

**DOES VITAMIN D IMPROVE  
COGNITIVE PROCESSING IN MS PATIENTS?  
An event-related potential study.**

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Master's thesis  
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March 2008

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HAKKARAINEN, ELINA KRISTIINA Does vitamin D improve cognitive processing in MS patients? An event-related potential study.

Master's thesis, 32 pages

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Psychology

March 2008

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Impairments in cognitive skills are found in 40-65% of patients with multiple sclerosis (MS). A link between MS and vitamin D has been shown, and vitamin D's advantages in central nervous system have been recently studied. In the present study, the effects of a high-dose (i.e. 1 µg) vitamin D's prestage Etalpa on cognitive processing of MS patients were investigated. Cognitive processing was investigated by measuring event-related potentials (ERP) in a visual oddball paradigm. Four visual ERP components (P1, MMN, PN, and P3) were investigated. Both active and passive oddball conditions were employed, by asking subjects to respond to stimuli or to ignore them. ERPs were measured both before and ca. 24 hours after the drug intake. The aim of the present study was threefold: (i) to clarify whether the frequently presented standard stimuli and infrequently presented deviant stimuli are discriminated by the responses of the MS patients, (ii) to test whether the discrimination is dependent on the allocation of attention, and (iii) to clarify whether there is difference in discrimination before vitamin D intake and after it. 14 MS patients (5 men, 9 women, age range 17 years to 47 years, mean age 33 years) were investigated. The results of the present study revealed that three out of four ERP components discriminated the standard stimuli from the deviant stimuli. The early visual MMN component, however, was not elicited. Early exogenous components (P1 and MMN) did not show any sensitivity for cognitive effort, while subsequent endogenous components (PN and P3) did. The results revealed no significant drug effect for vitamin D in the amplitudes of the ERPs, but further investigation of effects of vitamin D to P3 latencies and MMN compared with a healthy control group is recommended.

Keywords: ERP, Multiple sclerosis, Vitamin D

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## 1. INTRODUCTION

### 1.1 Multiple sclerosis and cognitive functioning

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system, and it is also characterized by progressive neuronal loss (Compston & Coles, 2002). MS is caused by interplay between environmental factors and genes (Compston & Coles, 2002), the concordance rate between monozygotic twins for MS being 30% (Cantorna, 2006). MS is nearly twice as common in women as in men and typically manifests during the reproductive age (Compston & Coles, 2002). Patients can be classified clinically as having relapsing remitting (RR), secondary progressive (SP), or primary progressive (PP) multiple sclerosis (Tajouri et al., 2005). Symptoms of MS include fatigue, weakness, spasticity, balance problems, numbness, vision loss, tremors, and bowel problems (Huijbregts, Kalkers, Sonnevile, de Groot & Polman, 2006).

Cognitive dysfunction is one of the main symptoms of multiple sclerosis (Achiron & Barak, 2006; Gonzales-Rosa et al., 2006; Kujala, Portin & Ruutiainen, 1997; Penner & Kappos, 2006; Sartori & Edan, 2006; Schwid, Goodman, Weinstein, McDermott & Johnson, 2007). Impairments in cognitive skills are found in 40-65% of MS patients (Amato, Zipoli & Portaccio, 2006; Dujardin, Donze & Hauteceur, 1998; Ellger et al., 2002; Gonzales-Rosa et al., 2006). At the early stages of the disease, the cognitive decline is specific, rather than general (Dujardin et al., 1998). The most impaired cognitive domains are attention, information processing speed, and verbal fluency (Gonzalez-Rosa et al., 2006; Magnano, Aiello & Piras, 2006). Also working memory (Pelosi, Geesken, Holly, Hayward & Blumhardt, 1997; Ruchkin et al., 1994; Sartori & Edan, 2006) and episodic memory (Sartori & Edan, 2006) are affected in MS patients. According to results by Litvan, Grafman, Vendrell and Martinez (1988), slowed information processing is a deficit that contributes to long term memory impairment in patients with MS. MS patients at early stage of the disease, however, differ from each other in clinical presentation, level of disability, anatomical location, and number of demyelinating lesions and severity of cognitive deficits (Achiron & Barak, 2006). In addition, disease duration and neuropsychological performance do not correlate in MS patients (Gainotti, 2006; Kujala et al., 1997).

Kujala et al. (1997) studied how cognitive functioning evolves over time in MS patients by comparing cognitively preserved, mildly deteriorated, and controls in a 3-year follow-up study. They concluded that cognitive deficits in initially cognitively deteriorated patients tended to progress over time, while initially preserved patients stayed stable in their cognitive functioning. Results by Schwid et al. (2007) are, however, in discrepancy with those by Kujala et al. They studied changes in cognitive functions of MS patients in a 10-year follow-up study, and found that the strongest baseline predictors of cognitive decline were the initial cognitive test scores, those with highest initial scores showing the greatest decline. In a review of neuropsychological literature of multiple sclerosis, Zakzanis (2000) concludes that there are differences in cognitive deficits between MS subgroups: patients with progressive MS display maximal deficits on frontal-executive tasks, while patients with relapse-remitting MS display maximal deficits on memory tasks. According to Amato et al. (2006), patients of SP consistently exhibit worse cognitive performance than RR or PP patients.

## **1.2 ERP techniques and components**

Event related potentials (ERP) represent activation of considerable populations of synchronously active neurons (Coles & Rugg, 1995). Measurement of event related potentials ERPs is an objective tool to assess certain aspects of cognitive processing and, for example, to investigate subtle and subclinical changes in development of the cognitive disturbances (Ellger et al., 2002; Newton, Barrett, Callanan & Towell, 1989; Pelosi et al., 1997). One advantage of ERPs is the revelation of the selective processing of specific stimulus features without any overt motor responses (Hansen & Hillyard, 1983). In addition, ERP allows obtaining a spatio-temporal picture of the flow of processing events in the brain before, during, and after the stimulus (Näätänen, 1992). The temporal resolution of the scalp-recorded ERP-measurements is accurate, while the spatial resolution is limited both by theory and present technology (Picton et al., 2000).

ERPs involve various negative and positive deviations, called components. The components are typically named in terms of their polarity and latency, but also by the psychological or experimental conditions controlling the potential or the scalp location of the maximal potential (Coles et al., 1990). ERP components can be divided into flexible endogenous components mostly depending on subject's intentions and actions and into more stable exogenous components mainly determined by

the external stimuli (Näätänen, 1992), also considered as obligatory or sensory potentials (Coles et al., 1990). Endogenous brain potentials occur in a timeframe of 50 to 500 ms post-stimulus and are increased in size when near threshold sensory stimuli are detected (Knight, 1985). The exogenous brain potentials occur within the first 100 ms of stimulus presentation (Coles & Rugg, 1995), the amplitude of sensory evoked potentials being directly proportional to stimulus magnitude (Knight, 1985). Although exogenous ERPs are determined primarily by the physical characteristics of the eliciting stimulus and endogenous ERPs vary with the state of the subject, they should still be viewed on a continuum, rather than as alternatives of each other (Picton & Hillyard, 1988).

P1 is an attention-sensitive component with latencies varying between 80 and 130 ms (Heinze et al., 1994; Mangun, 1995; Klimesch et al., 2003). All the stimuli presented to the attended location in the visual field elicit an enhanced exogenous P1 component (Näätänen, 1992). The effects of both temporal and spatial attention and the attention allocation to P1 have been considered in studies. Correa, Lupiáñez, Madrid and Tudela (2006) showed that temporally cued targets elicit larger P1 than unattended targets, early cues eliciting larger amplitude than late cues. Handy and Khoe (2005) found attention-related increases in sensory-evoked cortical activity, measured by the amplitude of the lateral occipital P1 component, only at the parafoveal (above fixation) target location but not at the foveal (fixation) target location. Handy, Soltani and Mangun (2001) showed that the effects of load on early visuocortical processing reflect changes of the attention capacity to visual locations, showing that the amplitude of the P1 component for task-irrelevant parafoveal stimuli decreases when the perceptual load of foveal task increases. Again, Mangun, Hopfinger, Kussmaul, Fletcher and Heinze (1997) showed that the P1 component was of greater magnitude when the task was perceptually more demanding within the focus of spatial attention than in less demanding task situation.

Mismatch negativity (MMN) is brain's response to any discriminable change in an otherwise homogenous sequence of stimuli (Kathmann, Frodl-Bauch & Hegerl, 1999; Pazo-Alvarez et al., 2003). It is the first change detection response of the long-latency-ERPs, and the latencies occur between 80 and 250 ms (Gaeta, Friedman, Ritter & Cheng, 2001; Kathmann et al., 1999; Laamanen, 2004; Kujala, Tervaniemi & Schröger, 2007). MMN requires a deviant stimulus and it occurs independent of conscious detection of the change (Gaeta et al., 2001; Kujala et al., 2007; Laamanen, 2004; Picton & Hillyard, 1988;). Kathmann et al. (1999) suggest that MMN is fully independent from the attention condition; whereas Pazo-Alvarez, Cadveira and Amenedo (2003) and Picton et al. (2000) share the view that mismatch negativity is best recorded when the subject is not attending to

the stimuli. The amplitude of the MMN is directly proportional to, and its latency inversely proportional to the degree of difference between the standard and the deviant stimulus (Gaeta et al., 2001). MMN has been recorded to auditory deviant stimuli differing from the standards, for example, in frequency, intensity, duration, and inter-stimulus interval (Horimoto, Inagaki, Yano, Sata & Kaga, 2002; Laamanen, 2004).

The phenomenon of MMN can be explained by rareness (refractory theory) or deviation (memory-based explanation) of a deviant stimulus. There are some studies supporting the refractory theory (see Kenemans, Grent-'t Jong & Verbaten, 2003; Tales, Newton, Troscianco & Butler, 1999). According to the prevailing memory-based explanation, however, MMN is elicited when the incoming stimulus does not fit to the representation of the preceding stimulation (Cowan et al., 1993; Czigler, Balázs & Winkler, 2002; Jacobsen & Schröger, 2003; Laamanen, 2004; Näätänen, Paavilainen, Alho, Reinikainen & Sams, 1988; Pazo-Alvarez et al., 2003; Pincze, Lakatos, Rajkai, Ulbert & Karmos, 2002). Studies by Astikainen, Ruusuvirta, Wikgren & Korhonen (2004), Näätänen et al. (1988), and Pincze et al. (2002) support the memory trace theory.

Though the existence of auditory MMN is approved, its existence in visual modality is still controversial (Czigler et al., 2002) and the theory on the MMN is primarily based on the empirical evidence obtained in the auditory modality (Kujala et al., 2007). Pazo-Alvarez et al. (2003) reviewed studies related to visual MMN and concluded that visual MMN is an automatic component insensitive to attentional manipulations, although a greater difference between standards and deviants is necessary to elicit it as compared with the auditory MMN. Studies by Tales et al. (1999), Laamanen (2004), and Horimoto et al. (2002) also demonstrate that MMN also occurs in the visual modality.

Processing Negativity, PN, is an endogenous negative component associated with selective attention (Näätänen, 1982; 1992). Näätänen, Gaillard and Mäntysalo (1978) were the first to represent the term processing negativity for a slow endogenous negative component, referring to processing that is mainly under the subject's control. PN is perhaps best obtained by comparing attended-stimulus ERPs with those elicited when the whole stimulus block is ignored (Näätänen, 1992). The onset latency of the PN appears to vary between 50-200 msec (Näätänen & Michie, 1979), being positively dependent on ISI (Näätänen, 1982) and the difficulty of the discrimination task (Hansen & Hillyard, 1982; Näätänen, 1992). The amplitude of PN is also positively

dependent on ISI and the difficulty of the discrimination task (Mäntysalo, 1987; Näätänen, 1982).

The P3 wave is an objective electrophysiological index of cognitive function (Gil et al., 1993). P3, also referred as P300, is an endogenous, scalp-recorded response with a latency of 300 msec or more (Buchwald, 1990). Its amplitude varies between 5 and 20  $\mu$ V (Coles & Rugg, 1995) and is affected by a variety of variables including probability, stimulus quality, and attention or task relevance (Hoffman, 1990). The latency of the P3 positively depends on stimulus evaluation time (Hoffman, 1990; Magnano et al., 2006). A P3 waveform is generated when an infrequent sensory event is correctly detected by a subject and it is maximal over parietal regions (Knight, 1985; Magnano et al., 2006; Polich & Comerchero, 2003). The P3 reflects both the stimulus evaluation and orientation capability of the subject and does not require an overt motor response for its generation (Knight, 1985). The P3 is dependent on the subjective probability of task-relevant effects, the value or meaning of the event in the context of the task, and the psychological resources allocated to the processing of the event (Coles et al., 1990). The P300 wave reflects the timing and processing of mental activity during a simple task (Piras et al., 2003) and it is not emitted until the event has been categorized (Coles et al., 1990).

An oddball paradigm, where a stream of high-probability standard stimuli is presented with infrequent deviant stimuli (oddballs) embedded in it, is applied in most of the MMN studies (Cacace & McFarland, 2003; Fu, Fan & Chen, 2003; Laamanen, 2004; Lyytinen et al., 1992) and in P3 studies (Buchwald, 1990; Newton et al., 1989; Polich & Comerchero, 2003). Task-irrelevant oddball stimulation elicits MMN even when the subject is performing a highly demanding primary task (Näätänen, 1992). In an oddball situation, the P3 amplitude depends on probability: the rarer the event, the larger the P3 (Coles & Rugg, 1995), presuming that the rareness of an event must be established prior to the P3 process (Coles et al., 1990). In an oddball paradigm, subjects can be instructed to an active condition or passive condition by asking them to respond to deviants or targets or to ignore them (Laamanen, 2004).

### 1.3 ERP studies in MS patients

Recording of ERPs provides a useful tool as an objective measure of cognitive function in patients with MS (Aminoff & Goodin, 2001; Comi, Martinelli, Locatelli, Leocani & Medaglini, 1998; Ellger et al., 2002; Magnano et al., 2006; Newton et al., 1989). Studies measuring P1, MMN, and P3 waveforms have revealed alterations in the latencies and amplitudes of the components in MS patients compared to the healthy control groups. Jung, Morlet, Mercier, Confavreux and Fischer (2006) concluded that the auditory MMN in MS patients was reduced, suggesting that pre-attentive auditory processing is altered by the disease. In a study by Polich, Romine, Sipe, Aung and Dalessio (1992), the visual P1 potential in MS patients was delayed compared to control group.

According to Compston & Coles (2002), demyelination characteristically delays the latencies of visual evoked potentials, leaving the amplitude of responses unchanged. Studies have revealed an increased P3 latency in MS patients compared to control groups (Aminoff & Goodin, 2001; Gil et al., 1993; Honig, 1992; Gonzalez-Rosa et al., 2006; Polich et al., 1992), suggesting that increased latencies are associated with prolonged information processing (Magnano et al., 2006), cognitive decline (Honig, 1992; Gonzalez-Rose et al., 2006), disease duration, and increased demyelination seen in MRI (Honig, 1992). Diminished amplitudes are also observed in MS patients. (Aminoff & Goodin, 2001; Polich et al., 1992; Ruchkin et al., 1994). Diminished amplitudes are associated with a failure in the activation of some neural generators (Magnano et al., 2006).

Ellger et al. (2002) studied whether there are differences between the different diagnostic subgroups of MS (PP, SP, RR) with respect to the course of cognitive impairment. They concluded that patients with secondary progressive MS showed significantly increased P3 latencies as compared to the other subgroups. In addition, they demonstrated that there was a significant correlation between Expanded Disability Status Scale (EDSS) score and P3 latency.

Patients with MS are sensitive to tasks requiring controlled information processing (Dujardin et al., 1998). Therefore, the effectiveness of a treatment can be assessed by improvement in cognitive functioning (Comi et al., 1998). P3 has been frequently used as an indicator of changes in information processing in MS patients. To improve delayed information processing, a variety of drugs have been tested. Filipović, Drulović, Stojsavljević and Lević (1997) found that generally

prolonged P3 latency of ERP in patients with clinically active MS became significantly shorter after administration of HDMP (high-dose intravenous methylprednisolone) therapy. Gerschlager et al. (2000) found no drug effect for Interferon  $\beta$ -1b, but 3 out of 14 MS patients developed abnormal P3 latencies after 1 year of INF-  $\beta$ -1b-therapy.

#### **1.4 Vitamin D and multiple sclerosis**

Vitamin D is a fat-soluble vitamin and steroid hormone found for instance in fish, eggs, and vegetable oils (McGrath, 1999). Actually, vitamin D is a hormone and not a vitamin (Holick, 1994). Vitamin D deficiency is caused by insufficient sunlight exposure or low dietary vitamin D<sub>3</sub> intake (Cantorna, 2006; Mark & Carson, 2006). Recent studies link vitamin D with several autoimmune diseases, including multiple sclerosis (Cantorna & Mahon, 2004; Mark & Carson, 2006). Interest in vitamin D and MS originated from identification of a negative correlation between exposure to sunlight and prevalence of MS (Mark & Carson, 2006). The disorder is more prevalent in higher latitudes (Chaudhuri, 2004; Mark & Carson, 2006; Tajouri et al., 2005), whereas at the equator MS occurrence is near 0% (Mark & Carson, 2006). Epidemiological data also associate poor dietary vitamin D with incidence of MS (Cantorna, 2006; Mark & Carson, 2006). Vitamin D supplementation in pregnancy and early life may prevent the symptomatic manifestation of MS in later life (Chaudhuri, 2004), and, according to results by Mahon, Gordon, Cruz, Cosman and Cantorna (2003), vitamin D supplementation could be beneficial in patients with MS.

More generally, vitamin D's advantages in central nervous system have been recently studied. Vitamin D may affect to neurons and glial cells (Garcion, 2002; Eyles et al., 2003). A positive association between vitamin D level and cognitive functioning in older adults (Przybelski & Binkley, 2007) and in rats (Becker et al., 2005) has been shown. Low prenatal vitamin D has been proposed as a candidate risk factor for schizophrenia in the human (Becker, Eyles, McGrath & Grecksch, 2005; McGrath, 1999) and associated with subtle and discrete learning and memory impairments in the rat (Becker et al., 2005). Eyles, Brown, Mackay-Sim, McGrath and Feron (2003) studied the effects of mother's D<sub>3</sub>-deficiency to brain development in rats concluding that low maternal vitamin D<sub>3</sub> has important direct consequences for the developing brain at birth, but long-term consequences remained unclear. Vitamin D has also a role in preventing ischemia, Alzheimer's disease, Parkinson's disease, AIDS, infection, multiple sclerosis, and experimental

autoimmune encephalomyelitis (Garcion, Wion-Barbot, Montero-Menei, Berger & Wion, 2002). Brachet, Neveu and Naveilahan (2005) have listed neurochemical findings of vitamin D's advantages in central nervous system. They conclude that vitamin D distinctively behaves as a neuroactive compound mainly implicated in the control of brain homeostasis. According to Eyles et al. (2003), vitamin D may affect neuronal and glial population dynamics because it directly regulates the expression of several neurotrophic factors.

### **1.5 The present study**

In this study, it is hypothesized that weakened information processing speed in central nervous system caused by MS could be improved by vitamin D. An association between cognitive decline and white matter loss in MS patients has been demonstrated (e. g. Edwards, Liu & Blumhardt, 2001). Experimental data suggest that cerebral white matter is responsive to vitamin D (Chaudhuri, 2004). The generation of ERPs is partly dependent on the integrity of cerebral white matter (Newton et al., 1989) and evoked potentials can provide information on the white matter lesions load and on the disease activity (Comi, Leocani, Locatelli, Medaglioni & Martinelli, 1999). According to Compston and Coles (2002), demyelination characteristically delays the latencies of visual evoked potentials, leaving the amplitude of responses unchanged. While ERP amplitudes are sensitive to neuronal loss rather than demyelination, the interest of the present study is in possible effects of vitamin D in repairing neuronal loss. The effects of the vitamin D to ERPs have not been studied before.

The aim of the present study is to investigate, whether vitamin D improves cognitive processing in MS patients. ERP techniques are employed to detect possible covert changes in cognitive functions. Both endogenous and exogenous processes are supposed to be activated in two kinds of experiments. Attention allocation is required in an active condition, while in a passive condition no active cognitive processing is present. Subjects are detecting stimulus changes in a visual oddball paradigm and the effects on vitamin D on ERPs are measured before and ca. 24 hours after the drug intake.

In the present study, it is hypothesized that vitamin D could have positive effects to cognitive processing of MS patients. The assumption is based on the findings supporting the vitamin D's

recently noticed remarkable role in central nervous system. It is also hypothesized that changes in the ERP amplitudes would reveal possible recoveries caused by vitamin D in white matter. Recovery would be perceived in amplitudes of the ERPs. The effect of a high-dose vitamin D is tested to clarify its possible positive influence on cognitive functioning perceived in four ERP components. Early components P1 and MMN are supposed to reveal early, exogenous information processing, while endogenous components PN and P3 are supposed to reveal changes in controlled information processing. The aim of this study is threefold: (i) to clarify whether the standards and deviants are discriminated by the MS patients, (ii) to test whether the discrimination is dependent on the allocation of attention, and (iii) to clarify whether there is difference in discrimination before vitamin D intake and after it.

## 2. MATERIALS AND METHODS

### 2.1 Participants

The participants of the present study were 14 MS patients (5 men, 9 women, age range 17 years to 47 years, mean age 33 years). All of them reported having normal vision (with correction if necessary).

### 2.2 Stimuli

White rectangles (width 25 mm, height 100 mm) on a black background were used as stimulus (fig. 1). In standard and deviant stimuli, the rectangles were in 45° angles, while in a target stimulus, the rectangle was presented in a vertical position. There were 1500 stimuli per condition. There were two stimulus conditions in the experiment: an ignore condition and a target condition. In the ignore condition, deviants pseudo-randomly ( $P = 0.1$ ) replaced standards ( $P = 0.9$ ) that were repeated at 100 ms onset-to-onset intervals. In the target condition, in addition to standards ( $P = 0.8$ ) and deviants ( $P = 0.10$ ), also target stimuli ( $P = 0.1$ ) were displayed.



Fig. 1. The stimuli.

### **2.3 Procedure**

Participants were seated 80 cm away from the computer screen while two stimulus conditions were presented. During the first (ignore) condition, they were asked to attend to a story presented by a CD-player and to passively fixate to the blue cross which was continuously present in the middle of the computer screen. During the second (target) condition participants were told to push a button on the keyboard whenever they noticed a target stimulus. Half of the subjects started with rectangles inclined to right, the rest started with rectangles inclined to left. Each task took ca. 20 minutes and between the tasks the participants had a chance to stretch or correct their position for a few minutes. After the first day's experiment participants immediately took a dose of vitamin D's pre-stage (E $\alpha$ , 1 $\mu$ g). Local hospital ethics committee approval was obtained and all subjects were veraciously informed of the possible effects of the drug. After ca. 24 hours they completed the same tasks that they had completed during the first day.

### **2.4 EEG recording and data analysis**

The electroencephalogram (EEG) was recorded at Fz, Cz, Pz, Oz, O1, and O2. The electro-oculogram was recorded with two electrodes, one placed below the canthus of the right eye and the other above the centre of the right eyebrow, in order to control for the contribution of eye-blinks to EEG-signal. The reference electrode was placed to the right side of the nose. The impedances of all recording electrodes were less than 5 k $\Omega$ . Blink artefacts were corrected by a VEOG correction method. The EEG was filtered off-line between 1Hz and 30 Hz. Single EEG-sweeps (from 100 ms before to 600 ms after stimulus onset) were corrected by their baseline. Sweeps exceeding 100  $\mu$ V in any recording electrode were then discarded. The remaining sweeps were averaged separately for deviants and for standards immediately preceding the deviants.

### 3. RESULTS

The data were analyzed with four-way analyses of variance (ANOVA) [*treatment* (day 1 and 2) X *stimulus type* (standard, deviant) X *electrode site* X *condition* (ignore, target)]. If there was no treatment effect or interaction between treatment and any other factor, the measurements of two days were pooled, and a three-way ANOVA was performed.

The ERPs at 80-120 ms from stimulus onset (a P1 component) were analyzed from electrodes O1, OZ and O2. No main effect [ $F_{1,13} = 0,93$ ,  $p = 0,354$ ] or interaction effect for treatment was found. Subsequently, a repeated measures ANOVA revealed a significant main effect of stimulus type (standard versus deviant) [ $F_{1,13} = 23,63$ ,  $p < .001$ ], indicating that, over the electrodes, ERPs to deviants were negatively displaced in comparison to ERPs to standards (fig. 2a and 2b). A significant interaction between the stimulus type and electrode site [ $F_{2,26} = 6,10$ ,  $p < .01$ ] was found, indicating that the difference between ERPs to deviants and standards was unequal on different electrode sites. Paired t-tests further revealed that deviants and standards were significantly discriminated at O1 [ $t_{13} = -4,16$ ,  $p < .01$ ], Oz [ $t_{13} = -5,15$ ,  $p < .001$ ], and O2 [ $t_{13} = -5,12$ ,  $p < .001$ ], ERPs to standards being more positive than ERPs to deviants (fig. 2a and 2b). No main effect was found for condition [ $F = 1,05$ ,  $p = .323$ ], thus attention did not contribute to P1 component of the ERPs.

The ERPs at 180-220 ms from stimulus onset (mismatch negativity, MMN) were analyzed from electrodes O1, OZ and O2. No main effect [ $F_{1,13} = 0,20$ ,  $p = .665$ ] or interaction effect was found for treatment. A repeated measures ANOVA further revealed a significant interaction between the stimulus type and electrode site [ $F_{2,26} = 5,01$ ,  $p < .05$ ], indicating that the difference between ERPs to deviants and ERPs to standards on different electrode sites was not equivalent. However, paired t-tests revealed that standards and deviants were not discriminated at any occipital electrode sites, O1 [ $t_{13} = -0,68$ ,  $p = .509$ ], Oz [ $t_{13} = -0,236$ ,  $p = .817$ ], and O2 [ $t_{13} = -1,11$ ,  $p = .288$ ] (fig. 2a and 2b). There was also a significant main effect of electrode site [ $F_{2,26} = 4.54$ ,  $p < .05$ ], indicating that ERPs differed according to electrode site. No main effect was found for condition [ $F = 4,19$ ,  $p = .061$ ], indicating that attention did not contribute to the stimulus discrimination (fig. 3).

The ERPs at 260-300 ms from stimulus onset (Processing Negativity, PN) were analyzed from electrodes Fz and Cz. No main effect [ $F_{1,13} = 0,339$ ,  $p = .570$ ] or interaction effect was found for

treatment or electrode site [ $F_{1,13} = 4,51, p = .053$ ]. The measurements of two days were pooled over the electrode sites and a repeated measures ANOVA revealed a significant main effect of stimulus type (standard versus deviant) [ $F_{1,13} = 5,92, p < .05$ ]. Over the electrodes, ERPs to deviants were negatively displaced in comparison to ERPs to standards (fig. 2a and 2b). There was also a significant interaction between stimulus type and condition [ $F_{1,13} = 25,56, p < .001$ ], indicating that discrimination of standards and deviants was unequal in target and ignore conditions. Paired t-tests further revealed that ERPs to deviants and standards were significantly discriminated in the target condition [ $t_{13} = 4,11, p < .01$ ], ERPs to standards being stronger than ERPs to deviants, whereas in the ignore condition ERPs to deviants and standards were not discriminated [ $t_{13} = -0,53, p = .607$ ] (fig. 2a and 2b).

The ERPs at 370-410 ms from stimulus onset (a P3 component) were analyzed from electrodes Fz, Cz and Pz. Again, no main effect [ $F_{1,13} = 1,29, p = .277$ ] or interaction effect was found for treatment, so that the measurements of two days were pooled. A repeated measures ANOVA revealed a significant main effect of stimulus type (standard versus deviant) [ $F_{1,13} = 33,88, p < .001$ ], indicating that, over the electrodes, ERPs to deviants were negatively displaced in comparison to ERPs to standards (fig. 2a and 2b). There was also a significant main effect for electrode site [ $F_{1,14} = 5,53, p < .05$ ] That is, the ERPs did differ according to electrode site. A significant main effect was also found for condition [ $F_{1,13} = 22,69, p < .001$ ], indicating that attention did contribute to ERPs. There was also a significant interaction between stimulus type and condition [ $F_{1,13} = 5,07, p < .05$ ], indicating that standards and deviants were discriminated differently between ignore and target condition (fig. 3). Paired t-tests further revealed that standards and deviants were significantly discriminated both in ignore condition [ $t_{1,13} = -5,988, p < .001$ ] and in target condition [ $t_{1,13} = -4,747, p < .01$ ]. ERPs in target condition were more positive than ERPs in ignore condition (fig. 2a and 2b).

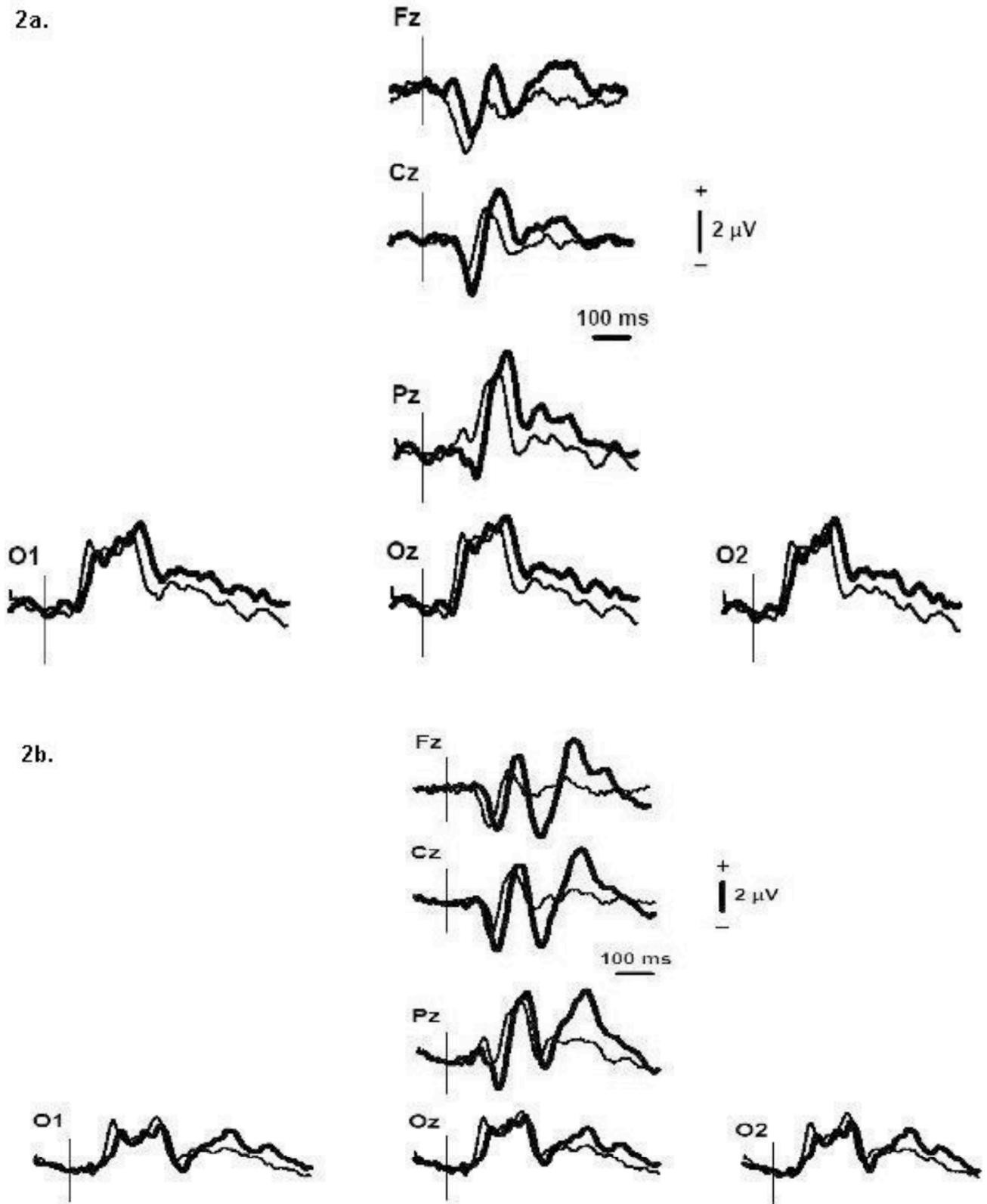


Fig. 2a and 2b. Grand-averaged ERPs to standard (thin line) and deviant (thick line) stimuli in the ignore condition (a) and in the target condition (b). Vertical axes indicate stimulus onset.

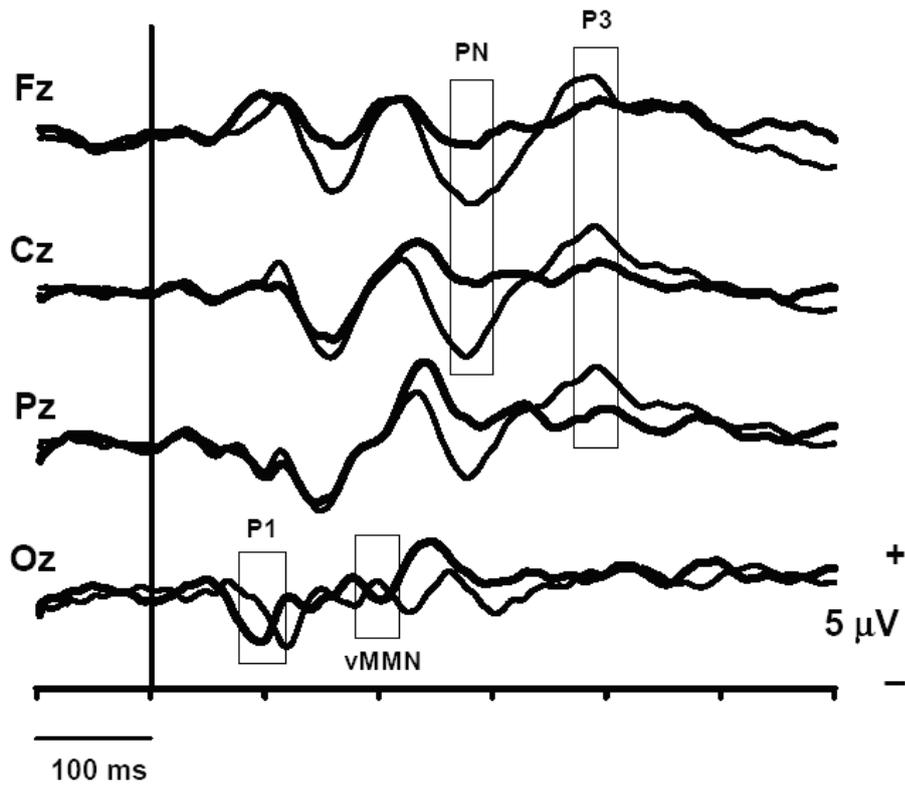


Fig. 3. Grand-averaged difference ERPs (deviant ERPs - standard ERPs) in the target (thin line) and ignore (thick line) conditions. The vertical axis indicates stimulus onset and the rectangles show the time windows for the data upon which the statistical analyses were applied.

## 4. DISCUSSION

### 4.1 ERP findings

In the present study, the effects of a vitamin D's prestage Etalpa to the cognitive processing of MS patients were investigated. An oddball paradigm was employed to discover possible differences in the amplitudes of the ERP components before and after the drug intake. On the whole, the aim of this study was threefold: The first aim was to investigate, whether the participants' responses discriminate the frequently presented standard stimuli from the infrequently presented deviant stimuli. The results indicate that three ERP components of the MS patients out of four discriminated between the standards and deviants. The early visual MMN, however, was not elicited. The second aim was to investigate, whether allocation of attention has an effect on the discrimination in the patients with MS. Results were consistent with previous findings considering ERPs in the patients with MS (e.g. Aminoff & Goodin, 2001), showing that early exogenous components (P1 and MMN) did not show any sensitivity for cognitive effort, while subsequent endogenous components (PN and P3) did. Most importantly, the third aim was to investigate whether the intake of vitamin D influences to the discrimination. There were no significant differences in the P1, MMN, PN or P3 amplitudes before and after the drug intake.

P1 amplitude was measured to find out if the standard and deviant stimuli were discriminated and whether the attention allocation influenced to the discrimination. A P1 wave was elicited and standards and deviants were discriminated. Attention allocation did not contribute to the discrimination. Since P1 is an early exogenous component expressing pre-attentive processing of information, the result was presumed. While conscious detection did not contribute to the discrimination, some other qualities of attention do affect to the P1 amplitude. Effects of attention to the P1 component have been studied and results have been diverse. One reason for the diverse results is that the nature of the attention has an effect to the amplitude of the P1 component. For example, a temporally cued stimulus elicits a larger P1 than an unattended stimulus (Correa et al., 2006), and parafoveal (above fixation) target location increases the P1 amplitude compared to foveal (fixation) target location (Handy & Khoe, 2005). In the present study, the gaze was fixed to the foveal target location both in active and passive condition. The appearance of the deviant and standard stimuli was regular (ISI = 500 ms) while the timing of presentation of the deviant stimuli was randomized. These qualities of the stimulus setting may have affected to the amplitudes of the P1 component, but conscious observation did not.

Mismatch negativity was measured to assess pre-attentive detection mechanism in the visual modality in patients with MS during a passive and active oddball condition. The extinction of the MMN suggests that patients with MS are prone to pre-attentive visual information processing deficits. Results are consistent with those by Jung et al. (2006). In their study, MMN reduction was perceived in MS patients in auditory modality. According to Comi et al. (1998), the absence of ERP responses, if persistent for some months, is indicative of an axonal degeneration. In accordance with previous findings (Picton & Hillyard, 1988; Kujala et al., 2007; Laamanen, 2004; Gaeta et al., 2001), allocation of attention did not affect the MMN. Kathmann et al. (1999) also remark that the MMN to frequency deviants is not severely affected by the withdrawal of attentional resources.

Controlled information processing in patients with MS was measured by later endogenous components PN and P3. Processing negativity is associated with selective attention, and it is best obtained by comparing a component elicited in a passive condition with one elicited under active observation (Näätänen, 1992). In the present study, the processing negativity for standard and deviant stimuli was measured both in active and passive condition. Standards and deviants were discriminated in active condition, while in passive condition no discrimination occurred. Diminished amplitudes in P3 component in MS patients have been shown earlier and they have been associated with possible cognitive decline (e. g. Ruchkin et al., 1994; Polich et al., 1992; Aminoff & Goodin, 2001). In this study, a P3 wave sensitive to stimulus change and attention allocation was discovered. Although the effect of the attention allocation was not significant, the change occurring in the stimuli was better perceived in active condition than in passive one.

The results of the present study suggest that MS disease has altered pre-attentive information processing, manifested by extinction of early exogenous ERP component visual MMN. No control group was involved, but the existence of visual MMN in healthy subjects is established before (e. g. Pazo-Alvarez et al., 2003; Tales et al., 1999; Laamanen, 2004; Horimoto et al., 2002). Later components associated to active information processing, however, were elicited. In this study, both endogenous and exogenous mechanisms were present. In the ignore condition, exogenous mechanisms were supposed to be activated by asking subjects to passively follow a stream of randomized stimuli and listen to a story from a CD-player. Respectively, cognitively active endogenous mechanisms were supposed to be activated in the target condition, when subjects were instructed to observe the stimuli and to respond to the target stimuli by tapping a space bar at the keyboard.

According to Aminoff and Goodin (2001), any observed latency prolongation in MS patients could be either the result of subcortical demyelination or demyelination in an afferent pathway leading to the brain. They remark that an observed ERP change can derive from either of the damages, while cognitive dysfunction is only associated to the central demyelination. They suggest that the changes in the later ERP components are not simply the result of alterations in the primary afferent pathways but are the consequence of central demyelination. The elimination of the MMN in the present study may thereby reflect demyelination both in the primary afferent pathways and in the central nervous system. The existence of later components PN and P3 was shown, but possible alterations in their amplitudes could not be examined due to the absence of a control group.

## **4.2 Reliability**

To assess the reliability of the present study, some matters of reliability of ERP techniques must be considered proportioned to this study. ERP techniques are an objective tool to assess cognitive functions, because motivational and emotional factors do not affect to the measurements the way they may, for example, contribute to psychological testing. According to Aminoff and Goodin (2001) and Comi et al. (1998), the recording of ERPs may provide a useful tool as an aid in the evaluation of response in treatment. In addition, Fuhr and Kappos (2001) state that evoked potentials are suitable as objective outcome measure in therapeutic trials even with relatively small patient numbers. In the present study, the ERPs were used to assess a treatment effect of vitamin D to the information processing deficits in MS patients. The number of patients was quite small, but it was sufficient for this kind of clinical purposes. A 3-stimuli paradigm (standard, deviant, and target) recommended by Magnano (2006) was employed. In this study, no control group was involved. The comparison is solely based on the measurements of the amplitudes before and after the drug intake in the patients of MS.

ERP abnormalities observed in MS patients may consist of a delay of latency of one or more components, morphological abnormalities, wave cancellation and increased refractory period (Comi et al., 1999). However, there are some standpoints to take into account when considering the measurements. Firstly, even if an experimental manipulation has no effect on the ERP, we cannot conclude that it does not influence brain processes, because it is possible that a sizeable portion of

the information-processing transactions that occur after or before the anchor event are silent as far as ERPs are concerned (Coles et al., 1990). According to Comi et al. (1998), the origin of ERP abnormalities in MS is complex and not completely understood. Amplitude reduction or absence of an expected wave may also occur because of technical problems and in order to be accepted they have to be consistently repeated in repeated exams (Comi et al., 1998). Clinical symptoms and ERP findings often change independently in MS patients, a complex interplay of degenerative and regenerative processes being typical for the disease (Comi et al., 1999). That is why the longitudinal studies can be questioned. In the present study, however, such alterations in generative processes could have not taken place because of the short period between the measurements.

### **4.3 Conclusions and further investigation**

In the present study, it was hypothesized that vitamin D could have positive effects to cognitive processing in MS patients. No effects for treatment, however, were found in this experiment. Differing from the prior drug studies in MS patients employing ERP techniques, in this study the main interest was to investigate the amplitude alterations instead of the latency alterations. Diminished amplitudes in MS patients have been found in earlier studies (e. g. Ruchkin et al., 1994; Polich et al., 1992; Aminoff & Goodin, 2001), associated with a failure in the activation of some generators (Magnano et al., 2006).

Early diagnosis, rehabilitation and treatment are important for MS patients. According to Liu et al. (1999), there is adaptive capacity of neuronal systems and plasticity of the brain during early stages of multiple sclerosis. Furthermore, Kuhlmann, Lingfeld, Bitsch, Schuchardt and Brück (2002) remark that an acute axonal damage within multiple sclerosis lesions is highest during the initial stages of the disease and a treatment aimed at axon protection should be started as early as possible and should be continued for at least some years. Investigating possible remedies for cognitive decline caused by multiple sclerosis is essential. Cognitive dysfunction affects patients' quality of life (Achiron & Barak, 2006), and impacts social activities (Sartori & Edan, 2006). Limitations in patients' work and social activities are also in association with the extent of cognitive impairment, independent of degree of physical disability (Amato, Ponziani, Siracusa, & Sorbi, 2001), the cognitive disturbance on everyday activities probably being the most critical question from the

patients' vantage point (Amato et al., 1995). According to Amato et al. (2006), however, very little is known about effective strategies for managing cognitive decline in MS patients.

Further investigation of vitamin D's effects to the cognitive processing in MS patients is thus recommended. Patients at the early stage of the disease could be recruited and medication could be carried out for a longer period. An oddball paradigm design utilized in the present study has turned out to be viable for eliciting desired components. Instead of the amplitudes of the ERP components, the latencies of the late components, especially P3, could be dissected. Comparison with a healthy control group is also recommended to assess the differences between P3 latencies before and after the medication in patients and controls. Finally, the effects to the MMN could be investigated in comparison with a control group.

### **Acknowledgements**

The author thanks Dr. Piia Astikainen for drawing figures 2a, 2b, and 3.

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