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Rapid cerebral hemodynamic modulation during set shifting: Evidence of time-locked associations with cognitive control in females ☆

Daniel Schuepbach [a,*], Mariëtte Huizinga [b], Stefan Duschek [c], Simone Grimm [a], Heinz Boeker [a], Daniel Hell [a]

[a] Psychiatric University Hospital Zürich, Lenggstrasse 31, 8032 Zürich, Switzerland
[b] Department of Psychology, University of Amsterdam, Roetersstraat 15, 1018 WB Amsterdam, The Netherlands
[c] University of Munich, Department of Psychology, Leopoldstrasse 13, 80802 München, Germany

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ABSTRACT

Set shifting provokes specific alterations of cerebral hemodynamics in basal cerebral arteries. However, no gender differences have been reported. In the following functional transcranial Doppler study, we introduced cerebral hemodynamic modulation to the aspects of set shifting during Wisconsin Card Sorting Test (WCST). Twenty-one subjects underwent the WCST during insonation of the middle cerebral arteries. We examined gender effects on task performance and cerebral hemodynamic modulation. Further, we investigated the linkage between performance and cerebral hemodynamic modulation. In females, maximum positive modulation was restricted to the behaviorally relevant time point of set shifting, and there were time-locked associations between mental slowing during set shifting and rapid cerebral hemodynamic modulation exclusively in females. This study provides evidence of gender-related cerebral hemodynamic modulation during set shifting, and we detected time-locked brain–behavior relationship during cognitive control in females.

1. Introduction

Rapid adjustment to changing cognitive demands is an essential characteristic of cognitive control (Braver, Reynolds, & Donaldson, 2003). Important prerequisites to solve respective neuropsychological paradigms are constant representation of internal task-set information and task-set reconfiguration (Monsell, 2003). One of the most widely used cognitive tasks with features of set shifting and set maintenance is the Wisconsin Card Sorting Test (WCST) (Huizinga & van der Molen, 2007). The test itself is a difficult task of executive functioning (Feldmann, Schuepbach, von Rickenbach, Theodoridou, & Hell, 2006). It assesses cognitive flexibility that is the ability to alter a behavioral response mode in the face of changing contingencies (set shifting) (Monchi, Petrides, Petre, Worsley, & Dagher, 2001).

During WCST, Monchi et al. (2001) observed dorsolateral prefrontal cortex (DLPFC) activity during set shifting and a network comprising frontal areas, basal ganglia and the thalamus. Parts of the lateral prefrontal cortex may be involved in monitoring working memory performance, in shifting attentional sets or in selection of the appropriate response during performance of WCST. Selecting the relevant action among competing motor responses has been associated with activity of the striatum and the putamen.

We applied this task using functional transcranial Doppler sonography (fTCD) to healthy subjects and found specific alterations of cerebral hemodynamics (Schuepbach et al., 2002). Further, we demonstrated that set shifting during WCST comprises elements of difficult mental and online planning (Feldmann et al., 2006). Only few neurophysiological studies addressed gender issues of that paradigm (Esposito, Van Horn, Weinberger, & Berman, 1996; Feldmann et al., 2006) with at best inconclusive results. Gender differences are well known for other neuropsychological domains, e.g. males exhibit stronger performance in visuo-spatial abilities, whereas females solve tasks of verbal and language domains more efficiently, and there is evidence of distinct brain activity between males and females during mental rotation, verbal and visuo-spatial tasks (Jordan, Würstenberg, Heinze, Peters, & Jäncke, 2002; Neubauer, Grabner, Fink, & Neuper, 2005). Bell, Willson, Wilman, Dave and Silverstone (2006) found differential patterns of activation in males and females during a variety of cognitive tasks, even though there was no performance difference in some. A number of reasons exist that help explaining functional differences between males and females, such as evidence from diffusion tension imaging (DTI) suggesting a sexual dimorphism in the white matter of deep temporal regions as well as in precentral, cingulate and anterior temporal areas (Hsu et al., 2006), or structural differences

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* Corresponding author. Address: Psychiatric University Hospital Zurich, Lenggstrasse 31, P.O. Box 1931, 8032 Zurich, Switzerland. Fax: +41 44 383 44 56.
E-mail address: daniel.schuepbach@puk.zh.ch (D. Schuepbach).

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in various brain regions such as the parietal and occipital regions (Raz et al., 2004).

In the light of the multitude of reasons for differences in neural tissue between males and females and given the widespread use of WCST, it is surprising to note that no studies on cerebral blood flow and metabolism exist, which explored gender differences during set shifting of WCST. Concerning fTCD, one reason may lie in the fact that averaging peak mean cerebral blood flow velocity (MFV) over larger time intervals prevails from the detection of differences. In that context, we recently introduced a novel measure of cerebral hemodynamics namely cerebral hemodynamic modulation, which assesses flow modulation on a second-wise level (Schuepbach, Boeker, Duschek, & Hell, 2007; Schuepbach, Weber, Kawohl, & Hell, 2007), enabling to analyze very brief time intervals. Interestingly, we were able to demonstrate that there is evidence of time-locked association between rapid cerebral hemodynamic modulation and test performance during difficult planning (Schuepbach, Weber et al., 2007).

Given the complete absence of studies that applied rapid cerebral hemodynamic modulation during set shifting, the following issues were of interest in this study: first, does rapid cerebral hemodynamic modulation occur during set shifting? Second, does rapid cerebral hemodynamic modulation during set shifting differ between genders, and if yes, do males and females regulate brain perfusion differently over time? Third, is there evidence of time-locked association between rapid cerebral hemodynamic modulation and mental slowing during set shifting?

2. Method

2.1. Participants

Twenty-one right-handed healthy subjects (11 men, 10 women; age: 28.9 ± 6.9 yrs vs. 28.0 ± 4.4 yrs, $t(19) = 0.35$, $P = 0.73$) were included in this study. No subject had previously undergone neuropsychological testing. All subjects denied consumption of caffeine or nicotine in the 2 h prior to the experiment. The local ethical committee approved the study, and all subjects gave written informed consent.

2.2. Stimulus

The WCST was presented through a 15″ computer display, with four key cards at the upper half of the screen and a stack of response cards at the lower half of the screen (always depicting symbols on the top card). The top response card had to be attributed to one of the four key cards according to one of the three sorting rules color (red, green, yellow, blue), shape (triangle, star, cross, circle) and number (one, two, three, four). Feedback was given through a high (i.e. correct) or low (i.e. false) pitched tone. After 10 correct card sorts, which represented one category, the matching principle altered, and the participant had to infer the new sorting strategy. Each category was presented twice until a maximum of six categories were achieved or a maximum of 128 trials was achieved. The subject controlled card sorting by means of a conventional computer keyboard, using their fingers of the right hand on the numeric block (keys 1, 2, 3 and 4 indicated the four possible key card positions on the computer screen). Participants were instructed to sort the cards as swiftly as possible. The WCST was repeated once.

2.3. Technical specifications

Doppler measurements were performed with a Multi-Dop TCD X4 instrument (DWL Elektronische Systeme GmbH, Sipplingen, Germany). Two dual 2 MHz transducers were attached and fixed with a headband. Both middle cerebral arteries (MCA) were insonated at depths of 48–55 mm through the temporal bone window (Aaslid, Markwalder, & Nornes, 1982). MFV was assessed in all examined vessels. The distance between the participant and the test monitor was 1 m, adjusted at the height of the subject's eyes. A second monitor, which showed a standard screen saver program (starfield, Microsoft Corp., USA, c.f. Schuepbach et al., 2002), was positioned beside the test screen.

2.4. Procedures

Thirty minutes prior to the experiment, participants received instructions and a practice session to solve WCST. During testing, subjects were instructed to remain silent and avoid any confounding motor activity.

2.5. Data collection

2.5.1. Performance

The ratio between RT during set shifting and RT during set maintenance was calculated to achieve a measure of mental slowing during set shifting (mean of first and second runs); hence, an adaptation from the so-called switch cost was made (Monsell, 2003). For the sake of completeness, information is also provided on numbers of categories, percentage of perseverative errors, reaction times (RT) of 2nd and 3rd trials as means of set shift, and RT of 9th and 10th correct trials as means of set maintenance (Schuepbach, Hell, & Baumgartner, 2005).

2.5.2. Mean cerebral blood flow velocity (MFV)

Offline analysis of MFV (mean of first and second runs) comprised the following steps (Feldmann et al., 2006): (a) integration of absolute MFV to one value per heartbeat, (b) offline export of the digitized MFV data to a commercially available spreadsheet program (MS-Excel, Microsoft Corp., US), (c) normalization of digitized data with reference to pre- and post-task rest phases (90 s intervals of rest with 60 s between the first and last 15 s, yielding one absolute and averaged baseline MFV, recalculation to percent values) and (d) conversion from heartbeat to second-wise frequency. The steepness of the increasing slope (S_{inc}) (Schuepbach and Boeker et al., 2007; Schuepbach and Weber et al., 2007) as a means of rapid cerebral hemodynamic modulation was obtained as % MFV change/s (Fig. 1). More precisely, we calculated S_{inc} using

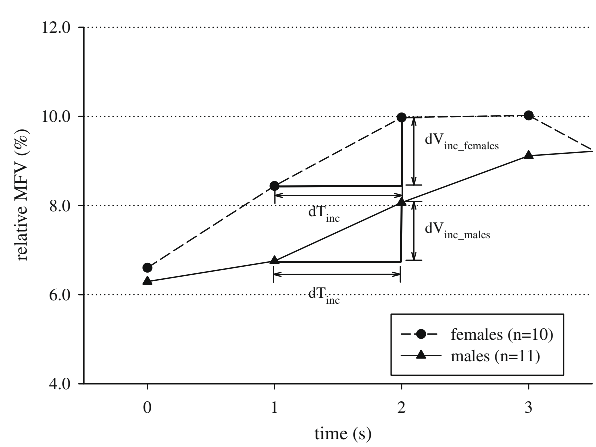

Fig. 1. Schematic illustration of how mean S_{inc} (%/s) has been calculated in male and female subjects. *x*-axis: time (s) and *y*-axis: relative MFV (%). Abbreviations: d, difference; S_{inc}, steepness of the increasing slope between 1 and 2 s; dV_{inc}, difference of MFV during 1 and 2 s; *T*, time and *V*, mean cerebral blood flow velocity.