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Attention orienting dysfunction with preserved automatic auditory change detection in migraine

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HIGHLIGHTS

- The mismatch negativity (MMN) is normal in migraine patients.
- The N1 orienting component and the N2b are increased in migraine patients.
- Auditory processes up to attention triggering are preserved in migraine patients.
- Attention orienting to sound income and sound deviance are exacerbated in migraine.
- These observations suggest abnormal activation of attention-related frontal networks.

ABSTRACT

Objective: To investigate automatic event-related potentials (ERPs) to an auditory change in migraine patients.
Methods: Auditory ERPs were recorded in 22 female patients suffering from menstrually-related migraine and in 20 age-matched control subjects, in three sessions: in the middle of the menstrual cycle, before and during menses. In each session, 200 trains of tone-bursts each including two duration deviants were presented in a passive listening condition.
Results: In all sessions, duration deviance elicited a mismatch negativity (MMN) showing no difference between the two groups. However, migraine patients showed an increased N1 orienting component to all incoming stimuli and a prolonged N2b to deviance. They also presented a different modulation of P3a amplitude along the menstrual cycle, which tended to normalise during migraine attacks. None of the studied ERP components showed a default of habituation.
Conclusions: This passive paradigm highlighted increased automatic attention orienting to auditory changes but normal auditory sensory processing in migraineurs.
Significance: Our observations suggest normal auditory processing up to attention triggering but enhanced activation of attention-related frontal networks in migraineurs.

1. Introduction

Migraine is one of the most common headache disorders and affects 11% of the adult population (Stovner et al., 2007). Attacks are characterised by recurrent throbbing headaches accompanied by nausea, vomiting, photophobia, and/or phonophobia and are aggravated by movements (ICHD, 2004). Between attacks,

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migraine patients may also show a hypersensitivity to visual, auditory, or olfactory stimuli (Main et al., 1997, 2000). Moreover, sound/light-induced headaches are frequent in migraine patients (Vingen et al., 1999; ICHD, 2004). The pathophysiological basis of such hypersensitivity to external stimuli is currently not completely elucidated.

In line with these symptoms, electrophysiological studies have revealed changes in cortical excitability between migraine attacks. Increased attention orienting to new incoming stimuli had been long ago demonstrated in migraine patients. The initial (or early) contingent negative variation (iCNV), which reflects the orienting properties of a warning stimulus in an active paradigm, has been found to be increased in migraine (Maertens de Noordhout et al., 1986), preferentially just before an attack (Kropp and Gerber, 1998), but not systematically (Böcker et al., 1990; Mulder et al., 2001). A default in the habituation of several event-related potentials (ERPs) to visual and auditory stimuli has also been observed in migraine patients in numerous studies (for a review, see Coppola et al., 2009), although not systematically (Oelkers et al., 1999; Sand and Vanagaite, 2000; Omland et al., 2013). Using an auditory habituation paradigm made of small consecutive trains of tones (Woods and Elmasian, 1986), we also found normal habituation pattern of the sensory N1 in migraineurs (Demarquay et al., 2011). Interestingly, this passive paradigm allowed to investigate the automatic response to the first stimuli of stimulation trains, and revealed that migraine patients exhibited a drastically augmented N1 orienting component, a fronto-central negative component appearing after the obligatory sensory N1 when the inter-stimulus interval is greater than 4 s (Näätänen and Picton, 1987; Alcaini et al., 1994). The response to standard stimuli inside the trains also exhibited enhanced negative potentials in the descending slope of the N1 wave. By comparison with the augmented N1 orienting component observed in response to the first stimuli of the trains, we called this additional component "residual orienting component" and we concluded that migraine patients showed exacerbated attention orienting not only to first stimuli after a silent gap but also to repeated similar incoming stimuli.

The electrophysiological studies described above showed abnormal responses not only to attended warning stimuli but also to passively endured stimuli. They emphasized attention-orienting exacerbation and/or habituation deficit in migraine without clearly disentangling basic auditory processing dysfunction and abnormal orienting processes. The use of passive oddball paradigms is of particular interest here because it allows studying both automatic sensory responses to auditory changes and automatic attention triggering. Indeed, in those paradigms, a rare and random change in repetitive stimulation elicits a negative response (mismatch negativity or MMN) disclosed when the response to the standard is subtracted from the response to the deviant. MMN is attributed to discriminative processes using memory traces developed from the previous stimulation (review in Näätänen et al., 2001, 2007, 2011). It is noteworthy that the memory traces probed by the MMN are thought to reflect the outcome of perceptual processing (Näätänen and Winkler, 1999; Näätänen et al., 2011) and further that MMN occurs automatically, even if subject's attention is not directed to the sounds (Näätänen et al., 1993). Nevertheless, if deviant stimuli are salient enough, attention-orienting processes can be triggered, and an N2b–P3a complex (brain orienting response) is further obtained following the MMN (Näätänen et al., 1982). In contrast, presenting a second consecutive deviant drastically diminishes the MMN (and subsequent orienting responses), which has been called "short-term habituation of the MMN" (Sams et al., 1984). This phenomenon was explained by the simultaneous occurrence, for the repeated deviant, of mismatch processes with the (declining) neuronal model of the standard and match processes with the neuronal model of the deviant. Altogether, the study of ERPs triggered by a rare change in auditory stimulation thus offers the advantage to assess, in a passive listening situation, the integrity of pre-attentive stages of perceptual processing, as indexed by the MMN, as well as the automatic triggering of attention, indexed by the N2b–P3a complex. For these reasons, passive auditory oddball paradigms have been used in a very large number of ERP studies in various pathologies (review in Näätänen, 2003; Näätänen et al., 2012), but surprisingly very rarely in migraine.

Indeed, most of the oddball paradigm studies in migraine have required an active detection of deviant tones and they mainly focused on the P300 in response to targets, which was found to be altered in migraine patients (Drake et al., 1989; Mazzotta et al., 1995; Wang et al., 1995). The investigation of brain mechanisms to a stimulus change during passive listening has been rarely reported in migraine patients. Only one study investigated the MMN in adult migraineurs and reported increased N1 and MMN latencies, suggesting a hypo-activity of automatic cortical processes (de Tommaso et al., 2004). Two recent paediatric migraine studies also pointed to subtle MMN alterations in these patients (Valeriani et al., 2009; Korostenskaja et al., 2011). One study (Wang and Schoenen, 1998) explored the amplitude of an N2–P3a complex in response to deviant stimuli and reported for migraine patients a potentiation of this response in successive blocks, contrasting with a habituation in controls.

The aim of the present study was thus to investigate the specific response to deviant stimuli in migraine patients, from the pre-attentive processes (MMN) to the attention-orienting processes (N2b, P3a), and to assess the habituation of the different components. Abnormalities of the MMN would suggest dysfunction in basic auditory processing of migraine patients. In light of our previous results, we expected a pathological brain orienting response to deviants.

2. Methods

The present analysis is the second part of a larger auditory ERP study conducted in migraineurs using small trains of repeated standard tones with occasional deviant stimuli. The first part of the analysis focused on the responses to standards and their habituation patterns (Demarquay et al., 2011). Here we explore the response to deviant stimuli.

2.1. Migraine patients and healthy subjects

Twenty-two female migraine patients suffering from menstrually-related migraine without aura (A1.1.2 in ICHD 2004) were included in the study (mean age ± SD: 27 years ± 7; disease duration: 12 years ± 8; attack frequency: 2 ± 1 per month). Migraine patients and controls were recruited through advertising in Lyon University and INSERM administration. A neurologist (CF, FB or GD) subsequently examined eligible subjects.

Twenty age-matched female controls participated in the study (28 years ± 9). Exclusion criteria for all subjects included chronic daily headache, known morphological brain abnormality, current substance abuse, and migraine preventive medication. 14 migraine patients and 11 controls took oral contraceptives ($\chi^2 = 0.0649$, $p = 0.799$).

All subjects gave their written informed consent (CCPPRB centre Léon-Bérard, Lyon, A 06-107, 04/20/06) and were remunerated for their contribution.

2.2. Recording procedure

The recording procedure has been described in detail previously (Demarquay et al., 2011).