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Gender characteristics of cerebral hemodynamics during complex cognitive functioning ☆

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ABSTRACT

Functional Transcranial Doppler sonography (fTCD) has been applied to assess peak mean cerebral blood flow velocity (MFV) with a high temporal resolution during cognitive activation. Yet, little attention has been devoted to gender-related alterations of MFV, including spectral analysis. In healthy subjects, fTCD was used to investigate a series of cerebral hemodynamic parameters in the middle cerebral arteries (MCA) during the Trail Making Tests (TMT), a means of selective attention and complex cognitive functioning. In females, there was a frequency peak at 0.375 Hz in both MCA, and we observed a dynamic shift in hemispheric dominance during that condition. Further, after the start phase, there was an MFV decline during complex functioning for the entire sample. These novel results suggest condition-specific features of cerebral hemodynamics in females, and it adds to the notion that gender is a fundamental confounder of brain physiology.

1. Introduction

Functional Transcranial Doppler sonography (fTCD) of basal cerebral arteries has been successfully used to measure discrete phases of peak mean cerebral blood flow velocity (MFV) during planning and abstraction tasks (Frauenfelder, Schuepbach, Baumgartner, & Hell, 2004; Schuepbach, Boeker, Duschek, & Hell, 2007; Schuepbach et al., 2002, 2009) and also during attention (Duschek, Schuepbach, & Schandry, 2008). One advantage of fTCD consists in the high temporal resolution, allowing pinpointing instant MFV changes (for review see Duschek & Schandry, 2003; Stroobant & Vingerhoets, 2000), whereas the spatial resolution of this technique is restricted to the arterial territories. Gender may play an important role in lateralization of cerebral hemodynamics during higher cognitive functioning. For example females activate the left hemisphere during Raven Progressive Matrices, a paradigm thought to be a measure of general intelligence and also working memory. Conversely, males exhibit right hemispheric dominance (Njemanze, 1991, 1996, 2005a). A further strategy to characterize gender differences of cerebral hemodynamics is the application of Fourier analysis that gives information within the frequency domain. Njemanze (2007) found gender specific features during facial processing by means of Fourier transformation of the MFV signal. There were gender-related differences of spectral density peaks recorded at frequencies of 0.125 Hz and 0.375 Hz. This author suggested that the frequency of 0.375 Hz originated from subcortical terminals while the frequency of 0.125 Hz stemmed from cortical branches of the middle cerebral arteries (MCA). The underlying thought of applying spectral analysis to the fTCD signal is that cerebral blood flow (CBF) is coupled to neuronal activity, and both the vascular and neuronal systems oscillate at similar frequencies of such coupling. In the case of TMT, the examination of condition and gender-related frequencies of cerebral hemodynamics is interesting, since there is evidence that TMT-B is more complex and challenging than TMT-A. Most studies on cognitive activation assessed MFV in the middle cerebral arteries. In this context it is of relevance to note that the arterial supply of MCA comprises the lateral hemisphere of the frontal and parietal lobes (Tatu, Moulin, Bogousslavsky, & Duvernoy, 1998). There is evidence that relative MFV is significantly associated with cerebral blood flow (CBF) (Bishop, Powell, Rutt, & Browse, 1986; Dahl et al., 1992) and also with results of functional magnetic resonance imaging (fMRI) (Schmidt et al., 1999).

One of the most widely used neuropsychological paradigms of attention and complex functioning is the Trail Making Test (Lezak, Howieson, & Loring, 2004). It is sensitive to frontal lobe

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functioning. Neuroimaging evidence suggests left dorsolateral and medial frontal activity (Zakzanis, Mraz, & Graham, 2005), but also a widely distributed pattern of cerebral activation. A study using subjects with brain lesions (Stuss et al., 2001) found a notable slowing of speed of solution in frontally impaired patients. Concerning the more complex sub form, subjects with dorsolateral frontal lesions were more severely impaired. In other words, dorsolateral areas, i.e. areas within the MCA territory, play a pivotal role in TMT performance. Interestingly, gender effects have not been reported in those studies despite solid evidence that males and females show distinct neuroanatomical substrates (Hsu et al., 2006; Raz et al., 2004). One explanation may be that there is no clear evidence of performance differences between males and females (Tombaugh, 2004). There have been TMT studies using near-infrared spectroscopy, indicating that cerebral blood flow increases in the prefrontal cortex during performance of that task, and that both hemispheres are required, especially for TMT-B (Kubo et al., 2008; Nakahachi et al., 2010; Shibuya-Tayoshi et al., 2007). Across those studies, there was neither a consistent gender effect nor hemispheric dominance.

Time sensitive alterations of cerebral hemodynamics due to discrete cognitive stimuli pose an intriguing new domain of neurophysiological research. In that context, we recently measured a means of rapid change of cerebral hemodynamics, so called cerebral hemodynamic modulation, in a series of complex cognitive functions (Schuepbach, Weber, Kawohl, & Hell, 2007; Schuepbach et al., 2009). In an fTCD study, we were able to show increased oscillations of that measure during cognitive activation, with a gender specific profile (Schuepbach et al., 2009). To the best of our knowledge, there have been no TMT studies on cerebral hemodynamic modulation using the high temporal resolution of fTCD, and corresponding gender aspects have not been investigated with this technique. The gender wise examination of rapid alterations of cerebral hemodynamics is interesting, because electrophysiological evidence suggests that oscillations due to stimulation are increased in females as compared to males (Güntekin & Başar, 2007). Further, the TMT is carried out at two separate difficulty levels, and evidence from aforementioned neuroimaging (Zakzanis et al., 2005) and lesion studies (Stuss et al., 2001) suggests that the more difficult version of TMT has distinct neurobiological properties. It is therefore appealing to investigate variations in cerebral hemodynamics due to such graded stimuli and also in relation to gender.

In an attempt to comprehensively examine second wise cerebral hemodynamics during the TMT, the following questions were of relevance for this study: First, does TMT provoke specific cerebral hemodynamics that is different from a visuomotor control task? Second, are there gender-related differences, particularly with respect to hemispheric dominance? Third, given the examination of cerebral hemodynamic modulations and hence oscillations of cerebral hemodynamics, are there distinct frequencies of cerebral hemodynamic modulation, be it for the entire sample or gender wise?

2. Method

2.1. Participants

Thirty healthy and right-handed subjects were included in this study (15 males and 15 females, age 31.0 ± 8.0 and 31.5 ± 7.0 yrs, $t(28) = 0.19$, $P = 0.85$). All subjects denied consumption of caffeine or nicotine in the 2 h prior to the experiment, and they were free of psychotropic medications, general medical, neurological and psychiatric disease. Further, all participants denied a recent traumatic burden. The local ethical committee approved the study, and all subjects gave written informed consent.

2.2. Stimulus

The TMT was applied as a conventional paper and pencil test. There are two parts of this paradigm, namely Part A and B. In the Trail Making Test, Part A (TMT-A), 25 numbers are depicted that have to be connected in an incrementing way (1, 2, 3…25) as fast as possible. The test assesses graphomotor speed, visual scanning and selective attention, called in the following "selective attention". In the Trail Making Test, Part B (TMT-B), numbers (1 until 13) and letters (A until L) must be linked in a mutually and incrementing fashion, and it provides information on mental flexibility and executive functioning, in the following called "complex cognitive functioning" (Tombaugh, 2004) (Fig. 1a and b). Subjects were required to solve the tasks as quickly and accurately as possible.

Before the measurements, subjects underwent a short standardized practice session of both parts of the task, i.e. they were instructed about the nature of the paradigm and had the opportunity to connect several ascending numbers or number and letters with

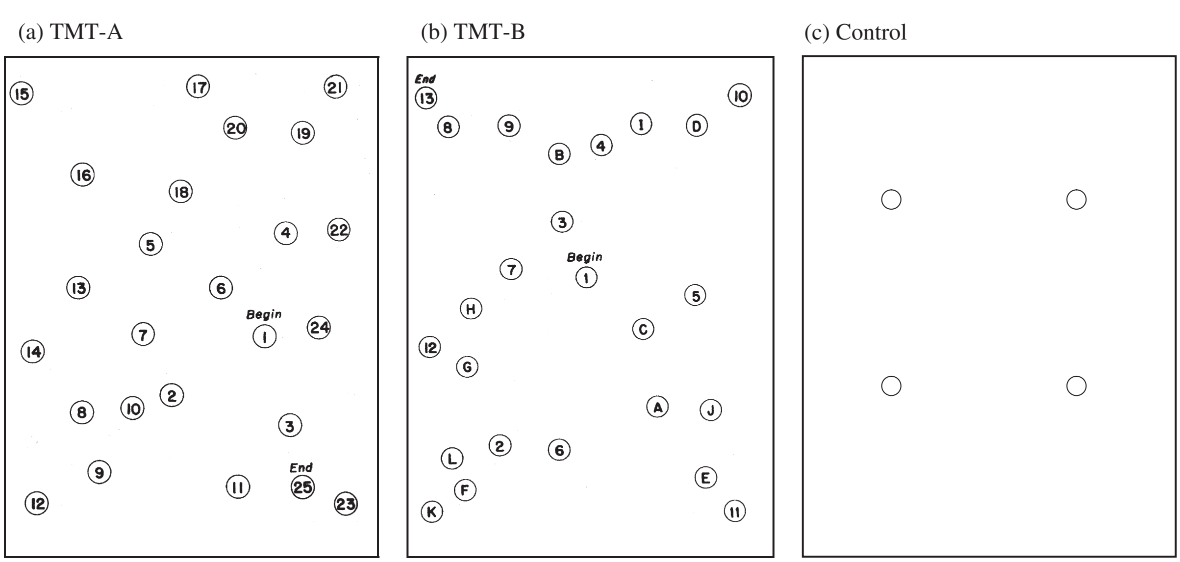

Fig. 1. Paper and pencil versions of (a) TMT-A; (b) TMT-B; (c) control. Abbreviations: TMT-A or -B: Trail Making Test, Part A or B.