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Rapid event-related near-infrared spectroscopy detects age-related qualitative changes in the neural correlates of response inhibition

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ABSTRACT

Near-infrared spectroscopy (NIRS) is a promising neuroimaging tool for the study of human cognition. Here, we show that event-related NIRS is able to detect age-related differences in the neural processing in a simple visual Go/NoGo task using a relatively fast (stimulus onset asynchrony approx. 1.4 s) event-related design together with a model-based analysis approach. Subjects were healthy young (<30 years) and elderly (>60 years) adults. Behaviorally, old adults were slower but more accurate than young adults. The event-related analysis approach of NIRS data allowed us to contrast activation of successfully inhibited NoGo stimuli with that of correctly answered Go stimuli. Both age-groups showed frontal activation differences between these events in oxy- (HbO; increase) and deoxyhemoglobin (HbR; decrease). Between age groups, differences in HbR were found in right dorsolateral frontal (old>young), right temporal/postcentral/precentral and left precentral/inferior frontal (young>old) channels. These differences are in line with age-associated activation changes in inhibition detected with functional magnetic resonance imaging. The present study successfully separated the neural correlates of response inhibition from errors of commission/omission and provides data from multiple simultaneously recorded optodes. Furthermore, these results demonstrate the feasibility of using NIRS to investigate neural processes related to aging and dementia, in particular in patients for which other neuroimaging techniques are contraindicated. In the future, functional phenotyping of successful aging in respect to executive performance may be feasible.

Introduction

Near-infrared spectroscopy (NIRS) is an optical technique that can be used to assess variations in the content of oxy- (HbO) and deoxyhemoglobin (HbR) in superficial layers of brain tissue through the intact skull (Jöbsis, 1977; for review see Hillman, 2007). NIRS measurements are correlated with signals obtained by functional magnetic resonance imaging (fMRI) in which a closely related vascular signal, the BOLD contrast, is measured (for review see Steinbrink et al., 2006). Although inferior to fMRI in spatial resolution, NIRS has several advantages: there are few restrictions in the type of experimental paradigm that can be investigated and subjects are not confined to the supine position which facilitates application of complex stimuli and response characteristics (e.g. Strangman et al., 2002). Also, unlike fMRI, subjects with cardiac pacemakers, metal implants or large tattoos need not to be excluded. The time resolution of NIRS is superior to that of fMRI in that the sampling rate is an order of magnitude higher, although a similar, inherently slow, hemodynamic response is measured with both techniques. In fMRI research, a significant leap has been made through the use of event-related compared to block designs (Josephs et al., 1997). Whereas in the latter a task of interest is performed for a period of 30 s or so, event related designs allow to measure brain responses to individual, short duration stimuli. Event-related designs have several advantages compared to block designs, among which is the ability of post hoc trial-by-trial sorting according to subject performance and a greater overall flexibility in experimental design (Burock et al., 1998; Zarahn et al., 1997). A number of event-related NIRS experiments have shown that the same rationale can also be applied to this imaging technique (Boecker et al., 2007; Obrig et al., 2000; Schroeter et al., 2002; Taga and Asakawa, 2007). Schroeter et al. (2004) have shown that the length of the intertrial interval can be shortened to 2 s without a reduction of the HbR amplitude. Different analysis approaches have been explored with regard to NIRS data. Many researchers analyze NIRS studies by simply measuring concentration changes in HbO and HbR in response to task blocks (e.g. Herrmann et al., 2005) or single events (Boecker et al., 2007). A different way is a model-based general linear model

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(GLM) approach which is widely used in fMRI research. Plichta et al. (2007) have shown that analyzing fast event-related NIRS data with this approach is feasible.

A research area for which the above mentioned advantages of NIRS seem especially important is the field of aging and dementia as many elderly and demented patients have contraindications against examinations with fMRI or show excessive movement artifacts. Also, the versatility of the NIRS technique appears to be a major asset when higher cognitive functions are to be investigated. In the past, cognitive inhibition has been of particular interest to scientists, as a decline on various levels of this domain was observed both in normal aging (reviewed by Hasher and Zacks, 1988 and by West, 1996; see also Nielson et al., 2002; Spieler et al., 1996) and early Alzheimer's disease (reviewed by Amieva et al., 2004). Inhibition is a separable entity within the metacognitive executive function framework (Miyake et al., 2000), which is considered to have general importance for a variety of other downstream cognitive functions such as language, reading, memory, attention and working memory. However, there appear to be different aspects of cognitive inhibition, which, in respect to aging, may show different trajectories (reviewed by McDowd, 1997). A widely used paradigm in cognitive neuroimaging is the Go/NoGo task in which a prepotent motor response has to be actively inhibited. As there are a number of event-related fMRI studies using various Go/NoGo tasks (see Discussion), we chose this paradigm for our feasibility investigation with respect to cognitive inhibition. Moreover, there exists a large body of literature which compares young and old populations using fMRI research, also with respect to executive function (for a meta-analysis see Spreng et al., 2010). Thus, we are interested in whether event-related NIRS with short intertrial intervals and a GLM based analysis approach is similarly able to detect age-associated changes in neural correlates of simple motor response inhibition. To this end, we measure healthy young (<30 years) and elderly (>60 years) subjects performing a simple Go/NoGo task to explore potential changes in brain activation evoked by response inhibition between age-groups using rapid event-related NIRS. As mentioned, our primary aspect of interest is to test the feasibility of this expansion to the rapid event-related nature of the experiment, similar to investigations in fMRI research (Burock et al., 1998; Dale, 1999; Dale and Buckner, 1997). There are several competing theories on functional activation changes during healthy cognitive aging (reviewed by Dennis and Cabeza, 2008) which make different predictions, often tied to specific paradigms. Apart from the general feasibility hypothesis, we do therefore not predict the exact nature of the age effects between groups but are rather interested in whether both within- as well as between-group differences can be observed using this approach. In an attempt to align the obtained results with existing evidence on the cognitive neuroimaging of healthy aging (see Spreng et al., 2010), we therefore conduct post-hoc exploratory analyses, focusing on differential activation patterns in the two age groups.

Material and methods

Participants

Young subjects (<30 years) were recruited via a student social network, and old subjects (>60 years) were recruited by contacting representatives of the senior lecturing program of the University of Magdeburg and through the subject database of the German Center for Neurodegenerative Diseases (Magdeburg). All subjects were informed about the procedures of the experiment in written form. Additionally, subjects had to fill out a short questionnaire about their general health status and life habits. Data from 22 old and 27 young participants were acquired. After data acquisition 14 (6 old; 8 young) participants were excluded from the analysis because of technical problems during data acquisition (4 young), health reasons (assessed by a medical doctor (TFM): 3 old due to depression and/or psychotropic medication; 2 young, one participant with frequent migraine attacks, one participant due to recreational drug use on the evening preceding the experiment), or because they exceeded the a-priori set criterion of 50% failed inhibitions (2 old; 1 young). The remaining 2 subjects (1 old; 1 young) were excluded because the data on their handedness was either not collected (1 young) or did not match that of the other subjects (1 old left-handed subject). All analyzed participants had a high school diploma that entitled them to access higher (college-level) education ("Abitur" or "Fachhochschulreife"). The finally analyzed sample consisted of 16 old (68.4 ± 1.4 (mean ± SEM) years, range 60–76, 5 women) and 19 young (23.1 ± 0.4 years of age, range 20–26, 9 women) subjects. The study was approved by the Ethics Council of the Faculty of Medicine of the Otto-von-Guericke University Magdeburg.

Experimental procedure

A fast event-related design (Burock et al., 1998; Dale, 1999; Dale and Buckner, 1997) was used to exploit the possibility of post-hoc response sorting. In each run, participants saw a stream of + (Go) and × (NoGo) symbols which were presented in pseudorandom order (optimized for efficiency; see below) for 100 ms each. A total of 1083 stimuli appeared during the experiment (20.2% of these were NoGo stimuli) in five runs. Participants had to press a mouse button for frequent Go stimuli and had to inhibit this prepotent response when a NoGo stimulus occurred. Before the actual experiment, subjects completed a short test run to become familiar with the task. They had the possibility to rest between runs and continue the experiment in a self-paced manner. The mean stimulus onset asynchrony (SOA) was approximately 1.4 s and was jittered between 1 and 2.5 s, optimized for both power and efficiency of the event-related design (Dale, 1999).

Near-infrared spectroscopy

We recorded the concentration of oxygenated and deoxygenated hemoglobin at a sampling rate of 10 Hz using a Hitachi ETG-4000 Optical Topography System (Hitachi Medical Systems) which uses a modified Beer–Lambert Law to calculate hemoglobin concentrations. A thin plastic stick with a smooth ending was used to remove hair under the sockets in the optode grid to ensure direct skin contact of the optodes. Thirty-three optodes were placed on the subject's forehead from which 52 channels were recorded (see Fig. 1). The positioning of the optode grid was performed such that the middle optode of the most inferior row on the 3×11 optode grid was located on the point Fpz of the international 10/20 electroencephalography (EEG) system (Jasper, 1958). Also, the distances between the optode grid and both preauricular points were kept equivalent. The built-in 3D digitizer of the Hitachi system was used to record individual channel positions in each subject and to transform these to Montreal Neurological Institute (MNI) space during analysis using the toolbox of NFRI functions (Singh et al., 2005) included in the analysis software NIRS-SPM (Ye et al., 2009; see below). In three subjects, several (not more than three) channels failed to record a meaningful signal. In these cases, the channels were excluded from further analysis. Following transformation of individual channel positions to MNI space, we used the mean MNI coordinates of all subjects to visualize the channel positions on the MNI brain (Fig. 1).

Data analysis

Behavioral data and beta weights yielded by the NIRS analysis (see below) were analyzed with the software package R (version 2.12.1; R Development Core Team, 2010) with the package nlme (Pinheiro et al., 2011). Reaction times for Go stimuli and error rates (ERs) on NoGo trials were compared between age groups using unpaired