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Menstrual cycle corrupts reliable and valid assessment of language dominance: Consequences for presurgical evaluation of patients with epilepsy☆

Christoph Helmstaedter*, Christiane Jockwitz, Juri-Alexander Witt

Department of Epileptology, University of Bonn, Bonn, Germany

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ABSTRACT

Purpose: Functional transcranial Doppler sonography (fTCD) is a valid and non-invasive tool for determining language dominance, e.g. in the context of presurgical evaluations. Beyond this, fTCD might be an ideal tool to study dynamics in language dominance over time. However, an essential prerequisite would be a high test–retest reliability. This was addressed in the present study.
Methods: Test–retest reliability of hemispheric hemodynamics during open speech was determined in 11 male and 11 female healthy volunteers using the Animation Description Paradigm. Expressive language dominance was assessed weekly over an interval of 4–5 weeks.
Results: Internal consistency of the four measurements was excellent (split-half reliability 0.85–0.95), but test–retest reliability of the lateralization index was poor to moderate (rtt = 0.37–0.74). Controlling for gender, test–retest reliabilities were better in men (rtt = 0.67–0.78) as compared to women (rtt = 0.04–0.70). When arranging the assessments in women around day one of menstruation – all were on contraceptives – a significant shift from left hemisphere dominance toward bilaterality ($t = 2.2$ $p = 0.04$) was evident around menstruation with significant reversal afterwards ($t = -3.4$ $p = 0.005$).
Conclusion: A high intraindividual variability of language dominance patterns is indicated in women when assessed repeatedly by fTCD. Menstrual cycle appeared to be the source of inconsistency. The finding challenges the use of non-deactivating methods for language dominance assessment in epilepsy. Support for this is demonstrated with a female patient with epilepsy in whom language dominance assessed by repeated fMRI and fTCD varied concordantly with cycle but not so the repeated intracarotidal amobarbital test.

1. Introduction

In the context of epilepsy surgery the intracarotidal amobarbital test (IAT; also Wada test [1]) still represents the gold standard for determination of the language dominant hemisphere [2–4]. This procedure, however, is invasive and today it appears mainly indicated if brain surgery may directly affect suggested eloquent cortex subserving language function. During the IAT a barbiturate is injected via a femoral catheter which terminates within the left/right arteria carotis interna. Because of its invasiveness, the IAT is neither suited for research questions beyond its strict clinical indication, nor for routinely performed follow-up assessments. Repeated measurement would for example be appreciated to answer questions regarding changes in language dominance along with language development or processes of functional recovery and plasticity in the context of chronic or reversible cerebral pathology (in epilepsy: lesions, surgery vs. seizures, interictal activity).

Among the non-invasive methods discussed as alternatives for the IAT functional MRI (fMRI) in particular meets all the criteria for utilization in clinical settings [5]. Another non-invasive alternative to the IAT is the functional transcranial Doppler sonography (fTCD), which had been introduced by Aaslid and colleagues in 1982 [6]. FTCD like fMRI assesses task-dependent changes of cerebral blood flow and is therefore an indirect measure of brain activation. During cognitive performance (e.g. word generation, picture

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* Corresponding author at: Department of Epileptology, University of Bonn, Sigmund-Freud-Str. 25, 53105 Bonn, Germany.
Tel.: +49 228 287 16108; fax: +49 228 287 90 16108.
E-mail address: C.Helmstaedter@uni-bonn.de (C. Helmstaedter).

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description), the increased need for energy (glucose and oxygen) in the activated brain regions leads to increased regional blood flow that is accompanied by blood flow velocity changes within major cerebral arteries. As a result, change in neuronal activity can be indirectly assessed by experimentally measuring changes in blood flow velocity along with different mental states. FTCD is non-invasive, inexpensive, and easily applied in both children and adults. FTCD has proven to be a valid tool for the assessment of language dominance and is increasingly used in the presurgical evaluation of patients with epilepsy [7–10].

In a newer activation paradigm, the so called *Animation Description Paradigm*, which was developed by Bishop et al. [11], the subject is asked to watch brief cartoon clips which have to be described in a fixed time interval immediately after presentation. The description period is followed by a silent resting phase (see Fig. 1). Different from the classical word generation paradigm, this task is easy to perform and eligible for adults, children and disabled persons as well, there is no right or wrong, the resting intervals are short, and overt speech allows for direct monitoring of the requested behavioral response. In a still ongoing validation study in patients with epilepsy the fTCD results obtained with this *Animation Description Paradigm* are compared to those of the IAT and/or language fMRI. Preliminary results had shown perfect correspondence between fTCD and IAT (100%, $n = 10$) and good concordance between fTCD and fMRI (89%; $n = 27$) and fMRI and IAT (90%; $n = 10$) [12].

The present study was set up to determine the internal consistency and test-retest reliability of fTCD lateralization indices in healthy subjects. Following the reliability study applying the classical silent word generation paradigm [9] the a-priori hypothesis was that the results should be stable over time. Due to its low demanding properties, we did not expect practice or habituation effects.

We did, however, control for the possibility of gender effects. In this regard there is an ongoing discussion that women may have more bilateral language representation as compared to men [13,14]. Own evidence from IATs in patients with epilepsy indicated that women might be more prone to have bilateral language than men [15]. Apart from this, it has been demonstrated in healthy subjects that menstrual cycle causes intraindividual fluctuations in language dominance patterns as assessed by fMRI using a semantic decision task [16]. In the study by Fernandez there was greater right hemisphere activation during the luteal phase. Similarly another fMRI study showed different fMRI activation at the luteal phase and menstruation using a word generation task [17]. Therefore, we asked all women about the time of menstruation during the study phase.

2. Methods

2.1. Participants

Twelve male and 12 female healthy volunteers were recruited to participate in this prospective longitudinal study. Past neurological psychiatric diseases led to an exclusion from the study. An inclusion criterion for women was hormonal contraceptives to eliminate fluctuations of dominance patterns in women as described by Fernandez et al. [16]. Taking this nevertheless into consideration, all female participants had to indicate the first day of their menstruation. From the original sample of 24 participants, one subject had to be excluded because of insufficient quality of the fTCD signal, probably due to a deficient temporal bone window. Another subject was not able to attend all sessions because of illness and therefore had to be excluded as well. This resulted in a total sample of 22 participants. The participant́s chronological age ranged from 20 to 55 years (mean: 27.3 years; SD: 7.3). Twenty-three of the participants were right-handed and one participant was left-handed. German was the first language for all subjects. The participants took part in the study on a voluntary basis and did not receive any monetary compensation. Written informed consent was given in the first session by all participants.

2.2. Design and procedure

All subjects attended four sessions (T1–T4). In women a fifth session was added to have a session before during and after the menstruation. The assessments were carried out within four/five weeks; every week at the same day (plus minus one day). We employed the Animation Description paradigm which comprises

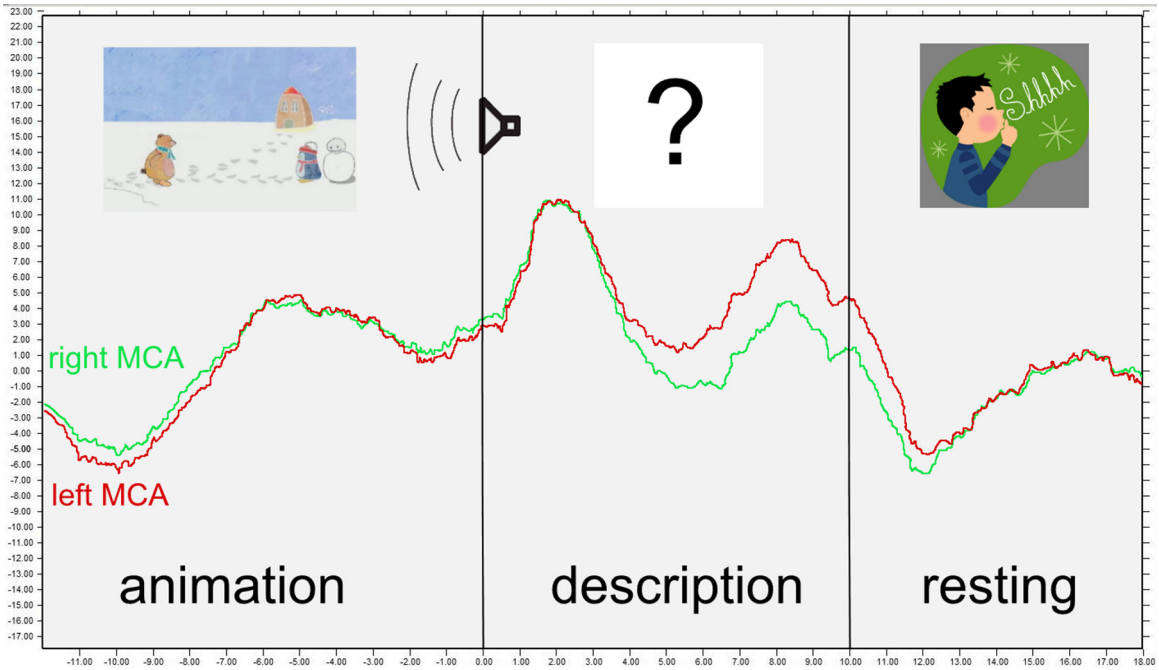

Fig. 1. Mean blood flow velocity changes within the left (red) and right (green) middle cerebral artery registered during the Animation Description paradigm (fTCD-LI: +4.0 ± 0.39).