Analýza zdrojů EEG pomocí standardizované elektromagnetické tomografie (sLORETA) u pacientů s panickou poruchou

EEG source analysis using standardized electromagnetic tomography (sLORETA) in panic disorder

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SOUHRN

U pacientů s panickou poruchou byla nalezena vyšší relativní pravostranná frontální EEG aktivita v porovnání se zdravými kontrolami, stejně jako abnormality v zastoupení frekvenčních pásem v EEG spektru. Dosud však chybí práce zaměřená na lokalizaci zdrojů EEG, a tedy i informace o tom, kde je abnormální EEG aktivita generována. Do studie bylo zařazeno 14 pacientů s panickou poruchou (F40.01 a F41.0 podle MKN-10) a 14 zdravých kontrol. Skupiny se nelišily vzhledem k věku, pohlaví a lateralitě. EEG bylo snímáno standardní metodikou v klidovém stavu a při zavřených očích z 19 lokalit na skalpu. Pomocí modelu sLORETA (standardizovaná elektromagnetická tomografie s nízkým rozlišením) byla u každého jednotlivce spočítána absolutní a relativní proudová hustota v 2394 voxelech mozkové kůry a 8 frekvenčních pásmech. Skupiny byly porovnány pomocí randomizačně-permutační statistiky a výsledky byly korigovány na mnohočetná srovnávání. Za signifikantní byly považovány clustery obsahující minimálně 50 signifikantních voxelů. Pacienti s panickou poruchou vykazovali vyšší aktivitu v pásmu absolutní beta1 (12,5–16 Hz) a beta2 (16,5–21,5 Hz) v laterální prefrontální kůře a s výraznou převahou vpravo. Beta2 byla u pacientů navíc snížena v levé dolní parietální kůře. Nálezy ukazují na hyperaktivitu pravé frontální kůry u pacientů s panickou poruchou.

Klíčová slova: panická porucha, standardizovaná elektromagnetická tomografie s nízkým rozlišením (sLORETA), frontální kortex

SUMMARY

Studies in panic patients reported higher relative right frontal EEG activity compared with healthy controls as well EEG spectral abnormalities. However, EEG source localization studies that would indicate where is the abnormal EEG activity generated are missing in panic disorder. 14 patients with panic disorder (F40.01 and F41.0 according to ICD-10) and 14 healthy controls were included in the study. The groups were equivalent for age, sex and handedness. EEG was recorderd during eyes-closed resting state from 19 standard scalp locations. Absolute and relative current density in each subject were computed in 2394 cortical voxels and 8 frequency bands according to sLORETA model (standardized low-resolution electromagnetic tomography). The groups were compared by means of randomization-permutation statistic and the results were corrected for multiple comparison. Only clusters containing at least 50 significant voxels were considered significant. Panic patients showed higher absolute power in beta1 (12.5–16 Hz) and beta2 (16.5–21.5 Hz) frequency bands in lateral prefrontal cortex, significantly more pronounced in the right hemisphere. Moreover, beta2 was lower in patients in the left inferior parietal region. These findings indicate right frontal hyperactivation in patients with panic disorder.

Key words: panic disorder, standardized low-resolution electromagnetic tomography (sLORETA), frontal cortex

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Úvod

V posledních 25 letech došlo k prudkému nárůstu výzkumu zaměřeného na asymetrii mozkových hemisfér a její možný vztah k pozitivním a negativním emocím, osobnosti a psychopatologii. Značné množství elektroencefalografických (EEG) studií zjistilo zejména souvislost mezi hemisferální asymetrií ve frontálních kortikálních oblastech a depresivními příznaky. Tyto výsledky byly interpretovány v kontextu teorie o specializaci kortikálních systémů hemisfér zodpovědných za motivační a emoční procesy. V tomto modelu (Davidson et al., 1992) zprostředkují levé frontální regiony motivaci k přiblížení se a/nebo pozitivní emoce, zatímco pravé frontální regiony zprostředkují motivaci ke stažení se a/nebo negativní emoce. Byl navržen systém vulnerability vůči stresu (Coan a Allen, 2004), ve kterém atypický vzorec frontální kortikální asymetrie v klidovém stavu značí stabilní, charakterovému rysu podobný rizikový faktor pro následný rozvoj deprese nebo jiných s emocemi spojených poruch. Další výzkum ukázal, že klidová frontální EEG asymetrie

není výhradně spojena s depresí, ale také s jinými emočními stavy, jako je úzkost. Existují důkazy o tom, že různé podtypy úzkosti (např. panika vs. obava) mají odlišný odraz v klidové frontální asymetrii (Heller et al., 1997). Funkce pravého frontálního kortexu v motivaci ke stažení se a/nebo negativní emoci naznačuje, že by úzkostní jedinci měli vykazovat vyšší relativní pravostrannou frontální aktivitu v porovnání s neúzkostnými protějšky. Byla publikována data, která podporují tento názor. U lidí se sociální fobií (Davidson, 2000) a panickou poruchou (Wiedemann et al., 1999) byla nalezena vyšší relativní pravostranná frontální aktivita v porovnání se zdravými kontrolami. Navíc klidová frontální EEG asymetrie signifikantně koreluje s měřením stavu nebo rysu úzkosti (Tomarken et al., 1994; Wiedemann et al., 1999). Jedna studie také prokázala vztah mezi depresí s komorbidní úzkostí na jedné straně a klidovou frontální asymetrií na straně druhé. V této studii komorbidní úzkostní účastníci, ne však čistě depresivní účastníci, vykazovali relativní pravostrannou asymetrii v porovnání se zdravými kontrolami (Bruder et al., 1997).

EEG studie u pacientů s panickou poruchou zjistily kromě frontální asymetrie (Wiedemann et al., 1999) nižší interhemisferální konektivitu mezi frontálními regiony a nižší intrahemisferální konektivitu v temporálních oblastech (Hanaoka et al., 2005) a různé změny v zastoupení frekvenčních pásem ve spektru (Knott et al., 1996; Gordeev, 2008). Dosud však chybí práce zaměřená na lokalizaci zdrojů EEG, a tedy i informace o tom, kde je abnormální EEG aktivita generována. V následující studii jsme použili metodu sLORETA (standardizovaná elektromagnetická tomografie s nízkým rozlišením), která pomocí matematického modelu odhaduje lokalizaci zdrojů EEG signálu v jednotlivých voxelech mozkové kůry. Metoda není zaměřena na sledování asymetrie mezi hemisférami, ale na srovnání aktivity v korespondujících oblastech u pacientů a kontrol. Případné rozdíly mohou být v závislosti na frekvenci a lokalizaci interpretovány jako snížení či zvýšení aktivace dané oblasti. Naším cílem bylo odpovědět na otázku, zda se EEG aktivita pacientů s panickou poruchou liší od EEG aktivity kontrol. Na základě výše uvedených studií o frontální asymetrii u panické poruchy a o souvislosti pravostranné hyperakvitace s negativními emocemi jsme předpokládali, že pacienti s panickou poruchou budou mít ve srovnání s kontrolami více aktivity v pásmu excitačních frekvencí beta v pravé frontální kůře.

Metody

Soubor

Do studie bylo zařazeno 14 nemedikovaných pacientů s primární diagnózou panické poruchy diagnostikované podle MKN-10 jako agorafobie s panickou poruchou (F40.01, 7 pacientů) nebo panická porucha (F41.0, 7 pacientů) a 14 zdravých kontrol (tab. 1). Vylučovací kritéria zahrnovala současné závážné nebo chronické onemocnění, zneužívání návykových látek, mentální retardaci, organickou duševní poruchu, anamnestický výskyt psychózy, poruchu nálady, vážný úraz hlavy nebo neurochirurgický zákrok. Studie byla schválena místní etickou komisí.

Tabulka 1: ***Demografické charakteristiky souboru.***

	Pacienti (N = 14)		Kontroly (N = 14)	
Charakteristiky souboru	průměr	SD	průměr	SD
věk (roky)	33,3	10,4	33,3	10,0
pohlaví (muži:ženy)	5:9	NA	5:9	NA
lateralita (praváci:leváci)	14:0	NA	14:0	NA

Zkratky: SD - standardní odchylka, NA – neaplikovatelné

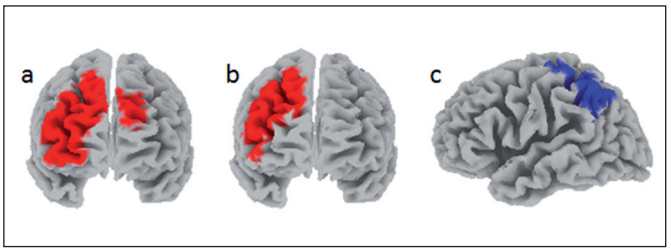
Snímání a analýza EEG dat

EEG bylo snímáno v klidovém stavu a při zavřených očích z 19 standardních lokalit na skalpu pomocí diferenčního zesilovače BrainScope (Unimedis, Česká republika) vůči referenci Afz, FCz nebo Cz se vzorkovací frekvencí 250 nebo 256 Hz. Data byla importována do softwaru Eureka (NovaTechEEG, Arizona, USA), kde byly odstraněny artefakty. Pokud záznam obsahoval kontinuální svalové artefakty nebo příliš mnoho očních artefaktů, byly odstraněny jako nezávislé komponenty pomocí softwaru ICoN (NovaTechEEG, Arizona, USA). Před analýzou byla data převzorkována na 128 Hz a převedena vůči společné referenci (common average). Následně byla pro každého jednotlivce, 2394 voxelů mozkové kůry a v 8 frekvenčních pásmech (delta: 2–3,5 Hz; theta: 4–7,5 Hz; alfa1: 8–10 Hz; alfa2 10,5–12 Hz; beta1: 12,5–16 Hz; beta2: 16,5–21,5 Hz; beta3: 22–30 Hz; gama: 30,5–40 Hz) vypočtena absolutní a relativní proudová hustota podle modelu sLORETA. Na výsledná data byla aplikována logaritmická transformace a 14mm smoothing. Absolutní proudová hustota byla navíc u každého jedince normalizována vzhledem k celkovému výkonu v daném pásmu. Skupiny byly porovnány pomocí randomizačně-permutační statistiky (10 000 permutací) v softwaru MhyT (NovaTechEEG, Arizona, USA). Všechna pásma byla testována simultánně a výsledky byly korigovány na mnohočetná srovnávání pomocí t-sum statistiky založené na kombinaci t-statistik (Congedo et al., 2004). Za signifikantní byly považovány clustery obsahující minimálně 50 voxelů.

Tabulka 2: ***Lokalizace a počet voxelů mozkové kůry s odlišnou absolutní proudovou hustotou u pacientů s panickou poruchou ve srovnání s kontrolami (p < 0,05).***

	Pravá hemisféra		Levá hemisféra	
Frekvenční pásmo a lokalizace	**průměrné t**	**sign. voxely**	**průměrné t**	**sign. voxely**
beta1 (12,5 - 16 Hz)				
Horní frontální gyrus (BA 8, 9, 10)	3,68	48	NA	0
Střední frontální gyrus (BA 9, 10, 11, 46)	3,67	36	NA	0
Dolní frontální gyrus (BA 10, 46, 47)	3,54	10	NA	0
Mediální frontální gyrus (BA 9)	3,47	2	NA	0
Dolní parietální kůra (BA 40)	NA	0	-3,46	2
beta2 (16,5–21,5 Hz)				
Horní frontální gyrus (BA 8, 9, 10)	3,74	24	NA	0
Střední frontální gyrus (BA 8, 9, 10, 46)	3,62	37	NA	0
Dolní frontální gyrus (BA 10, 46)	3,44	9	NA	0
Dolní parietální kůra (BA 40)	NA	0	-3,75	51

Zkratky: BA – Brodmannova area, NA – neaplikováno



Obrázek 1: ***Lokalizace clusterů s odlišnou proudovou hustotou u pacientů s panickou poruchou ve srovnání s kontrolami (p < 0,05) v pásmu beta1 (a) a beta2 (b, c).***

Výsledky

Sledované demografické charakteristiky obou souborů se nelišily. Všichni respondenti byli praváci a skupiny byly ekvivalentní vzhledem k věku i pohlaví (tab. 1).

Pacienti s panickou poruchou měli ve srovnání s kontrolami vyšší výkon v normalizované absolutní proudové hustotě v pásmu beta1 a beta2 ve frontální kůře (práh $t = 3{,}39$, $p < 0{,}05$) (obr. 1, tab. 2). Vyšší aktivita v pásmu beta1 u pacientů ve srovnání s kontrolami byla lokalizována v oboustranné laterální prefrontální kůře s výraznou pravostrannou převahou. Vyšší aktivita v pásmu beta2 byla zjištěna pouze v pravé laterální prefrontální kůře. V pásmu beta2 vykazovali pacienti navíc nižší aktivitu v menším clusteru v oblasti dolní parietální kůry (tab. 2). V dalších frekvenčních pásmech a v relativní proudové hustotě nebyl mezi pacienty a kontrolami rozdíl.

Diskuze

Zvýšené množství beta aktivity u pacientů s panickou poruchou dominující v pravé hemisféře je v souladu s předchozími nálezy zobrazovacích a elektrofyziologických metod a, vzhledem k tomu, že beta aktivita je považována za projev excitační aktivity (Pascual-Marqui et al., 1999), ukazuje na pravohemisferální hyperaktivaci u pacientů s panickou poruchou. Vyšší množství beta aktivity v pravé hemisféře bylo v nedávné době popsáno u pacientů s panickou poruchou s agorafobií (Gordeev, 2008).

Pro hyperaktivaci pravé hemisféry u pacientů s panickou poruchou svědčí několik dříve zjištěných skutečností: 1) Pravá hemisféra kontroluje a zpracovává autonomní a interoceptivní signály (Katkin et al., 1991), které hrají významnou roli ve vývoji a udržování panické poruchy (Ehlers a Breuer, 1992). 2) Většina pacientů s panickou poruchou je charakterizována vyhýbavým chováním (Rachman a Levitt, 1985), které je zřejmě kontrolováno pravými frontálními oblastmi mozku (Sutton a Davidson, 1997). Předchozí práce popsaly trend k vyššímu regionálnímu krevnímu průtoku v pravém mediálním frontálním a pravém horním frontálním gyru u pacientů s panickou poruchou oproti kontrolám (Eren et al., 2003) a pomocí infračervené spektroskopie také zvýšenou aktivaci v pravé laterální prefrontální kůře u geneticky definované podskupiny panických pacientů (Tanii et al., 2009). Na abnormality pravé prefrontální kůry u pacientů s panickou poruchou ukazuje také zjištění vyšší aktivity benzodiazepinového receptoru v pravém středním a dolním frontálním gyru (Kuikka et al., 1995). Narušené informační zpracování v pravé prefrontální kůře se může, podle autorů, účastnit vzniku panické poruchy.

Vztah mezi pravostrannou frontální hyperaktivací a symptomy panické poruchy není plně objasněn, nicméně byla prokázána souvislost mezi aktivitou frontální kůry a aktivitou amygdaly (Wiedemann et al., 1999). PET studie zdravých dobrovolníků ukazují, že existuje reciproční vztah mezi metabolizmem glukózy v levé mediální a laterální prefrontální kůře a metabolizmem glukózy v amygdale (Abercrombie et al., 1996). Naopak lidé s větším relativním metabolizmem glukózy vpravo prefrontálně mají vyšší metabolickou aktivitu v amygdale, která se účastní vyjádření a zpracování negativních emocí a učení vztahujícímu se k ohrožujícím podnětům (Davidson, 2002). Zvýšená aktivace v oblasti pravé prefrontální kůry i amygdaly byla zjištěna u různých typů úzkostných poruch (Davidson, 2002) a zdá se, že redukce aktivity pravé prefrontální kůry souvisí se zlepšením klinických symptomů. Nízkofrekvenční repetitivní transkraniální magnetická stimulace u pacientů s panickou poruchou a komorbidní depresí cílená na pravý dorzolaterální prefrontální kortex vedla ke zlepšení symptomů panické poruchy i deprese a zároveň ke zvýšení motorického prahu v pravé hemisféře (Mantovani et al., 2007). Praško et al. (2004) prokázali, že úspěšná léčba (antidepresiva i kognitivně-behaviorální terapie) vedla u pacientů s panickou poruchou ke snížení metabolizmu glukózy v několika oblastech pravé hemisféry, včetně frontálních.

Levá dolní parietální oblast nepatří ke klíčovým oblastem, o nichž se předpokládá, že hrají roli v patofyziologii panické poruchy. Nižší aktivita v tomto regionu v pásmu beta2 u pacientů oproti kontrolám proto nebyla a priori očekávána. Nicméně dvě PET studie, které zjistily snížený krevní průtok v oblasti levé parietální kůry u pacientů s panickou poruchou (Nordahl et al., 1990; Meyer et al., 2000), podporují validitu tohoto nálezu. Navíc se ukazuje, že stejně jako frontální asymetrie se u pacientů s panickou poruchou může vyskytovat asymetrie parietální aktivity, opět s pravostrannou převahou, tedy s relativní levostrannou hypoaktivací a relativní pravostrannou hyperakivací (Wiedemann et al., 1999). Podle Hellera et al. (1997) je zvýšená aktivita pravé parietální kůry spojena s úzkostným nabuzením, zatímco aktivita levé parietální kůry se účastní úzkostných obav.

Limitujícím faktorem naší studie je kromě malého vzorku také skutečnost, že pacienti s agorafobií i bez agorafobie byli posuzováni společně. Přestože obě podskupiny nebývají ve většině studií hodnoceny zvlášť, není vyloučeno, že mohou mít odlišné neurobiologické charakteristiky včetně EEG (Gordeev, 2008).

Práce přináší první poznatky o lokalizaci zdrojů EEG u panické poruchy a její výsledky mohou přispět k hledání vodítek pro nefarmakologickou léčbu tohoto onemocnění, jako jsou repetitivní transkraniální magnetická stimulace a neurofeedback.

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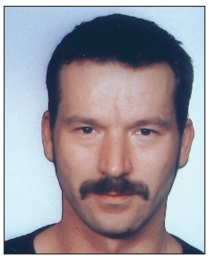

V rubrice zobrazovacích metod se dnes věnujeme výzkumně i klinicky vysoce aktuální problematice nových možností využití kvantitativní analýzy EEG záznamu u depresivní poruchy. Na kazuistické studii je demonstrováno použití hodnocení theta kordance a elektromagnetické tomografie (sLORETA) ve sledování efektu léčby a predikce terapeutické odpovědi. Sdělení je doplněno o podrobné vysvětlení patofyziologických korelátů změny obou proměnných.

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Využití kordanční analýzy a elektromagnetické tomografie ke sledování změn elektrické mozkové aktivity během léčby depresivní poruchy

Utilization of Cordance Analysis and Electromagnetic Tomography in Monitoring CHanges of Electric Brain Activity During Depressive Disorder Treatment

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SOUHRN

Na kazuistické studii pacientky s depresivní poruchou jsou demonstrovány možnosti využití informace o elektrické aktivitě mozku (EEG) při predikci odpovědi na léčbu a příp. predikci udržení této odpovědi. Klidový EEG záznam depresivní pacientky, která odpověděla na novou antidepresivní léčbu (venlafaxin), byl analyzován po 1, 4 a 14 týdnech pomocí metod kvantitativní elektroencefalografie (QEEG): kordanční analýzy a elektromagnetické tomografie (sLORETA – standardized Low-Resolution Electromagnetic Tomography). Byl zaznamenán pokles prefrontální EEG theta kordance již po prvním týdnu léčby (v čase, kdy nebyly zjevné klinické známky zlepšení) a stálost remise korelovala se zvyšujícím a rozšiřujícím se trendem proudové hustoty theta aktivity (4-8 Hz) v zadním cingulu.

Klíčová slova: depresivní porucha, elektromagnetická tomografie, sLORETA – standardized Low-Resolution Electromagnetic Tomography, EEG kordance, cingulární kortex

SUMMARY

The case report of a depressed patient demonstrates the use of QEEG information in the prediction of a treatment response to an antidepressant and possibly of the maintenance of this response. Resting EEG record of depressive patient, having responded to the new antidepressive treatment (venlafaxine), was analyzed after 1, 4 and 14 weeks using the methods of quantitative electroencephalography (QEEG): cordance analysis and electromagnetic tomography (sLORETA - standardized Low-Resolution Electromagnetic Tomography). Decrease in prefrontal EEG theta cordance was found after the first week of treatment (by the time, when no clinical evidence of improvement was apparent) and the response sustainment correlated with increasing and spreading trend of theta activity (4-8 Hz) current density in dorsal cingulum.

Key words: depressive disorder, electromagnetic tomography, sLORETA – standardized Low-Resolution Electromagnetic Tomography, EEG cordance, cingular cortex.

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Úvod

Současné funkčně zobrazovací studie ukazují na několik mozkových oblastí s odlišným metabolizmem a/nebo perfuzí u pacientů s depresivní poruchou. Nejlépe průkazné oblasti s odlišným vzorcem metabolizmu měřeným pomocí pozitronové emisní tomografie (PET) a jedno-fotonové emisní počítačové tomografie (SPECT) jsou prefrontální kortex (PFC), přední a zadní cingulární kortex a hippocampus (Drevets et al., 1997; Kennedy et al., 1997; Mayberg, 1997; Drevets, 1998; Mayberg et al., 1999; Videbech, 2000; Mayberg, 2003). Předpokládá se, že symptomatický depresivní stav je doprovázen poklesem aktivity dorsolaterálního PFC a vzestupem neuronální aktivity ventrolaterálního PFC a předního cingula (Drevets, 1998; Mayberg et al., 1999). Nejvíce konzistentní změnou klidového metabolizmu mozku u deprese je inverzní vztah mezi aktivitou PFC a závažností deprese (Videbech, 2000). Několik studií s PET nebo SPECT prokázalo redukci prefrontální kortikální perfuze a/nebo metabolizmu mozku, následující po efektivní antidepresivní léčbě (Nobler et al., 1994; Drevets, 1998; Brody et al., 2001; Saxena et al., 2002). Tři malé studie ukázaly, že u pacientů s depresivní poruchou může snížení frontální aktivity (měřené pomocí EEG kordance v theta pásmu) predikovat odpověď na léčbu již po jednom týdnu užívání antidepresiv (Cook, 2002; Cook et al., 2005; Bares et al., 2007). Hodnota EEG theta kordance pozitivně korelovala s kortikální perfuzí měřenou PET (Leuchter et al., 1999), proto předpokládáme, že pokles prefrontální theta kordance bude odpovídat poklesu prefrontální elektromagnetické aktivity. Pacienti s depresivní poruchou, kteří odpověděli na léčbu, měli před léčbou vyšší metabolizmus glukózy v rostrálních oblastech předního cingulárního kortexu (Brodmanova area, BA 24a/b) než non-respodéři a zdraví dobrovolníci (Mayberg et al., 1997; Mayberg et al., 2000).

Elektromagnetická tomografie (sLORETA – standardized Low-Resolution Electromagnetic Tomography) je relativně nová metoda zpracování EEG signálu, pomocí které lze odhadnout lokalizaci elektrické aktivity v mozkové kůře a části limbických struktur (Pascual-Marqui et al., 1994; Pascual-Marqui, 2002).

Vlastní kazuistika

Třiačtyřicetiletá žena, s anamnesticky diagnostikovanou úzkostně-depresivní poruchou a panickými stavy od 29 let a dále od 41 let s depresivní poruchou, byla přijata na kliniku PCP (Psychiatrické centrum Praha) pro druhou epizodu středně těžké deprese trvající cca dva měsíce. Osobnost byla hodnocena jako akcentovaná se závislými rysy.

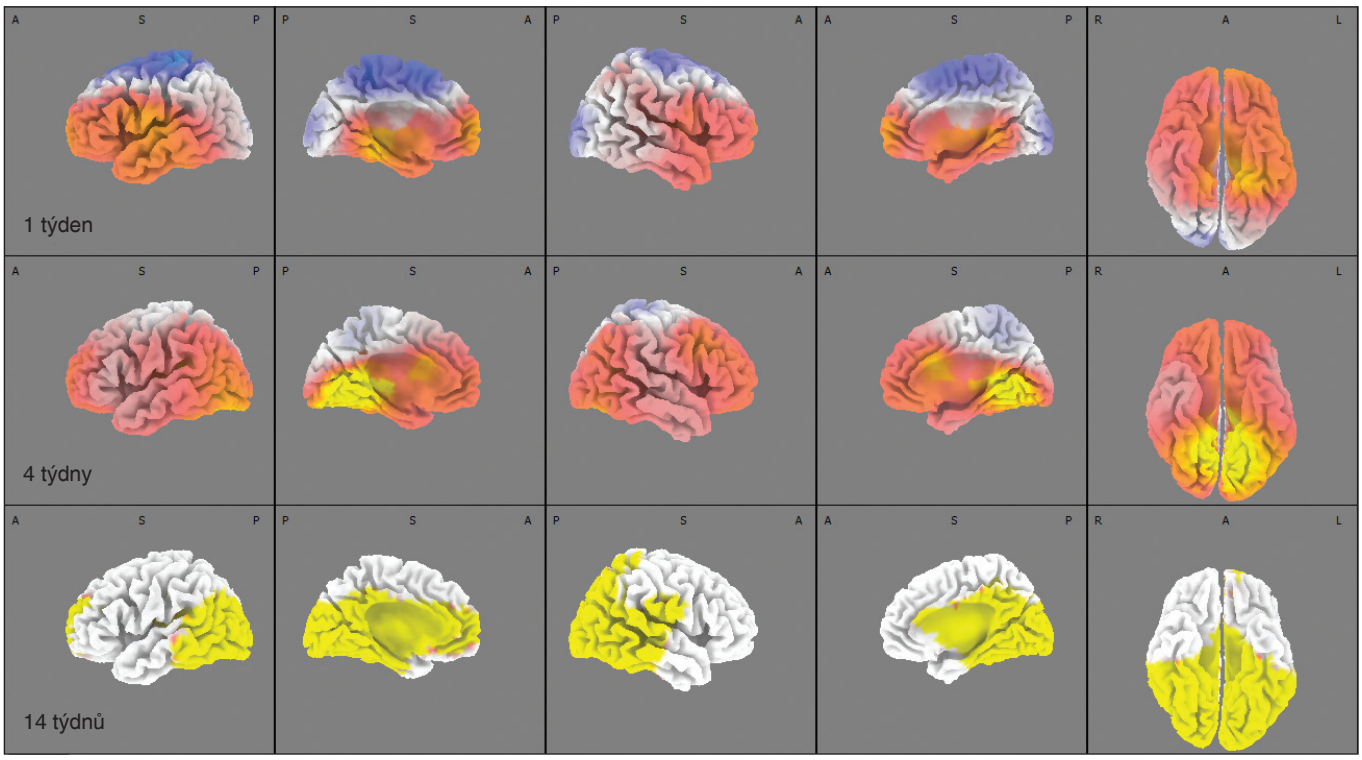
Matka pacientky, neléčená alkoholička, zemřela v 62 letech na karcinom vaječníku, léčila se pro hypofunkci štítné žlázy. Jinak bez další psychiatrické heredity. Porod a perinatální vývoj v normě, překonala běžná dětská onemocnění, dále nebyla vážněji somaticky nemocná. Úraz hlavy neměla, v bezvědomí nebyla, bez anamnézy křečí či epileptických paroxysmů, neuroinfekce negovala, endokrinologicky se neléčila. Alkohol pila příležitostně, nekouřila, drogy neužívala.

Otce pacientka nezná. Vyrůstala pouze s matkou, otec opustil rodinu záhy po jejím narození. Pacientka udávala pozdější obtíže s integrací do kolektivu. Matka si našla přítele, se kterým pacientka dobře vycházela. Vdala se a žije v relativně harmonickém manželství, je matkou dvou dětí. Dcera (15 let) se léčí pro hypofunkci štítné žlázy. Pacientka studovala střední pedagogickou školu se zaměřením na předškolní věk, nyní pracuje jako učitelka prvního stupně ZŠ.

Poprvé vyhledala psychiatrickou péči po prvním porodu v roce 1993 pro úzkostné a depresivní stavy. Trpěla četnými obavami, že nebude schopna dítě zaopatřit a nereálnými výčitkami, že jí dítě zemře. Po roce docházení do psychiatrické ambulance a užívání fluoxetinu absolvovala denní stacionář pro pacienty s anxiózními poruchami. Pro progredující ústup úzkostně-depresivní symptomatiky byl fluoxetin postupně vysazen. Relaps potíží nastal v roce 2006 návratem manžela do zaměstnání po delší době společného soužití. Depresivní symptomatika byla neúspěšně léčena řadou antidepresiv v kombinaci s anxiolytiky. Pacientka byla na jaře roku 2008 přijata na otevřené oddělení kliniky PCP (Psychiatrické centrum Praha). Po vysazení původní medikace a podepsání informovaného souhlasu byla zařazena do studie porovnávající efektivitu venlafaxinu a rTMS (repetitivní transkraniální magnetická stimulace). Léčena byla venlafaxinem, medikaci tolerovala bez obtíží. Relativně rychle dochází ke zlepšení nálady. Po 4 týdnech pobytu dosáhla odpovědi na léčbu, přetrvávala pouze iniciální dyssomnie a rezidua ranní úzkosti. Poslední 3 měsíce užívala stabilní medikaci: venlafaxin 225 mg/den, bromazepam 0,75 mg/den, hydroxyzin 50 mg/den, promethazin 1 tbl/den, hypnogen 1 tbl/den.

Metodika

Diagnóza středně těžké depresivní fáze dle MKN-10 byla potvrzena použitím Mini – International Neuropsychiatric Interview – M.I.N.I., česká verze 5.0.0 (Sheehan et al., 1998). Pacientka podstoupila v průběhu 6,5 měsíců vždy ve stejnou denní dobu celkem čtyřikrát klinické škálování pomocí MADRS (Montgomery-Ĺsberg Depression Rating Scale) (Montgomery and Ĺsberg 1979), CGI (Clinical Global Impression) (Guy, 1976) a BDI (Beck Depression Inventory) (BECK et al., 1961) a elektroencefalografické (EEG) vyšetření – na začátku léčby (baseline), po týdnu a po 4 týdnech od zahájení léčby venlafaxinem, dále pak v následném sledování 2,5 měsíce po propuštění z hospitalizace. Desetiminutový EEG záznam byl snímán v klidu při zavřených očích se vzorkovací frekvencí 250 Hz devatenácti elektrodami umístěnými na skalpu podle mezinárodního systému 10/20 oproti referenční elektrodě umístněné mezi elektrodami Cz a Fz ve střední čáře. EEG křivka byla hodnocena nejprve vizuálně a následně dvěma kvantitativními algoritmy: 1. kordanční analýzou (pomocí software WaveFinder v.2.80, Unimedis, Praha), 2. elektromagnetickou encefalografií – sLORETA (Standardized Low-Resolution Electromagnetic Tomography) (Pascual-Marqui, 2002). Po selekci třiceti dvousekundových bezartefaktových úseků z každého záznamu, digitální filtraci 0,5 až 30 Hz a přepočítání na referenci rovné průměru signálu všech elektrod, tzv. common average, byla data podrobena zpracování. Frekvenční pásma byla definována následovně: delta (0.5-4 Hz), theta (4-8 Hz), alfa (8-12 Hz) a beta (12-20 Hz). EEG kordance byla vypočtena využitím algoritmu určeného pro výzkumné účely (Leuchter, 1994). Následně byla vypočtena průměrná hodnota kordance ze tří frontálních elektrod (Fp1, Fp2 a Fz) v theta frekvenčním pásmu (podrobněji viz (Bares et al., 2007). Přibližná lokalizace elektrické aktivity v mozkové kůře a části limbických struktur byla určena a zobrazena pomocí softwaru sLORETA (Pascual-Marqui, 2002). Srovnávány byly jednotlivé záznamy po 1, 4 a 14 týdnech s baseline křivkou pomocí neparametrické statistiky – t-testu pro nezávislé výběry (popsáno již v Brunovský et al., 2006).



Obrázek 1: ***Distribuce proudové hustoty theta aktivity srovnáním po 1, 4 a 14 týdnech vs. baseline. Zvýšení aktivity je znázorněno červenou, výraznější zvýšení žlutou a snížení aktivity modrou barvou.***

Výsledky

Při vizuálním hodnocení EEG záznamů bylo patrno vyšší množství beta aktivity difuzně s převahou nad předními kvadranty, kde byl častější výskyt tzv. beta vřeten jako známek úzkostnosti pacientky a ovlivnění křivky aktuální medikací benzodiazepiny.

Klinické měření:

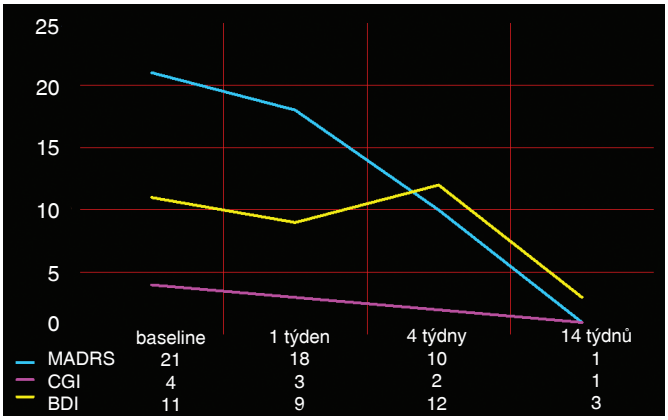
Pacientka se středně těžkou depresivní fází (MADRS 21, CGI 4, BDI 11), úspěšně odpověděla po 4 týdnech na terapii venlafaxinem (MADRS 10, CGI 2, BDI 12) a v následném sledování po 2,5 měsících od propuštění dosáhla spolehlivé remise (MADRS 1, CGI 1, BDI 3) (podrobněji viz graf 1).

Kvantitativní EEG analýza:

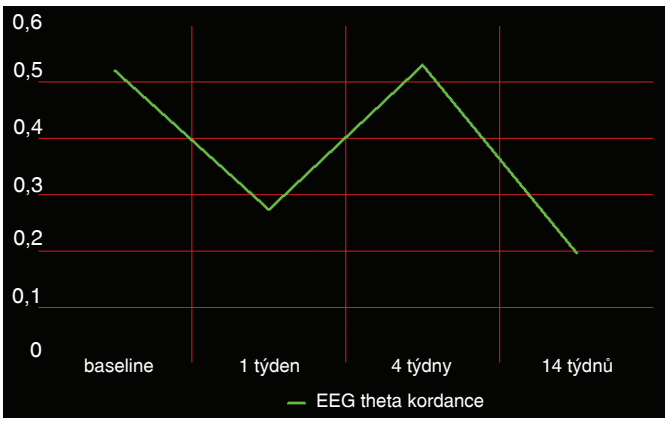
1. Po týdnu od zahájení léčby došlo k poklesu EEG kordance a zároveň k pouze hraničnímu bilaterálnímu zvýšení theta aktivity v parahipokampálním gyru ($p > 0,05$) (obr. 1).

2. Po čtyřech týdnech od zahájení léčby došlo ke zvýšení EEG kordance oproti baseline. Tato změna se odrazila ve výrazném bilaterálním zvýšení proudové hustoty theta aktivity v okcipitálním lobu včetně zadního cingula (BA 29, 30, 31).

3. Po čtrnácti týdnech od zahájení léčby došlo k poklesu EEG kordance (podrobněji viz graf 2) oproti baseline a ke zvýraznění bilaterálního zvýšení proudové hustoty theta aktivity v široké oblasti okcipitálního lobu včetně zadního cingula (podrobněji viz obr. 1).



Graf 1: ***Průběh výsledných hodnot klinických škál (MADRS, CGI) a dotazníku (BDI) po 1, 4 a 14 týdnech léčby venlafaxinem.***



Graf 2: ***Průběh prefrontální EEG theta kordance s poklesem v prvním týdnu jako predikce odpovědi na léčbu venlafaxinem.***

Diskuze

Sledovali jsme průběh středně těžké depresivní epizody u pacientky (MADRS 21), která po 4 týdnech úspěšně odpověděla na terapii venlafaxinem (MADRS 10) a v následném sledování po 2,5 měsících od propuštění dosáhla spolehlivé remise (MADRS 1). Ke sledování jsme kromě klinických škál využili EEG kordanční analýzu a elektromagnetickou tomografii (sLORETA).

Hodnota EEG kordance v sobě kombinuje komplementární informace z absolutního a relativního výkonového spektra a odráží perfuzi (popř. metabolizmus) mozku lépe než jiné metody kvantitativní EEG (Leuchter et al., 1999). Předchozí studie u farmakorezistentních depresivních pacientů ukázaly, že včasný pokles hodnot prefrontální EEG theta kordance (již po 1 týdnu) odliší respondery od non-responderů na nově nasazené antidepresivum (Bares et al., 2007; Bares et al., 2008; Cook 2002; Cook et al., 2005; Kopecek et al., 2007; Kopeček et al., 2007). Dosud není jednoznačně prokázáno, jaké děje odráží změna prefrontální kordance v pásmu theta. Předpokládáme, že by se mohlo jednat o snížení aktivity především v předním cingulu (Brodmanova area – BA 25). U pacientů reagujících na léčbu ukázala studie s pozitronovou emisní tomografií snížení metabolizmu právě v předním cingulu (BA 25) na rozdíl od pacientů, kteří na léčbu neodpověděli (Mayberg et al., 2000). Snížení aktivity předního cingula bylo detekováno také po spánkové deprivaci spolu s léčbou antidepresivy, což vedlo ke zlepšení depresivní symptomatiky (Smith et al., 1999). Hluboká mozková stimulace předního cingula (BA 25) vedla k odpovědi na léčbu u 66 % farmakorezistentních pacientů. Přerušení stimulace vedlo k opětovnému výskytu deprese a znovuzapojení stimulátoru vedlo opět k antidepresivnímu efektu (Mayberg et al., 2005).

Klinické zlepšení u deprese bylo jednoznačně asociováno s poklesem metabolizmu glukózy v subgenuálním cingulu (BA 25) a se vzestupem metabolizmu mozkového kmene a dorsálních kortikálních oblastí (prefrontální, parietální, přední a zadní cingulum) (Mayberg et al., 2000). Dlouhodobě persistující hypometabolizmus subgenuálního cingula u pacientů v remisi lze vysvětlit jako metabolické změny potřebné k udržení remise (Mayberg et al., 1998).

V naší kazuistické studii jsme pozorovali u odpovědi na léčbu již po týdnu terapie zřetelný nárůst theta aktivity zadního cingula, který přetrvával i po 14 týdnech a dále se rozšiřoval. Tyto výsledky korelují s předpokladem Maybergové o udržení remise.

Zatímco depresivní stav je doprovázen redukcí aktivity dorzálního předního cingula (kaudální část BA 24, 32 a cingulární motorická oblast), zvýšená aktivita rostrálního předního cingula (BA 25, 32, 33 a rostrální oblast BA 24) před léčbou charakterizuje pouze podskupinu responderů (Pizzagalli et al., 2001).

Studie využívající nízko-rozlišovací elektromagnetickou tomografii (LORETA) u depresivních pacientů ukázala, že vyšší aktivita v pásmu theta vedla k lepší odpovědi na léčbu než u pacientů s nízkou aktivitou před léčbou (Pizzagalli et al., 2001). Práce stejného autorského kolektivu ukázala vztah mezi metabolizmem předního cingula a theta aktivitou u zdravých dobrovolníků, nikoliv depresivních pacientů (Pizzagalli et al., 2003).

Přední cingulum je považováno za jeden z generátorů frontální theta aktivity (Pizzagalli et al., 2003), a tak předpokládáme, že nás frontální kordance informuje právě o jeho aktivitě. Skutečnost, že aktivita předního cingula je u depresivních nemocných ovlivněna antidepresivní léčbou vedoucí k léčebnému efektu a ne jen pouhou změnou psychopatologie, ukazuje studie (Leuchter, 2002), která u pacientů odpovídajících na léčbu placebem nalezla zvýšení theta kordance na rozdíl od jejího snížení u pacientů odpovídajících na léčbu antidepresivy. I když pravá podstata změny frontální kordance je zatím spekulativní, nebrání to jejímu potenciálnímu klinickému využití.

Závěry

Kazuistika demonstruje možnosti využití metod kvantitativní elektroencefalografie (kordance, sLORETA) k predikci odpovědi na léčbu a jejího udržení po nasazení antidepresiva (venlafaxin). Odpověď na léčbu u popsané pacientky byla zaznamenána poklesem EEG theta kordance již po týdnu léčby (v čase kdy nebyly zjevné klinické známky zlepšení) a stálost odpovědi na léčbu potvrzoval zvyšující a rozšiřující se trend proudové hustoty theta aktivity (4-8 Hz) v zadním cingulu.

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The change of prefrontal QEEG theta cordance as a predictor of response to bupropion treatment in patients who had failed to respond to previous antidepressant treatments

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Abstract

The aim of the study was to examine whether the reduction of theta prefrontal quantitative EEG (QEEG) cordance after one week of bupropion administration is a predictor of response to a 4-week treatment in patients that had failed to respond to previous antidepressant treatments. Method: EEG data of 18 inpatients were monitored at baseline and after one week. QEEG cordance was computed at 3 frontal electrodes (Fp1, Fp2, Fz). Response to treatment was defined as a $\geq$50% reduction of MADRS score. Results: Nine of the eleven responders and one of the seven non-responders showed decreased prefrontal cordance value after the first week of treatment (p=0.01). Positive and negative predictive values of cordance reduction for the prediction of response to the treatment were 0.9 and 0.75, respectively. Conclusion: Similar to other antidepressants, the reduction of prefrontal QEEG cordance might be helpful in the prediction of the acute outcome of bupropion treatment.

1. Introduction

Major depressive disorder (MDD) is considered to be a chronic, relapsing and remitting illness. A large percentage

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of patients (30–50%) fail to respond to an initial course of antidepressant treatment (Keller, 2005; Trivedi et al., 2006). Since a large number of patients fail to respond to antidepressants (AD), there is a clear need for methods that select the right treatment for the right patient. A considerable body of research supports the assertion that antidepressant medication effects are physiologically detectable in the EEG (for review see Hunter et al., 2007). QEEG cordance is one of the promising tools for the prediction of response which has generated research interest. Cordance is a QEEG method which combines complementary information from absolute (the amount of power in a frequency band at a given electrode) and relative power (the percentage of power contained in a frequency band relative to the total spectrum) of EEG spectra (Leuchter et al., 1994a). Since cordance values are correlated with regional cerebral blood flow, findings with this measure could be interpreted within the same conceptual framework as other functional neuroimaging studies (Leuchter et al., 1999, Leuchter et al., 1994b; Cook, 2008) demonstrating an abnormal pattern of metabolism or perfusion in the prefrontal cortex and the anterior cingulate in depressed patients (Drevets, 1998; Mayberg et al., 1997, Mayberg et al., 2000). Moreover, frontal electrical activity in theta frequency band has been associated with the function of these structures and previous research has linked higher pretreatment theta activity of the anterior cingulate with clinical response to nortriptyline and citalopram treatment (Asada et al., 1999; Mulert et al., 2007; Pizzagalli et al., 2001; Pizzagalli et al., 2003).

Several studies have demonstrated that a reduction of prefrontal QEEG theta cordance value after 1 or 2 weeks of treatment with selective serotonin reuptake inhibitors (SSRI) and selective serotonin–norepinephrine reuptake inhibitors (SNRI) can predict clinical response to 8-week treatment in non-resistant patients or non-responders to SSRI (Cook and Leuchter, 2001; Cook et al., 2002, 2005) and these changes were different from those observed in placebo responders (Leuchter et al., 2002). We have independently replicated a relationship between an early change in prefrontal cordance and clinical outcome for resistant patients treated with various AD ($n=17$) and venlafaxine monotherapy ($n=25$) in two open-label studies (Bares et al., 2007, 2008). The positive predictive values (PPV) and negative predictive values (NPV) for the reduction of theta cordance as a predictor of response were 0.7 and 1.0 in the first study, and 0.7 and 0.9 in the second one.

As far as we know, no study examining predictive value of prefrontal QEEG cordance changes for AD other than SSRI or SNRI in resistant subjects has been published. Bupropion, an antidepressant which does not act primary via serotonergic mechanism was selected for our study because it is generally well tolerated (including low rate of sexual side effects) and switching to bupropion is a popular strategy for the treatment of non-responders to SSRI (Fredman et al., 2000; Kennedy et al., 2006). Furthermore, there is some evidence about its efficacy in the treatment of resistant depression (Rush et al., 2006b; Papakostas et al., 2008).

We hypothesized that the reduction of theta prefrontal QEEG cordance value after 1 week of bupropion administration would be associated with response to 4-week treatment in patients resistant to previous antidepressive treatments.

The Prague Psychiatric Center Institutional Review Board reviewed and approved the study and written informed consent to participate in the research was obtained from all subjects. Study was carried out in accordance with the latest version of the Declaration of Helsinki.

2. Experimental procedures

This single-centre, open-label study was performed as a part of a grant project addressing the evaluation of the relationship between QEEG cordance and response to the treatment with various antidepressive interventions.

2.1. Subjects

Our sample comprised 18 inpatients (10 men, 8 women, mean age 46.1 ± 10.1 years) with major depressive disorder (recurrent or single episode) diagnosed according to DSM IV criteria (American Psychiatric Association, 1994), confirmed using The Mini-International Neuropsychiatric Interview–M.I.N.I., Czech version 5.0.0 (Sheehan et al., 1998). We included subjects who reached at least the total score of 20 in Montgomery–Åsberg Depression Rating Scale (MADRS, Montgomery and Asberg, 1979) and the score of 4 or more in the Clinical Global Impression (CGI, Guy, 1976). All patients were hospitalized at the Open Department of Prague Psychiatric Center between May 2006 and December 2008. They fulfilled at least Stage I criteria for resistant depression (≥1 adequate antidepressant treatment) according to Thase and Rush (1997). Evaluation of adequacy of previous medication in the index episode was based on the Antidepressant Treatment History Form (Sackeim, 2001) with a score of at least 3 (more than 4 weeks of treatment at an adequate dose). The most recent medications before enrollment to the study were SSRI ($n=6$), noradrenergic and specific serotonergic AD (NaSSA, $n=2$), SNRI ($n=1$), various combinations of AD ($n=4$) and augmentation of AD with atypical antipsychotics ($n=5$) – for more details see Table 1. We excluded subjects with suicidal risk assessed by clinical examination, current psychiatric comorbidity on Axes I and II, serious unstable medical illness or neurologic disorder (e.g., epilepsy, head trauma with loss of consciousness) and patients using any treatment (including electroconvulsive therapy within 3 months before start of study) which can strongly affect EEG, as well as patients who were resistant to bupropion in the past.

2.2. Treatment trial and clinical assessments

All patients were antidepressants and antipsychotics free at least one day before initializing of bupropion treatment – for more details see Table 1. The continuation of benzodiazepines was allowed in unchanged dosage in patients who used them before the study to avoid withdrawal effect and possible EEG changes. The last dose of benzodiazepines before EEG recording was given at 9 p.m. of previous day.

The length of bupropion treatment was four weeks. We used sustained-release form of bupropion. The bupropion was used in a minimal dose of 150 mg/p.d. with possibility of titration of dose after 5 days of treatment according to clinical status, tolerability and judgement of attending psychiatrist, with average daily doses of 183.3 ± 64.2 mg at week 1 and 287.5 ± 38.6 mg at week 4. Zolpidem and hydroxyzine were permitted as a concomitant (emergency) treatment in case of severe insomnia or anxiety.

The primary outcome measure for the study was the score change in the MADRS. Clinical response was defined as equal to or more than 50% reduction of the MADRS score. The patients were assessed with MADRS, Beck Depression Inventory–Short Form (BDI-S, Beck et al., 1974) and CGI before a wash-out period of 1 to 5 days, at baseline and after 1 and 4 weeks of treatment. Ratings were made by experienced clinical psychiatrists (M.B., T.N., M.K., P.S.) who were

Table 1 Baseline characteristics of subjects and clinical features of depression.

	Responders ($n=11$) median (IQR)	Non-responders ($n=7$) median (IQR)	Statistical significance level
Age (years)	48 (43–50)	43 (32–54)	NS [a]
Gender (F:M)	8:3	0:7	$p<0.004$ [b]
Duration of depressive disorder (months)	60 (7–108)	39 (6–140)	NS [a]
Number of previous depressive episodes	2 (0–3)	1 (0–4)	NS [a]
Duration of index episode before enrollment (weeks)	22 (8–32)	24 (16–24)	NS [a]
Number of previous treatment trials of index episode	2 (1–2)	2 (1–2)	NS [a]
Number of subjects taking benzodiazepines	10	4	NS [b]
Duration of wash-out period (days)	4 (1–5)	3 (2–4)	NS [a]
Last treatment before enrollment	citalopram-1, escitalopram-2, mirtazapine-1, sertraline-1, venlafaxine-1, clomipramine + nortriptyline-1, escitalopram + trazodone-1, citalopram + risperidone-1, mirtazapine + olanzapine-1, dibenzepine + quetiapine-1	citalopram-1, mirtazapine-1, sertraline-1, venlafaxine + trazodone-2 escitalopram + olanzapine-1, mirtazapine + olanzapine-1	NA
Dose of benzodiazepines (diazepam equivalent, mg/p.d.)	11.3 (7.5–15.0)	12.5 (8.75–25.0)	NS [a]
Dose of bupropion at week 1 (mg/p.d.)	150 (150–300)	150 (150–150)	NS [a]
Final dose of bupropion (mg/p.d.)	300 (300–300)	300 (300–300)	NS [a]

IQR—interquartile range, NA—not applicable, NS—nonsignificant, p.d.—per day.
[a] Mann–Whitney *U* Test.
[b] Fisher Exact Test.

trained to the criterion of intraclass correlation >0.80 for each clinician prior to conducting ratings.

2.3. Apparatus and physiological recording

EEG data were collected at baseline and after 1st week of treatment. The EEG examination was regularly carried out between 8 a.m. and 9 a.m. We used a standard 32-channel digital EEG amplifier BrainScope (unimedis, Prague) with 21 Ag/AgCl surface electrodes placed according to the international 10/20 system and referenced to the electrode situated between electrodes Fz and Cz in the midline (FCz). All scalp electrode impedances were below 5 kΩ (within 1 kΩ of homologous sites). The EEG recording system acquires the data with a 16 bit depth and 7.63 nV/bit resolution (i.e. ~130 bit/μV) with the dynamic range of ±250 μV. The data sampling rate was 250 Hz and the acquired signals were filtered with digital high- and low-pass filtering at 0.15 and 70 Hz, respectively. The EEG was recorded with the patients in a semi- recumbent position, with eyes closed in a maximally alert state in a sound-attenuated room with subdued lighting. During the recording the alertness was controlled. If the patterns of drowsiness appeared in the EEG, the subjects were aroused by acoustic stimuli.

2.4. EEG data reduction and analyses

The first 50 sequential, non-overlapping, 2-second epochs collected during resting periods with eyes closed were selected to be processed for each recording. Before analysis of the data, artifact detection was performed visually to exclude all epochs containing eye blink, eye rolling artifact, head movements, muscle artifacts, decrease in alertness or epoch in which any channel had a voltage deflection greater than ±75 μV. EEG reviewer was blind to the outcome of treatment. The number of artifact-free, 2-seconds epochs averaged 18.4±2.5 (range 15–23) across subjects, indicating that on average, at least 30 s of the available recordings were submitted to a spectral analysis. The number of epochs we processed did not differ between responders and non-responders. Preceding the Fast Fourier Transform (FFT), a linear interpolation between adjacent raw values (sampled at a frequency of 250 Hz) was carried out, followed by a second sampling procedure at a frequency of 256 Hz, yielding 512 values in the 2.0 s spectral window. With this algorithm, the frequency resolution of the power spectra is 0.5 Hz. FFT was used to calculate absolute and relative power in each of four non-overlapping frequency bands (Nuwer et al., 1999): delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–20 Hz).

2.5. Cordance calculations

QEEG cordance was calculated by our EEG software (WaveFinder v.1.70, unimedis, Prague) using the algorithm for the cordance calculation which has been described elsewhere in greater detail (Leuchter et al., 1994a,b). This algorithm normalizes power across both electrode sites and frequency bands in three consecutive steps: first, absolute power values are reattributed to each individual electrode by averaging power from all bipolar electrode pairs sharing that electrode (for example, the reattributed absolute power for Fp1

electrode is calculated as an average of the bipolar absolute power of pairs Fp1–F7, Fp1–F3, and Fp1–Fp2) (Cook et al., 1998). This electrode referencing method is similar to the single source method of Hjorth (1975), in which voltage signals are recombined, except that the current method averages power from neighboring electrode pairs whereas the Hjorth transformation averages voltage amplitudes. It has been previously shown that electrode referencing on the basis of power averaging provides a stronger association between QEEG measures and perfusion of underlying brain than either the linked-ears reference or the conventional Hjorth method (Cook et al., 1998). Then the relative power values (percentage of power in each frequency band) are calculated on the basis of dividing reattributed absolute power values by total power values for each electrode site in each frequency band. In the second step, for each individual EEG recording the maximum absolute and relative power values ($AMAX_f$, $RMAX_f$) in each frequency band (f) are determined to obtain normalized absolute ($A_{NORM\ (s,f)}$) and normalized relative ($R_{NORM\ (s,f)}$) power values (each absolute and relative power values are divided by $AMAX_f$ and $RMAX_f$ respectively). This normalization process places absolute and relative power values into a common unit (yielding values between 0 and 1) which allows them to be combined. In the third step, the cordance values at each electrode site (s) for each frequency band (f) are calculated by summing the A_{NORM} and R_{NORM} values, after a half-maximal value (0.5 on the normalized scale) are subtracted:

$$CORDANCE_{(s,f)} = \left(A_{NORM\,(s,f)} - 0.5\right) + \left(R_{NORM\,(s,f)} - 0.5\right).$$

For each individual EEG record, the cordance values from 3 frontal electrodes (Fp1, Fp2 and Fz) in theta frequency band (4–8 Hz) were averaged and subjected to statistical analysis similar to previous studies (Cook et al., 2002, 2005; Leuchter et al., 2002; Bares et al., 2007, 2008).

2.6. Statistical methods and data analyses

Analyses were performed using SPPS version 13. Due to the small sample size and non-normal data distribution we used nonparametric statistical tests (Fisher Exact Test, Mann–Whitney U Test, Spearman's Rho). All tests were 2-sided and an exact significance level of 0.05 was adopted. The baseline characteristics, scores in rating scales as well as values of cordance were expressed as a median and interquartile ratio (IQR). The primary analysis was conducted to detect difference between the number of responders and non-responders who decreased cordance (Fisher Exact Test). The difference in cordance value changes between responders and non-responders after one week of treatment was assessed using Mann–Whitney U Test. PPV, NPV, number need to diagnose (NND) with exact binomial 95% confidence intervals (95 CI%) as well as post-hoc effect size were also calculated. Based on our previous results (Bares et al., 2007, 2008), we planned our sample size to detect a large effect size (difference between responders and non-responders who reduced prefrontal cordance). Total sample size of 18 patients would be sufficient to detect an effect size (w) of 0.66 with 81% power at a 5% level of statistical significance.

3. Results

3.1. Baseline and treatment characteristics and clinical measures

We analyzed 18 patients who finished 4 weeks of treatment. Eleven (61%) out of 18 subjects responded to the treatment. With the exception of gender, no baseline differences were found between responders and non-responders in demographic and clinical characteristics, duration of wash-out period or in average daily doses of bupropion at week 1 and week 4 (see Table 1). We also did not find any significant difference in the number of patients taking zolpidem and hydroxyzine in both groups at week 1 (a day before the 2nd EEG session) and week 4. The scores of the clinical rating scales in patients over time are summarized in Table 2 and there were no differences between responders and non-responders at baseline. Both groups differed in MADRS and CGI after first week of treatment but were not significantly different in the reductions of MADRS and CGI scores.

Table 2 Results of the clinical rating scales.

	Responders (n=11) median (IQR)	Non-responders (n=7) median (IQR)	Statistical significance level [a]
MADRS baseline	28 (24–33)	29 (28–36)	NS
MADRS week 1	24 (19–28)	31 (26–36)	p=0.04
Reduction of MADRS score after week 1	4 (0–8)	1 (−2–3)	NS
MADRS week 4	12 (10–16)	24 (22–27)	p<0.001
Reduction of MADRS score after week 4	15 (13–18)	4 (2–14)	p<0.01
CGI baseline	5 (4–5)	5 (5–6)	NS
CGI week 1	4 (4–5)	5 (5–6)	p=0.04
Reduction of CGI score after week 1	0 (0–1)	0 (0–0)	NS
CGI week 4	2 (2–3)	4 (4–5)	p<0.001
BDI-S baseline	19 (11–23)	19 (17–21)	NS
BDI-S week 1	17 (11–22)	21 (17–24)	NS
BDI-S week 4	10 (6–15)	19 (18–21)	p=0.001

BDI-S—Beck Depression Inventory—Short Form, CGI—Clinical Global Impression, IQR—interquartile range, MADRS—Montgomery and Åsberg Depression Rating Scale, NS—nonsignificant.
[a] Mann–Whitney U Test.

3.2. Predictive value of prefrontal cordance reduction

Nine of eleven responders and only one of seven non-responders showed a decrease in prefrontal QEEG cordance after the first week of drug administration (Fisher Exact Test, $p=0.01$). Using the decrease of prefrontal cordance value after one week of treatment as an indicator of response to bupropion, PPV and NPV of this test were 0.9 (95% CI, 0.56–1.0) and 0.75 (95% CI, 0.35–0.97), respectively. NND for response was 1.48 (95% CI, 1.16–4.17) with the effect size (w) for response of 0.7. When cordance values were analyzed as continuous variables, we detected significant difference in prefrontal cordance value changes between responders and non-responders (Mann–Whitney U Test, $U=15$, $p=0.03$) after first week of bupropion treatment. The higher baseline cordance value was found in responders (Mann–Whitney U Test, $U=6$, $p=0.002$). For numerical details see Table 3.

We found significant relationships between percentage reduction of MADRS score from baseline to final visit and both the baseline cordance (Spearmen's Rho, $r_s=0.64$, $p=0.004$) and the change of cordance value after week 1 (Spearmen's Rho, $r_s=-0.55$, $p=0.02$). There were no correlations between baseline cordance value and severity of depression (baseline MADRS score).

We also did not detect any relationship between benzodiazepine equivalent dose (Bazire, 2003) and baseline cordance value for all patients ($r_s=0.02$, $p=0.94$) as well as between benzodiazepine equivalent dose and the change of cordance value after week 1 ($r_s=0.21$, $p=0.4$). The baseline cordance values were not different between patients with benzodiazepines (0.64, IQR 0.60–0.69) and without benzodiazepines (0.50, IQR 0.31–0.70, Mann–Whitney U Test, $U=18$, $p=0.33$) as well as the change of cordance value after week 1 (−0.02, IQR −0.06–0.07 and 0.02, IQR −0.12–0.13, resp.; Mann–Whitney U Test, $U=27$, $p=0.96$).

Although we observed significant gender difference in final response rate, there was no significant difference in the change of cordance value after week 1 between males and females (Mann–Whitney U Test, $U=32$, $p=0.51$). The same result was achieved by comparing the cordance change between males and females who responded to the treatment (Mann–Whitney U test, $U=6$, $p=0.28$). We found significantly higher baseline cordance value in females (0.68, IQR 0.64–0.72) comparing to males (0.57, IQR 0.46–0.62) in whole sample (Mann–Whitney U test, $U=13$, $p=0.02$) and no gender difference of baseline cordance value in responders group (Mann–Whitney U test, $U=10$, $p=0.78$).

In addition, we calculated predictive parameters of cordance reduction for remission ($n=6$) defined as a MADRS score ≤ 12 points. PPV and NPV were 0.6 (95%CI, 0.26–0.88) and 1.0 (95%CI, 0.63–1.0) respectively.

4. Discussion

The primary finding of this study was that the reduction of prefrontal QEEG cordance value in theta frequency band after one week of bupropion treatment predicted clinical response to 4-week treatment in patients who had failed to previous antidepressant treatments. We also found intergroup difference (responders vs. non-responders) in cordance value changes at this time point. As far as we know, this is the first study using the frontal theta band QEEG cordance as an early predictor of response to an antidepressant whose mechanism of action does not involve inhibition of serotonin reuptake. Previous study demonstrated predictive effect of a reduction of prefrontal cordance for SSRI or SNRI (Cook et al., 2002; Cook and Leuchter, 2001; Bares et al., 2008).

The decrease of theta prefrontal cordance we observed might be a potential correlate of early activity changes in anterior cingulate and prefrontal cortex coupling with antidepressant response. The changes of metabolic activity in anterior cingulate and adjacent orbital and prefrontal cortices were associated with response to treatment with chronic deep brain stimulation (Lozano et al., 2008, Mayberg et al., 2005) and antidepressants as well (Drevets et al., 2008). However, the link between decrease of theta prefrontal cordance and early activity changes in anterior cingulate and prefrontal cortex is currently supported by very limited data (Leuchter et al., 1994a,b, 1999). We also observed significantly higher baseline cordance value in responders as well as the relationship between baseline prefrontal cordance value and a reduction of MADRS in the whole sample that were not seen in previous studies (Cook et al., 2002; Bares et al., 2007, 2008). If the frontal electrical activity in theta frequency band reflects mainly the function of the anterior cingulate cortex (Asada et al., 1999; Pizzagalli et al., 2003) and the cordance values correlate with regional cerebral blood flow (Leuchter et al., 1994a,b, 1999), our finding could be hypothetically consistent with the results of previous studies linking higher baseline metabolism as well as higher theta activity of anterior cingulate with response to antidepressant treatment (Mayberg et al., 1997; Mayberg et al., 2000; Mulert et al., 2007; Pizzagalli et al., 2001).

Reviewing previous "cordance" studies we identified the same pattern of results (higher cordance value in responders) in three studies (Cook et al., 2002; Leuchter et al., 2002;

Table 3 Prefrontal cordance values during study.

	Responders ($n=11$) median (IQR)	Non-responders ($n=7$) median (IQR)	Statistical significance level [a]
Prefrontal cordance value at baseline	0.68 (0.62–0.73)	0.49 (0.40–0.60)	$p=0.002$
Change in prefrontal cordance values after week 1 (CF2 − CF1)	−0.06 (−0.18 to −0.02)	0.12 (0.03–0.14)	$p=0.03$

CF1—cordance value at baseline, CF2—cordance value after week 1, IQR—interquartile range.
[a] Mann–Whitney U Test.

Bares et al., 2007), but none reached statistical significance. Based on our data we hypothesize that both parameters (baseline cordance value and early change of cordance) closely interact and may predict changes in depressive symptoms.

We suppose that reduction of cordance value outlined as a dichotomous variable is more suitable for prediction of treatment outcome in clinical practice than baseline cordance because there is no cut-off of cordance value to be used in individual setting.

The increase of cordance value in non-responders observed in our study might be also a promising predictor but it has not yet been supported by sufficient body of evidence contrary to cordance decrease in responders (Cook et al., 2002; Bares et al., 2007, 2008). It is not clear what processes are coupled with increase of cordance in non-responders. It might be due to non-response to treatment or a consequence of the ongoing changes related to pathophysiological processes of depression.

Accidentally, we detected significant gender difference in the response rate. Several analyses have found that gender, menopausal status, and age can affect response to AD, whereas others have failed to show such differences (Kornstein and Sloan, 2006). The recent pooled analysis did not find gender-related difference in the antidepressant efficacy of bupropion and SSRI (Papakostas et al., 2007a). In our study, we found a gender difference in baseline cordance value in whole sample but not in responders and no differences were observed between males and females in changes of cordance values after week 1 in whole sample or responders. We are not able to say if baseline cordance gender difference is a true gender difference or a consequence of baseline cordance difference between responders and non-responders combined with unequal response gender ratio in our study. The study is too small to elucidate this question. Since a previous study did not detect gender baseline difference in cordance value (Morgan et al., 2005) in depressive patients we do not suppose any robust influence of gender on cordance prediction, however we cannot exclude some smaller effect in patients treated with bupropion.

We evaluated confounding influence of benzodiazepines administration (stable dose during the study) on prefrontal cordance change. We examined the relationship between benzodiazepine equivalent dose and baseline cordance value for all patients as well as between benzodiazepine equivalent dose and the change of cordance value after week 1 and found no significant correlation. Moreover, there was no difference between patients with and without benzodiazepines in baseline cordance values and in the change of cordance value after week 1. The relation between cordance and benzodiazepines, if present, did not appear to influence the results of our study.

It is important to note several limitations of the current study. First, the duration of 4 weeks might be too short to assess clinical response to bupropion (Rush et al., 2006a) and we cannot exclude the possibility of further clinical change emerging during longer treatment. In an outpatients' fluoxetine study, non-responders after 4 weeks of treatment achieved better remission rate at week 12 but the response rate after week 4 of treatment was still substantial — 50% (Quitkin et al., 2003). The period of 4 weeks is frequently used as a cut-off point of antidepressant treatment adequacy (Antidepressant Treatment History Form — Sackeim, 2001, Souery et al., 2007) and 4 weeks was a median of treatment duration to response in responders to bupropion in Level 2 of STAR*D study that involved patients with similar degree of failure to previous AD treatment as in our project (Rush et al., 2006b). Moreover, at least four previous studies found that the change after the first 2 or 4 weeks of treatment predicted the outcome at 6, 8 and 12 weeks (Nierenberg et al., 2000; Papakostas et al., 2007b; Trivedi et al., 2005, Szegedi et al., 2009).

Second, we used only a short wash-out period to prevent potential side effects of rapid switching as in our venlafaxine study (Bares et al., 2008). Since a previous study with randomized clinical trial design employed a wash-out and a placebo lead-in period prior to enrollment (Cook et al., 2002) and detected similiar sensitivity, specificity and predictive values as a study without a wash-out period (Cook et al., 2005), we supposed that the wash-out period might not be essential for the correct detection of prefrontal cordance change in patients with a new antidepressant intervention.

Third, we did not include placebo control arm because Institutional Review Board of Prague Psychiatric Centre would not have approved a placebo-controlled study in the treatment of resistant patients.

Fourth, the raters were not blind to medication; however, they were blind to EEG results during the study. Next, the relatively small sample size could be a further limitation. Nevertheless, our sample size calculation was based on effect sizes observed in previous studies (Bares et al., 2007, 2008) and post-hoc effect size (w) estimated from this sample for response was in the large range (Cohen, 1988). Final limitation of our study is that we did not record EEG in the end of study in all patients as it was not a part of our a priori hypothesis. We collected EEG records after finishing the study only in responders in the framework of another study (not yet published) evaluating stability of various EEG parameters in responders to acute treatment. Calculating cordance value we found four responders who did not reduce cordance after finishing the study. Two responders with increase of cordance value after week 1 continued as cordance non-reducers. Since a previous study has demonstrated a different pattern of cordance changes in placebo responders (increase of cordance value) in comparison with medication responders after 4 weeks of treatment, cordance changes might possibly differentiate true medication responders and false (placebo) medication responders (Leuchter et al., 2002). However, there is no clear evidence supporting such approach in individual patients.

Despite the limitations of this and other cordance studies the early change of cordance value remains a promising tool in the prediction of antidepressant response. The data of our study together with the results of previous clinical trials (Cook et al., 2002, 2005; Cook and Leuchter, 2001; Bares et al., 2007, 2008) suggest usefulness of this method in the decision whether to stop or continue with a given AD and thus to reduce the period of ineffective treatment.

There is a clear need of cordance studies combined with some neuroimaging or other neurophysiological methods to clearly determine physiological or pathophysiological meanings of cordance. This approach and combination or comparison of cordance with other potential predictors of

response will define the role and significance of cordance in clinical practice.

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Contributors

Dr. Bares designed the study, wrote protocol, coordinated all project activities, participated in clinical part of project and wrote the manuscript.

Dr. Brunovsky designed the study, wrote protocol and provided assistance with EEG hardware and contributed to the analysis of the EEG data.

Dr. Novak assessed the patients throughout the study and performed statistical analysis.

Dr. Kopecek designed study, wrote the protocol, assessed patients and managed literature searches.

Dr. Stopkova participated in clinical part of project, discussed results and wrote the manuscript.

Dr. Sos undertook EEG analysis.

Mr. Krajca provided assistance with EEG hardware and software.

Dr. Höschl designed study and discussed results.

All authors contributed, revised and approved the final manuscript.

Conflict of interest

In the last three years, Dr. Höschl has received travel grant from Eli Lilly and comp. He has been a consultant for Servier, and he has been a speaker for Eli Lilly & Co. and Bristol-Myers Squibb Company. He is also a faculty member, Lundbeck International Neuroscience Foundation. He has received consulting honoraria from United Biosource Corporation. He has no shares, no other conflicts of interests.

Other authors declare that they have no conflicts of interests.

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QEEG changes during switch from depression to hypomania/mania: A case report

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Abstract

BACKGROUND: QEEG cordance and low-resolution electromagnetic tomography (LORETA) are relatively new applications of QEEG. Four small-scale studies have shown that decreases of QEEG prefrontal theta cordance after the first week on new antidepressants predict clinical response to treatment in patients with unipolar depression.

METHODS: We calculated prefrontal theta cordance and changes in 3D distribution of brain electrical activity using LORETA in the case of a 54-year old man experiencing his third depressive episode.

RESULTS: We did not detect a decrease of prefrontal theta cordance after one week of new treatment and the patient did not respond to this therapy after four weeks. However, we observed a decrease of prefrontal theta cordance after the first week of clomipramine therapy. Manic symptoms emerged after two weeks of clomipramine treatment. A decrease of prefrontal theta cordance preceded the clomipramine induced switch to hypomania during the next episode of depression also. LORETA before and during clomipramine therapies detected a significant increase of theta in the right postcentralis gyrus in the parietal lobe, and a borderline increase of alfa2 in the right middle frontal gyrus.

DISCUSSION: In a patient with bipolar spectrum disorder we found that a treefold change in theta prefrontal cordance preceded mood changes in a similar way as in patients with unipolar depression. We speculate that the changes detected by LORETA can attributed to the anticholinergic activity of clomipramine and the specific effects of a mood switch. Our data suggest that the new applications of QEEG can be sensitive to mood changes and have potential in bipolar disorder research.

CASE REPORT

Abbreviations and units:

BA – Brodmann area
BD – Bipolar Depression
BDI-SF – Short Form of Beck Depression Inventory
CGI – Clinical Global Impression
EEG – electroencephalography
fMRI – functional Magnetic Resonance Imaging
LORETA – Low Resolution Electromagnetic Tomography
MADRS – Montgomery-Åsberg Depression Rating Scale
mg – milligram
mIU/l – milli-International Units per liter
mmol/l – millimol/liter
PET – Positron Emission Tomography
QEEG – Quantitative Electroencephalography
rTMS – repetitive Transcranial Magnetic Stimulation
SPECT – Single Photon Emission Tomography
SSRI – Selective Serotonin Reuptake Inhibitor
TCA – tricyclic antidepressant
YMRS – Young Mania Rating Scale

INTRODUCTION

The switch to hypomania/mania during treatment of unipolar depressive disorder with antidepressants was described with frequencies occurring between 0–22.4% [30,45]. Using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), these patients are diagnosed with a manic or hypomanic episode associated with antidepressants. Some authors have proposed that these patients should be classified in the bipolar spectrum [1,30], while others do not [7]. Antidepressant induced switch to hypomania/mania are estimated to occur in 0–84.2% patiens with bipolar depression (BD) [4,24]. Swich phenomena have been described during treatment with almost every antidepressant modality even nonpharmacological ones [5,16,61,63].

The neurobiologic basis of a drug induced switch is unknown, as is a spontaneous switch to mania. Antidepressant-related switches could be considered a subtype of switches [14], occurring in predisposed individuals because of the eliciting action of antidepressants [57]. The switch to mania after specific antidepressant treatment could reflect an endophenotype which could be composed of a more homogenous group of patients than the phenotype of bipolar disorder.

In this study, we present a case series of antidepressant induced switches together with detected electrophysiological changes. We used two types of new EEG analyses (theta QEEG cordance and Low Resolution Electromagnetic Tomography – LORETA) to describe EEG changes before the switch to mania.

QEEG cordance is a new EEG method, that combines complementary information from the absolute (the amount of power in a frequency band at a given electrode) and relative power (the percentage of power contatined in a frequency band relative to the total spectrum) of EEG spectra. Cordance combines these parameters to achieve a stronger association with cerebral perfusion than either measure alone. Of the three QEEG measures (absolute power, relative power, and cordance) examined, cordance had the strongest relationship with perfusion [40].

LORETA is a neurophysiological method, that allows truly three-dimensional tomography of brain electrical activity [51].

QEEG techniques

Nineteen surface electrodes were placed according to the international 10/20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2), with all electrode impedances kept below 5 kΩ. We used the BrainScope amplifier system (unimedis, Prague), with the Cz as a reference electrode. The EEG was recorded with the patient in a semi recumbent position, with eyes closed in a maximally alert state in a sound-attenuated room with subdued lighting. The data, 30 minutes in duration, were collected with an on-line computer system. All signals were sampled with a frequency of 250 Hz with 0.5–70 Hz filters, and the data were stored for further computer off-line analysis. Before analysis of the data, artifact detection was performed visually with the exclusion of all EEG segments which contained obvious eye and head movements, muscle artifacts or decrease of alertness. After re-computation to average reference, spectral analysis was performed for at least 30s of artifact-free data. The cross-spectra were averaged across the overlapping windows which yielded into seven frequency bands delta (1.5–6 Hz), theta (6.5–8 Hz), alpha-1 (8.5–10 Hz), alpha-2 (10.5–12 Hz), beta-1 (12.5–18 Hz), beta-2 (18.5–21 Hz) and beta-3 (21.5–30 Hz) [37].

Theta prefrontal cordance and LORETA analysis

According to previous studies [8–10,17,39], average cordance values from three frontal electrodes (Fp1, Fp2 and Fz) in theta frequency band (4–8 Hz) were subjected to statistical analysis.

Subsequently, LORETA was used to estimate changes in 3D intracerebral current density distribution. LORETA 3D images were compared with voxel-by voxel t tests, resulting in t statistic 3D images. In these images, cortical voxels of statistically significant differences were identified by a nonparametric approach using a randomization strategy that determined the critical probability threshold values for the actually observed statistic with corrections for multiple testing of single voxels. Only the voxels with t-values, that exceeded the critical threshold for $p = 0.05$ were taken into account. Statistical analysis of LORETA data was made by the comparison (by paired t-tests of log-transformated LORETA power spectra) of two EEG recordings in the clomipramine treatment (after 1st week of 1st and 2nd clomipramine therapy, before switch to mania) with two EEG recordings in the depressive episode, before clomipramine therapy.

Table 1. Clinical characteristics and EEG cordance before and after switch to 1st episode of mania. Yellow color marks how change in theta frontal cordance after one week on new medication predict mood change.

Scales	Treatment and scores in scales					
	Baseline scores	Ven 1st week	Ven 4th week	Clo 1st week	Clo 2nd week	Li+Ris
MADRS	24	30	25	25	4	0
CGI-D	4	5	4	4	1	1. 4*
BDI-SF	16	20	16	16	2	0
YMRS	X	X	X	X	12	24
cordance value	0.63	0.66 (↑)	0.83 (↑)	0.77 (↓)	X	X

MADRS, CGI-D – Depressive - Clinical Global Impression scale, * - Mania - Clinical Global Impression Scale, BDI-SF - Beck Depression Inventory – Short Form [11], YMRS - Young Mania Rating Scale [64], Clo – clomipramine, Li – lithium, Ris – risperidone, Ven – venlafaxine ER, X – No observed. ↓ - decrease, ↑ - increase

Table 2. Clinical characteristics and EEG cordance before and after switch to 2nd hypomania episode. Yellow color marks how change in theta frontal cordance after one week on new medication predict mood change.

Scales	Treatment and scores in scales				
	baseline scores Ser+Li+Ris	1st week Clo+Li+Ris	2nd week Clo+Li+Ris	3rd week ↓Clo+Li+Ris	4th week Ola+Li
MADRS	24	24	8	2	2
CGI-D	4	3	2	1.3*	1.2*
BDI-SF	19	19	11	1	1
YMRS	0	0	14	16	8
cordance value	0.827	0.727 (↓)	0.687 (↓)	0.727(↑)	0.757(↑)

MADRS – Montgomery-Åsberg Depression Rating Scale, CGI-D – Depressive - Clinical Global Impression scale, * - Mania - Clinical Global Impression Scale, BDI-SF - Beck Depression Inventory – Short Form [11], YMRS - Young Mania Rating Scale [64], Clo – clomipramine, Li – lithium, Ola – olanzapin, Ris – risperidone, Ser – sertralin, X – No observed, ↓ - decrease, ↑ - increase.

Case report and the change of theta prefrontal cordance

A 54-year old man experiencing his third depressive episode was admitted to The Prague Psychiatric Centre (PPC). His brother suffered from BD 1 and his sister was healthy. No parent had suffered from mental illness. He was married, had one son and worked as a teacher in the high school. He used tamsulosin (an α1a-selective alpha blocker) for treatment of benign prostatic hyperplasia. His first depressive episode occurred when he was 52 years old, and for which he took citalopram followed by escitalopram, bupropion and underwent psychotherapy. He did not reach full remission and was not able to go back to his work. He had no history of manic or hypomanic episodes. During his second depressive episode at age 54, he was treated with mirtazapine 45 mg/d and amisulpride 50 mg/d. With treatment his mood improved, but he still did not reach full remission. After six months of treatment with mirtazapine and amisulpride he experienced two months of full recovery, but than suddenly experienced his third depressive episode for which he was hospitalized at the PPC. After admission to the PPC he consented to participate in a clinical study. At The PPC the diagnosis of recurrent major depressive disorder was evaluated according to DSM IV criteria and confirmed using The Mini – International Neuropsychiatric Interview – M.I. N. I., Czech version 5.0.0. [58]. The patient suffered from depressive mood, abulia, mental slowing, decreased appetite, weight loss, insomnia, working incapacity and tiredness. He underwent an EEG examination, baseline mood evaluation (Table 1) and than started a four week monotherapy course of venlafaxine ER up to 225 mg/d. No decrease in theta prefrontal cordance value occurred after one week of venlafaxine therapy (Table 1), and he did not reach a significant antidepressant response after four weeks of therapy (reduction of ≥ 50% in total MADRS – Montgomery-Åsberg Depression Rating Scale [46]). Subsequently, the therapy was changed to clomipramine given up to 100 mg/d by the intravenous route given along with oxazepam 30 mg/d and nitrazepam 5 mg/d. After the first week of the clomipramine therapy was started, prefrontal cordance decreased (Table 1). The mood switched to mania in the second week

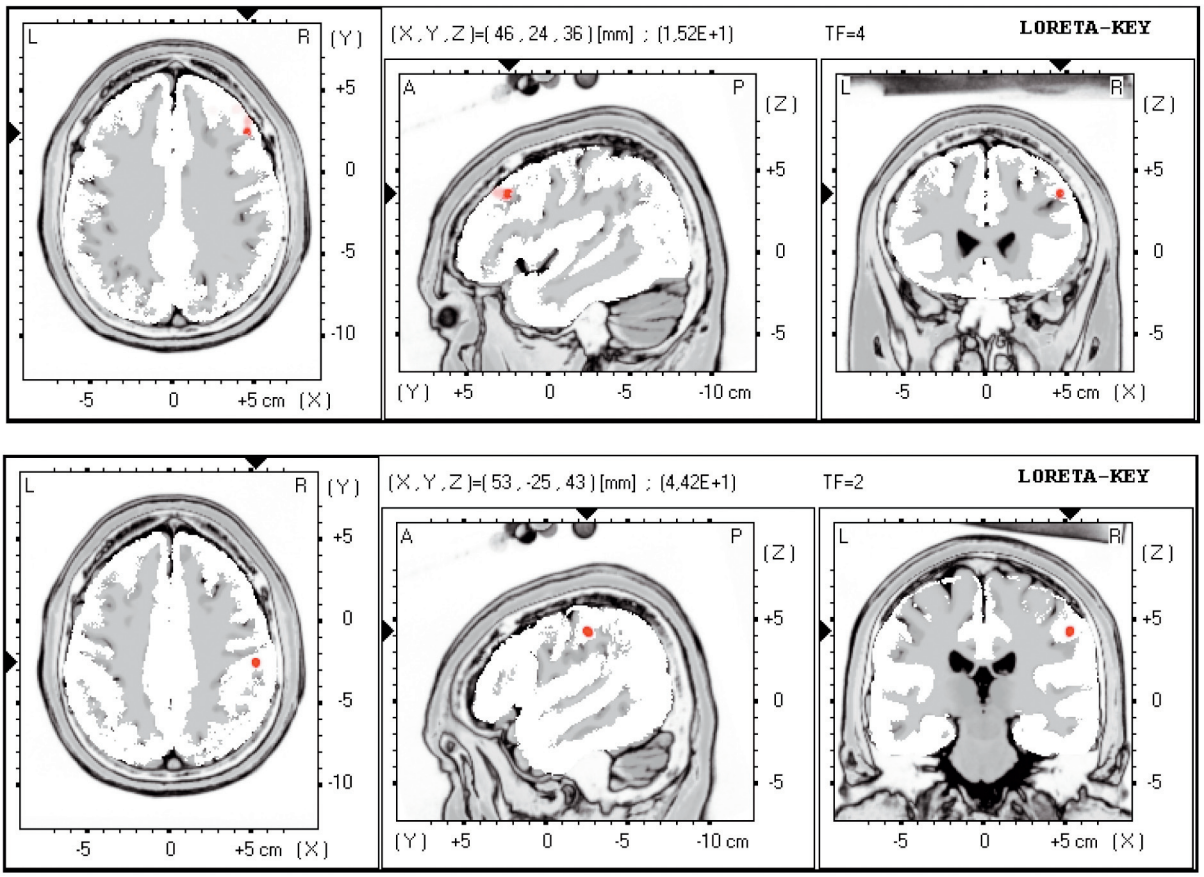

Figure 1. Images of voxel-by-voxel t-statistic of brain regional electrical activity using LORETA, comparing before-after one week clomipramine power density in patient in theta and alfa 2 band. An increase of current density after clomipramine is indicated by red. Upper figure shows an increase of current density in the alfa2 band in the Middle Frontal Gyrus, Brodmann area 9 (X= 46, Y= 24, Z= 36), lower figure shows an increase of current density in the theta band in the Postcentral Gyrus, Parietal Lobe, Brodmann area 2, (X= 53, Y= -25, Z= 43). Structural anatomy is shown in gray scale (white-to-black). Left: axial slices, seen from above, nose up; center: sagittal slices, seen from the left; right: coronal slices, seen from the rear. The extreme t-values are given as (X,Y,Z) coordinates in Talairach space, and are graphically indicated by black triangles on the coordinate axes. Talairach coordinates: X from left (L) to right (R); Y from posterior (P) to anterior (A); Z from inferior to superior.

of clomipramine treatment. The patient was euphoric, hyperactive and talkative. He had a decreased need for sleep, described racing thoughts and his behavior was deliberate and inappropriate (he wore women's clothes as he walked around the hospital). He was transferred to a locked psychiatric unit, tapered off clomipramine and started antimanic treatment. Manic symptoms disappeared after six weeks of lithium (900 mg/d) and risperidone (5 mg/d) therapy. The patient was in full remission for the next four months after which the next depressive episode started. His psychiatrist added sertraline 200 mg/d to lithium (900 mg/d) and risperidone (2 mg/d). Six-weeks of outpatient sertraline therapy had no effect and the patient was rehospitalized in PPC. The symptoms were same as in the previous depressive episodes (Table 2). His lithium plasma level was within the therapeutic range (0.69 mmol/l) and elevation of plasma prolactin (675 mIU/l) was consistent with low dose risperidone therapy [34]. After unsuccessful treatment of the depression with sertraline, it was decided use an oral form of clomipramine. The patient was informed that during clomipramine therapy, he was at risk of the induction of hypomania/mania but that use of lithium and risperidone could reduce this risk [12,48]. The patient agreed to have clomipramine therapy and further EEG assessments. Thus oral clomipramin 100 mg/d was added to lithium (900 mg/d) and risperidone (2 mg/d). After one week of clomipramine therapy, we observed a decrease of theta prefrontal cordance and further decreased two weeks later (Table 2). During the second week of this clomipramine therapy, morning tiredness promptly disappeared and the first signs of the switch to hypomania occurred (the patient was hyperactive, cheerful and talkative). In the third week clomipramine was decreased to 50 mg/d and the theta prefrontal cordance increased. Due to continuing mood elevation, we tapered the patient off clomipramine and switched the risperidone to olanzapine. A week after this new treatment, theta prefrontal cordance increased again and mood was euthymic during next eight weeks.

Table 3. Affinity of antidepressants used in the case

	NE	5– HT	DA	Alfa– 1	H1	M
escitalopram	+/–	++++++	0	+/–	+/–	+/–
citalopram	+/–	+++++	0	+	+	+/–
bupropion	0	+/–	+	+/–	+/–	0
sertraline	+	++++++	+++	++	0	+
venlafaxine	+	++++	+/–	0	0	0
Mirtazapine	+/–	0	0	+	++++++	+
Clomipramine	+++	++++++	+/–	+++	+++	+++

NE= norepinephrine; 5- HT= serotonin; DA= dopamine, Alfa-1 = alpha adrenergic, H1 = h istaminic, M = muscarinic; ++++++=most potent; +/-=weak effect; 0 = no effect. Addapted from [50,55]

LORETA changes

We also used LORETA analysis changes before and after the first week of the first and second clomipramine treatment phases to elucidate electrophysiological changes that preceded the switch to mania/hypomania. We combined data from both trials to increase power. We found significant increases in the theta band (p=0.002) in the right parietal lobe (postcentral gyrus, Brodmann area – BA 2) and borderline increases of alfa2 in the right middle frontal gyrus (BA 9) p= 0.056 (Figure 1).

DISCUSSION

To the best of our knowledge, this is the first description of the application of theta prefrontal cordance to the study of patients with bipolar disorder. The absence of a prefrontal theta cordance decrease after venlafaxine therapy in our patient predicted non-response, in agreement to previous studies in patients with unipolar depression [8–10,17,18]. Further therapy with intravenous clomipramine was associated with a decrease of theta prefrontal cordance and a switch to mania which occured a week later. Previous reports have described that decreases in prefrontal theta cordance predict antidepressive responses to drugs [8–10,17,18] and rTMS [36]. Increase of prefrontal theta cordance was associated with placebo response [39] and or dissimulation [35]. However, no reference to a switch to mania was mentioned. The patient was treated with lithium and risperidone as antimanic therapy and later as mood stabilizing therapy, but this combination did not prevent a further depressive episode. We were not sure that the switch was due to clomipramine induced mania, a spontaneous switch to mania with random co-occurrence, or a switch after benzodiazepine medication [19,26].

A second trial with oral clomipramine treatment induced hypomania despite the possibility that lithium and risperidone might be effective in the prevention of mania, because it has been effective as an antimanic treatment before. The lithium plasma level was stable, and the patient treated with 2 mg/d of risperidone, a lower dose than used during the acute treatment of mania. In our opinion, the second occurrence of hypomania during clomipramine therapy excluded the possibility of a spontaneous switch to hypomania or a benzodiazepine induced mania, and made clomipramine more probable as a causal agent of the switch. Also after the first and second depressive episodes, no spontaneous switch occurred during treatment with antidepressants. For both manic episodes, the switch was preceded by a decrease of prefrontal theta cordance (Table 2). Rather than measurement of absolute value previous studies have used a decrease in theta prefrontal cordance after treatment with a new drug to predict response, and a non-decrease to predict non-response [8–10,17,18].

It is not clear which brain processes underlie decreases of theta prefrontal cordance. Previous human studies suggest that theta band reflects the actitivity of anterior cingulate gyrus [6,54], that support recent EEG and default mode fMRI study [59]. Abnormity in anterior cingulate gyrus in patients with mood disorders were detected using structural MRI [28] and PET [20]. Responders and nonresponders to antidepressants treatment had different frontal theta activity using EEG [47,53], glucose metabolism [44] and blood flow using fMRI [27,29] or SPECT [38] in anterior cingulate gyrus. Based on this data, we suppose that the change of theta prefrontal cordance might be the main correlate of early activity changes in the anterior cingulate.

The patient did not experience manic symptoms after receiving escitalopram, citalopram or bupropion, which act as serotonin reuptake inhibitors and a norepinephrine-dopamine reuptake inhibitor (Table 3). We did not observe a switch to mania after sertraline or venlafaxine which act as a serotonin and a weak dopamine reuptake inhibitor and serotonin-norepinephrine reuptake inhibitor respectively, and which have no antihistaminic or significant anticholinergic activity [55]. The switch to mania did not occur after mirtazapine therapy which increases serotonin via ac-

Table 4. - EEG cordance and EEG findings in patients with unipolar depression after 1 week of antidepressant, in patient with clomipramine induced mania/hypomania and in healthy controls after acute intravenous application of scopolamine and during drug induced euphoria

	EEG cordance	LORETA	EEG
Patients with unipolar depression	Reduction predicts later response. Absence of reduction predicts non-response.	Decrease of theta band in BA 8, 9 [13]	
Patient with switch after clomipramine	Reduction preceded twice early switch to mania/hypomania. Absence of reduction preceded once no antidepressant effect.	1) marginal increase of the alpha-2 band in BA 9 2) an increase in the theta band in the right parietal lobe	
healthy volunteers after scopolamine intake [33]			1) a decrease of the alpha-2 band, mainly over frontal regions 2) Increased delta and theta activity in central and parieto-occipital regions
healthy volunteers after alcohol induced euphoria intake [43]			increase of the frontal alpha

tivity on presynaptic α2-noradrenergic receptors and blocks 5-HT2A and histamine receptors [55] or after the addition of low doses of amisulpride, a drug that increases dopamine in prefrontal cortex [60].

Clomipramine has a high affinity for serotonin reuptake inhibition, high antagonistic activity on histamine H1 and muscarinic acetylcholine receptors, and medium affinity for norepinephrine reuptake inhibition [55]. The antihistaminic activity is not related to an antidepressive effect but blockade of muscarinic receptors may be related to an antidepressant effect [22,31,32].

We speculate that the anticholinergic activity of clomipramine played a role in the switches to hypomania/mania in our patient. A recent study demonstrated antidepressant activity for an anticholinergic drug – scopolamine in depressive patients [22] and another showed reduced muscarinic type 2 receptor binding in the anterior cingulate in patients with bipolar disorders [15]. These studies have caused renewed interest in the acetylcholine hypothesis in affective disorder [31,32]. Anticholinergic drugs such as scopolamine have been recently studied in healthy volunteers, mainly to evaluate cholinergic hypothesis of Alzheimer diseases using QEEG. These studies detected increased delta and theta activity in central and parieto-occipital regions [33,56] that agree with our observation of an increase in the theta band in the right parietal lobe using LORETA. This change seems more related to an anticholinergic effect of clomipramine.

Of course we could not rule out synergic effect between anticholinergic activity and norepinephrine and/or serotonine reuptake inhibition during clomipramine use. This is a typical receptor profile of tricyclic antidepressants (TCA). TCA are associated with an increased risk of switch to mania during treatment of bipolar depression than treatment with other antidepressants [25,52]. TCA is also probably associted with induction of rapid cycling in patients with bipolar disorder [3,62].

A decrease of the alpha-2 band, mainly over frontal regions, was detected in healthy volunteers after scopolamine administration [21,33]. We observed a marginal increase of the alpha-2 band, using LORETA, that indicated a reaction to the clomipramine treatment in our patient or a prospective sign of a pending manic/hypomanic state. However, we interpreted these changes carefully, due to a marginal statistical effect. Nevertheless, we did not detect similar changes in patients with unipolar depression after one week of antidepressant treatment using LORETA [13]. This lack of change suggests that this effect is not connected to an antidepressant response in patients with unipolar depression, and could be potentially connected with clomipramine induced mania/hypomania (table 4). Increased frontal alpha activity were detected in alcohol, cocaine and mariuhana induced euphoria [41–43] that indicate possible association between increased frontal alpha and switch to mania. Moreover, abnormalities in the right frontal cortex were described during secondary [23,49] and primary mania [2] and recently were observed changes in glucose metabolism in the frontal cortex during a switch to mania after subthalamic deep brain stimulation [61].

We are aware of the difficulty generalizing from a case report and the necessity to confirm our findings in large controlled study. Nevertheless, the data from our case report should indicate more extensive research for this new application of QEEG as cordance or LORETA in patients with bipolar disorder. Our data suggest that the new application of QEEG can be sensitive to mood changes and have potential in the research of bipolar disorder. The advantage of QEEG, being that it uses a

conventional EEG recorder and so has a larger potential for application in clinical practice than functional MRI, PET or SPECT.

Anticholinergic mechanisms could play a role in some patients with TCA-induced switches and this information could be used to find a more homogenous population for genetic studies in patients with BD. In our case, we did not see a prophylactic effect of lithium on the switch, which is in agreement with other studies that did not find a prophylactic effect of lithium in TCA-induced switches and for that lithium is less effective in the case of the rapid cycling that can also be induced by TCA.

CONCLUSION

This case report is interesting from four points of view: i) It presents repeated switches to mania/hypomania after clomipramine therapy in which antimuscarinic activity could play a role, ii) it shows that theta prefrontal cordance can precede changes in mood not only in unipolar depression but in bipolar depression too iii) it shows that changes detected by LORETA in the parietal cortex seems to reflect antimuscarinic activity and iv) it allows speculation that changes in activity in the right frontal cortex indicate an area responsible for switches to hypomania/mania.

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Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression

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Abstract

OBJECTIVES: Ketamine and other NMDA (N-methyl-D-aspartate) antagonists produce fast-acting antidepressant-like effects, although the underlying mechanism is unclear. Furthermore, high affinity NMDA antagonists such as ketamine are associated with psychotomimetic effects. To date the link between the antidepressant and psychotomimetic effects of ketamine has not been explored. We examined the relationship between the antidepressant and psychotomimetic effects of a single ketamine infusion in subjects diagnosed with major depressive disorder.

METHODS: In a double-blind, cross-over, placebo-controlled, two weeks clinical trial we studied the effects of ketamine (0.54 mg/kg within 30 min) in a group of 27 hospitalized depressive patients.

RESULTS: Higher intensity of psychotomimetic symptoms, measured using BPRS, during ketamine administration correlated with alleviation in mood ratings during the following week with maximum on day seven. Ketamine was superior to placebo in all visits (day 1, 4, and 7) assessed by MADRS with effect size (Cohen´s d) of 0.62, 0.57, and 0.44 respectively. There was no significant correlation between ketamine and nor-ketamine plasma levels and MADRS score change at any study time point.

CONCLUSION: The substantial relationship between ketamine's antidepressant and psychotomimetic effects was found. This relationship could be mediated by the initial steps of ketamine's action, trough NMDA receptors, shared by both ketamine's clinical effects.

Abbreviations:

BPRS	- Brief Psychiatric Rating Scale
GC-MS	- Gas Chromatography–Mass Spectrometry
HDRS	- Hamilton Depression Rating Scale
ITT	- intent-to-treat
LLOQ	- lower limit of quantification
LOD	- limit of detection
MADRS	- Montgomery-Åsberg Depression Rating Scale
M.I.N.I.	- Mini-International Neuropsychiatric Interview
NMDA	- N-methyl-D-aspartate

ORIGINAL ARTICLE

INTRODUCTION

The antidepressant effect of the dissociative anesthetic ketamine has been increasingly studied over the last ten years (Berman *et al.* 2000; Zarate *et al.* 2006; Diaz-Granados *et al.* 2010a). Ketamine and other NMDA (N-methyl-D-aspartate) antagonists produce fast-acting antidepressant-like effects, although the underlying mechanism is unclear (Dazert & Hall 2011). Furthermore, high affinity NMDA antagonists such as ketamine, are associated with psychotomimetic effects (Skolnick 1999; Johnson *et al.* 2013). To date, the link between the antidepressant and psychotomimetic effects of ketamine has not been examined.

Depending on the individuals, their expectations, the setting and the dose, ketamine produces a wide range of psychotomimetic states (Dalgarno & Shewan 1996). Dissociative anesthetics mimic the positive and the negative symptoms (social withdrawal and apathy) of schizophrenia through antagonism at NMDA glutamate receptors (Krystal *et al.* 1994; Anis *et al.* 1983). These effects are usually mild to moderate at subanesthetic doses, although they can be more pronounced in a minority of cases (Murrough 2012). The intensity of these alterations of consciousness and perception is dose-dependent (Vollenweider & Kometer 2010). It is often claimed that the psychotomimetic effects of ketamine may limit clinical use, despite its reported efficacy (Skolnick *et al.* 2009).

The improvement associated with ketamine infusion reflects a lessening of core symptoms of depression and is disconnected from ketamine-induced psychotomimetic symptoms (Berman *et al.* 2000). Zarate *et al.* reported that the higher change in positive BPRS (Brief Psychiatric Rating Scale) symptoms during ketamine infusion have trended to predict a greater decrease in Hamilton Depression Rating Scale (HDRS) scores the next day (Zarate *et al.* 2006). The pharmaceutical industry has tried to develop new NMDA antagonists with antidepressant, without provoking psychotomimetic symptoms, and the relationship between these two factors has yet to be examined.

The purpose of our study was the evaluation of ketamine‘s antidepressant properties, and to determine the link between the antidepressant and psychotomimetic effects. We also examined the role of plasma levels of ketamine and its metabolite nor-ketamine. A priori we hypothesized that the single infusion of ketamine in subanesthetic dose induces a higher decrease in depression scale score than placebo infusion. We also hypothesized greater antidepressant effect in subjects with more psychotomimetic effects during the infusion.

MATERIAL AND METHODS

Subjects

Right-handed ketamine-naive inpatients aged between 18 and 65 years old with major depressive disorder (recurrent or single episode) diagnosed according to DSM-IV criteria (Thakurta *et al.* 2012), established by means of the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan *et al.* 1998), Czech version 5.0.0 were assessed for study eligibility. Subjects were included who reached at least the total score of 20 on the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg 1979). All patients were hospitalized at the Department of Affective Disorders of Prague Psychiatric Centre between December 2009 and December 2011. All subjects were on a stable dose of antidepressant medication for a minimum of three weeks prior to admission and remained on the same medications and dosages throughout the duration of the study (Table 1). Exclusion criteria were: any suicidal risk assessed by clinical examination, current psychiatric comorbidity on Axis I and II, serious unstable medical illness or neurological disorder (e.g. epilepsy, head trauma with loss of consciousness), lifetime history of psychotic symptoms and psychotic disorder in first- or second-degree relatives and electroconvulsive therapy within 3 months before the start of the study. The study was approved by the Prague Psychiatric Centre Institutional Review Board and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki 1975, revised Hong Kong 1989. Written informed consent was obtained from all subjects before inclusion in the study. The study was registered with the European Clinical Trials Database (EudraCT number 2009-010625-39).

Study design and procedures

In this two week, double-blind, placebo controlled, crossover study each participant attended one ketamine and one placebo session in a randomized order in one week intervals. Both sessions were performed at the same time from 8 a.m. to 10 a.m. A unilateral intravenous catheter was inserted into the subjects' forearm for ketamine infusion. Racemic ketamine hydrochloride (Calypsol, Gedeon Richter Plc., Czech Republic) or a placebo (0.9% saline solution) was administered into the right cubital vein using an infusion pump (ID 20/50, Polymed medical CZ Ltd). Ketamine was administered in a loading dose of 0.27 mg/kg for the first 10 min, followed by a maintenance infusion of 0.27 mg/kg within 20 min. These infusion rates were calculated with respect to the pharmacokinetics of ketamine (Hetem *et al.* 2000; Horacek *et al.* 2010) in order to: (a) produce stable ketamine blood levels, (b) apply a total dose very close to clinical studies in depression (Berman *et al.* 2000; Zarate *et al.* 2006), and (c) maximize safety by using a loading dose over 10 min. Ketamine has an elimination half-life of 2 to 2.5 hours with a distribution half-life of 10 to 15 min when given parenterally. To measure ketamine and nor-ketamine serum levels, 2 ml of vein blood was sampled from the left arm 5 min before and 10 and 30 min after the beginning of the infusion.

The possibility of occurrence of side effects such as vivid dreaming, floating sensations, dizziness and blurred vision were explained before treatment and subjects were assured that if the occurred, they would be temporary. Each participant was interviewed and evaluated with the Brief Psychiatric Rating Scale (BPRS) (Overall & Donald 1962) before and 30 minutes after the ketamine/placebo infusion. During and three hours after the session each subject was monitored for any adverse effects.

The subjects were assessed by MADRS, at baseline and subsequently one, four and seven days after each session. Ratings were made by two independent experienced clinical psychiatrists who were trained to the criterion of the intra-class correlation >0.80 for each clinician prior to conducting the ratings.

The primary outcome measures for the study were MADRS score change at day 1, 4 and 7 between ketamine and placebo. The secondary outcomes included response rates (defined as equal to or more than a 50% reduction of the MADRS score) and plasma levels of ketamine and its metabolite nor-ketamine during ketamine infusion (baseline, 10 minutes, 30minutes of the infusion) between ketamine and placebo at the same time points.

Gas Chromatography–Mass Spectrometry (GC-MS)

The GC-MS toxicological method was developed and validated according to international standards (Penders & Verstraete, 2006) for determination of ketamine and nor-ketamine serum levels. The analytical standards nor-ketamine, ketamine and deuterated ketamine (ketamine-D4), supplied as hydrochlorides from Cerilliant, USA, were used for toxicological analyses. For quantitation, the internal standard method was applied using ketamine-D4. Isolation of analytes from blood serum samples was performed using SPEC-DAU discs and analyses were performed with acetyl derivatives using an HP 6890–5973 instrument (Agilent, Germany) operating in electron impact single ion monitoring (SIM) mode. The lower limit of quantification (LLOQ) for ketamine was 50 ng/ml and for nor-ketamine 8 ng/ml. The limit of detection (LOD) for ketamine was 20 ng/ml and for nor-ketamine 1 ng/ml (Horacek *et al.* 2010).

Statistical analyses

Data are expressed as means (standard deviation) or in the case of non-Gaussian distributed measures as medians (inter-quartile range). The baseline clinical data of the groups according to the treatment sequence were compared using the Mann-Whitney test or unpaired t-test, and by Fisher's exact test. The primary efficacy analyses were based on a modified intent-to-treat (ITT) data set, which was defined as the subset of patients who completed a baseline and at least one post-baseline visit after the cross-over. A general linear model for a two-period crossover design with BPRS change during ketamine infusion as a covariate, sequence (placebo-ketamine, ketamine-placebo) as a between-subjects factor, and period (week 1, week 2), treatment (ketamine, placebo) and time (baseline, day 1, day 4, day 7) as the within-subjects factors followed by Bonferroni post-hoc tests was used to compare the changes in MADRS between ketamine and placebo over the study period All repeated measures effects are reported with the original degrees of freedom and Greenhouse-Geisser corrected *p*-values. The differences between treatments were expressed as both the mean score change treatment difference with 95% confidence intervals and Cohen's d. Prescott's test for crossover trials with binary outcomes was used to test for a treatment difference in response rate (≥50% reduction in MADRS) at day 1, 4 and 7. These associations were analysed by Pearson's correlation coefficient: a) between BPRS score change during ketamine administration and MADRS score change at day 1, 4 and 7; b) between ketamine and/or nor-ketamine plasma levels and change in psychometric scales. The statistical analyses were performed using Statistica 9.0 (StatSoft, Inc.).

RESULTS

Demographics

Thirty-eight subjects were screened, of whom 30 depressive subjects who met the inclusion criteria and agreed to participate, were randomized by a flip of a coin (Kishimoto *et al.* 2012). Eight subjects were not included, four of them had comorbidity on Axis I, one of them had a MADRS score under twenty points, three of them decided not to participate. Eleven subjects received ketamine and nineteen received the placebo in Week 1. Two subjects discontinued the study due to a worsening of their depression after the placebo infusion and one subject did not receive ketamine after the placebo infusion (Week 2) because of a maintained placebo response for the week (Figure 1). Thus, twenty-seven patients received the intended treatment and were included in all analyses (intention-to-treat analysis; ITT), 9 of whom were randomized into the K-P group and 18 into the P-K group. In five patients who did not complete all of the visits after crossover analyses were performed using the last observation analysis (LOAN) (Figure 1). The K-P and P-K groups differed in MADRS scores at baseline (t=2.23, df=25, p=0.03). Otherwise, both groups were comparable under the relevant demographic and clinical characteristics (Table 1).

Adverse effects

Ketamine was well-tolerated and no serious adverse or side-effects (other than the expected acute psychotomimetic effect) occurred during the study. Typical effects occurring at subanesthetic doses of ketamine were dissociation/perceptual disturbances, confusion, mild increases in blood pressure, emotional blunting and euphoria. The majority of these effects ceased within 30 minutes after the ketamine infusion. In no case did emotional blunting, euphoria or dissociation persist beyond 60 minutes.

Tab. 1. Demographic and outcome data according to the treatment sequence.

	ketamine first (K-P) (n=11) mean ± SD	placebo first (P-K) (n=19) mean ± SD	Statistical significance level
Age (years)	42.2±15.1	44.6±10.9	NS [a]
Gender (M : F)	5:6	10:9	NS [b]
Duration of depressive disorder (years)	10.2±9.4	10.4±8.3	NS [c]
Duration of current episode (months)	11.2±9.9	11.6±11.5	NS [c]
Number of previous psychiatric hospitalizations	2.2±1.2	3.6±2.4	NS [c]
Baseline MADRS score	20.4±4.7	24.6±4.8	p=0.04 [c]
Treatment before enrolment	SSRI (n=2) NaSSA (n=1) SNRI (n=1) AD comb. (n=5) AD augm. (n=2) BZD (n=6)	SSRI (n=2) NaSSA (n=2) SNRI (n=3) AD comb. (n=7) AD augm. (n=5) BZD (n=7)	NA

[a] Student's t-test; [b] Fisher Exact Test; [c] Mann-Whitney U Test; NA – not applicable; NS – not significant; AD – antidepressant; NaSSA – Noradrenergic and Specific Serotonergic AD; SNRI – Serotonin–Norepinephrine Reuptake Inhibitor; AD comb. – various combinations of AD; AD augm. – augmentation of AD with atypical antipsychotics; BZD – benzodiazepines

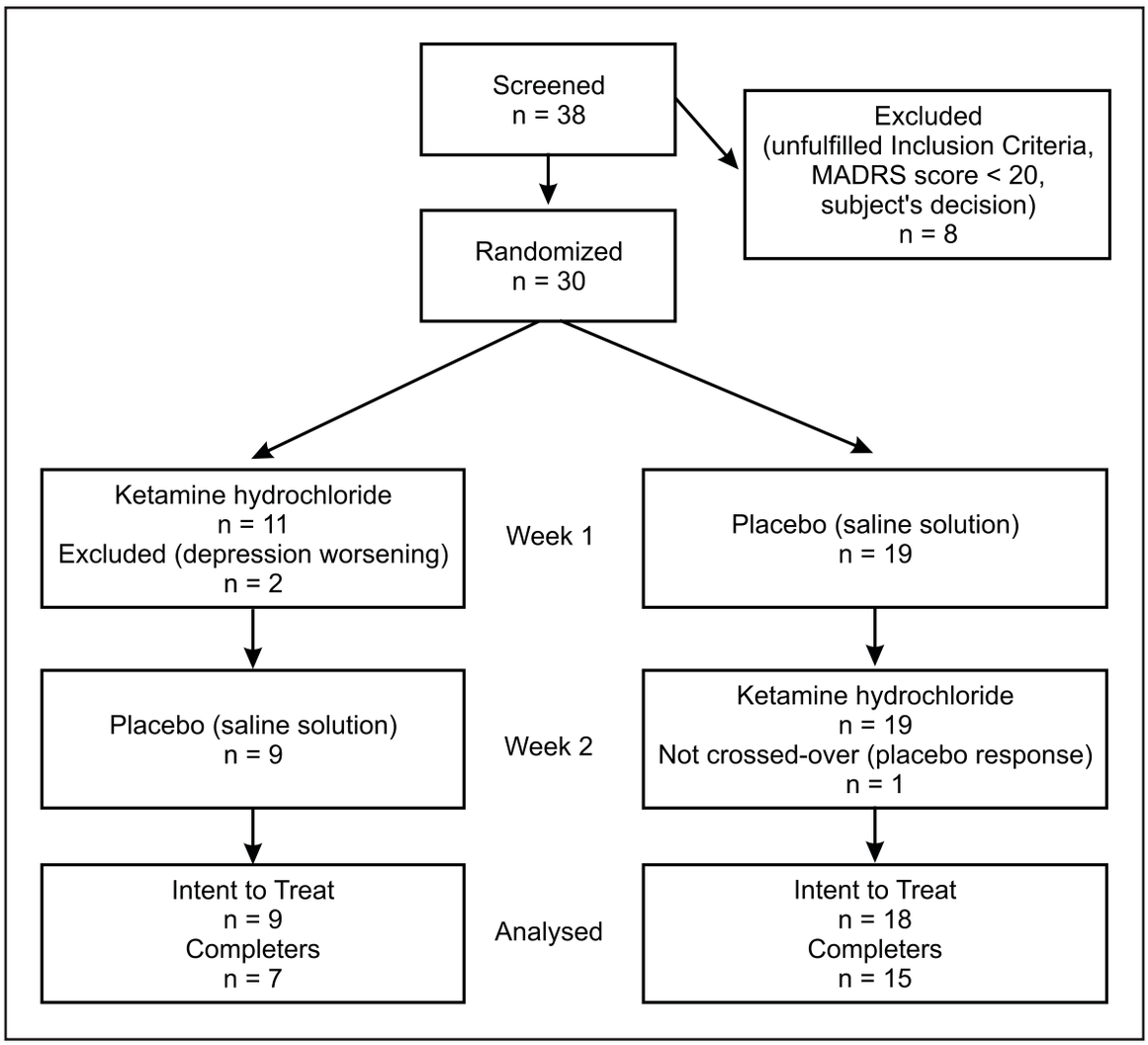

Fig. 1. Patient flow chart

Efficacy

General linear model revealed a treatment effect (F(1,24)=5.87, p=0.03), time effect (F(3,72)=5.58, p=0.002) and treatment to time interaction (F(3,72)=4.11, p=0.01) irrespectively to effect of sequence (F(1,24)=2.05, p=0.17) and period (F(1,24)=3.49, p=0.07), i.e. there were no significant carry-over effects. BPRS score change as a covariate did not achieve statistical significance (p=0.10). In post hoc analysis superiority of ketamine over placebo at all post-infusion visits was found (day 1: p<0.001 day 4: p=0.002; day 7: p=0.02). The mean MADRS total score change differences were 5.7 (95%CI 3.4–7.9) at day 1, 4.7 (95%CI 2.5–7.0) day 4 and 4.0 (95% CI 1.8–6.2) at day 7 (Figure 2). Effect sizes (Cohen's d) were 0.62 at day 1, 0.57 at day 4, and 0.44 at day 7.

Comparison of categorial responses to the placebo vs. ketamine showed a significantly higher number of responders to ketamine compared to the placebo at day 1 (ketamine n=10 (37.0%), placebo n=1 (3.7%); Prescott's test, p=0.008) at day 4 (ketamine n=11 (40.7%), placebo n=1 (3.7%); Prescott's test, p=0.003) and at day 7 (ketamine n=10 (37.0%), placebo n=3 (11.1%); Prescott's test p=0.02, respectively). Additionally, 10 patients were classified as responders to ketamine on at least two visits and 5 of them remained responders from day 1 to day 7 in comparison with none such responder to placebo.

When we analysed association between the BPRS total score and the MADRS score changes there was a significant correlation at day 7 (r=–0.40, p=0.04) and trend toward to significance at day 1 (r=–0.37, p=0.06) and day 4 (r=–0.36, p<0.07) were found (Figure 3). No significant correlations were demonstrated when the same analyses were applied to the BPRS subscales.

Ketamine and nor-ketamine serum levels

Neither ketamine nor its metabolite nor-ketamine was detectable in the placebo or in the active ketamine session at baseline. In the case of ketamine infusion, the serum levels increased after 10 min and 30 min for ketamine (306±136 ng/ml, resp. 237±95 ng/ml) and its metabolite nor-ketamine (11±7 ng/ml, resp. 50±21 ng/ml). There were no differences found between responders and non-responders in ketamine and/or nor-ketamine serum levels.

Further, no correlations were found between change in total BPRS score and ketamine or nor-ketamine plasma levels. Significant correlation was found only between BPRS Anergia Factor (emotional withdrawal, motor retardation, blunted affect and disorientation) and nor-ketamine plasma level after 10 min of infusion (r=–0.47, p<0.05).

DISCUSSION

To our knowledge, this study is the first *a priori* to examine the relationship between psychotomimetic symptoms and antidepressant efficacy of a single ketamine infusion in patients with major depressive disorder.

We found a significant correlation between, the two temporally distinct ketamine's effects, the intensity of transient altered mental function (as measured by the BPRS score) during ketamine administration and lessening of core symptoms of depression (as measured by the MADRS score) during the following week with maximum on day seven. The extent of psychotomimetic symptoms was similar to that reported in other ketamine studies of major depressive disorder and bipolar depression (Diazgranados *et al.* 2010b). As

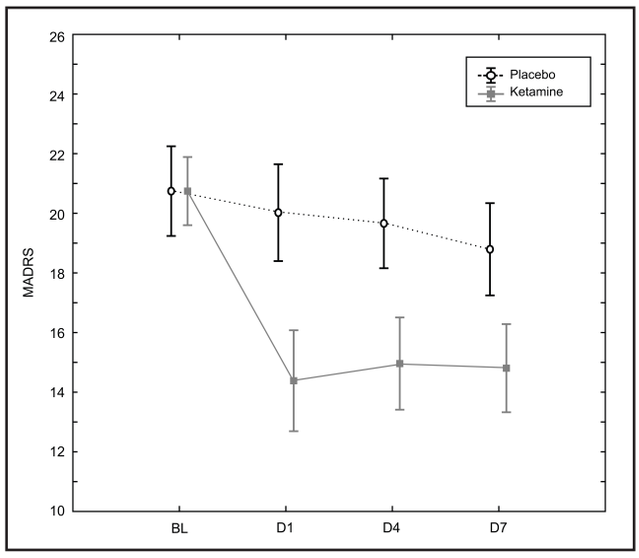

Fig. 2. Superiority of ketamine over placebo at all post-infusion visits was found (day 1: p<0.001 day 4: p=0.002; day 7: p=0.02).

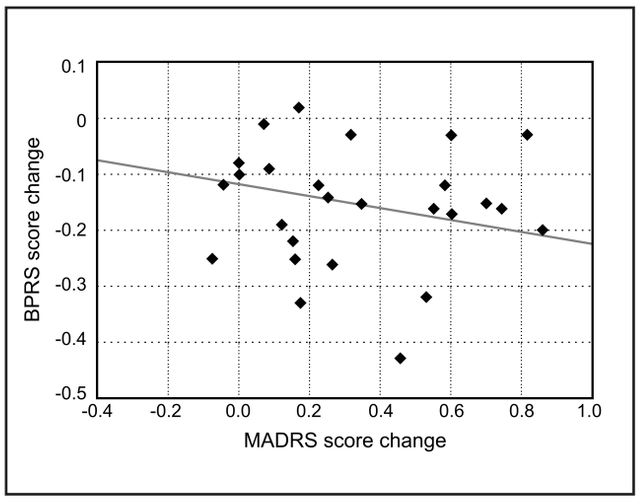

Fig. 3. Association between BPRS score change during acute administration of ketamine and MADRS score change at day seven, analysed by Pearson's correlation coefficient (r=–0.40, p=0.04).

noted by others, (Zarate *et al.* 2006), there was a trend, but not significance, for an inverse relationship between HDRS (Hamilton Depression Rating Scale) scores at day 1 and peak change in BPRS positive symptoms subscale scores.

This study supports previous findings of robust, rapid (hours), and relatively prolonged (1 week) antidepressant action with single dose of ketamine (summarized in Bunney & Bunney 2011). In our study, the strongest effect size was found at the first day after infusion during a one week period. When comparing our results with the study by Zarate *et al.* (2006), we found smaller effect-size for the drug difference (0.44 vs. 0.68), but similar magnitude of response rate (37% vs. 35%) one week after the ketamine infusion.

Both, the intensity of transient altered mental function (Passie *et al.* 2003), and improvement in mood ratings, are dose-dependent and occur with low to medium doses (Horacek *et al.* 2010). In our study, a moderate correlation was found between BPRS Anergia Factor (emotional withdrawal, motor retardation, blunted affect and disorientation) and nor-ketamine plasma level after 10 mins of infusion ($r=-0.47$, $p<0.05$). This can be supported by evidence that ketamine may primarily induce negative symptoms through its direct inhibition of the NMDA receptor (Stone *et al.* 2008). No correlations were found between psychotomimetic (positive BPRS) symptoms or depressive symptoms (MADRS score) change and ketamine or nor-ketamine plasma levels. This fact supports our hypothesis that the early ketamine effects initiate subsequent downstream signalling processes, which are not directly related to ketamine and nor-ketamine blood levels (Horacek *et al.* 2010).

The leading neurobiological theory for the antidepressant effects of ketamine is that its antagonistic activity at NMDA receptors leads to diversion of glutamate signalling to AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionate) receptors. Increased extracellular glutamate or serotonin in the prefrontal cortex could contribute to the psychotropic effects of ketamine (Skolnick *et al.* 2010). Furthermore, the incidence of psychotomimetic effects after administration of NMDA receptor antagonists appears to correlate with the following factors: 1) the affinity of the drug for the PCP binding site of the NMDA receptor complex (Kornhuber & Weller 1997); 2) individuals expectations; 3) the setting; and 4) the dose of the drug (Dalgarno & Shewan 1996). In addition, it can be speculated that the sensitivity of NMDA receptors to ketamine predicts the acute subjective effects and the outcome of antidepressant treatment.

Several factors limit interpretations of our data. Despite our sample size was relatively small, in comparison with previous randomized, placebo controlled studies with ketamine (summarized in Bunney & Bunney 2011), it ranks among the most populated studies and the effect sizes were relatively large. Consistent with previous studies, we also used inactive placebo without psychotomimetic properties, which could have affected the study blind. Rather than the flip of a coin a block randomization design with equal sizes of the sample groups would have been preferable.

CONCLUSION

The results of our study show the substantial relationship between ketamine's antidepressant and psychotomimetic effects. This relationship could be mediated by the initial steps of ketamine's action, trough NMDA receptors, shared by both ketamine's clinical effects. These effects are not directly related to ketamine and nor-ketamine blood levels. Further studies should address the question if the sensitivity of NMDA receptors to ketamine predicts the acute subjective effects and the outcome of antidepressant treatment.

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Conflict of Interest Statement

The Authors declare that there is no conflict of interest.

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