Masarykova univerzita v Brně

Lékařská fakulta

Studium elektrofyziologických projevů vyšších funkcí mozku člověka pomocí intracerebrálních elektrod

Habilitační práce

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Souhrn

Schopnost člověka odpovědět dohodnutým způsobem na definovaný podnět je podmíněna řadou mozkových procesů, které jsou podkladem senzorického zpracování podnětů, kognitivních a exekutivních funkcí. V předkládaném souboru prací jsme se zaměřili na studium jejich elektrofyziologických korelátů registrovaných intracerebrálně u pacientů s farmakorezistentí formou epilepsie. Tito pacienti souhlasili s účastí ve studiích, schválených etickou komisí Masarykovy univerzity, probíhajících v rámci epileptochirurgické léčby epilepsie na 1. neurologické klinice u Sv. Anny v Brně. V průběhu hospitalizace pacienti prováděli různé kognitivní úkoly při současné intracerebrální registraci EEG. Výzkumně se přímá registrace elektrické aktivity neuronálních populací lidského mozku využívá pouze na několika specializovaných světových pracovištích. Umožňuje však vyšetřit pouze omezený rozsah oblastí mozku, protože hluboké elektrody jsou implantovány v limitovaném počtu a výhradně na základě klinické potřeby bez jakékoli vazby na výzkumné úkoly.

V úvodní části habilitační práce je popsána metodika intracerebrální (intrakraniální) registrace elektrické aktivity mozku člověka a její výzkumné využití. V navazující části jsou komentovány výsledky prací, zaměřených na studium jednotlivých složek elektrofyziologické odpovědi mozku snímané v průběhu kognitivních úkolů. Základním přístupem byla analýza evokovaných potenciálů, označovaných jako „event-related potentials“ (ERPs), které získáme zprůměrněním obvykle několika desítek EEG odpovědí od okamžiku prezentace podnětů. V nejvíce studovaném zrakovém oddball úkolu byla náhodně prezentována písmena „X“ (terčové podněty) a „O“ (neterčové podněty) v poměru 1:5. Pacienti byli instruováni reagovat stiskem tlačítka pouze na výskyt terčového podnětu, který současně počítali. Výsledky našich studií potvrdily, že terčové a neterčové podněty jsou v mozku zpracovávány dvěma různými způsoby. První, obecnější způsob zahrnuje procesy senzorické, pozornostní, paměťové a rozhodovací, které jsou součástí základní analýzy externích podnětů bez ohledu na jejich význam. V řadě vyšetřených struktur (např. gyrus cinguli, gyrus parahipokampalis, gyrus temporalis superior, medius a inferior, hipokampus a frontoorbitální kortex) by tomu odpovídal nález identických ERP komponent po obou typech podnětů. Druhý způsob zpracování již zohledňuje asociaci podnětu s dohodnutou odpovědí, případně jeho méně častý výskyt v rámci úkolu, a zahrnuje opět kognitivní, ale také exekutivní a kontrolní funkce. Elektrofyziologickým korelátem těchto funkcí jsou pravděpodobně jednotlivé kognitivní komponenty ERPs, např. vlna P3. Na základě analýzy časového vztahu této vlny k okamžiku prezentace podnětu a

motorické odpovědi se nám podařilo prokázat, že intracerebrální vlna P3 je heterogenní fenomén. Velmi pravděpodobně odráží buď vyhodnocení významu podnětu, nebo exekutivní funkce anebo pozornostní a integrativní funkce. Ve studii zaměřené na analýzu kognitivního ERP generovaného v hipokampu člověka v průběhu jednoduchého senzorimotorického úkolu jsme následně ukázali, že hipokampální kognitivní potenciál s latencí kolem 420 ms nesouvisí s provedením motorické odpovědi a zřejmě odráží vyhodnocení významu podnětu v kontextu experimentální situace.

V další studii jsme se zaměřili na lokalizaci neuronálních populací, které v průběhu oddball úkolu po prezentaci podnětů vykazují fázově nekoherentní změny EEG aktivity. Signifikantní změny amplitudy EEG oscilací ve frekvenčním pásmu alfa a beta byly identifikovány v různých oblastech mozku bez specifické vazby na konkrétní struktury. Po terčových podnětech jsme častěji pozorovali nárůst výkonu EEG oscilací v alfa pásmu, který by mohl ukazovat na aktivaci neuronálních sítí zajišťujících motorickou odpověď. Po neterčových podnětech byl převažujícím nálezem pokles výkonu EEG oscilací v alfa i beta pásmu, který by mohl odrážet převahu inhibičních procesů souvisejících s neprovedením stisku tlačítka. Identifikované změny výkonu jsou zjevně vázány na odpověď subjektů, jejich jasná interpretace však doposud chybí.

Intracerebrální registraci EEG dat jsme také využili k mapování potenciálů, které odrážejí aktivaci neuronálních systémů zajišťujících kontrolu správnosti odpovědi jedince na podněty z jeho okolí. Generátory tzv. „error“ potenciálů vázaných na chybnou odpověď subjektu v Go/NoGo úkolu jsme našli v řadě oblastí frontálního a temporálního laloku, např. v gyrus cinguli anterior (ACC), gyrus frontalis medialis, dorzolaterálním prefrontálním kortexu (DLPFC), orbitofrontálním a laterálním temporálním kortexu. Z našich výsledků navíc vyplynulo, že kaudální a rostrální část ACC patrně hrají odlišnou roli při zpracování chybné odpovědi. V další studii jsme se zaměřili na lokalizaci jiné skupiny potenciálů vyvolaných v oddball úkolu až po provedení odpovědi správné. Opět se ukázalo se, že v rámci vyšetřených mozkových struktur existují minimálně dvě funkčně odlišné neuronální sítě, přičemž účast jedné byla specifická pouze pro terčové odpovědi, u druhé byla její aktivace na typu podnětu nezávislá. Navíc se podařilo identifikovat některá místa v ACC, DLPFC, primárním motorickém a laterálním temporálním kortexu, která se podílela současně i na hodnocení odpovědí chybných. Z výsledků výše uvedených prací vyplývá, že jedna anatomická struktura může být součástí několika neuronálních sítí, které jsou strukturálním podkladem různých funkcí.

Intracerebrální EEG data snímaná ve zrakovém oddball úkolu nám však také umožnila studovat hierarchicky vyšší úroveň organizace mozkových funkcí, konkrétně funkční konektivitu aktivovaných oblastí. Výpočtem korelací EEG signálů ve frekvenčním pásmu beta se ukázalo, že nejvýznamnější roli při komunikaci mezi frontálními a temporálními oblastmi mozku hraje gyrus cinguli. S použitím výpočtu „directed transformation function“ se nám podařilo také demonstrovat, že při zpracování podnětů spojených s aktivní odpovědí se v rámci frontálního laloku informace šíří směrem z gyrus cinguli do dorzolaterálního prefrontálního kortexu. Výsledky těchto studií dokládají klíčové postavení předního gyrus cinguli při řízení chování jedince.

Summary

The human ability to respond to specific stimuli arises from neuronal activity associated with sensory processing of information as well as cognitive and executive functions. The presented set of original papers studies intracerebrally recorded electrophysiological correlates of neuronal processing in patients with medically intractable epilepsy. All studies were approved by the Ethical Committee of Masaryk University and all patients agreed to participate and perform several cognitive tasks while their intracerebral EEG was continuously recorded during their stay in the hospital. Such direct investigation of the electrical activity of the human brain is possible only at very few clinical departments in the world. The possible limitation of the intracerebral EEG method, however, is the fact that the depth electrodes are implanted solely on clinical grounds and without any reference to the experimental protocols.

The first part of the text introduces the method of intracranial electroencephalography and explains its value for research. The following part includes comments of our papers where we examined different components of the electrophysiological brain responses recorded during various cognitive tasks. We used the analysis of evoked potentials, i.e. event-related potentials (ERPs), obtained by averaging of several EEG epochs triggered by the presented stimuli. In the most investigated oddball paradigm, the letter "X" was used as a target stimulus and the letter "O" as a nontarget stimulus in the ratio 1:5. Patients were instructed to press a button after the target stimuli and count them silently. Our findings confirmed that the brain processes the target and non-target stimuli in two different ways. The first, more general processing, could represent a basic analysis of the external stimuli regardless of their specific meaning and includes e.g. sensory processing, attention, memory and decision making. The evidence comes from the findings of identical early and late ERP components evoked after the target and non-target stimuli in various brain structures, e.g. cingulate gyrus, parahippocampal gyrus, superior, middle and inferior temporal gyri, hippocampus, and frontoorbital cortex. The second type of processing takes into account the association between the stimulus and the required response or the salience of the stimulus. Electrophysiological correlates of such processes can be represented by intracerebrally recorded cognitive ERP components, e.g. the P3-like waveform, that can be associated with cognitive, executive and control functions. Our analysis of the temporal relationship of the P3-like waveform to the stimulus and motor response demonstrated that this component is a heterogeneous phenomenon. It might reflect stimulus evaluation, executive functions or attentional and integrative functions. Our next study analysed

the temporal characteristics of large negative ERP generated in the human hippocampus during a simple sensorimotor task. We demonstrated that the hippocampal cognitive potential with latency of about 420 ms occurs independently of motor execution and within the context of situation it is most likely related to the evaluation of stimulus meaning.

Our next study aimed to localize neuronal populations that exhibit changes of non-phase locked EEG oscillatory activity after a presentation of stimuli during a cognitive task. The significant changes in alpha and beta frequency bands were identified in different frontal and temporal areas without a specific relationship to a particular structure. The target stimuli induced power increase in EEG oscillations in alpha frequency band. This could be related to the activation of neuronal networks functionally linked to the motor response. The non-target stimuli induced power decrease in EEG oscillations in alpha and in beta frequency bands that could reflect inhibition processes associated with refraining from motor response. It is evident that identified power changes are locked to the subject`s response but their functional meaning is not known yet.

We also utilised the intracerebral EEG data to map the distribution of the ERPs related to the activation of the brain's performance monitoring system. We found generators of the potentials elicited after erroneous responses during Go/NoGo task in various cortical areas of frontal and temporal lobes, e.g. anterior cingulate gyrus (ACC), medial frontal gyrus, dorsolateral prefrontal cortex (DLPFC), orbitofrontal and lateral temporal cortices. Our findings demonstrated a different involvement of the rostral and caudal ACC in error processing. A follow-up study aimed to localise late postperformance ERPs evoked after correct responses to the oddball task. We found two functionally distinct neural networks within the examinand brain regions. While the first network responded only to the target stimuli, the second network responded independently of a stimulus type. Furthermore, we were able to identify several sites in ACC, DLPFC, primary motor and lateral temporal cortices that were simultaneously engaged in evaluation of erroneous responses. Overall, our findings demonstrated that one anatomical structure can be part of functionally distinct neuronal networks.

The intracerebral EEG data recorded during the visual oddball task allowed us the investigation of functional organization of the brain and particularly the investigation of functional connectivity between the activated brain areas. Correlation analysis of EEG signals in beta2 frequency band revealed a prominent role of cingulate gyrus in communication between frontal and temporal brain areas. Using the calculation of "directed transformation

function", we also showed that the directionality of the information flux in frontal lobe during processing of stimuli associated with active response was from anterior cingulate gyrus to dorsolateral prefrontal cortex. The findings of these two studies demonstrate the key role of cingulate gyrus in human behaviour control.

Obsah

Seznam použitých zkratek

ACC	anterior cingulate cortex (přední cingulární kortex)
CNS	centrální nervový systém
CRN	correct-related negativity
DLPFC	dorsolateral prefrontal cortex (dorzolaterální prefrontální kortex)
DTF	directed transformation function
EEG	elektroencefalografie, elektroencefalogram
ERD	event-related desynchronization
ERN	error-related negativity
ERPs	event-related potentials
ERS	event-related synchronization
FFT	fast Fourier transform (rychlá Fourierova transformace)
iEEG	intracerebrální (intrakraniální) elektroencefalografie
fMRI	functional magnetic resonance imaging (funkční magnetická rezonance)
LFPs	local field potentials
MEG	magnetoencefalografie
MRI	magnetic resonance imaging (magnetická rezonance)
P3	vlna P3
P3-like	intracerebrální vlna P3
SEEG	stereoelektroenecefalografie
SMA	suplementární motorická area

I. Úvod

Při studiu mozku a chování se používá řada vyšetřovacích technik, např. elektroencefalografie (EEG), magnetoencefalografie (MEG) nebo funkční magnetická rezonance (fMRI). Elektroencefalografie má ve zmíněné skupině technik zvláštní postavení, protože umožňuje zaznamenávat jeden ze základních projevů činnosti nervového systému, tedy elektrickou aktivitu mozku. Vedle rutinního skalpového způsobu snímání lze elektrickou aktivitu neuronů a neuronálních populací registrovat také přímo pomocí elektrod implantovaných do mozku člověka. V takovém případě hovoříme o intracerebrální elektroencefalografii (iEEG; někdy se používá obecnější název intrakraniální EEG, který označuje i snímání subdurálními nebo intrakortikálními elektrodami). Metodu iEEG zavedl do klinické praxe v České republice v 90. letech minulého století prof. MUDr. I. Rektor, CSc. z 1. neurologické kliniky u Sv. Anny v Brně. Dodnes je na tomto pracovišti využívána za účelem lokalizace epileptického ložiska u pacientů s farmakorezistentním typem epilepsie vybraných do epileptochirurgického programu.

Po mém nástupu na Fyziologický ústav LF MU bylo klíčovým momentem volby mé vědecké orientace navázání spolupráce prof. MUDr. M. Kuklety, CSc. z našeho ústavu s prof. MUDr. I. Rektorem, CSc. z 1. neurologické kliniky u Sv. Anny v Brně v rámci projektu „Plasticita řídicích systémů centrálního nervového systému a možnosti jejího ovlivnění (MSM141100001)“ a následně projektu „Vnitřní organizace a neurobiologické mechanismy funkčních systémů CNS (MSM0021622404)“, na jejichž řešení jsem se podílel. V rámci obou projektů probíhaly na neurologické klinice studie schválené etickou komisí Masarykovy univerzity, ve kterých pacienti se zavedenými hlubokými elektrodami v průběhu diagnostického monitorování souhlasili s tím, že budou provádět různé jednoduché kognitivní úkoly při současném iEEG nahrávání.

Stal jsem se členem řešitelského týmu, který spolupracoval na některých studiích s prof. MUDr. M. Brázdilem, PhD. Ze začátku jsme využili možnost analyzovat iEEG data, která prof. Brázdil nasnímal u skupiny 20 pacientů v průběhu jednoduchého zrakového oddball úkolu. V dalších letech jsme se vedle analýzy iEEG dat podíleli i na jejich získávání u dalších pacientů v průběhu jiných kognitivních úkolů, jako např. jednoduchého senzorimotorického úkolu nebo tzv. Go/NoGo úkolu. Jejich společným jmenovatelem je prezentace jednoho nebo střídavě dvou typů podnětů, přičemž úkolem subjektu je domluveným způsobem (např. stiskem tlačítka) reagovat na výskyt pouze jednoho typu podnětu. Uvedené úkoly tak nabízejí jedinečnou možnost studovat intracerebrální elektrofyziologické koreláty neuronálních procesů

souvisejících např. se senzorickou diskriminací podnětů, hodnocením významu podnětů, pamětí, rozhodováním, přípravou a provedením motorické odpovědi. Zmiňované funkce jsou podkladem schopnosti člověka odpovědět dohodnutým způsobem na definovaný podnět.

Všechny uvedené práce předloženého souboru vycházejí z analýz iEEG registrovaného v průběhu kognitivních úkolů u epileptických pacientů a jsou vždy výsledkem týmové spolupráce. Osobně jsem se různou měrou podílel na získávání, analýze dat a publikovaní výsledků, které v habilitační práci uvádím se souhlasem spoluautorů. V komentovaném souboru osmi prací jsem u čtyř z nich (příloha 1,2,4 a 6) první nebo korespodující autor, u zbývajících pak jako spoluator.

II. Intracerebrální (intrakraniální) elektroenecefalografie

S intracerebrálním EEG se poprvé setkáváme již ve 30. letech 20. století (Jaspers a Carmichael, 1935) relativně brzy po prvním použití skalpové elektroencefalografie u lidí (Berger, 1929). Za účelem diagnostickým a terapeutickým byla iEEG do klinické praxe zavedena ve 40. letech 20. století. V popředí zájmu byla v té době bazální ganglia (Meyers a Hayne, 1948; Knott et al., 1950) nebo thalamus (Ishikawa, 1957). Od 50. let se hluboké EEG začalo využívat u pacientů s epilepsií (Penfield a Baldwin, 1952; Rasmussen a Jasper, 1958), protože se v té době vylepšila technika umístění elektrod (Talairach et al., 1952, 1958). K širšímu využití se dostáváme až se vznikem stereotaktického atlasu, který poskytoval prostorové koordináty pro stereotaktickou exploraci různých struktur (Talairach a Tournoux, 1988; Talairach et al., 1967). Na základě vyšetření několika desítek epileptických pacientů potom vznikl i atlas intrakraniální elektroencefalografie (Sperling, 1993).

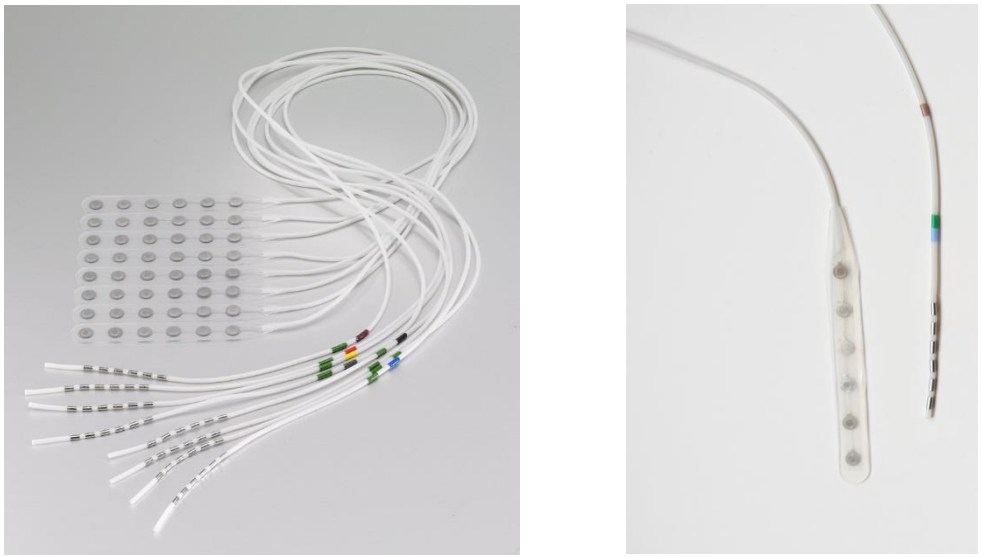
Metodou iEEG je nejvíce vyšetřovaná skupina pacientů s farmakorezistentním typem epilepsie, méně často pak pacienti s onemocněním bazálních ganglií, těžkými bolestmi anebo s mozkovým nádorem (Niedermeyer, 2005). U epileptických pacientů jsou elektrody ponechány v mozku několik dní za účelem lokalizace epileptogenní zóny v rámci přípravy operační léčby epilepsie. V průběhu hospitalizace pacienti mohou souhlasit, že budou provádět různé kognitivní úkoly při současném iEEG nahrávání. Na tomto místě je nutné uvést, že umístění elektrod a trvání diagnostického postupu je určeno výhradně klinickými požadavky bez jakékoli vazby na výzkumné úkoly. I přesto však získaná data poskytují unikátní pohled na fungování lidského mozku. Pacienti mohou z účasti ve zmiňovaných úkolech také profitovat, protože na základě získaných informací je možné určit specifické funkční oblasti mozku v blízkosti epileptického zdroje, které nemohou být chirurgicky odstraněny právě z důvodů

jejich prokázaného funkčního zapojení do klíčových kognitivních procesů. Zkoumání mozkových funkcí touto cestou navíc umožňuje pochopit, jak mohou kognitivní procesy souviset s mozkovou aktivitou, podílející se na vzniku záchvatu (Lachaux et al., 2003).

Intracerebrální (intrakraniální) EEG registruje extracelulární elektrickou aktivitu mozku dvojího typu. Jednak může snímat akční potenciály generované jednotlivými neurony nebo malým počtem neuronů – „single“ nebo „multi units recording“. Tento typ aktivity odpovídá výstupním signálům nervových buněk. Druhý typ představují elektrické signály, které jsou výsledkem činnosti větších populací neuronů v blízkosti snímacího kontaktu. V zahraniční literatuře se označují termínem „local field potentials“ (LFPs). Předpokládá se, že odrážejí sumární synaptickou aktivitu na dendritech neuronů, tedy vstupní signály neuronů (Mukamel et al., 2012; Lachaux et al., 2003).

II.1. Typy snímacích elektrod

Při registraci intrakraniální EEG se používá několik typů elektrod – subdurální, intrakortikální a hluboké (Marusič et al., 2006). Subdurální elektrody se implantují pod tvrdou plenu a umísťují se nejčastěji nad konvexitou hemisfér, případně mohou zasahovat i na jejich bazální plochu. Vyrábějí se ve dvou variantách, jako tzv. gridy nebo stripy (obr.1).

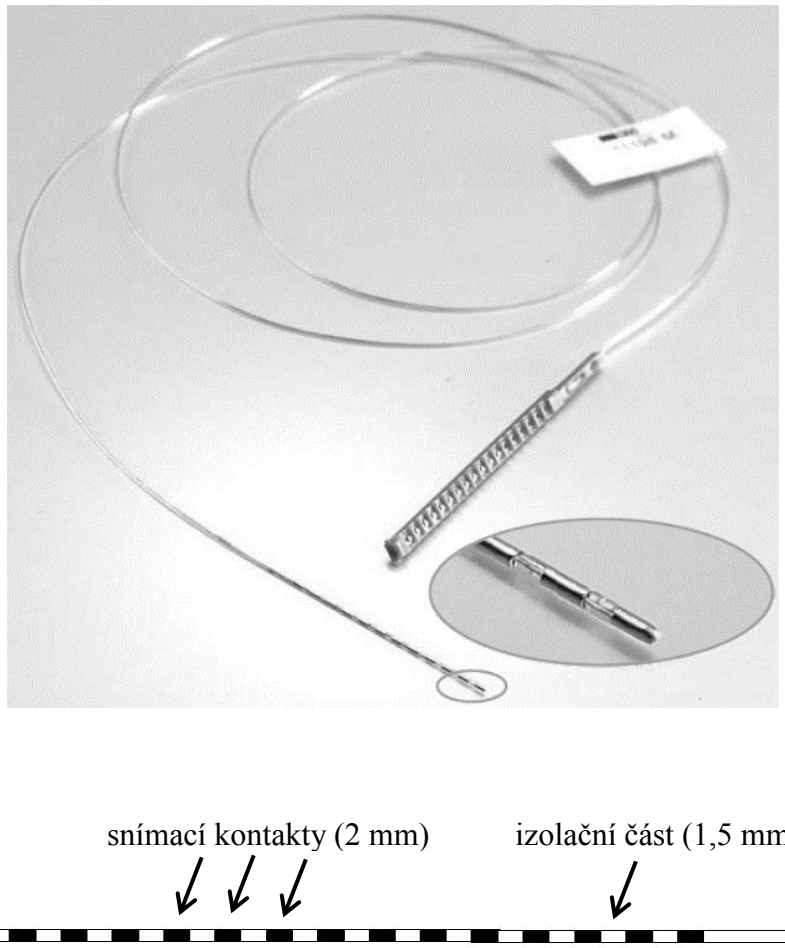


Obr. 1 Subdurální elektrody: vlevo - grid, vpravo - strip. (zdroj: http://www.diximedical.com)

V obou případech se jedná o diskové elektrodové kontakty z neparamagnetického kovu (platinové případně platino-iridiové) nebo z oceli o velikosti 2-5 mm, které jsou uchycené v biologicky inertním flexibilním materiálu. V provedení strip jsou kontakty seřazeny do jedné řady v počtu 4 až 8 na jednom proužku. Ve variantě grid jsou kontakty uspořádány do mřížky v počtu 8×2 až 8×8. Vzdálenost mezi středy sousedních kontaktů v obou variantách bývá 1 cm. Výhodou subdurálních elektrod (zejména gridů) je registrace LFPs z relativně velké plochy hemisfér.

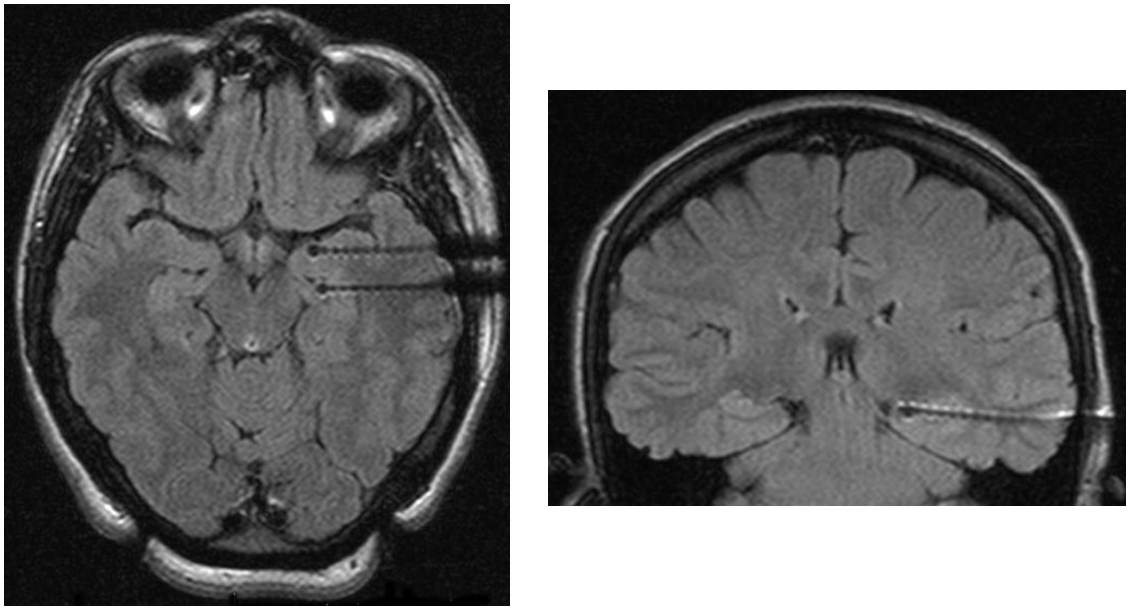
Intrakortikální elektrody jsou v porovnání se subdurálními elektrodami invazivnější, protože pronikají do kortexu do hloubky několika milimetrů. Registrovaným signálem v tomto případě je jednotková aktivita neuronů. Snímá se z malého prostoru např. ze 100 kontaktů při uspořádání elektrod do mřížky v počtu 10×10 na ploše cca 3×3 mm (tzv. „Utah array", Hochberg et al., 2006). Jiný způsob uspořádání kontaktů na jedné elektrodě tvaru připínáčku umožňuje snímání z 22-24 kontaktů o průměru 40 mikrometrů vzdálených od sebe 75-200 mikrometrů (Ulbert et al., 2001a). V souvislosti s prvním typem intrakortikální registrace může být zajímavé, že s pomocí těchto elektrod dlouhodobě implantovaných do primárního motorického kortexu kvadruplegického pacienta byl záznam aktivity neuronálních populací vázaných na zamýšlený pohyb počítačově dekódován a následně úspěšně využit k ovládání periferních zařízení - pohyb robotickou paží, zapínání televize a otevírání mailů. Jedná se o první studii dokládající možnosti funkčního použití rozhraní mozek-stroj (Hochberg et al., 2006).

Hluboké elektrody jsou nejinvazivnější variantou při snímání iEEG, protože pronikají hluboko do mozkového parenchymu. V české odborné literatuře se také označují termínem intracerebrální. Využívají se zejména pro registraci z hlubokých mozkových struktur, které nelze snímat výše uvedenými typy elektrod. Nejčastěji jsou vyšetřovány struktury meziotemporální – amygdala a hipokampální formace, dále inzulární, cingulární a frontoorbitální kortex, bazální ganglia, případně thalamus. Z důvodů MRI kompatibility se používají platinové kontakty v počtu 4 až 18 na jednu jednorázovou semiflexibilní elektrodu. Průměr elektrody je 0,8 mm, velikost kontaktu je 2 mm a vzdálenost mezi kontakty 1,5 mm (obr. 2). Používají se různé délky elektrod v závislosti na hloubce uložení cílové vyšetřované struktury - 5, 10, 15 nebo 18 kontaktů. Elektrody mohou být zaváděny ortogonálně (obr. 3), tedy z laterálního přístupu kolmo na sagitální rovinu nebo diagonálně, tzn. šikmo z frontálního nebo okcipitálního přístupu (Marusič et al., 2006).



Obr. 2 Nahoře: hluboká elektroda používaná v klinické praxi při registraci iEEG. V elipsovém výběru je detail koncové části elektrody se třemi kontakty. Dole: schematické znázornění elektrody. (Zdroj: http://www.diximedical.com).

Vlastní implantaci elektrod předchází získání detailních strukturálním MRI snímků, které se převádějí do trojrozměrného modelu mozku ve vztahu ke kontrastním značkám a stereotaktickému keramickému MRI kompatibilnímu rámu. Při následném plánování se hledá co možná nejpřesnější pozice elektrody ve vztahu k anatomické struktuře, která má být vyšetřena. Současně se vybírá cesta implantace s nejmenším rizikem poškození cévních struktur. Zavedení elektrody provádí neurochirurg pomocí speciální dvojité mřížky upevněné na stereotaktický rám (Marusič et al., 2006). Po zavedení elektrod se provádí kontrolní MRI k upřesnění jejich lokalizace. Vlivem nehomogenity magnetického pole na rozhraní elektroda-tkáň je šířka elektrody v tomto zobrazení větší, než je její šířka skutečná (obr. 3).



Obr. 3 Příklady MRI snímků mozku s hlubokými elektrodami implantovanými ortogonálně do temporálního laloku. Vlevo: řez horizontální, vpravo: řez koronální. Tloušťka zobrazených elektrod je na snímcích z důvodu nehomogenity magnetického pole větší než ve skutečnosti, kdy je její průměr 0,8 mm.

Popsané hluboké elektrody s kontakty o velikosti 2 mm a nízké impedanci registrují LFPs. Při určité modifikaci však mohou snímat i jednotkovou (nebo vícejednotkovou) aktivitu. Lze toho například dosáhnout umístěním mikrokontaktů na špičku makroelektrody (Fried et al., 1999). Jinou možností je tzv. hybridní elektroda, na které se střídají kontakty s nízkou impedancí s kontakty s vysokou impedancí (Howard et al., 1996).

Synonymem monitorace elektrické aktivity při použití hlubokých elektrod je termín stereoelektroencefalografie (SEEG), který začali prosazovat stoupenci Pařížské školy (Bancaud, 1959; Talairach et al., 1952). Tento pojem zdůrazňuje skutečnost, že metoda je založena na stereotaktických principech a s její pomocí se elektrická aktivita registruje ve 3D prostoru a navíc současně se skalpovým snímáním EEG (Niedermayer, 2005).

Dle trvání implantace elektrod do nervové tkáně lze snímání elektrické aktivity dělit na akutní (na operačním sále), krátkodobé (za hospitalizace v nemocnici) a dlouhodobé (pro rozhraní mozek-stroj). Akutní snímání se provádí během neurochirurgického výkonu a trvá řádově v minutách, zatímco u hospitalizovaných pacientů se zavedenými elektrodami se elektrická aktivita snímá kontinuálně řádově ve dnech.

II.2. Referenční elektroda

Stejně jako u skalpového EEG, i pro intrakraniální snímání je klíčová co možná nejvíc neutrální referenční elektroda, vůči které se signál na každém kontaktu měří. Kolísání elektrického pole v blízkosti referenční elektrody by mělo být minimálně o řád nižší než kolísání elektrického pole zachycené hlubokými elektrodami a to ve všech frekvenčních pásmech (Lachaux et al., 2003). Tuto podmínku splňují např. spojené elektrody ušní, které však na druhou stranu mohou být kontaminovány svalovými artefakty případně očními pohyby. Minimalizovat vliv externích zdrojů umožňují referenční elektrody umístěné uvnitř lebky. V praxi se používá tzv. snímání bipolární, kdy se měří napětí mezi sousedními kontakty a referenční elektroda je tak pro každou dvojici jiná. Druhou možností je použití průměrné hodnoty ze všech intrakraniálních kontaktů. K určení zdroje elektrické aktivity je pak výhodné data prohlížet v obou způsobech zapojení.

Poměr signál-šum je u iEEG vyšší než u skalpového EEG, protože mezi registrační elektrodou a nervovou tkání se nenachází bariéry (kost, kůže, vlasy), které by signály z mozku oslabovaly. Při použití vhodné referenční elektrody jsou iEEG data zatížena svalovými artefakty a pohyby očí minimálně. Díky uvedeným skutečnostem pak tato metoda umožňuje jako jediná snímat vysokofrekvenční složky elektrické aktivity mozku, které jsou jinými metodami nedostupné (Lachaux et al., 2012).

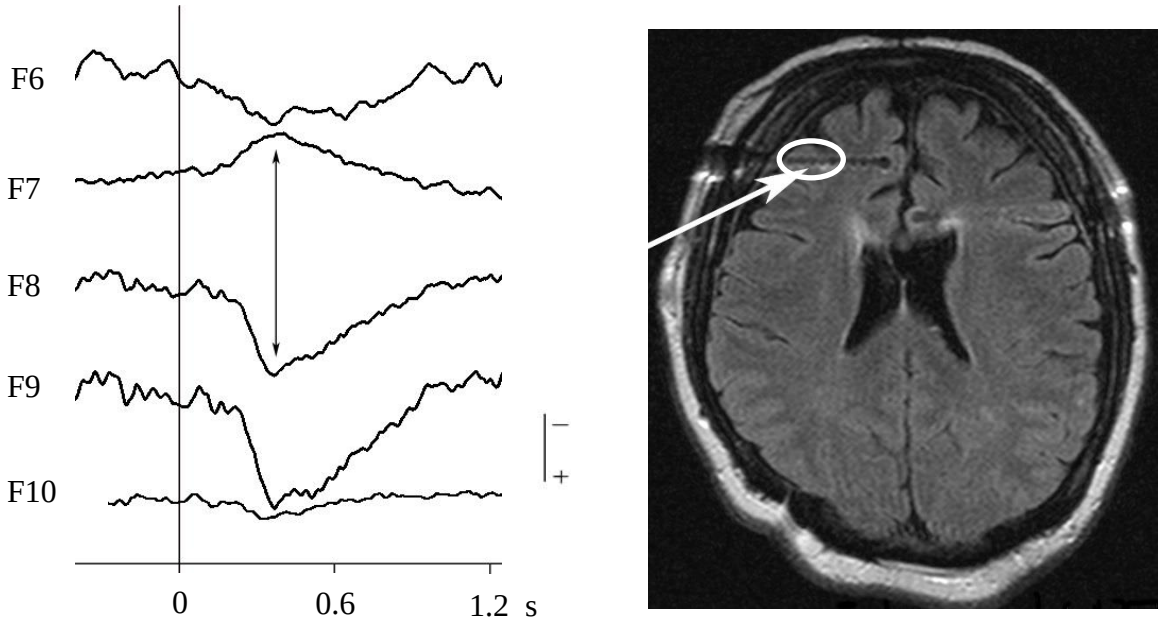
II.3. Časové a prostorové rozlišení iEEG

Časové rozlišení iEEG, stejně jako EEG a MEG, je v milisekundách. Je limitováno pouze vzorkovací frekvencí použitých registračních zařízení. V současné době se dostáváme k hodnotám 30 kHz, což umožňuje registrovat právě i jednotkovou aktivitu neuronů.

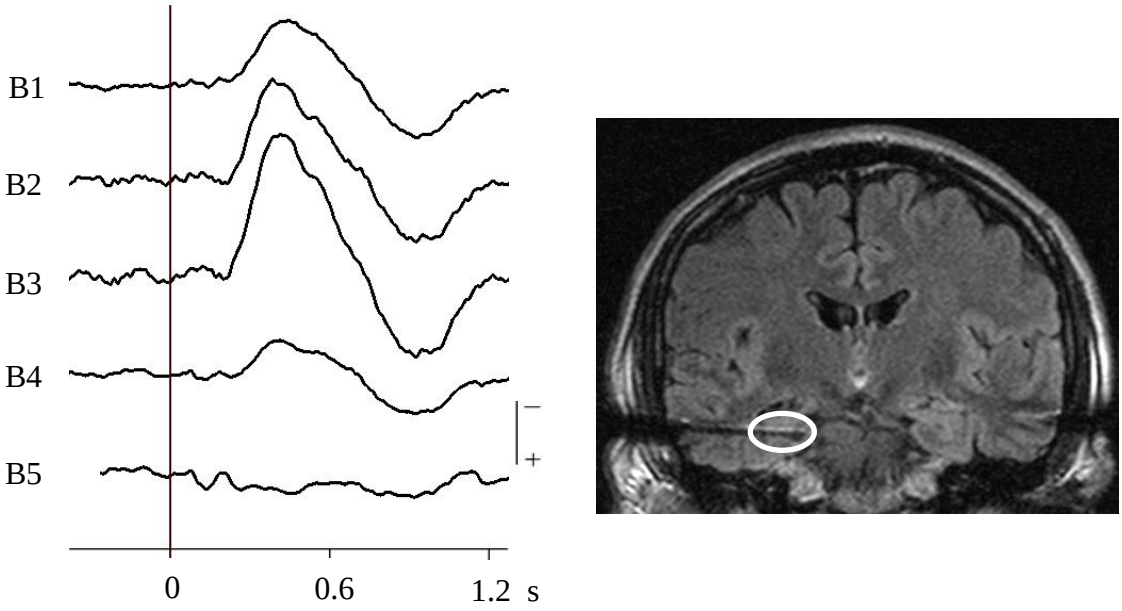
Jednou z dalších výhod intracerebrální registrace v porovnání se skalpovým EEG nebo jinými technikami je prostorové rozlišení. To je určeno typem snímací elektrody (impedancí a velikostí kontaktů), jejím umístěním a také vodivostí mozkové tkáně kolem elektrody. Při použití intrakortikálních elektrod nebo vysokoimpedančních mikroelektrod umístěných na těle nebo na špičce hlubokých elektrod je možné snímat jednotkovou aktivitu jednotlivých neuronů nebo vícejednotkovou aktivitu malé skupiny neuronů v bezprostřední blízkosti kontaktu. Takové extrémní rozlišení se využívá při mapování struktur během neurochirurgického zákroku. Například u pacientů s Parkinsonovou chorobou se postupně zavádí elektroda do bazálních ganglií a dle registrované neuronální aktivity se identifikují oblasti, které mohou být následně cíleně poškozeny nebo naopak chronicky stimulovány, čehož

se využívá při tzv. hluboké mozkové stimulaci. Při výzkumu kognitivních funkcí se registrace jednotkové aktivity na operačním sále využívá zřídka (např. Ojemann et al., 2002; Ulbert et al., 2001b), protože klade vysoké požadavky jak na technické provedení, tak na trvání a volbu kognitivního protokolu.

Lokalizovat zdroj iEEG odpovědi někdy nazývaný jako generátor, tedy oblast nervové tkáně, jejíž koherentní nervová aktivita vytváří měřitelné elektrické pole, je možné díky specifické prostorové distribuci elektrického potenciálu, který vytváří. Příkladem může být tzv. zvrat fáze sledovaného potenciálu na sousedních kontaktech (tzv. „phase reversal“, obr. 4). Zdroj charakteru dipólu bude v tomto případě se spojnicí kontaktů pravděpodobně orientován rovnoběžně. Jiným příkladem lokalizace zdroje je výrazná změna amplitudy signálu na sousedních kontaktech (tzv. „steep voltage gradient“, obr. 5).



Obr. 4 Příklad lokalizace generátoru evokované odpovědi zachycené na elektrodě F v průběhu jednoduchého senzorimotorického úkolu. Vlevo: mezi kontakty F7 a F8 má potenciál opačnou polaritu, jedná se o tzv. zvrat fáze („phase reversal“, označeno šipkou). Podněty jsou prezentovány v čase 0 s. Vpravo: MRI řez v rovině horizontální s elektrodou F zavedenou do přední části frontálního laloku, kontakty F6-F10 v bílé elipse se nacházejí v gyrus frontalis medius, Brodmannova area 9.

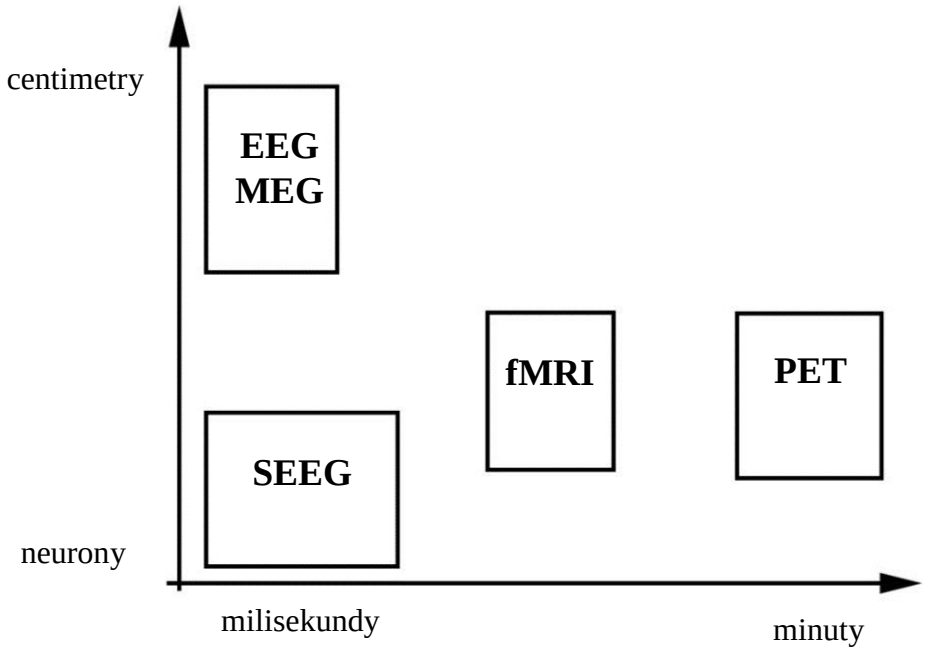


Obr. 5 Příklad lokalizace generátoru evokované odpovědi zachycené na elektrodě B v průběhu jednoduchého senzorimotorického úkolu. Vlevo: mezi sousedními kontakty B1 až B5 lze pozorovat výrazné změny amplitudy evokované odpovědi, kontakt B3 je pak nejblíže zdroji. Podněty jsou prezentovány v čase 0 s. Vpravo: MRI řez v rovině koronální s elektrodou B zavedenou do temporálního laloku, kontakty B1-B4 v bílé elipse se nacházejí v hipokampu, kontakt B5 v bílé hmotě.

Převážná většina intrakraniálního snímání u lidí využívá subdurálních nebo nízkoimpedančních kontaktů na hlubokých elektrodách, které snímají místní potenciály pole. Určit prostorové rozlišení v těchto případech není tak jednoduché, protože každý kontakt uvedených elektrod snímá sumární elektrickou aktivitu, která pochází z různých zdrojů v mozku. Síla elektrického pole zdrojů však klesá se čtvercem jejich vzdálenosti od kontaktu. To nevylučuje teoretickou možnost ovlivnění ze vzdálenějších zdrojů v případě, že tyto generují velmi silné elektrické pole v porovnání se zdroji bližšími. Lachaux a spol. (2003) však uvádějí, že vliv jednotlivých zdrojů vzdálenějších více než 1 cm od kontaktu je zanedbatelný.

I když jsou hluboké elektrody zaváděny do mozkové tkáně s milimetrovou přesností, je prostorová lokalizace zdrojů elektrické aktivity v mozkové tkáni limitována přesností určení anatomické pozice elektrod po jejich implantaci. V současné době nejčastěji používané MRI

zobrazení elektrod in situ umožňuje určit jejich pozici s přesností řádově v milimetrech. Shrneme-li výše uvedené informace, iEEG snímaná hlubokými elektrodami se srovnává s prostorovým rozlišením funkční magnetické rezonance a pozitronové emisní tomografie. Díky vysokému časovému rozlišení však představuje zajímavý nástroj pro funkční mapování mozku (obr. 6).



Obr. 6 Schematické porovnání časového (osa x) a prostorového (osa y) rozlišení některých vyšetřovacích technik (upraveno dle Lachaux et al., 2003).

K doplnění seznamu výhod je nutné také zmínit, že díky intracerebrálním elektrodám zavedeným do lidského mozku je, na rozdíl od téže techniky používané u zvířat, možné s vysokým časovým a prostorovým rozlišením studovat procesy související s funkcemi typickými pouze pro člověka, jako je např. řeč, představivost apod.

II.4. Limitace využití iEEG pro výzkumné účely

Na prvním místě je nutno uvést, že vyšetřovanými subjekty nejsou zdraví jedinci, ale pacienti s různými typy onemocnění. Při analýze intrakraniálních dat získaných nejčastěji u pacientů s farmakorezistentním typem epilepsie je vždy otázkou, zda jejich mozkové okruhy nejsou organizovány vlivem patologie nebo medikace jinak, než u zdravé populace. Výsledky

studií ukazují, že na behaviorální úrovni je většina pacientů schopna kognitivní úkoly provádět bez větších problémů. Předpokládá se, že vliv patologické tkáně není vázán na okamžiky prezentace podnětů a může měnit elektrickou aktivitu v průběhu času nezávisle na jednotlivých úkolech. Proto se při analýze dat vybírají pouze úseky bez zjevné epileptiformní aktivity a vybírají se signály z těch elektrod, které se nacházejí dále od epileptického ložiska. Z metodického hlediska je také nevýhodné, že vyšetřovaní pacienti tvoří méně homogenní skupinu, např. v parametrech věku nebo kognitivních schopnostech provádět požadované úkoly, než vybraní zdraví dobrovolníci ve studiích skalpových (Mukamel et al., 2012).

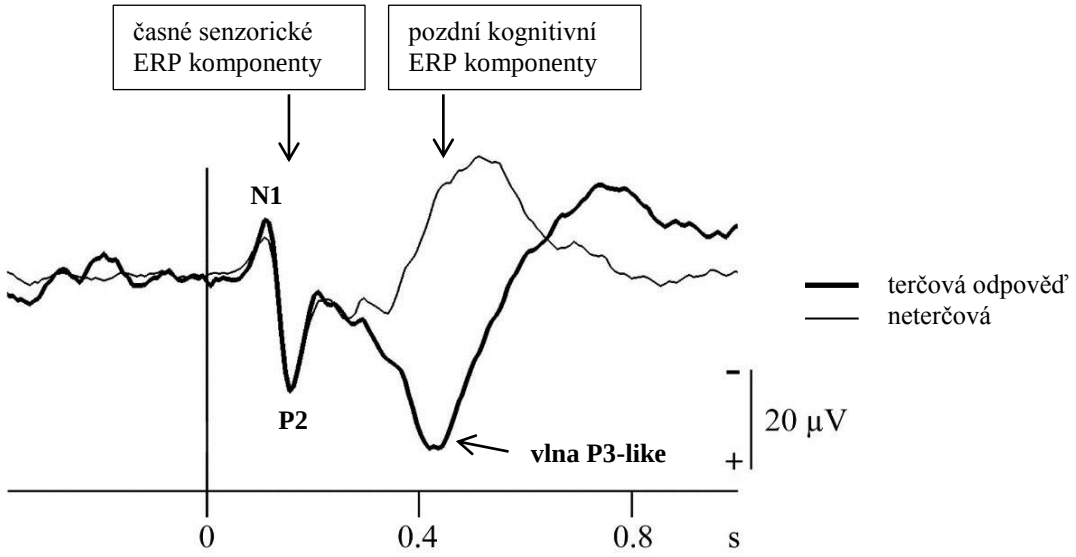
Podstatným omezením iEEG je možnost vyšetření pouze limitovaného objemu mozkové tkáně. Nelze tedy zachytit aktivitu všech částí neuronálních sítí, které se na experimentálních úkolech podílejí. Tento nedostatek je možné částečně eliminovat tak, že se porovnávají data iEEG a fMRI získaná např. u stejných pacientů ze stejného úkolu. Je zajímavé, že např. v oddball úkolu struktury generující vlnu P3 vykazují často zvýšenou aktivaci ve fMRI (Clark et al., 2000; Stevens et al., 2000). Ukazuje se, že nárůst tzv. „blood-oxygen-level dependent“ signálu v fMRI se v některých strukturách shoduje se zvýšením výkonu v pásmu 60-200 Hz (Brovelli et al., 2005), v pásmu 40-150 Hz (Lachaux et al., 2007), v pásmu 70-190 Hz (McDonald et al., 2010) nebo v pásmu 30-70 Hz (Privman et al., 2007). Jaký je vztah mezi metabolickou a elektrickou aktivitou neuronálních populací zatím není zcela jasné.

II.5. Elektrofyziologické koreláty mozkových operací

Jako jedna z metod funkčního mapování lidského mozku umožňuje intrakraniální EEG studovat neuronální pochody přinejmenším na dvou úrovních. Na jedné úrovni se vědci snaží identifikovat jednotlivé složky neuronálních sítí, tzn. hledají oblasti mozku, které vykazují změny elektrické aktivity (ať už jednotkové nebo LFPs) např. v průběhu kognitivních úkolů. Na druhé úrovni se studují dynamické vztahy v neuronálních sítích, tzn. časově-prostorová aktivace a synchronizace jednotlivých zúčastněných oblastí. V obou úrovních se studované děje odehrávají v určitých frekvenčních pásmech, jejichž označení nejčastěji vychází z klasické EEG klasifikace jako delta, theta, alfa, beta nebo gama pásma. Někdy se lze setkat s přesnějším dělením, např. na horní, dolní-1 a dolní-2 alfa pásmo (Klimesch, 2000). Protože se u různých autorů hranice jednotlivých pásem mohou lišit, užívá se vedle výše uvedeného také rozdělení s označením číselným, např. frekvenční pásmo 15-40 Hz, 8-15 Hz apod.

Při studiu kognitivních funkcí s pomocí intrakraniálních elektrod se používají stejné postupy analýzy, jako u registrace ze skalpu. Jednou z nich je zprůměrování EEG odpovědí

časově vázaných na opakovanou prezentaci stejného podnětu nebo na provedení jednoduché akce. Výpočet průměrné amplitudy EEG odpovědi umožňuje studovat fázově koherentní složku signálu („phase-locked“), tedy evokované děje, které jsou podkladem tzv. „event-related potentials“ (ERPs). Do češtiny lze přeložit jako „mozkové odpovědi na zaměřené události“ (Stejskal et al., 1993). Pro zkratku a srozumitelnost se však v české odborné literatuře používá označení ERP nebo ERPs. Ty se skládají z několika komponent – vln (obr. 7), které jsou definovány latencí, polaritou, distribucí na skalpu a behaviorálními koreláty (např. Halgren et al., 1998).



Obr. 7 Příklad ERPs po terčových (silná čára) a neterčových podnětech (tenká čára) registrovaných v průběhu zrakového oddball úkolu z gyrus cinguli anterior vpravo. Podněty jsou prezentovány v čase 0 s. Z časných ERP komponent je vidět vlnu N1 a P2. Kognitivní vlna P3 se v intracerebrálním EEG označuje jako P3-like.
(Obrázek z přednášky „Electrophysiological correlates of neuronal processing during cognitive tasks studied by the intracranial EEG in humans“ prezentované na 25. mezinárodní CIANS konferenci v Bratislavě, Slovensko, 2016).

Po sobě jdoucí vlny lze rozdělit na časné senzorické potenciály, které jsou zejména ovlivnitelné fyzikálními vlastnostmi vyvolávajícího podnětu (Jewett et al., 1970; Cracco a Cracco, 1976) a na pozdní kognitivní potenciály, podmíněné kognitivními procesy (Sutton et al., 1965; Donchin et al., 1978; Hillyard et al., 1978, Halgren et al., 1998). Mezi ERP

komponenty časné řadíme vlny s latencí obvykle kratší než 250ms, označované nejčastěji jako P1, N1, P2, výjimečně některými autory uváděná i N2 (Antal et al., 2000). ERP komponenty s latencí delší než 250 ms jsou pak označovány jako kognitivní a patří sem např. vlny N2, P3, N400. Použité dělení je však pouze orientační, protože přesná hranice mezi senzorickými a kognitivními potenciály není doposud jednoznačně určena. Na tomto místě je zapotřebí ještě uvést, že polarita jednotlivých komponent evokovaných odpovědí u intracerebrálních dat nemá stejnou výpovědní hodnotu, jako při registracích na skalpu. Navíc není také doposud jasné, jakým způsobem se v mozkové tkáni identifikované generátory ERP podílejí na skalpových signálech. Detailnější popis problematiky ERPs lze nalézt v dizertační práci (Roman, 2004).

Interpretace ERPs vychází z předpokladu, že při opakované prezentaci stejného podnětu se shodně mění i neuronální aktivita ve stejných anatomických oblastech a ve stejném časovém okně. Někteří autoři popisují tuto skutečnost jako „phase resetting“ (Brandt, 1997). Zprůměrněním takto vyvolaných EEG odpovědí se pravidelná aktivita zvýrazní, zatímco neuronální aktivita, která není vázána na prezentaci podnětu (šum), se potlačí. Tento jednoduchý matematický postup je použitelný i tehdy, když evokovaná odpověď při některé prezentaci podnětu chybí nebo, když její latence od podnětu není konstantní. Takové kolísání však musí být mnohem menší než trvání studovaného evokovaného potenciálu. Z uvedeného pak vyplývá i jisté omezení. Např. tímto postupem nelze detekovat evokované potenciály o frekvenci vyšší než 30 Hz, pokud jednotlivé odpovědi nejsou s podnětem synchronizovány s milisekundovou přesností (Lachaux et al., 2003).

Prezentace podnětů však vedle evokované odpovědi může vyvolat takové změny LFPs, při kterých jednotlivé EEG oscilace nejsou fázově koherentní. Hovoříme o tzv. odpovědi indukované. V tomto případě se analyzuje především změna amplitudy nebo výkonu oscilací, nikoliv fáze ("time-locked; nonphase-locked"), která se navíc obvykle objevuje s delším časovým odstupem od okamžiku stimulace než odpověď evokovaná. Předpokládaným podkladem tohoto typu EEG odpovědi je změna počtu aktivovaných oscilátorů (tj. oscilačních neuronálních celků) v daném frekvenčním pásmu (Klimesch, 1999).

U indukovaných odpovědí vyhodnocujeme především relativní změny amplitudy oscilací EEG signálu ve vymezeném frekvenčním pásmu vzhledem k amplitudě signálu v krátkém časovém okně před prezentací podnětu (Pfurtscheller, 1992). Nárůst amplitudy je označován ERS („event related synchronization“) a pokles ERD („event related desynchronization“). Pro analýzu indukovaných změn se používá výpočet amplitudových nebo výkonových obálek pomocí Hilbertovy transformace s využitím FFT nebo vlnkové

transformace. Pro různá frekvenční pásma lze vytvářet časově-frekvenční mapy. Jednotlivé mapy nebo obálky se průměrují po jednotlivých EEG epochách („EEG trials“).

Pro analýzu časově-prostorové aktivace zúčastněných neuronálních oblastí, tzn. míry jejich funkčního vztahu – tzv. funkční konektivity, se např. používá výpočet korelace signálů ze dvou a více míst mozku v časové oblasti (korelace; např. Kukleta et al., 2009) nebo ve frekvenční oblasti (koherence výkonových spekter; Rappelsberger et al., 1993). Kromě lineární korelace a koherence patří v současné době mezi nejpoužívanější metody analýzy funkční konektivity i metody založené na výpočtu okamžité fáze signálu, nelineární a kauzální metody. Z metod využívajících okamžitou fázi signálu lze uvést například „Phase Synchronization“, „Mean Phase Coherence“ (Mormann et al., 2000) nebo „Phase-lag Index“ (Stam et al., 2007). Kromě zachycení okamžitých fázových změn mezi dvojcí EEG signálů mají tyto postupy schopnost lépe potlačit společné, nežádoucí složky v signálech. Z nelineárních metod lze použít např. h2 – nelineární korelaci. I přesto, že je použití nelineárních analýz v signálech EEG z mnoha důvodů diskutabilní, dosahuje tato metoda dobrých výsledků, především v kontextu dynamických změn výrazných behaviorálních stavů, jako jsou například epileptické záchvaty (Wang et al., 2014, Jirsa et al., 2014).

Pro posouzení kauzality zkoumaných dějů v EEG, mohou výše zmíněné konvenční metody nabídnout pouze omezenou informaci. Pro popis časových posloupností v EEG signálech je proto často používána Grangerova kauzalita, která na základě predikce a výsledné chyby určuje, který EEG signál kauzálně ovlivňuje průběh signálů okolních (Granger, 1969). V případě zkoumání kauzální konektivity (tzv. efektivní konektivity) mezi více než dvěma EEG signály jsou využívány multivarietní metody založeny na principu Grangerovy kauzality – „Directed Transfer Function“ a „Partial Directed Coherence“ (Baccala a Sameshima, 2001). Při analýzách konektivity však obecně platí, že hodnota výsledných parametrů je významně závislá na strukturálních spojích mezi odpovídajícími anatomickými oblastmi a je ovlivněná přítomnou patologií (Tucker et al., 1986).

II.6. Výzkumné využití iEEG

Výzkumné využití iEEG u lidí představuje minoritní podíl mezi moderními technikami funkčního mapování mozku z důvodů vysoké náročnosti na její provedení a relativně malého počtu pacientů, kteří z klinických důvodů tuto exploraci podstoupí. K náročnosti do jisté míry přispívá nutnost multidisciplinárního přístupu - většinou se na výzkumu podílejí odborníci

z oboru neurologie, neurochirurgie, neurofyziologie, neuropsychologie a kognitivních neurověd. I přes uvedené skutečnosti však tato metoda poskytuje unikátní data díky její milimetrové a milisekundové rozlišovací schopnosti.

V následujících odstavcích jsou uvedeny některé zajímavé nálezy humánních iEEG studií, které přispěly k rozšíření našich znalostí v různých oblastech výzkumu mozku (řeč, motorika, percepce, emoce a paměť). Širší výčet prací lze nalézt v přehledových článcích Lachaux a spol. (2003), Jacobs a Kahana (2010) nebo Mukamel a Fried (2012).

Při výzkumu řeči a řečových funkcí Penfield a Roberts (1959) a později Ojemann a spol. (1989) prokázali účast mnoha kortikálních oblastí v řečově dominantní hemisféře pomocí elektrické stimulace kortexu během neurochirurgických zákroků. Sahin a spol. (2009) na základě registrace potenciálů místního pole zase ukazují, že lexikální, gramatické a fonologické procesy řeči jsou v Brokově oblasti zpracovávány v odlišných časových obdobích. Dalším zajímavým nálezem je, že např. premotorické oblasti během mluvení modulují neuronální aktivitu ve sluchovém kortexu (Greenlee et al., 2011).

Somatotopická organizace primárního motorického i senzorického kortexu byla prokázána pomocí elektrické stimulace kortexu (Penfield a Boldrey, 1937) a také sledováním výkonu v alfa, beta a gama pásmech pro pohyby různých částí těla (Crone et al., 1998a,b). S využitím stimulace nervus medianus se Allison a spol. (1989) podařilo zmapovat časově prostorovou reprezentaci odpovědi na tuto stimulaci v odpovídajícím senzorimotorickém kortexu. Fried a spol. (1991) jako první prokazují somatotopickou organizaci lidské suplementární motorické oblasti (SMA). Navíc elektrickou stimulací této oblasti spustili u pacientů potřebu provést pohyb, demonstrujíce tak spojení mezi SMA a volním pohybem. Podobný vztah k volnímu řízení pohybu nalézá Desmurget a spol. (2009) i u dolního parietálního kortexu, kdy jeho stimulace vedla k vyvolání pocitu, že pacient by měl provést pohyb. Při vyšší intenzitě stimulace dokonce došlo k navození iluze, že pohyb byl proveden. Nezávisle na vůli pacienta však skutečný pohyb spouští stimulace v premotorické korové oblasti (area 6). Tankus a spol. (2009) demonstrují, že neuronální aktivita SMA oblasti je nepřímo úměrná rychlosti prováděného pohybu. Odpovědi neuronů téže oblasti byly registrovány i při pouhé představě pohybů (Amador a Fried, 2004).

V lidském hipokampu a parahipokampálním gyru Ekstrom a spol. (2003) jako první demonstrují existenci „place“ a „view“ neuronů, jejichž aktivita je podkladem prostorové orientace. V jiné studii Allison a spol. (1999) identifikovali komponenty ERPs související s percepcí lidských tváří a podrobně zmapovali jejich lokalizaci v okcipitotemporálním

kortexu. V jiné studii byly meziotemporálně identifikovány takové neurony, které se aktivovaly jak při prohlížení zrakových podnětů, tak při jejich představování při zavřených očích (Kreiman et al., 2000a,b). Jiná studie ukázala, že stupeň fázové shody jednotkové aktivity s pomalými oscilacemi místních potenciálů pole v pásmu 3-8 Hz v hipokampu a amygdale je ukazatelem výkonnosti paměti (Rutishauser et al., 2010).

Dále při výzkumu emocí se např. ukázalo, že aktivita amygdaly se při rozlišování averzivních, neutrálních a pozitivních podnětů liší jak v indukované (Oya et al., 2002; Sato et al., 2010) tak v evokované odpovědi (Krolak-Salmon et al., 2004). Pocity znechucení byly vyvolány elektrickou stimulací těch oblastí inzuly, které vykazují nárůst amplituy ERP při pozorování výrazů znechucení (Krolak-Salmon et al., 2003). Další studie mapují lokalizaci tzv. zrcadlových neuronů, které se aktivují v případě, že vyšetřovaný subjekt sám provádí nějakou činnost nebo stejnou činnost pozoruje u ostatních. Jejich existence byla prokázána nejen v motorickém a senzorickém kortexu, ale i v SMA nebo hipokampu (Mukamel et al., 2010a). Analogicky aktivní neurony lze nalézt i v předním cingulárním kortexu u subjektů v situacích, kdy sami jsou vystaveni bolestivé stimulaci nebo když pozorují jiné osoby vystavené stejné bolestivé stimulaci (Hutchison et al., 1999).

III. Elektrofyziologické projevy mozkových funkcí studované v průběhu kognitivních úkolů.

V šesti předkládaných studiích (příloha 1,3,4,6,7,8) jsme zpracovávali prof. Brázdilem dříve nahraná intracerebrální EEG data, která byla získána v průběhu jednoduchého zrakového oddball úkolu u souboru 20 epileptických pacientů (ve věku od 23-45 let). V dalších studiích byl použit jednoduchý senzorimotorický úkol (příloha 2; vyšetřeno 11 epileptických pacientů, průměrný věk 35±11 let) a tzv. Go/NoGo úkol (příloha 5; vyšetřeno 7 epileptických pacientů, průměrný věk 29±4 roky), jejich detailnější popis je uveden v komentáři k dané publikaci.

Ve všech studiích byly při registraci EEG signálu použity standardní semiflexibilní vícekontaktové elektrody ALCIS o průměru 0,8 mm. EEG bylo nahráváno 128 kanálovým TrueScan EEG systémem na vzorkovací frekvenci 1024 Hz.

Studované elektrofyziologické koreláty jsou generovány v různých frekvenčních pásmech. Z toho důvodu jsou EEG data v každé studii po odstranění artefaktů a před vlastní segmentací filtrována offline ve frekvenčních pásmech odpovídajících studovanému korelátu. Následně pak do analýzy vstupují EEG přeběhy (synonyma: EEG segmenty, EEG epochy, „EEG trials“) v trvání několika stovek milisekund před a po okamžiku prezentace podnětů nebo registrované odpovědi.

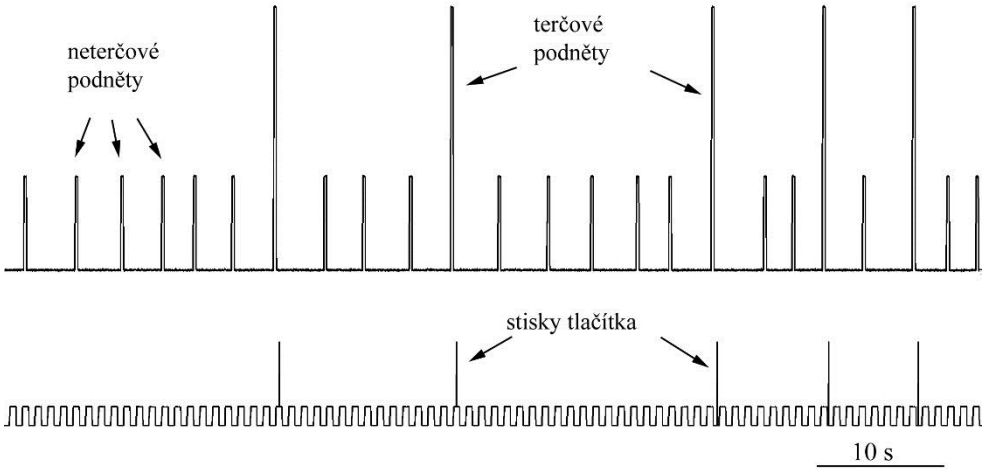
EEG data získaná při současné registraci ze skalpové CPz elektrody, umístěné v poloviční vzdálenosti mezi elektrodami Cz a Pz mezinárodního 10-20 systému, byla v našich studiích málo využitelná z důvodů nižšího poměru signál/šum a použitých analýz. Ojedinělé nálezy z této elektrody zmiňujeme v následujících komentářích jen výjimečně.

Pro analýzu iEEG dat jsme ve většině případů použili software ScopeWin, jehož autorem je ing. Pavel Jurák, CSc, případně software Physioplore, jehož autorem je ing. Jan Chládek, PhD., oba autoři jsou zaměstnanci Ústavu přístrojové techniky Akademie věd ČR, Brno.

Oddball úkol

V základní variantě oddball úkolu (jednoduchý rozhodovací úkol; pro anglické slovo „oddball“ nemáme v češtině překlad) jsou náhodně prezentovány dva typy senzorických podnětů stejné modality – terčové (synonymum vzácné; angl. „rare, target, deviant“) a neterčové (synonymum časté; anglicky standard, frequent, non-target“) v poměru 1:5 (obr. 4). Mezi jednotlivými podněty se nachází krátká pauza (cca 2-5 s). V našem případě zrakové stimulace s použitím písmen jako podnětů představovalo písmeno „X“ podněty terčové,

písmeno „O“ podněty neterčové. Pokusná osoba byla instruována reagovat na výskyt každého terčového podnětu stlačením ručního spínače a v duchu tyto podněty počítat, zatímco ostatní podněty nechávat bez povšimnutí (např. Polich, 2007).



Obr. 4 Schematické znázornění jednoduchého oddball úkolu. V naší studii bylo terčovým podnětem písmeno „X“ a neterčovým podnětem písmeno „O“ (horní záznam). Na výskyt terčového podnětu pokusná osoba reagovala stiskem tlačítka (dolní záznam). Oba záznamy jsou vždy nahrávány do přídavných kanálů zesilovače současně s kanály EEG.

Oddball úkol je do jisté míry značně jednoduchý (percepce dvou podnětů stejné modality) a tudíž velmi snadno použitelným pro základní i aplikovaný neurofyziologický výzkum s využitím různých vyšetřovacích metod. Na druhé straně však určení významu podnětů a jejich randomizovaný výskyt v průběhu úkolu vyžaduje zapojení mentálních operací, které jsou hlavním cílem zkoumání v této oblasti neurofyziologie a při kterých se angažuje řada kortikálních a subkortikálních struktur. S využitím moderních vyšetřovacích metod s lepším prostorovým i časovým rozlišením, jednou z nich je právě intracerebrální elektroencefalogarfie, je možné získat detailnější informace o zúčastněných neuronálních sítích a časo-prostorových vztazích mezi neuroanatomickými strukturami, které jsou aktivovány v průběhu základních mentálních operací.

III.1. Intracerebrální vlna P3-like je heterogenní fenomén

V naší první studii (příloha 1) jsme se zaměřili na detailnější analýzu kognitivní komponenty ERP označované jako vlna P3, konkrétně na její intracerebrální variantu označovanou jako vlna P3-like. V oddball úkolu je typicky přítomná po terčových podnětech. Její další název je vlna P300, což souvisí s průměrnou vrcholovou latencí této komponenty (kolem 300 ms) u zdravých jedinců při použití sluchové modality stimulace. Latence vizuální vlny P3 se pohybuje v rozmezí 250-600 ms od začátku podnětu a může se měnit v závislosti na typech podnětů, složitosti úkolu a na vyšetřovaných osobách (Comerchero a Polich, 1998). Časově se však často překrývá s okamžikem pohybu, může jej předcházet nebo následovat, a proto na pohyb-vázané potenciály mohou zkreslit její skalpovou distribuci a změnit její latenci (Jentzsch a Sommer, 2001; Salisbury et al., 2001; Brázdil et al., 2003).

I přes nejednoznačné nálezy ve studiích zaměřených na analýzu vztahu mezi latencí vlny P3 a reakční dobou (např. Gehring et al., 1992; Mecklinger et al., 1992; Gunter et al., 1994), považuje většina autorů vlnu P3 obecněji za korelát procesů souvisejících s vyhodnocováním podnětů („stimulus-related“) a nesouvisejících s procesy výběru a provedením odpovědi (Pfefferbaum et al., 1986). Tento kognitivní potenciál bývá tedy interpretován jako měřítko rychlosti zařazení nebo vyhodnocení podnětu (Polich, 1986), jako ukončení poznávacího procesu v mozku („cognitive closure“), či jako korelát aktualizace paměťových funkcí před další akcí nebo bývá spojován s mechanismy pozornosti a orientace (Paller et al., 1987).

Ve studiích využívajících intracerebrálních elektrod u epileptických pacientů byly nalezeny generátory vlny P3 v různých strukturách (Baudena et al., 1995; Halgren et al., 1995a,b; Brázdil et al., 1999). Byly popsány dva charakteristické, na modalitě podnětu nezávislé, intracerebrální vzorce vlny P3. První představuje trifázická vlna s ostrými vrcholy (negativní–pozitivní–negativní) označovaná jako N2a-P3a-SW. Bývá spojována se systémem zaměřené pozornosti a byla pozorována opakovaně v těchto oblastech: gyrus temporalis medius, gyrus fusiformis, gyrus parahipokampalis, gyrus cinguli, dorzolaterální prefrontální kortex a dolní parietální kortex. Druhým vzorcem je široká vlna P3b, která je součástí vlny N2b-P3b a která je spojována se systémem „kódujícím události“, byla nalezena např. v laterálním orbitofrontálním kortexu, amygdale a hipokampu (Halgren et al., 1995a,b; Brázdil et al., 1999).

Na rozdíl od všech do té doby známých intrakraniálních studií zabývajících se lokalizací kognitivních potenciálů v mozku jsme se v této studii zaměřili na časový vztah intracerebrální vlny P3-like k podnětu a motorické odpovědi. Využili jsme přitom skutečnosti, že 1) EEG záznamy z hlubokých elektrod mají vyšší poměr signál/šum a tudíž stačí zprůměrnit menší počet EEG přeběhů k vykreslení studovaného potenciálu; 2) u každého EEG přeběhu jsou vedle přesné časové identifikace prezentace podnětu ještě zaznamenány okamžiky stisku tlačítka; 3) reakční doba, tj. čas od prezentace podnětu po okamžik stisku tlačítka, není v jednotlivých EEG přebězích u každého subjektu stejná a individuálně je tak možné rozdělit EEG přeběhy do podskupin s krátkou a dlouhou reakční dobou.

Příloha 1. Roman R, Brazdil M, Jurak P, Rektor I, Kukleta M. Intracerebral P3-like waveforms and the length of the stimulus-response interval in a visual oddball paradigm. *Clinical Neurophysiology* 2005;116:160-171.

K analýze jsme použili intracerebrální data registrovaná v průběhu zrakového oddball úkolu u 17 epileptických pacientů (4 ženy a 13 mužů). K odstranění vlivu vysokofrekvenčních složek EEG signálu, které nepřispívají ke generování vlny P3-like, jsme EEG data nejdříve digitálně filtrovali (pásmová propust 0,5-5,5 Hz). U každého pacienta bylo zprůměrněno přibližně 50 přeběhů po terčových podnětech a 150 přeběhů po podnětech neterčových. Vlna P3-like v rozsahu latencí 250-600 ms byla identifikována ve 180 místech frontálního, temporálního a parietálního laloku. V dalším kroku jsme EEG přeběhy po terčových podnětech rozdělili do dvou podskupin s kratší a delší reakční dobou. Přeběhy (počet 16±3) v podskupinách byly poté zprůměrněny dvěma způsoby a to od podnětu a od stisku spínače.

Porovnání latencí vln P3-like v obou podskupinách při dvou způsobech zprůměrnění nám umožnilo rozdělit vlny P3-like na tři typy s difúzní intracerebrální distribucí. Jednotlivé typy nebyly specifické pro určité struktury a u většiny pacientů jsme mohli identifikovat více než jeden případ P3-like vlny každého typu v různých strukturách.

Prvním typem byla vlna časově vázaná na podnět (průměrná latence 393 ms). Zprůměrněním od podnětu vykazovala tato vlna stejnou latenci v obou podskupinách. Zprůměrněním od stisku spínače se však latence lišily (delší byla v podskupině s delší reakční dobou) rozdílem, který představoval průměrně 91,1±22,9 % odpovídajícího rozdílu v průměrné reakční době obou podskupin. Takový typ potenciálu může představovat procesy související se senzorickou diskriminací a vyhodnocením podnětu. Může být podkladem skalpových P3 vln generovaných po „distraktorech“ (Knight, 1998), registrovaných v pasivním oddball úkolu

(Polich, 1989) nebo P3 vln, jejichž latence se měnila s reakční dobou při snižování intenzity podnětů (Verleger et al., 1991) nebo při snižování diskriminability podnětu (Novak et al., 1990).

Druhým typem byla vlna časově vázaná na odpověď (průměrná latence 440 ms). Stejnou latenci v obou podskupinách vykazovala tato vlna při zprůměrnění od stisku spínače. Při zprůměrnění od podnětu se však latence lišily (byla delší v podskupině s delší reakční dobou) rozdílem, který představoval průměrně 95,1±20,1 % odpovídajícího rozdílu v průměrné reakční době obou podskupin. Taková vlna P3-like pravděpodobně reprezentuje procesy související s vytvořením vnitřní reprezentace odpovědi, její přípravou, zahájením a vlastním provedením. Její existence by mohla např. vysvětlit, proč v úkolech s minimálními požadavky na vyhodnocení podnětu vedlo provedení odpovědi k ovlivnění latenc skalpové vlny P3 (Doucet a Stelmack, 1999) nebo proč změnilo její skalpovou distribuci (Salisbury et al., 2001).

Nejčastěji jsme pozorovali třetí typ vlny bez jasné časové vazby na podnět a odpověď (průměrná latence 425 ms). U tohoto typu vlny představoval rozdíl latencí mezi oběma podskupinami při zprůměrnění od podnětu 57,4±26,0 % a při zprůměrnění od odpovědi 51,9±18,8 % rozdílu v průměrné reakční době obou podskupin. Zdá se, že poslední typ vlny P3-like by mohl souviset s paměťovými a pozornostními operacemi nebo procesy integrujícími zpracování podnětu a provedení odpovědi, tzn. rozhodnutí o odpovědi na základě analýzy senzorické informace. S těmito operacemi bývá asociována skalpová vlna P3b s centroparietálním maximem (McCarthy et al., 1997). Redukce vlny P3b u pacientů s temporoparietální lézí je doprovázena deficity pozornosti a paměti (Woods et al., 1993). Nálezy třetího typu P3-like vlny v hipokampu, parahipokampálním gyru, amygdale a na dalších místech mohou podpořit výše uvedené zjištění. Je pravděpodobné, že rozhodování, pozornostní a paměťové procesy nemusí být přesně časově vázány na okamžik prezentace podnětu a jejich časová vazba může kolísat v závislosti na okamžitých podmínkách. Stejné vysvětlení může být použito pro procesy počítání terčových podnětů, které pak mohou přispívat ke vzniku třetího typu vlny P3-like.

Výsledky naší studie tedy prokázaly, že vlna P3-like vyvolaná v průběhu zrakového oddball úkolu je heterogenní fenomén odrážející více mozkových funkcí. Zajímavým vedlejším nálezem bylo zjištění, že oba intracerebrální vzorce – trifázická vlna N2a-P3a-SW i široká vlna P3b – byly nalezeny u všech tří typů P3-like vln. Z uvedeného vyplývá, že tyto vzorce evokované EEG odpovědi registrované přímo v mozkové tkáni odrážejí spíše určitou elektrofyziologickou zákonitost než specifické kognitivní operace.

III.2. Hipokampální kognitivní potenciál s latencí kolem 420 ms vyvolaný v průběhu jednoduchého senzorimotorického úkolu nesouvisí s motorickou odpovědí

V práci Roman a spol. (2005) zaměřené na analýzu vlny P3-like vyvolané v oddball úkolu jsme pozorovali, že se v hipokampu člověka pravidelně vyskytuje významný pomalý ERP s latencí kolem 450 ms. Stejný nález při použití téhož úkolu popisuje také jiná skupina (Ludowig et al., 2010). Potenciál velmi podobného charakteru byl v hipokampu nalezen také při použití jiných experimentálních úkolů, např. při studiu paměťových procesů (Paller a McCarthy, 2002). Pro svoji přítomnost v řadě humánních studií (např. Grunwald et al., 1995; Brázdil et al., 2001; Fell et al., 2005; Boutros et al., 2008; Axmacher et al., 2010) je tento potenciál chápán jako korelát kognitivních procesů zprostředkovaných hipokampem v různých kognitivních úkolech. V některých studiích byl tento potenciál považován za jeden z generátorů skalpové vlny P300 a proto jej někteří autoři označují např. jako MTL-P300 (Fell et al., 2004), jako hluboká P3b (Halgren et al., 1995b) nebo P3-like vlna (Brázdil et al., 2003). Protože tento hipokampální ERP není vázán na některé funkce asociované s funkcemi vlny P300, Paller a McCarthy (2002) navrhují používat popisný termín „large negative ERP“.

Výsledky většiny intracerebrálních studií prokazují účast hipokampu v kognitivních procesech, jako jsou např. hodnocení významu podnětů (Rosburg et al., 2007; Grunwald et al., 1998; Strange a Dolan, 2001) a při paměťových úkolech - prostorová paměť (např. Watrous et al., 2011), kódování a vybavování epizodické paměti (např. Fernández el al., 2002; Amaral a Lavenex, 2007; Eichenbaum et al., 2012). Některé animální studie však ukazují, že hipokampální theta aktivita je spojena s motorickým chováním (Vanderwolf, 1969; Wyble et al., 2004; Shin, 2011). Intracerebrální studie u člověka také v hipokampu prokazují na pohyb vázaný nárůst theta oscilační aktivity (Ekstrom et al., 2005). Tyto nálezy jsou v souladu se senzorimotorickou integrační teorií, která předpokládá, že hipokampální theta aktivita odráží jak zpracování senzorických informací souvisejících s přípravou pohybu tak jeho provedením (Bland a Oddie, 2001).

Další doklady pro účast hipokampu při provádění pohybu pocházejí ze studií, které ukazují změny hipokampální evokované aktivity v průběhu motorické odpovědi. Například v oddball úkolech, je amplituda hipokampálního pomalého ERP vždy vyšší po terčových podnětech, vyžadujících stisk tlačítka, v porovnání s odpovědí po neterčových podnětech, kdy motorická odpověď není požadována (Brázdil et al., 1999; Fell et al., 2005; Ludowig et al., 2010). Amplituda hipokampálního pomalého ERP po terčových podnětech je také vyšší v případě, kdy pacient označí přítomnost terčového podnětu stiskem tlačítka v porovnání

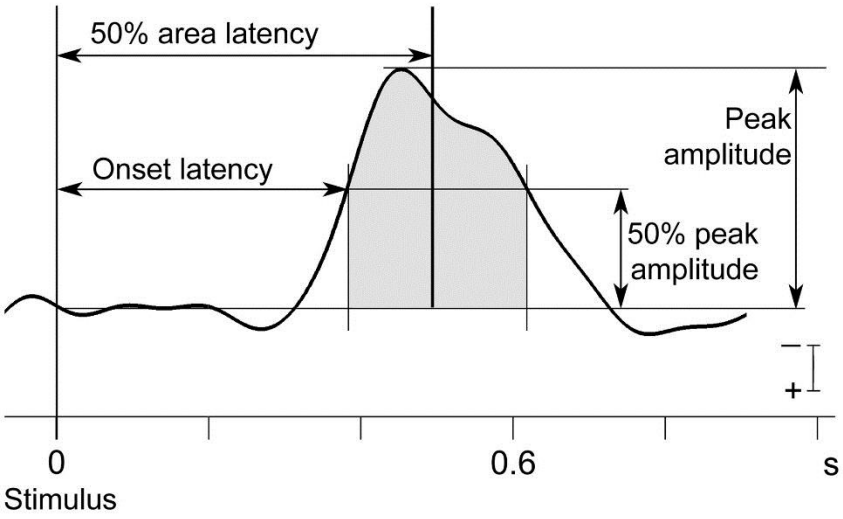
s mentálním počítáním (Brázdil et al., 2003). Navíc v naší předchozí studii (Roman et al., 2005) jsme pozorovali, že hipokampální P3-like vlna může být časově vázána jak na okamžik prezentace podnětu, tak na okamžik motorické odpovědi. Tyto nálezy naznačují, že hipokampální pomalá evokovaná aktivita může souviset vedle vyhodnocení podnětů a paměťových procesů také s provedením pohybu.

Abychom objasnili tuto možnou souvislost, zaměřili jsme se v další naší intracerebrální studii (příloha 2) na analýzu časového vztahu mezi latencí hipokampálního pomalého ERP a okamžikem motorické odpovědi. Zvolili jsme jednoduchý úkol, při kterém byl prezentován pouze jeden typ podnětu (1 kHz tón; celkem 150 podnětů; interstimulus interval 4-6s). Pacienti byli instruováni stisknout tlačítko spínače po zaznění tónu, přičemž nebyl kladen důraz na rychlost odpovědi.

Příloha 2. **Roman R**, Brázdil M, Chládek J, Rektro I, Jurák P, Světlák M, Damborská A, Shaw DJ, Kukleta M. Hippocampal negative event-related potential recorded in humans during a simple sensorimotor task occurs independently of motor execution. *Hippocampus* 2013;23(12):1337-1344.
Tato práce získala v roce 2014 ocenění České společnosti pro klinickou neurofyziologii ČLS JEP - 1.místo v soutěži o nejlepší vědeckou práci za rok 2013.

Z metodického hlediska se jedná o první iEEG studii, ve které byly pro stanovení latence intracerebrálního ERP použity parametry odvozené z plochy studovaného potenciálu. Vycházeli jsme z obdobné metodiky doporučené pro analýzu skalpových ERP (Luck, 2005). V našem případě jsme měřili latenci těžiště plochy potenciálu (tzv. „50% area latency“) v časovém okně, jehož počáteční a koncový bod ležely na průsečíku potenciálu a pomyslné čáry, která jej protínala v polovině jeho amplitudy („50% peak amplitude“).

Výhodou tohoto parametru je, že získané hodnoty jsou mnohem méně ovlivněny šumem. V porovnání s vrcholovou latencí tak přesněji odráží časovou pozici potenciálu od okamžiku prezentace podnětu a je proto pro analýzu vztahu latence studovaného potenciálu a reakční doby, konkrétně mediánu reakční doby, vhodnější. Počáteční bod vymezeného časového okna jsme potom použili i pro určení latence začátku studovaného potenciálu, tzv. „onset latency“ (obr. 5). Uvedená měření jsme prováděli pomocí software Physioplore, jehož autorem je ing. J. Chládek, Ph.D. z Ústavu přístrojové techniky Akademie věd ČR, Brno.



Obr. 5 Schematické znázornění parametrů odvozených z plochy studovaného potenciálu (popis parametrů je uveden v textu).

Vyšetřili jsme celkem 11 pacientů (9 žen a 2 muži) s farmakorezistentním typem epilepsie. Z celkového počtu 91 hlubokých elektrod implantovaných do frontálních, parietálních a temporálních laloků jsme analyzovali data z 22 elektrod (9 v pravé, 13 v levé hemisféře) umístěných do hipokampu.

Studovaný pomalý ERP je evokovanou odpovědí v pásmu delta (kolem 3 Hz) a proto jsme v prvním kroku analýzy EEG data filtrovali (pásmová propust 0,1-5,5 Hz). Vybrané EEG přeběhy bez artefaktů (průměrný počet 92±21) jsme zprůměrnili od okamžiku prezentace tónu. U všech vyšetřených hipokampů jsme našli lokálně generovaný pomalý ERP s průměrnou latencí kolem 420 ms a amplitudou -129±84 μV. Latence těžiště hipokampálního ERP byla ve 14 případech kratší než medián reakční doby, ve zbývajících 8 případech byla delší než medián reakční doby.

V dalším kroku analýzy jsme použili originální postup, při kterém jsme EEG přeběhy rozdělili dle reakční doby do pěti podskupin a odděleně zprůměrnili. U takto získaných potenciálů jsme opět změřili jejich latenci těžiště, které jsme navíc přepočítali na procentuální podíl reakční doby a získali jsme tak relativní latenci. Parametr latence a relativní latence jsme korelovali s reakční dobou měřenou v jednotlivých podskupinách. Výsledky korelační analýzy prokázaly, že latence hipokampálního pomalého ERP měřená v pěti podskupinách EEG

přeběhů nekorelovala s mediánem reakční doby těchto podskupin. Hodnota korelace relativní latence s mediánem reakční doby naopak dosáhla v 16 z 22 případů signifikantní hladiny významnosti. Výsledky naší analýzy ukázaly, že hipokampální pomalý ERP u člověka vyvolaný v průběhu jednoduchého senzorimotorického úkolu je časově nezávislý na okamžiku provedení motorické odpovědi. Jedná se tedy o elektrofyziologický korelát velmi pravděpodobně související s vyhodnocováním významu podnětu v kontextu situace.

III.3. Intracerebrální pozdní ERP komponenty neterčových odpovědí se mohou ve svém průběhu shodovat s odpovědí terčovou

Průběh evokované odpovědi přibližně od 200-250 ms po prezentaci terčových a neterčových podnětů v oddball úkolech je ve skalpových studiích odlišný. Po neterčových podnětech je evokovaná změna minimální, pokud vůbec, zatímco po terčových se např. objevuje významná vlna P3. Tato skutečnost se stala i jedním z kritérií pro identifikaci vlny P3. Podobný nález lze najít i u intrakraniálních registrací (např. Halgren et al., 1998; McCarthy et al., 1989; Ludowig et al., 2010). Nepřítomnost evokované odpovědi po neterčovém podnětu je dávána do souvislosti s tím, že po jeho detekci není vyžadována žádná akce, tj. pokusné osoby si jej nemají všímat. Z toho důvodu byla evokovaná odpověď po neterčových podnětech při analýzách ERP opomíjena.

Z podstaty oddball úkolu však lze předpokládat, že i neterčový podnět vyžaduje procesy navazující na základní senzorickou diskriminaci, jejímž korelátem jsou již známé časné ERP komponenty. Přinejmenším by se mohlo jednat o porovnání s informací uloženou v paměti, konkrétně, že s neterčovým podnětem není spojena žádná akce a z toho vyplývající rozhodnutí nic nedělat.

K ověření výše uvedeného předpokladu jsme zvolili opačný postup, než při identifikaci vlny P3-like. Hledali jsme, ve vyšetřených strukturách místa, kde se odpovědi po terčovém a neterčovém podnětu shodují. Pro zvýšení věrohodnosti analýzy jsme odpovědi po neterčových podnětech rozdělili do dvou skupin. Do jedné skupiny jsme vybrali odpovědi na každý první neterčový podnět prezentovaný po podnětu terčovém, označili jsme je jako „nehabituované“. Do druhé skupiny jsme zařadili odpovědi na každý šestý, sedmý případně další neterčový podnět, které následovaly po terčovém podnětu, označeny byly jako „habituované“ (příloha 3).

Příloha 3. Kukleta M, Brazdil A, **Roman R**, Jurak P. Identical event-related potentials to target and frequent stimuli of visual oddball task recorded by intracerebral electrodes. *Clinical Neurophysiology* 2003;114:1292-1297.

Do této studie byla zařazena data ze zrakového oddball úkolu od 20 pacientů (6 žen a 14 mužů). EEG signál jsme hodnotili v jeho celé šíři frekvenčního pásma 0,1-40 Hz. Celkem bylo vyšetřeno 660 míst ve frontálních, temporálních a parietálních lalocích. Počet vybraných EEG odpovědí po terčových podnětech byl průměrně 52. Do skupiny neterčových nehabituovaných bylo vybráno průměrně 42 a habituovaných průměrně 89 odpovědí. Průběhy zprůměrněných odpovědí po terčových a dvou skupinách neterčových podnětů byly vizuálně porovnány a hodnoceny jako identické nebo neidentické dvěma nezávislými pozorovateli.

ERPs byly identifikovány na 530 místech. Identický průběh ERP po terčových a neterčových podnětech byl pozorován v 88 případech, nejčastěji v amygdale, gyrus parahipokampalis, gyrus temporalis superior, medius a inferior, gyrus fusiformis a lingualis, méně často pak v senzorimotorickém kortexu, bazálním a dorzolaterálním prefrontálním kortexu a hipokampu. Ve zbylých 442 případech se evokované odpovědi po obou typech podnětů začaly ve svém průběhu lišit cca 300-470 ms od prezentace podnětů. Identické ERP nebyly nalezeny v bazálních gangliích a parietálním kortexu.

Výsledky této studie jako první ukazují, že v určitých strukturách mozku probíhá kognitivní zpracování senzorického podnětu bez vztahu k jeho významu (tzn. nezávisle na způsobu odpovědi). I přes zdánlivou „nevýznamnost“ neterčového podnětu v tomto úkolu se po jeho detekci velmi pravděpodobně musí aktivovat paměťové, případně rozhodovací nebo kontrolní procesy, které jsou potřebné pro správné plnění úkolu. V porovnání s výskytem odlišných ERPs se po obou typech podnětů shodné ERPs vyskytují 1) mnohem méně často a 2) hlavně v meziotemporálních strukturách. Uvedené skutečnosti by potom mohly vysvětlovat, proč tyto elektrofyziologické koreláty nejsou pozorovatelné na skalpu.

III.4. Terčové podněty častěji indukují pokles výkonu EEG aktivity v alfa pásmu, neterčové podněty naopak častěji nárůst výkonu EEG aktivity v alfa i beta pásmu

EEG aktivita během volního pohybu, paměťových a dalších kognitivních procesů souvisí se změnami výkonu alfa, beta a theta oscilací. Změny výkonu v theta pásmu jsou pozorovány v paměťových úkolech a souvisí pravděpodobně s kódováním a vybavováním informací v pracovní paměti (Klimesch, 1999). Snížení výkonu v alfa pásmu (ERD;

„event-related desynchronization“) bývá u skalpových studií interpretováno jako elektrofyziologický korelát aktivovaných procesů účastnících se zpracování senzorických a kognitivních informací, pozornosti nebo spuštění motorické odpovědi. Nárůst výkonu ve stejném pásmu (ERS; „event-related synchronization“) je chápán jako korelát inhibice zpracovávání informací nebo paměťových procesů (Klimesch, 1996; Mazaheri a Picton, 2005). Zvýšení výkonu v pásmu beta je pozorováno u řady senzorimotorických úkolů a v těchto případech je spojováno s inhibicí kortikálních procesů. Někteří jiní autoři však fenomén ERS v různých frekvenčních pásmech považují za korelát aktivního zpracování (Crone et al., 1998b, 2001).

Studium výkonových změn EEG signálu v průběhu oddball úkolu bylo v minulosti realizováno výjimečně. Ve skalpových studiích při zrakové stimulaci byl pouze po terčových podnětech prokázán signifikantní pokles výkonu v alfa pásmu (Sergeant et al., 1987), u sluchové varianty úkolu nárůst výkonu v gama pásmu s maximem kolem 37 Hz (Gurtubay et al., 2001). Jediná humánní intracerebrální studie, která se zaměřila na studium ERD/ERS fenoménů v oddball úkolu, prokázala po terčové odpovědi v hipokampu ERS v pásmu theta a ERD v pásmu alfa1 (Sochůrková et al., 2006). V této studii autoři analyzovali data pouze 6 pacientů a sledovali změny výkonu v definovaných frekvenčních pásmech a pouze v meziotemporálních strukturách.

Některé změny výkonu ve frekvenčních pásmech s fixně nastavenými hranicemi však nemusí dosáhnout hladiny signifikance. Toto omezení a malý počet vyšetřených pacientů ve studii Sochůrková et al. (2006) byl pro nás podnětem k detailnější analýze tohoto fenoménu (příloha 4).

Příloha 4. **Roman R**, Chládek J, Brázdil M, Jurák P, Rektor I, Kukleta M. Changes of oscillatory activity in a visual oddball task (sEEG study). *Homeostasis in Health and Disease* 2006;44(4):169-171.

V tomto případě jsme data ze zrakového oddball úkolu analyzovali u 16 pacientů (4 ženy a 12 mužů). Vyšetřili jsme celkem 150 míst ve frontálních, temporálních a parietálních lalocích (66 v levé a 84 v pravé hemisféře). U každého pacienta jsme nejdříve provedli časově frekvenční analýzu EEG odpovědi zvlášť pro terčové a neterčové podněty. Na jejím základě jsme vybrali pro každého pacienta specifická, různě široká frekvenční pásma, ve kterých došlo k signifikantní změně výkonu a která bylo možno zařadit do pásma alfa nebo beta. Cílem studie

byl popis struktur, ve kterých dochází k signifikantním změnám výkonu (ERD/ERS) a porovnání změn výkonu mezi terčovou a neterčovou odpovědí.

Signifikantní změny výkonu EEG aktivity jsme pozorovali u všech pacientů po terčové (95 míst) i neterčové odpovědi (84 míst) a to v různých mozkových strukturách v obou hemisférách – gyrus cinguli, gyrus fusiformis, gyrus angularis, hipokampus, gyrus parahipokampalis, gyrus temporalis superior, medius a inferior a frontoorbitálním kortexu. Po terčových podnětech jsme v alfa pásmu pozorovali ERD v 59 % a ERS ve 41 % případů, zatímco v beta pásmu ERD ve 46 % a ERS v 54 % případů. Po neterčových podnětech jsme v alfa pásmu pozorovali ERD v 38 % a ERS v 62 % případů, v beta pásmu pak ERD ve 29 % a ERS v 71 % případů. Po terčových podnětech v 17 případech a neterčových podnětech v 20 případech jsme na stejném kontaktu našli nárůst i pokles výkonu ve více pásmech současně.

Výsledky této studie ukázaly, že indukované EEG změny v oddball úkolu lze najít v celé řadě struktur temporálního a frontálního laloku a rozšiřují tak nálezy předchozí studie Sochůrkové a spol. (2006). Po terčových podnětech jsme častěji pozorovali ERD v alfa pásmu, která by mohla odrážet procesy související s motorickou odpovědí. Na druhou stranu běžnější nález ERS po neterčových podnětech by mohl v některých případech ukazovat na převahu inhibičních procesů souvisejících s neprovedením stisku tlačítka. Zachycené změny výkonu jsou zjevně vázány na odpověď subjektů, jejich jasná interpretace však doposud chybí. Z našich výsledků také vyplývá, že sledování ERD/ERS v individuálně vybraných frekvenčních pásmech může lépe zachytit i takové změny výkonu, které by nebyly patrné při fixně nastavených hodnotách frekvenčních pásem.

III.5. Mapování „error“ potenciálů ukazuje účast řady kortikálních oblastí v mozkovém systému detekce chybných odpovědí

Hodnocení správnosti vykonané odpovědi je pravděpodobně jedna z klíčových funkcí lidského mozku. Na začátku 90. let byla popsána negativní komponenta skalpového ERP, která se objevuje 50-100 ms po chybné motorické odpovědi (Falkenstein et al., 1991; Gehring et al., 1993). Tato negativita je maximální frontocentrálně a označuje se termínem „error negativity“ (Ne) nebo „error-related negativity“ (ERN). Předpokládá se, že tento na chybu vázaný potenciál je elektrofyziologickým korelátem detekce chybné odpovědi nebo kontroly odpovědi jako takové (Coles et al., 2001; Falkenstein et al., 2000; Vidal et al., 2000). Detekci chyby někteří autoři vysvětlují jako detekci neshody (konflikt) mezi provedenou chybnou odpovědí a neurální reprezentací správné odpovědi vytvořené v průběhu kontinuálního zpracování podnětu

(Botvinick et al., 2001; Yeung et al., 2004). Lokalizační analýzy komponent skalpových ERP ukazují na možné zdroje ERN v předním cingulárním kortexu nebo pre-suplementární motorické oblasti (Holroyd et al., 1998; Luu et al., 2000; Ridderinkhof et al., 2004). Aktivaci ACC po chybných odpovědích prokazují také některé fMRI studie (např. Braver et al., 2001; Carter et al., 1998; Fiehler et al., 2004; Garavan et al., 2003). Méně často se aktivace objevuje v pre-SMA, inzulárním kortexu, zadním cingulárním kortexu, thalamu, lobulus parietalis inferior a gyrus supramarginalis, (Menon et al., 2001; Ullsperger a von Cramon, 2001).

Intracerebrální registrace ERP u epileptických pacientů během předoperačního video-EEG monitorování nabízí možnost přímé lokalizace zdrojů evokovaných potenciálů. V souvislosti s mapováním mozkových oblastí účastnících se zpracování chybných odpovědí je bezesporu zajímavý výsledek naší intracerebrální studie z roku 2002. V průběhu zrakového oddball úkolu totiž někteří pacienti také někdy chybně stiskli tlačítko po terčových podnětech. Vybrali jsme 7 pacientů s dostatečným počtem chybných odpovědí (průměrně 9,3). Zprůměrněním těchto chybných odpovědí jsme získali typické „error“ potenciály, tedy ERN. Jejich zdroje jsme prokázali v řadě mozkových oblastí, zejména v gyrus cinguli anterior, meziotemporálních a prefrontálních korových oblastech (Brázdil et al., 2002). Naše výsledky však z důvodů použitého úkolu nebylo možno jednoduše srovnávat s ostatními ERP nebo fMRI studiemi.

K odstranění této nevýhody jsme pro mapování intracerebrálních generátorů ERN v nové studii (příloha 5) zvolili Go/NoGo úkol, používaný běžně v této oblasti výzkumu.

Příloha 5. Brazdil M, **Roman R**, Daniel P, Rektor I. Intracerebral error-related negativity in a simple Go/NoGo task. *Journal of Psychophysiology* 2005;19:244-255.

V Go/NoGo úkolu byly na monitoru prezentovány střídavě dva typy podnětů - velké písmeno „X“ a „K“ v poměru 4:1 (celkem 310 podnětů); přičemž „K“ nikdy dvakrát po sobě; trvání podnětu 240 ms, interstimulus interval byl náhodně 650 ms, 1650 ms nebo 2650 ms. Úkolem pacientů bylo stisknout co nejrychleji tlačítko pouze po písmenu „X“. Studie se zúčastnilo 7 pacientů (1 žena a 6 mužů). Celkem jsme vyšetřili 574 míst frontálního, temporálního a parietálního laloku. Při vlastní analýze jsme EEG data nejdříve filtrovali (pásmová propust 2-10 Hz). EEG epochy délky 600 ms (300 ms před a 300 ms po stisku tlačítka) jsme zprůměrnili od stisku tlačítka zvlášť pro správné odpovědi (tzn. stisk po „X“) a pro chybné odpovědi (stisk po „K“) a vzájemně porovnali.

Průměrná chybovost našich pacientů byla 46±18,7 %. Generátory „error“ potenciálů jsme nalezli v mnoha kortikálních oblastech – shodně s nálezy fMRI studií jsme je nejčastěji identifikovali mediálně frontálně (gyrus cinguli anterior, pre-SMA, gyrus frontalis medialis), dále pak v dorzolaterálním prefrontálním kortexu, orbitofrontálním kortexu, laterálním temporálním kortexu a v izolovaném případě také v gyrus supramarginalis. Zajímavý byl nález dvou zdrojů ERN v ACC – jeden v rostrální a druhý v kaudální části. To by mohlo souviset s odlišnými procesy, tj. emočním zpracováním a specifickou detekcí chybné odpovědi, protože rostrální část ACC funkčně souvisí s emocemi a dorzální část s kognitivními funkcemi a řízením motoriky (Bush et al., 2000; Devinsky et al., 1995; Paus et al., 1993). Přítomnost ERN v laterálním prefrontálním kortexu jsme prokázali i v naši předchozí studii (Brázdil et al., 2002). Současná aktivace laterálního prefrontálního kortexu s ACC během chybných odpovědí byla již prokázána Gehringem a Knightem (2000), ale její funkční význam není jasný.

Aktivace pre-SMA při kontrole provedení odpovědi je v fMRI studiích většinou asociována se zpracováním konfliktu a inhibicí odpovědi (Braver et al., 2001; Menon et al., 2001). Náš nález ERN v této oblasti však shodně se studií Garavana et al. (2004) potvrzuje její účast i při detekci chyby. Na rozdíl od neurozobrazovacích studií se nám podařilo prokázat ERN i ve frontoorbitálním kortexu, který je funkčně spojován s modulací impulzivity (Bechara et al., 2000). Přítomnost „error“ potenciálů v řadě kortikálních oblastí je důkazem existence rozsáhlé neuronální sítě, která může být v tomto případě podkladem mozkového systému kontroly chybných odpovědí.

III.6. Po provedení správné odpovědi v rámci oddball úkolu se aktivují dvě funkčně odlišné neuronální sítě, některé ze zúčastněných struktur jsou současně využívány i při hodnocení odpovědí chybných

Při studiu neuronálních systémů, které se podílejí na hodnocení správnosti vykonané odpovědi v jednoduchých kognitivních úkolech, se pozornost vědecké komunity většinou zaměřuje na tzv. „error“ potenciály generované po chybné odpovědi. Jejich detailnější popis je uveden v předchozím komentáři k práci Brázdila a spol. (2005) výše uvedené v III.5.

Elektrofyziologické koreláty vyvolané po provedení správné odpovědi jsou studovány v mnohem menší míře. Ve skalpových studiích se popisuje negativní potenciál vyvolaný po správně provedené odpovědi, tzv. „correct response-related negativity (Nc/CRN)“ s frontální (Mathalon et al., 2002; Meckler et al., 2011) a frontocentrální distribucí (Falkenstein

et al., 2000; Hajcak et al., 2005). Na základě těchto výsledků se za zdroj Nc považuje rostrální cingulární kortex (Carter et al., 1998; Roger et al., 2010). Podobně jako u skalpových „error" potenciálů lze u správných odpovědí po Nc nalézt i pozdější pozitivní komponentu, tzv. „correct response positivity (Pc)", která je studována minimálně a slouží obecně jako „klidová" aktivita při porovnávání s Pe (Bates et al., 2004). Na rozdíl od „error" potenciálů, které jsou studovány i s pomocí intrakraniálního EEG, analogické elektrofyziologické studie a hlubší interpretace evokovaných potenciálů po správné odpovědi chybí.

K doplnění chybějících poznatků z oblasti hodnocení správnosti provedených odpovědí při provádění kognitivních úkolů jsme opět analyzovali data pacientů vyšetřených v oddball úkolu (příloha 6). Pro účely této studie jsme navíc využili skutečnosti, že kromě naprosté většiny správných odpovědí pacienti také občas chybovali - po terčovém podnětu spínač nestiskli nebo po častém podnětu spínač stiskli. Tři pacienti dokonce chybovali po terčových i neterčových podnětech v dostatečném počtu vhodném pro zpracování ERP. Vedle mapování oblastí aktivovaných po správných motorických reakcích po terčových odpovědích jsme tak v této studii mohli současně posuzovat i možnou účast těchto oblastí v reakci na odpovědi chybné, což doposud v intrakraniálních studiích popsáno také nebylo.

Příloha 6. Damborska A, **Roman R**, Brazdil M, Rektor I, Kukleta M. Post-movement processing in visual oddball task - Evidence from intracerebral recording. *Clinical Neurophysiology* 2016;127(2):1297-1306.

Ve studii byla analyzována data 18 pacientů (4 ženy a 14 mužů). Bylo vyšetřeno celkem 205 míst ve frontálních, temporálních a parietálních lalocích. EEG signál byl filtrován ve frekvenčním pásmu 0,1-40 Hz. EEG epochy v trvání 1800 ms byly zprůměrněny od okamžiku prezentace podnětu pro správné odpovědi po terčových podnětech a od stisku tlačítka zvlášť pro odpovědi správné i chybné po obou typech podnětů. Počet chybných odpovědí v dostatečném počtu pro zprůměrnění (min. 13 chyb) měli pouze 3 pacienti, u kterých bylo možné srovnávat elektrofyziologické odpovědi po správných i chybných odpovědích.

Průměrná reakční doba u správných odpovědí po terčových podnětech v souboru 18 pacientů se pohybovala v rozmezí od 457±34ms po 644±78ms. Po zprůměrnění EEG epoch těchto odpovědí od okamžiku stisku tlačítka byly identifikovány „post-movement" potenciály (= po stisku tlačítka, tj. po pohybu) na 131 místech mozku. Jejich generátory byly často identifikovány v amygdale, hipokampu, laterálním temporálním kortexu, v dorsolaterálním prefrontálním, předním cingulárním a orbitofrontálním kortexu. Morfologicky se nejčastěji

jednalo o monofazické (80%), méně často o bifazické potenciály (v naší studii jsme tyto potenciály neoznačili zkratkami Nc/CRN nebo Pe pro jejich nejasný vztah k analogickým skalpovým ERP). Průměrná latence vrcholů potenciálů byla 295±184 ms po pohybu. Ve 27 % případů jim nepředcházely žádné ERP vlny v časovém intervalu od podnětu po stisk tlačítka.

Na 73 místech, kde byly identifikovány potenciály po pohybu u správných odpovědí na terčové podněty, byly při zprůměrnění od podnětu nalezeny potenciály také po správné odpovědi na neterčový podnět s latencí vrcholů (757±168ms) přesahující průměrnou reakční dobu subjektu. Při porovnání s latencemi potenciálů po terčových podnětech měřených při stejném způsobu zprůměrnění se ukázalo, že pozdní potenciály po neterčových podnětech vykazovaly bez specifické vazby na struktury kratší latenci o 174±118ms ve 34 místech, delší latenci o 166±88ms ve 26 místech a přibližně stejnou latenci v 7 místech.

Reakční doba po chybných odpovědích u třech pacientů byla delší v porovnání s reakční dobou po odpovědích správných. Pouze u dvou pacientů byly u chybných odpovědí („incorrect rejection, false alarms“) nalezeny pozdní potenciály a to v předním cingulárním, dorsolaterálním prefrontálním, primárním motorickém a laterálním temporálním kortexu. V těchto místech byly nalezeny současně i „post-movement“ potenciály po správné odpovědi na terčový podnět. U jednoho pacienta byly latence vrcholů těchto potenciálů delší než u potenciálů po správných odpovědích, u druhého pacienta se latence vrcholů nelišily více než o 20 ms.

V této studii se podařilo prokázat, že integrální součástí neuronálních sítí aktivovaných po správném provedení odpovědi v rámci oddball úkolu je kromě již dříve ve skalpových studiích identifikovaného předního cingulárního kortexu (Roger at al., 2010) také řada dalších struktur zejména temporálního a frontálního laloku. Účast některých z nich byla specifická pouze pro terčové odpovědi, u jiných byla na typu podnětu nezávislá. Z tohoto lze usuzovat na existenci dvou funkčně odlišných neuronálních sítí, které částečně sdílejí některé anatomické struktury. Aktivace neuronální sítě v prvním případě pak může odpovídat za mentální počítání podnětů s nezbytnou aktualizací pracovní paměti, případně zpracování somatosenzorických aferentních informací z aktivovaných svalů. Elektrofyziologické koreláty na typu podnětu nezávislé pak mohou reprezentovat procesy hodnotící správnost provedené odpovědi v porovnání s informací o významech jednotlivých podnětů uložených v paměti. Nález mozkových oblastí, které jsou aktivovány jak u správných tak u chybných odpovědí, potvrzuje dřívější předpoklady ze skalpových studií, že generátory „error“ a „correct“ potenciálů se pravděpodobně překrývají (Wessel et al., 2012).

III.7. Přední cingulární kortex hraje významnou roli v komunikaci s temporálními oblastmi mozku

V současné době se předpokládá, že podkladem kognitivních funkcí jsou mechanismy funkční integrace četných neuronálních populací aktivovaných v průběhu zpracování informací. Otázkou zůstává, zda v integraci neuronálních sítí velkého rozsahu („large-scale cognitive networks“) hraje klíčovou roli nějaká struktura nebo je to vlastnost kognitivních sítí jako takových (Bressler a Kelso, 2001; Fries et al., 2001; Jensen et al., 2007; Varela et al., 2001). Jedním z kandidátů strukturální lokalizace integrativních funkcí je přední cingulární kortex (ACC). Anatomicky je propojen s celou řadou oblastí mozku a jeho aktivaci v průběhu kognitivních úkolů ukazuje řada studií (např. Allman et al., 2001; Paus, 2001; van Veen a Carter, 2002). Experimentální doklady potvrzují jeho funkční účast např. při řešení problémů, rozpoznání chyb, rozpoznání a řešení konfliktních situací nebo při adaptivní odpovědi v měnících se podmínkách (Allman et al., 2001; Posner et al., 2007). Ze studií vyplývá, že ACC se podílí na motorické, kognitivní a motivační složce chování. Paus (2001) uvádí, že právě účast na třech složkách chování odlišuje ACC od ostatních frontálních kortikálních oblastí a umožňuje tak této struktuře převádět záměry k akcím. Dle Rueda a spol. (2004) spočívá hlavní příspěvek ACC k mozkovým funkcím v jeho řízení informačních vstupů z prostředí a tím k omezení vzniku konfliktních behaviorálních odpovědí.

Cingulární kortex, zejména jeho přední část, byl vedle dalších frontálních korových oblastí často vyšetřován v rámci hledání epileptického ložiska u naší skupiny epileptických pacientů, kteří prováděli zrakový oddball úkol. Současná představa o klíčovém postavení ACC v integraci aktivit různých neuronálních populací nás vedly k myšlence ověřit hypotézu, že míra funkční interakce ACC se vzdálenými mozkovými oblastmi odlišuje tuto strukturu od ostatních frontálních oblastí (příloha 7). Za tímto účelem jsme porovnávali úroveň synchronizace intracerebrálního EEG signálu ve frekvenčním pásmu beta2 (pásmová propust 25-35 Hz) mezi frontálními a temporálními laloky, přičemž některé frontální kontakty se nacházely v ACC a další v jiných frontálních oblastech. Frekvenční pásmo beta2 jsme vybrali na základě nálezu vyššího zastoupení synchronních oscilací právě v tomto pásmu v naší předchozí studii zaměřené na analýzu synchronizací mezi frontálními a temporálními oblastmi v různých frekvenčních pásmech (Kukleta et al., 2009).

Příloha 7. Kukleta M, Bob P, Brazdil M, **Roman R**, Rektor I. The level of frontal-temporal beta-2 band EEG synchronization distinguishes anterior cingulate cortex from other frontal regions. *Consciousness and Cognition* 2010;19:879-886.

V předkládané studii jsme vyšetřili EEG data ze zrakového oddball úkolu u 8 pacientů původního souboru. V prvním kroku jsme vybrali 180 fronto-temporálních párů intracerebrálních kontaktů. EEG signál ve frontálních lalocích byl ve 41 případech snímán v předním cingulárním kortexu, v 60 případech v orbitofrontálním kortexu, v 41 případech v dorzolaterálním prefrontálním kortexu a v 38 případech v mesiálním frontálním kortexu. Druhý kontakt vybraných párů se nacházel v temporálním laloku (většinou v laterálních korových oblastech, méně často v gyrus parahipokampalis a fusiformis, amygdale a hipokampu). Následoval výpočet korelačních koeficientů filtrovaného (25-35 Hz) EEG signálu a porovnání jejich průměrných hodnot ve všech 180 párech ve třech funkčně odlišných obdobích: a) v osmnácti 30s úsecích vybraných v průběhu celého oddball úkolu nezávisle na okamžiku prezentace podnětů; b) v 1s úseku předcházejícím prezentaci podnětu; c) v 1s úseku po prezentaci podnětu. V případě b) a c) jsme výpočet korelace provedli na zprůměrněných EEG odpovědích a to jenom po neterčových podnětech (nebyly kontaminovány motorickou aktivitou).

Výsledky studie ukázaly, že průměrné hodnoty korelačních koeficientů ve fronto-temporálních párech, které měly frontální kontakt v ACC, byly signifikantně vyšší než v párech s kontaktem v jiných frontálních oblastech a to ve všech třech funkčně odlišných obdobích, tedy v průběhu celého experimentu, v období zvýšeného očekávání dalšího podnětu a v období senzorického a kognitivního zpracovávání neterčového podnětu. V souladu s výsledky jiných autorů (Paus, 2001; Posner et al., 2007) tyto nálezy dokládají významnou roli předního cingulárního kortexu v neuronálních sítích velkého rozsahu, která může být podkladem integračních funkcí v průběhu kognitivních procesů.

III.8. Při zpracování podnětů spojených s aktivní odpovědí se v rámci frontálního laloku informace šíří směrem z gyrus cinguli do dorzolaterálního prefrontálního kortexu

Jak bylo uvedeno dříve, podněty v oddball úkolu spouští v mozku řadu procesů, které jsou podkladem časného senzorického zpracování, pozornosti a exekutivních funkcí. Přední cingulární kortex (ACC) a dorzolaterální prefrontální kortex (DLPFC) jsou považovány

za struktury účastnící se pozornostních procesů vyvolaných neočekávanými změnami v prostředí nebo procesů souvisejících s výběrem správné odpovědi. V těchto oblastech byl opakovaně prokázán generátor hluboké vlny P3a (Baudena et al., 1995; Brázdil et al., 1999; Halgren et al., 1998). Předpokládá se, že tyto dvě oblasti při řízení chování spolupracují, přičemž ACC je důležitý pro sledování zpracování podnětu a s tím související vhodné odpovědi (Shallice, 1988; Shallice et al., 1989). V případě potřeby ACC zřejmě aktivuje DLPFC (a obecně arousal systém), jehož prostřednictvím by se selektivně posílily procesy související se zpracováním podnětu a jeho kortikální reprezentací v zadních kortikálních oblastech, aby mohly být splněny vnitřní cíle nebo dohodnuté instrukce (Barch et al., 2001; Botvinick et al., 1999; Carter et al., 1998; Cohen et al., 2000). V tomto smyslu může být ACC chápáno jako klíčová oblast při časné alokaci pozornosti (Gitelman et al., 1999; Woldorf et al., 2001).

Hierarchické funkční uspořádání ACC a DLPFC v kognitivních úlohách bylo prokázáno i v rámci oddball úkolu s využitím fMRI (Brázdil et al., 2007). Nízké časové rozlišení této techniky však limituje prokazování směru informačního toku (efektivní funkční konektivity) mezi kortikálními oblastmi během časově krátkého zpracování podnětů. Pro jeho detailnější studium lze využít výpočet směrové transformační funkce, anglicky „directed transformation function“ (DTF) z EEG záznamů (Kaminski a Blinowska, 1991). S použitím tohoto výpočetního algoritmu bylo např. prokázáno, že tok informací z parietookcipitálních do frontálních oblastí je převažující v období před usnutím nebo při kódování zrakových informací, zatímco opačný směr šíření informací je typický po usnutí (De Gennaro et al., 2004; Babiloni et al., 2006).

Relativně častá současná explorace předního cingulárního kortexu a dorzolaterálního prefrontálního kortexu u naší skupiny epileptických pacientů opět exkluzivně umožnila využít intracerebrálně registrovaný EEG signál tentokrát pro studium efektivní funkční konektivity mezi těmito dvěma oblastmi během zpracování podnětů v průběhu oddball úkolu (příloha 8). S použitím DTF algoritmu jsme se snažili ověřit hypotézu, že ACC ovlivňuje oscilační aktivitu DLPFC.

Příloha 8. Brazdil M, Babiloni C, **Roman R**, Daniel P, Bares M, Rektor I, Eusebi F, Rossini PM, Vecchio F. Directional Functional Coupling of Cerebral Rhythms Between Anterior Cingulate and Dorsolateral Prefrontal Areas During Rare Stimuli: A Directed Transfer Function Analysis of Human Depth EEG Signal. *Human Brain Mapping* 2009;30:138-146.

Za tímto účelem jsme analyzovali data ze zrakového oddball úkolu 8 pacientů (2 ženy a 6 mužů), u kterých byly v rámci předoperační léčby epilepsie současně vyšetřeny obě oblasti. Do analýzy byla použita EEG data po terčových i neterčových podnětech pouze z ACC (area 32 a 24) a DLPFC (area 9, 44, 45 a 46) a to v jednom časovém okně 500 ms před okamžikem prezentace podnětu a ve druhém časovém okně 500 ms po prezentaci podnětu. Dle standardizovaného postupu (Kaminsky a Blinowska,1991) byla EEG data nejdříve normalizována a poté použita jako vstupní parametry vícerozměrného autoregresního modelu pro výpočet DTF. Jednoduše lze říci, že použitý model určuje informační tok mezi místy A a B prostřednictvím výpočtu pravděpodobnosti, se kterou lze průběh EEG dat v místě A predikovat na základě průběhu EEG dat v místě B a naopak. DTF výpočet byl proveden pro terčové a neterčové EEG odpovědi ve frekvenčním pásmu theta, alfa, beta a gama.

V časovém okně 500 ms před prezentací podnětů byly DTF hodnoty pro směr toku informací ACC→DLPFC a DLPFC→ACC ve všech frekvenčních pásmech po terčovém i neterčovém podnětu přibližně shodné. V časovém okně 500 ms po prezentaci podnětů se DTF hodnoty zvýšily pro směr toku informací ACC→DLPFC, ale jen po terčovém podnětu, přičemž signifikantní změny bylo dosaženo pouze v pásmu theta.

Výsledky naší studie tedy potvrzují hypotézu, že při odpovědi mozku na terčový podnět v průběhu oddball úkolu, přední cingulární kortex ovlivňuje oscilační aktivitu dorzolaterálního prefrontálního kortexu zejména v theta frekvenčním pásmu. Na událost vázané modulace právě tohoto theta rytmu jsou důležitým elektrofyziologickým korelátem mozkových procesů souvisejících s integrací senzorimotorických a kognitivních informací (Basar et al., 1999b; Brankack et al., 1996; Pfurtscheller a Lopes da Silva, 1999). Předpokládá se, že neuronální oscilace v theta pásmu souvisejí se zaměřením pozornosti, pracovní pamětí, kódováním epizodické paměti a řízením akcí (Gevins a Smith, 2000; Sauseng et al., 2002, 2004; Sochůrková et al., 2006). V těchto souvislostech pak v naší studii identifikovaný informační tok z ACC do DLPFC může souviset s pozorností, aktualizací pracovní paměti a řízením motorické odpovědi na obtížně předvídatelný vzácný (terčový) podnět.

IV. Závěr

Intracerebrální elektroencefalografie je vyšetřovací metoda, která je používána u pacientů s neurologickým onemocněním výhradně na základě přesně definovaných klinických požadavků. Přesto tato metoda nabízí jedinečnou příležitost studovat elektrickou aktivitu neuronálních populací mozku u člověka při vědomí. V neurovědeckém výzkumu tvoří sice minoritní podíl, poskytuje však unikátní pohled na mechanismy mozkových funkcí, které nelze studovat u zvířat. Přispívá tak zásadně k detailnějšímu pochopení fungování lidského mozku, což je základním předpokladem pro vývoj sofistikovanějších diagnostických a terapeutických postupů použitelných při jeho poruchách.

Při zpracování intracerebrálních EEG dat snímaných v průběhu kognitivních úkolů se používají některé metodické postupy běžně využívané ve skalpových EEG studiích. Zprůměrnění několika desítek EEG odpovědí od okamžiku prezentace podnětu umožňuje např. analyzovat evokované (ERP) a indukované (ERD/ERS) děje a určit jejich intracerebrální distribuci. Pro svoje specifické vlastnosti, jako je např. vysoký poměr signál-šum, je možné iEEG data analyzovat i způsobem, který u skalpového EEG signálu lze použít výjimečně, pokud vůbec. Příkladem mohou být námi navržené analýzy pomalých kognitivních potenciálů v podskupinách s malým počtem EEG odpovědí. Nevýhodou intracerebrálních EEG dat je nemožnost jejich matematického zprůměrnění ve skupině pacientů, protože se hluboké elektrody implantují do různých oblastí a nikdy tak nejsou vyšetřena naprosto identická místa. Pro identifikaci zákonitých jevů je potom nutné např. vizuální porovnání EEG odpovědí snímaných z různých oblastí mozku u jednotlivých pacientů a hledání takových elektrofyziologických projevů, jako je např. morfologie a latence ERP komponent, které jsou vyšetřeným oblastem a skupině pacientů společné. Všechny zmiňované postupy jsme použili v naší práci s cílem hlouběji pochopit vztah mezi elektrofyziologickými koreláty registrovanými intracerebrálně a předpokládanými mentálními operacemi, přičemž část našich nálezů je komentována v předloženém souboru prací.

Při výzkumném použití iEEG platí dvojnásob, že vhodně navržený úkol a perfektně dodržená pravidla získávání dat s detailní dokumentací okolností nahrávání mohou poskytnout data s vysokým informačním obsahem. Je potom jen otázkou času a vůle nové zákonitosti objevovat a popsat.

Příloha č. 1

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Intracerebral P3-like waveforms and the length of the stimulus–response interval in a visual oddball paradigm

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Abstract

Objective: This study investigated the possible linkage of intracerebrally recorded P3-like waveforms to the processes induced by stimulus perception or motor response formation.

Methods: Event-related potentials were recorded from 560 cerebral sites in 17 patients suffering from intractable epilepsy during visual oddball task. Potentials evoked by the target stimuli were sorted according to button-pressing response times, and the P3 waveform was analyzed both in stimulus-locked and response-locked averages, which were separately averaged for fast and slow responses.

Results: P3-like waveforms were identified in 180 sites in 17 patients. Three different types of P3-like waveforms, diffusely distributed within the brain, were found: (1) time-locked to the stimulus (30 sites in 11 patients); (2) time-locked to the motor response (52 sites in 13 patients); and (3) with ambiguous time relationship to stimulus and motor response (98 sites in 16 patients).

Conclusions: The intracerebral P3-like waveform could represent different processes involved in performing active oddball tasks. Therefore, our results support the hypothesis that the P3 waveform registered by surface electrodes could be a heterogeneous phenomenon.

Significance: These results provide evidence that the P3 waveform is not only related to stimulus processing, which differs from what has been generally claimed in the literature.

Keywords: P3 waveform; ERPs; Intracerebral recordings; Visual oddball paradigm

1. Introduction

Event-related potentials (ERPs) are composed of a series of waveforms, each defined by its latency, polarity, scalp topography, and behavioural correlates (Halgren et al., 1998). Successive waveforms can be divided into early sensory, or exogenous, potentials primarily influenced by physical characteristics of the eliciting stimulus (Cracco and Cracco, 1976; Jewett et al., 1970), and late cognitive, or endogenous, potentials, primarily influenced by cognitive processes (Donchin et al., 1978; Halgren et al., 1998; Hillyard et al., 1978; Sutton et al., 1965).

One of the most studied waveforms of endogenous or 'cognitive' ERPs is the P3 (P300) waveform, which was first described by Sutton and colleagues in 1965. It is usually elicited in the oddball paradigm, wherein two stimuli are presented in a random order with different probabilities. In the active form of this paradigm, a subject is required to discriminate between the infrequent target stimulus and the frequent standard stimulus by noting the occurrence of the target, usually by pressing a button or mentally counting. The P3 waveform can also be obtained with alternative tasks: a passive oddball paradigm, a single stimulus paradigm, or a 3-stimulus paradigm (Bennington and Polich, 1999; Jeon and Polich, 2001; Polich, 1998). Using the 3-stimulus paradigm, two types of P3 waveform have been described: the novelty 'P3a' waveform, with frontal/central maximum scalp distribution, elicited by novel

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stimuli (Squires et al., 1975), and the later 'P3b' waveform, with the largest amplitudes over parietal areas, elicited by the infrequent target stimuli (Comerchero and Polich, 1999). A kind of P3 potential has even been recorded in a modified visual oddball paradigm after subliminally presented target stimuli (Brázdil et al., 2001).

In a task requiring specific motor response to a target stimulus, distinct movement-related 'P3-like' potentials (MRPs) are also generated intracerebrally that coincide with P3 potentials (Brázdil et al., 2003). The temporal occurrence of these MRPs is related to the occurrence of the movement and, therefore, they are time-locked to the button-pressing (Vaughan et al., 1968). The P3 usually coincides with the movement or precedes it, and thus these MRPs can distort the P3 scalp topography and can modify P3 amplitude and latency (Brázdil et al., 2003; Jentzsch and Sommer, 2001; Kok, 1988; Salisbury et al., 2001). Since the scalp potentials only reflect the sum of electrical activity propagated in a given area, it is hard to distinguish this MRP from the cognitive P3 waveform. This MRP contamination, however, can be at least partially eradicated by the use of a trial-by-trial reaction time (RT) matching procedure, which creates a variance-matched and temporally aligned MRP-correction waveform (Kok, 1988; Salisbury et al., 2001).

The P3 latency ranges from 250 to 600 ms after the stimulus onset, and can vary depending on the task complexity, stimulus, and subject (Comerchero and Polich, 1998; Mertens and Polich, 1997; Polich, 1998). The P3 latency is considered a measure of the stimulus classification speed (Kutas et al., 1977; Polich, 1986a,b). It is generally unrelated to response selection and execution processes (McCarthy and Donchin, 1981; Pfefferbaum et al., 1986), and is therefore, independent of behavioural RT (Duncan-Johnson, 1981). This view is supported by many studies where the manipulations with the stimuli resulted in an increase of the RT as well as of the P3 latency: the reduction of stimulus intensity (Verleger et al., 1991), the reduction of stimulus discriminability (Novak et al., 1990), increasing the number of irrelevant stimuli while randomly changing the location of the relevant stimulus (Magliero et al., 1984), presenting flanking stimuli to which the alternative response is assigned (Smid et al., 1990). In some other studies, the manipulation with responses was used in order to increase the RT but constant P3 latency was observed: using spatially incompatible stimulus–response (SR) assignments (Fitzpatrick et al., 1988). However, when presenting the stimulus on the side of the alternative response (Nandrino and El Massioui, 1995) or when increasing the number of response alternatives (Falkenstein et al., 1994a), the P3 latency became longer. There is some evidence that P3 latency is sensitive to response processing time, particularly when the response times in a given task are generally fast (Verleger, 1997). Indeed, the results of simple RT tasks suggest that motor execution can influence P3 latency. This effect, however, was observed only when stimulus evaluation demands were minimal. Increased stimulus evaluation demands are sufficient to mask the motor execution effect on P3 latency. In general, motor execution processes would not be considered a confounding factor in most P3 studies (Doucet and Stelmack, 1999; Rektor et al., 2003).

In studies using depth electrode recordings, P3 generators were found in different brain structures (Baudena et al., 1995; Brázdil et al., 1999; Halgren et al., 1995a,b). Two characteristic, modality non-specific intracerebral patterns of P3 were described. First, the triphasic waveform with sharp negative, positive, and negative peaks termed N2a-P3a-SW, associated with the system for the orientation of attention, was observed in the middle temporal, posterior parahippocampal and fusiform gyrus sites, and in dorsolateral prefrontal, inferior parietal and cingulate cortices. Second, a broad P3b waveform, coupled to the event-encoding system, was found in the hippocampus, amygdala, superior temporal sulcus, lateral orbitofrontal cortex, and intraparietal sulcus (Brázdil et al., 1999; Halgren et al., 1995a,b). Due to their similarity to the scalp-recorded P3 waveforms, these were labelled as the depth P3a and depth P3b, or generally P3-like waveforms. Their contribution to the scalp-recorded P3s remains unclear.

To date, the P3 waveform is generally viewed as reflecting decision or cognitive closure of the stimulus identification. It has also been linked to orientation, attentional mechanisms, and the update of working memory (Paller et al., 1987; Squires et al., 1975). This relationship between the P3 response and the fundamental aspects of cognitive function is used in clinical practice for the assessment of cognitive ability in normal subjects as well as in patients with neurological and psychiatric diseases. To obtain the most uniform P3 responses, specific stimulus characteristics, task factors, subject variables, and proper electrophysiological recording are recommended (Polich, 1998).

In the oddball paradigm, where recognition of the target stimulus is indicated by pressing the button, two events well defined in time are recorded simultaneously together with EEG. They are the stimulus presentation, which starts processing of this information and the button pressing which stands for the signal of the subject that he/she recognized the target stimulus. Approximately 50 target stimuli are used in order to be randomly presented within the oddball task. The behavioural RT, i.e. the time from the stimulus presentation to the moment of the button pressing, can vary across trials in each subject for 50–200 ms even though the subjects are instructed to respond as fast as possible. Therefore we can sort all 50 responses into fast and slow subgroups and average them separately. If the studied waveform of ERP represents process time locked to the stimulus, its peak latency will be the same in fast and slow subgroups averaged with the stimulus as a trigger. Back averaging, with the button pressing as a trigger, would reveal, in this case, that the peak latency of the waveform is longer in slow averages and shorter in fast averages. If the waveform

represents process time locked to the button pressing, the peak latency will be longer in slow and shorter in fast subgroups when averaged with the stimulus as a trigger. The averaging with the button pressing as a trigger would then reveal the same peak latency.

In our study, we analyzed intracerebrally-recorded P3-like waveforms obtained in a standard visual oddball paradigm in epileptic patients during their presurgical diagnostic exploration. We were interested in whether the unequivocal relationships between P3 latency and the processes underlying the experimental task, found in scalp recordings, could be also demonstrated on the depth-recorded P3-like waveform. To answer this question, we investigated the character of the relationship between the P3 latency and the SR interval. In each subject, we created one averaged curve from trials with short SR intervals and another curve from trials with long SR intervals. In both cases, two averaging procedures were performed: with the stimulus onset as a trigger and with button-pressing as a trigger. The comparison of P3-like waveforms obtained under these conditions enabled us to evaluate the possible link between them and the processes induced by stimulus perception or motor response formation.

2. Methods

2.1. Subjects

Seventeen patients (4 females and 13 males; see Table 1) with medically intractable epilepsy participated in the study (their mean age was 29.5 ± 5.5 years). All the subjects had normal or corrected-to-normal vision. Informed consent was obtained from each subject prior to the experiment, and the study received the approval of the Ethical Committee of Masaryk University.

2.2. EEG recordings

A total of 89 depth electrodes were implanted to localize the seizure origin prior to surgical treatment. 560 sites of the frontal, parietal, and temporal lobes (248 in the right and 312 in the left hemisphere; see Table 1) were explored with standard MicroDeep semiflexible multilead electrodes, each with diameters of 0.8 mm. Recordings contacts were 2.0 mm in length, and successive contacts were separated by 1.5 mm. Lesional anatomical structures and epileptogenic zone structures were not included in the analysis. The exact position of the electrodes and their contacts in the brain were verified using postplacement MRI with electrodes in situ.

The EEG signal was recorded simultaneously from various intracerebral structures and from CPz scalp electrodes (situated between Cz and Pz) during seizure-free periods using the 64-channel Brain Quick EEG system (Micromed). All the recordings were monopolar with respect to a reference electrode on the right processus mastoideus and were acquired at a 128 Hz sampling rate. All impedances were less than 5 kΩ. Button-pressing was recorded on a separate channel.

2.3. Behavioural task

A standard visual oddball paradigm was performed: two types of stimuli -target and frequent- were randomly presented in the centre of the screen. Clearly visible uppercase yellow letters X (target) and O (frequent) were presented on a white background as the experimental stimuli.

Table 1
Age, sex and handedness for 17 epileptic patients, along with the number of intracranial electrodes, recorded sites and brain lobes investigated

Patient ID	Age (years)	Sex	Handedness	Electrodes left/right hemisphere	Recording sites left/right hemisphere	Brain lobes
BS	25	M	R	4/1	14/2	T′, T, P′
DJ	20	M	R	1/1	13/13	F′, F, T′, T
DM	28	M	R	1/1	12/15	T′, T
FP	37	M	R	1/6	15/26	F′, F, T′, T
HZ	45	M	R	5/4	23/16	F′, F, T′, T
HP	30	M	R	5/2	28/12	F′, F, T′, T
JI	31	F	R	0/6	0/41	F, T
KM	32	M	R	1/1	14/14	F′, F, T′, T
KP	30	M	R	0/4	0/40	T, P
KJ	30	M	R	4/1	27/15	F′, F, T′, T
LL	27	F	R	0/4	0/22	T
PM	25	M	L	6/4	24/17	F′, F, T′, T
SM	34	M	R	0/5	0/34	F, T, P
SO	30	F	R	3/1	15/11	F, T′, T, P′
SI	23	M	R	4/5	16/25	F′, F, T′, T
VH	28	F	R	7/0	41/0	F′, T′
VP	27	M	R	1/0	15/0	F′, T′

F, frontal lobe; T, temporal lobe; P, parietal lobe; symbol (′) indicates left hemisphere.

The duration of stimuli exposure was constant at 200 ms; the ratio of target to frequent stimuli was 1:5. The interstimulus interval varied randomly between 2 and 5 s. Each subject was instructed to respond to the target stimulus as quickly and as accurately as possible by pressing a microswitch button in the dominant hand and, at the same time, he/she was instructed to silently count the target stimuli.

2.4. Data analysis

ScopeWin software was used for further off-line signal analysis. Each 1.7 s stimulus epoch beginning 500 ms prior to the stimulus onset (used as a prestimulus baseline; in figures only 300 ms before the stimulus onset is presented) was inspected visually and further processing was performed with artefact-free EEG periods. Because P3-like waveforms have a relatively low frequency (Polich, 1998), a digital filter with a bandpass of 0.5–5.5 Hz was used for the offline analysis.

In each subject, approximately 50 trials were averaged for target and 150 trials for frequent stimuli (unsorted averages; sections A in Figs. 1–4). The identification of P3-like waveforms in the latency range of 250–600 ms was based on a visual evaluation of the records by two independent experts. To reduce the contamination of P3-like waveforms by movement-accompanying slow potentials (Rektor et al., 1998), those with a latency longer than the mean SR interval of each patient were excluded from the analysis (11 from 191 cases). In each target trial, the SR interval was measured. From all the target trials in each patient, two subgroups with shorter and longer SR intervals were created arbitrarily (see Table 2). In creating the subgroups, we attempted to meet the following general demands: sufficient number of trials for averaging in each subgroup; identical number of trials in both subgroups; corresponding range of SR intervals in each subgroup; and the largest possible difference of the mean values of SR intervals between the two subgroups. Selected trials were then averaged in two procedures: (i) with the stimulus onset as a trigger (sorted averages; sections B1 in Figs. 1–4), (ii) with the button-pressing as a trigger (sorted averages; sections B2 in Figs. 1–4). The peak P3 latencies in each subgroup for both averaging procedures were then analyzed. The differences of P3 peak latencies were considered as identical if the difference between them reached no more than 8 ms (with the sampling rate of 128 Hz, the difference of 8 ms corresponds to the difference of 1 sample).

For statistical purposes, one-way ANOVA, post hoc Spjotvoll/Stoline test (a variant of Tukey's HSD test) and regression analysis were performed. Statistics were obtained using the routines included in the Statistica program (StatSoft).

3. Results

The mean number of averaged target trials in each subgroup of patients was 16±3 (minimum 9, maximum 24;

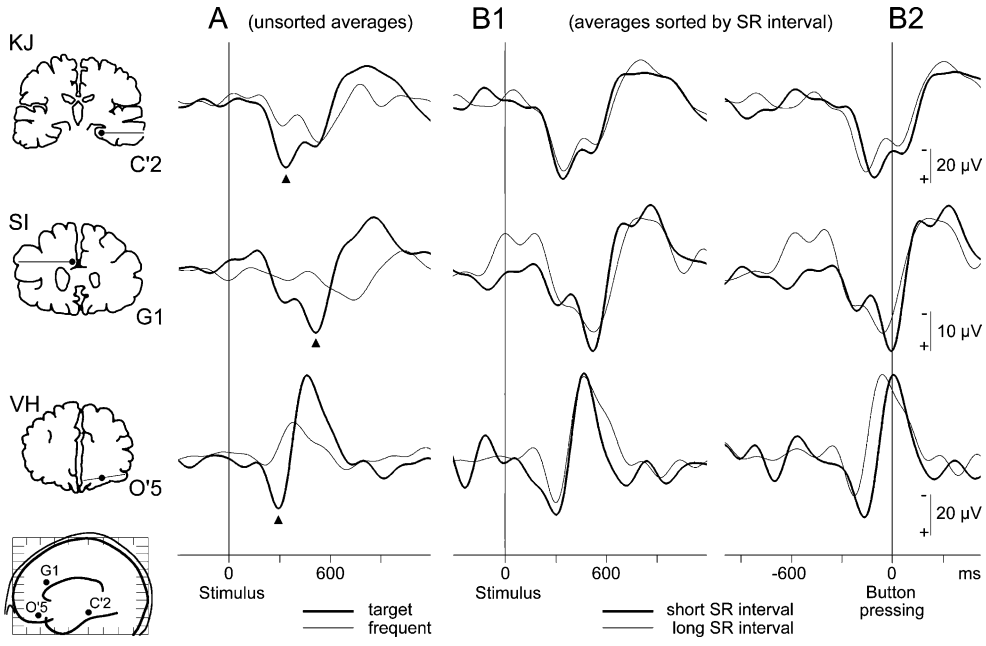

Fig. 1. Three examples of P3-like waveforms time-locked to the stimulus. Coronal sections representing electrode and contact position in each patient are not proportional. Patient KJ (C′2, left parahippocampal gyrus), patient SI (G1, right anterior cingulate gyrus) and patient VH (O′5, left orbitofrontal cortex). (A) ERPs to target (thick line) and non-target (thin line) stimulus, unsorted averages. (B1, B2) Target ERPs from the same sites and patients averaged from the subgroup of trials with short SR intervals (thick line) and long SR intervals (thin line), with the stimulus onset as a trigger (on the left, B1) and the button-pressing as a trigger (on the right, B2). The peak P3 latency difference between the two subgroups averaged with the stimulus as a trigger was 0 ms (KJ), 0 ms (SI), 8 ms (VH), whereas averaged with the button-pressing as a trigger it was 47 ms (KJ), 47 ms (SI) and 63 ms (VH). Symbol ▲ indicates P3-like waveform.

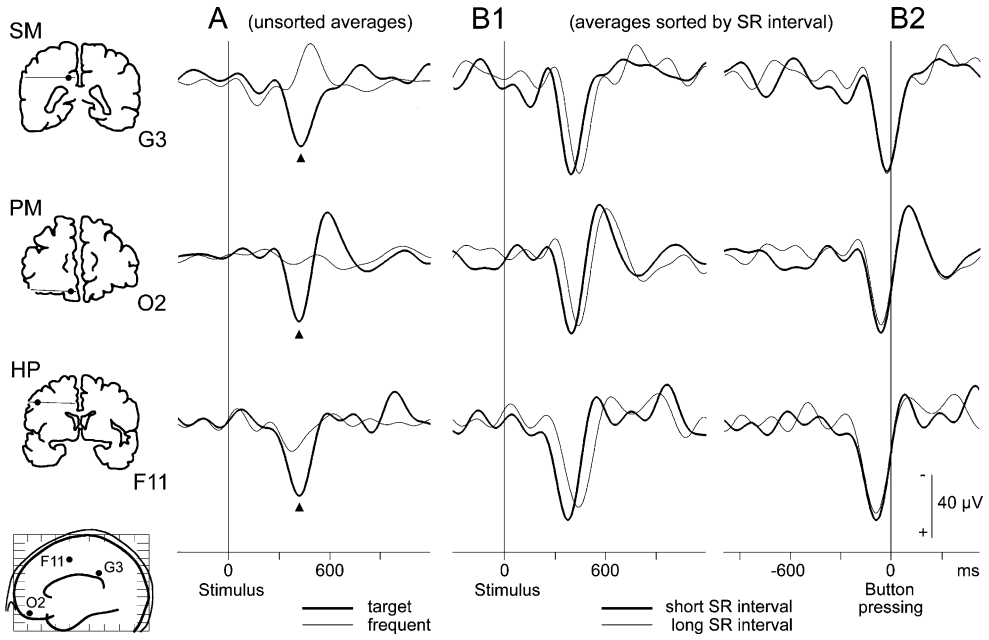

Fig. 2. Three examples of P3-like waveforms time-locked to the motor response. Coronal sections representing electrode and contact position in each patient are not proportional. Patient SM (G3, right posterior cingulate gyrus), patient PM (O2, right rectus gyrus) and patient HP (F11, right premotor cortex, Brodmann's area 6). (A) ERPs to target (thick line) and non-target (thin line) stimulus, unsorted averages. (B1, B2) Target ERPs from the same sites and patients averaged from the subgroup of trials with short SR intervals (thick line) and long SR intervals (thin line), with the stimulus onset as a trigger (on the left, B1) and the button-pressing as a trigger (on the right, B2). The peak P3 latency difference between the two subgroups averaged with the stimulus as a trigger was 47 ms (SM), 40 ms (PM) and 63 ms (HP), whereas averaged with the button-pressing as a trigger it was 0 ms (SM), 0 ms (PM), 8 ms (HP). Symbol ▲ indicates P3-like waveform.

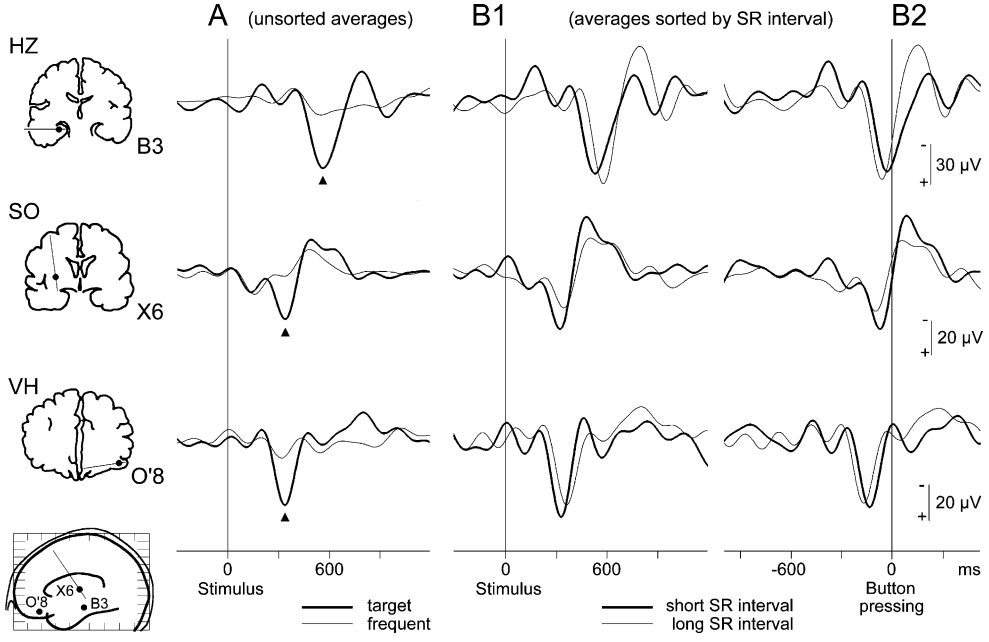

Fig. 3. Three examples of P3-like waveforms with ambiguous time relationship to stimulus and motor response. Coronal sections representing electrode and contact position in each patient are not proportional. Patient HZ (B3, right hippocampus posterior), patient SO (X6, right putamen) and patient VH (O′8, left ventrolateral prefrontal cortex). (A) ERPs to target (thick line) and non-target (thin line) stimulus, unsorted averages. (B1, B2) Target ERPs from the same sites and patients averaged from the subgroup of trials with short SR intervals (thick line) and long SR intervals (thin line), with the stimulus onset as a trigger (on the left, B1) and the button-pressing as a trigger (on the right, B2). The peak P3 latency difference between the two subgroups averaged with the stimulus as a trigger was 47 ms (HZ), 24 ms (SO), 31 ms (VH), whereas averaged with the button-pressing as a trigger it was 31 ms (HZ), 24 ms (SO) and 31 ms (VH). Symbol ▲ indicates P3-like waveform.

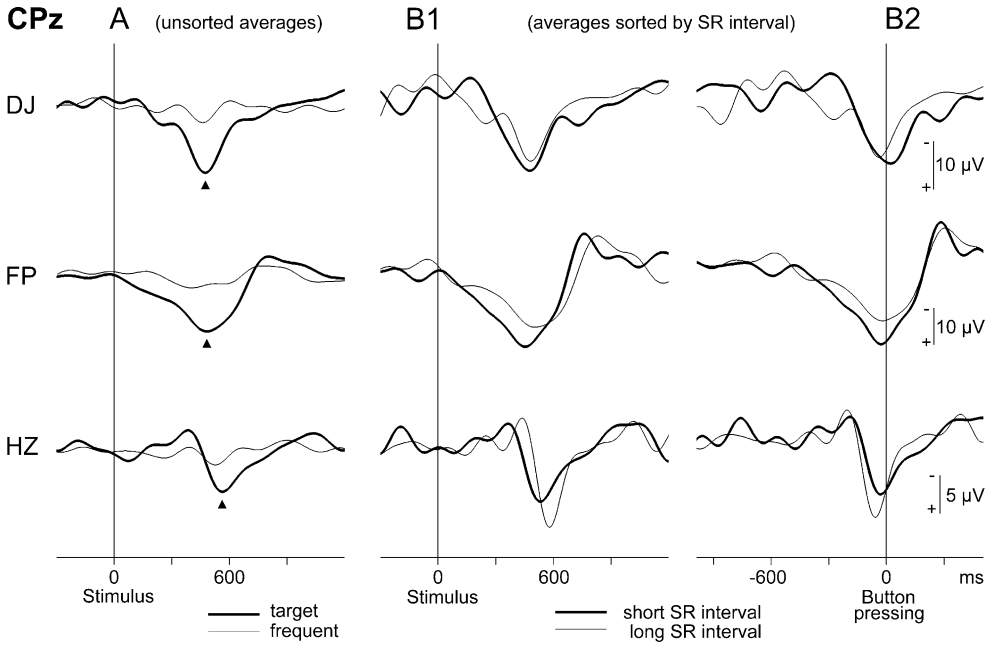

Fig. 4. Three examples of P3 waveforms recorded with the scalp CPz electrodes. Patient DJ, P3 waveform with the latency of 477 ms time-locked to the stimulus; patient FP, P3 waveform with the latency of 484 ms time-locked to the motor response; patient HZ, P3 waveform with the latency of 562 ms with ambiguous time relationship to stimulus and motor response. (A) ERPs to target (thick line) and non-target (thin line) stimulus, unsorted averages. (B1, B2) Target ERPs from the same sites and patients averaged from the subgroup of trials with short SR intervals (thick line) and long SR intervals (thin line), with the stimulus onset as a trigger (on the left, B1) and the button-pressing as a trigger (on the right, B2). The peak P3 latency difference between the two subgroups averaged with the stimulus as a trigger was 7 ms (DJ), 55 ms (FP), 47 ms (HZ), whereas averaged with the button-pressing as a trigger it was 62 ms (DJ), 0 ms (FP) and 24 ms (HZ). Symbol ▲ indicates P3 waveform.

see Table 2). We compared the morphology of P3-like waveforms obtained from our subgroups with short and long SR intervals with those obtained from all target trials in each patient. A very similar shape was found in all of the cases. Nine selected examples are presented in Figs. 1–3; compare left (A) and middle (B1) columns of curves.

P3-like waveforms were identified in 180 sites in 17 patients diffusely in the frontal, temporal, and parietal lobes

Table 2
Number of target trials, mean SR intervals (ms) and standard deviations (ms) in each patient; difference between the mean SR intervals of subgroups with long and short SR intervals (ms)

Patient ID	All target trials		Subgroups of target trials				Difference between mean long and mean short SR intervals (ms)
			Short SR interval		Long SR interval		
	n	Mean SR int. ± SD (ms)	*n*	Mean SR int. ± SD (ms)	*n*	Mean SR int. ± SD (ms)	
BS	50	429 ± 29.7	19	413 ± 9.6	21	448 ± 10.9	35
DJ	46	511 ± 55.8	17	468 ± 11.9	17	525 ± 15.2	57
DM	43	606 ± 71.8	15	546 ± 9.0	14	622 ± 11.5	76
FP	49	523 ± 64.2	13	489 ± 14.0	21	532 ± 11.9	43
HZ	30	665 ± 114.4	10	566 ± 14.5	9	650 ± 14.2	84
HP	52	575 ± 157.0	18	479 ± 15.1	14	547 ± 15.9	68
JI	55	602 ± 156.8	17	512 ± 13.4	13	560 ± 15.0	48
KM	49	565 ± 58.3	15	514 ± 12.8	13	566 ± 14.7	52
KP	48	533 ± 84.9	14	477 ± 16.8	14	577 ± 17.5	100
KJ	51	470 ± 38.9	24	467 ± 10.1	13	519 ± 12.1	52
LL	56	587 ± 91.5	14	514 ± 13.6	16	582 ± 12.3	68
PM	60	506 ± 55.0	18	472 ± 8.7	17	512 ± 10.0	40
SM	57	477 ± 50.7	16	438 ± 15.4	22	480 ± 8.7	42
SO	53	446 ± 44.0	16	407 ± 12.4	16	457 ± 11.1	50
SI	61	587 ± 87.9	22	547 ± 10.9	14	598 ± 12.2	51
VH	55	521 ± 67.7	13	470 ± 13.5	21	540 ± 13.8	70
VP	53	458 ± 50.1	16	418 ± 11.1	15	483 ± 13.7	65

structures (9 selected examples are presented in Figs. 1–3, section A). The mean percentage of task performance errors taken across patients was 1.2±0.7%.

The comparison of the differences of peak latencies between the two subgroups, averaged with the stimulus onset as a trigger and with a button-pressing as a trigger, made it possible to distinguish 3 different types of intracerebral P3-like waveforms.

(1) *P3-like waveforms time-locked to the stimulus* (3 examples in 3 patients in the parahippocampal gyrus (KJ), the anterior cingulate gyrus (SI), and the orbitofrontal cortex (VH) are shown in Fig. 1).

When averaged with the stimulus onset as a trigger, these responses exhibited identical P3 peak latencies in the short and long SR interval averages. Using the averaging with a button-pressing as a trigger, the peak latencies differed between the two subgroups (they were longer in the long SR interval averages).

This type of P3-like waveforms was identified in 30 sites in 11 patients (a summary of their intracerebral distribution is presented in Table 3). The peaks were located on the time axis at the point corresponding to 71.1±12.7% of the mean SR interval (393.7±81.5 ms in absolute values).

(2) *P3-like waveforms time-locked to the motor response* (3 examples in 3 patients in the posterior cingulate gyrus (SM), the rectus gyrus (PM) and the premotor cortex (HP) are shown in Fig. 2).

When averaged with a button-pressing as a trigger, these responses exhibited identical P3 peak latencies in the short and long SR interval averages. Using the averaging with the stimulus as a trigger, the peak latencies differed between the two subgroups (they were longer in the long SR interval averages).

This type of P3-like waveforms was identified in 52 sites in 13 patients (a summary of their intracerebral distribution is presented in Table 3). The peaks were located on the time axis at the point corresponding to 85.5±7.9% of the mean SR interval (439.6±53.6 ms in absolute values).

(3) *P3-like waveforms with ambiguous time relationship to stimulus and motor response* (3 examples in 3 patients in the hippocampus posterior (HZ), the putamen (SO), and the ventrolateral prefrontal cortex (VH) are shown in Fig. 3).

For the third type of P3-like waveforms, the peak P3 latency differences between the two subgroups obtained by averaging the stimulus and button-pressing as triggers were 32.5±16.0 and 28.3±15.2 ms, respectively.

This type of P3-like waveform was identified in 98 sites in 16 patients (a summary of their intracerebral distribution is presented in Table 3). The peaks were located on the time axis at the point corresponding to 78.1±12.9% of the mean SR interval (425.3±82.2 ms in absolute values).

The one-way ANOVA revealed the main effect for the peak P3 latencies expressed as the percentage value of the corresponding mean SR interval, i.e. 71.1±12.7% for the first type of P3-like waveform, 85.5±7.9% for the second type of P3-like waveform, and 78.1±12.9% for the third type of P3-like waveform (F (2,177)=14.89, $P<0.000$). A post hoc Spjotvoll/Stoline test showed statistically significant differences between the first and the second type of P3-like waveform ($P<0.000$) and the second and the third types of P3-like waveform ($P<0.004$). The one-way ANOVA revealed the main effect also for

Table 3
Total number of investigated sites in each structure and intracerebral distribution of 3 types of the P3-like waveform

Structures	Investigated sites hemisphere left/right	P3-like waveforms time-locked to		P3-like waveforms with ambiguous time relationship to stimulus and motor response (sites/patients)
		Stimulus (sites/patients)	Motor response (sites/patients)	
Cingulate gyrus	10/18	1L 3R/4	2R[a]/2	1L 6R/5
Parahippocampal gyrus	18/22	1L 1R/2	0	4L 2R/5
Hippocampus	33/38	2R/2	6R/4	3L 8R/5
Amygdala	28/16	0	1L 1R/2	3L 3R/5
Basal ganglia	23/23	2R/1	2L/2	4L 2R/4
Temporal gyri (superior, middle, inferior)	64/78	3L 4R/6	3L 12R/9	12L 8R/9
Fusiform gyrus	6/10	0	3R/3	2L 1R/3
Angular gyrus	2/0	0	0	1L/1
Sensorimotor cortex	0/10	0	3R/2	2R/2
Dorsolateral prefrontal cortex	23/15	3L 1R/1	2L 5R/5	14L 7R/5
Basal and medial frontal cortex	28/26	2L 1R/2	1L 6R/2	5L 6R/6
Parietal cortex	4/16	2R/1	1L 1R/1	2R/2
White matter				
Frontal lobe	9/19	2L 1R/2	1L 1R/2	3L 2R/4
Temporal lobe	5/14	1R/1	0	1L 2R/3
Parietal lobe	0/3	0	1R/1	0

L, R indicate the left and right hemispheres.
[a] In the cingulate gyrus one site from two was found in left handed patient PM.

the peak P3 latencies expressed in absolute values, i.e. 393.7, 439.6, and 425.3 ms, respectively (F (2,177) = 3.54, $P < 0.031$). A post hoc Spjotvoll/Stoline test showed statistically significant differences between the first and the second type of P3-like waveforms ($P < 0.049$).

In a number of patients we could identify more then one P3-like waveform of each type with different latencies diffusely distributed within the brain. For example, in patient HP we found P3-like waveforms time-locked to the stimulus in the inferior temporal gyrus (312 ms), in the superior temporal gyrus (383 ms), in the parahippocampal gyrus (305 ms) and in the cingulate gyrus (430 ms); P3-like waveform time-locked to the motor response in the premotor cortex (398 ms); P3-like waveform with ambiguous time relationship to stimulus and motor response in the cingulate gyrus (391 ms), in the frontoorbital cortex (336 ms), in the fusiform gyrus (297 ms), in the parahippocampal gyrus (328 ms), in the inferior temporal gyrus (297 ms) and in the middle temporal gyrus (328 ms). Furthermore, the localization of electrodes in each patient was not identical. Even as we describe the position of certain contact in several patients, for example in the hippocampus, in each patient these contacts can record a signal from different functional populations of neurons. That is why the ANOVA was applied for statistical analysis of the differences between the 3 types of P3-like waveforms and it used all 180 sites as independent samples.

For each type of P3-like waveform, the differences of peak P3 latencies between the long and short SR interval averages were correlated with the differences of SR intervals between the long and short subgroups. For the first type of P3-like waveform, time-locked to the stimulus, the correlation coefficient was 0.132 ($P < 0.485$; $N = 30$); for the second type of P3-like waveform, time-locked to the motor response, the correlation coefficient was 0.784 ($P < 0.000$; $N = 52$); for the third type of P3-like waveform, with ambiguous time relationship to stimulus and motor response, the correlation coefficient was 0.278 ($P < 0.005$; $N = 98$).

The two most common intracerebral patterns, the triphasic N2a–P3a-SW (see Fig. 2, column A, patient PM) and the broad P3b (see Fig. 1, column A, patient KJ), were identified in all the 3 types of P3-like waveforms. In the groups of P3-like waveforms time-locked to the stimulus and with an ambiguous time relationship to stimulus and motor response, they were found approximately in a 3:1 ratio, whereas in the group of P3-like waveforms time-locked to the motor response, they were present almost equally.

Records from CPz electrodes were obtained only in 14 subjects. Due to the number of target trials in subgroups with short and long SR intervals, which was mostly too small for scalp averaging, we could reliably identify and analyze the P3 waveform only in 5 subjects. In patients DJ and JI it was time-locked to the stimulus (with the latencies of 477 and 508 ms, respectively), in patient FP it was time-locked to the motor response (with the latency of 484 ms) and in patients HZ and PM it represented P3 waveform with an ambiguous time relationship to stimulus and motor response (with the latencies of 562 and 555 ms, respectively). Examples of scalp recorded P3 waveforms are presented in Fig. 4.

4. Discussion

4.1. Methodological remarks about intracerebral EEG

Like scalp EEG, intracranial (iEEG) has a very high temporal resolution, limited only by sampling frequency (in this study, 8 ms). Unlike scalp EEG, iEEG also has very high spatial resolution, limited only by the electrode size and spacing. However, depth electrodes are implanted only into a limited region for strictly clinical purposes in patients with medically intractable epilepsies and, thus, they may record abnormal responses. Nonetheless, it is possible to select sites and epochs for analyses that are electrographically normal. Furthermore, the localization of electrophysiological correlates is not really accurate until it is supported by finding its local generator. These facts have to be considered when interpreting intracerebrally recorded data.

Due to the 8 ms temporal resolution, we were limited in our separation of the P3-like waveforms into the 3 types according to their latency difference, which could be 0, 8, 16, 24 ms and so on. In light of the measured latency differences, we created the rule that the latency difference of 0 or 8 ms, when averaged from the stimulus onset as a trigger or button-pressing as a trigger, means that the waveform is time-locked to the stimulus or the motor response, respectively. It is clear that using a higher sampling frequency would probably provide slightly different data separation into all the 3 types of P3-like waveforms.

A unique aspect of this study has been the finding that a smaller number of EEG epochs is sufficient for averaging to produce the depth P3-like waveform. The recommended minimum for the scalp ERPs is 20 single epochs (Cohen and Polich, 1997; Polich, 1986a,b). In our analysis of the relationship between the P3-like waveform and the length of SR interval, we averaged from 9 to 24 EEG epochs and obtained curves basically identical with those averaged from all the recorded epochs (approximate mean number of 50). Similarly, a small number of trials was sufficient in intracerebral error-related potentials recording in our previous study (Brázdil et al., 2002). It can be explained by the presumption that the small region surrounding the electrode contacts provides distinctive responses, and the signal is recorded with higher signal-to-noise ratio than is the case with scalp-recorded ERPs. These matters have been treated more formally by Effern et al. (2000). This fact enabled the selection of trials with shorter and longer SR

intervals and to create two individual groups, which could then be averaged and compared separately in each patient.

To classify P3 potentials as stimulus- and response-related, it is also possible to use the comparison of the peak amplitudes between stimulus- and response-locked averages. If the stimulus-locked amplitude is larger than response-locked amplitude, the potential is more stimulus-related than response-related, and vice versa in the other case. This analysis has already been applied to our data, and preliminary results were published by Damborská et al. (2001).

4.2. Types of P3-like waveforms

Studies in normal subjects, intracranial recording in epileptic patients, and lesional studies in neurological patients show that P3 does not correspond to one cognitive process or a unitary brain potential arising from a discrete brain region; rather, it is related to the activation of multiple cortical and subcortical structures which are involved during the performance of the experimental paradigms. According to the different time relationship of P3-like waveform to the stimulus presentation or motor response, we were able to divide the intracerebral P3-like waveforms into the 3 types, which could explain the sometimes contradictory findings in scalp-recorded ERPs. Two facts are obvious: (1) there is a diffuse, rather than a specific, distribution of all 3 P3 types within the brain and (2) it remains unclear how the intracerebral P3 generators contribute to the scalp-recorded potentials.

The first type is characterized by constant latency of the peak in relation to the stimulus occurrence and is independent of the length of SR interval. This potential could be probably strictly related to the stimulus detection and evaluation processes. This type of P3-like waveform could possibly contribute to the scalp-recorded P3 in paradigms where, on some presented stimuli, no response is required, for example, in a passive oddball paradigm (Polich, 1989) or in studies where the manipulations with the stimuli resulted in an increase of the RT as well as of the P3 latency: the reduction of stimulus intensity (Verleger et al., 1991), the reduction of stimulus discriminability (Novak et al., 1990), increasing the number of irrelevant stimuli while randomly changing the location of the relevant stimulus (Magliero et al., 1984), presenting flanking stimuli to which the alternative response is assigned (Smid et al., 1990). In the 3-stimulus variant of the oddball paradigm, there is an additional infrequent non-target stimulus inserted into the sequence of infrequent target and frequent standard stimuli (Katayama and Polich, 1999). Even with the absence of a response, this unexpected and novel stimulus generates P3a waveform which probably reflects activities engaged during involuntary response to novel events (Knight and Scabini, 1998). Therefore, it is also possible that the first type of P3-like waveform time-locked to the stimulus could partially represent an electrophysiological correlate of the orienting response. In support of this hypothesis, this type of P3-like waveform occurred in the N2a–P3a-SW pattern markedly often. However, it may also contribute to the generation of all the scalp-recorded potentials evoked by any kind of stimuli.

The second type of P3-like waveform is time-locked to the moment of motor response, i.e. it is dependent on the length of SR interval. This can be explained by the activation of structures engaged in response-related processes, such as timing, decision to perform the movement, preparation for, initiation and execution of the movement. Unfortunately the design of the oddball paradigm, with only a button-pressing response, used in our study does not allow distinguishing between intracerebrally recorded MRPs or P3-like potentials influenced by response-related processes. In our previous paper (Brázdil et al., 2003), the effect of the response type on the P3-like potential was investigated with respect to button-pressing versus mental counting conditions from the same intracerebral sites. Task-specific P3-like potentials for the button-pressing task were observed in the lateral premotor cortex and sporadically in the orbitofrontal, cingulate, lateral parietal, and mesiotemporal cortex (amygdala and fusiform gyrus), but mostly without the character of its local origin in these sites. These findings are in accordance with the intracerebral distribution of the second type of P3-like waveform, which could be linked to the family of MRPs.

The influence of response execution on P3 latency was explored during the performance of simple RT and SR compatibility tasks. When the stimulus evaluation demands were minimal, response execution affected P3 latency, however, these movement effects were modest (Doucet and Stelmack, 1999). Another study focused on the effect of button-pressing on P3, with the result that button-pressing generated smaller P3 than silent-counting, and P3 topography in button-pressing tasks was confounded by motor potentials (Salisbury et al., 2001). As in the study by Kok (1988), they assumed that motor processes on a simple RT task were roughly equivalent to a ‘go’ trial in an oddball task. The existence of the second type of P3-like waveform demonstrated in our study could possibly explain these findings.

The third type of P3-like waveform, which is not strictly time-locked to stimulus or motor response, could be interpreted as an integration of stimulus- and response-processing (more precisely, as a decision to respond on the basis of perceptual analysis) and a representation of attentional and memory processes. The scalp-recorded P3b with the central/parietal maximum is associated with these processes (McCarthy et al., 1997). The P3b reductions in patients with temporoparietal lesions are accompanied with attention and memory deficits (Woods et al., 1993). Temporoparietal lesions in monkeys also result in auditory memory deficits (Colombo et al., 1990). Ruchkin et al. (1990, 1992) provided evidence that longer latency scalp positivities index activity in phonologic and visuospatial

systems of working memory. Our finding of this third type of P3-like waveform in structures such as the hippocampus, parahippocampal gyrus, amygdala and others can further corroborate the interpretation above. It is possible that decision making, and attentional and memory processes need not be strictly time-locked to the stimulus occurrence, and their time relationship can vary from trial to trial depending on instantaneous conditions. The same reasoning can also be used for mental counting processes required in the task, which can contribute to generation of the third type of P3-like waveform.

Only 5 cases of our CPz recordings yielded P3 waveform, which could be identified and analyzed in both short and long averages. Two of them (patients DJ and JI) would match up with the first type, one case (patient FP) with the second type and the last two cases (patients HZ and PM) with the third type of P3-like waveform. In patient JI, FP and PM we found simultaneously all the 3 types of P3-like waveforms with different latencies in the various brain structures. In patients DJ and HZ we did not find any stimulus-related P3-like waveform. Limited number of CPz records did not allow any detailed analysis of the correlation between scalp-recorded and intracerebrally recorded P3 waveforms.

The presence of both kinds of typical intracerebral patterns, the triphasic N2a–P3a-SW and the broad P3b, in all 3 types of P3-like waveforms evokes the explanation that these patterns could more likely represent a distinctive electrophysiological rule, when they are recorded directly from the nervous tissue, than a certain linkage to specific cognitive processes.

4.3. P3-like waveform and the time axis

Our interpretation of each P3-like waveform type can be further supported by the fact that the first type occurs on the average on the time axis more closely to the stimulus, the second type more closely to the motor response, and the third type somewhere between them, i.e. 394, 440, and 425 ms, respectively. If we assume that the first type of depth P3 can be similar to the scalp P3a, and that the third type of depth P3 could be similar to the scalp P3b, then the difference of 31 ms between the two types does not really correspond to the difference of 60–80 ms between scalp P3a and P3b (Knight and Scabini, 1998). On the other hand, it is found that intracranial putative generators of scalp-recorded P3 do not have the same latencies as corresponding scalp P3a and P3b. It is also obvious that we could not register EEG responses from all the possible intracerebral generators, and thus our latency measurement is limited.

To determine the relation between the P3 latency and the length of SR interval for each type of P3-like waveform, the differences of peak P3 latencies between the long and short SR intervals averages were correlated with the differences of SR intervals between the long and short subgroups. No correlation for the first type of P3-like waveform was expected because the peak latency difference of 0–8 ms was selected as a criterion for this type of response. For the second type of P3-like waveform, the correlation coefficients showed that the peak latency was dependent on the length of SR interval, which was less evident for the third type P3-like waveform.

4.4. Other relevant intracerebral studies

Kropotov and Ponomarev (1991) recorded the ERPs in visual oddball paradigm from the globus pallidus and ventro-lateral nucleus of the thalamus in parkinsonian patients. In both structures, they identified 3 different neuronal populations: stimulus-bound, response-bound, and group of neurons which did not react significantly in an oddball task. Such stimulus- and response-bound neuronal populations were involved in generation of P3-like waveforms. The authors included these results in their hypothesis of action programming; P3-like activity was considered as an electrophysiological reflection of several mental operations (Kropotov, 1989). Turak et al. (2002) investigated the cingulate gyrus, which was activated during various experimental tasks. They concluded that this area appears to be multimodal, and is involved in several types of cognitive activity. In accordance with this conclusion, our study showed all 3 types of P3-like waveform in this area, too, as well as in the superior, middle and inferior temporal gyri, hippocampus, dorsolateral prefrontal, basal and medial frontal and parietal cortices. Our findings extend recent knowledge that not only the cingulate gyrus, globus pallidus, and ventro-lateral nucleus of the thalamus, but also some areas and structures in the frontal, temporal, and parietal lobes are involved in several type of processes engaged in an oddball paradigm.

Our results suggest that intracerebral P3-like waveform represents different processes diffusely distributed within the brain. In addition to higher cognitive processes, e.g. stimulus identification or decision-making, there must be brain structures responsible for planning, preparation, and execution of the response given by the task. It seems that P3-like waveform could be either stimulus-related or response-related or not strictly related to the stimulus or motor response. Therefore our results support the hypothesis that the P3 waveform registered by surface electrodes represents a heterogeneous phenomenon.

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Příloha č. 2

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Hippocampal Negative Event-Related Potential Recorded in Humans During a Simple Sensorimotor Task Occurs Independently of Motor Execution

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ABSTRACT: A hippocampal-prominent event-related potential (ERP) with a peak latency at around 450 ms is consistently observed as a correlate of hippocampal activity during various cognitive tasks. Some intracranial EEG studies demonstrated that the amplitude of this hippocampal potential was greater in response to stimuli requiring an overt motor response, in comparison with stimuli for which no motor response is required. These findings could indicate that hippocampal-evoked activity is related to movement execution as well as stimulus evaluation and associated memory processes. The aim of the present study was to investigate the temporal relationship between the hippocampal negative potential latency and motor responses. We analyzed ERPs recorded with 22 depth electrodes implanted into the hippocampi of 11 epileptic patients. Subjects were instructed to press a button after the presentation of a tone. All investigated hippocampi generated a prominent negative ERP peaking at ~420 ms. In 16 from 22 cases, we found that the ERP latency did not correlate with the reaction time; in different subjects, this potential could either precede or follow the motor response. Our results indicate that the hippocampal negative ERP occurs independently of motor execution. We suggest that hippocampal-evoked activity, recorded in a simple sensorimotor task, is related to the evaluation of stimulus meaning within the context of situation. © 2013 Wiley Periodicals, Inc.

KEY WORDS: intracranial recordings; auditory task; hippocampus; ERP latency; motor response

INTRODUCTION

Electrophysiological recordings from the hippocampus in humans (e.g., Halgren et al., 1980; Stapleton and Halgren, 1987; Grunwald et al., 1995; Brázdil et al., 2001; Fell et al., 2005; Boutros et al., 2008; Axmacher et al., 2010) and in animals (e.g., Paller et al., 1992; Shinba et al., 1996; Shin, 2011) reveal a large, mostly negative, event-related potential (ERP) with a peak latency of around 450 ms. There is no consensus on the terminology used to refer to this cognitive potential. Some authors regard it as one of the putative generators of the scalp recorded P300 and label this ERP accordingly; Grunwald et al. (1999) and Fell et al. (2004), for example, used the term MTL-P300, while Halgren et al. (1995) labeled it the depth P3b. Likewise, similar ERPs recorded from the hippocampus and various other brain structures have been referred to as P3-like waveforms (Brázdil et al., 2003; Roman et al., 2005; Damborská et al., 2012). Hippocampal activity is not related to some functions associated with scalp P300, however, and it can be observed also after frequent stimuli in oddball task (Kukleta et al., 2003). We believe that the descriptive term "large negative ERP" used by Paller and McCarthy (2002) seems to be the most accurate so far, and hereafter, we refer to this potential as the hippocampal negative ERP, or simply the negative potential, rather than the MTL-P300 or the P3-like waveform.

McCarthy et al. (1989) have speculated that this hippocampal ERP is generated by the synchronous activation of spatially aligned hippocampal pyramidal cells. Later, these same authors suggested that this potential may reflect the arrival into the hippocampus of neocortical information, of modulatory inputs from diffusely projecting brain systems, or of recurrent inhibition from hippocampal pyramidal cells (Paller and McCarthy, 2002). As such, this ERP has been used as an index of hippocampal activity during various cognitive tasks.

One view on the medial temporal lobe functional arrangement is the hierarchically organized set of associational networks. Associational connections within the perirhinal, parahippocampal, and entorhinal cortices enable a significant amount of integration of unimodal and polymodal inputs, so that only highly integrated information reaches the remainder of the hippocampal formation (Lavenex and Amaral, 2000). Sensory inputs to the long axis of the hippocampus are organized topographically, as are its efferent connections. Studies report an anterior–posterior

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differentiation of hippocampal activation during various tasks (Paller and McCarthy, 2002; Crottaz-Herbette et al., 2005; Ludowig et al., 2010). Such functional organization is likely based on interconnections between transverse circuits within the longitudinal axis of hippocampus (Small, 2002; Aggleton, 2010; Aggleton et al., 2012).

The hippocampus is involved in novelty detection (Grunwald et al., 1998; Cohen et al., 1999; Strange and Dolan, 2001), salience detection (Rosburg et al., 2007), spatial memory and navigation (e.g., Watrous et al., 2011), and in encoding and recollection of episodic memory (e.g., Fernández el al., 2002; Eichenbaum, 2004; Amaral and Lavenex, 2007; Ranganath, 2010; Lega et al., 2012; Eichenbaum et al., 2012). In a recently published review, Olsen et al. (2012) suggest that the hippocampus supports multiple cognitive processes through relational binding and comparison, with or without conscious awareness for the relational representations that are formed, retrieved, and/or compared.

Despite the fact that most evidence points to cognition variables, some animal studies showed hippocampal theta activity associated with motor behavior (Vanderwolf, 1969; Wyble et al., 2004; Bland et al., 2006; Shin, 2011). Intracranial recordings from human hippocampi have also demonstrated movement-related increase in theta oscillatory activity (Ekstrom et al., 2005). These findings are consistent with sensorimotor integration theory, according to which hippocampal theta activity may reflect both the processing of sensory information related to the preparation for movement and the execution of movement (Bland and Oddie, 2001).

Besides theta oscillatory power changes, additional evidence for the role of the hippocampus in motor execution comes from studies demonstrating a modulation of hippocampal-evoked activity during motor responses. In studies employing the oddball task, for example, the amplitude of the hippocampal ERP is consistently reported to be higher after target stimuli requiring a motor response, relative to frequent stimuli for which no motor response is required (e.g., Brázdil et al., 1999; Fell et al., 2005; Ludowig et al., 2010). The amplitude of this potential was also found to be significantly greater after button pressing compared to mental counting (Brázdil et al., 2003). Furthermore, in our previous study (Roman et al., 2005) we observed that hippocampal P3-like waveforms to target stimuli could be time-locked to the onset of the stimulus or the motor response. These findings could indicate that this potential partially reflects processes also related to the motor response and not just to stimulus evaluation and associated memory functions. To explore this possibility, we investigated the temporal relationship between the hippocampal negative potential latency and the onset of a stimulus-cued movement. To do so, we employed a simple stimulus-response task, during which subjects were required to press a single button in response to a single, unchanging auditory stimulus. The subjects were instructed to respond at their own pace—that is, not to respond as fast as possible. The latency parameter of the examined hippocampal ERPs was then analyzed in subgroups of EEG trials with slower and faster responses.

MATERIAL AND METHODS

Subjects

Eleven patients (nine females and two males; one male subject was left-handed; mean age 35 ± 11 yrs) with medically intractable epilepsy participated in the study. All subjects had normal or corrected-to-normal vision. Informed consent was obtained from each subject before the experiment, and the study received the approval of the Ethical Committee of Masaryk University.

Intracranial Recordings

For clinical purposes a total of 91 depth multicontact electrodes were implanted orthogonally to the frontal, parietal, and temporal lobes to localize seizure origin before surgical treatment. In this study, we investigated ERP data from 22 electrodes that were positioned at the anterior (electrodes B mostly in hippocampal head, occasionally in the anterior part of hippocampal body) or posterior part of the hippocampi (electrodes C mostly in hippocampal body or its posterior part) in both right (nine electrodes) and left hemispheres (13 electrodes). The number of contacts located in hippocampal tissue ranged from two to four per electrode. The number of electrodes implanted into the hippocampi per patient varied from one to four (see Table 1); no electrodes recorded from epileptic foci.

ERPs were recorded with standard semiflexible multilead electrodes (ALCIS), each with a diameter of 0.8 mm. Recording contacts were 2.0 mm in length, and successive contacts were separated by 1.5 mm. The exact position of the electrodes and their contacts in the brain were verified using postplacement MRI with electrodes in situ.

The EEG was recorded with a sampling rate of 1,024 Hz during seizure-free periods using the 128-channel TrueScan EEG system (Deymed Diagnostic). All recordings were monopolar, with a linked earlobe reference. All impedances were less than 5 kΩ. Eye movements were recorded from a cathode placed 1 cm lateral and 1 cm above the canthus of the left eye, and from an anode 1 cm lateral and 1 cm below the canthus of the right eye.

Behavioral Task

A single-stimulus auditory task was performed, consisting of five sessions of 30 trials (i.e., 150 trials). On a given trial, we presented a single 1-kHz tone. The duration of auditory stimuli was constant at 200 ms. The interstimulus interval varied randomly between 4,000 and 6,000 ms. The intersession interval was 1 min. Subjects were instructed to press a button with their dominant hand after presentation of the tone. They were also instructed not to respond as fast as possible.

Data Analysis

ScopeWin and Physioplore software were used for offline analysis. EEG data were digitally filtered with pass band from 0.1 to

TABLE 1.

Reaction Time and Hippocampal Negative ERP Parameters Measured in All Investigated Contacts, for All Subjects

Subject	Reaction time mean ± SD (ms)	Reaction time median (ms)	Contact	Onset latency (ms)	50% area latency (ms)	Peak latency (ms)	Peak amplitude (μV)
1	387 ± 58	371	B4	300	468	512	−125
			C3	324	552	528	−94
			B′1	214	423	462	−37
			C′2	300	503	522	−92
2	660 ± 61	654	B′1	270	389	385	−136
3	260 ± 31	259	B3	296	453	427	−205
			C′3	321	478	465	−239
4	384 ± 64	387	C′2	268	426	445	−80
5	608 ± 144	566	B2	227	369	330	−133
			B′2	226	358	339	−77
			C′2	283	430	437	−61
6	649 ± 134	636	B′2	239	420	361	−40
7	668 ± 160	652	B4	240	355	341	−94
			C4	226	388	407	−145
8	440 ± 64	444	B3	272	430	386	−188
			C3	274	442	384	−202
			B′3	295	464	494	−59
9	1,113 ± 269	1,117	B′1	265	366	351	−65
			C′2	279	401	383	−51
10	693 ± 93	688	C′3	260	405	353	−78
11	552 ± 45	552	B3	267	372	370	−300
			B′4	290	434	396	−338

B = anterior hippocampus, C = posterior hippocampus, ′ = left hemisphere.

5.5 Hz. This filter was chosen because the most informative aspect of the signal we were analyzing resides within frequencies below 5 Hz (Jacobs et al., 2007; Lega et al., 2012; Watrous et al., 2011, 2013). Furthermore, we wanted to exclude possible influence of higher frequency components on the shape of the ERPs obtained from subgroups with a low number of trials. The filtered signal was then segmented according to the stimulation trigger onset, and segment lengths were 2,000 ms with a 600-ms prestimulus period used as baseline (−700 to −100 ms before stimulus onset). In Figures 2–4, only a short prestimulus period (∼500 ms) is depicted, resulting in a shorter time axis. Segments containing artefacts were rejected manually on the basis of visual inspection. In each subject, the reaction time (RT) was measured in artifact-free EEG segments. Outliers, i.e., 5% of segments with extremely long or short RT, were excluded from subsequent averaging. For further analysis, we selected in each electrode the one contact with the highest peak amplitude of negative ERP.

We evaluated ERP parameters derived from fractional area measures (Luck, 2005). We used a measurement window delimited by a line intersecting the waveform at the 50% peak amplitude level. The time point at which the waveform reached 50% of its peak amplitude represented the "onset latency." The 50% "area latency" was obtained by computing the area under the ERP waveform above the aforementioned measurement window and then identifying the time point that bisected that area. We used this latter parameter as a measure of the latency of a given potential, and it is this particular measure that is the focus of our analyses; for the sake of brevity, we refer to this parameter as "ERP latency." We also expressed ERP latency as a relative value—i.e., the percentage fraction of RT. This gave us a measure of "relative latency." We measured also the "peak latency," allowing the comparison of our results with the majority of other studies. Figure 1 illustrates all parameters measured in the present study.

To investigate whether or not any temporal relationship existed between the hippocampal negative potential and the motor response (i.e., the moment of button pressing) we performed the following procedure. In each subject, the artifact-free EEG segments were sorted according to the respective RT from the fastest to the slowest responses. Subsequently, the segments were divided into five subgroups and averaged separately (sorted averages). In creating the subgroups, we attempted to fulfill the following criteria: a sufficient number of segments for averaging in each subgroup; an identical number of segments in all subgroups; and similar variability of the RT across subgroups. Finally, the ERP latency and relative latency, obtained from all five sorted averages, were correlated with the median RT for each subgroup.

Nonparametric statistics—Spearman correlation and Wilcoxon pair test—were performed using the routines included in the Statistica program (StatSoft).

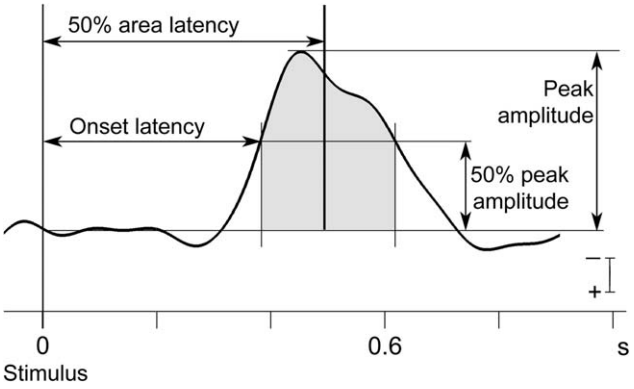

FIGURE 1. Schematic representation of event-related potential (ERP) parameters derived from fractional area measurements. The 50% area latency was used as the primary measure of ERP latency. The time point at which the waveform reached 50% of the peak amplitude represented the onset latency.

RESULTS

All the subjects responded to all presented stimuli. RT in a group of 11 subjects measured only from artifact-free EEG segments was 583 ± 227 ms (mean ± SD) and individual RT values are listed in Table 1. The average number of artifact-free segments across all subjects was 92 ± 21, ranging from 61 to 126. The shortest responses were measured in subject 3 (260 ± 31 ms), while subject 9 responded very slowly with the highest variability of responses (1,113 ± 269 ms). For the rest of the subjects, mean RTs and standard deviations ranged, respectively, 384–693 and 45–160 ms.

We found prominent hippocampal negative potentials characterized by a local origin, indicated by a steep voltage gradient change, in all investigated electrodes. Two examples of locally generated ERPs are demonstrated in Figure 2. The values of our selected ERP parameter measurements (mean ± SD) across 22 cases were as follows: 50% area latency = 424 ± 49 ms; peak latency = 413 ± 62 ms; onset latency = 270 ± 31 ms; peak amplitude = −129 ± 84 μV. Parameter values from each individual subject are presented in Table 1.

In all investigated contacts, averages created from sorted subgroups of segments revealed waveforms comparable to the waveform averaged from all artifact-free segments (compare one example in Figs. 3A,B). The number of segments included in each subgroup varied from 14 ± 1 to 25 ± 4.

To test the temporal relationship between the negative potential latency and motor responses, in each subject, we performed correlation analyses between two measures of ERP latency—both absolute (50% area latency) and relative latency—with median RT obtained from sorted subgroup averages (Table 2). First, we observed nonsignificant correlations between ERP latency and median RT in all but two cases; specifically, C′2 in subject 1 and C′3 in subject 3. These findings reflect relatively constant hippocampal negative potential latency that is independent of RT. Second, we found significant negative correlations between ERP relative latency and median RT in 16 of 22 cases. These results demonstrate that with longer RT the hippocampal negative potential latency, expressed as a relative value of corresponding RT, became correspondingly lower. Although many of the correlations observed are far more robust than those reported typically in the literature, yet they failed to reach statistical significance. This is unsurprising given the low degrees of freedom. Nevertheless, we performed resampled procedures and we obtained very similar results: for the coefficient of −0.8 (i.e., subject 1, C′2), $P > 0.067$; and for the coefficient −0.7 (i.e., subject 1, B′1), $P = 0.119$.

In the light of the previous results, we also correlated median RT and ERP latency parameters but measured from

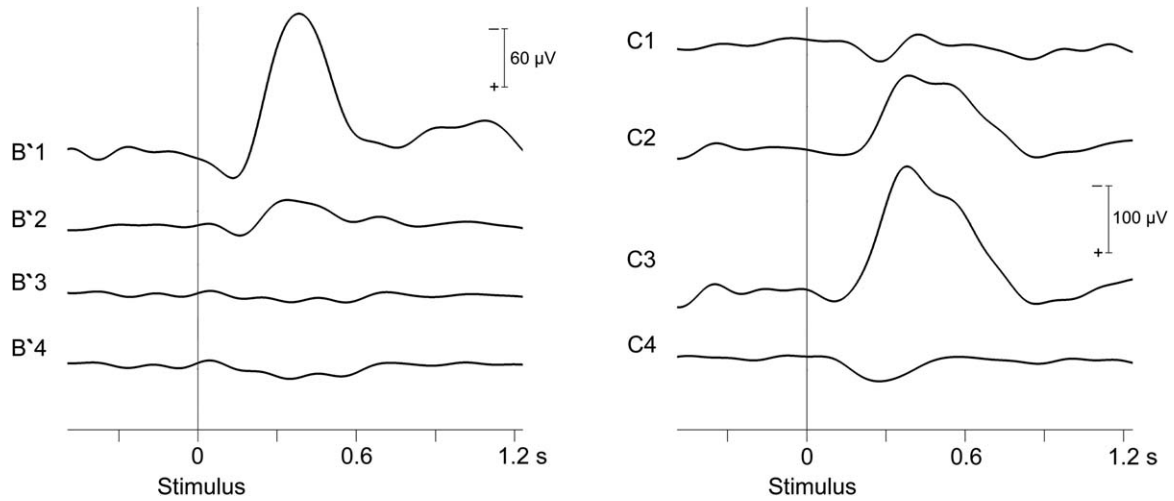

FIGURE 2. Two examples of locally generated hippocampal negative ERP revealed by steep voltage gradient changes. In subject 2 (left), contact B′1 was located in the left hippocampal head, while contacts B′2–4 were located outside this structure; In subject 8 (right), contacts C1–3 penetrate right hippocampal body, while contact C4 lay outside this structure.

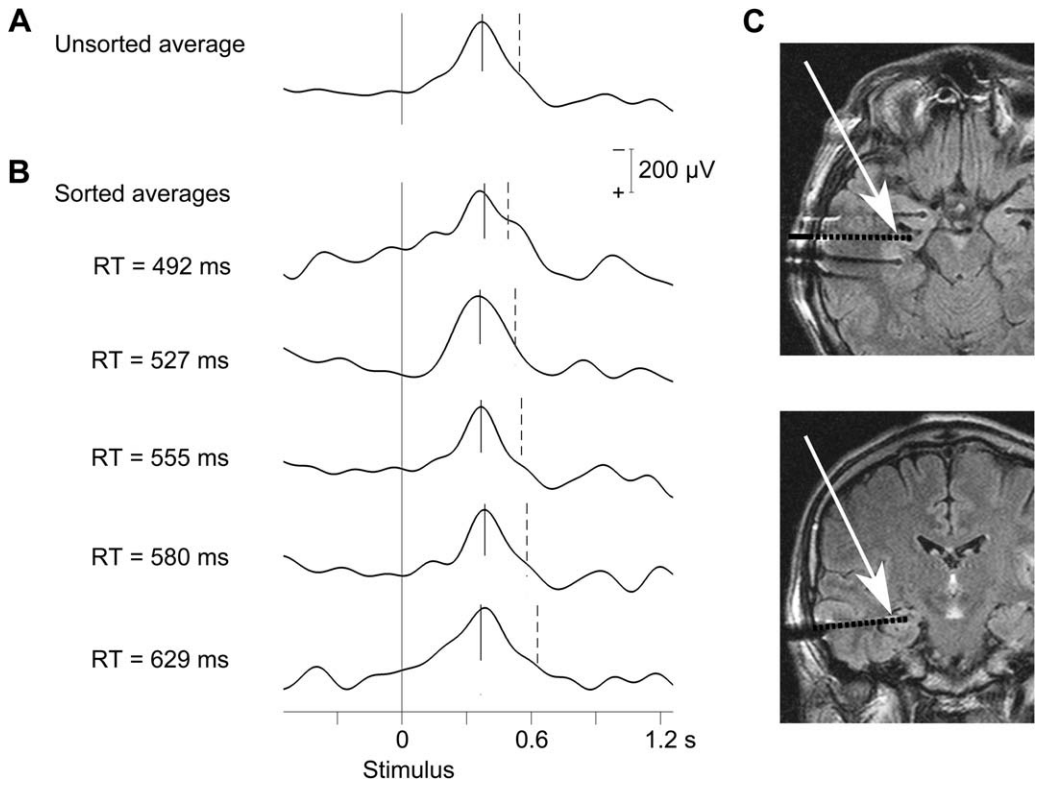

FIGURE 3. Hippocampal negative ERP recorded from the right hippocampal head in subject 11, contact B3. A: ERP averaged from 88 artifact-free EEG segments (unsorted average). B: ERPs recorded from the same contact and patient, averaged from five subgroups of EEG segments defined according to median RT (sorted averages), ordered from the shortest (upper) to the longest (lower). ERP latency is indicated by short vertical solid lines crossing the waveforms. The vertical dashed lines depict median RT expressed numerically on the left. C: Transversal and coronal MR images demonstrate the location of electrode B, with the B3 contact position indicated by a white arrow.

unsorted averages across subjects. For this analysis, if the studied ERP is related to the motor response one would expect high positive correlations. On the contrary, however, we observed significant negative correlations between median RT and ERP latency ($r = -0.77$, $P < 0.001$) and between median RT and onset latency ($r = -0.55$, $P < 0.01$). This finding supports the proposal that the studied ERP is unrelated to the motor response.

In all investigated sites, the hippocampal ERP latency—our primary measure—varied along the time axis in relation to the motor response (see Table 1). In 14 cases, it was shorter than the median RT and preceded the motor response—in two cases in subject 9, it was shorter by 751 and 716 ms; in 12 cases, it varied from 297 to 2 ms (mean value 182 ± 98 ms) before the average motor response. In eight cases, the hippocampal ERP latency was longer than the median RT; this is true especially for subject 3, who provided the fastest responses, whereby ERP latency was longer by 219 ms in C′3 and 194 ms in B3. In the six other remaining cases, it varied from 20 to 181 ms (mean value 87 ± 62 ms) after the motor response (see examples in Fig. 4). In contrast, our other measure of ERP latency—onset latency—preceded the motor response in all interrogated contacts except two in subject 3. It also demonstrates that there is no fixed relationship between the studied ERP and the motor response.

Differences in the measured parameters between anterior and posterior parts of the hippocampus were assessed in six pairs of contacts for subjects 1, 5, 7, 8, and 9 (Wilcoxon pair test). A significant anterior—posterior difference ($P < 0.05$) revealed that ERP latency was shorter in the anterior compared with posterior hippocampi—i.e., 400 ± 47 and 452 ± 63 ms, respectively. No significant differences were found between right and left hippocampi in any of the measured parameters in five investigated pairs of contacts (subjects 1, 5, 8, and 11).

DISCUSSION

In the present study, we found that the human hippocampi consistently generate a large negative ERP during simple auditory stimulus-response task. Analyses focusing on the latency of this hippocampal ERP suggested that it is not time-locked to the motor response (i.e., to movement execution). First, the

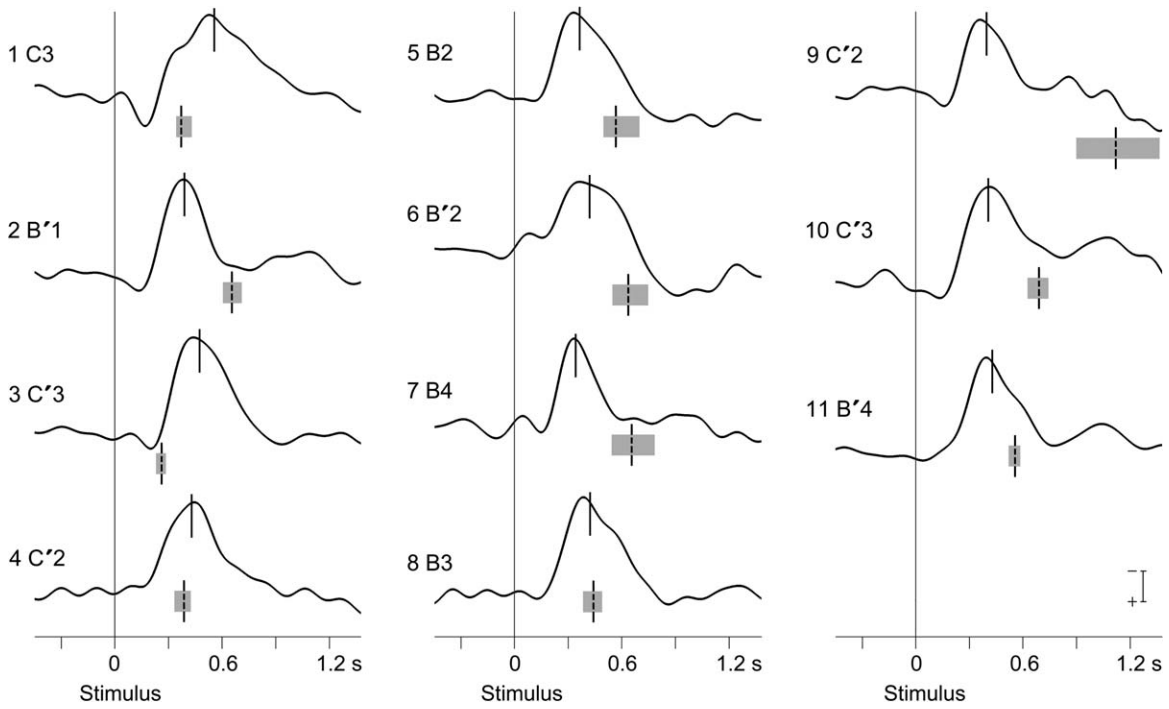

FIGURE 4. Examples of hippocampal negative ERPs from each subject. Contacts B are located in hippocampal head or in the anterior part of the hippocampal body, and contacts C are positioned within the posterior part of hippocampal body; apostrophes indicate left-hemisphere locations. ERP latency is indicated by vertical solid lines crossing the waveforms. Shadow rectangles below each waveform represent reaction times quartile ranges and vertical dashed lines, crossing the rectangles, signify median RT. Scaling was adjusted separately for each waveform so as to optimize amplitude.

hippocampal negative ERP latency measured in five sorted subgroups of segments did not correlate with median RT. When the same latency parameter was expressed as a relative value of RT, however, it correlated highly with median RT in most of the cases. Second, there is no fixed temporal relationship between the hippocampal negative ERP and the motor response expressed as median RT. In some cases, the ERP latency was shorter and, in other cases, it was longer than median RT, i.e., negative potential preceded or followed the motor response, respectively. Third, across the entire group of subjects, the variability of the ERP latency and the onset latency was at least four times lower than the variability of RTs.

Our conclusion is based on a simplified conceptualization of sensorimotor tasks; specifically, we assume that the hippocampal ERP reflects activity related either to the stimulus presentation *or* to the execution of the response. The results of our correlation analyses between RT and the latency (absolute and relative) of the hippocampal negative potential should then reveal the temporal relationship between this ERP and the stimulus or the response. In the first case, the latency of the ERP should be independent of RT. The opposite would be expected if the studied ERP reflects processes linked to the execution of the response; the ERP latency should depend entirely on RT. By averaging subgroups of EEG segments sorted according to RT in each subject, we measured an almost constant potential latency in all sorted averages. Moreover, when this potential latency was expressed as a relative value of RT, it was lower for longer RTs. In other words, we revealed that the hippocampal ERP is linked to the auditory stimulus rather than the motor response.

One of the suggested hippocampal functions is its support in multiple cognitive processes through relational binding and comparison. The comparison occurs when recently processed perceptual information is evaluated with respect to associated relevant information that is maintained in the memory (Vinogradova, 2001). In our study, the auditory stimulus was given a task-relevant meaning by verbal instruction. After each presentation of the stimulus, its identification and comparison with memorized representation had to be accomplished. We believe that the hippocampal negative potential could represent an electrophysiological correlate of such evaluation processing.

In our study, several subjects performed the task so quickly that the latency of hippocampal waveform followed the execution of instructed movement. This could be explained by the existence of a short-cut pathway from auditory areas to secondary motor areas involved in movement programming (Bender et al., 2006). This is in line with the finding of early processing of auditory stimuli in the frontal cortex as well (Kukleta et al., 2010). It demonstrates that aforementioned hippocampal evaluation is not critical for movement execution.

TABLE 2.

Spearman Correlation Coefficients (df = 4) for the Relationship Between Median RT and ERP Latency, and Between Median RT and ERP Relative Latency (the Percentage Fraction of Reaction Time

Subject	Contact	Latency	Relative latency
1	B4	0.7	−0.9*
	C3	0.5	−0.8
	B′1	0.1	−0.7
	C′2	0.9*	−0.8
2	B′1	0.7	−0.1
3	B3	0.2	−1.0*
	C′3	0.9*	−1.0*
4	C′2	0.6	−0.9*
5	B2	0.5	−0.9*
	B′2	0.5	−0.9*
	C′2	−0.2	−1.0*
6	B′2	0.6	−0.9*
7	B4	−0.3	−1.0*
	C4	−0.3	−0.9*
8	B3	−0.4	−0.9*
	C3	−0.3	−0.9*
	B′3	0.1	−0.6
9	B′1	0.3	−0.9*
	C′2	0.3	−0.9*
10	C′3	−0.6	−1.0*
11	B3	−0.3	−0.9*
	B′4	0.5	−0.7

B = anterior hippocampus, C = posterior hippocampus, ′ = left hemisphere.
*$P < 0.05$.

Low variability of RTs in some subjects represented a certain limitation for our analysis. In such cases, we obtained very small differences of median RT between the subgroups we created. Since the ERP latency varied minimally in the sorted averages also, this may have influenced the correlation coefficients we obtained in subjects 1 and 3.

Another finding from the present study is the primarily shorter ERP latencies recorded from anterior relative to posterior orthogonal electrodes; i.e., 400 ± 47 and 452 ± 63 ms, respectively. The small number of cases did not allow deeper statistical evaluation, however. Very similar but nonsignificant anterior–posterior differences in peak latencies were also observed in axial electrodes penetrating the hippocampal head 429 ± 96 ms and hippocampal body 486 ± 69 ms (Ludowig et al., 2010). These findings seem to be in accordance with a model of memory recall that assumes a spreading of hippocampal activation from anterior to posterior during information retrieval (Small, 2002). The recent finding of traveling theta waves with the same direction of propagation observed in hippocampi of freely behaving rats is not in contradiction with this model (Lubenov and Siapas, 2009).

The hippocampal negative ERP was found to be uniform in shape and polarity across all subjects and investigated sites. It is for this reason that we chose to employ parameters derived from fractional area measures for the description of this potential. The 50% area latency parameter is obtained by computing the area under the ERP waveform over a delimited measurement window, and then identifying the time point that bisects that area. Thus, it can be related to RT more directly because this is similar to the median RT, which is the point separating the fastest and slowest halves of RTs. It also has several other advantages over peak latency that is used in the majority of ERP studies; the same value is expected irrespective of the noise level of the data, for example, rendering it less sensitive to noise (Luck, 2005). That is why we use the 50% area latency parameter as a measure of the latency of the investigated negative potential instead of the peak latency. Concerning RT, we use the mean RT for description of group behavioral performance and median RT to compare the size of the latency effect to the size of the RT effect.

The primary finding of the present study is that during a simple sensorimotor task, human hippocampi generate a prominent negative ERP that occurs independently of motor execution. We suggest that this electrophysiological phenomenon is related to evaluation of stimulus meaning within the context of the current situation.

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Příloha č. 3

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Identical event-related potentials to target and frequent stimuli of visual oddball task recorded by intracerebral electrodes

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Abstract

Objective: The shape of visually elicited event-related potentials (ERP) of epileptic patients during their presurgical evaluation with intracerebral electrodes was investigated in the study.

Methods: Twenty intractable epileptic patients with depth electrodes at several intracranial locations in the frontal, temporal, parietal lobes, and in the amygdalo-hippocampal complex participated in the study. To evoke the ERP, a standard visual oddball task was used with target stimuli, and frequent non-habituated and habituated stimuli. The averaged responses of the 3 groups were superimposed and visually analyzed whether the shape appeared identical or non-identical.

Results: The EEG response to target and frequent stimuli was recorded in 660 intra-cerebral sites. In 88 sites (14 different patients) localized in the amygdala, parahippocampal gyrus, superior, middle, and inferior temporal gyri, fusiform and lingual gyri, sensorimotor cortex, prefrontal cortex, hippocampus, and cingulated gyrus, the identical ERPs to target and both groups of frequent stimuli were observed. In 442 sites located in the above listed structures, and in the basal ganglia and parietal cortex, the shape of the ERP differed from 0.3 to 0.47 s on after the stimulus. The remaining 130 sites did not yield the task-specific potential change.

Conclusions: The existence of identical ERPs to target and frequent stimuli in the oddball task suggests that a part of mental operations underlying the brain engagement in this task is not dependent on the way of responding.

Keywords: Event-related potential; Intra-cerebral EEG recording in humans; Oddball task

1. Introduction

In the cognitive brain research, the registration of event-related potentials (ERP) continues to be a basic and ever-productive method. Especially the P3 component, firstly described by Sutton et al. (1965) and Desmedt et al. (1965), has been attracting the attention of researchers for decades. This wave appears in averaged records after rare (target) external stimuli presented, in a random order, with frequent ones. It is peaking about 300 ms after an acoustic signal, and some 100–150 ms later after a visual signal. In the scalp recordings, its amplitude is largest over the centroparietal regions for acoustic as well as visual stimulation. The P3 evoked by a visual signal has been analyzed thoroughly since the 1960s, and available evidence demonstrates its large dependence on experimental conditions of psychological character (Donchin et al., 1978; Hillyard and Picton, 1987). This long-latency positive waveform is generally viewed as reflecting decision or cognitive closure of the recognition processing, or as the updating of memory for future actions (Smith et al., 1970; Hillyard et al., 1971; Hillyard and Picton, 1987; Iragui et al., 1993). Actually, the P3 is mostly considered as an electrophysiological concomitant of mental processes linked with the cognitive elaboration of target signals. Frequent signals are believed to be unable to produce comparable electrophysiological changes.

Many studies using scalp electroencephalography (EEG), intracerebral EEG, and myoelectroencephalography (MEG) have attempted to localize structures where the P3 is generated (Basile et al., 1997; ; Baudena et al., 1995; Brázdil, et al., 1999; Goto et al., 1996; Halgren et al., 1995a,b, 1998; Kropotov and Ponomarev, 1991; McCarthy et al.,

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1989; Puce et al., 1991; Rogers et al., 1991; Seeck et al., 1995; Smith et al., 1990; Tarkka et al., 1995; Tarkka and Stokic, 1998; Tesche et al., 1996; Yamazaki et al., 2000; Yamazaki et al., 2001). These studies have shown that the P3 (and P3 magnetic) is a complicated phenomenon, which involves many areas of the brain in space and time. The evidence emerging shows that the P3 reflects parallel and serial neuronal activity in numerous structures, and that this activity underlies, very probably, a number of mental operations necessary for accomplishing the experimental task. It also becomes clear that the whole set of these operations has not been delineated unequivocally so far.

In this study, the shape of visually elicited ERP of epileptic patients with intracerebral electrodes in an oddball setup has been investigated. Contrary to the common approach in this method, which consists in differentiating responses to target and frequent stimuli we were looking for identical ERP after target and frequent stimuli. The existence of such responses could be expected when considering the demands on signal discrimination and decision-making in the case of frequent stimuli. There is no reason to believe that these demands are principally different from those induced by target ones. To confirm this hypothesis, we chose a simple methodological procedure. We superimposed and analyzed visually all the ERPs elicited by target, frequent non-habituated, and frequent habituated stimuli with the aim to see whether the shape of these 3 curves appeared identical or non-identical.

2. Methods and materials

2.1. Subjects

Twenty patients (14 males, 6 females; aged 19–47 years; all with medically intractable epilepsies; 19 right handed, one left handed) participated in the study. Depth orthogonal platinum electrodes were implanted to localize the seizure origin prior to surgical treatment in the frontal, temporal, and/or parietal lobes using the methodology of Talairach et al. (1967). In 7 patients, additional diagonal electrodes were inserted stereotactically into the amygdalo-hippocampal complex (via the frontal approach, passing through the basal ganglia in 6 patients, via the occipital approach in one patient). The electrodes were placed bilaterally in 14 patients and unilaterally in 6 patients. Standard MicroDeep semi-flexible electrodes (DIXI) with the diameter of 0.8 mm, length of each contact of 2 mm, and inter-contact intervals of 1.5 mm were used for invasive EEG monitoring. Contacts at the electrode (5–15) were always numbered from the medial to lateral sites. Their positions were indicated in relation to the axes defined by the Talairach system using the '*x*, *z*, *y*' format where '*x*' is lateral, millimeters to midline, positive right hemisphere, '*z*' is antero-posterior, millimeters to the AC (anterior commissure) line, positive anterior, and '*y*' is vertical, millimeters to the AC/PC (posterior commissure) line, positive up. The exact positions of the electrodes and their contacts in the brain were verified using post-placement magnetic resonance imaging (MRI) with electrodes in situ. The recordings from lesional structures and epileptogenic zones were not included into the analysis. No patient from the group examined has had bilateral hippocampal sclerosis or bilateral temporal lobe epilepsy. All the patients had normal or corrected-to-normal vision. Informed consent was obtained from each patient prior to the experiment, and the study received an approval from the Ethical Committee of Masaryk University.

2.2. Procedure

The patients were seated comfortably in a moderately lighted room with a monitor screen positioned approximately 100 cm in front of their eyes. During the examination, they were asked to focus the gaze continuously on the point in the center of the monitor screen and to respond, as quickly as possible, to a target stimulus (yellow letter X on the white background) by pressing a micro-switch button in the dominant hand and counting the number of these stimuli in their heads, and to ignore frequent stimuli (yellow letter O on the white background). Both stimuli were displayed on a black screen, subtended at the visual angle of 3°. Their duration was 200 ms. The inter-stimulus interval varied randomly between 2 and 5 s, the ratio of target to frequent stimuli was 1:5.

2.3. EEG recording

The EEG signal was recorded simultaneously from various intra-cerebral structures using 64 channel Brain Quick EEG system (Micromed). All the recordings were monopolar with respect to a reference electrode placed in all the cases on the right processus mastoideus. EEGs were amplified with the bandwidth of 0.1–40 Hz at the sampling rate of 128 Hz. Further processing was performed with artifact-free EEG periods (selection was based on visual inspection of the periods by an experienced person). EEG periods of 2 s were averaged off-line using the stimulus onset as the trigger (−500 and +1500 ms from stimulus onset). ScopeWin software was used for the signal analysis, which included up to 44 channels recorded simultaneously. Responses to frequent stimuli were distributed to a subgroup of 'non-habituated responses' and to a subgroup of 'habituated responses', and averaged independently. The former subgroup gathered responses to the first frequent stimulus following the target response, the latter one gathered responses to the sixth, seventh and next (if any) frequent stimuli following the target response. The mean value of averaged records was 52 records in the groups of target responses (median 54, maximum 61, minimum 36), 42 records in the group of frequent 'non-habituated' responses (median 44, maximum 53, minimum 29), and

89 records in the group of frequent 'habituated' responses (median 88, maximum 128, minimum 56).

2.4. Data analysis

In total, 660 averaged electrophysiological responses to target stimuli, 660 averaged responses to non-habituated frequent stimuli, and 660 averaged responses to habituated frequent stimuli from different anatomical sites were evaluated. The number of explored sites in one patient varied from 14 to 42 sites (median 35 sites). The potential change after the stimulus has been considered as an ERP if its amplitude was greater than the twofold of the maximal potential change seen in the period prior to the stimulus onset. The decision whether the shape of ERPs to target and frequent stimuli is identical or non-identical was based on the visual comparison of superimposed averaged curves from these 3 conditions. The agreement of two independent observers was used to decrease a possible subjective factor in the assessment.

3. Results

Responses from 530 sites (80% of all the investigated sites) could be considered as event-related potentials (ERPs). The remaining 20% of sites did not yield task-specific potential changes. In 88 sites (14 different patients) of several structures, the identical ERPs to target and both groups of frequent stimuli were observed (Table 1). These sites were situated ipsilaterally in 64% and contralaterally in 36% of cases with regard to the performing hand. As evident, the occurrence of identical ERPs was more frequent in the amygdala, parahippocampal gyrus, superior, middle, and inferior temporal gyrus, in fusiform gyrus and lingual gyrus. The occurrence of identical responses was less frequent in the sensorimotor cortex, basal and dorsolateral prefrontal cortex, hippocampus, and very rare in the cingulate gyrus. In 72 sites located in the basal ganglia and parietal cortex, the identical ERP was not found.

Fig. 1 presents 12 cases of identical ERPs induced by target and frequent stimuli that were selected with the intention to demonstrate typical ones. The shape of these potentials varied across different structures as well as within the same structure. Simple forms, mostly biphasic curves, were observed frequently in the amygdala. In the other structures, the shape of identical ERPs was more complex. In the majority of cases, these potentials included late components located in the periods, which followed the execution of movement in responses to a target stimulus.

In another 442 sites of all the investigated structures, the response to a target stimulus quit the initially identical course with responses to frequent stimuli, and started its own course. The instant of these dissociations varied between 0.30 and 0.47 s. Fig. 2 demonstrates 12 such cases. In the great proportion of cases, these sites exhibited, after the dissociation point, task-specific EEG activity even in response to frequent stimuli (though different from target responses). The simultaneous occurrence of identical and non-identical ERPs to target and frequent stimuli in the same patient and in the same structure was a common finding. This phenomenon has been observed almost in all the patients in whom identical responses were demonstrated (12 out of 14 patients).

The data in Fig. 3 demonstrate 3 regions exhibiting signs of a local generator. Two of these generators concern the ERP evoked by a target stimulus only (contacts X′4, X′5, and G1, G2, respectively), the third one could be considered, at least in its early half, as the generator of identical ERP (contacts D4, D5).

4. Discussion

The first question to be discussed is the relevance of the results for understanding the functioning of the healthy brain.

Table 1
The prevalence of identical and non-identical ERPs induced by target and frequent stimuli across different brain structures

Structure	Total	Identical	Non-identical	No response
Amygdala	39 (11 patients)	12 (5 patients)	15 (6 patients)	12 (3 patients)
Parahippocampal gyrus	34 (8 patients)	10 (3 patients)	17 (6 patients)	8 (6 patients)
Temporal gyri (superior, middle, inferior)	190 (17 patients)	33 (8 patients)	91 (13 patients)	65 (14 patients)
Fusiform gyrus	15 (8 patients)	5 (2 patients)	9 (6 patients)	1 (1 patient)
Lingual gyrus	5 (1 patient)	3 (1 patient)	2 (1 patient)	0
Sensorimotor cortex	41 (4 patients)	4 (1 patient)	32 (4 patients)	5 (1 patient)
Prefrontal cortex (basal, dorsolateral)	144 (12 patients)	13 (3 patients)	125 (12 patients)	6 (3 patients)
Hippocampus	80 (14 patients)	7 (3 patients)	47 (10 patients)	25 (8 patients)
Cingulate gyrus	40 (11 patients)	1 (1 patient)	34 (10 patients)	5 (1 patient)
Parietal cortex	23 (3 patients)	0	23 (3 patients)	0
Basal ganglia	49 (6 patients)	0	47 (6 patients)	2 (1 patient)

Total, the number of all the explored sites; Identical, the number of sites from which identical ERPs to target and frequent stimuli were derived; Non-identical, the number of sites from which non-identical ERPs to target and frequent stimuli were derived; No response, absence of task-specific EEG change after a stimulus.

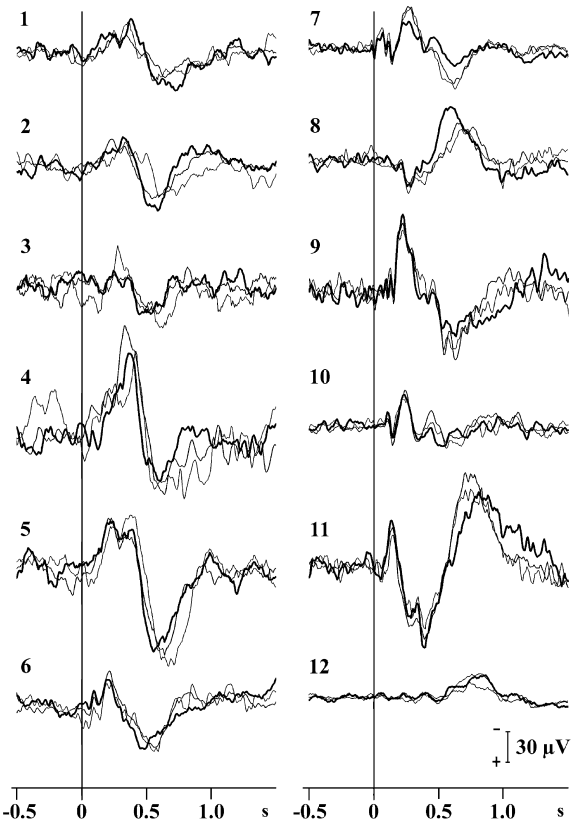

Fig. 1. Identical averaged ERPs evoked by target (thick line), habituated, and non-habituated frequent stimuli (thin lines). No of the case, initials of the patient, location of recording contact, side with respect to the movement, Talairach's coordinates: (1) DJ, amygdala, ipsilateral, +23, −6, −15; (2) FP, amygdala, ipsilateral, +21, −5, −16; (3) VP, amygdala, contralateral, −21, −6, −16; (4) KJ, amygdala, contralateral, −23, −6, −16; (5) PM, amygdala, ipsilateral, −23, −5, +15; (6) KJ, fusiform gyrus, contralateral, −29, −25, −16; (7) KP, superior temporal gyrus, ipsilateral, +60.5, −33, +17; (8) KZ, supplementary motor area, ipsilateral, +13, −12, +52; (9) DM, parahippocampal gyrus, ipsilateral, +18, −43, 0; (10) MP, lingual gyrus, ipsilateral, +23, −45, −1; (11) KZ, dorsolateral prefrontal cortex, ipsilateral, +54, +4, +31; (12) MP, middle temporal gyrus, ipsilateral, −64, −44, +2.

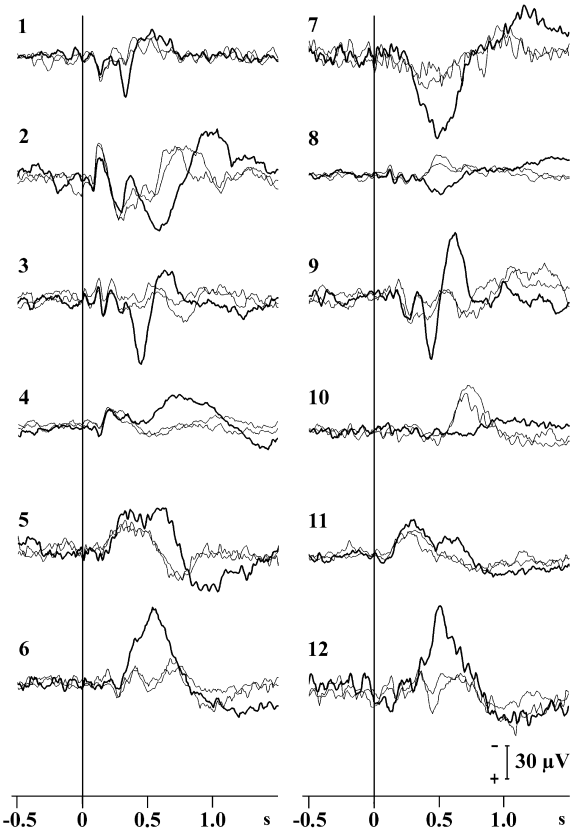

Fig. 2. Non-identical average ERPs evoked by target (thick line), habituated, and non-habituated frequent stimuli (thin lines). No of the case, initials of the patient, location of recording contact, side with respect to the movement, Talairach's coordinates: (1) SM, putamen, ipsilateral, +26, −7, +8; (2) HZ, fusiform gyrus, ipsilateral, +34, −42, −5; (3) PM, middle frontal gyrus, ipsilateral, −14, +44, −8; (4) FP, parahippocampal gyrus, ipsilateral, +18, −34, −3; (5) DM, amygdala, contralateral, −25, −5, −17; (6) KZ, suplementary motor area, contralateral , −1, −9, +51; (7) DM, hippocampus posterior, contralateral, −25, −27, −8; (8) SM, inferior temporal gyrus, ipsilateral, +58, −26, −13; (9) PM, anterior cingulated gyrus, contralateral, +4, +22, +32; (10) KZ, sensorimotor cortex, contralateral, −28.5, −9, −51; (11) JI, parahippocampal gyrus, ipsilateral, +24, −13, −24; (12) DJ, parahippocampal gyrus, contralateral, −23, −6, −4.5.

The intracerebral ERP data analyzed in this study as well as those published previously by various authors were obtained from intractable epileptic patients in the course of their clinical presurgical evaluation. Unfortunately, we are always dealing with the diseased brain tissue in this kind of research. Considering the presence of functional and possibly structural focal lesions in epileptic patients, only EEG signal from carefully selected extralesional sites can be evaluated. In this study, recordings from lesional anatomical structures, epileptogenic zones and sites with obvious epileptiform discharges were not included in the analysis. Despite the fact it is impossible to eliminate unequivocally the possible impact of spreading epileptic activity on the normal function of other parts of the brain, wherever they are located and whatever their distance from epileptogenic focus is. Another negative consequence of focal epileptic activity can be a compensatory shift of physiological functions into distinct cortical locations.

Other limitations of such studies are imposed by ethical imperatives. In our patients, the locations of electrodes were strictly determined by diagnostic purposes. Therefore, the recordings and evaluations of this study can only give information on the brain areas, which were limited in number and which were selected unsystematically with regard to the studied function. For the same reason, simultaneous or subsequent recordings from the scalp have not been performed in our patients. Nevertheless, while keeping in mind all the limitations of the method, its value for understanding the ERP genesis is currently unquestionable.

The demonstration of identical intracerebral ERPs to target and frequent stimuli in oddball task is the main result of the study presented. This result represents no contradiction to the consistent findings of different EEG responses to targets and non-targets. It simply demonstrates that, apart

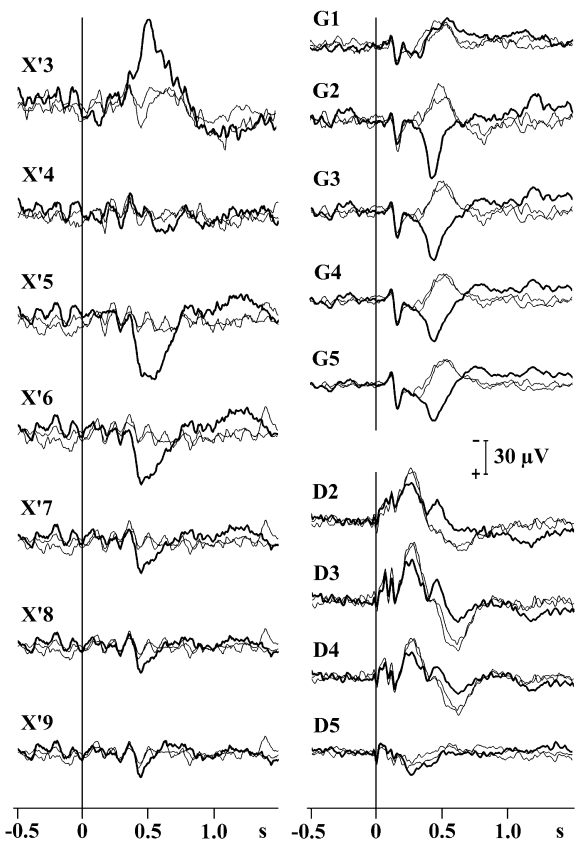

Fig. 3. The averaged ERPs evoked by target (thick line), habituated, and non-habituated frequent stimuli (thin lines), recorded from neighboring electrode contacts exhibiting phase reversal and steep voltage gradients. Left half: patient DJ, plots in parahippocampal gyrus (X′3, −23, −6, −4.5), amygdala (X′4, −23, −5, −21), amygdala (X′5, −23, −4, −17.5), amygdala (X′6, −23, −3, −14), amygdala (X′7, −23, −2, −10.5), white matter (X′8, −23, −1, −7), putamen (X′9, −23, 0, −3.5); side contralateral with respect to the movement. Right half, above: patient SM, plots in cingulated gyrus (G1, +3, −35, +28; G2, +6.5, −35, +28; G3, +10, −35, +28; G4, +13.5, −35, +28; G5, +17, −35, +28); side ipsilateral with respect to the movement. Right half, below: patient KP, superior temporal gyrus (D2, +53.5, −33, +17; D3, +57, −33, +17; D4, +60.5, −33, +17; D5, +64, −33, +17); side ipsilateral with respect to the movement.

from sites where target stimuli are processed specifically, there can be found other sites, in which the processing of targets and frequents is going identically. We have not found, in the pertinent literature, a study looking for identical ERP after target and non-target stimuli with intracranial electrodes. The identical ERP had predominantly a form of slow biphasic potential change that extinguished about 1 s after the signal. The shape of identical ERPs varied across the structures explored and, sometimes, even across different contacts located in the same structure. The unstable form of ERPs was a frequent finding, and it reflected, very probably, the complexity of factors in space and time that determined the characteristics of electrical field in the surroundings of recording contacts. The orientation of functional dipoles, which generated these fields, their power, form, and number as well as the tissue conductivity – these are some possibilities of determining factors. In such a situation, the comparison of records obtained from the same site under various conditions can only provide reliable results. In the present study, the creation of two subgroups of frequent responses (non-habituated and habituated subgroups) was inspired by this methodological requirement. The increased number of curves superimposed in evaluating their shape and the resulting increase of reliability of this procedure was the only reason of this subdivision.

As demonstrated, the identical and non-identical responses occurred frequently in the same patient and in the same structure. Identical responses were less frequent; they represented 17% of identified ERPs only. Another aspect of the results necessitates a comment. Amongst 88 identical ERPs recorded in different brain structures, the generator was demonstrated on one occasion only (Fig. 3, contacts D4, D5). All the other evaluated identical ERPs have been generated in the sites more or less remote from the recording contacts. This fact has considerably limited any attempt of localizing the structures responsible for their generation.

The study has not yielded sufficient data for the interpretation of behavioral significance of identical ERP. Nevertheless, it is clear that the demonstration of identical ERP further corroborate the complicated image of the P3 phenomenon emerging from relevant EEG studies. The demonstration of simultaneous occurrence of identical and non-identical ERPs to target and frequent stimuli in an oddball task allows differentiating between response-dependent and response-independent intra-cerebral ERPs. This suggests the existence of response-dependent and response-independent mental operations that, at least in some cases (see Fig. 3, contacts G1 and G2), are organized in a parallel fashion. This reasoning is not supported directly by the data presented; nevertheless, it has an inspiring quality for orienting further research in this field.

Acknowledgements

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Příloha č. 4

Roman R, Chládek J, Brázdil M, Jurák P, Rektor I, Kukleta M. Changes of oscillatory activity in a visual oddball task (sEEG study). *Homeostasis in Health and Disease* 2006;44(4):169-171.

Changes of oscillatory activity in a visual oddball task (sEEG study)

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INTRODUCTION

Two types of changes in the electrical activity of the cortex may occur upon sensory stimulation: one change is time-locked and phase-locked (evoked) and can be extracted from the ongoing activity by simple linear methods such as averaging; the other is time-locked but not phase-locked (induced) and can only be extracted through some nonlinear methods such as envelope detection or power spectral analysis. The EEG activity during voluntary movement, memory and cognitive tasks corresponds to different reactivity of alpha, beta and theta rhythms expressed as a decrease and increase in power quantified by the method of event-related desynchronization (ERD) and synchronization (ERS), respectively. Event-related changes in the theta band appear to be related to encoding and retrieval processes of working memory systems (Klimesch, 1999). ERD in the alpha band can be interpreted as an electrophysiological correlate of activated cortical areas involved in processing of sensory or cognitive information, attention or production of motor behavior while ERS can be assumed as a correlate of a depressed state of active processing of information in the underlying cortical neuronal populations, for example, the blocking of memory search (Klimesch, 1996; Mazaheri and Picton, 2005). Beta ERS is observed after the performance of various sensorimotor tasks and in these cases it is associated with a deactivated (inhibited) cortical state.

The aim of the present study was to investigate ERD and ERS in various brain structures during a visual oddball task.

METHODS

In 16 patients (4 females and 12 males, mean age 27±5 years) with medically intractable epilepsies depth electrodes were implanted to localize the seizure origin prior to surgical treatment. A total of 150 sites (66 in the left and 84 in the right hemispheres) of the frontal, parietal and temporal lobes were investigated. Informed consent was obtained from each subject prior to the experiment.

A standard visual oddball paradigm was performed: two types of stimuli – target (letter X) and frequent (letter O) – were presented in the center of the screen in the random order. The duration of stimuli exposure was constant at 200 ms; the ratio of target to frequent stimuli was 1:5. The interstimulus interval varied randomly between 2 and 5s. Each subject was instructed to respond to the target stimulus as quickly and accurately as possible by pressing a microswitch button by the dominant hand and, at the same time, he/she was instructed to count the target stimuli mentally.

The EEG signal was recorded with 64-channel Brain Quick EEG system (Micromed) with the sampling frequency of 128 Hz. All the recordings were monopolar with respect to a reference electrode on the processus mastoideus. ScopeWin software was used for off-line signal analysis. Further processing was performed with arti-

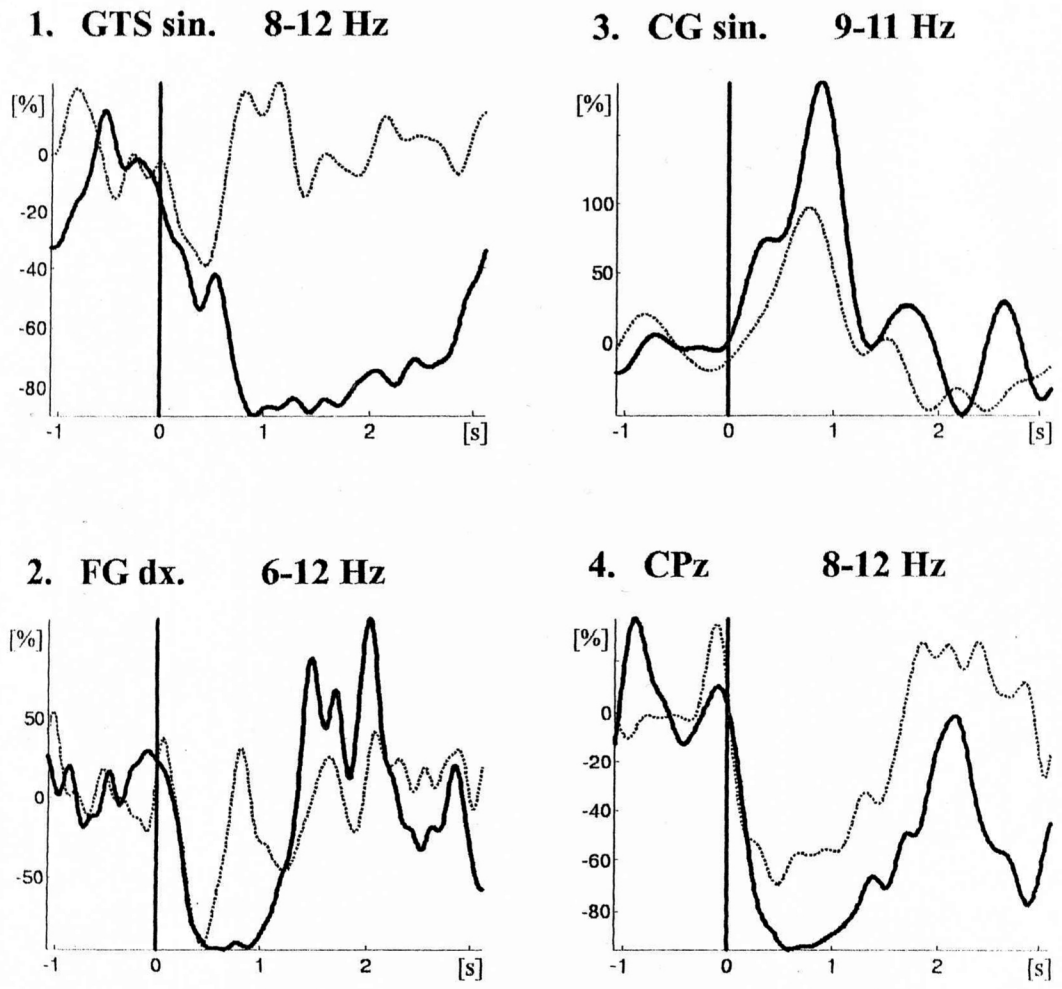
fact-free 4 seconds epochs beginning 1 s prior to the stimulus onset. In each patient, time-frequency analysis was performed separately for target and frequent stimuli. ERD and ERS were calculated by Hilbert transform in individual alpha and beta bands, which were selected from time-frequency plots according to the most prominent changes of EEG power. ERD and ERS after target and frequent stimuli in the same frequency bands were investigated.

For statistical processing, Wilcoxon paired-matched test was used.

RESULTS

Significant changes in EEG oscillatory activity ($p<0.05$) were observed after both target and frequent stimuli in alpha and beta bands in all the patients in various brain structures – cingulate gyrus, fusiform gyrus, angular gyrus, hippocampus, parahippocampal gyrus, temporal gyrus superior, middle and inferior and orbitofrontal cortex (Fig.1).

Figure 1. Examples of EEG power changes within selected range of frequencies in different patients expressed as percentage difference compared to the baseline value of 100%. Target response – bold line, frequent response – dotted line, 0 s – stimulus onset, GTS – superior temporal gyrus, CG – cingulate gyrus, FG – Fusiform gyrus, CPz scalp electrode.



ERD and ERS were identified in both hemispheres in 95 sites after target stimuli and in 84 sites after frequent stimuli, which correspond to 63% and 56% of all the investigated sites, respectively. After target stimuli ERD in alpha bands represented 59% and ERS 41% of cases while in beta bands ERD was observed in 46% and ERS in 54% of cases. After frequent stimuli ERD in alpha bands represented 38% and ERS 62% of cases and in beta bands ERD was observed in 29% and ERS in 71% of cases. In 17 cases after target stimuli and 20 cases after frequent stimuli, both ERD and ERS in the same or different frequency band were found in the same contact.

Simultaneous scalp CPz recordings were analyzed in 13 patients and ERD/ERS was observed in 9 patients after target stimuli (ERD in 8 and ERS in 4 cases) and in 6 patients after frequent stimuli (ERD in 5 and ERS in 5 cases).

DISCUSSION AND CONCLUSION

Our results show ERD and ERS during visual oddball task after both target and frequent stimuli in different brain structures. It broadens recent intracerebral findings describing alpha desynchronization after target stimuli recorded from the hippocampus in the same task (Sochurková et al., 2006). Nevertheless our observations have revealed no regular ERD or ERS within one structure which is probably due to electrode position given by clinical demands. More frequent observation of ERD after target stimuli probably represents the activation of processes involved in a subject's motor response. After frequent stimuli, more frequent observation of ERS or an absence of ERS/ERD phenomenon in some cases could correspond to the inhibition or exclusion of such processing, respectively, leading the subject not to respond to a frequent stimulus.

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Příloha č. 5

Brazdil M, **Roman R**, Daniel P, Rektor I. Intracerebral error-related negativity in a simple Go/NoGo task. *Journal of Psychophysiology* 2005;19:244-255. **IF (2005) = 0,968**

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Intracerebral Error-Related Negativity in a Simple Go/NoGo Task

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Abstract. Performance monitoring represents a critical executive function of the human brain. In an effort to identify its anatomical and physiological aspects, a negative component of event-related potentials (ERPs), which occurs only on incorrect trials, has been used in the extensive investigation of error processing. This component has been termed "error-negativity" (Ne) or error-related negativity (ERN) and has been interpreted as a correlate of error detection. The aim of the present intracerebral ERP study was to contribute knowledge of the sources of the Ne/ERN, with a particular focus on the involvement of a frontomedian wall (FMW) in the genesis of this negativity. Seven patients with intractable epilepsy participated in the study. Depth electrodes were implanted to localize the seizure origin prior to surgical treatment. A total of 574 sites in the frontal, temporal, and parietal lobes were investigated. A simple Go/NoGo task was performed and EEG epochs with correct and erroneous motor responses were averaged independently using the response as the trigger.
Ne/ERN was generated in multiple cortical structures, with the most consistent involvement being that of the FMW structures. Ne/ERN generators were revealed there in both the rostral and caudal anterior cingulate cortex (ACC), but also in the pre-SMA and in the parts of the medial frontal gyrus adjacent to the ACC. Different timing of activations between the rostral and caudal anterior cingulate Ne/ERN sources was observed in this study. Other neural sources of the Ne/ERN were found in the dorsolateral prefrontal cortex, in the orbitofrontal cortex, in the lateral temporal neocortex, and in one isolated case in the supramarginal gyrus. Our findings support the key role of the FMW in the genesis of Ne/ERN. At the same time, our findings suggest a different functional significance for the rostral and caudal ACC involvement in error processing. In addition to the FMW, the other prefrontal cortical sites, the lateral temporal neocortex, and the supramarginal gyrus seem to represent integral components of the brain's error monitoring system.

Keywords: error processing, event-related potentials, intracerebral recordings, Go/NoGo task

In the early 1990s, two groups independently discovered a negative component of event-related potentials (ERPs), which occurred only on incorrect trials (Falkenstein, Hohnsbein, & Hoormann, 1991; Gehring et al., 1993). This negativity shows a frontocentral maximum in scalp recordings, peaking about 50–100 ms after the erroneous motor response. It has been termed "error negativity" (Ne) or "error-related negativity" (ERN) and has generally been interpreted as a correlate of error detection, or alternatively as a correlate of response checking itself (Coles, Scheffers, & Holroyd, 2000; Falkenstein et al., 2000; Vidal, Hasbroucq, & Bonnet, 2000). It is noteworthy, however, that many individuals also exhibit a smaller response-locked frontocentral negativity after the execution of correct responses. This component is known as the "correct response negativity" (CRN); its amplitude is usually much smaller than that of the Ne/ERN (Falkenstein et al., 2000; Ford, 1999; Vidal et al., 2000). Ne/ERN is an online index of performance monitoring that may be independent of response conflict because it is observed in simple choice-reaction tasks without response competition (Falkenstein et al., 2000). However, it is possible that Ne/ERN can also signal the detection of conflict between the executed error and the correct response that becomes activated through continued processing of the stimulus (Botvinick et al., 2001; Yeung, Cohen, & Botvinick, 2004). Thus, despite its complexity, Ne/ERN can be favorably used in the study of the neural substrates of error processing.

An increasingly animated issue in the research of performance monitoring concerns the site where the specific error-detection system is implemented in the brain. Earlier dipole source localization analyses suggested a local genesis of the Ne/ERN within structures of the

Table 1. Patient characteristics.

Pt. No	Sex	Age (years)	Dominant hand	Implanted sites*	Recording sites	Error rate (%)	Reaction time (ms)
1	M	31	R	LF, RF	84	35.6	381 ± 82.5
2	M	29	R	LTFP	68	39.6	372 ± 71.7
3	M	31	L	LTF, RT	84	79.7	286 ± 42.3
4	M	35	R	LT, RT	65	36.7	316 ± 36.5
5	M	23	R	LTF	59	62.1	337 ± 41.3
6	F	23	R	RTF	114	28.3	410 ± 29.0
7	M	34	R	LTF, RTFP	100	40.0	422 ± 40.5

*T = temporal; F = frontal; P = parietal; R = right; L = left.

frontomedian wall (FMW) – most probably in the anterior cingulate cortex (ACC) or presupplementary motor area (pre-SMA) (Dehaene, Posner, & Tucker, 1994; Holroyd, Dien, & Coles, 1998; Luu, Flaisch, & Tucker, 2000; Miltner et al., 1998; Ridderinkhof et al., 2004; Van Veen & Carter, 2002a, b). It must be noted that source modeling of electrical components of the ERPs is limited in its spatial resolution because there is no unique solution to the inverse problem. Nevertheless, recent studies using functional magnetic resonance imaging (fMRI) have also revealed significant activation of the ACC during erroneous trials (Braver et al., 2001; Carter et al., 1998; Fiehler, Ullsperger, & von Cramon, 2004; Garavan et al., 2002, 2003; Kiehl, Liddle, & Hopfinger, 2000; Menon et al., 2001; Ullsperger & von Cramon, 2001, 2004). Less frequently, additional activations were also observed in the pre-SMA, the insular cortex, the inferior parietal lobule, the supramarginal gyrus, the orbitofrontal cortex, the posterior cingulate, and the thalamus (Garavan, Hester, & Fassbender, 2004; Menon et al., 2001; Ullsperger & von Cramon, 2001). However, the theory that the Ne/ERN originates in the ACC, or within other brain sites with significant hemodynamic response to errors, has not yet been directly confirmed.

Intracerebral ERP recordings, performed in epilepsy surgery candidates during preoperative invasive long-term video-EEG monitoring, represent a good opportunity for directly defining the generators of cognitive evoked potentials. Error-related potentials elicited by incorrect responses to frequent stimuli in a visual oddball task were recently analyzed using standard methodology (Brázdil et al., 2002). The results stressed the role of multiple cortical structures in the genesis of observed Ne/ERN. In addition to the anterior cingulate, the mesiotemporal, and some prefrontal cortical sites repeatedly generated Ne/ERN-like potentials during the performed task. In terms of experimental tasks, this analysis differed significantly from previous ERP and fMRI studies on error processing, so mutual comparisons of the results remain somewhat problematic. The aim of the present intracerebral ERP study was to contribute more accurately to the knowledge of cerebral generators of the Ne/ERN by using a standard Go/NoGo task. Special attention was devoted to the involvement of the FMW in the genesis of Ne/ERN.

Methods

Subjects

Seven patients (six males and one female) ranging in age from 23 to 35 years (with an average age of 29.4 years), all with medically intractable epilepsies, participated in the study (Table 1). The epileptogenic zone was found in the mesiotemporal regions in four subjects (three left, one right), within the frontal lobe structures in two subjects (one ACC right, one frontopolar cortex left); and in the parietal lobe in one subject (postcentral region left). A comprehensive neuropsychological examination excluded severe cognitive disturbances and dementia in each patient. Depth electrodes were implanted to localize the seizure origin prior to surgical treatment. Each patient received 5–11 orthogonal multicontact electrodes using the methodology of Talairach et al. (1967). A total of 574 sites in the frontal, temporal, and parietal lobes were investigated. The number of sites per patient varied from 59 to 114. Standard MicroDeep semiflexible electrodes (DIXI Medical, Besançon, France) with diameters of 0.8 mm, contact lengths of 2 mm, and intercontact intervals of 1.5 mm were used for invasive EEG monitoring. Contacts at the electrodes (5–15) were always numbered from the medial to the lateral side. Their positions were indicated in relation to the axes defined by the Talairach system using the "x,y,z" format where "x" = lateral, mm to midline, positive right hemisphere; "y" = anteroposterior, mm to the AC line, positive anterior; and "z" = vertical, mm to the AC-PC (anterior commissure-posterior commissure) line, positive up. The exact positions of the electrodes and their contacts in the brain were verified using postplacement magnetic resonance imaging (MRI) with electrodes *in situ*. The recordings from

lesional anatomical structures and epileptogenic zones were not included in the analysis. All subjects had normal or corrected-to-normal vision. Informed consent was obtained from each subject prior to the experiment and the study received the approval of the Ethics Committee of Masaryk University.

Procedure

The experiment was conducted on each patient in the morning hours during a long-term video-EEG monitoring. Subjects were seated comfortably in a moderately lighted room with a monitor screen positioned approximately 60 cm in front of their eyes. During the examination, they were requested to focus their eyes continuously on the small fixation point in the center of the screen, and to minimize blinking. Two types of visual stimuli – clearly visible, yellow uppercase letters "X" (0.80 probability; approx. 250 trials) and "K" (0.20 probability; 60 trials) – were presented in the center of the screen. With the exception that two "K"s were never presented sequentially, the order of "X"s and "K"s was completely random. The stimuli were approximately 3 × 5 visual degrees and were presented for 240 ms on a black background. The interstimulus interval varied randomly between 650, 1650, and 2650 ms. Participants were instructed to respond as quickly and as accurately as possible with their dominant index finger on a computer keyboard every time the "X" appeared, and to not respond to the "K." Reaction time and accuracy were equally stressed. In this task, subjects relatively often made erroneous responses (false alarms) to the "K"s (i.e., incorrectly hit the keyboard). Prior to the recording, each participant performed a block of 10 practice trials twice to ensure that they understood the instructions. After the recording session, reaction times for false alarms and error rates were computed for each subject.

EEG Recording

The EEG signal was simultaneously recorded from various intracerebral structures, and from standard Fz, Cz, and Pz scalp electrodes, using the 96 channel Brain Scope EEG system (M&I; Patients 1–5) or the 128 channel TrueScan EEG system (Deymed Diagnostic; Patients 6–7). All recordings were monopolar, with a linked earlobe reference. All impedances were less than 5 kΩ. Eye movements were recorded from a cathode placed 1 cm lateral and 1 cm above the canthus of the left eye, and from an anode 1 cm lateral and 1 cm below the canthus of the right eye. In each subject, simultaneous bipolar surface EMG recordings from the dominant finger interossei muscle were obtained as a control of the subject's motor response. EEGs were amplified with a complete bandwidth at a sampling rate of 256 Hz. Occasional EEG artifacts were rejected manually during off-line analysis and further processing was performed with artifact-free EEG periods. For each patient, EEGs were analyzed using ScopeWin software. EEG data was digitally filtered with a zero-phase shift 10 Hz low-pass filter, and a zero-phase shift 2 Hz high-pass filter. EEG epochs of 600 ms were averaged off-line using the motor response as the trigger (response-triggered averages [RTA]; 300 and +300 ms from the response). EEG epochs with correct and incorrect motor reactions were averaged separately for each subject. All averages were baseline corrected to a 50 ms period beginning 200 ms before subject response. The main ERP components in the latency range of –100 ms – +200 ms were independently identified by visual inspection by two authors, and quantified by latency measures. The most valuable discoveries were the less frequent intracerebral findings of polarity reversals (identical potentials with opposite polarity in recordings from two adjacent contacts of the same intracerebral electrode) and the steep voltage gradients of the recorded potentials that uniquely proved the focal origin of the waveform (Vaughan et al., 1986). To prevent confusing the intracerebral P3-like potentials with the error-related potentials (see Results), the stimulus-triggered ERPs (–100 and +500 ms from the stimulus) were subsequently computed for error and correct trials after rare "K"s in the brain regions, where the Ne/ERN generators were clearly revealed in the response-triggered averages. For each anatomical structure investigated by depth electrode, the measurement values from the recording channel (single electrode contact) with the most prominent potential responses were chosen for further analysis.

Two-way MANOVAs (electrode × response type) were used for repeated measurements in the experiment to test the effect of the response type (correct hits vs. false alarms) at the three scalp electrode sites (Fz, Cz, and Pz) on the negative peak voltage (measured to a baseline) and latency. Subsequently a paired *t*-test was used for evaluating the effect of the response type on the ERP latencies and amplitudes at each scalp electrode separately. Statistics were obtained by using the routines included in the Statistica program (StatSoft).

Results

Satisfactory cooperation of all subjects was observed during the experiment. The mean false-alarm rate in our investigated subjects was 46% (*SD* = 18.17). The mean reaction time for false alarms was 361 ms (*SD* = 49.8).

Table 2. Mean Ne/ERN and CRN amplitude and latency values at Fz, Cz, and Pz.

		Ne/ERN		CRN	
		Mean	*SD*	Mean	*SD*
Amplitudes	**Fz**	–7.6	3.20	–3.0	1.52
	Cz	–6.0	4.17	–1.6	3.59
	Pz	–3.9	3.53	–2.7	3.71
Latencies	**Fz**	84.3	35.10	29.4	39.38
	Cz	74.2	46.61	45.7	52.08
	Pz	110.7	37.99	27.8	49.22

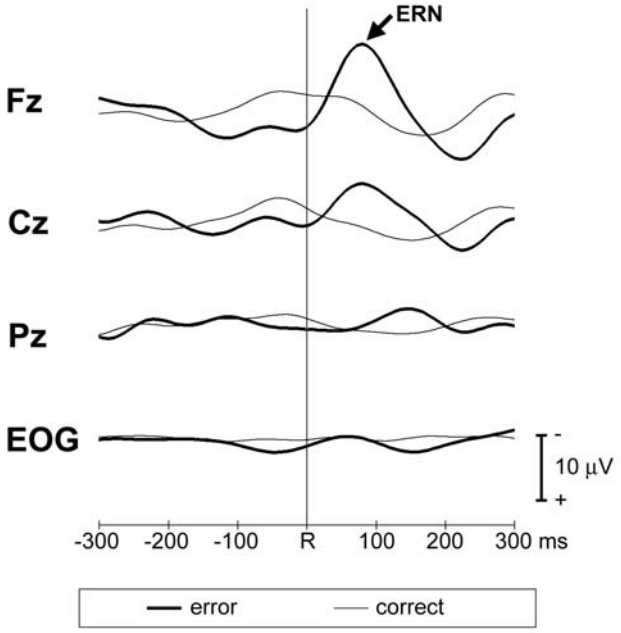

Figure 1. Grand averages of the RTA for correct responses (thin lines) and error trials (thick lines) at the scalp electrodes (Fz, Cz, Pz) and EOG. R = motor response.

In scalp recordings, Ne/ERN was clearly expressed after erroneous responses in most subjects and generally it was maximal at the Fz electrode (mean amplitude –7.6 µV; mean latency 84 ms). The grand averages of scalp ERPs for response-locked correct trials and response-locked error trials across the investigated subjects are presented in Figure 1. Mean latencies and amplitudes of scalp ERPs for error trials (Ne/ERN) and for correct trials (CRN) can be found in Table 2. The response type had a significant effect on the ERN/CRN amplitude, $F(1,30) = 8.89$, $p = .005$, with higher values for the false alarm than for the correct hit condition. A strongly significant effect of the response type on the ERN/CRN latency was also observed, $F(1,30) = 14.38$, $p = .0007$. In contrast, the electrode site did not have a significant effect on the negativity amplitudes, $F(2,30) = 1.15$, $p = .330$, or their latencies, $F(2,30) = 0.26$, $p = .772$. No significant effect on ERN/CRN amplitude and latency was found in reference to interactions between the recording site and response type, $F(2,30) = 0.91$, $p =$

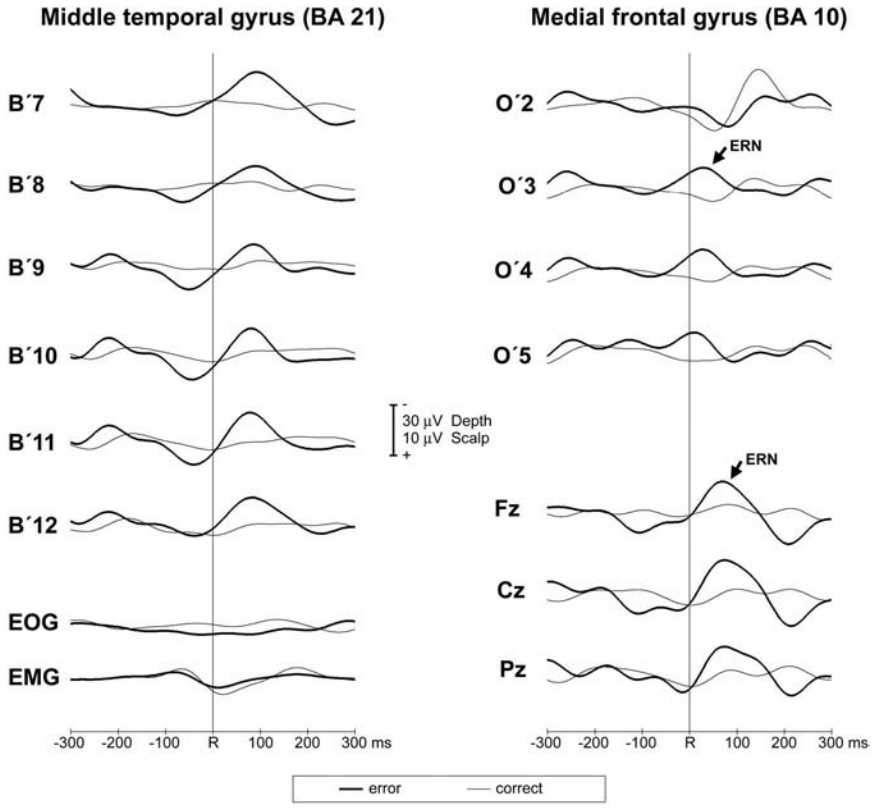

Figure 2. Response-triggered averaged intracerebral and scalp ERPs for correct (thin lines) and error (thick lines) trials. Averaged responses to errors reveal Ne/ERN-like potential without considerable voltage variation in a number of adjacent electrode contacts within the left temporal lobe (B'7–12; approximate coordinates in the Talairach axes of $x = –41$ – –61 mm, $y =$ –22 mm, $z = –9$ mm) = far field (on the left). On the right, steep voltage gradients in adjacent contacts O'2–3 indicate focal origin of Ne/ERN in the left-sided medial frontal gyrus (Talairach's coordinates, –7, 40, –10). Subject no. 5.

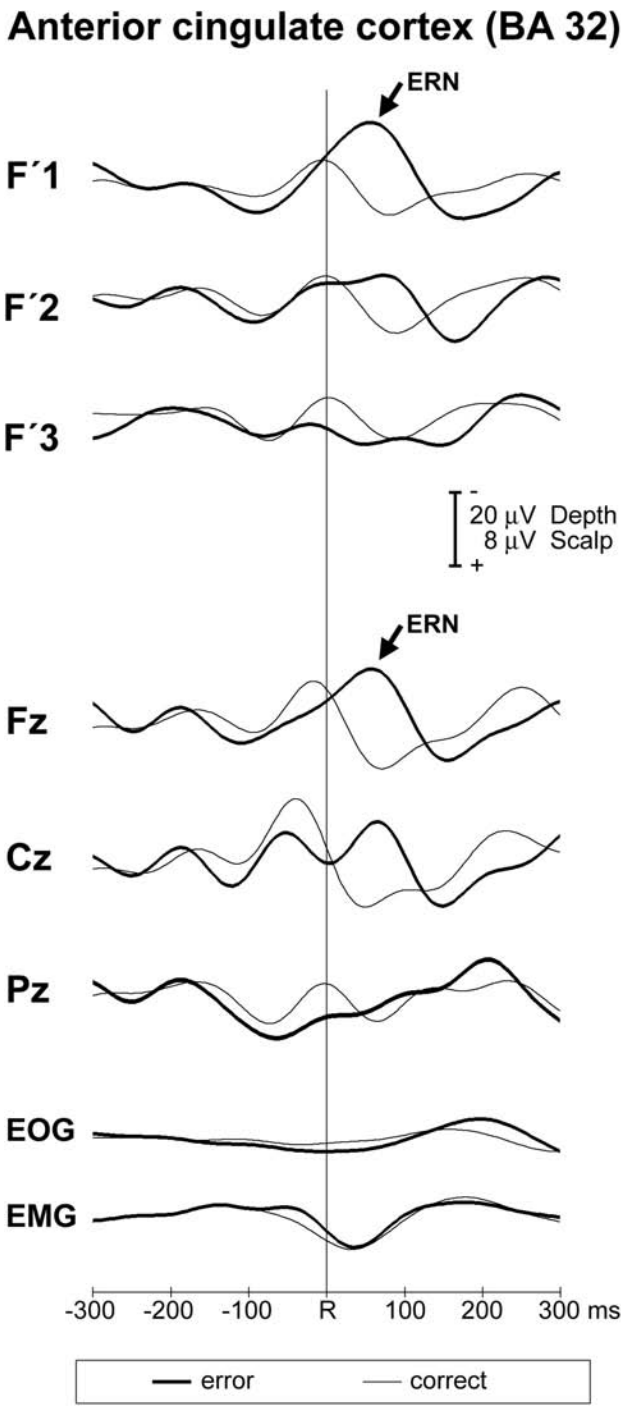

Figure 3. Intracerebral Ne/ERN with a character indicating its local source. Recordings from the left-sided rostral cingulate motor area (F'1–2: Talairach's coordinates, –5, 15, 40). Simultaneous recordings from scalp Fz, Cz, and Pz electrodes, EOG and EMG. Subject no. 3.

.413; $F(2,30) = 1.15$, $p = .325$. The effect of the response type on the Ne/ERN amplitude was at its greatest at Fz ($t = –2.77$; $df = 5$; $p = .039$), lower at Cz ($t = –2.21$; $df = 5$; $p = .078$), and absent at Pz ($t = –1.04$; $df = 5$; $p = .344$).

Intracerebral recordings in a number of cortical locations revealed prominent Ne/ERN-like potentials (with RTA-latency in the range of –100 ms – +200 ms) after false alarms that were not present after correct hits. These potentials occurred either in a number of adjacent electrode contacts without considerable voltage variation (this finding proves a far field of the recorded potential – spreading from a more or less distant neural source; see Figure 2), or restrictively with a phase reversal or steep voltage gradients in adjacent electrode contacts. This finding proves the focal origin of the waveform (neural source; see Figures 2 and 3). The number of negative findings (i.e., no evident difference in averages on correct and incorrect trials, classified as "absent Ne/ERN"), far fields, and generators within the investigated brain regions for all participating subjects is given in Table 3. Despite extensive investigation by means of depth electrodes, we never found a focal origin of Ne/ERN-like potentials within the amygdala, or the superior temporal, fusiform, or precentral gyri. Far fields of the recorded distinct ERP to false alarms were frequently observed in middle temporal gyrus and amygdala. The most interesting finding was that the focal origin of the ERPs to false alarms were proven in a number of brain sites – the hippocampus, the ACC, the medial frontal gyrus, the middle temporal gyrus, the middle frontal gyrus, the orbito-frontal cortex, the pre-SMA, and the inferior frontal, inferior temporal, and supramarginal gyri. As the rarely-presented "K" stimuli in the performed task were hypothetically potent enough to activate the neural populations involved in the genesis of P3 potential (which would not be activated by the frequent "X" stimuli), the stimulus-

Table 3. Summary of the intracerebral findings for investigated anatomical sites. Number of negative findings, far fields, and generators of Ne/ERN-like potentials as revealed by RTA technique.

Anatomical site (Brodmann area)	Negative finding	Far field	Focal origin
Anterior cingulate cortex (32)	2	4	3
Anterior cingulate cortex (24)	3	2	2
Medial frontal gyrus (8,9,10)	3	1	5
Pre-SMA (6)	1	1	2
Orbito-frontal cortex (11)	1	2	3
Middle frontal gyrus (6, 8, 9, 10, 46)	8	2	3
Inferior frontal gyrus (45, 46, 47)	3	3	2
Precentral gyrus (4, 6)	2	2	0
Amygdala	2	8	0
Hippocampus	1	1	11
Fusiform gyrus (36)	1	0	0
Superior temporal gyrus (22, 38, 42)	7	2	0
Middle temporal gyrus (21)	9	13	5
Inferior temporal gyrus (20)	0	0	1
Angular gyrus (39)	1	0	0
Supramarginal gyrus (40)	0	0	1

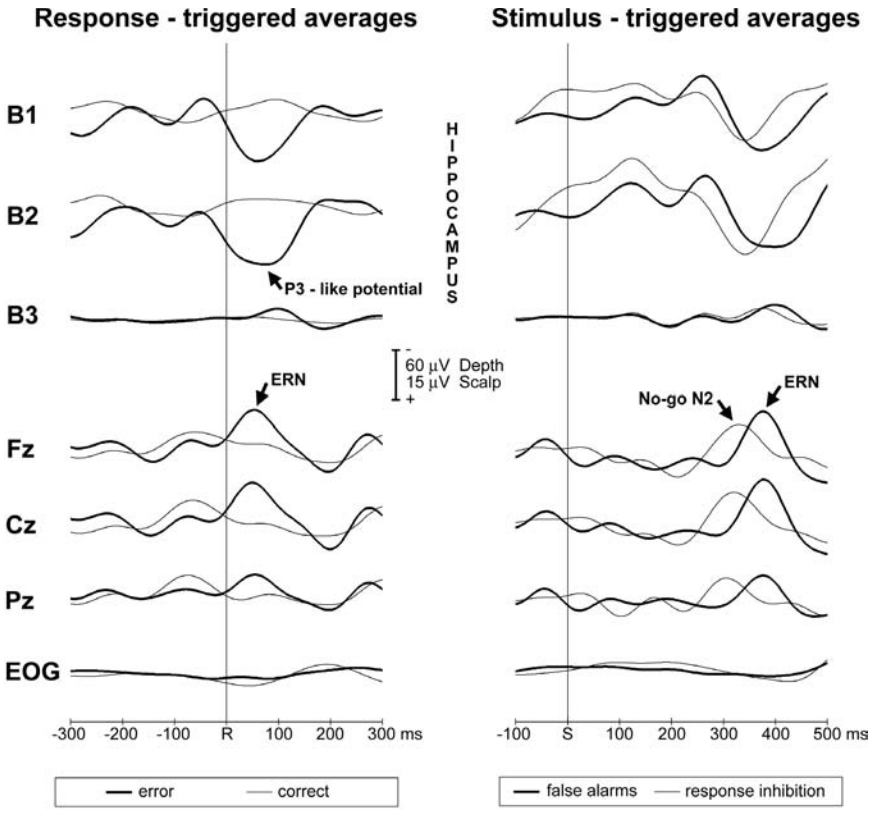

Figure 4. RTAs (for correct and error trials) and STAs (for erroneously hit and correctly ignored "K"s) for the intracerebral (right-sided hippocampus – B1–3: 27–36, –19, –12) and scalp recordings. Intrahippocampal ERPs of analogous configuration to false alarms and response inhibition in STAs dispute the direct relationship of the hippocampal activation to the error-detection in the task used. S = stimulus presentation. Typical NoGo N2 potential after correctly ignored trials is indicated in scalp STAs. Subject no. 4.

Table 4. List of Ne/ERN generators with their approximate coordinates in the Talairach axes and individual latencies.

Anatomical site	Brodmann area	Subject no.	Talairach's coordinates (x,y,z)	Ne/ERN latency (ms)
ACC	BA 32	3	–5, 15, 40	56
	BA 32	1	–7, 20, 30	0
	BA 32	1	–5, 34, –5	20
	BA 24	1	–2, 31, 14	0
Medial frontal gyrus	BA 10	5	–7, 40, –10	45
	BA 9	2	–5, 38, 32	70
	BA 10	7	3, 41, –10	48
	BA 10	7	–4,45, –12	91
Pre-SMA	BA 6	2	–4, –5, 53	70
	BA 6	6	3, 2, 56	82
Orbito-frontal cortex	BA 11	5	–25, 40, –10	22
	BA 11	7	–37, 45, –12	28
Middle frontal gyrus	BA 8	3	–48, 15, 42	59
	BA 46	6	45, 34, 21	20
	BA 6	6	30, 2, 56	37
Inferior frontal gyrus	BA 46	6	50, 40, 11	37
	BA 45	7	53, 24, 19	51
Middle temporal gyrus	BA 21	3	–61, –12, –12	14
	BA 21	3	–61, –24, –9	50
	BA 21	7	53, –19, –9	162
Inferior temporal gyrus	BA 20	6	45, –27, –11	–9
Supramarginal gyrus	BA 40	7	54, –48, 37	–37

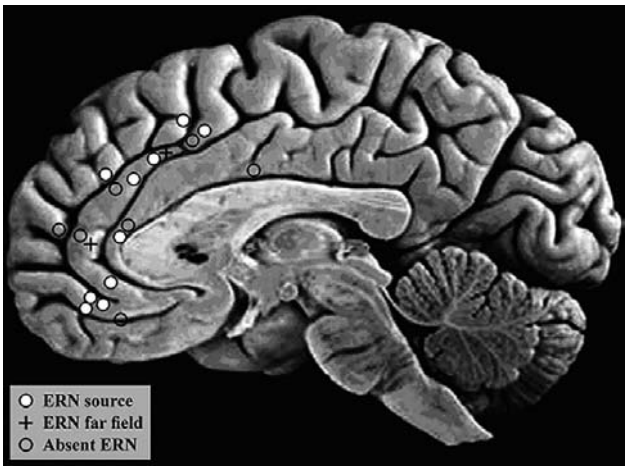

Figure 5. Schematic map of Ne/ERN findings on the mesial aspect of the frontal lobe (group data).

triggered ERPs were further computed for error and correct responses after the presentation of the "K" stimuli to differentiate the effects of "rare events" (as errors could only occur on rare trials). This analysis was performed in brain regions with proof of Ne/ERN-like potential generators as detected in response-triggered averages. Analogous ERPs in error and correct responses to "K"s were repeatedly found in different brain regions. A typical situation was observed in the intrahippocampal recordings, where stimulus-triggered averages showed identical waveforms after both erroneously hit and correctly ignored "K"s in all the sites with generators of Ne/ERN-like potentials (Figure 4). Similarly, several other neural sources of Ne/ERN-like potentials within the middle temporal gyrus, the orbito-frontal cortex, and some mesiofrontal sites (Brodmann areas 24 and 10) were proven to be involved in the processing of rare stimuli, and not exclusively in specific error processing. However this behavior was only observed in some recordings from the described brain structures, and was not typical for the extrahippocampal structures. Excluding sources of these pseudo-ERN potentials, we obtained the list of definite Ne/ERN generators presented in this study (Table 4). In all of these sites there were obvious differences in the waveforms obtained from stimulus-triggered averaging (false alarms after "K"s vs. correct response inhibition after "K"s). At the same time, RTAs showed Ne/ERN after error hits with a character indicating focal origin (see above). It is clear that true Ne/ERN was generated in multiple cortical structures, with in-

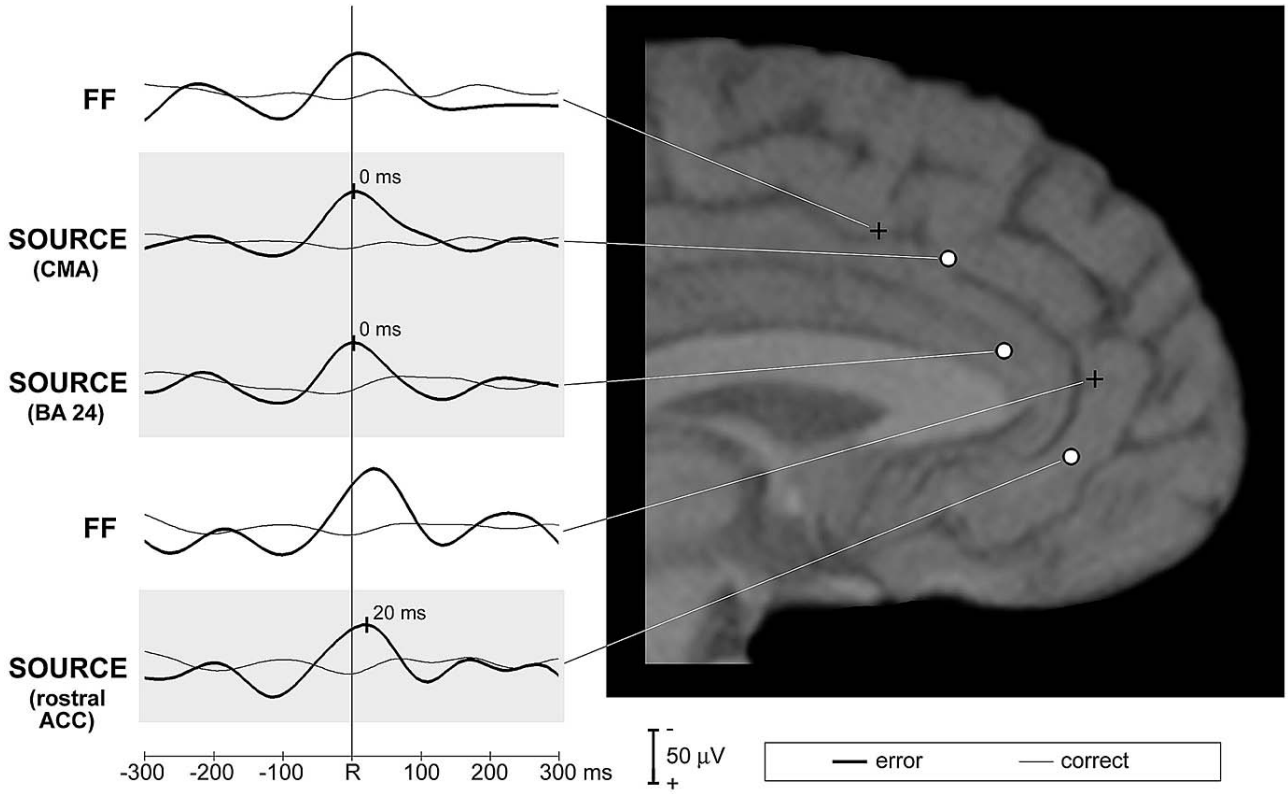

Figure 6. A time delay between intracerebral Ne/ERNs generated within different ACC sub-areas (response-triggered averages from cingulate motor area – CMA: –7, 20, 30 – Ne/ERN latency = 0 ms; BA 24: –2, 31, 14 – Ne/ERN latency = 0 ms; rostral ACC: –5, 34, –5 – Ne/ERN latency = +20 ms). The position of the recording sites (right) is precisely indicated on the subject's MRI scan (verified using postplacement MRI). Subject no. 1. FF – far field (spreading of the Ne/ERN activity).

volvement of the FMW structures being the most consistent. Ne/ERN generators were revealed there at 10 locations: most frequently in the rostral and caudal ACC, in the adjacent medial frontal gyrus (mainly within the ventral bank of the paracingulate sulcus, in which cytoarchitectonic and functional properties can be identical or very similar to those of the paralimbic cortex – BAs 32 and 24c; Paus, 2001), but also in the pre-SMA. A schematic map of Ne/ERN findings on the mesial aspect of the frontal lobe is given in Figure 5. A mutual comparison of Ne/ERN latencies among several generators within the FMW was possible in one subject (No. 1). This intraindividual analysis detected at least two separate Ne/ERN sources in the left-sided FMW. Clearly different Ne/ERN latencies were found in the left-sided FMW, with a time delay of 20 ms in the rostral anterior cingulate in comparison to the latency of Ne/ERN generated in a more caudal ACC (Figure 6). Other neural sources of Ne/ERN were proven in the dorsolateral prefrontal cortex, in the orbito-frontal cortex, in the lateral temporal neocortex, and in one isolated case within the supramarginal gyrus. The latency values of intracerebral Ne/ERNs at the sites of their focal origin are indicated in Table 4. Because of the limited number of the values obtained for the distinct brain regions, no further statistical analysis was performed.

Discussion

Performance monitoring represents a critical executive function of the human brain. A major resource in this research is to investigate the correlates of error processing and conflict monitoring. Distinguishing between errors and conflict is made difficult by the fact that conflict may accompany errors and vice versa. Nevertheless, recent evidence suggests that error-monitoring can be viewed as separate from conflict-monitoring, and that both functions may be subserved by distinct neural substrates (Braver et al., 2001; Garavan et al., 2003; Kiehl et al., 2000; Swick & Turken, 2002; Ullsperger & von Cramon, 2001). The Ne/ERN phenomenon is, then, generally thought to reflect the activity of the neural system responsible for error monitoring (Falkenstein et al., 2000, 2004; Gehring et al., 1993; Masaki and Segalowitz, 2004). In recent years, an increased interest in the neural sources of the Ne/ERN can be observed in the effort to identify the neuroanatomical bases of an error-detection system. Dipole modeling ERP analyses, congruent with neuroimaging studies, have repeatedly provided evidence that a crucial source of the Ne/ERN lies in the FMW. It was recently suggested that the ACC is responsible for the modulation of autonomic nervous system activity, which has been shown to be recruited during error processing (Hajcak, McDonald, & Simons, 2003). In agreement with all these findings, the most consistent proof of the Ne/ERN generators in our study was obtained from FMW structures. Ne/ERN sources were repeatedly revealed in the caudal ACC (BA 32) and its vicinity – within the medial frontal gyrus on the ventral bank of paracingulate sulcus (BA 9). It is noteworthy that clear-cut generators of error-related potentials were revealed in the identical sub-area of the ACC in our previous intracerebral study on performance monitoring (Brázdil et al., 2002). Two of the indubitable Ne/ERN sources were found in the present study on the ventral bank of the cingulate sulcus, where the rostral cingulate motor area (CMA) is located (see Figures 3, 5, and 6). These findings are consistent with the suggestion by Holroyd (2001) that Ne/ERN is elicited by the activity of neurons located within the CMA, and also with the results of a recent fMRI study in which the authors observed preferential activation of the human homolog of the CMA during error processing (Ullsperger & von Cramon, 2001). Another region that clearly elicited Ne/ERN in our subjects was the rostral ACC – BAs 24 and 32, and the adjacent medial frontal gyrus (BA 10). Significant activation in the rostral ACC during the commission of the errors, compared with during correct trials, was congruently demonstrated in two fMRI studies of a Go/NoGo task (Kiehl et al., 2000; Menon et al., 2001). The responsiveness of the rostral ACC to errors may reflect the role that this area plays in emotional processes. This hypothesis can simply explain a discrepancy between our results and those of Ullsperger's fMRI study. In the flankers task used in Ullsperger's fMRI experiment, errors can be corrected by a second key press. This may lead to a less negative affective valence of errors for the participants (Ullsperger & von Cramon, 2001). The different functional significance of the rostral ACC involvement in error processing also supports our finding of an unequivocal time delay of Ne/ERNs within the rostral ACC compared to the more caudal sub-areas of ACC. It makes sense that emotional processing of the error would be slightly delayed after the specific error-detection. Our results match well with the contemporary view of the ACC function, placing this region in a unique position to translate intentions into actions (Paus, 2001). Certainly the ACC is not dedicated exclusively to one process, but it is activated in a huge number of conditions. Most are related neither to errors nor to response conflict. The anterior cingulate has been proposed to be an essential part of the "anterior attention system," and as such it is importantly involved in target detection (Baudena et al., 1995; Brázdil et al., 1999; Halgren, Marinkovic K, & Chauvel, 1998; Posner et al., 1988; Posner & Peterson, 1990). At the same time, the rostral division

of the ACC has been linked to emotion, and the dorsal region has been associated with cognition and higher-order motor control (Bush, Luu, & Posner, 2000; Devinsky, Morrel, & Vogt, 1995; Paus et al., 1993). Therefore, it is very unlikely that just single a neural source of the Ne/ERN will be present within the ACC. Instead, functionally different sub-areas of the ACC (subserving different cognitive/affective functions) have to be involved in error processing and, hence, participate in the genesis of scalp Ne/ERN. In addition to a specific error-detection system and the neural substrate for emotional processing of the error, other systems should be activated by error trials within a performed Go/NoGo task (e.g., the attentional system, the systems for response selection, movement execution, etc.). On the other hand, most of these systems are also activated by correct trials and, consequently, they can be reflected in the scalp CRN.

Neural sources of the Ne/ERN were repeatedly observed in our study within the pre-SMA. The significant hemodynamic response in the pre-SMA also has been described in most fMRI studies on performance monitoring, but this response was not specific to errors. Rather, it was sensitive to conflict processing and to response inhibition (Braver et al., 2001; Garavan et al., 2003; Menon et al., 2001; Ullsperger & von Cramon, 2001; van Veen et al., 2001). There is, nevertheless, clear-cut recent evidence that pre-SMA shows both error and conflict effects in a Go/NoGo task, and that this FMW structure can be significantly activated by incorrect responses (Garavan et al., 2004). In this sense, the pre-SMA very likely contributes to the creation of the Ne/ERN phenomenon. This statement is entirely congruent with our results.

Another brain region where undisputed Ne/ERN neural sources were revealed in this study is the lateral prefrontal cortex (PFC), namely the middle and inferior frontal gyri. In the relevant literature, the congruently lateral PFC has been shown to be involved in error processing. The importance of this region and of the lateral PFC-ACC interactions for the genesis of the Ne/ERN was established in a study published by Gehring and Knight (2000). Several neuroimaging studies also found lateral prefrontal activations during errors (Carter et al., 1998; Kiehl et al., 2000; Menon et al., 2001). Obvious generators of error-related potentials were also detected in the lateral PFC in our previous intracerebral study (Brázdil et al., 2002). Because of the widespread reciprocal cortico-cortical connections of the lateral PFC with the supracallosal cingulate areas 24 and 32, these findings are not truly surprising. Actually, coactivations of the lateral PFC and the ACC during the performance of a variety of tasks have been noticed frequently. Even if the functional significance of such interactions remains unclear, it was suggested that the lateral PFC computes and maintains online information necessary for the selection of an appropriate response, whereas the ACC facilitates the implementation of the selected action (Paus et al., 1993). Our results produced no evidence to support the possible lateralization of the PFC involvement in error processing.

Our observations of Ne/ERN sources in the orbitofrontal cortex, the supramarginal gyrus, and the lateral temporal neocortex are less consistent than findings within the FMW and PFC structures. The orbito-frontal cortex is known to be importantly involved in the modulation of impulsivity (Bechara, Damasio, & Damasio, 2000; Fuster, 1995). This fits well with our evidence of local Ne/ERN sources within BA 11 in two subjects. However, neuroimaging studies have not yet revealed any activation in this structure related to error processing. On the other hand, the orbito-frontal cortex is a part of the brain that is well known to be extremely prone to susceptibility artifacts in fMRI experiments. Thus, false negative findings in hemodynamic studies might be obtained. In contrast, our separate proof of the neural source of the Ne/ERN in the supramarginal gyrus (SMG) is in agreement with the results of the Ullsperger and von Cramon's fMRI study (2001). But significant hemodynamic response within a parietal lobe was described extremely rarely in previous fMRI studies focused on Go/NoGo tasks (Garavan et al., 2004). An important contribution to the understanding of the neurophysiological aspects of error processing may arise from our finding of the shortest Ne/ERN latency within SMG. By analogy, intracerebral investigations of P3 potential disclosed the earliest involvement in the detection of targets as that of the parietal lobe structures (Halgren et al., 1998). Finally, the clear-cut latency differences between the P3 and error-related potentials across distinct brain lobes observed in our previous study suggest that the Ne/ERN is also primarily elicited in parietal regions, and only later in frontal and temporal regions (Brázdil et al., 2002). The substantially different peak latencies in distinct Ne/ERN neural sources seen in the present study support that hypothesis and link different cognitive processes in the human brain.

The role of the hippocampus in the processing of error trials and the functional significance of the common local activation after both erroneous hits and correct rejections of rare stimuli should be discussed. The hippocampus is known to be a structure importantly engaged in the cognitive processing of external as well as internal stimuli. It has also been identified as a powerful neural source of some cognitive potentials including P3 (see Halgren et al., 1998). This mesiotemporal structure is evidently simultaneously involved in affective processing. In terms of discussed emotional aspects in error processing, the mesiotemporal structures (including the hippocam-

pus) were coherently identified as additional generators of error-related potentials in our previous study using an oddball task. In that oddball study, erroneous motor responses to frequent stimuli were analyzed and compared to the correct motor responses to rare stimuli. A P3 potential was observed after correctly hit targets, while errors evoked undisputed Ne/Pe complexes in several brain sites, with the most consistent proof of their generators within the mesiotemporal region (Brázdil et al., 2002). The design of the Go/NoGo task used in the present study unfortunately impedes a meaningful assessment of the role of the hippocampus in the genesis of Ne/ERN. It could be expected that both error and correct reactions to the rarely presented "K" stimuli would activate hippocampal neurons and, thus, produce an ERP. This was the case for all the hippocampal recordings. However, an interpretation of the obtained ERP remains speculative. Certainly neuronal populations responsible for target detection would be activated in both conditions, and, thus, the P3 potential should be present in both STAs. On the other hand, neuronal populations engaged in successful response inhibition and conflict monitoring (and hence producing NoGo N2; Nieuwenhuis et al., 2002) will also be involved in processing of the correctly rejected "K"s and the distinct neuronal substrate for error processing will produce similar Ne/ERNs after error trials. If there is a brain region with a common involvement of its neuronal populations both in error-processing and response inhibition, then similar responses will be seen in STAs. Even if it is conceivable that response inhibition and error processing activate different brain areas, some evidence has been accumulated from hemodynamic studies that indicate that the error-processing network indeed overlaps partly with the distributed network involved in response inhibition. Brain regions that are involved in both functions were identified to be the pre-SMA, the caudal ACC, and the lateral prefrontal cortex (Carter et al., 1998; Fiehler et al., 2004; Ford, Whitfield, & Mathalon, 2004; Menon et al., 2001; Ullsperger & von Cramon, 2001). Absolutely no information is available for mesiotemporal regions that addresses their potential role in conflict monitoring. The reason for this may be the low sensitivity of fMRI methodology for the detection of transient neural activity within the mesiotemporal regions during some cognitive tasks. In contrast, this "hidden" activity can be clearly detected in intracerebral ERP recordings (Brázdil et al., 2005). Given the knowledge currently available, one can assume that analogous intracerebral ERPs in stimulus-triggered averages within the hippocampi reflect the activation of the hippocampal neural substrate for target detection, as well as the involvement of hippocampal neurons in error processing, and possibly response inhibition also. The hippocampal P3 response is extremely strong and, thus, the Ne/ERN, and possibly the NoGo N2, are still covered by this P3 response. An analogous situation can be seen in a few other generators of Ne/ERN-like potentials, with identical responses to error hits and correct rejections in STAs (i.e., ACC /1/, medial frontal gyrus /1/, orbito-frontal cortex /1/, and middle temporal gyrus /2/). An intracerebral ERP study using a Go/NoGo task with equal rates of Go and NoGo stimuli is suggested to eliminate the problem of this P3 effect on Ne/ERN.

To summarize, our results clearly confirmed the key role of ACC and the adjacent FMW in the genesis of error-related negativity. However, our results show that error processing involves an extensively distributed network of different brain regions. In addition to FMW, other cortical structures were proven to be engaged – the lateral and basal prefrontal cortex, the lateral temporal neocortex, and the supramarginal gyrus. At the same time, it can be expected that the brain's error-checking systems include some other regions that are involved in parallel fashion both in error processing and conflict monitoring, but still participating in the genesis of scalp Ne/ERN.

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Post-movement processing in visual oddball task – Evidence from intracerebral recording

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HIGHLIGHTS

- Multiple cortical structures are activated after correct motor performance including mesiotemporal structures, anterior midcingulate, prefrontal, and temporal cortices.
- Equivalent involvement of these structures in task-variant nonspecific and target specific processes is suggested.
- Networks generating correct and incorrect performance-related potentials probably share some common nodes.

ABSTRACT

Objective: To identify intracerebral sites activated after correct motor response during cognitive task and to assess associations of this activity with mental processes.
Methods: Intracerebral EEG was recorded from 205 sites of frontal, temporal and parietal lobes in 18 epileptic patients, who responded by button pressing together with mental counting to target stimuli in visual oddball task.
Results: Post-movement event-related potentials (ERPs) with mean latency 295 ± 184 ms after movement were found in all subjects in 64% of sites investigated. Generators were consistently observed in mesiotemporal structures, anterior midcingulate, prefrontal, and temporal cortices. Task-variant nonspecific and target specific post-movement ERPs were identified, displaying no significant differences in distribution among generating structures. Both after correct and incorrect performances the post-performance ERPs were observed in frontal and temporal cortices with latency sensitive to error commission in several frontal regions.
Conclusion: Mesiotemporal structures and regions in anterior midcingulate, prefrontal and temporal cortices seem to represent integral parts of network activated after correct motor response in visual oddball task with mental counting. Our results imply equivalent involvement of these structures in task-variant nonspecific and target specific processes, and suggest existence of common nodes for correct and incorrect responses.
Significance: Our results contribute to better understanding of neural mechanisms underlying goal-directed behavior.

1. Introduction

It is widely accepted that successive components of event-related potentials (ERPs) elicited during a cognitive task are related to successive stages in processing. Therefore, electrophysiological recording can be used to monitor the probable location, timing and intensity of brain activation during the task (Halgren et al., 1998). Recently, an increased interest in the neural sources of ERPs elicited in the post-performance period has been observed with the aim to identify anatomical structures engaged in performance monitoring. A well-known event-related potential provoked by errors, error-related negativity (Ne/ERN) typically peaking

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100–150 ms after an erroneous response (Falkenstein et al., 1990; Gehring et al., 1993) was proved by intracerebral studies to stem from activation of multiple sources, with the most consistent involvement being that of frontomedian wall and mesiotemporal lobe structures (Brázdil et al., 2002, 2005; Pourtois et al., 2010). A positive deflection occurring 200–500 ms after an incorrect response and following the Ne/ERN referred to as error positivity (Pe; Falkenstein et al., 1991, 1995, 2000) was suggested to be generated in the anterior cingulate cortex (ACC; Herrmann et al., 2004) and to have a common origin with the Ne/ERN (Brázdil et al., 2002). In patients and also in healthy subjects the so-called "correct response-related negativity" (Nc/CRN) is often seen as negative deflection following correct responses in surface electrophysiological recordings (Bonnefond et al., 2011; Coles et al., 2001; Ford, 1999; Gehring and Knight 2000; Scheffers and Coles, 2000; Vidal et al., 2000, 2003). Surprisingly, few studies carefully investigated neural sources of Nc/CRN. This ERP was observed at frontal (Mathalon et al., 2002; Meckler et al., 2011) and frontocentral electrodes (Falkenstein et al. 2000; Hajcak et al., 2005), and, therefore, generators in the rostral cingulate zone were suggested (Carter et al., 1998; Roger et al., 2010). Similarly to erroneous responses a small positivity can also be found for correct responses called the correct response positivity (Pc), but it has generally been used only as a baseline comparison for the Pe and little has been written about it (Bates et al., 2004; Mathalon et al., 2002). We believe, however, that studies focused on correct response processing could contribute to better understanding of neural mechanisms underlying successful goal-directed behavior. In addition to these theoretical implications, studying the functional significance of post-performance ERPs might also help to understand deficits in action control and behavior adaptation observed in psychopathological and neurological conditions (Taylor et al., 2007).

Scalp-recorded event-related potentials (ERPs) elicited during the so-called "oddball" task have been employed for decades as a useful tool for studying cognition processes. In the oddball task the subject responds by button pressing and/or mental counting only to the infrequent "target" stimulus, which is presented randomly and repeatedly among frequent "nontarget" stimuli. Two types of correct performance are observed – motor response in the target variant (correct hit) and refraining from movement in the nontarget variant (correct rejection). The oddball paradigm can also induce two types of errors – response omission in the target variant (incorrect rejection) and erroneous motor response (false alarm) in the nontarget variant. As such, the analysis of ERPs recorded in the post-performance period of this simple cognitive task seems to be very useful for studying mechanisms of performance monitoring. Previous intracerebral studies employing motor tasks, however, focused rather on P3-like potentials (Rektor et al. 2007) or ERPs appearing before and during a simple acral limb movement (Rektor et al. 1998; Rektor, 2000) and did not investigate ERP components that might appear later. To our knowledge, the activity following correct responses in motor tasks has not been systematically examined by any intracerebral study yet.

While multiple sources were proved for event-related activity in the post-performance period provoked by errors (Brázdil et al., 2002, 2005; Pourtois et al., 2010) we have hypothesized whether also in correct reactions to target stimuli of visual oddball task multiple brain regions might be involved in processes that take place there. If so, ERP activity in the post-movement period of correctly performed task might be observed within a large-scale neuronal network rather than limited to a single brain structure. To this end, the present intracerebral ERP study was designed to identify the cerebral sites consistently activated after correct motor reactions in a visual oddball task. Therefore we assessed across examined brain structures the occurrence frequency of post-movement ERP evoked during the target task variant. In an attempt to associate these ERPs with underlying mental processes, we decided to evaluate these potentials in relation to ERPs elicited after correct performance of nontarget task variant and after both types of errors induced during the task. If the post-movement ERP reflects different mental processes then in sites where this ERP was detected, differences in post-performance activity in the nontarget task variant should be observed. If the brain network related to incorrect responses shares some common nodes with that related to correct responses, then sites active in both conditions should be identified. To explore the character of mental processes underlying the post-movement ERPs we evaluated their latency and distribution among brain structures.

2. Methods and materials

2.1. Subjects

Eighteen patients (14 men) aged from 23 to 45 years (median 30) were employed in the study (Table 1). All subjects suffered from medically intractable epilepsy and were candidates for surgical treatment. They all were under antiepileptic drug therapy, which was determined by clinical considerations. During the period of diagnostic examination by intracerebral EEG recording, the doses of medicaments were reduced to allow seizures to develop spontaneously. All patients had normal or corrected-to-normal vision. The subjects gave us their informed consent to the experimental protocol that had been approved by the Ethical Committee of Masaryk University.

2.2. Experimental task

A visual oddball task was performed. The patients were sitting comfortably in a moderately lighted room and were focusing on the center of a monitor situated at about 100 cm from their eyes. Yellow capital letters X (target) or O (nontarget) appeared repeatedly on white background in random order as experimental stimuli. Each stimulus presentation lasted 200 ms and the interstimulus interval varied randomly between 2 and 5 s. The target stimuli were five times less frequent than the nontarget ones. The subjects were instructed to press a microswitch button with

Table 1
Patient characteristics and lobes investigated.

Patient	Sex*	Age	Lobes investigated *	Number of sites investigated
1	M	20	RFT, LFT	11
2	M	28	RFT, LT	7
3	M	37	RFT, LFT	13
4	M	45	RFT, LFT	15
5	M	30	RFT, LFT	14
6	F	31	RFT	12
7	M	32	RFT, LTF	4
8	M	30	RFT, LFT	10
9	M	19	RF, LF	12
10	F	31	RFT, LFT	14
11	F	27	RT	6
12	M	19	RT, LT	14
13	M	41	RF, LF	8
14	M	25	RFT, LFT	17
15	M	34	RFTP	14
16	M	23	RFT, LFT	16
17	F	28	LFT	10
18	M	27	LT	8

* M = male; F = female; R = right, L = left; F = frontal, T = temporal, P = parietal.

the dominant hand as quickly as possible, whenever a target stimulus appeared, to mentally count the target stimuli, and to ignore the nontarget stimuli.

2.3. Data acquisition

Electrical activity was recorded during the task simultaneously from various brain sites by means of standard Micro Deep semiflexible multicontact platinum electrodes. Having a diameter of 0.8 mm, each electrode carried 5–15 contacts 2.0 mm long separated by constant intervals of 1.5 mm. Strictly for diagnostic reasons 113 intracerebral depth electrodes were implanted into the structures of the frontal, temporal, and parietal lobes (Table 1). Every patient received 2–10 such electrodes exploring either or both hemispheres. Long electrodes examined both lateral and mesial cortical regions. The electrodes were placed using the methodology of Talairach et al. (1967) and their position was afterwards verified by magnetic resonance imaging with electrodes in situ. The registration was made with the help of a 64-channel Brain Quick EEG system (Micromed). All the recordings were monopolar with respect to a reference electrode attached to the right processus mastoideus. The impedances used were less than 5 kΩ. The EEG signal was amplified with a bandwidth of 0.1–40 Hz at a sampling rate of 128 Hz.

2.4. Analysis

The EEG signal was analyzed offline with the help of ScopeWin software. The recordings from lesions and epileptogenic zones and the trials with artefacts were rejected offline with visual inspection made by two experienced persons. Switching the button in response to a nontarget stimulus or its omission in response to a target stimulus was considered as error. In each subject all artefact-free trials with correct and at least 10 incorrect performances were used for calculation of average curves. Exclusion of a different number of trials and commission of a different number of errors explains the interindividual variability in the number of trials used for each average curve (target variant: 41–80 trials with correct hits, 14 and 25 trials with incorrect refraining from movement; nontarget variant: 191–342 trials with correct refraining from movement, and 13, 14 and 18 trials with false alarms). Post-movement ERP waves in the latency range of 0–900 ms from movement were analyzed. Periresponse EEG periods (from −900 to +900 ms from the movement onset) were averaged for target correct responses using movement onset as a trigger. Peristimulus EEG periods (from −300 to +1500 ms from the stimulus onset) were averaged separately for target and nontarget correct and incorrect performances using the stimulus onset as a trigger. The statistical significance of ERP waves was computed between the mean amplitude observed during the baseline period (from −600 to −100 ms from the stimulus onset) and the mean value computed as a mean from the neighborhood of each point (170 ms length) after stimuli or responses using a nonparametric Wilcoxon Rank Sum (Signed Rank) test for paired samples. Records from one contact of each multicontact intracerebral electrode implanted in a particular anatomical structure were included in the analysis selecting the one with the largest amplitude of ERP. The intracerebral findings of steep voltage gradients uniquely proved the focal origin of the waveform (Fig. 1).

The statistical analysis of recorded potentials was performed by comparing the presence with the absence of the post-movement ERP in correct reactions to target stimuli. The frequency differences between brain structures were examined using the binomial test. Involvement of these structures after correct performance in nontarget task variant was compared using Fischer's exact test. To test the statistical significance of differences in latency of ERPs the *t*-test for independent samples was used. In all tests the threshold for statistical significance was set to $P < 0.05$.

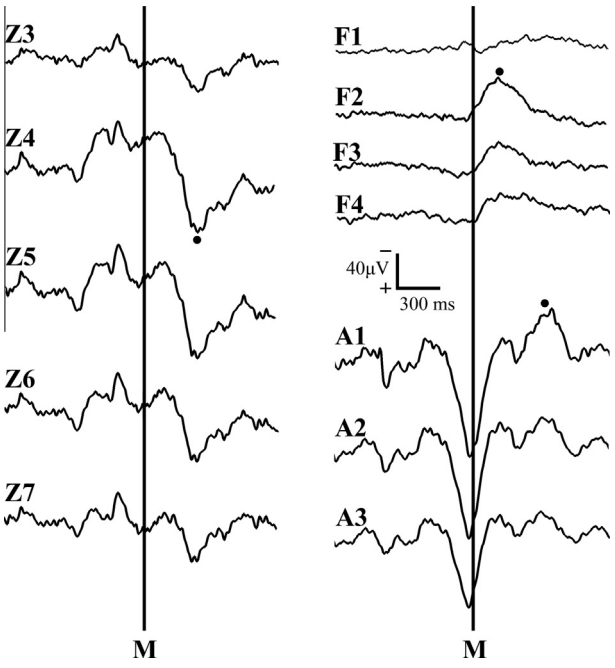

Fig. 1. The response-triggered averaged ERPs for correct target trials recorded from neighboring electrode contacts exhibiting steep voltage gradients in post-movement period in right hippocampus in patient No. 2 (Z3–Z7), right anterior midcingulate cortex in patient No. 9 (F1–F4), and right amygdala in patient No. 4 (A1–A3). Note the voltage variations across contacts with maximal peak amplitude marked with black point (M = movement).

3. Results

The performance of the subjects during the task was very accurate; only three subjects (Nos. 5, 9, and 12) committed higher number of errors (Table 2). The mean reaction time in correct responses ranged from 457 ± 34 ms to 644 ± 78 ms (median 522 ms). In the response-triggered averages (RTAs) of correct reactions to target stimulus a prominent event-related potential in the post-performance period (see Fig. 2) was detected in all subjects in 131 sites, i.e. 64% of sites investigated, with no significant difference in localization within well examined frontal and temporal lobes. These sites were distributed among multiple brain structures (see Table 3); involving mesiotemporal structures, lateral temporal, prefrontal, cingulate, frontal and parietal cortices, and basal ganglia. The occurrence of the post-movement ERP in enough examined (at least 5 investigated sites) brain structures ranged from 43% to 100% (mean 67 ± 15%) of investigated sites. The binomial test revealed no significant differences in frequency of findings of post-movement ERP among these eleven structures. The only exception were basal ganglia where finding of post-movement ERP was significantly more frequent than in several, mostly temporal, sufficiently examined brain structures (Table 4), and anterior midcingulate cortex with borderline significantly higher post-movement ERP occurrence than in inferior temporal gyrus ($P = 0.0485$). When we restrict our results to observation of generators, however, the list of presumably consistently involved structures is shorter (see Table 5). The data in Fig. 1 demonstrate three regions exhibiting signs of a local generator. Most frequently (53% of sites investigated) the post-movement ERP was generated in amygdala. Quite frequently, with occurrence not significantly different from amygdala, generators were also observed in

Table 2
Number of artefact-free trials.

Patient	Target		Nontarget	
	Correct hit	Incorrect rejection	Correct rejection	False alarm
1	49	0	281	3
2	45	0	236	1
3	62	6	266	1
4	41	5	221	1
5	65	1	332	18
6	57	3	328	2
7	49	0	261	0
8	52	0	247	0
9	77	25	343	14
10	46	3	267	0
11	59	1	243	2
12	80	14	282	13
13	53	3	201	0
14	61	1	316	4
15	63	1	242	0
16	66	3	305	3
17	57	0	222	0
18	57	2	270	1

Correct hit = motor response to target stimulus; Incorrect rejection = movement omission after target stimulus; Correct rejection = refraining from movement in nontarget task variant; False alarm = erroneous motor response in nontarget task variant.

hippocampus, parahippocampal and middle temporal gyri, anterior midcingulate cortex, medial frontal, orbitofrontal, and dorsolateral prefrontal gyri. On the other hand, despite sufficient examination, the post-movement ERP was generated significantly less frequently than in amygdala in superior and inferior temporal gyri and no generator was found in basal ganglia. The comparison between brain lobes revealed no significant differences in post-movement ERP generator occurrence. In post-movement ERPs generated in temporal and frontal lobes the mean peak latency relative to motor response was 288.9 ± 171.6 ms and 248.7 ± 176.4 ms, respectively. This difference, however, did not reach the statistical significance.

The observed post-movement ERPs were mostly (80% sites) monophasic, less frequently complex biphasic (14% sites) with waveforms of opposite polarities, only occasionally (6% sites) two separate waves of the same polarity were detected. In total, 157 ERP waves were observed in the post-movement period in the target task variant. Their peak latency ranged from 14 to 726 ms (mean 295 ± 184 ms, median 258 ms) with approximately half of them (48%) appearing between 100 and 300 ms after movement onset. Less than one third of post-movement ERPs (27%) were observed in sites where no ERP component was detected during the stimulus–response interval. This was revealed by the analysis of stimulus-triggered averages (STAs) of correct reactions to target stimulus. In these cases the post-movement ERP was observed as a very late isolated ERP with a latency exceeding the mean reaction time (e.g. in contact X′8 in patient 3, see Fig. 3A); in the majority of brain sites, however, this potential appeared only after components elicited within the stimulus–response interval (e.g. in contact D′2 in patient 14, see Fig. 3A).

Approximately in 50% of the sites where post-movement ERP was detected in the RTA of correct reactions to target stimuli, no very late ERP was observed in the STA of correctly ignored nontarget stimuli (e.g. examples in Fig. 3A). In the other half of the sites, however, one (61 sites) or two (6 sites) potential waves with a latency exceeding the subject's mean reaction time were observed (e.g. examples in Fig. 3B–D). The latency of all these 73 nontarget post-performance ERP waves ranged from 500 to 1162 ms (mean 757 ± 168 ms) after the stimulus onset. A comparison of the first nontarget with the first target post-performance ERP wave in the STAs revealed that the latency of the nontarget ERP was shorter

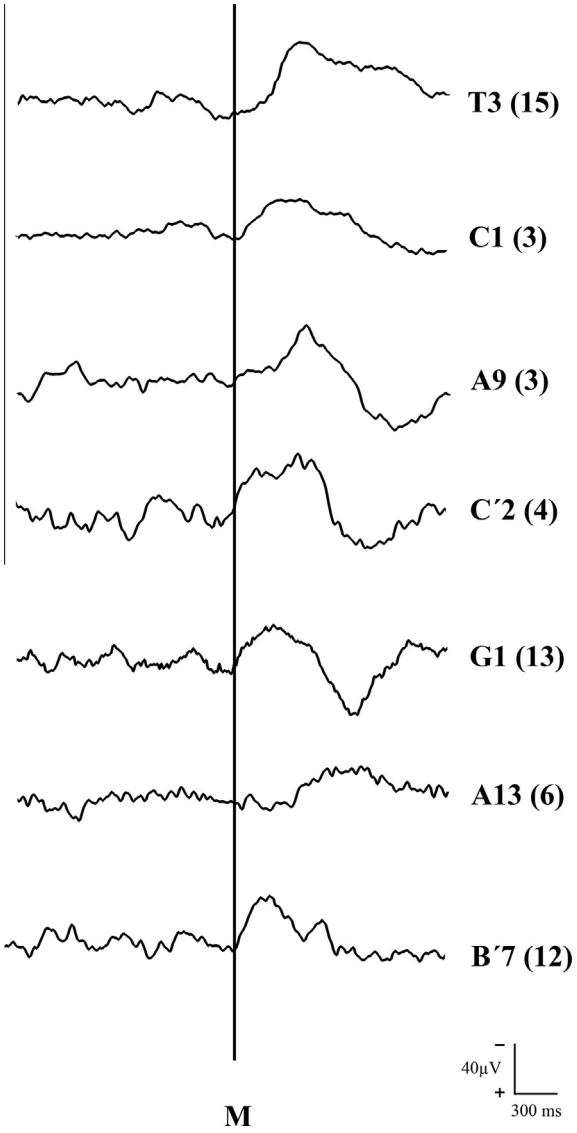

Fig. 2. Response-triggered averaged post-movement ERPs for correct target trials (M = movement). Contact (subject), anatomical structure: T3 (15), right superior temporal gyrus; C1 (3), right fusiform gyrus; A9 (3), right middle temporal gyrus; C′2 (4), left parahippocampal gyrus; G1 (13), right anterior cingulate cortex; A13 (6), right middle temporal gyrus; B′7 (12), left superior temporal gyrus.

by 174 ± 118 ms in 34 sites (Fig. 3B) and longer by 166 ± 88 ms in 26 sites (Fig. 3C). In the remaining 7 sites the latencies were almost identical differing by less than 20 ms (Fig. 3D).

In most anatomical structures examined both task-variant nonspecific and target specific post-movement ERPs were observed (Table 3). In the former case an ERP was detected both in target post-movement and nontarget post-performance periods while in the latter case the potential was found only in target task variant. Mean latency of task-variant nonspecific (244.6 ± 142.1 ms) and target specific (251.3 ± 164.5 ms) post-movement ERPs differed only slightly and the differences did not reach a statistical significance. Both the task-variant nonspecific and target specific post-movement ERPs were observed in all but two patients. Only the former or latter types of ERP were observed in subject No. 9 and 11, respectively. The occurrence frequency of task-variant nonspecific and target specific ERP types did not significantly differ between frontal and temporal lobes neither among individual brain structures investigated. The only exception were the basal

Table 3
Distribution of ERPs across brain regions in correct reactions to target stimulus.

Anatomical structure	Post-movement ERP[a]	Sites examined/subjects	Target specific ERP/subjects[b]	Task-variant nonspecific ERP/subjects[c]
Anterior midcingulate cortex	9(82)	11/7	3/3	6/5
Pregenual anterior cingulate cortex	2(67)	3/2	2/1	0/0
Rostro- and dorsomedial prefrontal cortices	6(75)	8/5	2/2	4/2
Orbitofrontal cortex	8(57)	14/8	6/5	2/2
Dorsolateral prefrontal cortex	15(71)	21/10	8/5	7/3
Supplementary motor area	0(0)	2/1	0/0	0/0
Premotor cortex	1(100)	1/1	1/1	0/0
Primary motor cortex	3(75)	4/2	0/0	3/2
Basal ganglia	7(100)	7/5	7/5	0/0
Amygdala	10(67)	15/12	5/5	5/5
Hippocampus	17(65)	26/15	10/8	7/6
Parahippocampal gyrus	6(55)	11/8	1/1	5/3
Fusiform gyrus	4(100)	4/5	1/1	3/3
Superior temporal gyrus	13(57)	23/11	5/5	8/4
Middle temporal gyrus	19(61)	31/15	9/6	10/7
Inferior temporal gyrus	6(43)	14/8	1/1	5/4
Lingual gyrus	1(50)	2/1	0/0	1/1
Posterior cingulate cortex	0(0)	2/1	0/0	0/0
Inferior parietal lobule	2(67)	3/1	1/1	1/1
Somatosensory cortex	2(67)	3/2	1/1	1/1
Frontal lobe	51(72)	71/14	29/13	22/7
Temporal lobe	76(60)	126/17	32/14	44/14
Parietal lobe	4(50)	8/2	2/1	2/1
Total	131(64)	205/18	63/17	68/17

[a] Number of sites (% of sites examined) with positive observations of post-movement ERP in response-triggered averages of correct reactions to target stimulus.
[b] Number of sites/subjects with observed target post-movement ERP but with negative finding in post-performance period of nontarget task variant.
[c] Number of sites where ERP was observed both in target post-movement and nontarget post-performance periods.

Table 4
Comparison between basal ganglia and other brain structures (*P*-values).

Anatomical structure	Binominal test	Fisher's exact test
Anterior midcingulate cortex	0.2341	0.0114*
Rostro- and dorsomedial prefrontal cortices	0.1553	0.0210*
Orbitofrontal cortex	0.0400*	0.4667
Dorsolateral prefrontal cortex	0.1073	0.0513
Amygdala	0.0843	0.0441*
Hippocampus	0.0663	0.0648
Parahippocampal gyrus	0.0037*	0.0047*
Superior temporal gyrus	0.0341*	0.0147*
Middle temporal gyrus	0.0454*	0.0227*
Inferior temporal gyrus	0.0112*	0.0047*

* $P < 0.05$, significant difference in numbers of post-movement ERPs (binominal test) or in frequency of target specific and task-variant nonspecific ERPs (Fisher's exact test) between basal ganglia and other sufficiently examined brain structures.

ganglia in which only target specific ERPs were found (e.g. Fig. 3A) and thus this result was significantly different from several brain structures (see the last column in Table 4). No significant differences in ERP type distribution, however, were found among generating brain structures (see Table 5).

Errors, i.e. erroneously omitted (incorrect rejection) or erroneously performed (false alarm) motor responses, were committed quite frequently in three of the patients (Nos. 5, 9, and 12; see Table 2). The subject's mean reaction time was longer for false alarms (RTf) compared to correct hits (RTc) by 56 ms, 23 ms, and 138 ms in patients Nos. 5, 9, and 12, respectively. In patient No. 5 no ERP was found after false alarms in sites where post-movement ERP was recorded in correct reactions to target stimuli. In both remaining patients, however, a very late ERP with latency exceeding both RTc and RTf was observed in stimulus-triggered

Table 5
Distribution of generators across brain regions in correct reactions to target stimulus.

Anatomical structure	Generators[a]	Target specific ERP[b]	Task-variant nonspecific ERP[c]
Anterior midcingulate cortex	5(42)	1	4
Pregenual anterior cingulate cortex	1(50)	1	0
Rostro- and dorsomedial prefrontal cortices	2(25)	1	1
Orbito-frontal cortex	3(21)	2	1
Dorsolateral prefrontal cortex	8(38)	3	5
Supplementary motor area	0(0)	0	0
Premotor cortex	1(100)	1	0
Primary motor cortex	1(25)	0	1
Basal ganglia	0(0)	0	0
Amygdala	8(53)	4	4
Hippocampus	8(31)	4	4
Parahippocampal gyrus	5(45)	1	4
Fusiform gyrus	1(25)	1	0
Superior temporal gyrus	5(22)	3	2
Middle temporal gyrus	10(32)	5	5
Inferior temporal gyrus	2(14)	0	2
Lingual gyrus	0(0)	0	0
Posterior cingulate cortex	0(0)	0	0
Inferior parietal lobule	0(0)	0	0
Somatosensory cortex	1(33)	0	1
Frontal lobe	21	9	12
Temporal lobe	39	18	21
Parietal lobe	1	0	1
Total	61	27	34

Sufficiently examined brain structures (at least 5 sites investigated) with high occurrence of generators are in bold format.
[a] Number of sites (% of sites examined) displaying signs of proximity to structure generating the target post-movement ERP either.
[b] With negative finding in nontarget post-performance period,
[c] With ERP observed in nontarget post-performance period.

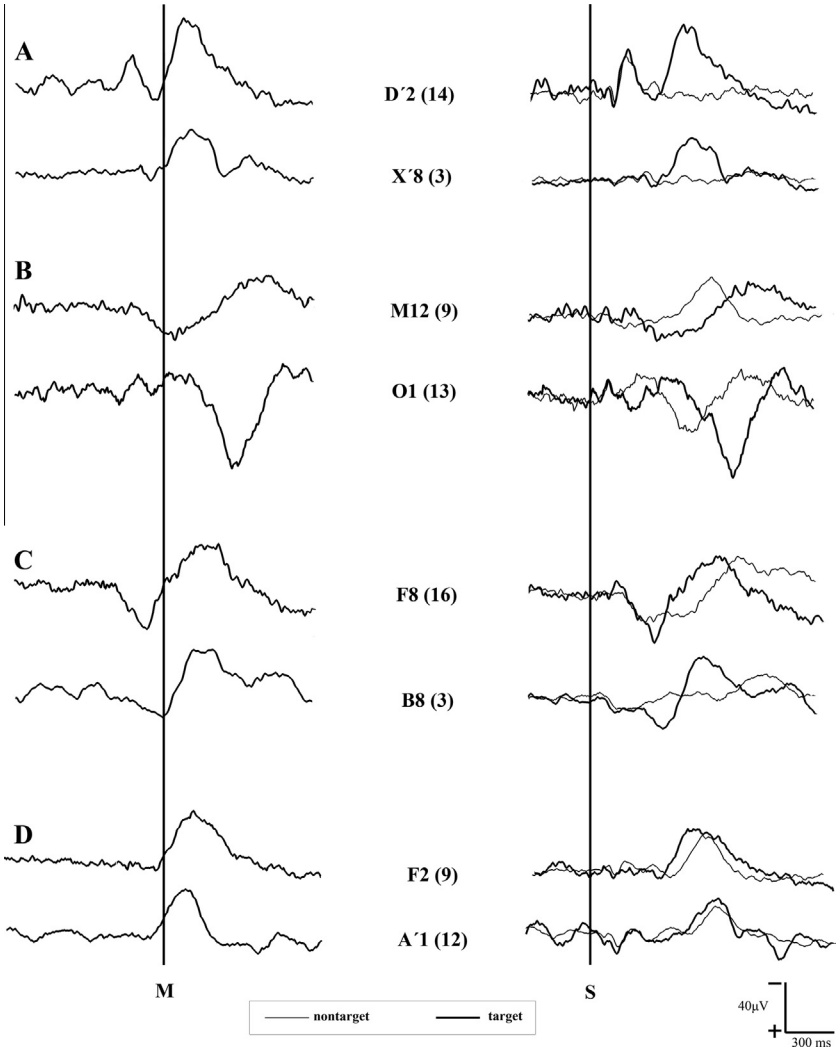

Fig. 3. Post-performance ERP: (A) prominent in target but absent in nontarget trials; (B) with shorter latency in nontarget than in target trials; (C) with longer latency in nontarget than in target trials; (D) with almost identical latency in target and nontarget trials. On the left side, response-triggered (M = movement) averaged ERPs for correct target trials; on the right side, stimulus-triggered (S = stimulus) averaged ERPs for correct target (thick lines) and correct nontarget (thin lines) trials in the same contact. Note that post-performance target ERP is either preceded by clear-cut earlier components or not, e.g. in D′2(14) or X′8(3) in section A, respectively. Contact (subject), anatomical structure: D′2(14), left superior temporal gyrus; X′8(3), left putamen; M12(9), right primary motor cortex; O1(13), right orbitofrontal cortex; F8(16), right dorsolateral prefrontal cortex; B8(3), right middle temporal gyrus; F2(9), right anterior cingulate cortex; A′1(12), left superior temporal gyrus.

averages of erroneous responses. Tables 6 and 7 show distribution of these ERPs across brain regions. Latencies of stimulus-triggered averaged ERPs detected after correct and incorrect performances are displayed in Table 8. In patient No. 9 the latency after incorrect rejection or false alarm was either longer, with a delay of up to 469 ms (Fig. 4A), or almost identical, with a difference no greater than 20 ms (Fig. 4B), compared to the latency observed after correct hit or correct rejection, respectively. In patient No. 12 the latencies after correct and incorrect performances differed less than by 20 ms (Fig. 4B).

In an attempt to associate the post-movement ERP observed in the target variant of a visual oddball task with underlying mental processes the following competent characteristics of post-performance ERPs were identified: (1) a waveform prominent to target but absent to nontarget stimuli; (2) a waveform prominent both to target and nontarget stimuli; (3) a longer latency of ERP when motor response was erroneously omitted in reaction to target stimulus; (4) a longer latency of ERP when motor response was erroneously performed in reaction to nontarget stimulus.

4. Discussion

This study examined the electrophysiological indicators of post-performance brain activity. By using depth EEG recording during a visual oddball task we have demonstrated that: (1) post-movement ERPs in correct target trials were observed in multiple cortical structures; (2) ERPs recorded after correct performance were either specific for the target task variant or were observed in both variants of the visual oddball task; (3) in several brain sites both after correct and incorrect performances clear-cut ERP components were observed; (4) in brain sites sensitive to error commission the latency of the post-performance ERP was longer in incorrect compared to correct performance.

4.1. Generators of post-performance ERPs in correctly performed target trials are distributed in multiple brain regions

Two recent source localization studies on performance monitoring focused on identifying ICA components reflecting the post-performance ERPs for correct and incorrect responses (Hoffmann

Table 6
Distribution of ERPs across brain regions in correct reactions to target and erroneous reactions to nontarget stimuli.

Anatomical structure	Post-movement ERPs[a]	Sites examined/ subjects	False alarm/ subjects[b]
Anterior cingulate cortex	3	4/2	0/0
Orbitofrontal cortex	0	2/1	–
Dorsolateral prefrontal cortex	3	3/1	3/1
Supplementary motor area	0	2/1	–
Premotor cortex	1	1/1	0/0
Primary motor cortex	2	3/1	2/1
Amygdala	1	1/1	0/0
Hippocampus	1	2/1	0/0
Parahippocampal gyrus	3	3/1	0/0
Superior temporal gyrus	7	9/2	1/1
Middle temporal gyrus	2	3/2	1/1
Inferior temporal gyrus	0	4/1	–
Lingual gyrus	1	2/1	0/0
Somatosensory cortex	0	1/1	–
Frontal lobe	9	15/2	5/1
Temporal lobe	15	24/2	2/1
Parietal lobe	0	1/1	–
Total	24	40/3	7/2

[a] Number of sites with positive observations of post-movement ERP in response-triggered averages of correct reactions to target stimulus.
[b] Number of sites/subjects with positive observation of ERP elicited both after correct reactions to target and erroneous reactions to nontarget stimuli.

Table 7
Distribution of ERPs across brain regions in correct and erroneous reactions to target stimuli.

Anatomical structure	Post-movement ERPs[a]	Sites examined/ subjects	Incorrect rejection/ subjects[b]
Anterior cingulate cortex	2	3/1	2/1
Dorsolateral prefrontal cortex	3	3/1	3/1
Supplementary motor area	0	2/1	–
Primary motor cortex	2	3/1	2/1
Hippocampus	1	2/1	0/0
Superior temporal gyrus	6	8/1	2/1
Middle temporal gyrus	2	2/1	1/1
Lingual gyrus	1	2/1	0/0
Somatosensory cortex	0	1/1	–
Frontal lobe	7	11/1	7/1
Temporal lobe	10	14/1	3/1
Parietal lobe	0	1/1	–
Total	17	26/2	10/2

[a] Number of sites with positive observations of post-movement ERP in response-triggered averages of correct reactions to target stimulus.
[b] Number of sites/subjects with positive observation of ERP elicited both after correct and erroneous reactions to target stimuli.

Table 8
Latency (ms) of post-performance ERP measured from stimulus onset in two patients.

Anatomical structure/contact	Target			Nontarget		
	Correct hit	Incorrect rejection	Delay	Correct rejection	False alarm	Delay
Patient No 9 (RTc = 474 ms, RTf = 497 ms)						
aMCC/*G1*	617	1086	469	703	–	–
aMCC/F2	601	1062	461	693	–	–
DLPFC/G14	804	1062	258	742	875	133
DLPFC/F14	688	1070	382	742	968	226
DLPFC/F9	601	1055	454	727	723	−4
PMC/M12	1046	1125	79	734	1117	383
PMC/M′11	950	966	16	727	1009	282
Patient No 12 (RTc = 594 ms, RTf = 732 ms)						
STG/T4	1018	999	−19	–	–	–
STG/T′5	836	827	−9	774	789	15
MTG/D′12	824	827	3	768	762	−6

Correct hit = motor response to target stimulus; Incorrect rejection = movement omission after target stimulus; Correct rejection = refraining from movement in nontarget task variant; False alarm = erroneous motor response in nontarget task variant; Delay = the ERP latency difference between incorrect and correct performances; RTc = mean reaction time for correct hit condition; RTf = mean reaction time for false alarm condition; aMCC = anterior midcingulate cortex; DLPFC = dorsolateral prefrontal cortex; PMC = primary motor cortex; STG = superior temporal gyrus; MTG = middle temporal gyrus; ′ = left side; regions generating post-movement ERP are written in *italics* format.

and Falkenstein, 2010; Roger et al., 2010). Both studies, however, aimed to identify ICA components related to the ERN/Ne, and the component selection was based on error trials (Roger et al., 2010) or on differences between error and correct trials (Hoffmann and Falkenstein, 2010). To the best of our knowledge, no source localization or even intracerebral study primarily aimed at identifying sources of post-performance ERPs for correct responses. Similarly, several EEG/fMRI studies identified correlations between the hemodynamic response in the rostral cingulate zone and scalp recorded ERN (for review see Ullsperger et al., 2014) but none of them was focused on correct response-related activity. From this point of view, the current study provides unique intracerebral data suggesting the existence of multiple sources of ERPs elicited after correct performance. We observed clear-cut correct response-related activation in many different brain regions (Table 3). Since converging observations seem to indicate that the field created by neurons more than one centimeter away from the recording site account for only a negligible portion of the intracranially recorded EEG signal (Lachaux et al., 2003), these ERPs might be considered to emerge from the brain structure in which they were observed. Most convincingly, our results suggest engagement of mesiotemporal structures, anterior midcingulate, prefrontal and lateral temporal cortices, in which steep voltage gradient across neighbouring contacts was observed as an unequivocal evidence of a potential generation. Thus, besides ACC whose involvement was previously documented by source localization study (Roger et al., 2010) in correct response-related negativity generation; our results suggest recruitment of several other brain structures following correct motor responses. Our results support the view, that the post-movement brain processes in correct responses of visual oddball task are realized through activation of large-scale neuronal networks. In the present study most brain structures that form these networks were active in discrete sites while in other sites no evoked electrophysiological activity was recorded. No difference in occurrence frequency was found among involved brain structures except for basal ganglia where post-movement ERP was found in all examined sites. Due to the fact that recording sites were selected according to diagnostic concerns, and most regions were not explored, the possibility to use this result for quantitative comparison of activation of different brain structures is limited. Thus, it still remains in question as to whether some structures generate the post-movement ERP in a greater portion of its volume than other structures.

4.2. Parallel systems of correct performance processing

In all well examined structures except for basal ganglia, i.e. in mesiotemporal structures, anterior midcingulate, prefrontal and lateral temporal cortices, we observed task-variant nonspecific post-movement ERP type. This suggests that the studied post-movement ERP might reflect some processes that are supposed to take place in both variants of the task, such as stimulus evaluation

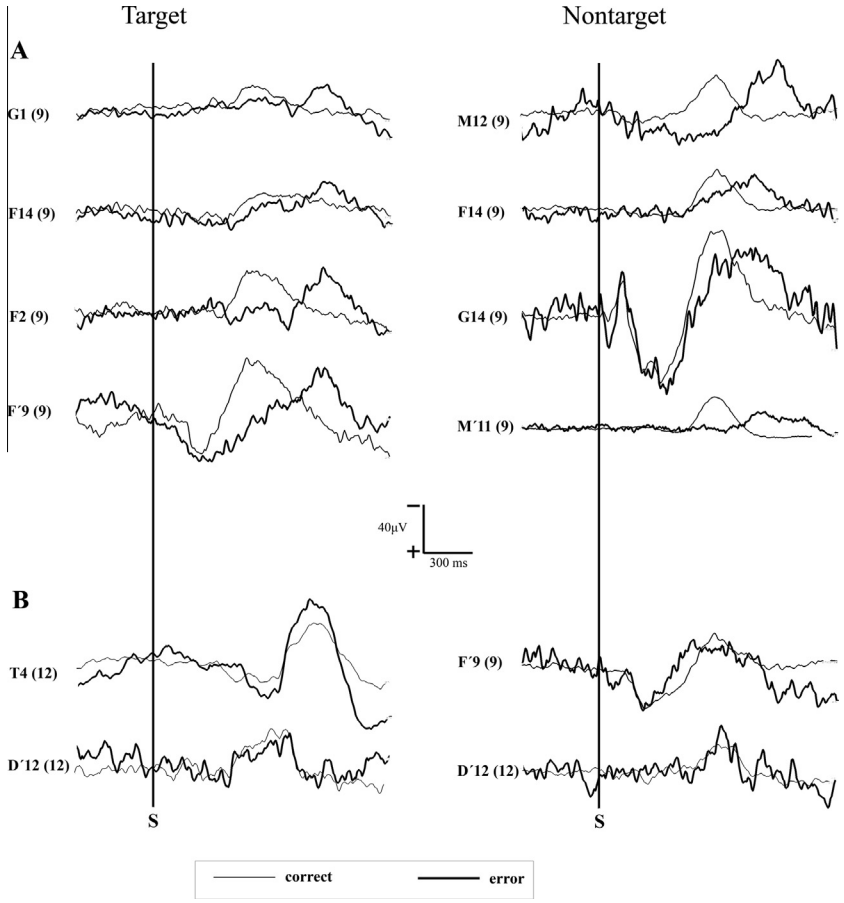

Fig. 4. Stimulus-triggered (S = stimulus) averaged ERPs for correct (thin line) and incorrect (thick line) trials. (A) Longer latency of post-performance ERP when motor response was erroneously omitted in reaction to target stimulus (left section) or erroneously performed in reaction to nontarget stimulus (right section). (B) Almost identical latency of post-performance ERP after correct and incorrect performance of target (left section) or nontarget (right section) task variant. Contact (subject), anatomical structure: G1(9), right anterior cingulate cortex; F14(9), right dorsolateral prefrontal cortex; F2(9), right anterior cingulate cortex; F′9(9), left dorsolateral prefrontal cortex; T4(12), right superior temporal gyrus; D′12(12), left middle temporal gyrus; M12(9), right primary motor cortex; G14(9), right dorsolateral prefrontal cortex; M′11(9), left primary motor cortex.

processing, attentional processes or performance monitoring. This interpretation is in line for instance with our previous study where we provided evidence that hippocampal ERPs, either preceding or following correct motor responses, could represent some stimulus evaluation processing (Roman et al., 2013) or with widely accepted role of frontal lobe for monitoring the effect of actions on the external environment (Stuss and Benson, 1986; Stuss, 2011). Such a monitoring process could just follow each correctly performed task, irrespective of whether the required behavior was movement execution and mental counting or movement inhibition and ignoring of the stimuli.

The finding of target specific ERPs in all well examined brain structures of frontal and temporal lobes may indicate their involvement in counting related brain processes. Previous observations of counting related brain activity in the lateral temporal neocortex and ACC (Brázdil et al., 2003) support this view. Since higher demands on memory functions in the target task variant with mental counting are expected, participation of these structures in memory processes might be suggested. Nevertheless, this type of ERP could as well only reflect more attention or higher cognitive load related to arithmetic without any specific relation to maintenance of episodic information in short term memory. Some processes underlying target specific activity may also be related to previous movement execution. In case of basal ganglia, in which we have found only target specific ERPs, this interpretation would perfectly fit with their prominent role in motor functions. According to another interpretation, this ERP could simply reflect passive re-entrance of somatosensory signals or a post-performance resetting of brain circuits without any elaboration or use of the performance features.

Both the task variant nonspecific and target specific ERP types were consistently generated in the same structures (see Table 5). The mere existence of these two types of post-movement ERP favors the view that after correct movement execution parallel processing in at least two distinct systems takes place sharing at least partially the same anatomical substrate. Parallel activation of two different systems, i.e. performance-monitoring and movement-monitoring, was also identified to be responsible for Ne/ERN generation (Yordanova et al., 2004).

4.3. Common nodes of correct and incorrect behavior processing

In the present study we demonstrated that there are brain sites in which both correct and incorrect performances may elicit a prominent potential in the post-performance period. We found sites in which ERPs were recorded both after correct motor response and its erroneous omission in the target variant of the task. In some of these sites we even recorded ERPs both after correct refraining from movement and erroneous movement execution in the nontarget task variant. Our findings suggest that

cortical networks engaged in the generation of correct and incorrect performance-related potentials could have some common nodes. The fact that in several sites post-performance ERPs were observed both in correct hit and false alarm conditions seems to further support findings of recent studies using independent component analysis, which strongly suggest that Ne/ERN and Nc/CRN stem from largely overlapping generators (Roger et al., 2010; Wessel et al., 2012). The demonstration of post-performance ERPs in false alarms stands in line with a large body of literature on error processing and supports the existence of an already known and well-described Ne/ERN and Pe complex (Wessel, 2012). On the other hand, our finding of post-performance ERPs after erroneous movement omission is rather unique. Our finding suggests that some kind of error processing might take place also after incorrect movement inhibition. Actually, it should not be surprising that also after this type of error some monitoring process might take place that compares the predicted behavior with the actual one.

Another interesting finding of the present study is that there are sites in anterior midcingulate, dorsolateral prefrontal and primary motor cortices, where the error commission has an influence on the latency of post-performance ERP with higher values for incorrect performance (Fig. 4A). Erroneous refraining from movement in the target variant of the task revealed a longer latency of the ERP than the correct hit condition. Similarly, erroneously performed movement in the nontarget variant of the task revealed a longer latency than correct inhibition of motor response. If the observed latency differences indicated that the preceding processes are prolonged or higher in number in case of error commission, then both correct and incorrect post-performance ERP components might represent some final evaluation processes related to finished action. Our findings of latency differences are analogous with those reported in a recent intracerebral study (Pourtois et al., 2010). In a go/nogo task the authors demonstrated local field potentials in the amygdala with evident temporal unfolding. A monophasic ERP around motor execution for correct hits was delayed by ~300 ms for false alarms, even though the actual reaction times were almost identical in these two conditions. Our findings not only confirmed typical involvement of ACC in action monitoring and cognitive control (Ridderinkhof et al., 2004) but also suggested recruitment of the dorsolateral prefrontal cortex and the primary motor cortex in error detection mechanisms.

A striking result of our current study was activation of the primary motor cortex in nonmotor task conditions, both after erroneous and correct movement inhibition (Table 8 and Fig. 4). This result extends the recent hypothesis of rostral premotor-subcortical networks serving as a gateway between the cognitive and motor networks (Hanakawa, 2011) suggesting that the primary motor cortex might be also involved in processes not directly associated with motor action.

5. Conclusions

Although the present study was limited by non-systematic examination of the brain due to strictly diagnostic purposes of electrode implantation, the results clearly suggest that besides the anterior cingulate cortex, also the mesiotemporal structures, and lateral temporal and prefrontal cortices are activated following correct responses. The spatiotemporal characteristics, task-variant specificity, and sensitivity to errors demonstrated that the observed post-movement activity might code various pieces of information needed for cognitive control, movement- and performance monitoring, and evaluation processes. It appears, however, that a one-to-one matching of post-movement ERP type and type of information is beyond the limitations of our study.

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The level of frontal-temporal beta-2 band EEG synchronization distinguishes anterior cingulate cortex from other frontal regions

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ABSTRACT

Recent findings indicate that complex cognitive functions are organized at a global level in the brain and rely on large-scale information processing requiring functional integration of multiple disparate neural assemblies. The critical question of the integration of distributed brain activities is whether the essential integrative role can be attributed to a specific structure in the brain or whether this ability is inherent to the cognitive network as a whole. The results of the present study show that mean values of the running correlation function in frontal-temporal EEG pairs with one electrode in the anterior cingulate cortex (ACC) are significantly higher than the same values in other frontal-temporal pairs. These findings indicate a particular role of the ACC in large-scale communication, which could reflect its unique integrative functions in cognitive processing.

1. Introduction

Today it is widely recognized that complex cognitive functions are organized at a global level in the brain, and that they arise from more primitive functions organized in localized brain regions. The global mode of functioning relies on large-scale information processing that requires mechanisms of functional integration of multiple disparate neural assemblies (Bressler & Kelso, 2001; Fries, Reynolds, Rorie, & Desimone, 2001; Jensen, Kaiser, & Lachaux, 2007; Varela, Lachaux, Rodriguez, & Martinerie, 2001). The critical question of the integration of distributed brain activities is whether the essential integrative role can be attributed to a specific structure in the brain or whether this ability is inherent to the cognitive network as a whole. Recent conceptions concerning the integrative role of the anterior cingulate cortex (ACC) seem to support the first possibility, which emphasizes structural localization of integrative functions (Paus, 2001; Posner, Rothbart, Sheese, & Tang, 2007; van Veen & Carter, 2002). In principle, these concepts are supported by findings of anatomical connectivity of the ACC and its structural particularities, especially the presence of spindle-shaped neurons with their widespread connections and their putative role in long-range activity coordination, and by data obtained by neuroimaging methods during the performance of cognitive tasks (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001; Paus, 2001; van Veen & Carter, 2002). Numerous experimental findings demonstrated the involvement of this structure in functions central to intelligent behavior, such as problem-solving, error recognition, conflict detection and resolution, and adaptive responses to changing conditions (Allman et al., 2001; Posner et al., 2007). This experimental evidence indicates that the role of the ACC in behavioral control includes three main issues, i.e. its involvement in motor control, its proposed role in cognition, and its relationship to the motivation states of the organism. On the basis of synthesis of available data, Paus (2001) proposed a hypothesis that the functional

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overlap of these three domains distinguishes the ACC from other frontocortical regions and that this overlap provides the ACC with the potential to translate intentions into actions. A similar conceptual approach was developed by Rueda and Posner (Posner et al., 2007; Rueda, Posner, & Rothbart, 2004), who based their proposal of the ACC role on the results of studies designed to examine the mechanisms of self-regulation. They proposed that the major contribution of the ACC to brain functions relies on its ability to regulate information influx from the environment in order to avoid conflicting responses in behavior (Rueda et al., 2004).

Following the idea about the particular role of ACC in integrating distributed brain activities, the aim of the present study was to test directly a hypothesis that functional interactions of the ACC with other remote brain regions distinguished this structure from other frontocortical regions. With this aim we investigated the level of EEG synchrony in the beta-2 frequency band between frontal and temporal depth electrode recordings in three different states occurring during a visual oddball experiment: (i) throughout the whole experiment, i.e. regardless of the fact that several distinct mental operations subserved the experimental task; (ii) 1 s before the stimulus, i.e. during the period of heightened expectation of the stimulus presentation; (iii) 1 s after the stimulus, i.e. during the period of stimulus processing. The choice of the beta-2 frequency band was based on demonstration of frequent occurrence of coherent oscillations in this band (Kukleta, Brazdil, Roman, Bob, & Rektor, 2009). In data analysis we compared mean values of the running correlation function calculated in 41 frontal-temporal pairs of EEG records, which had their frontal electrodes in the gyrus cinguli, with values obtained in 139 frontal-temporal pairs with their frontal electrodes in other parts of the frontal lobe.

2. Methods

2.1. Subjects

Eight patients (5 males, 3 females; aged 25–45 years; mean 32.4 years; all with medically intractable epilepsies; all right-handed) participated in the study. Standard MicroDeep multilead depth electrodes (DIXI) with a diameter of 0.8 mm, length of each recording contact 2 mm, and intercontact intervals of 1.5 mm were used for invasive EEG monitoring. The orthogonal electrodes were implanted in the frontal, temporal, and/or parietal lobes using the methodology by Talairach et al. (1967). In 2 patients, additional diagonal electrodes were inserted stereotactically into the amygdalohippocampal complex (via frontal approach, passing through the basal ganglia in 1 patient, via occipital approach in 1 patient). The electrodes were placed bilaterally in 6 patients and unilaterally in 2 patients. The recording contacts at the electrode (5–15) were always numbered from the medial to lateral sites. Their positions were indicated in relation to the axes defined by the Talairach system (1967) using the '*x*, *y*, *z*' format where '*x*' is lateral, millimeters to midline, positive right hemisphere, '*y*' is anteroposterior, millimeters to the AC (anterior commissure) line, positive anterior, and '*z*' is vertical, millimeters to the AC/PC (posterior commissure) line, positive up. The exact positions of the electrodes in the brain were verified using post-placement magnetic resonance imaging (MRI) with electrodes in situ. In all cases, both the number and positioning of the exploring electrodes were determined by a diagnostic procedure the aim of which was to localize the seizure origin prior to a surgical treatment. The recordings from lesional structures and epileptogenic zones were not included into the experimental analysis. No patient from the group examined had bilateral hippocampal sclerosis or bilateral temporal lobe epilepsy. All the patients had normal or corrected-to-normal vision and their performance in the experimental task was very good (median of errors 1.3%, minimum 0%, maximum 4.8%). The analysis of error responses to both non-target and target stimuli was taken as a demonstration that they really processed the stimuli according to the experimental instructions. Informed consent was obtained from each patient prior to the experiment, and the study received an approval from the Ethical Committee of Masaryk University.

2.2. Procedure

The patients were seated comfortably in a moderately lighted room with a monitor screen positioned approximately 100 cm in front of their eyes. During the examination they were asked to focus the gaze continuously on the point in the center of the monitor screen and to respond, as quickly as possible, to a target stimulus (a yellow letter X on white background) by pressing a microswitch button in the dominant hand and counting the number of these stimuli in their heads, and to ignore frequent stimuli (a yellow letter O on white background). Both stimuli were displayed on the black screen, subtended at a visual angle of 3°. Their duration was 200 ms. The interstimulus intervals varied randomly between 2 and 5 s, the ratio of target to frequent, non-target stimuli was 1:5. The mean duration of the whole experiment was 17.4 min (minimum 12.8 min, maximum 20.7 min).

2.3. EEG recording

The EEG signal was recorded simultaneously from various intra-cerebral structures using 64-channel Brain Quick EEG system (Micromed). The recordings were monopolar with respect to a reference electrode placed on the right processus mastoideus in all the cases. The EEGs were amplified with a bandwidth of 0.1–40 Hz at a sampling rate of 128 Hz. ScopeWin software was used for the data analysis, which included up to 44 channels recorded simultaneously.

2.4. Data analysis

In the data analysis EEG records from 180 frontal-temporal pairs were used. Frontal records were obtained from 27 sites; temporal records from 56 sites (see Table 1A). The pairs were homolateral in 114 cases (52 pairs in the left, 62 pairs in the right hemisphere), and heterolateral in the remaining 66 cases. According to the location of the frontal recording site these pairs were divided into four groups (ACC – anterior cingulate cortex, OFC – orbital frontal cortex, DLFC – dorsolateral frontal cortex, and MFC – mesial frontal cortex). More precise information about the location of the frontal recording sites is given in Fig. 1. As demonstrated in Table 1B, records from anterior cingulate sites were paired with approximately the same set of temporal sites as records from other frontal locations. All the investigated recording sites exhibited an evoked response to target and non-target stimuli. One record from an electrode or two records derived from remote contacts of an electrode were taken for the analysis only. As a rule, the largest response from similar ones was selected. The offline processing of each record started with its frequency decomposition and reduction to the beta-2 frequency band (25–35 Hz) via a digital band pass filter. The procedure comprised a spectrum computation using the Fast Fourier Transform, zeroing all the spectral components outside the selected frequency interval, and an inverse complex Fast Fourier Transform computation. Then, in each frontal-temporal pair of such filtered records, the correlation coefficients were calculated using the technique of running correlation. The expert's recommendation for the length of the sliding window in the computation of successive correlation coefficients (94 ms) took into account the sampling frequency and the frequency band used.

Three correlation indicators were derived from each of the resulting correlation curves: (1) mean *r*-value of 30 s segment of the correlation curve (18 values representing the whole experiment were obtained from each curve); (2) mean prestimulus *r*-value calculated from averaged 1 s segments which preceded the stimulus onset; (3) mean poststimulus *r*-value calculated from averaged 1 s segments which followed the stimulus onset. The second and third indicators were derived from averaged data. In this case, 5 s segments of the correlation curves were averaged using the stimulus onset as the trigger (−2.5 and +2.5 from stimulus onset). Segments linked to non-target stimuli were used only. One advantage of this selection was the fact that the data obtained were not contaminated by efferent actions linked with movement; the other advantage was the greater number of available responses, which allowed calculating the average curves with a more favorable signal/noise ratio. The mean number of averaged stimuli was 136 (minimum 90, maximum 165). Only artifact-free segments were included into the processing of both raw and averaged data (the selection was based on visual inspection of the segments by an experienced person).

3. Results

The sequence of correlation coefficients obtained by the running correlation technique from the 180 frontal-temporal pairs of filtered EEG records represented the source of data for analysis in this study. A typical time course of these correlation curves is shown in Fig. 2, section A. The curves consisted of irregular oscillations between the maximal and the minimal *r*-values; maximal peaks frequently attained values higher than +0.9. For the demonstration of the main characteristics of these curves we chose the mean correlation coefficient calculated in 18 consecutive 30 s segments of each curve (the "30 s *r*-values"). In a total of 3240 measurements obtained from 180 curves, their mean was 0.18 ± 0.13 (median 0.14, minimum −0.10, maximum +0.71) and their distribution was quasi-normal (skewness 0.6, kurtosis 0.4). The values of this indicator obtained from four different brain areas of four patients (64 individual measurements) are presented in Fig. 3, left section. These data illustrate the most conspicuous feature of the indicator, i.e. its high and relatively constant standard deviations. In

Table 1
Number and location of recording sites from which 180 frontal-temporal pairs were created (A) and the percentage of temporal recording sites paired with sites in the anterior cingulate gyrus and sites in other frontal locations (B).

A

Structure	Number of sites (left/right hemisphere)	Number of subjects
ACC (anterior cingulate gyrus)	3/4	6
OC (gyri orbitales)	4/4	7
DLFC (gyrus frontalis superior, medius, inferior, gyrus praecentralis)	3/3	5
MFC (gyrus frontalis medialis, gyrus rectus)	2/4	4
LTC (gyrus temporalis superior, medialis and inferior)	17/10	8
BTC (gyrus fusiformis and parahippocampalis)	5/4	5
HIPP (hippocampus)	7/4	6
AMY (amygdala)	5/4	7

B

Frontal sites	Number of pairs	LTC (%)	BTC (%)	HIPP (%)	AMY (%)
ACC	41	49	14	20	17
OC	60	50	15	18	17
DLFC	41	46	15	20	19
MFC	38	50	8	21	21

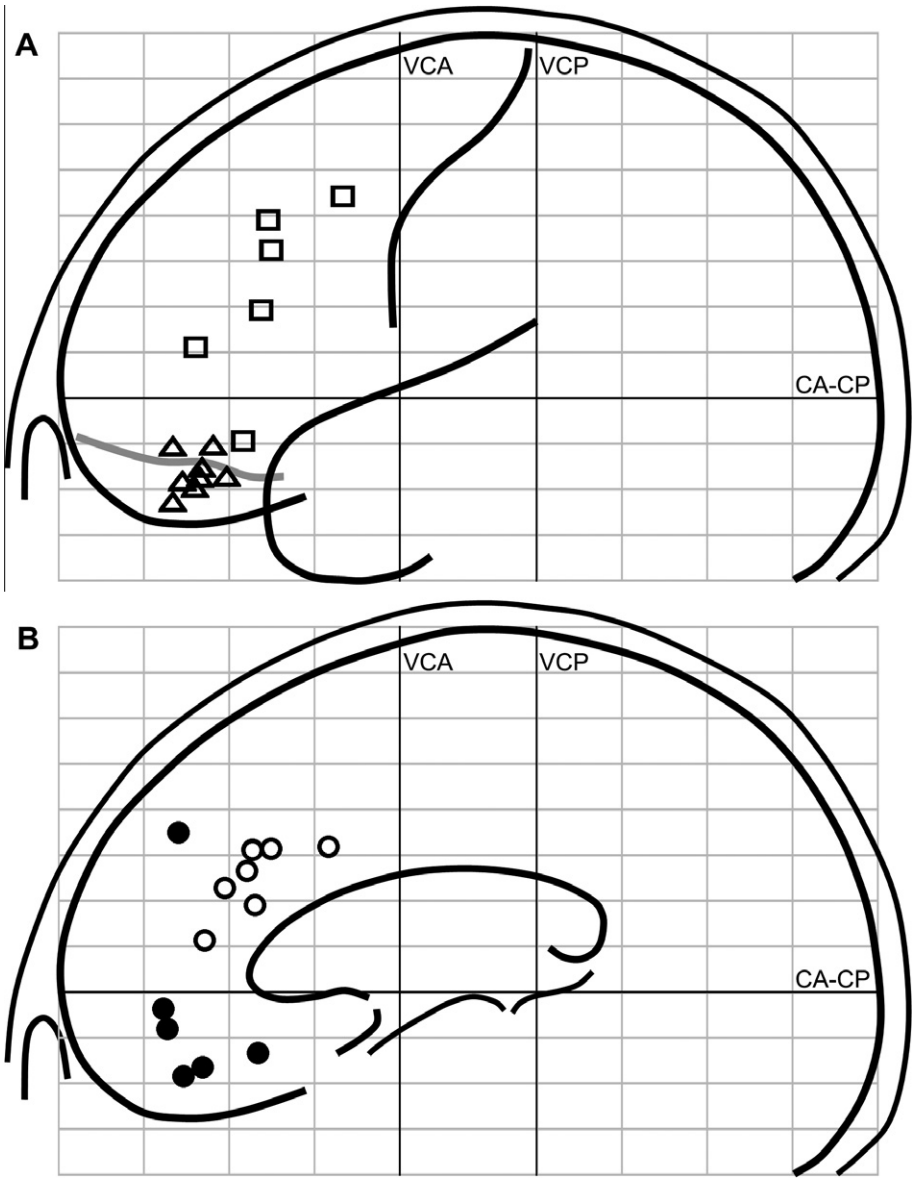

Fig. 1. Projection of 27 depth frontal orthogonal electrodes on lateral (A) or mesial (B) hemispheric surfaces. All electrodes, either right or left, were positioned in the same scheme (left convexity, right mesial surface), according to the standard Talairach's stereotaxic coordinate system. Allocation of single recording sites for one of the four groups is represented by identical geometric symbols.

a total of 3240 analyzed measurements their mean value was 0.52 ± 0.03. We thought that this steadily high variability of the indicator reflected the oscillatory nature of the mechanisms underlying the correlation curves.

Fig. 4, upper section, presents the "30 s *r*-values" of groups created according to the location of frontal recording sites. As is evident, the level of frontotemporal activity correlation was highest in pairs with frontal recording sites in the anterior cingulate cortex.

Statistical evaluation (Main effects ANOVA) showed a significant main effect of the recording site position ($F(3, 3229) = 66.3$; $p < .001$); the *p*-values of the post hoc Scheffé test of differences between the anterior cingulate group (ACC) on the one hand and OFC, DLFC, and MFC groups on the other hand were lower than .001 in all three comparisons. The statistical procedure used took into account a possible influence of the position of the 30 s segment in the time course of the experiment, and individual differences of the mechanisms underlying the correlation results. A more detailed investigation of these two factors was beyond the scope of the present study.

With respect to the final interpretation of the results, the finding of a high correlation between the "30 s *r*-values" and the number of peaks on the correlation curves, which exceeded the level of +0.9, was particularly important (Spearman R 0.84;

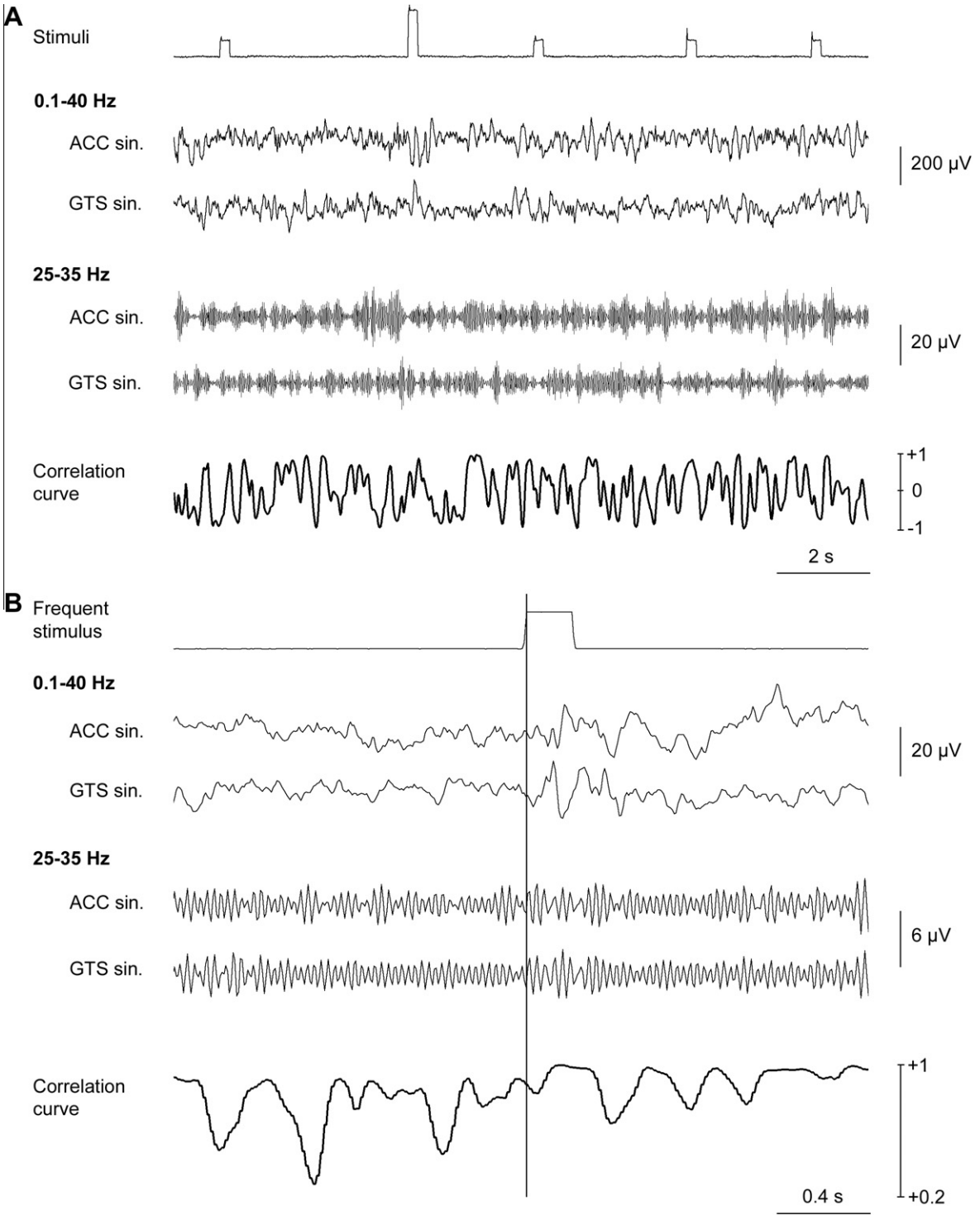

Fig. 2. An illustration of the correlation curves calculated from non-averaged, raw data (section A) and from averaged data (section B). In section A the curves represent, taken from top to bottom, the position of non-target (smaller marks) and target (higher mark) stimuli, the whole-band EEG records from the left anterior cingulate cortex (ACC), and from the left superior temporal gyrus (GTS) of patient 1, filtered derivatives of these two records in the frequency band of 25–35 Hz, and the resulting correlation curve. In section B the curves represent the position of non-target stimuli, the averaged pre- and poststimulus whole-band records from the left anterior cingulate cortex (ACC) and the left superior temporal gyrus (GTS) of patient 1, the filtered derivatives of these two records in the frequency band of 25–35 Hz, and the resulting correlation curve. The vertical line passing through all curves marks the stimulus onset.

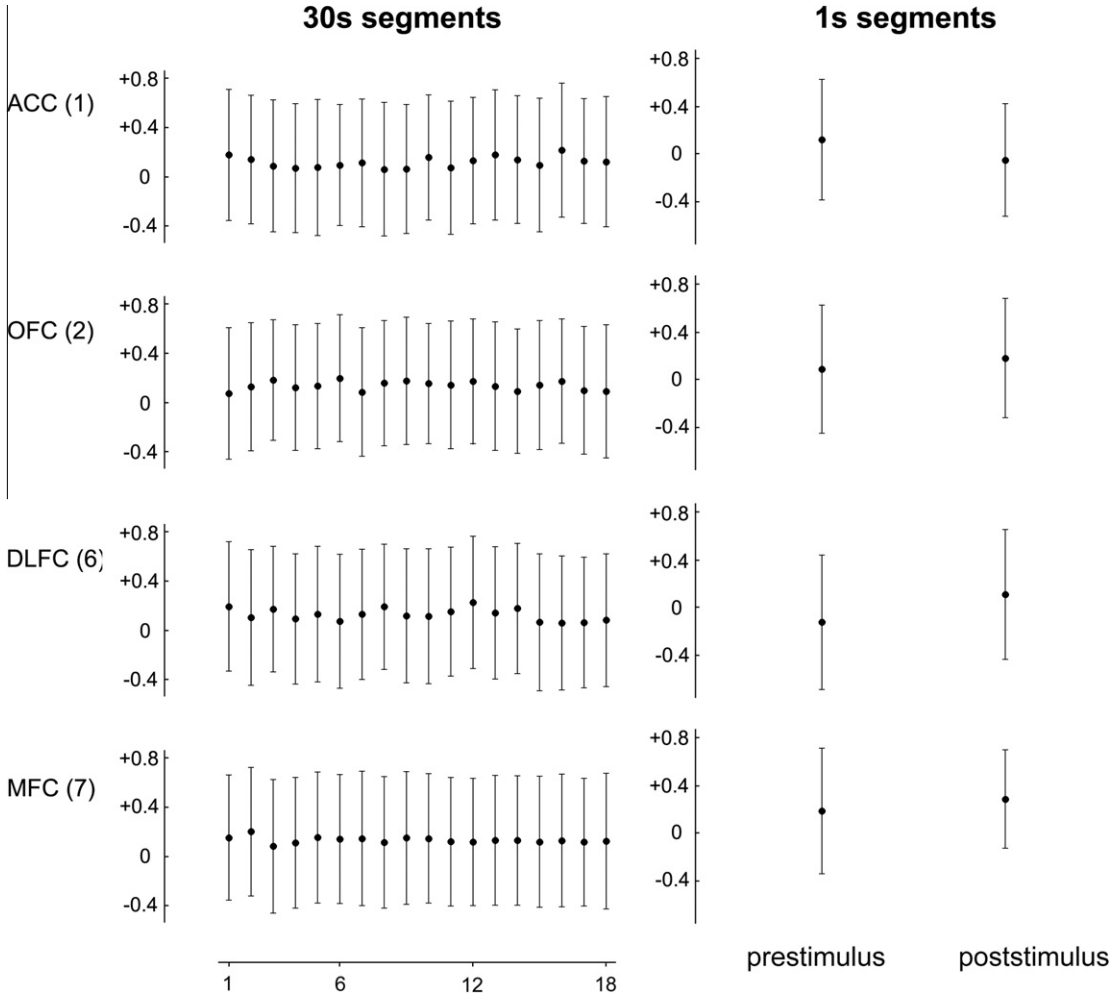

Fig. 3. An illustration of mean values of the correlation coefficient and their standard deviation calculated from four different brain areas of four patients in eighteen successive 30 s segments of raw correlation curves (left section) and in 1 s prestimulus and poststimulus epochs of averaged correlation curves (right section). The frontal recording site was in the anterior cingulate cortex of patient 1 (ACC), in the orbital frontal cortex of patient 2 (OFC), in the dorsolateral frontal cortex of patient 3 (DLFC), and in the mesial frontal cortex of patient 4 (MFC).

$p < .001$). This finding allowed considering the "30 s *r*-values" as a measure of interregional activity synchronization. The number of such peaks in one 30 s segment varied from 2 to 73 (median 14) and the distribution of its values was not normal.

Mean *r*-values in the 1 s segments, which preceded and followed the non-target stimulus onset, represented another two correlation indicators analyzed in the study. Both indicators varied largely in a total of 180 averaged correlation curves. The mean prestimulus *r*-value was 0.19 ± 0.24 (median 0.19, minimum −0.37, maximum +0.78), the mean poststimulus *r*-value was 0.25 ± 0.24 (median 0.25, minimum −0.35, maximum +0.81). The middle and bottom sections of Fig. 4 present mean prestimulus and poststimulus *r*-values of groups created according to the location of frontal recording sites. Even these indicators showed that the pairs with frontal recording sites in the cingulate cortex had higher mean *r*-values than pairs from other frontal locations. ANOVA showed a significant main effect for the recording site position in both cases ($F(3169) = 13.2$ in the first and 8.0 in the second case; $p < .001$ in both cases). The *p*-values of the post hoc Scheffé test evaluating the significance of differences between the anterior cingulate group (ACC) on the one hand and OFC, DLFC, and MFC groups on the other hand were lower than .001, .001 and .012, respectively, in comparisons of prestimulus values, and .001, .002 and equal to .120, respectively, in comparisons of poststimulus values. In other words, the pairs with their frontal recording sites in the cingulate cortex had higher mean *r*-values than had pairs from other frontal locations in five of six comparisons.

A comparison of eleven ACC pairs located in the right hemisphere and of eleven ACC pairs in the left hemisphere revealed a significant main effect of hemisphere location in the case of the "30 s *r*-values" (ANOVA, $F(1372) = 5.9$, $p = .016$; means 0.26 ± 0.10 in the right and 0.13 ± 0.08 in the left hemisphere). Prestimulus and poststimulus ACC *r*-values in the right and the left hemisphere did not differ significantly (ANOVA, $F(1, 15) = 0.7$ and 2.7, respectively, $p > .05$ in both cases). Due to the limited number pairs and inconsistency of the result, the difference between right and left locations of the recording site pairs was not analyzed in greater detail.

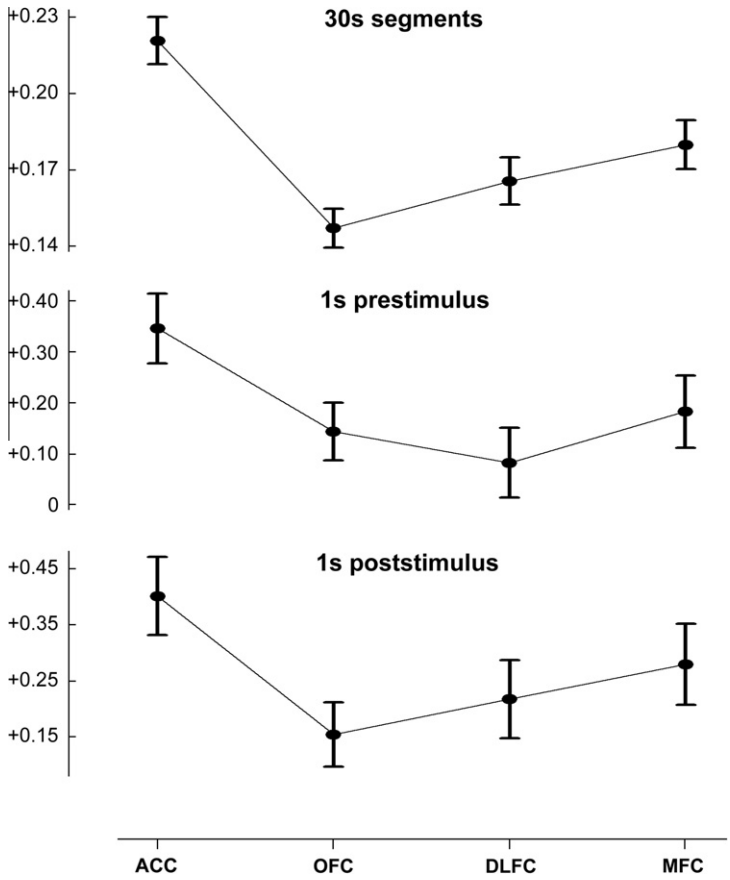

Fig. 4. Mean *r*-values in groups of correlated frontotemporal pairs created according to the location of their frontal recording site (ACC – anterior cingulate cortex; OFC – orbital frontal cortex; DLFC – dorsolateral frontal cortex; MFC – mesial frontal cortex). The upper section presents the means from the 30 s segments of correlation curves (N 738, 1080, 738, and 684, respectively), the middle and bottom sections present the means from the 1 s prestimulus and poststimulus epochs (N 41, 60, 41, and 38, respectively, in both indicators). Vertical bars denote 0.95 confidence intervals.

4. Discussion

The results of the present study support recent findings suggesting a specific integrative role of the ACC (Paus, 2001; Posner et al., 2007). Particularly, these results show that mean values of the running correlation function in frontal-temporal EEG pairs with one recording contact in the cingulate cortex (ACC pairs) are significantly higher than mean values of running correlation in other frontal-temporal pairs. This regional difference in the phase synchrony was found in three distinct functional states: (i) throughout the whole experiment; (ii) during the period of heightened expectation of the next stimulus; (iii) during the cognitive elaboration of the stimulus. The finding suggests a state-independent stronger communication of the ACC with other components of the cognitive network. A crucial interpretation of this finding is that higher synchrony in the ACC pairs in comparison with other frontal-temporal pairs may represent a particular role of the ACC in large-scale communication, which could reflect its unique integrative functions in cognitive processing. This interpretation could have key consequences for the understanding of the neural correlate of consciousness, which although it is spatially distributed and related to large-scale integration may have its "extraordinary places" with a specific integrative role.

The majority of recent studies on integrative or binding mechanisms have focused on EEG analysis and observed functionally relevant epochs of synchronization mainly in the gamma frequency band in various species and brain structures during attention, perception, motor and memory tasks (Jensen et al., 2007; Lee, Williams, Breakspear, & Gordon, 2003; Singer, 2001). A crucial result of these studies, which presents a direct link between visual perception and gamma synchrony, was reported by Eckhorn, Singer and colleagues in the cat visual cortex (Eckhorn et al., 1988). Following this finding, the functional significance of synchronous gamma activity in selective attention, perceptual processing, and recognition was repeatedly demonstrated in animal and human studies (Fries et al., 2001; Jensen et al., 2007; Meador, Ray, Echauz, Loring, & Vachtsevanos, 2005; Rodriguez, Kallenbach, Singer, & Munk, 2004). The interpretation of all these findings seems to imply a common assumption that transient and precise synchronization of neuronal discharges represents a crucial binding mechanism and is related to the emergence of conscious mental states. The concept of dynamic binding by synchronization of

distributed neuronal activity has been developed mainly in the context of perceptual processing. With respect to visual awareness, the available evidence shows that singular object features such as color, shape, texture, size, brightness, etc. produce activity, at least to some degree, in separate areas of the visual cortex (Bressler & Kelso, 2001; Crick & Koch, 1992; Singer, 2001). Recent neuroscience, however, has not located a distinct place in the brain, in which distributed visual information comes together (Bartels & Zeki, 2006; Crick & Koch, 1992). Additionally, there is evidence that the concept of binding is useful to apply to other domains of brain functioning such as attention, memory formation and recall, motor control, sensorimotor integration, language processing, and logical inference (Singer, 1993, 2001). Following these findings the large majority of authors share the view that consciousness results from a cooperative process in a highly distributed network, and is not attributable to a single brain structure or process. Instead of a single central place (“Cartesian theatre”), there are various events of content fixation that occur in various places at various times in the brain (Dennett, 1991, pp. 365). The evidence for this view of consciousness is presented by a whole series of experimental results in cognitive neuroscience and psychology (van der Velde & de Kamps, 2006; Varela et al., 2001; Zeki, 2003).

According to this view, the neural correlate of consciousness represents a part of the nervous system that transforms neural activity in reportable subjective experiences. A major hypothesis concerning its functioning is that the network can compare and bind activity patterns only if they arrive at the system simultaneously (van der Grind, 2002). Consciousness combines the present multimodal sensory information with relevant elements of the past and creates spatiotemporal memory. Information from each modality is continuously distributed into distinct features and locally processed in different relatively specialized brain regions and globally integrated by interactions among these regions. The resulting subjective experience is then represented by integration through levels of synchronization within neuronal populations and by large-scale integration among multiple brain regions (Bob, 2009; John, 2002; King, 2009; Singer, 2001).

Within this context the results of this study present the first reported evidence that the level of binding between structures could be significantly spatially differentiated and, although the synchronization underlying cognitive processes presents a global phenomenon related to large-scale integration, there are “extraordinary places” within the brain with a specific integrative role.

Acknowledgments

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Directional Functional Coupling of Cerebral Rhythms Between Anterior Cingulate and Dorsolateral Prefrontal Areas During Rare Stimuli: A Directed Transfer Function Analysis of Human Depth EEG Signal

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Abstract: What is the neural substrate of our capability to properly react to changes in the environment? It can be hypothesized that the anterior cingulate cortex (ACC) manages repetitive stimuli in routine conditions and alerts the dorsolateral prefrontal cortex (PFC) when stimulation unexpectedly changes. To provide evidence in favor of this hypothesis, intracerebral stereoelectroencephalographic (SEEG) data were recorded from the anterior cingulate and dorsolateral PFC of eight epileptic patients in a standard visual oddball task during presurgical monitoring. Two types of stimuli (200 ms duration) such as the letters O (frequent stimuli; 80% of probability) and X (rare stimuli) were presented in random order, with an interstimulus interval between 2 and 5 s. Subjects had to mentally count the rare (target) stimuli and to press a button with their dominant hand as quickly and accurately as possible. EEG frequency bands of interest were θ (4–8 Hz), α (8–12 Hz), β (14–30 Hz), and γ (30–45 Hz). The directionality of the information flux within the EEG rhythms was indexed by a directed transfer function (DTF). The results showed that compared with the frequent stimuli, the target stimuli induced a statistically significant increase of DTF values from the anterior cingulate to the dorsolateral PFC at the θ rhythms ($P < 0.01$). These results provide support to the hypothesis that ACC directly or indirectly affects the oscillatory activity of dorsolateral PFC by a selective frequency code under typical oddball conditions. *Hum Brain Mapp 30:138–146, 2009.*

Key words: connectivity; information flow; oddball paradigm; directed transfer function method (DTF); prefrontal cortex; stereoEEG

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INTRODUCTION

One of the most widely utilized experimental paradigms in cognitive neuroscience is the oddball task, which has been used extensively to study target rare stimulus processing in the human brain. It is a simple discrimination task with a randomly alternating presentation of two types of sensory stimuli: one frequent and one rare. The subject performing the oddball task is instructed to ignore frequent stimuli and to perform a certain task (motor response, counting, etc.) when rare (target) stimuli are detected. Target stimuli in this task indubitably trigger in the brain a whole set of cognitive processes that are mostly linked to attentional mechanisms, but concurrently they also reflect other functions collectively called "executive" including short term memory, assessment of stimulus relevance, decision making, and response. It is noteworthy that most of these processes are not triggered by frequent stimuli. Interestingly, a P3 component of event-related potentials, evoked by rare (target) stimuli in the subject's averaged electroencephalogram, can be subdivided into two subcomponents. A frontal P3a is enhanced by nontarget rare and by novel (distractor) stimuli in an extended oddball task (three types of stimuli—target, standard, and distractor). A later parietal P3b is enhanced by the certainty of target detection [Snyder and Hillyard, 1976; Squires et al., 1975]. The P3a seems to reflect the attentional functions, while P3b has been suggested to embody the closure of the cognitive event-encoding cycle or to reflect a whole set of processes that mediate between perceptual analysis and response initiation [Halgren et al., 1998; Verleger et al., 2005].

Among the attention-related brain regions under study, two frontal regions, the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (PFC), appear to be particularly involved in the attentional processes induced by unpredictable changes in the environment and also in a relative selection of proper reactions. These areas are also unequivocal generators of P3a potential, as revealed repeatedly by intracranial event-related potential studies [Baudena et al., 1995; Brázdil et al., 1999; Halgren et al., 1998]. To capture their strict functional relationship, it has been speculated that the ACC and the PFC cooperate to regulate behavior. The ACC would be specifically responsible for monitoring stimulus processing/responding and for signaling to the PFC and general arousal systems when extra-activation is needed. The PFC would be specifically responsible for selectively enhancing task-related processes and stimulus representations in posterior cortical areas, to meet endogenous plans and instructions [Banich et al., 2000; Barch et al., 2001; Botvinick et al., 1999; Braver et al., 2001; Carter et al., 1998; Cohen et al., 2000; Luks et al., 2002]. In this sense, the ACC may be considered as a key area in the tuning of earlier stages of task-driven allocation of attention prior to stimulus processing [Gitelman et al., 1999; Woldorf et al., 2001]. It can be maintained that the ACC plays a function quite similar to that of a "supervisory attentional system" [Shallice, 1988; Shallice et al., 1989], which would manage repetitive stimulation in routine conditions and would alert the dorsolateral PFC when the environment unexpectedly changes and proper cognitive processes and reactions have to be set [Luks et al., 2002; MacDonald et al., 2000].

Studies on functional integration between the ACC and the dorsolateral PFC have described how these functionally specialized areas interact and how these interactions depend on changes of context. In a recent fMRI study of effective connectivity during a visual oddball task [Brázdil et al., 2007], a simple hierarchy within the right frontal lobe has been revealed, with the ACC exerting influence over the PFC. This finding has supported the Norman-Shallice model of action control [Shallice, 1988] with the presumed central role of the ACC.

Keeping in mind the above results [Brázdil et al., 2007], one may argue that due to its low temporal resolution, fMRI cannot provide definitive evidence on the directionality of functional connectivity between cortical areas during quick stimulus processing, especially if the functional coupling of brain rhythms is implied in that connectivity.

The direction of the cortico–cortical information flows can be studied by the computation of directed transformation function (DTF) from electroencephalographic (EEG) rhythms [Kaminski and Blinowska, 1991]. With the DTF technique, it has recently been shown that the presleep period is characterized by a parietooccipital-to-frontal cortical information flow, while the opposite holds at sleep onset [De Gennaro et al., 2004]. It has been also demonstrated that fronto-parietal directional flows varied during memory processes [Babiloni et al., 2004, 2006]. During mere encoding of visual information, the parietooccipital-to-frontal direction of the cortical information flow predominates. The direction of fronto-parietal fluxes is balanced during short- or long (retrieval)-memory processes [Babiloni et al., 2004, 2006]. However, to our knowledge, DTF technique has been used neither for the investigation of attentional functions during oddball tasks nor for the estimation of interactions between the ACC and the dorsolateral PFC after rare stimuli.

The aim of the present study was to investigate the effective functional connectivity between the ACC and the dorsolateral PFC during task-relevant processing of rare events (visual oddball paradigm). The DTF method was applied to human intracerebral EEG data recorded from the ACC and the PFC. The directionality of the information flow between these two regions of interest was estimated from SEEG rhythms, in order to evaluate the working hypothesis that the ACC directly or indirectly affects the oscillatory activity of the PFC under oddball conditions.

METHODS AND MATERIALS

Subjects

Eight patients (six males and two females) ranging in age from 19 to 37 years (with an average age of 27.9 ± 1.9 SE),

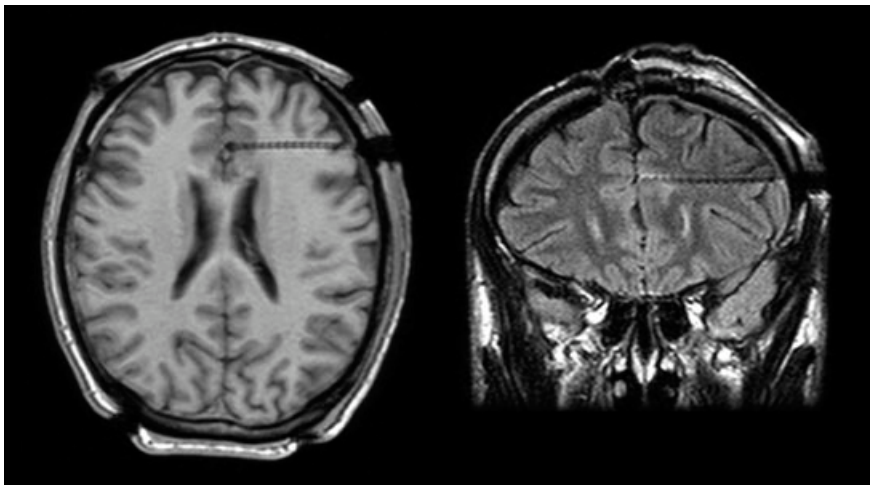

Figure 1.
Position of orthogonal depth electrode [passing through PFC into ACC]. The real volume of the electrode is about 10% of the displayed artifact.

all with medically intractable epilepsies, participated in the study. Depth electrodes were implanted to localize the seizure origin before surgical treatment. The intracerebral electrodes were implanted orthogonally under stereotaxic conditions (stereoEEG, SEEG) using the methodology of Talairach et al. [1967]. Standard MicroDeep semiflexible electrodes (DIXI) with a diameter of 0.8 mm, a length of each contact of 2 mm, and an intercontact interval of 1.5 mm were used for invasive EEG monitoring. The exact positions of the electrode contacts in the brain were verified using postplacement MRI with electrodes in situ (see Fig. 1). Lesional anatomical structures and epileptogenic zone structures were not included in the analysis. All subjects had normal or corrected-to-normal vision. All the patients were able to fully understand and perform the experimental task. Informed consent was obtained from each subject before the investigation and the study received approval from the Ethics Committee of Masaryk University Brno.

Visual Oddball Task

Subjects were seated comfortably in a moderately lighted room with a monitor screen positioned ~100 cm in front of their eyes. During the examination, they were requested to continuously focus their eyes on the small fixation point in the center of the screen and to minimize blinking. A standard visual oddball task was performed; two types of stimuli (frequent and rare) were presented in the center of the screen in random order. Clearly visible yellow capital letters O (frequent) and X (rare; ~50 trials) on a white background were used. The duration of stimuli exposure was constant at 200 ms; the ratio of rare to frequent stimuli was 1:5. The interstimulus interval randomly varied between 2 and 5 s. Each subject was instructed to respond to the rare (target) stimulus as quickly and accurately as possible by pressing a microswitch button in the dominant hand, and at the same time was instructed to mentally count the target stimuli.

EEG Recordings

The EEG signal was simultaneously recorded from various intracerebral structures and from the CPz scalp electrode (situated between Cz and Pz) using the 64-channel Brain Quick EEG system (Micromed). All recordings were monopolar with respect to a reference electrode on the processus mastoideus. All impedances were less then 5 kΩ. EEGs were amplified with a bandwidth of 0.1–40 Hz at a sampling rate of 128 Hz. Further processing was performed with artifact-free EEG periods. Eye movement artifacts were monitored via an electrooculogram (EOG) recorded by electrodes at the lateral canthus of the eyes. Surface electromyographic activity of bilateral extensor digitorum muscles was also recorded to monitor the voluntary movements as well as involuntary mirror movements and muscle activations.

In all subjects, we considered the depth electrodes crossing the dorsolateral PFC (Brodmann areas—BAs 9, 44, 45, 46) and ACC (BAs 24 and 32). To evaluate the effect of the rare stimulus independently by hemisphere, we considered the right hemisphere for half of the subjects, and the left hemisphere for the other half.

The collected SEEG data were segmented in single trials. For both rare (target) and frequent stimuli, the data windows for the spectral analysis were two 0.5 s windows: pre (a period of 0.5 s just before the stimulus) and post (a period of 0.5 s after the stimulus). The SEEG segments showing motor or instrumental artifacts were rejected. Eight SEEG recording sites from the PFC and eight SEEG recording sites from the ACC were considered for the data analysis (see Fig. 2).

"Direction" of the Functional Connectivity Estimated by the MVAR Model

Before computing the DTF, the SEEG data were preliminarily normalized by subtracting the mean value and by dividing for the variance, according to standardized rules by Kaminski and Blinowska [1991]. The DTF can be

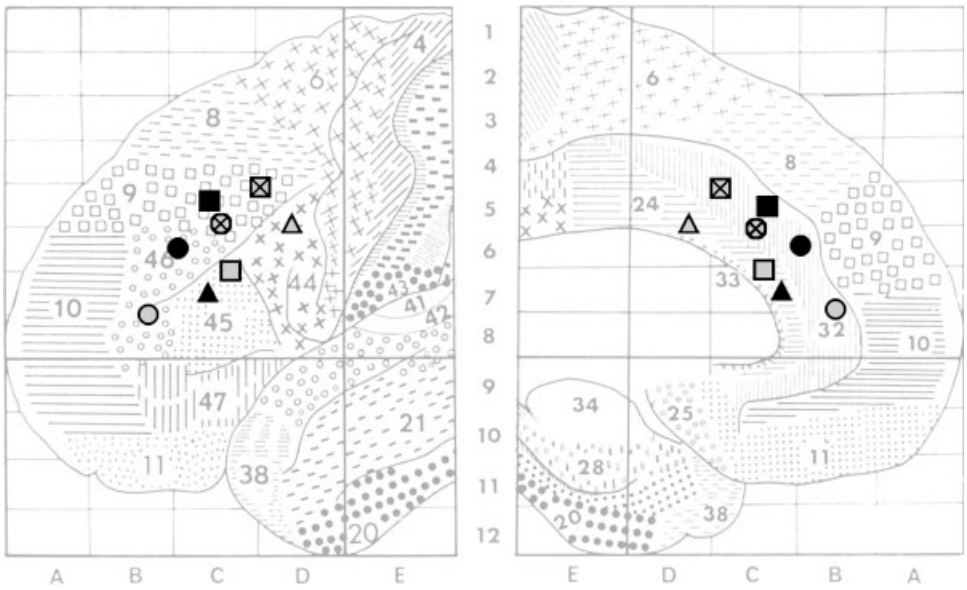

Figure 2.
Schematic distribution of recording sites within the lateral prefrontal cortex (left) and the anterior cingulate (right). The recording sites of each subject are labeled with specific symbols; each subject has its own distinguishing symbol.

considered as a normalized value ranging from 0 to 1. An important step of the DTF method was the computation of the so-called MVAR model [Blinowska et al., 2004; Kaminski and Blinowska, 1991; Kaminski et al., 1997]. SEEG data at all the electrode contacts inside the two regions of interest (anterior cingulate and dorsolateral prefrontal cortices) were simultaneously given as an input to the MVAR model for the computation of the DTF among all combinations of electrode pairs. The DTF values were obtained as the mean between the direction among each electrode contact of the ACC and all the contacts of the dorsolateral PFC. This procedure guaranteed the comparability of the results across subjects. The same procedure was true for the evaluation of the opposite direction of the DTF values between the two cortical regions of interest. In nonmathematical terms, the MVAR model estimates information flow between recording sites A and B by computing the extent to which the EEG data at recording sites A can be predicted based on the EEG data of recording sites B and vice-versa. A direction of the information flow from A to B is stated when that case is statistically more probable than directionality from B to A.

The mathematical core of the MVAR algorithm is based on the ARfit programs running on the platform (Matlab 5.3, MathWorks, Natick, MA). The model order was 7, as estimated by the Akaike criterion suggested in previous DTF studies [Kaminski and Blinowska, 1991; Kaminski et al., 1997]. The goodness of fit was evaluated by visual inspection of the values of noise matrix V of the MVAR model.

The MVAR model is defined as

$$\sum_{j=0}^{p} A_j X_{t-j} = E_t$$

where X_t is the L-dimensional vector representing the L-channel signal at time t; E_t is white noise; A_j is the $L \times L$ matrix of the model coefficients; and p is the number of time points considered in the model. From the identified coefficients of the model A_j, spectral properties of the signals can be obtained by the following z-transformation of the above equation:

$$X(z) = H(z)E(z)$$

where $H(z)$ is a transfer function of the system and

$$H(z) = \left(\sum_{j=0}^{p} A_j Z^{-j} \right)^{-1}$$

$$z^{-i} = \exp(-i2\pi f dt)$$

Since the transfer function $H(f)$ is not a symmetric matrix, the information transmission from the jth to the ith channel is different from that from the ith to the jth channel. The DTF from the jth channel to the ith channel is defined as the square of the element of $H(f)$ divided by the squared sum of all elements of the relevant row.

$$\mathrm{DTF}_{ij}(f) = \frac{|H_{ij}|^2}{\sum_{m=1}^{L} |H_{im}(f)|^2}$$

A substantial difference between $\mathrm{DTF}(f)_{ij}$ and $\mathrm{DTF}(f)_{ji}$ may suggest an asymmetric information flow from electrode i to electrode j. When $\mathrm{DTF}(f)_{ij}$ is greater in magnitude than $\mathrm{DTF}(f)_{ji}$, the "direction" of the information flow is from electrode j to electrode i. On the other hand, the "direction" of the information flow is from electrode i to electrode j, when $\mathrm{DTF}(f)_{ji}$ is greater in magnitude than $\mathrm{DTF}(f)_{ij}$. Noteworthy, the present procedure is based on the assumption that AR model is quasi stationary over the 500 ms window used for the MVAR analysis. This assumption is reasonable for short period of the brain activity and is the basis of the countless literature commonly

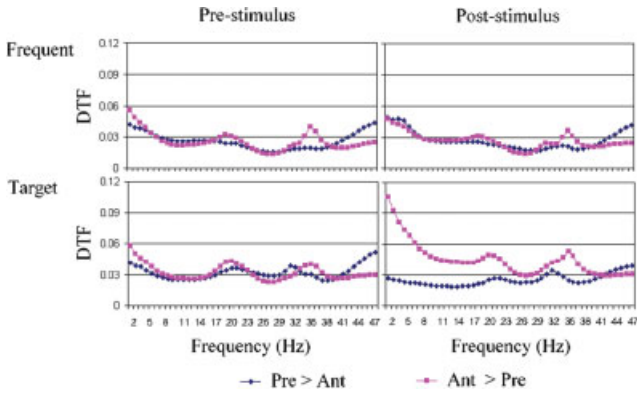

Figure 3.

Grand average ($N = 8$) of the DTF values (1–48 Hz) relative to the "anterior cingulate-to-dorsolateral prefrontal cortex" direction and the "dorsolateral prefrontal-to-anterior cingulate cortex" direction for the frequent and target trials in both pre- and post-stimulus periods. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

using fast Fourier transform, spectral coherence, and DTF measurements in event-related paradigms.

The DTF values were evaluated as the maximum DTF peak value at each of the following EEG bands of interest: θ (4–8 Hz), α (8–12 Hz), β (14–30 Hz), and γ (30–45 Hz). The DTF values were computed for the frequent and rare/target conditions and for the pre and poststimulus periods defined as the period of 0.5 s before and 0.5 s after the onset of the frequent or rare/target stimulus.

Statistical Analysis

A preliminary Kolgomorov-Smirnoff test evaluated the Gaussian distribution of the DTF data The results showed that all the variables were Gaussian so that DTF data were given as an input to repeated measures ANOVA. The Mauchley test evaluated the sphericity assumption and correction of the degrees of freedom was carried out using the Greenhouse-Geisser procedure. The Duncan test was used for post-hoc comparisons ($P < 0.05$). The side of the electrode position (namely left or right hemisphere) was used as covariate. Because of the small number of the subjects, no statistical analysis could address the effects of hemispherical lateralization or those the activity within subregions of prefrontal (Brodmann areas—BAs 9, 44, 45, 46) and ACC (BAs 24 and 32).

To simplify the visualization and statistical analysis of the DTF results, the directional flow of information was given as "anterior cingulate-to-dorsolateral PFC" minus "dorsolateral prefrontal-to-ACC" direction of the DTF. Positive values of this subtraction (DTFdiff values higher than zero) showed the predominance of the "anterior cingulate-to-dorsolateral PFC" direction over the "dorsolateral prefrontal-to-ACC" direction of the DTF. On the other hand, negative values of this subtraction (DTFdiff values lower than zero) showed the predominance of the "dorsolateral prefrontal-to-ACC" direction over the "anterior cingulate-to-dorsolateral PFC" direction of the DTF. We performed four different ANOVA analyses using DTFDiff values as a dependent variable; each ANOVA regarded a single band of interest (θ, α, β, and γ). The ANOVA factors were Condition (frequent, target) and Period (prestimulus, poststimulus).

RESULTS

Behavioral Results

Satisfactory co-operation of all subjects was observed during the experiment. The mean reaction time in the group of patients was 502 ms (±SD 31.3). The mean counting accuracy (i.e., accuracy of subjects' reports at the end of the experiment) was 88.6% (±SD 11.03).

Electrophysiological Results

Figure 3 illustrates the across-subjects mean DTF values (1–48 Hz) relative to the "anterior cingulate-to-dorsolateral PFC" direction and the "dorsolateral prefrontal-to-ACC" direction for the frequent and target trials in both pre and poststimulus periods. Similar DTF values are noted relative to the "anterior cingulate-to-dorsolateral PFC" and the "dorsolateral prefrontal-to-ACC" directions in the prestimulus periods of both frequent and target stimuli as well as in the poststimulus period of the frequent stimuli. With respect to these DTF values, there is a clear increment of the DTF values relative to the "anterior cingulate-to-dorsolateral PFC" in the poststimulus period of the target stimuli, especially at low EEG frequencies. These DTF values

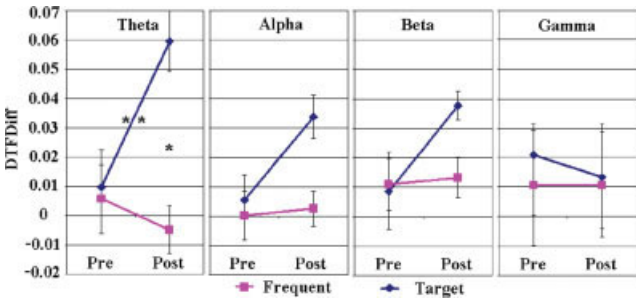

Figure 4.

Mean DTFdiff values (±standard error, SE) relative to the bands of interest (θ, α, β, and γ). Of note, positive DTFdiff values illustrate the predominance of the "anterior cingulate-to-dorsolateral prefrontal cortex" direction over the "dorsolateral prefrontal-to-anterior cingulate cortex" direction of the DTF; the opposite is true for the negative DTFdiff values. A statistical significance of the changes is depicted by asterisks (* $P < 0.0292$; ** $P = 0.006$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

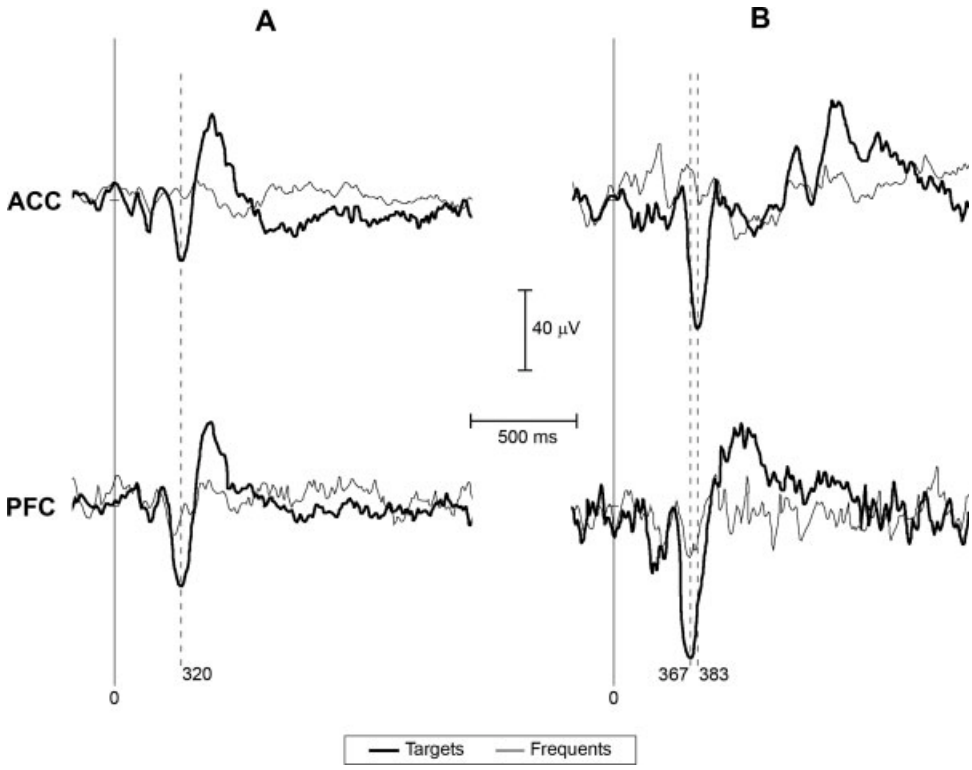

Figure 5.
Intracerebral event-related potentials from two of our subjects (A and B) recorded from ACC and dorsolateral PFC [for methodology see Brázdil et al., 1999]. Note exactly the same latency of P3 potential in mesial and lateral aspect of the frontal lobe in subject A, and somewhat earlier P3 latency within PFC in subject B.

were used as an input for the computation of the DTFDiff values. Figure 4 plots mean DTFdiff values (±standard error, SE) relative to the bands of interest (θ, α, β, and γ). Of note, positive DTFdiff values illustrate the predominance of the "anterior cingulate-to-dorsolateral PFC" direction over the "dorsolateral prefrontal-to-ACC" direction of the DTF; the opposite is true for the negative DTFdiff values. In line with the results relative to the DTF values, DTFdiff values point to the increment of the directionality "anterior cingulate-to-dorsolateral PFC" in the poststimulus period of the target stimuli at α, β, and θ bands.

The ANOVA analyses of the DTFDiff values showed a statistically significant interaction between the Condition (frequent, target) and Period (prestimulus, poststimulus) factors only for the θ band ($F(1,7) = 7.47$; $P < 0.0292$). Post hoc analysis disclosed a statistically significant increment of the positive values of the DTFdiff in the poststimulus period of the target stimuli when compared with the prestimulus period ($P = 0.006$), indicating a global prevalence of "anterior cingulate-to-dorsolateral PFC" direction over "dorsolateral prefrontal-to-ACC" direction of the DTF. Furthermore, there was a statistically significant increment of the positive values of the DTFdiff in the poststimulus period of the target stimuli in comparison to the frequent stimuli ($P = 0.01$), confirming the specificity of the result mentioned earlier.

One may argue that the above results merely reflected the anticipation of P3 in the ACC with respect to the dorsolateral PFC. To address this issue, we averaged SEEG trials to form the P3 in the ACC and dorsolateral PFC [for methodology see Brázdil et al., 1999]. The latency of the P3 was computed for the two regions of interest (ROI) and compared. Figure 5 shows the P3 in these regions for two representative subjects. If independent local generators of P3 potentials were observed in both ACC and PFC (which was the situation in three cases), either identical P3 latencies were found in both ROI or a shorter latency of P3 was even found in PFC (in one subject). In five subjects, typical P3 sources have been proven just in one recording site (ACC or PFC), whilst obvious far field potentials were observed in the other ROI (PFC in 2 cases; ACC in one case) or P3 was even completely missing there (PFC in two cases). In the majority of records, the comparison of the P3 latencies therefore could not be justified. From this simple analysis, it can be seen that the P3 peak was not earlier in latency in the ACC when compared with dorsolateral PFC. It is therefore unlikely that our DTF results are due to differences in the P3 latency between ACC and dorsolateral PFC.

DISCUSSION

Does the ACC affect the oscillatory activity of dorsolateral PFC activity, to properly react to unpredictable changes in the environment? To explore this issue, we proposed an advanced methodological approach applying the DTF analysis of directional information fluxes within

the brain oscillations on SEEG data having both high temporal (milliseconds) and spatial (millimeters) resolution. The SEEG data were recorded from the ACC and the dorsolateral PFC in drug-resistant epileptic patients engaged in a standard visual oddball task. It was shown that compared with the frequent stimuli, the rare (target) stimuli and relative responses (stimulus counting and movement) induced an increase of the DTF values from the ACC to the dorsolateral PFC, which was statistically significant at θ rhythms ($P < 0.05$).

The first few questions raised by our results concern the physiological meaning of θ rhythms in the experimental conditions present. It has been shown that event-related modulation of θ rhythms is an important neural correlate of brain processes for the integration of sensorimotor and cognitive information [Basar et al., 1999; Brankack et al., 1996; Klimesch, 1999; Pfurtscheller and Lopes da Silva, 1999]. In brief, θ rhythms functionally connect the activity of hippocampal systems and cortical mantle in many species [Buzsaki and Draguhn, 2004], and are supposed to be related to focused attention, working memory, encoding processes of episodic memory, and control of action [Gevins and Smith, 2000; Klimesch, 1999; Klimesch et al., 2001, 2006; Sauseng et al., 2002, 2004; Sochůrková et al., 2006]. Furthermore, hippocampal θ rhythms are coordinated with several motor patterns, including locomotion, orienting, rearing, and exploratory whisking [Berg and Kleinfeld, 2003; Hasselmo et al., 2002; Kleinfeld et al., 1999; Vanderwolf, 1969; Whishaw and Schallert, 1977]. In light of these data, it can be speculated that the flux of information within θ rhythms from the ACC (BAs 32, 24) to the dorsolateral PFC (BAs 9, 44, 45, 46) would be related to the attentional-control functions, updating of working memory, and the control of motor response to unpredictable rare (target) stimuli. Indeed, here the mere observation of the frequent stimuli was not able to modulate the directionality of the SEEG information flux between the ACC and the dorsolateral PFC.

A second important issue raised by these results is the physiological meaning of the unveiled directional information flux from the ACC to the dorsolateral PFC. This represents a step forward with respect to the notion of "coactivation/strict cooperation" between these areas previously revealed by fMRI during oddball tasks [Brázdil et al., 2007]. Indeed, such a directional information flux supports the hypothesis of a peculiar triggering role of the ACC over the dorsolateral PFC within cognitive functions. When activated by sudden changes in the subject's environment, ACC may operate as a "supervisory attentional system," able to promote the activity of the dorsolateral PFC for the integration of plans, instructions, stimulus processing, decision making, short-term memory updating, and response control [Shallice, 1988]. In this sense, the present results extend previous evidence suggesting that the directed attention is organized at the level of a distributed large-scale network revolving around three cortical epicentres (or local networks)—ACC, dorsolateral PFC, and posterior parietal cortex [Mesulam, 1981, 1990, 1999; Nebel et al., 2005], which would provide a slightly different but interactive and complementary type of top-down attentional functions [Corbetta and Shulman, 2002; Fan et al., 2005; Kondo et al., 2004; Konrad et al., 2005; Luks et al., 2002; MacDonald et al., 2000; Milham et al., 2003].

The oddball task used in the present study can be favorably employed in research of the attentional functions. Rare target stimuli are well known to activate a large network of regions as revealed by studies using SEEG [Brázdil et al., 1999; Baudena et al., 1995; Halgren et al., 1998] and fMRI (Brázdil et al., 2005; Clark et al., 2000; Kiehl et al., 2001, 2005; Stevens et al., 2000; Yoshiura et al., 1999]. Specifically, P3a potential of oddball tasks is unambiguously generated in frontoparietocingulate system, namely in dorsolateral PFC, supramarginal gyrus and cingulate gyrus [Halgren et al., 1998]. All these regions are significantly activated after targets in fMRI studies too. In addition other cortical regions play important role in target detection, including ventrolateral PFC, medial temporal regions, intraparietal, and superior temporal sulci as revealed consonantly by electrophysiological and haemodynamic studies. All these regions are involved in the complete set of cognitive processes resulting in target detection and related execution. Their involvement is nevertheless time-dependent to stimuli. The P3 potential has a significantly shorter latency in frontal sites than in parietal or temporal sites (but not in ACC than in PFC). These literature findings suggest that cognitive activation after targets is widespread and highly organized in functional systems. In this line, the present results should be interpreted as a demonstration of directionality in the information processing flow within the frontal lobe during oddball conditions, within a spatially complex network of several areas. Indeed, correlations and causalities could also be mediated by regions not included in the present analysis. As a novel result of the study, the results showed a central role of ACC in the attentional functions and its direct functional connectivity with PFC, in agreement with the strong evidence that the dorsolateral prefrontal and cingulate cortices are highly interconnected anatomically, and lesions in these sites are associated with neglect and other attentional deficits [Mesulam, 1990, 1999]. The extent of structural links between ACC and lateral PFC is one of the most striking features of cortico–cortical connectivity in the primate frontal cortex. As pointed out by Barbas and Pandya [1989], intrinsic connections of the cingulate cortices with other frontocortical areas are not limited to immediate neighbors, but also reach the more distant prefrontal regions, particularly those in the dorsolateral PFC. It seems therefore reasonable that in the task used, there is an influence of ACC exerting over the PFC directly through these anatomical interconnections. These data importantly extend our previous fMRI analysis in which directionality could be not determined at the level of cerebral rhythms [Brázdil et al., 2007].

CONCLUSIONS

Results of the present SEEG study showed that compared with the frequent stimuli, the rare (target) stimuli of an oddball task induced a frequency-specific increase of directional information fluxes in humans (as revealed by DTF of cerebral rhythms) from the ACC to the dorsolateral PFC. These results suggest that when people have to react to certain infrequent changes in the environment, the ACC may affect the oscillatory activity of the dorsolateral PFC by a selective frequency code. Future studies should define the features of the stimuli able to modulate the mentioned directional information fluxes in the two hemispheres.

The present results have an important heuristic values and constitutes a basis for further experiments aimed at addressing corollary working hypotheses. Does ACC interact with dorsolateral PFC when subjects have to select proper processes and response as a reaction to unpredictable changes in the environment and/or when they simply attend and perceive specific, albeit infrequent, relevant objects? Are the relationships between ACC and dorsolateral PFC affected by functional hemispherical asymmetry or do they depend on the different specialization of area 24 or area 32 [BA 24 but not BA 32 is close to the projection to motor areas; Bush et al., 2000]? Future experiments should require subjects to reconfigure their response based on changes in the environment (e.g., task switching) or action value, the type of tasks commonly associated with medial PFC activity. Here, we performed the first step towards a challenging scientific venture.

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