that comprised a wider frequency range and longer duration in the analyzed areas in the "on" stimulation state than in the "off" stimulation state; see Figure 1. This reactivity probably correlates with improved motor-cognitive functioning during the "on" condition. Distractors were followed by weak ERD that was accompanied by low-frequency ERS which probably represents the inhibition of involuntary motor response. Distractor-related changes did not differ significantly during "on" and "off" stimulation conditions. For these reasons further correlations were not performed.

Figure 1

Individual results were correlated to the behavior parameters. The most important finding was the variability in reaction times among the subjects; see Figures 3. The subjects were sorted into three subgroups according to the reaction times modified by DBS. Group +1 contained

12 subjects with decreased reaction time; Group 0 contained 14 subjects with no statistically significant difference in reaction times in the DBS “on” and “off”; and Group -1 comprised 6 subjects with a negative effect of DBS: the reaction times were longer during the DBS “on”- see patients characteristics in supplementary material. There were no statistically significant differences in response accuracy. Group -1 differs from the majority of patients in electrophysiological, cognitive, and motor reaction to DBS. Neuropsychological battery showed significantly decreased results in semantic memory test WL3 (word list recognition) for Group -1, and this trend was also detectable in WL1 and WL2 (word list 1- immediate verbal memory, 2- delayed verbal memory) tests; see Figure 3. The clinical effect of DBS on motor symptoms was also lower in Group -1 as measured by UPDRS scores in “off” and “on” conditions. The UPDRS “on” scores were higher in Group -1 than in the other subgroups and the “on”/ “off” state UPDRS difference was significantly lower than in Group +1; see Figure 3. On the other hand, Group +1 patients were the best responders to the DBS therapy: their “off” state scores were the highest and the “on” state scores were the lowest, and their “on”/ “off” state UPDRS difference was significantly the highest compared to Groups 0 and -1. ERD/S were computed as GA separately for the three groups of patients as the reconstructed signal from the regions of interest. For Group -1, we observed DBS-related alpha ERD reactivity to target stimuli that appeared opposite to most patients. The alpha and beta ERDs were decreased in the DBS “on” stimulation condition in Group -1. This was a reverse reactivity from the subjects in Groups 0 and +1, where alpha ERD was enhanced during the “on” stimulation state. Beta ERD was present on a comparable level in Groups +1 and 0 during both conditions. Group -1 differed from the other groups even in the DBS “off” condition: the alpha and beta ERD levels were significantly higher ($p < 0.05$) than in Group 0 and the trend was also observed for Group +1; see Figure 2.

Figure 2

Figure 3

4. Discussion

The established indication criteria reduced the risk of adverse effects of STN-DBS in PD. However, cognitive and neuropsychiatric adverse events still may occur in clinical practice. The effect of STN-DBS on motor symptoms is generally very good, but the degree of the response may vary among individual patients, and there are some patients with insufficient efficacy. We lack a consistent definition and prediction for such patients. Markers identifying patients with suboptimal responses to DBS could be useful. The identification of suboptimal responses to DBS could lead to the optimization of stimulation and the individualization of stimulation parameters. Our data indicate that the time frequency analysis based on source space analysis of scalp HD-EEG could serve as a potential biomarker of the clinical response to STN-DBS therapy.

We studied the impact of DBS on cognitive and motor functions. As surface EEG is an easy and generally accessible method, we tested whether the cortical oscillatory activities induced by a cognitive and motor task might be useful for identifying a suboptimal response to DBS. A three-stimulus visual experimental paradigm was used with frequent, target, and distractor stimuli. The distractor does not require any response, is task-irrelevant, and evokes an early attentional and orientation activity with response inhibition. In this study, the distractor-related response did not appear to be useful for identifying a response to DBS. Target stimuli are followed by motor reactions and are associated with complex cognitive processes in temporal-parietal cognitive circuits (Polich, 2007 [24]; Bočková et al., 2013 [4]). Therefore,

in addition to the premotor cortex, the temporal and parietal cortices and thalamus areas were selected for the GA analysis. These areas are known to be functionally coupled with the STN (Litvak et al., 2010 [20]; Litvak et al., 2011 [21]; Hirschmann et al., 2011 [16]). Two different functional networks with frequency-specific couplings have been described between the STN and cortical structures in PD. The motor and premotor regions are coupled to the STN at beta frequencies (13–30 Hz). The temporo-parietal areas are coupled to the STN at the alpha band (7–12 Hz).

The clinical effect of DBS on motor symptoms is known to be linked (similarly as the effect of levodopa) with the reduction of an excessive beta hypersynchrony in the STN and subsequently in the basal ganglia-thalamo-cortical motor circuit (Brown, 2003 [7], 2006 [8]; Kühn et al., 2006 [18]; Androulidakis et al., 2007 [1]; Giannicola et al., 2010 [15]; Chen et al., 2010 [10]). The non-motor functions are related to the reactivity in the theta-alpha band, for example conflictual decision-making is related to an increase in the 5–13 Hz frequency range (Fumagalli et al., 2011 [14]) or a local decrease in alpha power is related to processing emotional stimuli and depression (Huebl et al., 2014 [17]). Increased theta-alpha activity is also associated with impulse control disorders (ICD) and pathological gambling in PD (Rodriguez-Oroz et al., 2011 [25]; Rosa et al., 2013 [26]).

In this study, in the majority of patients, we were able to confirm the known reactivity of cortical oscillatory response to motor-cognitive stimuli to DBS. The expected lack of significant change (Group 0) or the shortening of RT (Group 1) was linked with enhanced ERD in the alpha range. ERD is considered to be an expression of cortical activation (Pfurtscheller, 2001 [22]).

We further identified a subgroup of patients with opposite behavioral and electrophysiological responses to target stimuli. The identification of this subgroup (Group -1) was based on significantly longer RT in the DBS “on” state than in the DBS “off” state. In this subgroup,

longer RT was accompanied with decreased desynchronization (i.e. diminished cortical activation), mainly in the alpha frequency range. Moreover, the clinical impact of the DBS therapy on motor symptoms was less effective. The neuropsychological examination showed no signs of dementia at the current stage, but the Group -1 subjects had significantly worse results in semantic memory tests. The task performance appears to be disturbed in these patients; the prolongation of the reaction times was probably caused by a decreased cognitive performance as there is no reason to presume a significant difference in the motor part of the response. The difference in oscillatory patterns, RT, and clinical scores in Group -1 subjects was not caused by incorrect electrode positioning in the STN. Electrode positions were verified in all subjects and no important deviations from the planned trajectory were detected. In our center, postoperative CT scans under stereotactic conditions covering the entire length of the implanted electrodes are routinely performed. The series of images are reimported to the planning workstation and subsequently the coordinates are correlated with the real position of implanted electrodes. The change of electrode position is evident in the planning data sets so that the final electrode position can be evaluated without being burdened by artifacts caused by electrode material in CT or MRI scans.

Our results suggest that the analysis of oscillatory activities via scalp EEG could identify patients with poorer response to DBS and possibly higher risk of cognitive deterioration. Here, in Group -1 we detected larger “off” state ERD than in the other Groups. This was present mainly in the alpha but also in the beta band. In Group -1, the DBS led to ERD reduction. Whether a higher level of alpha ERD in the “off” stimulation state that is decreased by DBS could serve as a potential biomarker for DBS-related cognitive adverse effects remains to be clarified. The small size of subgroups that resulted from sorting the patients according the obtained data limited the statistical analysis. A larger prospective study would

be needed to verify our finding of patients with suboptimal responses to DBS and possibly introduce criteria for defining this suboptimal response in clinical practice.

Attention should be focused on the individual oscillatory reactivity related to DBS. It has been shown that there is variability in oscillatory responses to DBS even in such well-known phenomena as beta hypersynchrony reduction, which was absent in some patients (Giannicola et al., 2010 [15]). Frequency peaks in the STN vary among subjects (Tsang et al., 2012 [29]). The development of adaptive neurostimulators enabling therapeutic progress represents the most important recent development (Little et al., 2013 [19]). However, these stimulators reflect beta oscillations only; changes in other frequency bands are not considered. Attention should be paid to alpha reactivity in the subcortico-cortical cognitive circuits, as the DBS modifications of the cortical alpha activity reflect the clinical response to DBS. It remains to be clarified whether this modification can be linked or if it precedes clinically relevant cognitive or behavioral disturbances in DBS patients. Different reactivity of brain oscillations reflecting a suboptimal response in some patients should be taken in account during adaptive DBS therapy.

5. Conclusion:

An expected DBS-related improvement in cognitive-motor task performance with typical reactivity of brain oscillations was observed in most patients. A minority of patients reacted differently, with opposite brain electrophysiological modifications, lower clinical motor response to DBS, decreased memory performance, and prolonged reaction times. Scalp-recorded cerebral oscillatory activities should be analyzed prospectively as a potential biomarker identifying patients with less favorable responses to STN-DBS.

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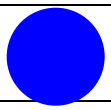
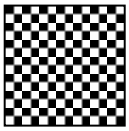
Table 1: Experimental paradigm

Stimulus	Description	Image	Response	Trials	Proportion
Target	Large blue circle		press a button	30	15%
Non-target	Small blue circle		no response	140	70%
Distractor	black & white checkerboard		no response	30	15%

Legend: Distractor-related responses are related to frontal focal attention and working memory, and target-related responses are related to temporal-parietal activity and subsequent memory processing (Polich, 2007 [24]).

Figure 1

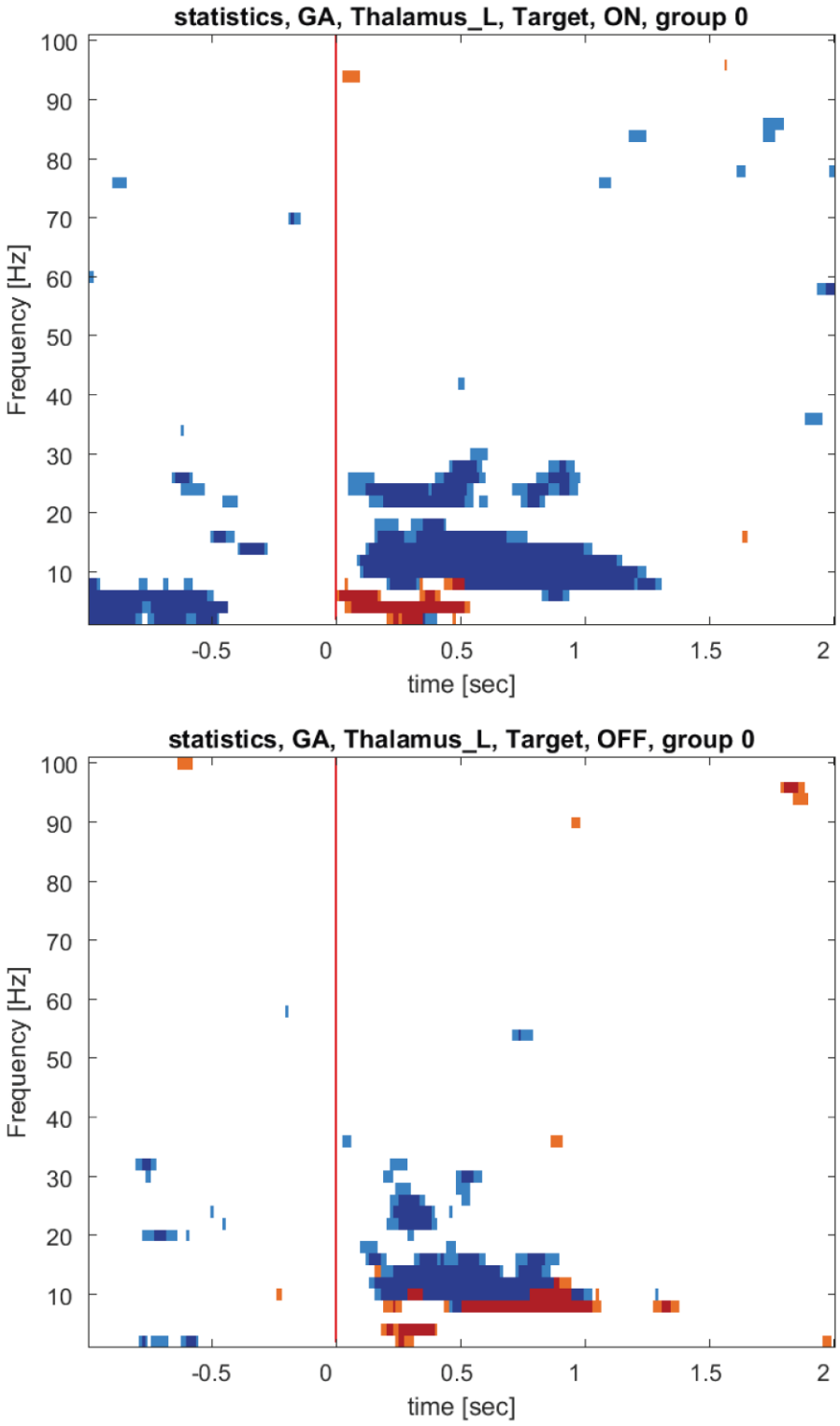

statistics, GA, Thalamus_L, Target, ON, group 0
Frequency [Hz]
time [sec]
statistics, GA, Thalamus_L, Target, OFF, group 0
Frequency [Hz]
time [sec]

Figure 2

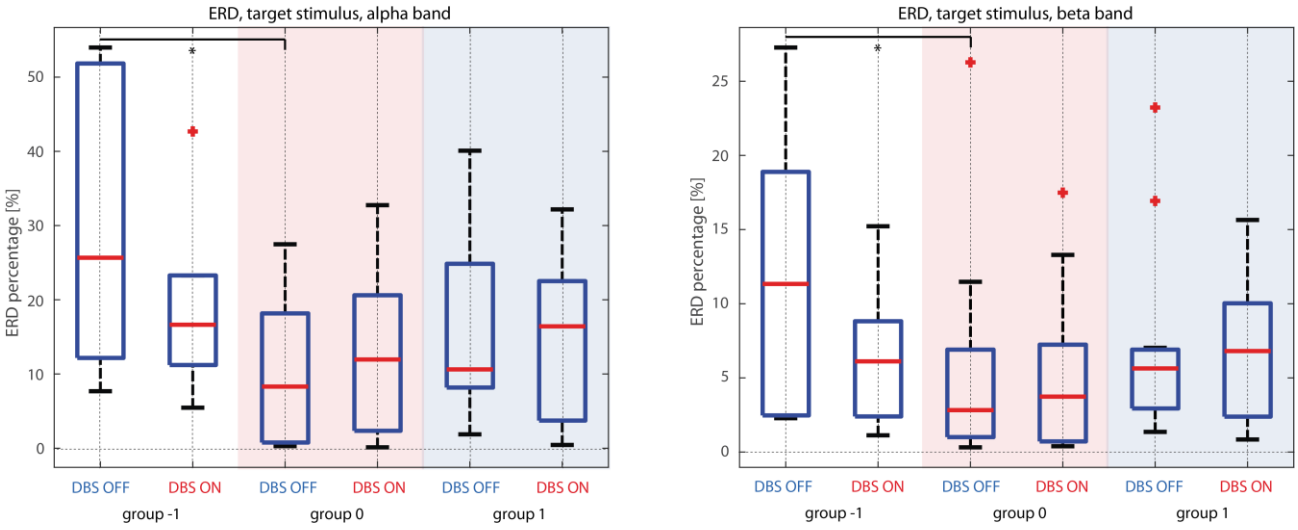


Figure 3

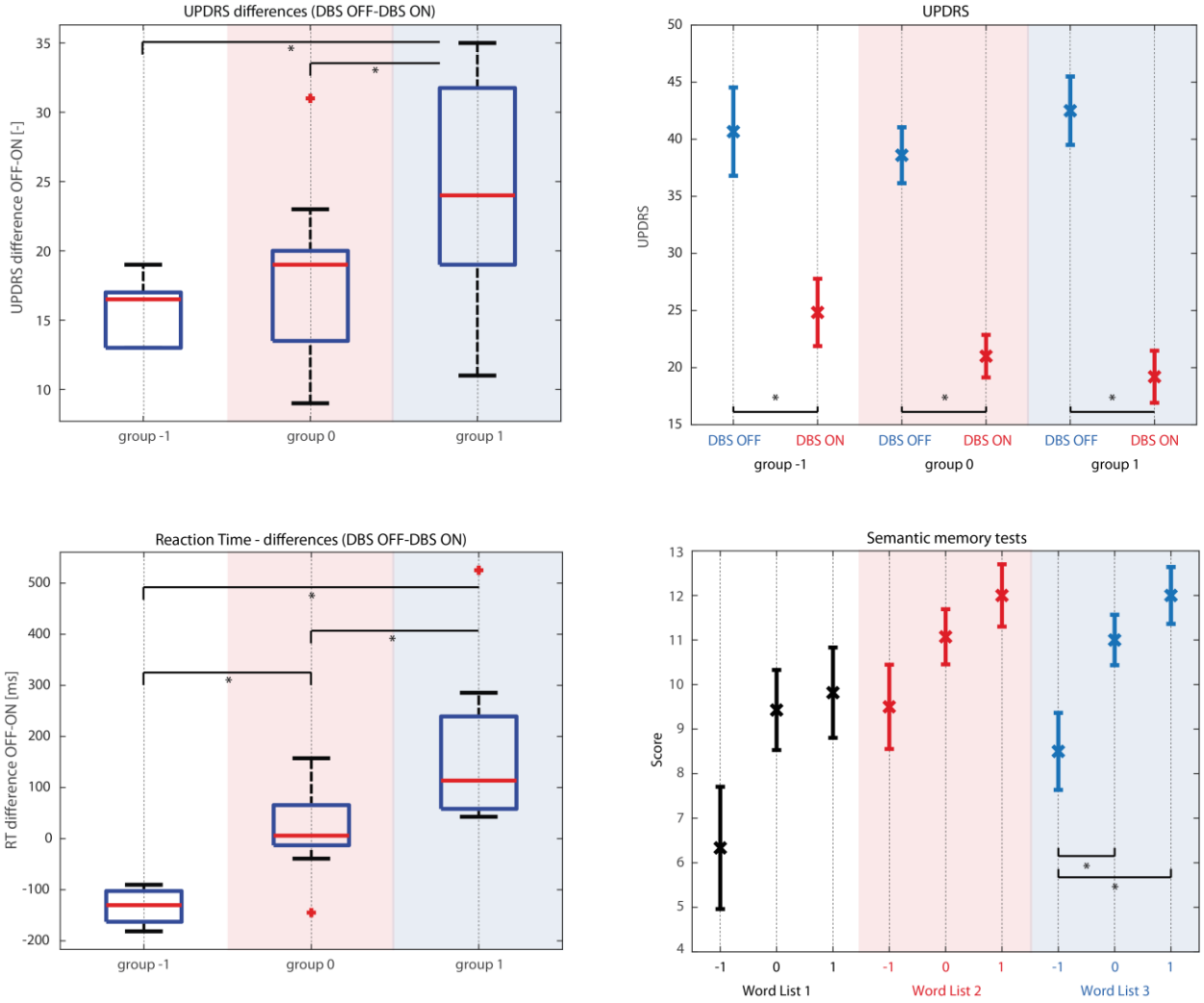


Figure 1: Examples of typical target-related responses during DBS “on” and “off”

Legend: Statistically significant Event Related Desynchronization (ERD)/Event Related Synchronization (ERS) in 0-100 Hz in interval 1 second before and 2 seconds after stimuli expressed by Time Frequency Analysis. Red identifies a power increase (ERS) - dark red $p<0.01$, light red $p<0.05$; blue indicates a power decrease (ERD) - dark blue $p<0.01$, light blue $p<0.05$. Upper panel = DBS “on” target-related response; lower panel = DBS “off” target-related response. The alpha ERD was increased in the “on” stimulation state in the majority of the subjects.

Figure 2: Alpha and beta Event Related Desynchronization (ERD) differences within the groups of subjects and frequency bands, calculated as the size of ERD from the selected areas (temporal and parietal cortex, premotor regions, and the thalamus).

Legend: Each box covers the data from 25th to 75th percentiles, the line in each box represents the median of explained variability over subjects, and whiskers represent 1.5 times the interquartile range (IQR). Red crosses show the outliers. Black stars represent significant differences using non-parametric Wilcoxon rank-sum test ($p<0.05$). Left panel: alpha ERD differences, right panel: ERD in beta frequencies. Different reactivity of Group -1 subjects was present mainly in the alpha range. The “off” state level of alpha and beta ERD is higher than in the other Groups.

Figure 3: Behavioral parameters

Legend: Upper panels: left - comparison of DBS “off” and DBS “on” differences in UPDRS scores. Each box covers the data from 25th to 75th percentiles, the line in each box represents the median of explained variability over subjects, and whiskers represent 1.5 times the interquartile range (IQR). Red crosses show the outliers. Black stars represent significant

differences using non-parametric Wilcoxon rank-sum test ($p<0.05$). Right - UPDRS scores real values. Crosses show score means, whiskers represent standard error.

Lower panels: Left - comparison of DBS "off" and DBS "on" differences in reaction times. Right - semantic memory test results.

UPDRS scores real values and semantic memory test results are statistically analyzed using multiway analysis of variance (ANOVA).

Table 1- Patient characteristics

Su. No.	**age**	**sex**	**DBS setting**	**medication**	**UPDRS**	
					off	**on**
1	65	F	2,5mA bilat./130Hz/91usec (Libra)	L-dopa, Ent, Rop	28	11
2	71	M	3,0V bilat./130Hz/ 90usec (Activa)	L-dopa, Rop	45	25
3	68	F	3,2V bilat/130Hz/90usec (Activa)	L-dopa, Ent, Rop	34	17
4	58	M	1,1mA bilat./130Hz/143usec (Libra)	L-dopa, Rop	40	26
5	52	M	3,3V bilat./130Hz/90usec (Activa)	L-dopa, Rot	42	14
6	55	M	1,5V bilat./130Hz/60usec (Activa)	L-dopa, Pra	46	29
7	64	F	2,4V bilat./130Hz/90usec (Activa)	L-dopa, Ent	50	17
8	61	F	2,4V bilat./130Hz/90usec (Activa)	L-dopa, Ent, Rop	35	15
9	39	M	3,9mA(bip)/3,0mA(bip)/130Hz/78usec (Libra)	L-dopa, Ent, Rop	48	13
10	60	M	1,9V bilat./130Hz/90usec (Activa)	L-dopa, Ent	31	18
11	65	F	3,2mA bilat. (bip)/130Hz/65usec (Libra)	L-dopa, Rop	44	31
12	53	M	2,2 V bilat./130Hz/90usec (Activa)	L-dopa, Ent, Rop	48	28

13	58	M	3,3V/4,3V/130Hz/90usec (Activa)	L-dopa, Rop, Rot, Bipe	53	37
14	55	F	1,4 mA/1,8mA/130Hz/91usec (Libra)	L-dopa, Ent, Pra	55	31
15	65	F	1,6V/1,4V/130Hz/90usec (Activa)	L-dopa, Pra	36	17
16	56	M	2,1V/2,1V(bip)/130Hz/90usec (Activa)	L-dopa, Ent	30	17
17	58	M	1,2V/2,5V/130Hz/90usec (Activa)	L-dopa, Ent, Rop	49	26
18	63	M	2,1V bilat./90usec/130Hz (Activa)	L-dopa, Ent, Rop, Sel	24	15
19	66	M	2,5V bilat./90usec/130Hz (Activa)	L-dopa, Ent, Rop	50	24
20	73	M	2,5V/ 3,0V /90usec/130Hz (Activa)	L-dopa, Ent	30	11
21	59	M	2,6V bilat/90usec/130Hz (Activa)	L-dopa	40	21
22	64	M	2,2V/90usec/130Hz (Activa)	L-dopa, Rop	38	14
23	66	M	2,8V/90usec/130Hz (Activa)	L-dopa, Pra	36	25
24	54	M	3,6V/60usec/130Hz (Activa)	L-dopa, Ent, Rop	36	17
25	65	M	1,4V/90usec/130Hz (Activa)	L-dopa, Pra	44	24
26	68	F	2,2mA/91usec/130Hz (Libra)	L-dopa, Ent, Ama	29	9
27	66	M	2,9V a 2,7V/90usec/130Hz (Activa)	L-dopa, Ent	36	21
28	54	M	3,2V/90usec/130Hz (Activa)	L-dopa, Ent, Rop, Ama	58	24
29	68	F	0,5 a 1,7V/90usec/130Hz (Activa)	L-dopa, Rop	42	23
30	64	M	2,6V/90usec/130Hz (Activa)	L-dopa, Ent, Rop	64	33
31	58	M	1,0V/90usec/180Hz (Activa)	L-dopa, Ent, Pra	26	17
32	69	M	3,3V/90usec/130Hz (Activa)	0	39	30

bip- bipolar

Ama- amantadine, Bipe- biperiden, Ent- entacapone, L-dopa- levodopa, Pra- pramipexole, Rop- ropinirole, Rot- rotigotine, Sel- selegiline, Tol- tolcapone

Green color- Group +1, Black color- Group 0, Red color- Group -1

Table 2- Neuropsychological examination

Su	DS	WL1	WL2	WL3	SW	SC	SWC	SI	MA	MI	MC	MCO	MM	MT	VFa	VFc	MS
1	6	6	10	9	48	60	53	50	35	31	6	39	25	136	25	25	0
2	10	12	13	12	28	33	45	57	37	35	6	39	25	142	62	50	0
3	6	11	13	14	42	43	35	37	37	36	6	39	25	143	75	75	3
4	13	15	15	14	42	45	52	57	37	34	6	39	25	141	10	10	0
5	8	8	12	13	52	52	42	37	36	34	6	39	25	140	9	20	0
6	6	5	10	8	22	30	37	57	36	36	6	39	25	142	30	8	0
7	9	12	12	11	33	53	47	50	36	36	6	39	25	142	25	90	5
8	13	15	13	14	63	35	50	53	37	37	6	39	25	144	90	25	4
9	6	11	12	12	40	33	35	38	37	33	6	39	25	140	10	30	1
10	9	9	12	8	35	43	50	55	37	36	6	39	25	134	50	25	0
11	10	4	5	5	25	40	27	35	37	36	6	39	25	144	75	75	7
12	11	11	9	11	62	65	58	50	37	37	6	39	25	144	75	25	6
13	9	8	10	10	28	27	30	42	37	37	6	39	25	144	75	25	4
14	11	12	10	11	20	28	40	63	37	32	6	39	25	139	10	9	10
15	7	4	10	11	35	33	37	48	37	34	6	39	25	141	17	14	0
16	13	11	12	8	28	42	40	40	37	30	6	39	25	137	13	8	1
17	6	4	9	10	33	38	25	33	37	36	6	39	25	143	20	7	3
18	10	8	12	14	50	67	53	47	37	37	4	39	25	142	90	50	0

19	10	7	14	14	47	47	45	47	37	34	6	39	25	141	50	50	0
20	8	6	11	11	53	45	16	32	37	27	5	39	25	133	5	25	0
21	5	11	15	14	28	33	37	45	34	36	6	39	24	139	75	60	0
22	9	14	13	14	63	62	65	62	37	37	6	39	25	144	90	90	0
23	12	4	11	10	35	37	40	48	37	25	6	39	25	132	5	40	0
24	7	9	11	11	42	48	52	57	35	37	6	39	25	142	90	50	0
25	6	7	10	11	23	30	33	50	35	32	5	39	25	136	50	50	0
26	7	9	6	11	55	38	33	33	37	30	6	39	24	146	10	75	6
27	9	4	6	6	40	40	35	37	37	31	6	39	25	138	5	25	0
28	NA																
29	10	6	10	11	42	37	27	30	34	37	4	39	25	139	50	75	2
30	6	10	13	11	22	40	50	75	37	36	5	39	25	141	90	50	0
31	7	8	12	8	42	47	48	48	35	30	6	39	25	135	5	10	17
32	7	3	12	11	65	55	70	98	36	28	6	39	25	134	10	10	12

DS – Digit Span; WL - Word List: 1- immediate verbal memory, 2- delayed verbal memory, 3- recognition; SW- Stroop Test Words, SC- Stroop Test Colors, SWC- Stroop Test Words/Colors, SI- Stroop Test Interference; MA- Mattis attention, MI- Mattis initiation, MC- Mattis construction, MCO- Mattis conception, MM- Mattis memory, MT- Mattis total; VFa- Verbal Fluency Test animals, VFc- Verbal Fluency Test clothes; MS- Montgomery-Asberg Depression Rating Scale (MADRS)

Green color- Group +1, Black color- Group 0, Red color- Group -1

6.11. Příloha 11- Suboptimal response to STN-DBS in PD is related to cortical large scale network dysfunction.

Martina Bočková, Eva Výtvarová, Martin Lamoš, Petr Klimeš, Pavel Jurák, Josef Halámek, Sabina Goldemundová , Marek Baláž, Ivan Rektor. Suboptimal response to STN-DBS in PD is related to cortical large scale network dysfunction.

Submitováno

Na stejném souboru subjektů jako ve výše uvedené práci, byla počítána síťová analýza pomocí teorie grafů. Hodnotili jsme změny globální a lokální konektivity při vypnuté a zapnuté stimulaci. U většiny pacientů se globální konektivita neměnila. Při hodnocení lokálních změn jsme zaznamenali zvýšení síly uzlu nebo eigenvector centrality pro oblasti levé i pravé SMA při DBS on, což zřejmě souvisí s obnovením fyziologického postavení této struktury v síti při řízení hybnosti. U podskupiny výše uvedených šesti subopotimálních respondéru byl patrný pokles globální konektivity během stimulace v pásmu 1-8 Hz, nebyla přítomna změna konektivity pro oblast SMA a navíc byl přítomen pokles konektivity (síly ulzu v pásmu 1-8 Hz) pro celou řadu především frontálních struktur. Síťová analýza tedy může být rovněž nápomocná pro detekci suboptimálních respodérů na DBS a pacientů se zvýšením rizikem vzniků nežádoucích účinků této terapie.

Suboptimal response to STN-DBS in PD is related to cortical large scale network dysfunction.

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Abstract

Objective: The degree of response to the subthalamic nucleus deep brain stimulation (STN-DBS) treatment is individual and the level of improvement and of adverse effects is hardly predictable. We hypothesized that dysfunction on cortical level linked to dysfunction of the cortico-subcortical circuits may be related to the suboptimal response to STN-DBS.

Methods: Network analysis based on graph theory was used to evaluate the high-density EEG signal (HDEEG) recorded in 32 Parkinson´s disease (PD) patients treated by STN-DBS. HDEEG was recorded during the performance of a visual three-stimulus oddball paradigm during STN-DBS "off" and "on" states. Pre-processed scalp data were reconstructed into the source space and correlated to the behavioral parameters.

Results: In the majority of patients, STN-DBS did not lead to changes in global network organization in large scale brain networks. Only in a subgroup of suboptimal responders with lower clinical motor response and worse memory test results decreased global connectivity in the 1-8Hz frequency range and decreased regional node strength of frontal areas was observed indicating that the topological organization in patients with suboptimal response was disturbed. The important role of the supplementary motor area for the optimal DBS response was demonstrated by the increased node strength and eigenvector centrality in good responders. This regional response was missing in the suboptimal responders.

Conclusions: The differences in global and local network measures during STN-DBS on/off estimated by network analysis of HDEEG could be helpful in identifying suboptimal responders to STN-DBS therapy in PD.

Key words: subthalamic nucleus, deep brain stimulation, high- density EEG, network analysis

1. Introduction

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is an effective and well-established treatment of motor symptoms in Parkinson´s disease (PD) (Schuepbach et al. 2013). As the STN is a part of the basal ganglia (BG)-thalamocortical circuits that is involved also in various non-motor functions, cognitive and affective activities can also be influenced by STN-DBS (Bostan et al. 2018). Recommended indication and exclusion criteria (Benabid et al. 2009) have reduced the risk of side effects; however, they still sometimes complicate the otherwise successful therapy. The phenotype of PD varies among patients; the progression of the motor and non-motor symptoms is individual (Eggers et al. 2012). It is known from the clinical practice, that the degree of response to the STN-DBS treatment is individual and that the level of clinical improvement and occurrence of adverse effects in each patient is hardly predictable. In this study we focused on the identification of optimal and suboptimal responders to STN-DBS. We presumed that brain bioelectrical activity measured on the scalp using High-Density EEG (HDEEG) could improve our understanding of the responses to DBS (Bočková and Rektor 2019). We hypothesized that cortical response to STN-DBS may contribute to the clinical response and that dysfunction on cortical level leading to or resulting from dysfunction of the cortico-basal ganglia-thalamo-cortical circuits may be related to the suboptimal response.

2. Methods

2.1. Subjects

PD patients (n=32) with late motor complications treated with STN-DBS (Activa PC or Libra XP stimulators) participated in the study (see supplementary material, Table 1). The duration

of the treatment varied among patients from a minimum 6 months to a maximum of 8 years. All subjects were informed about the nature of this study and gave their informed consent. The study received the approval of the local ethics committee. The Unified Parkinson's Disease Rating Scale (UPDRS) at the time of experimental recording and a neuropsychological examination were used to evaluate each patient's current clinical condition., The neuropsychological tests performed were: Digit Span (Wechsler Adult Intelligence Scale-III), Word List (Wechsler Memory Scale-III), Stroop Test, Mattis Dementia Rating Scale, Verbal Fluency Test, and Montgomery-Åsberg Depression Rating Scale. Patients did not express signs of dementia or major depression and did not have any other important neuropsychological disorders. The therapeutic parameters were used for recording during the STN-DBS "on" condition; see Supplementary material.

Supplementary material- Patient characteristics

2.2. Experimental protocol and recordings

Recordings were performed in a Faraday shielded room with a constant temperature. Subjects were instructed to remain calm, to keep their eyes fixed on the monitor, and to avoid unnecessary movements. A HDEEG system with 256 channels from Electrical Geodesics, Inc. (EGI) was used for the scalp EEG recording. The sampling rate was 1 kHz. For motor and cognitive testing, a visual oddball three-stimuli protocol was used (Conroy and Polich, 2007; Polich, 2007, Bočková et al. 2013); see Table 1. The frequent (non-target, standard) stimuli, which were 70% of all the stimuli, were small blue circles. These were not to be followed by any reaction. The target stimuli, which were 15% of all the stimuli, were larger blue circles, and the subjects had to press a response button at the time of the target detection. The distractors (rare non-target stimuli), which were 15% of the stimuli, were black and white

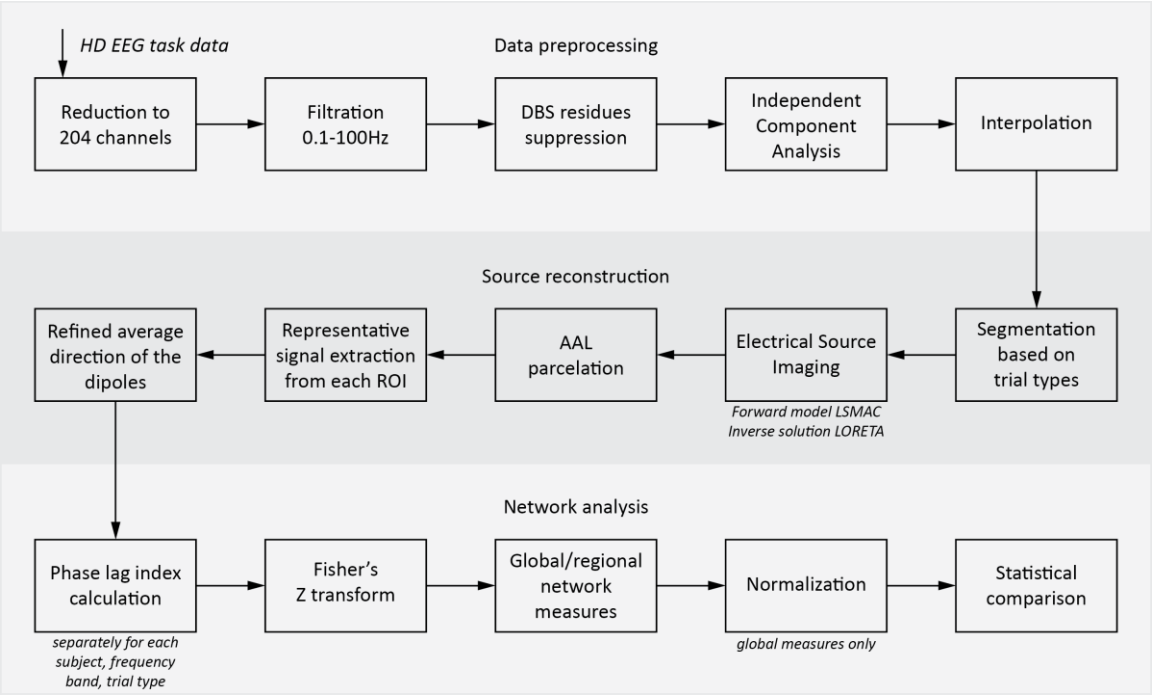
checkerboards; no response was required. The interstimulus interval was 4 seconds. The duration of the stimulus exposure was 200 ms. The visual stimuli were presented in random order on a monitor. Subjects were in the “off” medication condition (12-hour medication withdrawal) and repeated the experimental paradigm in both STN-DBS “on” and “off” states. Fourteen subjects were recorded first in “off” and later in “on” state, 18 subjects were recorded first in “on” and then in “off” condition to exclude the effect of learning.

Table 1

2.3. Data analysis

The whole analytical process is shown in figure 1 and described in the paragraphs. This process includes 3 phases: pre-processing, source reconstruction, and network analysis. Recordings from both conditions (DBS “on” and “off”) in each patient underwent the same processing steps. Statistical evaluation of the findings obtained from electrophysiological data was done by nonparametric Wilcoxon tests. Neuropsychological battery and UPDRS scores were assessed by a multiway analysis of variance (ANOVA).

Figure 1 - EEG data pre-processing and analysis pipeline



2.3.1. Reaction times

Reaction times (RT) during target stimulation in "off" and "on" states were determined for each patient. RT was measured as the delay between the target stimulus and the patient's reaction (button press). Subsequently, the statistical difference between RT-DBS-"on" and RT-DBS-"off" in each patient was tested using the Wilcoxon rank-sum test. Based on this difference and significance, three groups of patients were distinguished. RT faster in DBS "on" (Group 1), RT faster in DBS "off" (Group -1), and no significant RT difference between DBS "on" and DBS "off" (Group 0). Response accuracy was measured as the percentage of correct responses. However, no significant difference between groups was found. The mean accuracy was 96%.

2.3.2. High-Density EEG pre-processing and artifact suppression

The EEG data were processed off-line using the EEGLAB toolbox (Delorme and Makeig, 2004) complemented by an in-house solution running under MATLAB 2014b (The MathWorks, Inc, Natick, USA). We reduced the number of channels to 204, discarding facial and neck-line electrodes. Data were filtered to 0.1-100 Hz bandwidth. Residues of DBS-related artifacts under 100 Hz were visually detected in the frequency domain (several sharp peaks with substantially higher magnitude than background activity) in each subject and suppressed by a fast Fourier transform (FFT) filter. Independent component analysis (ICA) was used to eliminate common artificial signals from blinking and ECG. Data were visually inspected in SignalPlant software (Plesinger et al., 2016). Bad trials were marked to be discarded from further analysis and channels with frequent artifacts were interpolated using spherical spline method.

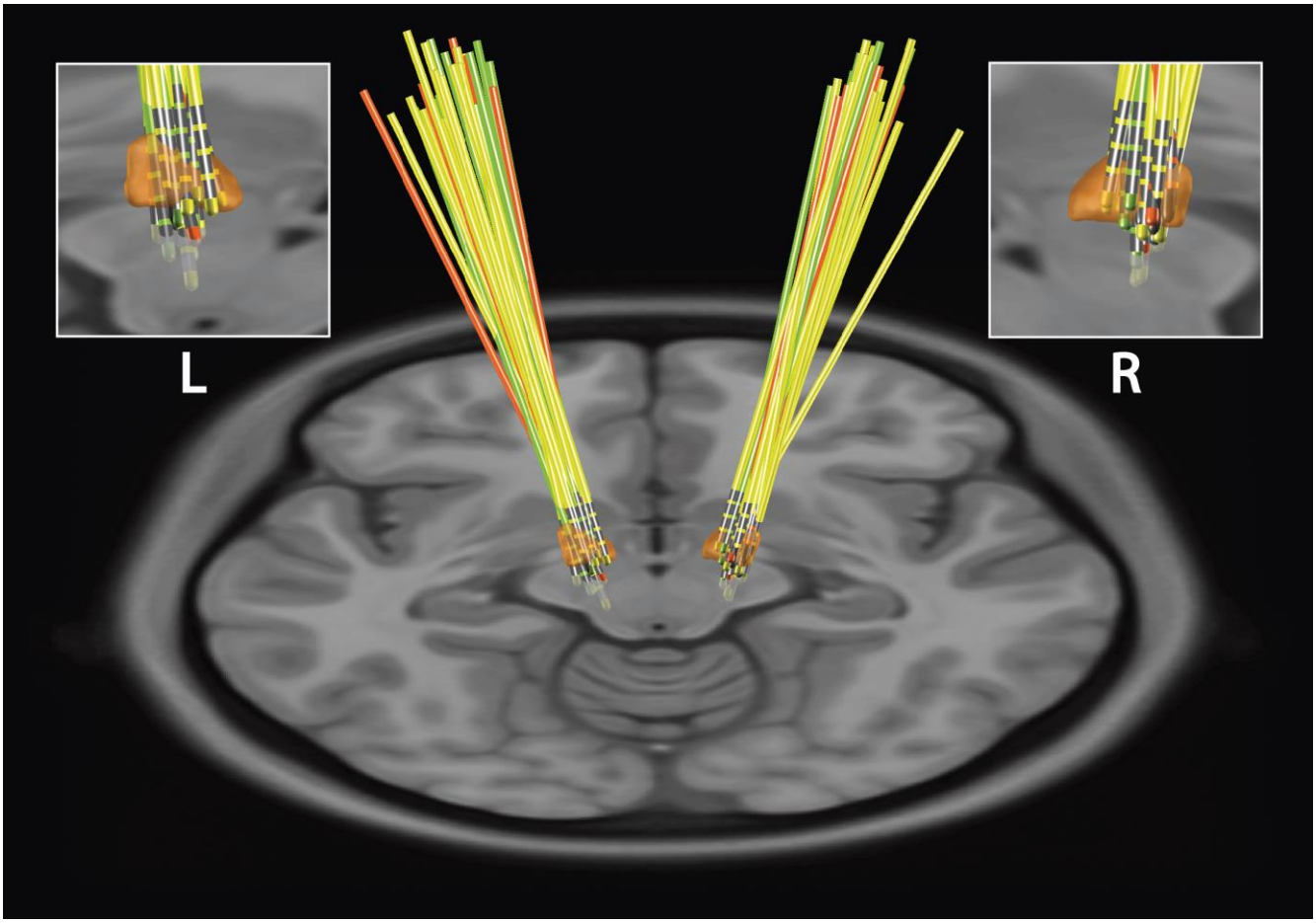
2.3.3. Source reconstruction

Electrical source imaging (ESI) was performed in Cartool software by Denis Brunet (cartoolcommunity.unige.ch), complemented by an in-house solution running under MATLAB 2014b. The Montreal Neurological Institute (MNI) template was used for forward Locally Spherical Model with Anatomical Constraints (LSMAC) model construction and Low-Resolution Electromagnetic Tomography (LORETA) was used for inversion. Reconstructed signals were parcellated based on the automatic anatomical labelling (AAL) atlas (90 areas excluding cerebellum and vermis). Electrical dipoles from each area were projected to the refined average dipole orientation based on the approach by Coito et al., (2016). Only the centroid signal from each area was selected to subsequent analysis.

2.3.4. Electrode positions

DBS electrodes positions were verified in all subjects using Lead-DBS software (www.lead-dbs.org, Horn et al. 2015) - see Figure 2. Postoperative CT images were coregistered to preoperative MRI using Advanced Normalization Tools (ANTs). Images were normalized into MNI ICBM 2009b NLIN ASYM space by ANTs based on preoperative MRI. Each step was manually checked in each patient. DBS electrodes were then localized within MNI space and overlaid with DISTAL atlas (Ewert et al. 2018).

Figure 2 – Deep brain stimulation electrodes localization.



DBS electrodes location in the STN. Green- electrodes in patients from Group 1;yellow – electrodes in patients in Group 0; red- electrodes in patients in Group -1. Notice that the grouping in the three groups is not related to the position of the electrodes

2.3.5. Network analysis

90 AAL regions of interest (ROIs) were used as nodes of a network. The edges were defined by phase-lag index (PLI) as a measure of phase synchronization (Stam, 2007) separately for these frequency bands: 1-8 Hz, 8-20 Hz, 20-45 Hz, and 55-80 Hz; PLI equals to zero means no phase coupling, PLI equals to one means perfect phase locking. Followed by Fisher's Z transformation (Lowe, 1998), a weighted connectivity matrix was established for each subject, frequency band and stimulus type, and analyzed by global and regional measures.

Brain connectivity toolbox (Rubinov and Sporns, 2010) was used and the average node strength, average clustering coefficient, characteristic path length and modularity were computed on a global level. Further, normalized measures of average clustering coefficient and characteristic path length were adapted – normalization ensured by dividing the unnormalized values by values computed and averaged for 50 networks of the null model (random network with preserved strength and degree distribution). On the regional level, node strength and eigenvector centrality were computed as measures of a ROI's importance in the network.

For each frequency band, stimulus type and patient subgroup the statistical differences between DBS "on" and DBS "off" were tested by Wilcoxon rank-sum test ($p < 0.05$).

3. Results

The differences in reaction times between DBS „on“ and „off“ conditions identified three subgroups: Group +1 containing 12 subjects was defined by decreased reaction times in DBS „on“ state; Group 0 containing 14 subjects with no statistically significant difference in reaction times; and Group -1 comprising 6 subjects displayed negative effect of DBS: the reaction times were longer during the DBS “on”. Further analysis led to distinction between the optimal responders (Group +1), good responders (Group 0) and suboptimal responders (Group -1). The neuropsychological battery showed significantly decreased results in semantic memory test WL3 (word list recognition) for Group -1, and this trend was also detectable in WL1 and WL2 (word list 1- immediate verbal memory, 2- delayed verbal memory) tests; see Figure 3. The clinical effect of DBS on motor symptoms was also lower in Group -1 as measured by UPDRS scores. The UPDRS “on” scores were higher in Group -1 than in the other subgroups and the “on”/ “off” state UPDRS difference was significantly lower than in Group +1; see Figure 3. On the other hand, Group +1 patients were the best responders to the DBS therapy: their “off” state scores were the highest and the “on” state scores were the lowest, and their “on”/ “off” state UPDRS difference was significantly the highest compared to Groups 0 and -1.

Figure 3- Clinical parameters

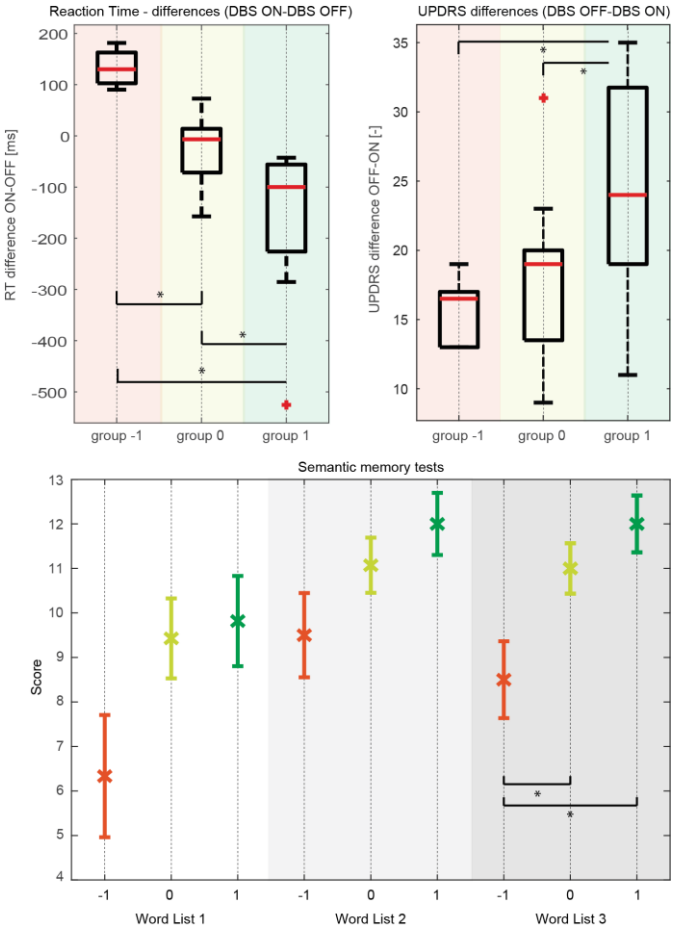


Figure 3: Clinical parameters

Legend: Upper panels: Each box covers the data from 25th to 75th percentiles, the red line in each box represents the median of explained variability over subjects, and whiskers represent 1.5 times the interquartile range (IQR). Red crosses show the outliers. Black stars represent significant differences using the non-parametric Wilcoxon rank-sum test ($p<0.05$).

Lower panel: semantic memory test results. Crosses show score means, whiskers represent standard error. Semantic memory test results were statistically analyzed using multiway analysis of variance (ANOVA). Difference in memory testing results in subgroup -1 was significant in the word semantic memory test - word list 3. The difference in the word list 1 did not reach statistical significance, but the trend to decreased performance is evident.

Green color- Group 1, yellow- Group 0, and red- Group -1.

Global network organization:

There were no important changes in global network measures in higher frequency ranges 8-20 Hz and 20-45 Hz frequency bands in DBS „on“ condition compared to DBS „off“. However, overall connectivity in Group -1 was impaired in the 1-8 Hz band in reaction to target stimulus, while no modifications were observed in Group +1 and 0. The average node strength was decreased as well as the clustering coefficient and the characteristic path length was increased in DBS „on“ state in Group -1 (Figure 4). In the other groups, the opposite trend is noticeable, although not significant. In the 55-80 Hz bandpass we have detected different global network organization changes in “on” and “off” states as a reaction to all three stimulus types in the -1 and 0 Groups in contrast to Group +1, where no STN-DBS influence was observed in the gamma range connectivity- see Table 2 summarizing all global network significant changes.

Table 2

Figure 4: Global connectivity measures – average node strength in 1-8 Hz band.

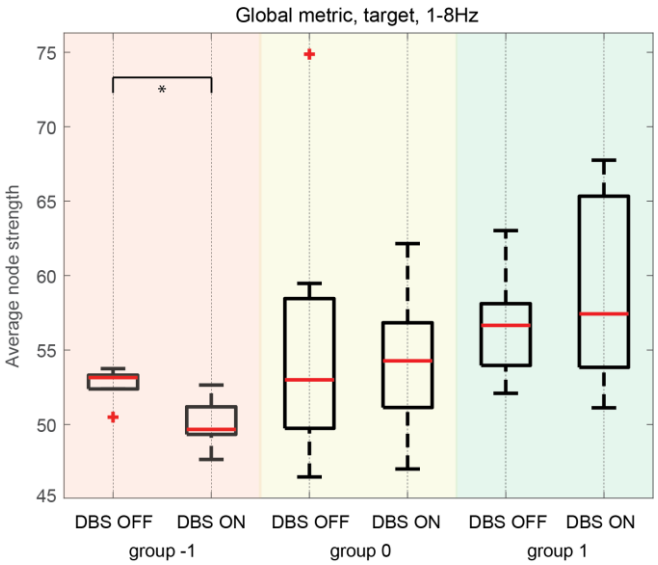


Figure 4: Global connectivity measures – average node strength in 1-8 Hz band.

Each box covers the data from 25th to 75th percentiles, the red line in each box represents the median of explained variability over subjects, and whiskers represent 1.5 times the interquartile range (IQR). Red crosses show the outliers. Black stars represent significant differences using the non-parametric Wilcoxon rank-sum test ($p<0.05$). Decreased global connectivity (decreased node strength and clustering coefficient, increased characteristic path length) was observed in Group -1 patients during stimulation in contrast to the other Groups where DBS produced no significant change.

Local network organization:

We have also found differences between "on" and "off" states in local network organization (using node strength and eigenvector centrality measures) among the three subgroups. Again, the Group -1 displayed a diverse pattern compared to Groups 0 and +1. The most important finding was significantly decreased node strength in 1-8 Hz frequency range in several mainly frontal areas during DBS "on" state after target stimulus, which was not present in the other groups. In contrast, Group +1 subjects displayed significantly increased node strength in the same frequency in the left and right supplementary motor area (SMA) in the "on" state after target stimulus. Group 0 was without changes in these parameters and frequency band, but here we have detected significantly increased eigenvector centrality in 8-20 Hz range in the left and right SMA and also in the left gyrus parietalis superior and left paracentral lobule- see Figure 5 and supplementary material (Table 3) with all regional differences. Increase in node strength in SMA in Group +1 equals to higher PLI coefficients in average to all ROIs (SMA is in average more phase-locked with signals from other ROIs in "on" than in "off" states). On the other hand, increase in EC in SMA in Group 0 suggests closer connection (better synchronization) to other EC-important ROIs in "on" than in "off" state.

Again, there were minimal changes in local network measures observed in the higher frequency ranges in Group +1 in contrast to the other two subgroups.

Figure 5: Local network measures in 1-8 Hz and 8-20 Hz bands

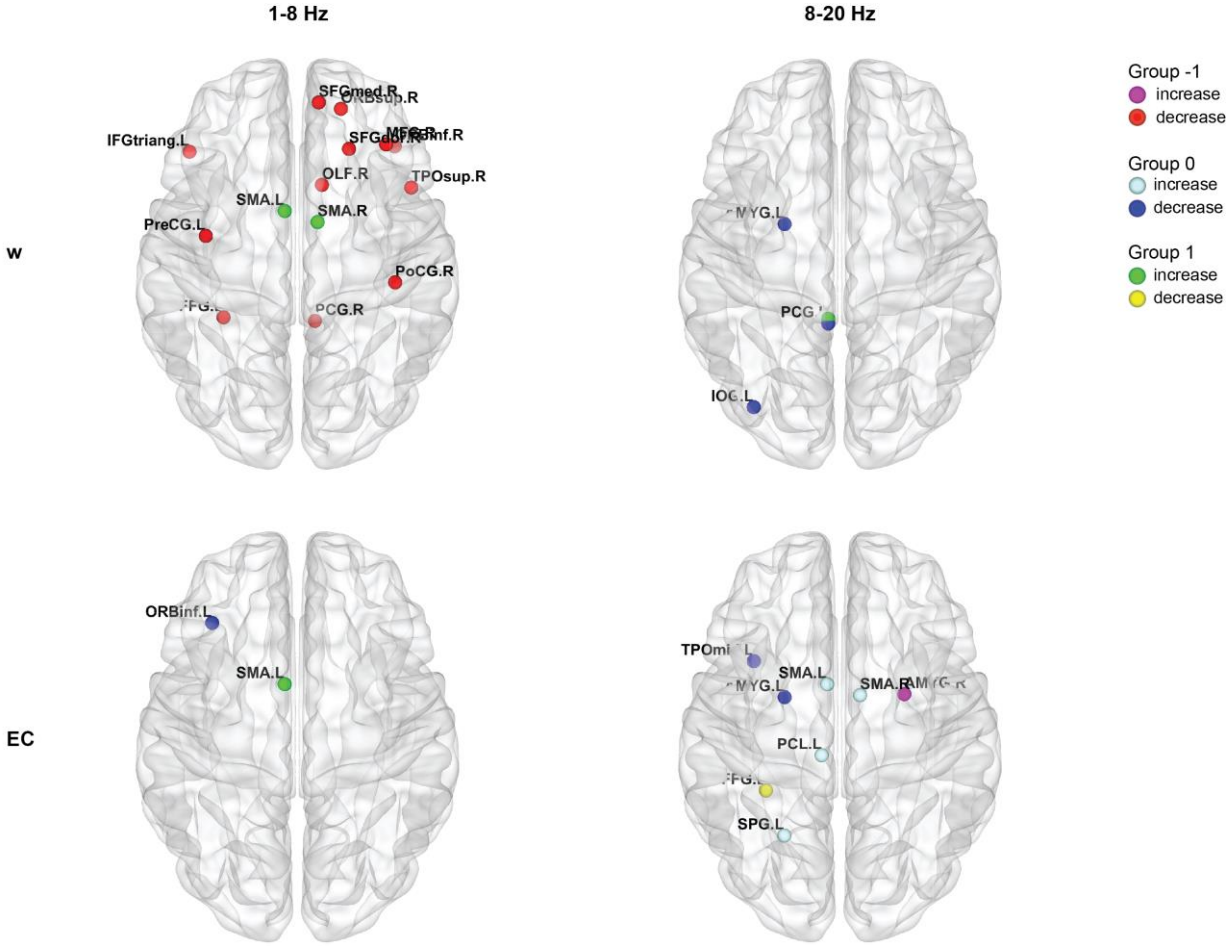


Figure 5: Local network measures in 1-8 Hz and 8-20 Hz bands

The increased importance of the SMA was observed in Groups 1 (increased node strength in 1-8Hz) and 0 (increased eigenvector centrality in 8-20Hz) during DBS. In contrast, this DBS related SMA change was absent in Group -1, where a decrease in importance was present (decreased node strength in 1-8 Hz) in several mainly frontal areas during DBS “on” state

EC- eigenvector centrality, w- node strength.

4. Discussion

We studied the influence of STN-DBS on large scale cortico-subcortical networks during processing of a cognitive and motor task. The aim was to identify the biomarkers of the individual responses to the STN-DBS. We were focused on the STN-DBS induced modifications in brain network organization underlying or leading to inter-individual differences in the clinical outcomes. To study the influence of STN-DBS on motor and cognitive circuits, a three-stimulus visual experimental paradigm was used (Conroy and Polich 2007, Polich 2007, Bočková et al. 2013). We focused on responses to target stimuli inducing a motor response that is associated with complex cognitive processes localized mainly in fronto-temporal-parietal cortex (Polich 2007, Bočková et al 2013). HDEEG was analyzed in 32 STN-DBS patients. All of our subjects have profited from STN-DBS in motor symptoms improvement and none of them had severe neuropsychiatric symptoms or global cognitive decline manifested. There was variability in reaction times (RT) of the motor response to the target stimulus. Based on differences in RT three subgroups could be constituted. In a group of 12 patients, the RT as expected was shortened under DBS "on" condition (Group + 1). In 14 patients, no significant difference was observed (Group 0). This subgroup may have slightly lower response to DBS STN than the Group +1, but the differences are mostly not significant and we consider both subgroups as good responders. Surprisingly, despite that all patients profited from motor improvement after DBS, a subgroup of 6 persons with suboptimal response to DBS could be defined (Group - 1). An unexpected prolongation of reactions times during "on" stimulation state as compared to DBS-off state was identified. This reverse motor reaction to DBS is a manifestation of a complex response to DBS that characterizes the suboptimal responders in contrast to good responders. The effect of DBS on motor PD symptoms was less expressed comparing to other patients. The neuropsychological examination has shown a decrease in semantic memory tests compared to

the other subgroups (Figure 3). As the UPDRS scores improved, even when in lesser degree, also in the suboptimal responders we presume that the prolongation of the reaction time to target stimulus under the DBS “on” condition was caused rather by a dysfunction of the cognitive than of the motor part in this cognitive-motor paradigm.

The network analysis approach indicates the dysfunction of the large-scale cerebral networks in suboptimal responders. From the brain global network organization perspective, the suboptimal responders differ from the good responders. The Group -1 patients displayed decreased average node strength and with it related (due to weighted approach to the computation of network measures) decrease in average clustering coefficient and increase in characteristic path length in 1-8 Hz band during DBS „on“. This means decreased connectivity and slower, however not less efficient, communication within the network. Reduction in overall functional connectivity was described to be linked to PD related dementia (Ponsen et al., 2012) and therefore we suspect that the development of cognitive deterioration is more probable in the suboptimal responders as in the optimal responders. However long-term follow-up study would be needed to confirm or de-confirm this hypothesis.

Importance of the supplementary motor area (SMA) for optimal DBS effect could be demonstrated. The functional role of SMA was enhanced in DBS “on” state, in Group +1 we have detected an increased node strength for left and right SMA in 1-8 Hz range and in Group 0 an increased eigenvector centrality for left and right SMA in 8-20 Hz range. Anatomic and functional connections between STN, SMA and frontal cortical structures are crucial in cognitive control over motor actions (Aron et al. 2007). SMA is known to be functionally coupled to STN mainly in beta frequency band and the beta activity underlies the main motor symptoms in PD i.e. bradykinesia and rigidity (Marsden et al. 2001, Williams et al. 2002, Brown 2003, Litvak et al. 2011, Oswal et al. 2016, Chung et al. 2018). Frequencies in theta-

alpha range in STN functional couplings reflect rather cognitive processes. STN is coupled with temporo-parietal areas at alpha frequencies (Litvak et al. 2011; Hirschmann et al. 2011) and with frontal areas via theta oscillations (Zavala et al. 2014, 2016). There was no DBS related difference in the area of SMA in Group -1 subjects. Moreover, a widespread decrease in node strength of several frontal areas and decreased global connectivity in low frequencies was observed in this subgroup indicating that the topological organization in particular of the frontal cortex was disturbed in patients with suboptimal response. Reduced functional connectivity and decreased local integration in alpha frequency band were proven in PD dementia and non-motor symptoms severity. These proposed markers might be useful in the screening process for deep brain stimulation (Utianski et al. 2016, Geraedts et al. 2018). Disrupted topological organization of brain networks reflects decreased information transmission efficiency in patients with suboptimal response to DBS.

Stimulation may lead to the modification of the physiological balance in network functioning and could impair behaviour and cognitive performance (Brittain et al. 2014), that was probably the case of our Group -1. On the other hand, our best responders Group +1 patients displayed no changes in overall connectivity and minimal changes in local connectivity were also detected in lower and higher gamma bandpasses. The suboptimal reactivity and clinical response in the Group -1 subjects was not linked to the electrode position (see Figure 2), specific PD phenotype, drug therapy or DBS parameters setting (see supplementary material). Our results have shown that the patients with prolonged reaction times in a motor-cognitive task after DBS were suboptimal responders with worse clinical outcomes. Reaction times evaluation and surface EEG can be used for identifying responsiveness to STN-DBS. Network analysis, along with modifications of oscillatory activities (Bočková et al., in preparation), may serve as biomarkers for the identification of optimal and suboptimal responders to STN-DBS. Our study confirmed the hypothesis of cortical networks

dysfunction in suboptimal responders to STN-DBS. It remains to be elucidated whether this dysfunction is primarily of cortical origin or a result of cortico-subcortical circuity dysfunction.

Limitations of the study: There is an ongoing discussion about reliability of the reconstructed electrophysiological activity into the deep brain areas from the scalp recordings. Recently, a positive response to this issue was presented in the work (Seeber et al. 2019), where they showed direct evidence that resting state scalp EEG data can detect subcortical activity. The electrical source imaging pipeline used in our work is very similar, and moreover our data are task-based. Signal to noise ratio is in our case probably higher because of the trial averaging process. In that sense, we believe that we are able to reconstruct meaningful data also into the deep regions of the brain.

The second limitation is linked to the small number of patients, mainly in Group -1 (n=6). Statistical comparison of the results between subgroups of patients have to be interpreted carefully. Due to the limited extent of studied cohort we consider our data as preliminary that need to be confirmed and further developed in a larger prospective study. An individualization of DBS parameters based on findings revealed in this study might be useful for clinical practice.

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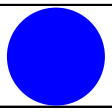
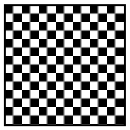
Table 1: Experimental paradigm

Stimulus	**Description**	**Image**	**Response**	**Trials**	**Proportion**
Target	Large blue circle		press a button	30	15%
Non-target	Small blue circle		no response	140	70%
Distractor	black & white checkerboard		no response	30	15%

Legend: Distractor-related responses are related to frontal focal attention and working memory, and target-related responses are related to temporal-parietal activity and subsequent memory processing (Polich, 2007 [24]).

Table 2: Significant ($p<0.05$) changes in global network measures.

	1-8 Hz	55-80 Hz
Group -1	TARGET: ↓ w, C; ↑ L	TARGET: ↑ w, C, Q, λ; ↓ L DISTRACTOR: ↑ w, C FREQUENT: ↑ λ
Group 0	-	TARGET: ↓ w, C; ↑ Q, γ, λ DISTRACTOR: ↓ w, C; ↑ L, Q, γ, λ FREQUENT: ↓ w, C; ↑ L, Q, γ, λ
Group 1	-	-

The ↑ and ↓ state for increase in DBS "on" as compared to DBS "off". Network measures are abbreviated as follows: w – average node strength, C – average clustering coefficient, L – characteristic path length, Q – modularity coefficient, γ – normalized average clustering coefficient, λ – normalized characteristic path length.

Supplementary material :

Table 1- Patient characteristics

Su. No.	age	sex	DBS setting	medication	UPDRS	
					off	on
1	65	F	2,5mA bilat./130Hz/91usec (Libra)	L-dopa, Ent, Rop	28	11
2	71	M	3,0V bilat./130Hz/ 90usec (Activa)	L-dopa, Rop	45	25
3	68	F	3,2V bilat/130Hz/90usec (Activa)	L-dopa, Ent, Rop	34	17
4	58	M	1,1mA bilat./130Hz/143usec (Libra)	L-dopa, Rop	40	26
5	52	M	3,3V bilat./130Hz/90usec (Activa)	L-dopa, Rot	42	14
6	55	M	1,5V bilat./130Hz/60usec (Activa)	L-dopa, Pra	46	29
7	64	F	2,4V bilat./130Hz/90usec (Activa)	L-dopa, Ent	50	17
8	61	F	2,4V bilat./130Hz/90usec (Activa)	L-dopa, Ent, Rop	35	15
9	39	M	3,9mA(bip)/3,0mA(bip)/130Hz/78usec (Libra)	L-dopa, Ent, Rop	48	13
10	60	M	1,9V bilat./130Hz/90usec (Activa)	L-dopa, Ent	31	18
11	65	F	3,2mA bilat. (bip)/130Hz/65usec (Libra)	L-dopa, Rop	44	31
12	53	M	2,2 V bilat./130Hz/90usec (Activa)	L-dopa, Ent, Rop	48	28
13	58	M	3,3V/4,3V/130Hz/90usec (Activa)	L-dopa, Rop, Rot, Bipe	53	37
14	55	F	1,4 mA/1,8mA/130Hz/91usec (Libra)	L-dopa, Ent, Pra	55	31
15	65	F	1,6V/1,4V/130Hz/90usec (Activa)	L-dopa, Pra	36	17
16	56	M	2,1V/2,1V(bip)/130Hz/90usec (Activa)	L-dopa, Ent	30	17
17	58	M	1,2V/2,5V/130Hz/90usec (Activa)	L-dopa, Ent, Rop	49	26

18	63	M	2,1V bilat./90usec/130Hz (Activa)	L-dopa, Ent, Rop, Sel	24	15
19	66	M	2,5V bilat./90usec/130Hz (Activa)	L-dopa, Ent, Rop	50	24
20	73	M	2,5V/ 3,0V /90usec/130Hz (Activa)	L-dopa, Ent	30	11
21	59	M	2,6V bilat/90usec/130Hz (Activa)	L-dopa	40	21
22	64	M	2,2V/90usec/130Hz (Activa)	L-dopa, Rop	38	14
23	66	M	2,8V/90usec/130Hz (Activa)	L-dopa, Pra	36	25
24	54	M	3,6V/60usec/130Hz (Activa)	L-dopa, Ent, Rop	36	17
25	65	M	1,4V/90usec/130Hz (Activa)	L-dopa, Pra	44	24
26	68	F	2,2mA/91usec/130Hz (Libra)	L-dopa, Ent, Ama	29	9
27	66	M	2,9V a 2,7V/90usec/130Hz (Activa)	L-dopa, Ent	36	21
28	54	M	3,2V/90usec/130Hz (Activa)	L-dopa, Ent, Rop, Ama	58	24
29	68	F	0,5 a 1,7V/90usec/130Hz (Activa)	L-dopa, Rop	42	23
30	64	M	2,6V/90usec/130Hz (Activa)	L-dopa, Ent, Rop	64	33
31	58	M	1,0V/90usec/180Hz (Activa)	L-dopa, Ent, Pra	26	17
32	69	M	3,3V/90usec/130Hz (Activa)	0	39	30

bip- bipolar

Ama- amantadine, Bipe- biperiden, Ent- entacapone, L-dopa- levodopa, Pra- pramipexole, Rop- ropinirole, Rot- rotigotine, Sel- selegiline, Tol- tolcapone

Green color- Group +1, Black color- Group 0, Red color- Group -1

Table 2- Neuropsychological examination

Su	DS	WL1	WL2	WL3	SW	SC	SWC	SI	MA	MI	MC	MCO	MM	MT	VFa	VFc	MS

1	6	6	10	9	48	60	53	50	35	31	6	39	25	136	25	25	0
2	10	12	13	12	28	33	45	57	37	35	6	39	25	142	62	50	0
3	6	11	13	14	42	43	35	37	37	36	6	39	25	143	75	75	3
4	13	15	15	14	42	45	52	57	37	34	6	39	25	141	10	10	0
5	8	8	12	13	52	52	42	37	36	34	6	39	25	140	9	20	0
6	6	5	10	8	22	30	37	57	36	36	6	39	25	142	30	8	0
7	9	12	12	11	33	53	47	50	36	36	6	39	25	142	25	90	5
8	13	15	13	14	63	35	50	53	37	37	6	39	25	144	90	25	4
9	6	11	12	12	40	33	35	38	37	33	6	39	25	140	10	30	1
10	9	9	12	8	35	43	50	55	37	36	6	39	25	134	50	25	0
11	10	4	5	5	25	40	27	35	37	36	6	39	25	144	75	75	7
12	11	11	9	11	62	65	58	50	37	37	6	39	25	144	75	25	6
13	9	8	10	10	28	27	30	42	37	37	6	39	25	144	75	25	4
14	11	12	10	11	20	28	40	63	37	32	6	39	25	139	10	9	10
15	7	4	10	11	35	33	37	48	37	34	6	39	25	141	17	14	0
16	13	11	12	8	28	42	40	40	37	30	6	39	25	137	13	8	1
17	6	4	9	10	33	38	25	33	37	36	6	39	25	143	20	7	3
18	10	8	12	14	50	67	53	47	37	37	4	39	25	142	90	50	0
19	10	7	14	14	47	47	45	47	37	34	6	39	25	141	50	50	0
20	8	6	11	11	53	45	16	32	37	27	5	39	25	133	5	25	0
21	5	11	15	14	28	33	37	45	34	36	6	39	24	139	75	60	0
22	9	14	13	14	63	62	65	62	37	37	6	39	25	144	90	90	0
23	12	4	11	10	35	37	40	48	37	25	6	39	25	132	5	40	0
24	7	9	11	11	42	48	52	57	35	37	6	39	25	142	90	50	0

25	6	7	10	11	23	30	33	50	35	32	5	39	25	136	50	50	0
26	7	9	6	11	55	38	33	33	37	30	6	39	24	146	10	75	6
27	9	4	6	6	40	40	35	37	37	31	6	39	25	138	5	25	0
28	NA																
29	10	6	10	11	42	37	27	30	34	37	4	39	25	139	50	75	2
30	6	10	13	11	22	40	50	75	37	36	5	39	25	141	90	50	0
31	7	8	12	8	42	47	48	48	35	30	6	39	25	135	5	10	17
32	7	3	12	11	65	55	70	98	36	28	6	39	25	134	10	10	12

DS – Digit Span; WL - Word List: 1- immediate verbal memory, 2- delayed verbal memory, 3- recognition; SW- Stroop Test Words, SC- Stroop Test Colors, SWC- Stroop Test Words/Colors, SI- Stroop Test Interference; MA- Mattis attention, MI- Mattis initiation, MC- Mattis construction, MCO- Mattis conception, MM- Mattis memory, MT- Mattis total; VFa- Verbal Fluency Test animals, VFc- Verbal Fluency Test clothes; MS- Montgomery-Asberg Depression Rating Scale (MADRS)

Green color- Group +1, Black color- Group 0, Red color- Group -1

Table 3: Significant ($p < 0.05$) regional network differences DBS ON x DBS OFF in -1, 0, 1 groups separately. No regressors (age, gender, …), no correction for multiple comparisons. The "d" indicates decrease in a given regional measure (*w* for node strength, *EC* for eigenvector centrality) and "i" increase in "on" state as compared to "off" state. *F*, *T* and *D* states for *frequent*, *target* and *distractor* stimuli types.

	1-8 Hz	**8-20 Hz**	**20-45 Hz**	**55-80 Hz**
Group -1 (N = 6)				
1 Precentral L	T: d w			

2 Precentral R				T: d EC
4 Frontal Sup R	T: d w			
6 Frontal Sup Orb R	T: d w			
8 Frontal Mid R	F: i EC T: d w			D: d EC
9 Frontal Mid Orb L				F: d EC
13 Frontal Inf Tri L	T: d w			
16 Frontal Inf Orb R	T: d w			
17 Rolandic Oper L				T: i w
19 SMA L			D: d EC	
22 Olfactory R	T: d w			
24 Frontal Sup Medial R	T: d w			F: d EC T: d EC
29 Insula L				T: i w
31 Cingulum Ant L	F: i EC			
32 Cingulum Ant R	F: i EC			
35 Cingulum Post L				T: i EC
36 Cingulum Post R	T: d w			
37 Hippocampus L			T: i w	D: i w, EC
39 Parahippocampal L				F: i w
41 Amygdala L			T: i w	
42 Amygdala R		T: i EC		
43 Calcarine L			T: d EC	

44 Calcarine R			F: d EC T: d EC	D: d w
48 Lingual R			D: d EC	
50 Occipital Sup R			D: d EC T: d EC	
55 Fusiform L	T: d w			
56 Fusiform R			F: d EC	
57 Postcentral L			T: i w	
58 Postcentral R	T: d w			
61 Parietal Inf L			D: i w	D: i w
63 Supramarginal L			D: i w F: i w	
65 Angular L			D: i w F: i w	F: i w
66 Angular R			D: d EC F: d EC T: d EC	
79 Heschl L			D: i w	F: i w, EC T: i w
81 Temporal Sup L			D: i w F: i w T: i w	T: i w
84 Temporal Pole Sup R	T: d w	F: i EC	D: i w F: i w	D: i w T: i w
85 Temporal Mid L	D: d w		D: i w	

86 Temporal Mid R			F: d EC	D: d EC
87 Temporal Pole Mid L				D: i w T: i w
90 Temporal Inf R			F: d EC	
Group 0 (N = 14)				
1 Precentral L	D: d w			D: d w F: d w
3 Frontal Sup L				D: d w
4 Frontal Sup R	D: i EC	F: i EC		
5 Frontal Sup Orb L				T: d w
7 Frontal Mid L				D: d w
8 Frontal Mid R				T: d w
14 Frontal Inf Tri R				F: d w T: d w
15 Frontal Inf Orb L	T: d EC			F: d w
19 SMA L		T: i EC		
20 SMA R		F: i EC T: i EC		
22 Olfactory R				D: d w
24 Frontal Sup Medial R	D: i EC			
26 Frontal Med Orb R	F: i EC			
28 Rectus R	F: i EC			
30 Insula R				T: d w, EC

31 Cingulum Ant L				T: d w
33 Cingulum Mid L		D: i EC		
34 Cingulum Mid R		F: i EC		
35 Cingulum Post L		T: d w		
36 Cingulum Post R				D: d w
37 Hippocampus L		F: d EC		
38 Hippocampus R				F: d w
41 Amygdala L		D: d EC T: d w, EC		
42 Amygdala R				T: d w
52 Occipital Mid R	F: d EC			
53 Occipital Inf L	F: d w, EC	T: d w		
57 Postcentral L				F: d w
58 Postcentral R				D: i EC
59 Parietal Sup L		T: i EC		
65 Angular L			T: d EC	
69 Paracentral Lobule L		T: i EC		
73 Putamen L				D: d w
75 Pallidum L			D: d w	
78 Thalamus R				D: d w, EC
80 Heschl R				D: d w F: d w T: d w
82 Temporal Sup R	D: i EC			

87 Temporal Pole Mid L		T: d EC		
88 Temporal Pole Mid R	F: i EC			F: d w
Group 1 (N = 12)				
3 Frontal Sup L	D: i w			
7 Frontal Mid L	D: i w F: i EC			
13 Frontal Inf Tri L				F: i EC
14 Frontal Inf Tri R			T: i w	
18 Rolandic Oper R				D: d w
19 SMA L	T: i w, EC			
20 SMA R	T: i w			
30 Insula R			T: i w, EC	
34 Cingulum Mid R	D: i w			
35 Cingulum Post L		F: i w T: i w		
39 Parahippocam. L		D: i w		
45 Cuneus L		D: d EC		
46 Cuneus R		D: d EC F: d EC		D: d w
53 Occipital Inf L				D: d EC
55 Fusiform L		T: d EC		
56 Fusiform R	F: i w			
57 Postcentral L			D: i w	

59 Parietal Sup L	D: i w			
61 Parietal Inf L	F: d EC			
62 Parietal Inf R			F: d EC	
66 Angular R				T: d w
77 Thalamus L		F: i EC		
86 Temporal Mid R			F: d w	
89 Temporal Inf L	F: i w			D: d w