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ORIGINAL ARTICLE

Lack of Visual Habituation in Multiple Sclerosis: An Electrophysiological Study*

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ABSTRACT

In this study, we aimed to investigate habituation of pattern-reversal visually evoked potentials (VEPs) in patients with relapsing remitting (RR) multiple sclerosis (MS). Twenty-one patients with this diagnosis and with a history of optic neuritis (ON), 29 such patients without a history of ON, and 25 normal controls were enrolled to study. One eye of each patient in the group with a history of ON and one eye of each subject in the control group was randomly selected. In the group with a past history of ON, the affected eye of the patients was selected in unilateral cases and the eye in which showed the greater latency delay of the P100 component in bilateral cases. P100 amplitudes were determined by visual inspection in 10 blocks of 512 responses and habituation was analysed as the percentage amplitude change between the 1st and 2nd–10th blocks. Amplitude of the P100 component of the VEP showed a significant clear-cut habituation after the first block in the control group but neither patient group showed a significant decrease in P100 amplitude. We conclude that our electrophysiological study has shown a lack of habituation in patients suffering from RR MS. This result could be important for the evaluation of visual system involvement in patients with MS, with or without a previous history of ON.

Keywords: Cortical responses, habituation deficit, relapsing remitting multiple sclerosis, visually evoked potentials

INTRODUCTION

In healthy subjects, the amplitude of evoked cortical responses normally decreases with repetitive presentation of a stimulus. This phenomenon is commonly referred to as habituation.[1] Habituation is also defined as a behavioural response that results from repeated stimulation and that does not involve sensory adaptation, sensory fatigue nor motor fatigue.[2] The mechanism of habituation is still not well understood. Many studies refer to habituation as a ''simple'' form of learning.[3] However, the physiological processes underlying habituation is not simple. Habituation requires a rich collection of cellular mechanisms involving different types of neurons, and stimulus paradigms that are differentially recruited in different parts of the nervous system.[1,3] In humans, habituation is studied through evoked potential stimulation and manifests as a reduction in the amplitude of the evoked response to repeated stimulation. Visual habituation has been consistently reported to be impaired in migraine and this impairment is considered a neuro-physiological hallmark of dysregulation of cortical sensory information processing; the subcortical activating system and reduced efficiency of intracortical inhibitory circuits have been implicated in the process.[4]

Visual habituation studies have been performed on other neurological conditions such as familial hemiplegic migraine and photosensitive epilepsy[5] but to our knowledge there is no study focusing on habituation patterns in multiple sclerosis (MS) patients. It is well known that, when properly performed, the visually evoked potential (VEP) can

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contribute important information on visual pathways in patients with optic neuritis (ON); MS; optic nerve and chiasm compressive lesions; non-compressive lesions affecting the visual pathways; and neurodegenerative diseases not primarily involving the visual pathways.[6] From the previous studied reviewed above, we hypothesise that disseminated lesions of the central nervous system in MS patients would affect visual habituation. Our study therefore aims to investigate habituation of the pattern-reversal VEP (PR-VEP) in relapsing remitting (RR) MS patients.

MATERIALS AND METHODS

Participants

Twenty-five healthy subjects and fifty patients who were diagnosed as definite RRMS according to the modified McDonald criteria 2010[7] were included to this study. All of the patients were in the remission phase of the disease which means the time elapsed from the patient's last attack was at least one month. Healthy volunteers were recruited from hospital and laboratory staff. Patients taking medication other than immunomodulators were not included in the study. Recorded parameters for the statistical analysis were as follows: age, gender, Expanded Disability Status Scale (EDSS) score, number of attacks, and history of ON. Informed consent was obtained from both the patients and healthy subjects. The study was conducted in accordance with the declaration of Helsinki and was approved by the Ethical Committee of University.

The patient group was classified according to existence of history of ON. The patients with a history of ON were classified as group 1 (WON) and the patients without a history of ON were classified as group 2 (WOON). One eye of each patient in the WOON and control group was randomly selected. In WON group, the affected eye of the patients was selected in unilateral cases and the worse affected eye according to VEP-P100 latency values was selected in bilateral cases.

Experimental Design and Recordings

Our VEP testing conditions were concordant with the International Society for Clinical Electrophysiology of Vision standards.[8] Patients were examined in a quiet room with dimmed light (30 Lux). For VEP recordings subjects were seated 1 m away from a television monitor and laboratory testing was performed by a computerised electromyography system (Medelec/Teca Premier Plus, England). Stimuli were presented as a checkerboard pattern of black and white squares. With one eye patched, subjects were instructed to look to a point in the middle of the screen. Needle electrodes were inserted into the scalp in the midline over the occipital region 2.5 cm above the inion (Oz: active electrode) and over the frontal region (Fz: reference). The ground electrode was placed on the forearm. During uninterrupted stimulation sequential blocks of 512 responses were averaged (band pass 1 ± 100 Hz, analysis time 200 ms). The conditions were 2.0 reversals per second with 0.23 cm check size. Ten blocks of 512 responses were analysed in terms of peak latencies and peak-to-peak amplitudes of the maximal negative and positive deflections determined by visual inspection: the N75 peak was defined as the most negative point, P100 as the most positive point following N75, N145 as the second most negative point following the P100. We analysed the 10 blocks of PR-VEP responses in terms of P100 amplitudes. Habituation was analysed as the percentage of amplitude change between the 1st and 2nd–10th blocks.

Statistical Analyses

We used the Kruskal–Wallis test to compare variables within three groups and the Mann–Whitney *U* test and *t*-test for between group comparisons and the paired samples test for within group comparisons.

RESULTS

Our study groups were consisting of 50 RRMS patients and 25 healthy subjects. Mean age of the patient group was 35.9 ± 11.4 years mean age of the control group was 35.3 ± 9.1. Sixty-four percent of the patients and 69.6% of the control group was female, 36.0% of the patients and 30.4% of the control group was male. There was no statistically significant difference in mean age and gender proportion between groups. The mean EDSS score was 1.4 ± 1.3 and the mean number of relapses was 3.0 ± 1.2 in the RRMS patients. The proportion of patients who had a history of ON was 41% ($n = 21$) with a history of right and left ON being found in 33.3% ($n = 7$), a history of only right ON was found in 33.3% ($n = 7$) and a history of only left ON in 33.3% ($n = 7$) of these patients.

On VEP examinations, the mean value of VEP-P100 latency was 124.4 ± 13.8 ms in WON group, 108.4 ± 14.7 ms in WOON group and 101 ± 5.8 ms in the control group. The differences were statistically significant (p value <0.001). Further intergroup comparisons between WON and WOON groups, WON and control groups and WOON and control groups showed significant difference between all groups (p values, respectively, 0.016, <0.001, and 0.002).

TABLE 1 Mean - VEP-P100 amplitude of blocks in the groups.

Blocks Mean VEP-P100 amplitude amplitude (μV ± SD)	WON ($n = 21$)	WOON ($n = 29$)	Control ($n = 25$)
Block 1	6.29 ± 3.19	5.86 ± 3.24	7.56 ± 3.75
Block 2	6.04 ± 3.42	6.43 ± 3.33	7.01 ± 3.13
Block 3	5.39 ± 2.29	5.51 ± 2.83	7.32 ± 3.14
Block 4	5.79 ± 2.79	5.25 ± 2.69	6.45 ± 3.16
Block 5	6.05 ± 2.83	5.14 ± 2.62	6.60 ± 2.88
Block 6	5.69 ± 3.13	5.43 ± 2.92	6.54 ± 3.34
Block 7	5.64 ± 3.39	5.19 ± 2.74	6.65 ± 3.28
Block 8	5.38 ± 3.1	5.12 ± 3.0	6.64 ± 3.55
Block 9	5.65 ± 2.92	5.57 ± 3.13	6.39 ± 3.78
Block 10	5.53 ± 3.21	5.27 ± 2.59	6.45 ± 3.12

WON; patients with ON, WOON; patients without ON.

TABLE 2 Ratios of 2nd–10th blocks' VEP-P100 amplitude to 1st block's VEP-P100 amplitude and significance (p) values of group comparisons.

	Ratio/p value		
Blocks	WON	WOON	Control
Block 2/Block 1	0.95/0.736	1.29/0.067	0.93/0.013
Block 3/Block 1	0.93/0.576	1.04/0.473	0.89/0.016
Block 4/Block 1	0.98/0.903	1.17/0.109	0.84/0.004
Block 5/Block 1	1.01/0.922	1.00/0.762	0.88/0.038
Block 6/Block 1	0.89/0.145	1.13/0.131	0.84/0.003
Block 7/Block 1	0.90/0.400	1.07/0.618	0.85/0.004
Block 8/Block 1	0.91/0.365	0.94/0.514	0.86/0.003
Block 9/Block 1	0.94/0.573	1.03/0.649	0.84/0.018
Block 10/Block 1	0.89/0.534	0.93/0.378	0.86/0.041

WON; patients with ON, WOON; patients without ON

The difference of the mean VEP-P100 amplitudes in the ten blocks was not significantly different between the patient group and the control group. Table 1 shows the mean values of the peak-to-peak VEP-P100 amplitudes in 10 blocks of averaged responses of WON, WOON and control groups.

Habituation was analysed as the amplitude change between the 1st and 2nd–10th blocks in three groups. For statistical analysis the ratio of the 2nd–10th blocks to the 1st block was calculated and the paired sample test was used for within group comparisons. We found that the VEP-P100 amplitudes showed a significant clear-cut habituation after the first block in the control group but a significant decrease in the VEP-P100 amplitudes was found in neither the WON nor the WOON groups.

Ratios of the VEP-P100 amplitude of the 2nd–10th blocks to the VEP-P100 amplitude of the 1st block and significance (p) values of group comparisons are shown in Table 2. Typical VEP examinations of a patient with history of ON (WON) and of a healthy subject are shown in Figures 1 and 2.

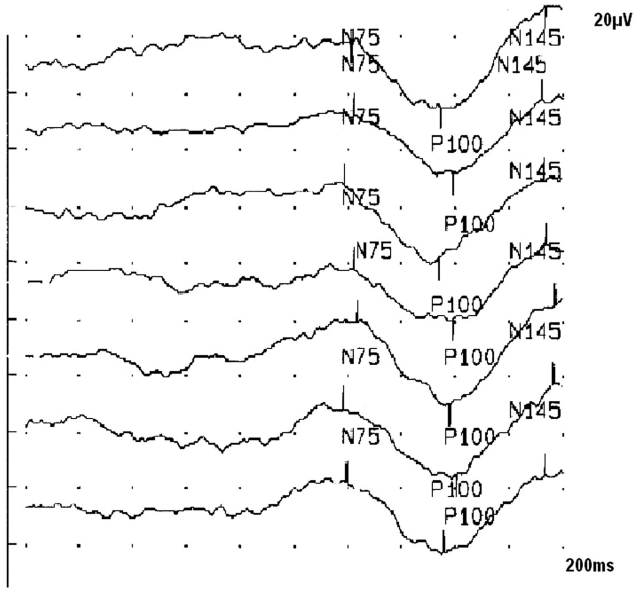

FIGURE 1 Lack of habituation and prolonged P100 latency in a patient with MS.

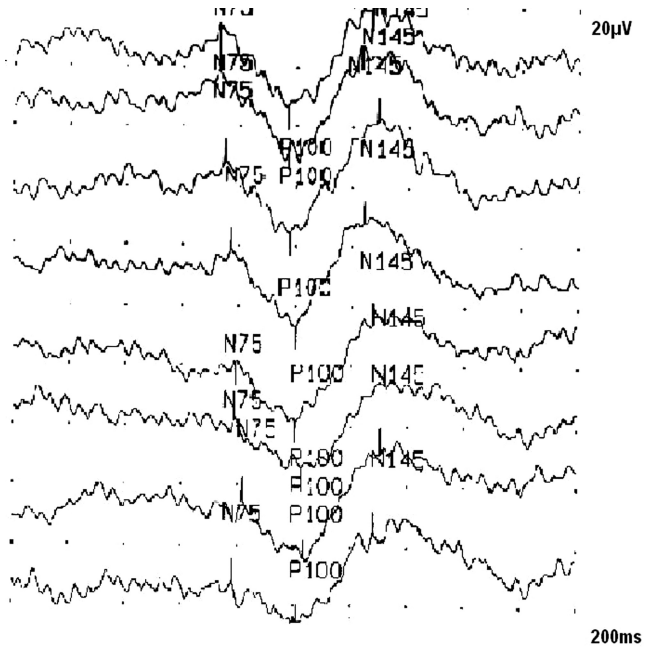

FIGURE 2 Typical habituation pattern in a healthy subject.

DISCUSSION

To the best of our knowledge, this is the first study to search for a visual habituation deficit in RRMS patients. In this study, we found that MS patients did not show a significant habituation to a visual stimulus using PR-VEP. During visual stimulation there is a local increase of cerebral blood flow together with glucose utilization in the activated cortex. After prolonged stimulation this increase tends to drop.[8,9]

Our results suggest either a direct or an indirect cortical activity deficit in the MS patients.

Habituation in normal subjects has been frequently reported[10,11] although the underlying mechanisms are still unknown. Healthy subjects showing normal activation levels of sensory cortex rapidly reach maximal response activity during repeated sensory stimulation and show habituation.[12] In our opinion, lack of visual habituation may be due to both defective cortical neuronal activity and disturbed visual sensorial systems in MS patients.

Although habituation is a complex neurobiological phenomenon, it might depend crucially, for cortical evoked potentials, on the cortical preactivation excitability level.[13] Thus the habituation deficit of patients may reflect cortical pathology in MS. It is well-known that disability shows a correlation with cortical atrophy in MS[14] and to perform PR-VEP studies, which may be more easily accessible and practical in neurology clinics than neuroimaging, may be helpful in predicting cortical functional deficits. In addition habituation is defined as a behavioural response decrement that results from repeated stimulation and that does not involve sensory adaptation/sensory fatigue nor motor fatigue.[3] Therefore to investigate habituation in MS could be more useful in the assessment of cortical functions of MS patients than neuro-cognitive tests which are easily affected by fatigue of the patients.

Habituation of event-related potentials has been reported for the auditory and visual systems and cognitive functions. Lack of habituation is reported in interictal migraine patients and this result was interpreted as demonstrating an the interictal abnormality of sensory processing in migraineurs.[15] As our study is the first showing lack of habituation in MS patients, we can do no more than speculate on the mechanism of habituation loss in MS.

As habituation may be considered a form of learning, it could be influenced by changes in the interplay between GABA, NMDA, and cholinergic receptors.[4] MS is characterised by dissemination of lesions both in time and space.[16] Such disseminated lesions may disrupt multiple brain areas responsible for normal habituation phenomena. It has been suggested that different properties such as check size and reversal rate of the magnocellular and parvocellular systems may be important for PR-VEP habituation[17] but in our study, we used the same laboratory and electrophysiological procedures for both patient and control groups.

CONCLUSION

To summarise, our electrophysiological study has demonstrated a lack of the normally seen habituation is RRMS patients. MS patients without a history of ON also show a lack of habituation. As visual system involvement is one of the red flags for MS this test may be used for patients who are in the early phase of the disease to evaluate the visual systems.

One limitation of our study is that we included only definite RRMS patients. To include a different patient group with isolated ON without MS would be informative and to perform the VEP examinations in different time periods of the disease would be helpful in understanding the pathological process of the habituation loss. Furthermore additional studies would be necessary to elucidate the pathophysiological mechanism underlying the visual habituation deficit in MS.

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REFERENCES

[1] Thomas E, Sandor PS, Ambrosini A, Schoenen J. A neural network model of sensitization of evoked cortical responses in migraine. *Cephalalgia* 2001;22:48–53.

[2] Judit A, Sandor PS, Schoenen J. Habituation of visual and intensity dependence of auditory evoked cortical potentials tends to normalise just before and during the migraine attack. *Cephalalgia* 2000;20:714–719.

[3] Rankin CH, Abrams T, Barry RJ, Bhatnagar S, Clayton DF, Colombo J, Coppola G, Geyer MA, Glanzman DL, Marsland S, McSweeney FK, Wilson DA, Wu CF, Thompson RF. Habituation revisited: an updated and revised description of the behavioral characteristics of habituation. *Neurobiol Learn Mem* 2009;92:135–138.

[4] Palermo A, Giglia G, Vigneri S, Cosentino G, Fierro B, Brighina F. Does habituation depend on cortical inhibition? Results of a rTMS study in healthy subjects. *Exp Brain Res* 2011;212:101–107.

[5] Brazzo D, Di Lorenzo G, Bill P, Fasce M, Papalia G, Veggiotti P, Seri S. Abnormal visual habituation in pediatric photosensitive epilepsy. *Clin Neurophysiol* 2011; 122:16–20.

[6] Cohen SN, Syndulko K, Tourtellotte WW. Clinical applications of visual evoked potentials in neurology. *Bull Los Angeles Neurol Soc* 1982;47:13–29.

[7] Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;69:292–302.

[8] Odom JV, Bach M, Brigell M, Holder GE, McCulloch DL, Tormene AP, Vaegan. ISCEV standard for clinical visual evoked potentials (2009 update). *Doc Ophthalmol* 2010; 120:111–119.

[9] Kremlacek J, Kuba M, Kubova Z, Langrova J, Vit F, Szanyi J. Within-session reproducibility of motion-onset VEPs: effect of adaptation/habituation or fatigue on N2 peak amplitude and latency. *Doc Ophthalmol* 2007;115: 95–103.

[10] Afra J, Cecchini AP, De Pasqua V, Albert A, Schoenen J. Visual evoked potentials during long periods of pattern-reversal stimulation in migraine. *Brain* 1998; 121:233–241.
[11] Brighina F, Piazza A, Daniele O, Fierro B. Modulation of visual cortical excitability in migraine with aura: effects of 1 Hz repetitive transcranial magnetic stimulation. *Exp Brain Res* 2002;145:177–181.
[12] Schoenen J. Deficient habituation of evoked cortical potentials in migraine: a link between brain biology, behavior and trigeminovascular activation? *Biomed Pharmacother* 1996;50:71–78.
[13] Ambrosini A, Schoenen J. The electrophysiology of migraine. *Curr Opin Neurol* 2003;16:327–331.
[14] Calabrese M, Rinaldi F, Grossi P, Gallo P. Cortical pathology and cognitive impairment in multiple sclerosis. *Expert Rev Neurother* 2011;11:425–432.
[15] Obrig H, Israel H, Kohl-Bareis M, Uludag K, Wenzel R, Müller B, Arnold G, Villringer A. Habituation of the visually evoked potential and its vascular response: implications for neurovascular coupling in the healthy adult. *Neuroimage* 2007;17:1–18.
[16] Fox RJ. Picturing multiple sclerosis: conventional and diffusion tensor imaging. *Semin Neurol* 2008;28:453–466.
[17] Omland PM, Nilsen KB, Sand T. Habituation measured by pattern reversal visual evoked potentials depends more on check size than reversal rate. *Clin Neurophysiol* 2011; 122:1846–1853.