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Neural correlates of a standardized version of the trail making test in young and elderly adults: A functional near-infrared spectroscopy study

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ABSTRACT

The trail making test (TMT) is a widely applied diagnostic tool measuring executive functioning in order to discriminate between healthy and pathological aging processes. However, due to its paper-and-pencil nature it is difficult to adapt for functional brain imaging. Related neural underpinnings even in healthy aging are mostly unknown since no consistent administration for imaging is available. In this study a standardized implementation of the TMT for functional near-infrared spectroscopy (fNIRS) is proposed to investigate associated frontal cortex activation in healthy young (mean age 25.7 ± 3.02 years) and elderly adults (mean age 70.95 ± 3.55 years). The TMT consisted of a number condition (TMT-A), an alternating number and letter condition (TMT-B) as well as a control task. Behavioral results demonstrated that elderly participants performed slower but committed a similar number of errors compared to younger adults. The fNIRS results showed that particularly the TMT-B provoked bilateral activation in the ventro- and dorsolateral prefrontal cortex (vlPFC and dlPFC) as well as in premotor regions. Elderly participants displayed more significantly activated channels and a different activation pattern compared to younger participants especially manifesting in more bilateral dlPFC activation. In line with the hemispheric asymmetry reduction in elderly adults (HAROLD) model, the results were interpreted as an additional need for cognitive control resources in elderly participants. This study succeeded in implementing an appropriate version of the TMT for fNIRS and helps elucidating neural aging effects associated with this task.

1. Introduction

The trail making test (TMT) is a frequently applied neuropsychological paper-and-pencil test (Armitage, 1946; War Department, 1944) consisting of the TMT-A in which numbers (1–25) are connected in an ascending order (1–2–3…) and the TMT-B which requires connecting numbers (1–13) and letters (A–L) alternately (1-A–2-B…). While both subtasks are considered to measure motor speed and visual scanning abilities, the TMT-B additionally requires cognitive flexibility, working memory, set-shifting abilities, the ability to maintain two response sets as well as inhibitory functions (Arbuthnott & Frank, 2000; Crowe, 1998; Gaudino, Geisler, & Squires, 1995; Kortte, Horner, & Windham, 2002; Miner & Ferraro, 1998; Misdraji & Gass, 2010; Salthouse, 2011; Sanchez-Cubillo et al., 2009; Stuss et al., 2001). Therefore, especially the TMT-B is often a substantial component of the assessment of executive functioning in neurodegenerative disorders (Ashendorf et al., 2008; Baillon et al., 2003; Bossers, van der Woude, Boersma, Scherder, & van Heuvelen, 2012; O'Rourke et al., 2011; Roca et al., 2013; Weintraub et al., 2005). This is additionally supported by the fact that the TMT is part of the most frequently used screening battery for the detection of Alzheimer's Disease

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(AD), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-plus; Morris, Mohs, Rogers, Fillenbaum, & Heyman, 1988).

However, even though the TMT is one of the best established neuropsychological tests and seems to be a sensitive and commonly used measure for the investigation of cognitive functioning in different populations, the underlying neural correlates are only sparsely understood and no consistent implementation for the use in brain imaging studies is available. This can mainly be attributed to the test characteristics: The standard TMT is conducted in a paper-and-pencil fashion, the investigator corrects errors immediately and the individual completion time is the main outcome measure (Armitage, 1946; Reitan, 1955). Existing functional magnetic resonance imaging (fMRI) studies vary with regards to the study design and often lack important features of the standard administration: Moll, de Oliveira-Souza, Moll, Bramati, and Andreiuolo (2002) for instance investigated participants with a verbal version of the TMT while Zakzanis, Mraz, and Graham (2005) used a virtual stylus displaying randomly arranged numbers and others (Allen, Owens, Fong, & Richards, 2011; Jacobson, Blanchard, Connolly, Cannon, & Garavan, 2011) instructed participants to mentally connect numbers and letters displayed on a screen and press a button when the target circle was visually reached. In these studies the response modality of the standard TMT was changed, an additional response component was added or neither a motor control task nor the TMT-A was included. Due to the diverse forms of administration these studies vary to some degree regarding the identified underlying neural structures. The described prefrontal regions include parts of superior, inferior and middle frontal gyr as well as medial and dorsolateral prefrontal regions (dlPFC; Allen et al., 2011; Jacobson et al., 2011; Moll et al., 2002; Zakzanis et al., 2005).

An alternative is the use of functional near-infrared spectroscopy (fNIRS) which non-invasively measures changes of oxy- and deoxygenated concentrations of hemoglobin using near-infrared light. This method is able to overcome some of the difficulties of fMRI studies, i.e. horizontal body position, scanner noise, movement artifacts and therefore the standard TMT form of administration can be adapted more closely. However, some of the existing fNIRS studies investigating the TMT exhibit methodological difficulties. Two of these studies either do not use a control task or disregard it in the analysis (Kubo et al., 2008; Shibuya-Tayoshi et al., 2007). Some arrange the items in a pseudorandomized fashion across the paper and therefore cannot control for the level of difficulty, only administer the TMT-A or do not use standardized block lengths (Kubo et al., 2008; Nakahachi et al., 2010; Shibuya-Tayoshi et al., 2007; Weber, Lutschg, & Fahnenstich, 2004, 2005).

Nevertheless, all mentioned fNIRS studies agree on a wide spread bilateral frontal activation which seems to be stronger for the TMT-B in the studies involving this subtask (Kubo et al., 2008; Shibuya-Tayoshi et al., 2007; Takeda, Notoya, Sunahara, & Inoue, 2011). One fNIRS study which overcame most of the above mentioned methodological difficulties by using a more standardized version of the TMT did not further specify the involved frontal regions due to a different focus of this study (Takeda et al., 2011). A more precise description of involved regions is given by two previous studies. The first study described ventrolateral (vlPFC) and dlPFC activation using a modified version of the TMT-A (Nakahachi et al., 2010). The second study reported bilateral anterolateral and to a lesser extent posteromedial PFC activation both being more pronounced during the TMT-B (Kubo et al., 2008). All above mentioned studies investigating the TMT concentrate on the neural correlates of young subjects. One study by Hagen et al. (2014) for the first time investigated healthy subjects from different age groups using the TMT and fNIRS. This study found the dlPFC and Broca's area to be active during both subtasks with generally more pronounced activation in the left hemisphere. Additionally, the authors describe differential patterns of activation for the two age groups. However, this study only involved participants with an age range from 50 to 75 years which were divided via a median split into two age groups of a small sample size consisting of 7 subjects per group. Additionally, the implementation of the TMT did not include a control task and the investigator was present in the testing environment which might have influenced the brain activation.

Nevertheless, age effects on neural mechanisms of the TMT are expected and are an important basis for the investigation of pathological aging effects. Behavioral studies investigating the TMT depict an increase in completion time for both subtests subtasks, being more pronounced for the TMT-B in elderly adults most noticeable after the age of 70. This was interpreted as the result of several factors such as age-related deficits in attention, cognitive flexibility and processing speed (Drane, Yuspeh, Huthwaite, & Klingler, 2002; Tombaugh, 2004). A large amount of studies using a variety of cognitive tasks measuring perception, memory encoding, memory retrieval, working memory and executive functioning investigated the effects of healthy aging on the involved neural mechanisms. Recent studies reported a general frontal over-recruitment in elderly as compared to younger adults and executive functions were one of the major cognitive domains for studying this hyperfrontality (Grady, 2008; Spreng, Wojtowicz, & Grady, 2010). This can either be manifested through a decrease in lateralization in elderly participants, i.e. homologous regions in the contralateral hemisphere are additionally activated, or by a stronger activation of the same regions as in younger adults (Cabeza, Anderson, Locantore, & McIntosh, 2002; Grady, 2008). Depending on how successful these additional recruitments are in the light of the behavioral performance two underlying functions of age-related neural changes are being discussed. On the one hand “compensation” states that an additional recruitment of frontal activity is needed to assure a likewise behavioral performance as seen in younger adults. On the other hand “dedifferentiation” of task-specific and -unspecific brain regions might be a general byproduct of aging which is not connected to a specific function and simply reflects less specific recruitment of specialized neural mechanisms (Cabeza, 2002; Cabeza et al., 2002; Dolcos, Rice, & Cabeza, 2002; Grady, 2008; Spreng et al., 2010).

In sum, the discussion of age-related changes in cognitive performance and their underlying neural mechanisms is still proceeding. Executive functions are one major cognitive domain of interest. The TMT as a common measure of executive functioning can therefore help to clarify the neural substrates. However, only one brain imaging study investigating healthy aging effects of the TMT in a small sample exists (Hagen et al., 2014).

Therefore, the first aim of the present study was the standardized implementation of the TMT for brain imaging with fNIRS including a control task, parallel versions of the subtasks as well as equal block lengths in order to create a common basis for the investigation of the neural correlates of the TMT-A and the TMT-B in different populations. Based on previous studies, a recruitment of the PFC especially during the TMT-B was expected. The second aim of the study involved the comparison of young and elderly healthy adults regarding age-related differences in frontal cortex activation evoked by the TMT in order to extend the preliminary study of Hagen et al. (2014). It was expected that elderly adults would connect fewer circles than younger adults given the same amount of time. In addition, elderly adults were hypothesized to show a frontal over-recruitment manifesting in increased or more widespread activation compared to younger adults.