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Top–down control of visual cortex in migraine populations

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ABSTRACT

The pathophysiology of migraine includes a heightened excitability of visual cortex that persists between headache events and that has been linked to impaired inhibitory intracortical processes. Here we examined the hypothesis that this cortical pathophysiology would affect the top–down attentional control of visual cortex. We asked two groups of participants—migraineurs ($N = 29$) and non-migraine controls ($N = 29$)—to perform a probabilistic spatial orienting task as we measured visual sensory cortical responses via event-related potentials (ERPs). Data were then analyzed as a function of whether the ERP-eliciting stimulus was in the fovea vs. parafovea, and whether the stimulus' location was attended or unattended. In this regard, we found two key between-groups differences in the effect of attention on sensory-evoked visual-cortical activity. First, relative to controls, migraineurs showed a larger attention effect in the visual N1 ERP component for events at the fovea. Second, unlike controls, migraineurs showed no early-phase attention effect in the P1 ERP component for events in the parafovea. Despite these altered ERP responses in migraineurs, however, corresponding behavioral data indicated that they also had heightened response performance. Taken together, our results support the hypothesis that migraineurs have an altered top–down attentional control of visual cortex, with the data suggesting that the effect may be tied to a reduced ability to suppress sensory-evoked activity for unattended events in the visual periphery.

1. Introduction

Although migraine is medically classified as a headache disorder, a key part of its pathophysiology is a heightened excitability of visual cortex that chronically persists in between headache events (e.g., Aurora & Wilkinson, 2007; Pietrobon, 2005). Most notably, migraineurs show reduced sensory habituation to repetitive visual stimuli as measured via visual-evoked potentials. Whereas the amplitude of visual-evoked components to repeated stimuli normally diminish over time, migraineurs show no evidence of this sensory attenuation (e.g., Afra, Cecchini, De Pasqua, Albert, & Schoenen, 1998; Coppola, Pierelli, & Schoenen, 2009; Di Clemente et al., 2005; Giffin & Kaube, 2002; Siniatchkin, Kropp, & Gerber, 2003), an effect that has been linked to impaired inhibitory intracortical circuitry (e.g., Brighina, Palermo, & Fierro, 2009; Chronicle, Pearson, & Mulleners, 2006; Mulleners, Chronicle, Palmer, Koehler, & Vredeveld, 2001). In light of this inhibition-related visual cortical pathophysiology in migraine, here we examined the hypothesis that migraine may also include an altered ability to modulate visuocortical sensory responses via the volitional orienting of visual spatial attention.

Our question followed from the common neuroanatomical locus of heightened cortical excitability and spatial attention effects in visuocortical processing. In particular, combined event-related potential (ERP) and functional neuroimaging have demonstrated that the top–down control of visual spatial attention specifically modulates the sensory-evoked excitability of extrastriate visual cortex (e.g., Heinze et al., 1994; Woldorff et al., 1997), the same visuocortical region linked to several visual anomalies in migraineurs (e.g., Batelli, Black, & Wray, 2002; Ditchfield, McKendrick, & Badcock, 2005; Fierro et al., 2003). Moreover, a key receptor-level mechanism underlying modulation of sensory-evoked activity in extrastriate cortex—GABAergic inhibition (e.g., Eickhoff, Rottschy, & Zilles, 2007)—has been implicated in both the normal modulatory effects of spatial attention (e.g., Houghton & Tipper, 1996) and hyperexcitability in migraineur cortex (e.g., Brighina et al., 2009; Chronicle & Mulleners, 1996). Taken together, this raises the possibility that attentional control of these visual cortical regions may also be altered in migraineurs.

Our question itself was of interest for two primary reasons. First, in studying the altered excitability of visual cortex in migraineurs, the dominant methodology has been to examine how visual cortical function is modulated via external or exogenous signal sources, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS). For instance, applying TMS/tDCS to various visual cortical areas has been used to show that the perception of phosphenes can be artificially induced at

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a lower stimulation threshold in migraineurs relative to non-headache controls (e.g., Antal, Arlt, Nitsche, Chadaide, & Paulus, 2006; Aurora, Ahmad, Welch, Bhardhwaj, & Ramadan, 1998), and that the perception of distracting visual stimuli is more difficult to suppress in migraineurs (e.g., Chronicle et al., 2006; Mulleners et al., 2001). From this perspective, our goal here was to ask a very different but highly complimentary question—given the altered excitability of migraineurs' visual cortex as revealed via the application of exogenous modulatory signals, are there differences between migraineurs and controls in terms of how sensory-evoked excitability in visual cortex is affected by *endogenous* or top–down modulatory signals?

Second, in terms of understanding the neurocognitive basis of visual-spatial attention itself, the cortical pathophysiology of migraine offers a novel investigative opportunity. To the point, it has long been suggested that visual-spatial attention operates in a bipartite manner, such that stimuli in attended visual locations are perceptually facilitated, while in tandem, stimuli in unattended visual locations are perceptually attenuated (e.g., Luck, 1995; Slotnick, Hopfinger, Klein, & Sutter, 2002; Slotnick, Schwarzbach, & Y, 2003). If migraineurs do in fact have altered intracortical inhibition (e.g., Brighina et al., 2009; Mulleners et al., 2001; Chronicle et al., 2006), then the potential contributions these inhibitory processes make to the attentional facilitation and/or attenuation of visual stimuli can be illuminated by examining if—and how—migraineurs might differ in their ability to attentionally modulate stimulus-evoked activity in extrastriate cortex, relative to non-migraineurs.

To address these issues we tested migraineurs and non-migraine control participants in a canonical spatial orienting task (e.g., Posner, 1980) as we measured visual sensory cortical responses to attended and unattended stimuli via event-related potentials (or ERPs). The paradigm itself was a direct replication of Handy and Khoe (2005), where participants maintained fixation on a central location while on each trial being cued to orient their visual attention either to a parafoveal location several degrees above fixation along the vertical meridian, or to keep their visual attention aligned with their focus of gaze on the fixation point. A target stimulus was then briefly presented and immediately followed by a mask, with the target requiring a forced, two-choice discrimination. On 80% of the trials a target was presented at the cued location, and on the remaining of the trials the target was presented at the uncued location, a probability manipulation designed to entice participants to volitionally orient their attention to the cued target location (see Posner, 1980). At issue in the paradigm is the extent to which the ERP responses to targets vary as a function of target location (foveal vs. parafoveal) and whether or not the target was cued/attended.

Planned analyses focused on two ERP components of interest, the lateral occipital P1 and lateral occipitotemporal N1. The P1 indexes the sensory-evoked excitability of extrastriate visual cortex (e.g., Heinze et al., 1994; Woldorff et al., 1997), such that the P1 amplitude positively covaries with the amount of attention allocated to the location of the ERP-eliciting stimulus (e.g., Handy & Mangun, 2000; Handy, Soltani, & Mangun, 2001). The N1 is also sensitive to top–down attentional modulation (e.g., Eimer, 1994; Handy & Mangun, 2000; Luck et al., 1994; Mangun & Hillyard, 1991) and indexes the kind of visual discriminative processes that might be altered in migraineurs (e.g., Hopf, Vogel, Woodman, Heinze, & Luck, 2002; Vogel & Luck, 2000). Because Handy and Khoe (2005) found that P1 attention effects were present for parafoveal stimuli but were absent for foveal stimuli (in participants not screened for migraine status), we thus adopted their paradigm here in order to examine whether migraineurs may likewise show effects of retinal eccentricity on attentional modulation of the P1 and/or N1 components.

2. Materials and methods

2.1. Participants

58 paid volunteers participated; 29 were in the non-migraine control group (19 women and 10 men; age 18–27 years) and 29 were in the migraine group (25 women and 4 men; age 18–54 years). The migraineurs had 14.9 (24.6 SD) headaches a year, with each headache lasting 22.3 (20.5 SD) h. Because migraine hyperexcitability is thought to normalize prior to and during an attack (e.g., Schoenen, 2006) all migraineurs had not had a migraine within 72 h prior and 48 h after the testing period. All but one control participant were right-handed. All participants gave their informed consent and all testing procedures were approved by the University of British Columbia Clinical Review Ethics Board.

2.2. Headache classification

All migraine participants were required to meet the migraine criteria specified by the International Headache Society (Headache Classification Subcommittee, 2004) and determined by an interview. Specifically, in order to be included in the migraine group, participants had to meet basic minimum criterion including 5 or more attacks with headache lasting 4–72 h. The headache needed to include two of the following: unilateral pain; pulsating pain quality; moderate to severe pain; and pain aggravated by routine physical activity such as walking or climbing stairs. The headache also had to be accompanied by nausea and vomiting or photophobia and phonophobia. All our migraine participants had not suffered from a migraine for at least 48 h before testing nor did they have a migraine for at least 48 h after testing.

2.3. Stimuli

Our paradigm was designed to separately assess visual sensory gain control at the fovea and parafovea, and replicated the paradigm used by Handy and Khoe (2005). The sequence and timing of each trial type (foveal or parafoveal target) is presented in Fig. 1. On each trial, a central fixation cross was presented on the center of the screen. Next, a pair of attention-directing arrow cues (0.5° in length) were presented on either side of fixation, directing attention to where the targets would appear, at either fixation (on half of the trials) or 2.2° above fixation on the vertical meridian (on the other half of the trials). An A or an H (0.5% probability) target letter (0.85° in width and 1.0° in height) then appeared in either of these locations, followed immediately by a mask (also 0.85° in width and 1.0° in height) consisting of an array of randomly oriented lines, with the target being presented to the attended location 80% of the time and in the unattended location 20% of the time. All stimuli were presented in dark grey (0.28 cd/m^2) against a black background (0.02 cd/m^2), providing a contrast ratio of 1.4.

Each participant performed 10 blocks of 32 validly cued targets in each of the two target locations (i.e., the cue predicted the correct target location), and 8 invalidly cued targets in each of the two target locations (i.e., the cue incorrectly predicted the target location). Between-blocks, the ratio of the target duration and mask duration (i.e., the target signal-to-noise ratio) was varied as necessary (51/51 ms, 34/68 ms, or 17/85 ms) within each target location in order to maintain the participant's performance near 0.75% correct (see Handy & Mangun, 2000; Handy, Jha, & Mangun, 1999; Handy, Soltani, et al., 2001). This was done so as to avoid a floor or ceiling effect, thereby allowing for an optimal measure of response accuracy (e.g., MacMillan & Creelman, 2005). In this manner, the duration of the target/mask complex always remained 102 ms, but depending on individual performance, the ratio could be different for foveal relative to parafoveal targets. At the beginning of the study, each participant was given one letter as the "go" target and one letter as the "no-go" target, with the order counterbalanced between participants. As such, participants made a button press only when they discriminated their specific target letter. The hit rate for calculating d' was thus defined as the ratio of "target present" responses relative to the total number of "go" trials, and the false alarm rate was defined as the ratio of "target present" responses relative to the total number of "no-go" trials, averaged across all trial blocks for that participant. The reported RTs are for correct target responses only.

2.4. Electrophysiological recording

Scalp potentials were recorded from 32 Ag/AgCl active electrodes (Electro-Cap International) evenly distributed across the scalp based on a modified 10–20 layout, measured relative to the left mastoid. Actual electrode sites were FP1, FP2, F3, F4, F7, F8, FZ, CZ, C3, C4, T3, T4, P1, P2, P3, P4, P5, P6, P01, P02, PZ, OZ, T5, T6, OL, OR, O1, O2, LM, RM, HEOG, and VEOG. Electroencephalic (EEG) activity was amplified with a bandpass of 0.1–30 Hz, with a gain of 50,000, and digitized on-line at a sampling rate of 256 samples-per-second. To ensure proper eye fixation and allow for the correction and/or removal of events associated with eye movements, vertical and horizontal electrooculograms (EOGs) monitored eye movements, with the vertical EOG measured via an electrode inferior to the right eye, and the horizontal EOG from an electrode on the right outer canthus. Electrode impedances were kept below 5 kΩ for the scalp electrodes and below 20 kΩ for the facial electrodes. Off-line computerized artifact rejection was used to eliminate trials during which

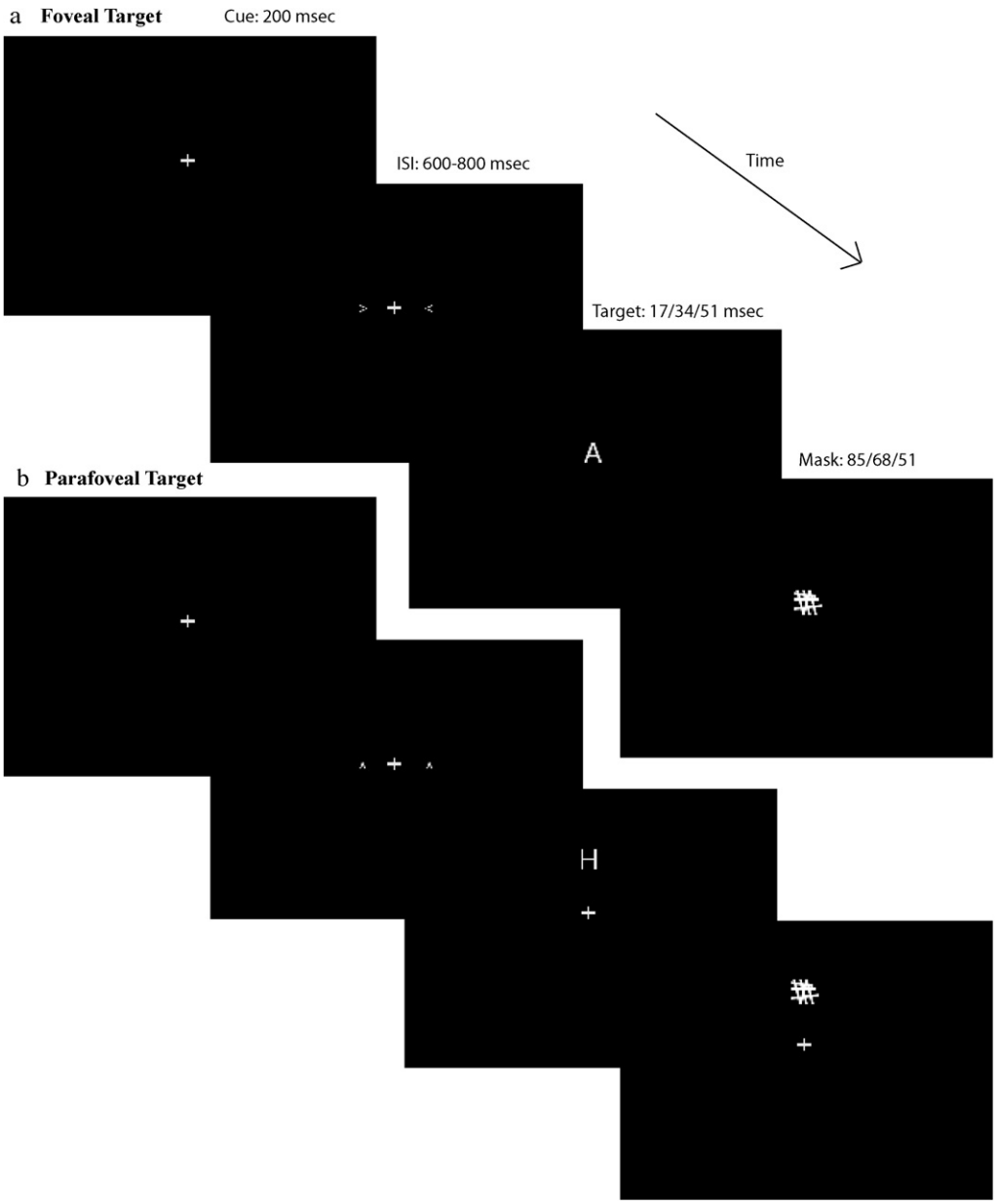

Fig. 1. Basic trial conditions. Shown are cued (or attended) trials for targets in the (a) foveal and (b) parafoveal locations, respectively. The relative ratio of target and mask durations are always summed to 102 ms, with the ratio varied within each participant on a run-to-run basis in order to avoid floor and/or ceiling effects in performance sensitivity. For uncued (or unattended) targets in the parafoveal location, the foveal location was cued; conversely, for uncued targets in the foveal location the parafoveal location was cued.

detectable eye movements (>1°), blinks, muscle potentials, or amplifier blocking occurred. For each subject, the waveforms for "go" and "no-go" trials were collapsed within each cue-target condition, and the resulting ERPs were derived into 3000 ms epochs, beginning 1500 ms before stimulus onset. Subsequently, all ERPS were algebraically re-referenced to the average of the left and right mastoid signals, and filtered with a low-pass Gaussian filter (25.6 Hz half-amplitude cut-off) to eliminate residual high-frequency artifacts in the waveforms. The resulting single-subject ERPs were used to derive group-averaged waveforms for display and analysis. Statistical quantification of ERP data were based on mean amplitude measures relative to a −200 to 0 pre-stimulus baseline.

3. Results

To examine possible age- and gender-related effects in our primary findings reported below, we initially ran repeated measures ANCOVAs with sigma-restricted coding of categorical predictors of sex and age covariates. As we found no significant effects of age or gender, either for behavioral (all $Fs < 0.393$; all $ps > 0.075$) or ERP measures (all $Fs < 1.715$; all $ps > 0.196$), we did not include these covariates in the main results.

3.1. Behavior

Mean reaction times (RTs) and perceptual sensitivity (d') for each group are reported in Tables 1a and 1b, respectively, as a function of headache classification, attention, and target location. We assessed these variables via repeated-measures ANOVAs that included headache category (migraine vs. control) as a between-subjects factor and attention (cued vs. uncued targets) as a within-subjects factor separately for each target location. Mean durations for foveal and parafoveal targets are reported in Table 2.

3.1.1. Foveal processing

As is apparent in Table 1a, each group showed faster RTs to cued than uncued targets, but the magnitude of the attention

Table 1a
Reaction times (ms) for target discrimination, as a function of headache classification, target location, and attention condition, averaged across participants. Standard deviation in parentheses.

Group	Attention	Target location	
		Fovea	Parafovea
Control	Cued	583.19 (144.67)	529.49 (125.07)
	Uncued	614.37 (131.27)	559.87 (107.02)
Migraine	Cued	503.83 (99.45)	469.63 (96.91)
	Uncued	571.69 (107.22)	510.15 (99.43)

effect appeared to be greater in migraineurs than it was in controls. This was confirmed statistically via a significant main effect of attention ($F(1,56) = 4.27$; $p < 0.001$) and a significant interaction between group and attention ($F(1,56) = 5.86$; $p < 0.05$). Follow-up statistics revealed that, indeed, both groups did show significant within-groups effect of attention (controls $F(1,28) = 1.14$, $p < 0.01$; migraineurs $F(1,28) = 31.9$, $p < 0.001$). There was also a trend for migraineurs to be faster than controls overall ($F(1,56) = 3.578$; $p = 0.064$).

For perceptual sensitivity as measured by d', both groups appeared to show an effect of attention, as can be seen in Table 1b. However, the direction of the effect appeared to differ between groups, with migraineurs having a higher d' value for cued vs. uncued targets, but for controls having a higher value for uncued vs. cued targets. This was confirmed statistically, where was no main effect of attention ($F(1,56) = 1.17$; $p = 0.295$), but there was a significant group by attention interaction ($F(1,56) = 5.330$; $p < 0.05$). Follow-up statistics confirmed that both groups showed significant within-groups effects of attention (controls $F(1,28) = 1.45$, $p < 0.01$; migraineurs $F(1,28) = 4.233$, $p < 0.05$).

3.1.2. Parafoveal processing

As can be seen in Table 1a, it appeared that responses to parafoveal targets were faster for cued than uncued targets, and that this effect did not differ between groups. This was confirmed statistically with a significant main effect of attention ($F(1,56) = 7.04$; $p < 0.001$), and no interaction with group ($F(1,56) = 1.442$; $p = 0.235$). There was also a trend for migraineurs to be faster than controls overall ($F(1,56) = 3.852$; $p = 0.055$).

For d', it appeared that responses to parafoveal targets were more accurate for cued than uncued targets, and that there were no group differences in the effect of attention on perceptual sensitivity, as can be seen in Table 1b. This was confirmed statistically with a significant main effect of attention ($F(1,56) = 9.872$; $p < 0.01$), but again no group by attention interaction ($F(1,56) = 1.44$; $p = 0.235$). In addition, migraineurs were more accurate than controls overall ($F(1,56) = 6.974$; $p < 0.05$).

3.2. Electrophysiology

Statistical interrogation of each of these ERP components/phases included repeated measures ANOVAs separately for the foveal and parafoveal locations, with headache category (control vs. migraine) as a between-subjects factor and attention (cued vs. uncued targets) as a within-subjects factor. Separate ANOVAs within each group were planned to follow-up any significant interactions between group and attention. All P1 measures were taken from lateral occipital electrode sites OL and OR, where this component is typically maximal (e.g., Handy & Mangun, 2000; Handy & Khoe, 2005; Mangun & Hillyard, 1991), and all N1 measures were taken from lateral occipital-temporal sites T5 and T6, where the N1 is typically maximal (e.g., Hopf et al., 2002; Mangun & Hillyard, 1991; Vogel & Luck, 2000).

Table 2
Mean target duration (ms), as a function of headache classification and target location, averaged across participants.

Group	Target location	
	Fovea	Parafovea
Control	37.93	26.82
Migraine	37.78	28.72

For the P1 component, it has been further subdivided into an "early phase" prior to the P1 peak that reflects the intensity of visual processing in dorsolateral extrastriate cortex of the middle occipital gyrus, and a "late phase" in the post-peak portion of the P1 tied to processing in ventral extrastriate cortex of the posterior fusiform gyrus (e.g., Di Russo, Martinez, Sereno, Pitzalis, & Hillyard, 2002). Given that the early and late phases of the P1 show differential sensitivity to various forms of visual attention (e.g., Fu, Caggiano, Greenwood, & Parasuraman, 2005; Hopfinger & Ries, 2005; Hopfinger & West, 2006), planned analysis of the P1 included a traditional mean amplitude measure centered on the P1 peak, as well as separate mean amplitude measures of the pre- and post-peak portions of the P1 component in order to independently examine the early and late P1 phases.

3.2.1. Foveal processing

3.2.1.1. Mean P1 peak. Mean amplitude of the lateral occipital P1 was measured over a 110–140 ms post-stimulus time window centered on the approximate peak of the P1 in the grand-averaged waveforms and are reported in Table 3 as a function of headache classification, attention, and target location. As can be seen in Fig. 2, the amplitude of the P1 appeared to be very similar for cued relative to uncued targets at the fovea in both groups, and this was confirmed statistically. We found no main effect of attention ($F(1,56) = 1.68$; $p = 0.20$), and no group by attention interaction ($F(1,56) = 0.31$; $p = 0.58$).

3.2.1.2. Early phase P1. Mean amplitude of the early phase of the P1 was measured over a 90–125 ms post-stimulus time window and are reported in Table 3 as a function of group and attention. As can be seen in Fig. 2, the amplitude of the early phase P1 appeared to be very similar for cued relative to uncued targets at the fovea in both groups, and this was confirmed statistically. We found no main effect of attention ($F(1,56) = 0.17$; $p = 0.68$), and no group by attention interaction ($F(1,56) = 0.13$; $p = 0.72$).

Table 1b
Perceptual sensitivity rates (hits, false alarms, d') for target discrimination, as a function of headache classification, target location, and attention condition, averaged across participants. Standard deviation in parentheses.

Group	Attention	Target location					
		Fovea			Parafovea		
		d'	Hits	FA	d'	Hits	FA
Control	Cued	2.09 (0.70)	0.79 (0.13)	0.14 (0.09)	3.05 (0.79)	0.92 (0.07)	0.12 (0.11)
	Uncued	2.22 (0.78)	0.81 (0.13)	0.14 (0.11)	2.74 .69)	0.91 (0.08)	0.16 (0.16)
Migraine	Cued	2.62 (0.63)	0.87 (0.08)	0.11 (0.07)	3.54 (0.98)	0.95 (0.05)	0.08 (0.06)
	Uncued	2.28 (0.89)	0.77 (0.16)	0.12 (0.12)	3.40 (1.00)	0.94 (0.05)	0.13 (0.12)

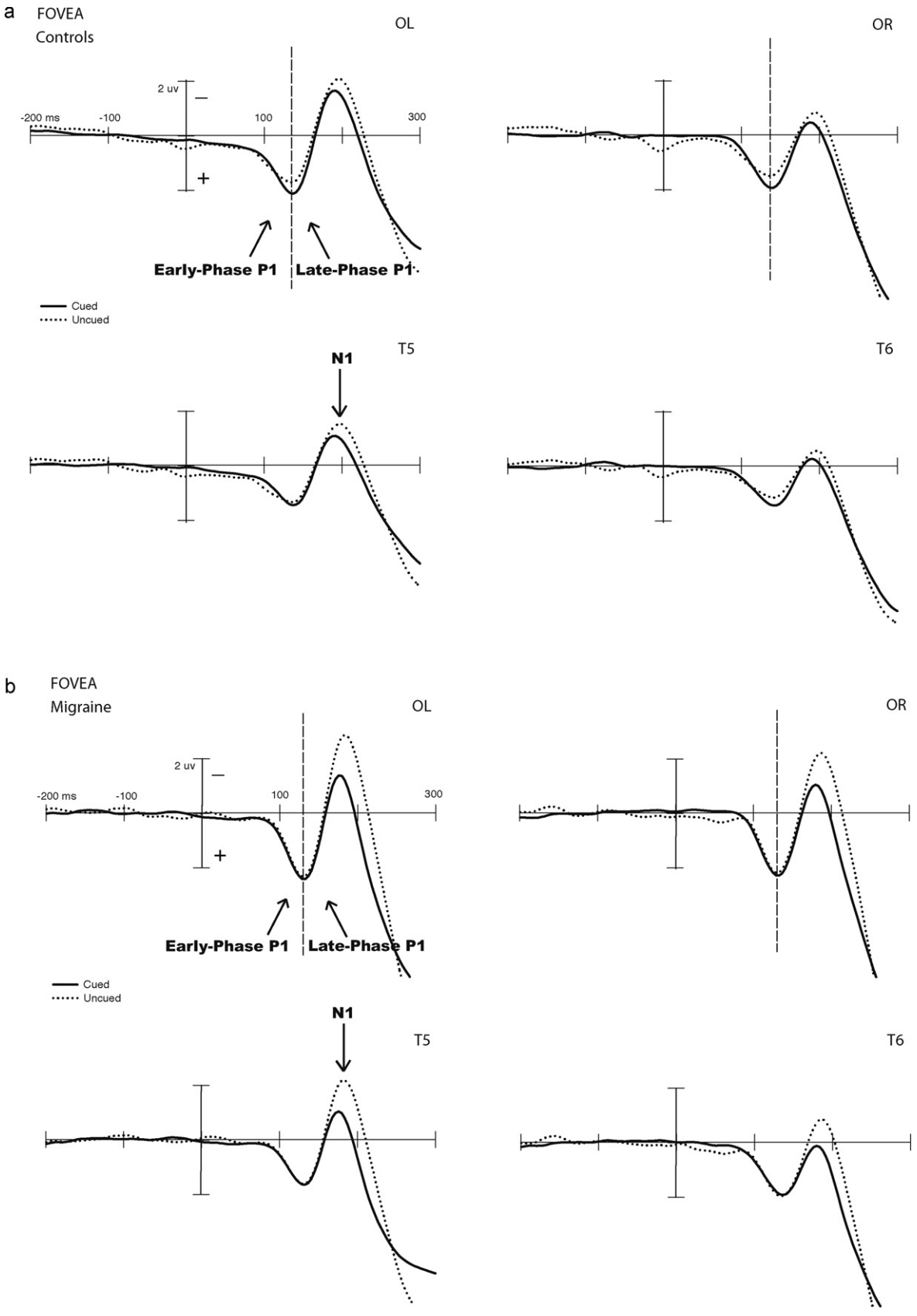

Fig. 2. P1 and N1 component responses to foveal targets. All waveforms are displayed relative to a baseline of −200 to 0 ms prestimulus. Shown are the waveforms from lateral posterior electrode sites for (a) control group and (b) migraine group.

Table 3
Mean amplitudes (μV) of the lateral occipital component, as a function of headache classification, target location, attention condition, component, and electrode location, averaged across participants. Standard error of the mean in parentheses.

Group	ERp component	Scalp location	Fovea		Parafovea	
			Cued	Uncued	Cued	Uncued
Control	P1	OL	1.85 (0.35)	1.59 (0.41)	3.78 (0.54)	2.96 (0.49)
		OR	1.64 (0.33)	1.36 (0.35)	3.94 (0.57)	3.04 (0.43)
	Early P1	OL	1.29 (0.26)	1.27 (0.36)	2.59 (0.44)	1.91 (0.40)
		OR	1.04 (0.24)	1.04 (0.27)	2.57 (0.41)	1.90 (0.33)
	Late P1	OL	0.96 (0.46)	0.63 (0.51)	3.30 (0.44)	2.47 (0.46)
		OR	1.22 (0.42)	0.87 (0.50)	3.80 (0.50)	2.99 (0.45)
	N1	T5	−0.61 (0.52)	−0.81 (0.47)	1.02 (0.31)	0.34 (0.37)
		T6	0.13 (0.43)	−0.06 (0.49)	1.50 (0.38)	0.76 (0.42)
Migraine	P1	OL	2.16 (0.29)	2.06 (0.35)	3.97 (0.40)	3.64 (0.37)
		OR	2.04 (34)	1.93 (0.35)	4.78 (0.48)	4.20 (0.44)
	Early P1	OL	1.52 (0.23)	1.42 (0.28)	2.42 (0.32)	2.46 (29)
		OR	1.38 (0.27)	1.27 (0.28)	2.87 (0.32)	2.64 (0.29)
	Late P1	OL	0.70 (0.51)	0.30 (0.53)	3.25 (0.42)	2.55 (0.52)
		OR	0.87 (0.50)	0.57 (0.60)	4.34 (0.50)	3.56 (0.50)
	N1	T5	−0.74 (0.52)	−1.81 (0.52)	0.78 (0.40)	0.01 (0.59)
		T6	0.33 (0.49)	−0.43 (0.49)	1.86 (0.40)	0.82 (0.47)

3.2.1.3. Late phase P1. Mean amplitude of the late phase of the P1 was measured from a 125–175 ms post-stimulus time window and are reported in Table 3 as a function of headache classification, attention, and target location. We found a main effect of attention ($F(1,56) = 5.43$; $p < 0.05$) such that the mean amplitude was larger for cued vs. uncued targets, but there was no group by attention interaction ($F(1,56) = 0.01$; $p = 0.96$).

3.2.1.4. N1 amplitude. Mean amplitude of the lateral occipital N1 was measured over a 160–190 ms post-stimulus time window centered on the approximate N1 peak in the grand-averaged waveforms, and are reported in Table 3 as a function of headache classification, attention, and target location. As can be seen in Fig. 2, the amplitude of the N1 appeared to be larger for uncued relative to cued targets at the fovea but more so in the migraine group, and this was confirmed statistically. We found significant main effects of attention ($F(1,56) = 9.92$; $p < 0.01$) and a significant group by attention interaction ($F(1,56) = 4.24$; $p < 0.05$). The planned follow-up ANOVA revealed that controls did not have an attention effect at the fovea ($F(1,28) = 0.28$; $p = 0.60$), while the migraineurs did ($F(1,28) = 19.58$; $p < 0.001$). Overall, this indicated that N1 amplitudes were larger for uncued relative to cued targets, and the main effect was driven by the migraine group.

3.2.2. Parafoveal processing

3.2.2.1. P1 amplitude. Mean amplitude of the lateral occipital P1 was measured over a 120–150 ms post-stimulus time window centered on the approximate peak of the P1 in the grand-averaged waveforms and are reported in Table 3 as a function of headache classification and attention. As can be seen in Fig. 3, the amplitude of the P1 appeared to be larger for cued relative to uncued targets at the parafovea in both groups, and this was confirmed statistically. We found significant main effects of attention ($F(1,56) = 13.78$; $p < 0.001$), but no group by attention interaction ($F(1,56) = 1.28$; $p = 0.26$). This indicated that overall P1 amplitudes were consistently larger for cued relative to uncued targets regardless of group.

3.2.2.2. Early phase P1. Mean amplitude of the early phase P1 was measured over a 90–135 ms post-stimulus time leading up to the peak of the P1 in the grand-averaged waveforms and are reported in Table 3 as a function of headache classification, attention, and target location. As can be seen in Fig. 3, the amplitude of this early phase of the P1 appeared to be different for cued relative to uncued targets at the parafovea between groups, such that there was an effect of attention for controls but not migraineurs, and this was confirmed statistically. We found a main effect of attention ($F(1,56) = 6.93$; $p < 0.05$), and a group by attention interaction ($F(1,56) = 3.82$; $p = 0.05$). ANOVAs within each group revealed that controls had a main effect of attention in the early phase P1 ($F(1,28) = 8.69$; $p < 0.01$) but migraineurs did not ($F(1,28) = 0.27$; $p = 0.61$).

3.2.2.3. Late phase P1. Mean amplitudes of the late phase of the lateral occipital P1 was measured over a 135–175 ms post-stimulus time window leading away from the peak of the P1 in the grand-averaged waveforms and are reported in Table 3 as a function of headache classification and attention and target location. As can be seen in Fig. 3, the amplitude of the late phase P1 appeared to be greater for cued relative to uncued targets at the parafovea in both groups, and this was confirmed statistically. We found a main effect of attention ($F(1,56) = 16.43$; $p < 0.001$), but no group by attention interaction ($F(1,56) = 0.05$; $p = 0.825$).

3.2.2.4. N1 amplitude. Mean amplitude of the lateral occipital N1 was measured over a 160–190 ms post-stimulus time window centered on the approximate N1 peak in the grand-averaged waveforms and are reported in Table 3 as a function of headache classification and attention and target location. As can be seen in Fig. 3, the amplitude of the N1 appeared to be larger for uncued relative to cued targets in both groups, and this was confirmed statistically. We found significant main effects of attention ($F(1,56) = 20.12$; $p < 0.001$), but no significant group by attention interaction ($F(1,56) = 0.31$; $p = 0.58$). This indicated that overall N1 amplitudes were larger for uncued relative to cued targets, and that this did not differ between groups.

3.3. Control analyses

In addition to the above analyses directly relating to our study's question of interest, we also wanted to examine two control issues associated with our migraine group. In particular, we wanted to determine whether the pattern of results we report for migraineurs varied as a function of (1) migraine sub-types in our migraine group (aura vs. non-aura), and (2) the age of migraineur participants, which included a broader range of older participants than our control group.

3.3.1. Migraine subtypes

In people presenting with migraine headaches, approximately 20% have visual auras as part of their constellation of migraine

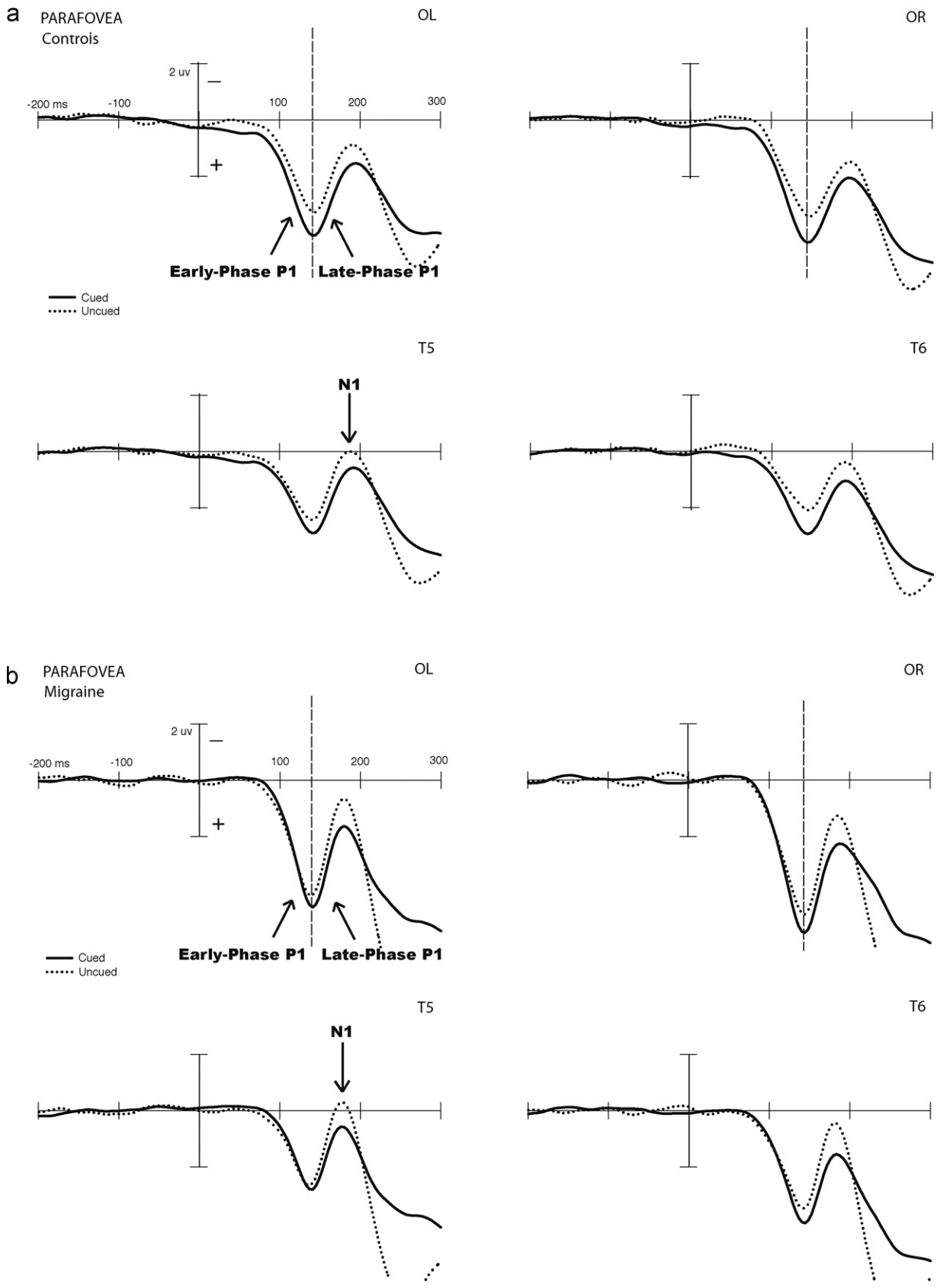

Fig. 3. P1 and N1 component responses to parafoveal targets. All waveforms are displayed relative to a baseline of −200 to 0 ms prestimulus. Shown are the waveforms from lateral posterior electrode sites for (a) control group and (b) migraine group.

symptoms. Our migraine group comprised 13 individuals who could be classified as migraine with aura and 16 participants who had migraine without aura. We compared these two groups to determine whether this sub-population of migraineurs manifest any differences in d' perceptual sensitivity, reaction time, P1 mean peak, early-phase P1, or late-phase P1 or N1 attention effects at the fovea or parafovea. Our reason for this comparison in the sub-populations of migraineurs was that, in assessments of neural and cognitive function, migraineurs with and without aura tend to show the same qualitative differences relative to controls, but in some experimental studies quantitative differences are more apparent or only found in migraineurs with aura (e.g., Chronicle, Wilkins, & Coleston, 1995). Statistical interrogation of each of the ERP components/phases included repeated measures ANOVAs with migraine subtype (13 migraine with aura vs. 16 migraine without aura) as a between-subjects factor, and location (fovea and parafovea) and attention (cued vs. uncued targets) as within-subjects factors. There were no differences in attention effects between the two migraine groups for early-phase P1, late-phase P1, mean peak P1, or N1 at either location (all $Fs(1,27) < 0.82$; all $ps > 0.374$). There were also no behavioral differences (reaction times or perceptual sensitivity) between the two migraine groups (all $Fs(1,27) < 0.903$; $ps > 0.350$).

3.3.2. Effect of age distribution

In addition to the ANCOVAs reported above for age as a covariate, to further demonstrate the group results were not affected by age in our migraine results, we divided the migraine group into two equal groups at the median age, dropping the median participant. Thus, the "younger" migraine group had 14 participants aged 18–25 and the "older" migraine group had 14 participants aged 25–54. We then ran repeated measures ANOVAs for each of the behavioral and ERP components of interest, comparing the two migraine age groups (14 "younger" migraineurs vs. 14 "older" migraineurs) as a between-subjects factor and attention (cued vs. uncued targets) as within-subjects factors at each location (fovea and parafovea). We found that neither of the behavioral measures differed between these two migraine age groups (all $Fs(1,27) < 2.413$; all $ps > 0.13$). We found that the N1 attention effect for foveal targets differed between these two migraine age groups ($F(1,27) = 4.67$; $p < 0.05$), whereas all the remaining components did not differ in attention effects between the two migraine groups (all $Fs(1,27) < 0.7056$; all $ps > 0.15$). Comparison of the means showed that both groups had an N1 greater for uncued than cued, but the magnitude was greater for the younger migraineurs. This suggests that, if anything, inclusion of older migraineurs actually attenuated the difference that we found between the migraineurs ($N = 29$) and controls ($N = 29$).

4. Discussion

Our study assessed the hypothesis that migraineurs may have an altered ability to modulate the sensory-evoked excitability of visual cortex in a goal-directed, top–down manner via visual-spatial attention. Towards answering this question, we found two significant differences between migraineurs relative to non-migraine controls. First, in the parafovea, migraineurs showed no early-phase attention effect in the P1 ERP component. Instead, attention effects were only found in the late phase of the P1, following the P1 peak. In comparison, control participants showed significant attention-related effects in both the early and late phase of the P1 component. Second, at the fovea, migraineurs had an increased N1 for unattended relative to attended targets, a data pattern that was present but not statistically significant in the control group. Taken together, our findings thus suggest that the altered excitability of visual cortex in migraineurs is not limited to bottom-up or external modulatory signal sources (e.g., Antal et al., 2006; Aurora et al., 1998; Mulleners et al., 2001), but extends to endogenously generated modulatory signal sources as well. In the following sections, we discuss the functional implications of our ERP findings, as well as the broader consequences for attention and migraine in general.

4.1. Sensory suppression in the parafovea

The hypothesis for our study—migraineurs may have an altered ability to modulate extrastriate visual cortex via visual spatial attention—was predicated on the common neuroanatomical locus of migraine visual anomalies and spatial attention effects in visuocortical processing—extrastriate cortex. Given the deficits in extrastriate cortex observed in migraineurs (e.g., Batelli et al., 2002; Ditchfield et al., 2005; Fierro et al., 2003), it is thus perhaps not surprising that we found migraineurs to have an absent attentional response in the early phase of the P1 ERP component, which has been shown to index the intensity of sensory-evoked activity in dorsolateral extrastriate cortex (e.g., Di Russo et al., 2002). Importantly, however, the effect itself was limited to parafoveal targets, such that the early-phase P1 response for these targets was equivalent in amplitude for both attended and unattended conditions.

How should this be interpreted functionally? Three lines of converging evidence suggest that it reflects a decreased level of "normal" suppression for unattended events outside the fovea. First, visual spatial attention is known to modulate sensory-evoked visual cortical activity by a combination of amplifying stimulus-evoked activity in attended locations while simultaneously suppressing or inhibiting stimulus-evoked activity in unattended locations in a manner analogous to the classic center-surround response properties of retinal ganglion cells (e.g., Slotnick et al., 2002, 2003). Within this context, attention effects in the P1—that is, amplitude differences in the P1s elicited by attended vs. unattended stimuli—are believed to reflect the active suppression of stimulus-evoked activity for unattended stimuli (Hillyard, Vogel, & Luck, 1998; Luck, 1995). In this model, the absence of an early-phase P1 attention effect in migraineurs for parafoveal targets would thus be explained by a lack of attention-related suppression of stimulus-evoked activity for unattended targets, rather than an absence of facilitation for attended targets.

Second, that migraineurs have an altered ability to suppress sensory-evoked activity for unattended stimuli also aligns with the inhibition-based model of migraine visual cortical pathophysiology. Briefly put, this theory holds that cortical hyperexcitability found in striate (e.g., Chronicle et al., 2006; Mulleners et al., 2001) and extrastriate (e.g., Batelli et al., 2002) cortex in migraineurs, arises in part from a lack of GABA-ergic inhibitory control (e.g., Brighina et al., 2009; Chronicle & Mulleners, 1996). To be sure, migraineurs may also have altered excitatory neurotransmitter activity in visual cortex, such as increased presynaptic glutamate release and/or decreased glutamate reuptake relative to non-migraine populations (e.g., Aurora & Wilkinson, 2007; Bussone, 2004). Nevertheless, models linking P1 attention effects to an active suppression of unattended visual-sensory inputs (e.g., Hillyard et al., 1998; Luck, 1995) predict exactly what was observed here for migraineurs: if there is reduced inhibitory control in visual cortex, there should be a corresponding reduction in the magnitude and extent of P1 attention effects.

Finally, our conclusion here also fits well with both anecdotal and empirical reports from migraineurs, who frequently remark on the distracting nature of extraneous visual inputs (e.g., Sacks, 1992). Indeed, recent laboratory evidence suggests that migraineurs' visual abnormalities may be considered signal-to-noise issues, where the ability to hone in on visual signals of interest is impaired by increased distraction from extraneous noise (e.g., Antal et al., 2006; Aurora & Wilkinson, 2007; Wagner, Manahilov, Loffler, Gordon, & Dutton, 2010). Moreover, not only did Wagner

et al. (2010) find that migraineurs have difficulties in excluding external noise sources, but also they attributed this difficulty to decreased GABA-mediated suppression in cortex. Notably, our data here directly parallel these reports and findings, where the apparent decreased suppression for unattended stimuli outside the fovea in migraineurs could be symptomatic of their increased sensitivity to visual noise.

4.2. Discriminative processing at the fovea

The second group difference we found in the ERP data was that migraineurs showed a significantly larger N1 for unattended vs. attended targets at the fovea, but controls did not. What does this reveal about visual processing in migraineurs? Whereas attention effects in the P1 have been tied to the suppression of stimulus-evoked activity for stimuli outside the focus of attention, attentional modulation of the N1 has been linked to the active facilitation of sensory-evoked activity for stimuli falling within the attended region of space (Hillyard et al., 1998; Luck, 1995). While at first pass it may be tempting to conclude that migraineurs simply show a heightened degree of facilitation for attended events at the fovea relative to non-migraineurs, two factors make this direct interpretation difficult.

First, the cortical locus of the visual N1 has not been well-characterized. Thus, unlike the P1, there is no clear mapping of the N1 effect we report here to known functional pathologies in migraine cortex. Second, the actual pattern of attention effects we observed here—the N1 amplitude for foveal targets in migraineurs was greater on unattended relative to attended trials—is reverse to the more typical finding of an increased N1 for attended events in the upper and lower visual field quadrants (e.g., Handy, Green, Klein, & Mangun, 2001; Handy & Mangun, 2000; Luck et al., 1994; Mangun & Hillyard, 1991). To be sure, our N1 pattern was not necessarily unexpected, in that not only did Handy and Khoe (2005) find the same "reversed" N1 effect using the identical paradigm, but other ERP studies have also reported similar N1 data patterns when using stimuli presented at the fovea or on the vertical meridian (e.g., Fu et al., 2009; Handy, Soltani, et al., 2001). Moreover, functional changes in the amplitude of sensory-evoked visual ERP components can vary depending on the retinotopic location of the ERP-eliciting stimulus. In particular, changing the location of a visual stimulus changes the orientation of the component-generating dipole in retinotopically mapped cortex relative to the scalp surface, which can in turn affect the amplitude of the component, it's polarity, and how it changes with attention (e.g., Clark and Hillyard, 1996; Mangun, Hillyard, & Luck, 1993). As such, it is possible that that what appears to be a larger N1 for unattended targets at the fovea may actually reflect enhanced processing for attended targets, as ERP-based models of attention would predict (e.g., Hillyard et al., 1998; Luck, 1995). However, in the absence of further evidence, such a proposal would be speculative at best.

Instead, the firmest statement that can be made regarding our N1 finding in migraineurs is that it reflects an altered level of visual discriminative processing in cortex, relative to the non-migraine population. This conclusion stems from the canonical view of the N1 as indexing the degree or intensity of visual discrimination afforded to sensory inputs (e.g., Vogel & Luck, 2000). And notably, as we discuss in the next section, it would appear that based on between-group differences in response performance, migraineurs actually show *heightened* discriminative functioning.

4.3. Migraine and attentional performance

Although ERPs were the primary dependent measure in our study, we were also able to compare behavioral performance between migraineurs and controls, in terms of both RTs and perceptual sensitivity (as indexed by d'). In this regard, migraineurs actually out-performed controls in two key ways. First, in the parafovea, while both groups showed greater perceptual sensitivity for attended relative to unattended targets, migraineurs also showed an overall greater perceptual sensitivity relative to controls, regardless of the attention condition. That this co-occurred with a trend towards faster overall RTs for migraineurs indicates that their increased level of perceptual sensitivity in the parafovea can't be dismissed as a simple speed-accuracy trade-off. Rather, the d' data in this case converge on the subjective reports of migraineurs outlined above, reports also suggesting that migraine is associated with an increased perceptual sensitivity to non-central visual inputs.

Second, at the fovea, whereas the controls and the participants in the study by Handy and Khoe (2005) showed greater perceptual sensitivity for unattended relative to attended targets, migraineurs showed the opposite pattern here, such that their perceptual sensitivity was greater for attended relative to unattended targets. In the context of the specific perceptual task here—identify a letter that is presented briefly and then rapidly masked—this indicates that in non-migraineurs (or in populations not screened for migraine status, as in the case of Handy & Khoe, 2005), whatever functional impact visual attention has on foveal processing leads to performance decrements in target discrimination. Conversely, however, migraineurs' attentional functioning at the fovea puts them at a perceptual advantage in our discrimination task. Although the underlying basis for this performance difference between migraineurs and controls remains unclear, migraineurs show the more beneficial attentional outcome.

In conclusion, whether or not migraine is consistently associated with perceptual advantages has been somewhat equivocal across studies, with some finding enhanced performance for migraineurs (e.g., Wray, Mijovic-Prelec, & Kosslyn, 1995) and others not (e.g., Conlon & Humphreys, 2001; Palmer & Chronicle, 1998; Shepherd, 2006). Although our study was not designed to resolve these differences, the data here nevertheless suggest that migraineurs do have altered top–down control of visual cortex, and that it does not necessarily come with perceptual costs. If anything, quite the opposite.

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