Clinical Neurophysiology 128 (2017) 604–621

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Event-related brain potential indices of cognitive function and brain resource reallocation during working memory in patients with Multiple Sclerosis

Thomas J. Covey, Janet L. Shucard, David W. Shucard *

Division of Cognitive and Behavioral Neurosciences, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, 114 Sherman Hall Annex, South Campus, Buffalo, NY 14214, USA
Neuroscience Program, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, 114 Sherman Hall Annex, South Campus, Buffalo, NY 14214, USA

ARTICLE INFO

Article history:
Accepted 26 December 2016
Available online 29 January 2017

Keywords:
Multiple Sclerosis
Working memory
P1
P3
Cognitive reserve

HIGHLIGHTS

- Event-related potentials (ERPs) were obtained during an n-back working memory task in Multiple Sclerosis (MS) patients and controls.
- MS patients exhibited attenuated P1 and P3 amplitudes compared to controls during the n-back.
- Anteriorization of the P3 was related to test performance in MS, indicating neural compensation.

ABSTRACT

Objective: To examine event-related brain potentials (ERPs) in Multiple Sclerosis (MS) during a visual n-back working memory (WM) task, and test the hypothesis that compensatory brain function may be associated with variance in task performance in MS patients.
Methods: Midline ERPs for 25 MS patients and 18 HCs were obtained for a visual n-back task that placed increasing demands on WM. N-back behavioral measures and neuropsychological performance measures of WM were also obtained.
Results: MS patients had slower reaction times (RTs) than HCs during the n-back task. Accuracy on the n-back and on neuropsychological tests did not differ between groups. P3 ERP amplitude decreased for both groups as WM demand increased. MS patients had lower overall P1 and P3 amplitudes compared to HCs. In MS, anteriorization of P3 amplitude was associated with better n-back performance. P1 and P3 amplitudes were also related to neuropsychological test performance in MS.
Conclusions: MS patients had reduced ERP amplitude compared to HCs during the n-back, and changes in ERP anterior–posterior midline amplitude distribution in MS were associated with cognitive performance.
Significance: ERPs, and in particular the P3 component obtained during a visual n-back task, are sensitive to subtle WM dysfunction in MS and may reflect compensatory reallocation of brain resources.

1. Introduction

1.1. Deficits in working memory and processing speed in Multiple Sclerosis

Multiple Sclerosis (MS) is a progressive neurodegenerative disorder of the central nervous system (CNS) characterized by demyelination (Cercignani et al., 2000; Kutzelnigg et al., 2005) and multifocal lesions. Cognitive impairments are prevalent in

* Corresponding author at: Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, Department of Neurology, Division of Cognitive and Behavioral Neurosciences, Sherman Hall Annex, Room 114, Buffalo, NY 14214, USA.
E-mail address: dshucard@buffalo.edu (D.W. Shucard).

http://dx.doi.org/10.1016/j.clinph.2016.12.030
1388-2457/

MS (Bagert et al., 2002; Beatty et al., 1989; Fischer, 1988; Rao, 1991), with impaired long-term memory, learning, processing speed (PS), executive function, and working memory (WM) being among the most common deficits (for reviews, see Benedict et al., 2008; Chiaravalloti and DeLuca, 2008; and Prakash et al., 2008a). Brain tissue abnormalities are commonly observed in both white and gray matter in MS (Deloire et al., 2005; Dineen et al., 2009; Pelletier et al., 2001; Reuter et al., 2009; Sanfilipo et al., 2005, 2006), and cognitive impairments in MS have been related to brain atrophy and lesion load (e.g., Covey et al., 2011; Lazeron et al., 2005; Sacco et al., 2015). Given the pathology and in particular the demyelinating processes characteristic of the disease, it is not surprising that PS and WM are among the most commonly affected cognitive domains in MS. WM is a core cognitive ability that involves the maintenance of information for short periods of time, while also manipulating or updating that information for the purpose of completing task-specific goals. The model of WM proposed by Baddeley and Hitch (1974) posits that information is held temporarily in specialized short-term memory buffers (i.e., the visual-spatial sketchpad, phonological loop, episodic buffer), and a supervisory central executive system serves to selectively manipulate and update information held in WM (Baddeley and Hitch, 1974; Repovs and Baddeley, 2006).

The role of PS as a distinct, and possibly mediating factor in WM function in MS has also been examined. Chiaravalloti et al. (2003) have provided evidence that WM is a distinct construct from PS, and several studies point towards PS as being a primary deficit in patients with MS, which in turn may result in difficulties in WM (DeLuca et al., 2004; Kail, 1998; Parmenter et al., 2006). Lengenfelder et al. (2006) found that when patients had more time to respond, they performed as well as healthy controls (HCs) on tests of PS and WM, indicating deficits specific to PS. However, Lengenfelder et al. also found that on tests with greater cognitive demand, some patients still underperformed even when given unlimited time to respond. These findings may indicate impairment in the central executive component of WM in those patients. Our laboratory has also shown that during a WM task, as cognitive demand increases, MS patients perform significantly worse than HCs, whereas they may perform equally as well under conditions with low cognitive demand (Parmenter et al., 2006, 2007). Other studies have found evidence of impairments in the central executive of WM in MS using dual-task paradigms (D'Esposito et al., 1996; McCarthy et al., 2005; Stablum et al., 2004). Lengenfelder et al. (2003) proposed that the central executive may be the main component of WM that is disrupted in cognitively impaired MS patients. This notion is supported indirectly by evidence that suggests that the dorsolateral prefrontal cortex, which is thought to underlie executive control, is commonly recruited when there is heavy demand placed on WM in individuals with brain injury and disease, in general (Hillary et al., 2006). Consistent with this notion, functional neuroimaging studies in MS patients have also found increased activation in frontal cortical regions (among other areas) during WM tasks (Chiaravalloti et al., 2005; Forn et al., 2007; Hillary et al., 2003).

There is evidence that MS patients with minimal or mild cognitive deficits have increased recruitment of frontal cortical regions during tasks of WM/PS, which has been interpreted to reflect compensatory changes in brain function (e.g., Audoin et al., 2003, 2005; Duong et al., 2005a,b; Forn et al., 2007). However, other studies have indicated reduced cortical activation in areas that include frontal cortex during WM tasks in patients with MS (Cader et al., 2006; Wishart et al., 2004). Roca et al. (2008) found an association between disrupted integrity of frontal-subcortical fiber tracts and deficits in performance on tasks of WM and executive function in MS patients. The notion of altered fronto-cortical functioning in MS is consistent with the emerging view in the aging literature that alterations in frontal cortical recruitment serve as a type of compensatory neuronal "scaffolding" in response to both neurological insult and normal neurocognitive aging (Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Cappell, 2008). Taken as a whole, these findings could reflect changes in the recruitment of frontal cortical resources, or diminished ability to recruit frontal cortical resources efficiently in MS. With respect to WM function specifically, frontal cortical compensation in MS is likely related to processes of the central executive of WM in particular.

1.2. Previous event-related brain potential research in Multiple Sclerosis

A number of studies have examined abnormal brain activity associated with PS and WM deficits in MS using electrophysiological techniques. Event-related brain potentials (ERPs) are derived by averaging the ongoing stimulus-locked electroencephalographic (EEG) signal across repeated presentations of discrete stimuli. ERPs have very good temporal resolution and therefore can provide measurement of brain processes, such as WM, that change dynamically over the course of milliseconds. Earlier occurring, exogenously driven components of the ERP, such as P1 and N1 (positive and negative peaks that occur at about 100 ms post stimulus when using visual stimuli), reflect early selective attention and the processing of the physical parameters of the stimulus. Later occurring, endogenously driven components, such as N2 and the P3 (or P300, P3a or P3b), which occur approximately 200–600 ms after stimulus onset, reflect higher order cognitive processes such as stimulus evaluation (for a review of these components, see Key et al., 2005).

The P3 component is not a unitary response but is a family of components, particularly the P3a and P3b. The P3a component typically has a frontal-central scalp topography and is thought to reflect involuntary attention and inhibition (Key et al., 2005; Polich, 2007). The P3b component has a parietal/posterior maximum amplitude scalp distribution. It is thought to relate specifically to event categorization (the matching of external stimuli to an internal representation), and therefore reflects activity associated with WM processes (Kok, 2001; Polich, 1991, 2007). P3b amplitude is suggested to be modulated by a complex set of factors, including the subjective probability of a stimulus, stimulus meaning (i.e., its category, complexity, and significance to the participant), the integrity of information transmission (Johnson 1986, 1993), and cognitive/brain resource allocation (Kok, 2001; Polich, 2007). P3 latency is related to the speed of classifying and discriminating stimuli that can occur during the updating of memory processes (Kutas et al., 1977; Magliero et al., 1984; Verleger, 1997); thus it can serve as an objective index of speed of processing in the CNS during WM.

Research examining ERPs in MS shows convergence with neuropsychological work and may help identify subtle cognitive dysfunction at the early stages of the disease (see Leocani and Comi, 2000; Magnano et al., 2006). Auditory and visual oddball tasks have frequently been used to examine differences in the P3 ERP component in MS patients and controls. MS patients tested with oddball paradigms have often exhibited longer latency and lower amplitude P3 components compared to HCs (Aminoff and Goodin, 2001; Ellger et al., 2002; Gil et al., 1993; Polich et al., 1992). ERP alterations also have been observed in MS that are more specific to the P3a component (Jung et al., 2006; Whelan et al., 2010). In addition, other ERP components have shown differences in MS patients compared to controls during oddball studies. These findings include prolonged P1 latency (Polich et al., 1992); prolonged N1, P2, and N2 latencies (Gil et al., 1993); decreased P2 amplitude (Aminoff and Goodin, 2001); reduced mismatch