NeuroImage 46 (2009) 584–588

Contents lists available at ScienceDirect

NeuroImage

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

Functional connectivity in the brain before and during intra-arterial amobarbital injection (Wada test)

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ARTICLE INFO

Article history:
Received 24 November 2008
Revised 6 February 2009
Accepted 19 February 2009
Available online 6 March 2009

Keywords:
Wada test
EEG
Synchronization
Functional connectivity
Epilepsy

ABSTRACT

We explored the effect of unilateral intracarotid sodium amobarbital injection during the Wada test (intra-arterial amobarbital procedure, IAP) on functional connectivity in the brain assessed by synchronization analysis of the EEG. Patients suffering from pharmaco-resistant epilepsy who were selected for epilepsy surgery and underwent a preoperative IAP to determine language dominance and contralateral memory capacity were eligible. All patients had brain abnormalities (mostly tumors) or mesial temporal sclerosis. Ipsilateral intrahemispheric, contralateral intrahemispheric, and interhemispheric synchronization likelihood (SL) was calculated in seven frequency bands before and during the IAP. Forty-two patients who underwent the IAP (34 left carotid injections, 32 right carotid injections) were included. In the delta and theta bands, SL increased over the hemisphere ipsilateral to injection, while contralateral and interhemispheric SL decreased. The SL increased in the beta band. In the gamma bands, differences between patients with right-sided and left-sided lesions were observed. When a left hemisphere lesion was present, SL increased after injection, while a more unequivocal pattern of change was present in patients with right hemisphere lesions. Our results indicate that amobarbital injection has effects on functional connectivity of both the anaesthetized and non-anaesthetized hemispheres. Synchronization consistently increases in the injected hemisphere. Functional connectivity in the contralateral hemisphere decreases in the lower frequency bands, while it tends to increase in the beta and gamma bands (depending on lesion lateralization). These results indicate that functional connectivity in both the injected as well as in the contralateral hemishere is strongly influenced by the IAP.

Introduction

The Wada test (intra-arterial amobarbital procedure, IAP) has been the most frequently used method to determine language dominance and memory capacity in temporal lobe epilepsy (TLE) surgery candidates for decades (Rosenow and Luders, 2001; Wada and Rasmussen, 1960). During the IAP, sodium amobarbital (or another sedative) is injected unilaterally into the internal carotid artery in order to selectively suppress activity in one hemisphere of the brain. After injection, functioning of the non-anaesthetized hemisphere can temporarily be assessed by means of neuropsychological testing. The IAP has for long been a clinically essential tool in determining patients' eligibility for epilepsy surgery. However, the popularity of the IAP has decreased in the past decade, mainly because of the possibly associated morbidity (Rausch, 1993), and interpretation issues concerning specificity and test–retest reliability (Kubu et al., 2000; Lee et al., 1995; Loddenkemper et al., 2007; Loring et al., 1990; Simkins-Bullock, 2000). At this moment, an estimated 40% of all centers performing epilepsy surgery use the IAP in most (i.e. more than 75% of all) epilepsy surgery candidates (Baxendale et al., 2008; Haag et al., 2008).

The IAP is a method of reversibly 'shutting down' one hemisphere of the brain, in order to mimic the functional effect of a resection of brain areas within the injected hemisphere. Most clinicians hold the view that the IAP affects only the injected hemisphere, while functioning within the contralateral hemisphere remains constant. However, 'shutting down' one half of the brain may also affect

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doi:10.1016/j.neuroimage.2009.02.034

functional properties of the contralateral hemisphere. Until now, the precise effects of lesions or suppression of circumscribed brain areas on functional connectivity in the rest of the brain are still unknown. This notion refers to the statistical interdependencies between time series (Aertsen et al., 1989), and is thought to reflect communication between different brain areas. Functional connectivity is probably essential for optimal brain functioning (Bressler, 2002; Reijneveld et al., 2007; Singer, 1999; Tononi and Edelman, 1998; Varela et al., 2001). Functional connectivity can be assessed by means of electroencephalography (EEG) and magnetoencephalography (MEG). Abnormalities in overall functional connectivity during resting state have been observed in primary brain tumor patients compared to healthy controls (Bartolomei et al., 2006a,b), which were correlated with decreased cognitive functioning (Bosma et al., 2008). These abnormalities, in particular the pathologically increased theta synchronization, normalized after tumor resection, and this normalization tended to be related to better epilepsy outcome (Douw et al., 2008; Engel et al., 1993). We also observed that brain tumors not only influence local communication, but also change connectivity in more remote, and even contralateral, brain areas (Bartolomei et al., 2006a,b; Bosma et al., 2008). To our knowledge, studies researching functional connectivity in other types of circumscribed brain lesions have not been performed yet.

Until now, the effects of the IAP on functional connectivity of the brain in resting state are unknown. A proper understanding of ipsilateral and contralateral changes induced by the IAP is important to comprehend fully the effects of amobarbital injection, and may contribute to our knowledge of functional plasticity in the brain. This reversible procedure may be highly useful to understand plasticity and adaptation in the brain when lesioned. Based on previous studies, we hypothesize that 'shutting down' one complete hemisphere through an IAP has strong effects on remote (i.e. contralateral) brain areas. This study explores the effect of sodium amobarbital injection during the IAP on functional connectivity in both the ipsilateral and contralateral hemispheres.

Methods

Patients

EEG data from all patients who underwent the IAP between November 2003 and October 2007 at the VU University Medical Center were visually inspected for this retrospective study. All patients suffered from pharmaco-resistant epilepsy and were selected for epilepsy surgery, warranting a preoperative IAP. Only patients of whom three artifact-free epochs of 10 s directly before and after amobarbital injection could be selected were included. The EEGs that were used were recorded as part of regular patient care, and data were analyzed anonymously in this study.

Electroencephalography and functional connectivity

Electroencephalography was performed continuously from approximately 1 h before to half an hour after the Wada procedure. Patients were asked to lie down, after which the electrodes were attached to the scalp. In order to inject the amobarbital selectively into the internal carotid artery, a 4F catheter was placed via a femoral artery approach, guided by angiography. In order to observe flow patterns through the circle of Willis, selective angiography of the internal carotid artery and visualisation in posterior–anterior and lateral projection was performed in all patients before injection of the sodium amobarbital. None of the patients showed cross-flow in to the contralateral arteria cerebri media. The injections of amobarbital were administered by hand through a catheter which was removed immediately after injection. Patients were typically injected with a slow bolus of 125 mg sodium amobarbital in 2.5 cm^3. There were at least 30 min between successive IAPs in the case of bilateral procedures. Patients had their eyes open, and were instructed to lie still as much as possible during the procedure.

EEGs were recorded with a digital EEG apparatus (Brainlab, manufactured by OSG) from Fp2, Fp1, F8, F7, F4, F3, A2, A1, T4, T3, C4, C3, T6, T5, P4, P3, O2, O1, Fz, Cz and Pz with Ag/AgCl electrodes. Impedance was kept below 5 kΩ. Initial filter settings were: time constant 1 s and high frequency cut-off 70 Hz. Sampling frequency was 500 Hz and A–D precision 16 bit. As reference for the EEG, an average montage was used during measurements.

The amobarbital effect is maximal up to the first minute of injection. Therefore, the three most artifact-free epochs of 10 s (i.e. 5000 samples) were visually selected [LD] both from the 40 s directly before ánd after injection, if possible after both left hemisphere injection and right hemisphere injection in the same patient. These six epochs per patient per injection were converted to ASCII files. The two frontoparietal electrodes (Fp1 and Fp2) were excluded to minimalize artifacts due to eye movements. Also, the midline electrodes (Fz, Cz, and Pz) were excluded, because we were specifically interested in intrahemispherical and interhemispherical functional connectivity. Further analyses of functional connectivity were performed off-line with software developed at the department of clinical neurophysiology of the VU University Medical Center (DIGEEGXP [CJS]). The synchronization likelihood (SL, see Stam and van Dijk, 2002) was used as an index of functional connectivity. We assume two dynamic systems, for instance, neural networks designated X and Y. Time series x_i and y_i are recorded from both neural networks. The general problem is to infer functional interactions between X and Y from x_i and y_i. The current assumption regarding functional connectivity states that the more x_i and y_i 'resemble', the stronger X and Y interact. This resemblance can be quantified by several measures, such as coherence or crosscorrelation. However, it has been shown that X and Y can interact even when x_i and y_i do not resemble each other in a simple way. This more complicated concept, called generalized synchronization, implies that the state of Y is a function of the state of X. The SL is a way to quantify this generalized synchronization (Rulkov et al., 1995), and takes linear as well as nonlinear synchronization between two time series into account. Synchronization likelihoods between all combinations of the 16 included electrodes were determined, providing us with a 16×16 matrix of SL values. These matrices were calculated in the following seven frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), lower alpha (8–10 Hz), upper alpha (10–13 Hz), beta (13–30 Hz), lower gamma (30–45 Hz), and upper gamma (55–80 Hz; see (Stam et al., 2006)). Further averaging of the obtained SL matrices took place to obtain three SL scores: left intrahemispheric, right intrahemispheric, and interhemispheric synchronization likelihoods. Recapitulating, we now had three SL scores per frequency band, both before injection and after, adding up to $3 \times 7 \times 2 = 42$ SLs. When patients had undergone bilateral IAPs, this number doubled to 84 SLs.

Statistical analysis

All statistical analyses were performed using SPSS 15.0 for Windows. Differences between included and excluded patients were assessed by means of a Student's *t*-test for independent samples (age) and Chi-square tests (sex, lesion type, lesion lateralization). To increase statistical power and because of the non-normality of SL data, we normalized SL scores by means of a logarithmic transformation, which has been used in previous studies regarding neurophysiological time series ($LN[x/[1-x]]$; see Gasser et al., 1982, and Bosma et al., 2008; Stoffers et al., 2007). In order to test whether the injection of sodium amobarbital had an effect on functional connectivity, we used a single repeated measures ANOVA, hereby controlling for multiple testing of our large number of variables. The ANOVA had four within-subject variables: frequency (including the seven aforementioned bands), side of injection (right vs. left), state (rest vs. injected),