Differences in early sensory-perceptual processing in synesthesia: A visual evoked potential study

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ABSTRACT

Synesthesia is a condition where stimulation of a single sensory modality or processing stream elicits an idiosyncratic, yet reliable perception in one or more other modalities or streams. Various models have been proposed to explain synesthesia, which have in common aberrant cross-activation of one cortical area by another. This has been observed directly in cases of linguistic-color synesthesia as cross-activation of the 'color area', V4, by stimulation of the grapheme area. The underlying neural substrates that mediate cross-activations in synesthesia are not well understood, however. In addition, the overall integrity of the visual system has never been assessed and it is not known whether wider differences in sensory-perceptual processing are associated with the condition. To assess whether fundamental differences in perceptual processing exist in synesthesia, we utilised high-density 128-channel electroencephalography (EEG) to measure sensory-perceptual processing using stimuli that differentially bias activation of the magnocellular and parvocellular pathways of the visual system. High and low spatial frequency gratings and luminance-contrast squares were presented to 15 synesthetes and 15 controls. We report, for the first time, early sensory-perceptual differences in synesthetes relative to non-synesthete controls in response to simple stimuli that do not elicit synesthetic color experiences. The differences are manifested in the early sensory components of the visual evoked potential (VEP) to stimuli that bias both magnocellular and parvocellular responses, but are opposite in direction, suggesting a differential effect on these two pathways. We discuss our results with reference to widespread connectivity differences as a broader phenotype of synesthesia.

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Introduction

It is now well established that synesthesia is a genuine perceptual phenomenon (reviewed in Hubbard et al., 2005; Hubbard and Ramachandran, 2005; Ward and Mattingley, 2006) yet its neural substrates are not well understood. For the synesthete, stimulation of a single sensory modality elicits an idiosyncratic, yet reliable perception in one or more other modalities. Various models have been proposed to explain synesthesia, which have in common the idea of aberrant cross-activation of one cortical area by another (Hubbard

and Ramachandran, 2005; Grossenbacher and Lovelace, 2001; Ramachandran and Hubard, 2001; Smilek et al., 2001). Such cross-activation has been observed directly in neuroimaging studies of one of the most common forms of synesthesia, which we term linguistic-color synesthesia (Barnett et al., 2008). In this form, letters of the alphabet, numbers, days of the week, months of the year and words each induce a consistent color percept or association. A number of neuroimaging studies have found that color-inducing stimuli for linguistic-color synesthetes (e.g., spoken words, visually presented letters of the alphabet) aberrantly activate area V4, known to be involved in color processing (Hubbard et al., 2005; Nunn et al., 2002; Sperling et al., 2005), as well as a number of other visual and parietal areas (Aleman et al., 2001; Paulesu et al., 1995; Rich et al., 2006; Weiss et al., 2005). However, the poor temporal resolution of fMRI leaves open the question of whether this cross-activation is direct, from one area (such as the grapheme area) to another (the adjacent area V4 in this case), or whether it arises later in time, consistent with post-perceptual feedback from processing in higher cortical areas. In

addition, the overall integrity of the visual system has never been assessed and it is not known whether wider differences in sensory-perceptual processing are associated with the condition.

Electroencephalography (EEG) offers a method to resolve the temporal characteristics of the synesthetic experience and also to assess early sensory processing. To the best of our knowledge only three studies have used evoked potentials to compare groups of synesthetes with matched controls. Schiltz et al. (1999) recorded EEG while synesthetes viewed numbers and letters that induced color and compared their responses to controls. Synesthetes had more positive responses over frontal and prefrontal regions that were evident at relatively late time points (200–600 ms). The frontal differences were interpreted as reflecting either prefrontal cortical inhibition or multisensory integration. A more recent study recorded auditory evoked potentials in response to words, letters and pseudowords that induced color percepts in synesthetes. In this study, differences between synesthetes and controls over inferior posterior temporal sites were present as early as 122 ms after the onset of an auditory stimulus (Beeli et al., 2008). These data were interpreted as evidence for a rapid, automatic cross-activation of the color area at early stages of processing, and this as the physiological basis for the synesthetic experience. More recently, Brang et al. (2008) reported that the contextual congruity of graphemes presented in sentences (i.e., whether the synesthetic color of the grapheme fit the context of the color-word it replaced in the sentence) affected the evoked responses to achromatic graphemes in synesthetes, who showed a more negative N1, more positive P2 and less negative N400 component in response to contextually appropriate graphemes. Thus, the interaction between the expectation induced by the preceding sentence and the synesthetic color effect was apparent in the evoked response to graphemes at a very early stage of processing.

In a preliminary experiment, designed to measure the time-course of synesthetic cross-activation, we measured visual evoked potentials (VEPs) in a set of linguistic-color synesthetes, using a 128-electrode array, in response to visual presentation of stimuli that induced synesthesia (e.g., letters) and control stimuli that did not induce synesthesia (e.g., Mondrian color patterns and scrambled letters). During this we noted a very surprising trend: synesthetes showed altered VEPs at very early stages of processing in response to control stimuli that did not induce synesthetic percepts (data not shown). To investigate this intriguing finding further, we conducted a more detailed experiment that we report here, designed specifically to assess early visual processing and to dissect the contributions of different visual processing streams.

The visual system is thought to be both structurally and functionally divided into two main parallel but interacting processing streams (Ungerleider and Mishkin, 1982). The 'dorsal' stream is largely driven by magnocellular lateral geniculate nucleus (LGN) inputs and involves projections from V1 to parietal cortex. Functional processing in the dorsal stream, sometimes referred to as the 'where' pathway, involves spatial perception, action-related behavior and attention. The 'ventral' stream, on the other hand, is largely driven by parvocellular inputs, and in the cortex, involves projections from V1 to the temporal cortex. The ventral visual stream is considered the 'what' pathway, being involved in processes such as object, face and word recognition (see Ungerleider and Mishkin, 1982). The functioning of each pathway at a basic sensory level can be assessed using simple stimuli that bias processing to one stream or the other, based on the preferred receptive field characteristics of the retinal ganglion cells that stimulate each pathway (Ungerleider and Mishkin, 1982). For example, magnocellular LGN neurons are sensitive to low luminance-contrast stimuli (1% to 10% contrast) and saturate at contrast levels of 16 to 32% (Kaplan, 1991). Additionally, the magnocellular system is sensitive to low spatial frequency (LSF) stimuli (Derrington and Lennie, 1984; Kaplan, 1991), but not chromatic stimuli. On the

other hand, parvocellular neurons do not begin responding vigorously until stimuli are at a contrast level of around 8–10% and show a non-saturating increase in amplitude across a range of luminance contrasts (Kaplan, 1991, Tootell et al., 1988). The parvocellular system prefers high spatial frequency (HSF) stimuli (Derrington and Lennie, 1984; Kaplan, 1991) and its neurons are highly responsive to color (Kaplan, 1991, Merrigan and Maunsell, 1993). The differential sensitivities of the two pathways mean that relatively simple stimuli such as Gabor patches and isolated luminance squares (i.e., check patterns) can be manipulated to bias each pathway and their integrity can then be assessed using VEPs.

The VEP from scalp recordings of electrical brain activity in response to visual stimulation have been well characterized in humans, providing precise information on the time-course of visual information processing in the brain and allowing for good estimations of the underlying neuronal generators. The C1, the first discernable VEP, has a central occipital scalp topography, peaks at about 90 ms, and reflects activity in both primary and secondary visual cortex (see Foxe and Simpson, 2002, for a detailed description). The subsequent P1 has a more dorsal bilateral occipital scalp topography and peaks at about 100 ms. The P1 has generators largely in the dorsal visual stream, but also reflects activity from the ventral visual stream (Di Russo et al., 2002). The N1, with a lateral occipito-temporal scalp distribution, peaks at about 160 ms, with major generators located in the ventral visual stream, in lateral occipito-temporal areas. Importantly, componentry arising from the dorsal or ventral visual stream can modulate independently (Doniger et al., 2000), indicating that the integrity of each can be independently assessed (see Butler et al., 2007).

The current study used high-density, 128-channel EEG to assess electrophysiological markers of sensory-perceptual processing in 15 linguistic-color synesthetes and 15 age- and sex-matched non-synesthete controls. Stimuli were designed to selectively bias the dorsal or the ventral visual stream. To date, early sensory-perceptual differences in synesthesia have not been assessed. Since linguistic-color synesthesia involves stimulus features that are largely processed in the ventral stream (i.e., letters and words), we reasoned that any early processing differences in synesthesia might be mainly found in the parvocellular, rather than the magnocellular pathway.

Methods

Participants

15 female linguistic-color synesthetes (mean age = 34.9, SE = 3.3 years) and 15 female, non-synesthete controls (mean age = 37.1, SE = 3.9 years) were tested. Recruitment criteria and consistency testing of synesthetes are described in detail in Barnett et al. (2008). Non-synesthetes were screened with a detailed questionnaire to ensure that they did not experience synesthesia or any associated traits (e.g., personalities for numbers). None of our participants reported a history of neurological disorders and all reported normal or corrected-to-normal vision without color blindness which we confirmed using the Ishihara test (Ishihara, 1992). The synesthesia group contained two left-handers and the control group one left-hander according to the Edinburgh Handedness Inventory (Oldfield, 1971). There were no between-group differences for age [$t_{(28)}$=.428, P=.627] or laterality quotient [$t_{(28)}$=.445, P=.660]. The average consistency score for synesthetes was 95.4% (SE=1.2). The majority of synesthetes in this sample (12 of the 15) reported experiencing concurrents (color to linguistic stimuli) in the 'mind's eye'. Three reported that concurrents are experienced both in the 'mind's eye' and projected externally. The experimental protocol was approved by the School of Psychology Ethics Committee, Trinity College Dublin and all participants gave written informed consent to participate prior to the study.
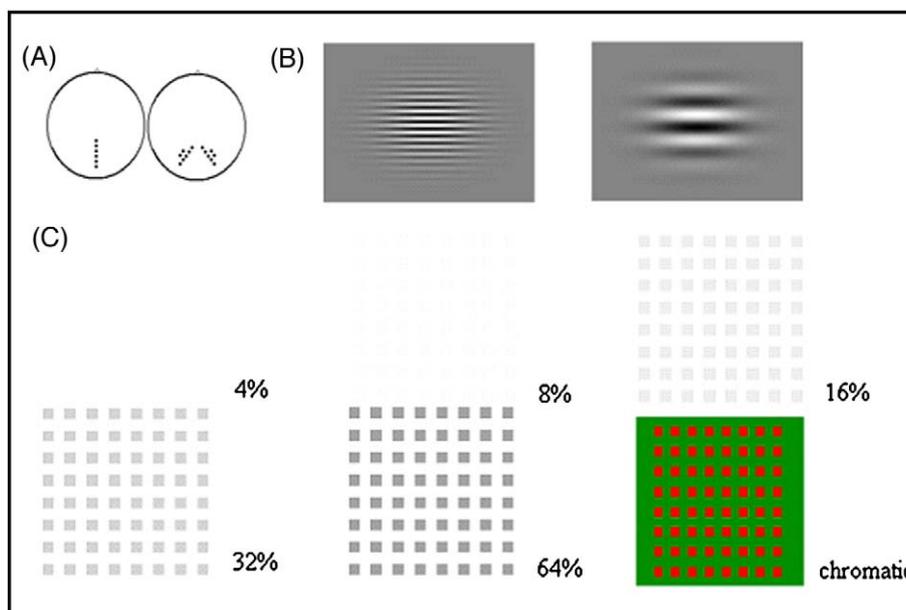
Fig. 1. Electrode location and stimuli. (A) Location of occipital electrodes subjected to ANOVA for (A) C1 (midline) and (B) P1/N1/P2 (left and right lateral occipital) components. Magnocellular and parvocellular stimuli. (B) Examples of spatial frequency Gabor patches (1 and 5 cycles/degree) used in experimental condition 1 and (C) check stimuli used in experimental condition 2. Check stimuli were presented at 5 different contrasts (4%, 8%, 16%, 32%, 64%) and in color.

Experimental stimuli

Stimuli were presented using Presentation® software (Neurobehavioural Systems, http://www.nbs.neuro-bs.com/). The EEG assessment was run in a quiet, dimly lit room and stimuli were presented on an Iyamaha CRT monitor with a frame rate of 100 Hz. See Fig. 1 for examples of stimuli.

Gabor stimuli

Gabor patches were presented against a light grey background that was isoluminant with the mean luminance of the stimuli. The spatial frequency of each stimulus was either 1.0 cycle/degree ('Low Spatial Frequency' or LSF) or 5 cycles/degree ('High Spatial Frequency' or HSF). Stimuli subtended 5.9 by 3.9° of visual angle with a viewing distance of 114 cm. Gabor stimuli were presented over 3 separate blocks in random order for 60 ms, with random ITIs of 750, 800, 850, 900, 950, 1000 and 1050 ms. To maintain attention, line drawings of 6 different animals were incorporated into the random sequence. Two different types of animal images were presented within each block, one of which was assigned as the target stimulus. Each block contained 100 presentations of each Gabor patch (for a total of 300 LSF and 300 HSF stimuli) and 40 animals, 20 of which were targets. Participants were required to respond to target animals and withhold responses to non-target animals. Performance was high for both groups and there was no difference in accuracy between controls (mean=96.0%, SE=1.5) and synesthetes (mean=98.7%, SE=3.8) [$t_{(28)}$=−1.798, P=.083].

Check stimuli

Each check stimulus comprised an 8 by 8 array of isolated squares presented against a white background. Check patterns subtended 7.2 by 7.2 of visual angle at a viewing distance of 114 cm and each square within the array measured 0.49 by 0.49° of visual angle. Stimuli were presented at 5 luminance contrasts (4%, 8%, 16%, 32%, 64%). A chromatic check pattern was presented in a separate block. This stimulus was red and appeared against a luminance-matched green background. Perceptual isoluminance of the chromatic check pattern was established for each participant using flicker photometry (Greenstein et al., 1998; Zemon et al., 1991). The achromatic check stimuli were presented over 6 blocks in random order for 60 ms, with

random ITIs of 750, 800, 850, 900, 950, 1000 and 1050 ms. Each block contained 50 presentations of each check stimulus at each contrast level (for a total of 300 presentations of each stimulus) and 20 animals, 10 of which were assigned as targets. The last, chromatic block consisted of 300 presentations of the colored check with the same ITIs and animals randomly distributed. Again, participants were required to respond to target animals and withhold responses to non-targets. Performance was high for both groups and there was no difference in accuracy between controls (mean=98.6%, SE=4.7) and synesthetes (mean=99.4%, SE=1.8) [$t_{(28)}$=−1.379, P=.229].

On completion of the EEG study, synesthetes completed a short questionnaire in which they were asked whether they experienced color associated with any of the stimuli involved in the experiment (e.g., Gabor patches, achromatic and chromatic checks or animals). None of the synesthetes reported color experiences elicited in response to any of these stimuli.

EEG acquisition

EEG was recorded continuously using an Active 2 system (Biosemi™, The Netherlands) from 128 scalp electrodes and two additional electrodes on the mastoids. The EEG was continuously sampled at 512 Hz and stored for offline analysis. The impedances at each electrode were kept below 25 kΩ. Eye movements were recorded using two electrodes at the outer canthi of the right and left eyes and two above and below the centre of the right eye. Data were analysed using Brain Electric Source Analysis (BESA) Version 5.18 software (http://www.besa.de/). To display and analyse the data, data were filtered with a 0.5 Hz high-pass filter and a 35 Hz low-pass filter and referenced to the electrode FPz. Stimulus-locked data were segmented into epochs of −100 to 300 ms.

Artifact removal

EEG signals were corrected for horizontal and vertical EOG artifacts using the movement correction procedure outlined by Berg and Scherg (1994). Data from noisy or flat electrodes was replaced using spherical spline interpolation (Perrin et al., 1989) implemented by BESA. All electrode channels were subjected to an artifact criterion

Table 1
Latencies at which data were exported for each experimental condition (Gabors, checks) for each component (C1, P1, N1, P2)

Component	Experiment 1: Gabors		Experiment 2: checks	
	Stimulus	Latency (ms)	Stimulus	Latency (ms)
C1	LSF	n/a	8%	66–86
	HSF	65–85	16%	56–76
			32%	56–76
			64%	50–70
			Chromatic	45–65
P1	LSF	105–125	8%	90–120
	HSF	135–155	16%	95–105
			32%	85–105
			64%	75–95
			Chromatic	85–105
N1	LSF	144–184	8%	150–170
	HSF	158–178	16%	130–150
			32%	115–135
			64%	115–135
			Chromatic	125–135
P2	LSF	210–230	8%	205–225
	HSF	214–234	16%	210–230
			32%	210–230
			64%	210–230
			Chromatic	180–200

of ±100 μV. Trials that passed this criterion were averaged separately for each condition and group. For the first main experimental condition (i.e. Gabor patches), 14.2% of all trials were rejected on average. There was no difference between groups for the number of trials that survived artifact correction (synesthetes: mean=519.3±9.3;

controls: mean=506.3±22.0) [$t_{(28)}$=.544, P=.591]. For the second experimental condition (i.e. check patterns), 18.2% of trials were rejected on average. Again, the groups did not differ in the number of trials that survived artifact correction (synesthetes: mean=1528.3±51.6; controls: mean=1415.8±80.6), [$t_{(28)}$=−1.503, P=.250].

Data analysis

Neither group elicited a C1 in response to the LSF Gabor patches. Independent samples t-tests were used to assess ERP components elicited by the HSF Gabor stimuli. Checks at 4% contrast did not elicit waveforms with an obvious C1, P1, N1 morphology. To assess group differences in this condition, grand-average waveforms were
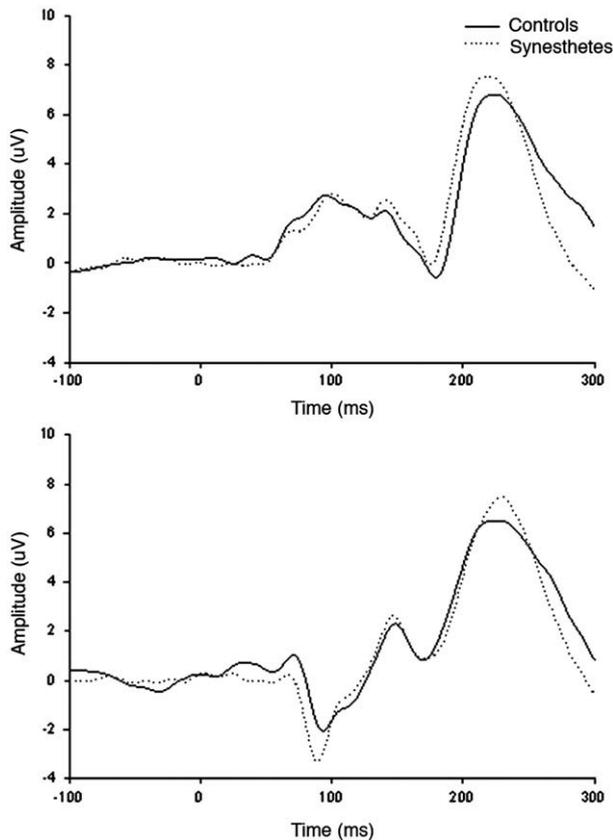
Fig. 2. Group averaged waveforms for controls (n=15) and synesthetes (n=15) in response to (A) LSF (1 cycle/degree) and (B) HSF (5 cycle/degree) Gabor patches. Waveforms show the mean amplitude (μV) of the C1 response at six midline sites.
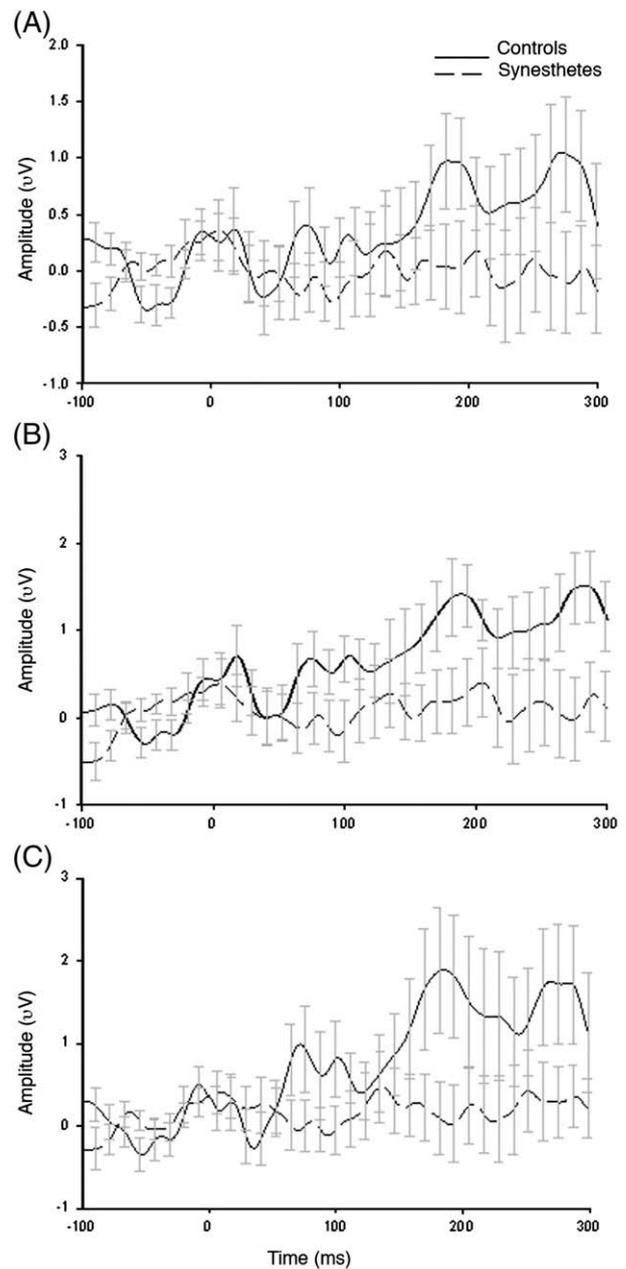
Fig. 3. Check stimuli presented at 4% contrast. Grand-average waveforms are shown for controls (n=15) and synesthetes (n=15). Error bars represent 1 SE of the mean and are plotted for waveforms obtained from (A) C1 midline electrodes and P1 electrodes in the left (B) and right (C) hemispheres respectively.

calculated for each group and plotted with 1 SE of the mean shown at each time window (Fig. 4). For all other stimuli, peaks were detected for each condition in the grand-average waveforms across groups. The latency at which the peak occurred was used to obtain individual subject amplitudes (μV)±1 ms around the peak latency (Table 1).

Amplitude (μV) data were analysed using SPSS software. Separate mixed repeated measures analyses of variance (ANOVAs) were run for each component (C1, P1, N1, P2) with group (controls or synesthetes) as the between-subjects factor and hemisphere (left, right) and either spatial frequency (HSF, LSF) or contrast (4%, 8%, 32%, 64%) as the within-subjects factors. For the N1 and P2 there was an additional within-subject factor of hemisphere (left, right). All tests were 2-tailed with an α level of $P < 0.05$. The ERP components elicited by the chromatic check patterns were analysed separately using independent t-tests.

Grand-average waveforms for each group in each condition were used to select electrode sites where C1, P1, N1 and P2 components were the most pronounced (Figs. 2A and B); these distributions were entirely consistent with the extant literature (e.g., Murray et al., 2001). For the C1 component, 6 midline occipital electrodes were chosen. For the P1, N1 and P2 components, a cluster of 7 electrodes in mirror image locations in each hemisphere was chosen. In the left hemisphere P1, N1 and P2 locations were close to or included O1, P3, PO7 and PO3. In the right hemisphere, locations were close to or included O2, P4, PO8 and PO4 (Fig. 1).

Results

Responses to Gabor patches

While LSF Gabor stimuli did not elicit a C1 response in either group, HSF Gabor stimuli elicited a robust C1 response. Synesthetes showed a significantly enhanced C1 component (negative peak at 90 ms) in response to HSF Gabor patches relative to controls [$t(28) = 2.412$, $P = .023$] (Fig. 3). It should be noted that differences appeared to precede the onset of the C1 response, which is considered the earliest discernable VEP cortical visual response (Molholm et al., 2002), raising the possibility of baseline differences.

In contrast, there were no between-group differences in amplitude for LSF or HSF Gabor stimuli for either the P1 [$F_{(1, 28)} = .001$, $P = .972$] or N1 [$F_{(1, 28)} = .171$, $P = .682$] components. There was no between-group difference for the P2 component for Gabor stimuli [$t_{(28)} = 1.295$, $P = .265$]. There was a trend towards a group by hemisphere interaction [$t_{(28)} = 3.964$, $P = .056$]. Synesthetes had higher amplitudes to Gabors in the left hemisphere, while controls had higher amplitudes to Gabors in the right hemisphere.

Responses to achromatic check patterns at 4% to 64% contrast

Stimuli presented at 4% contrast are known to be processed almost exclusively by the magnocellular system (Kaplan, 1991). We found that the responses from synesthetes were characterized by trend towards a decrease relative to controls at both the midline and lateral occipital electrode sites across all time points from 70 ms on (Fig. 4 and 5). However, checks at 4% contrast did not elicit waveforms with an obvious C1, P1, N1, P2 morphology in either group making it impossible to statistically compare amplitudes of specific components. Nevertheless, at both midline and lateral sites there are multiple time points where the amplitude of the average waveforms do not overlap at one SE of the mean and the overall, qualitative difference is consistent across all time points and across electrode sites (Fig. 3). We performed topographical analyses to compare the overall differences in amplitude in response to 4% contrast checks between synesthetes and controls in 4 ms time windows (Fig. 4). The maps show a clear decrease in response to stimuli presented at 4% contrast in the synesthesia group.

There were no differences in responses between the groups in the C1 component when stimuli were presented at 8% to 64% levels of contrast [$t_{(28)} = .324$, $P = .574$] (responses to the 4% level of contrast were not included because the peaks could not be identified). However, we found marked differences in P1 response amplitudes when checks were presented at contrast levels from 8% to 64% [$F_{(1, 28)} = 4.717$, $P = .038$]: P1 amplitudes were almost doubled in the synesthesia group (Figs. 5 and 6). This group difference was consistent across the 8–64% contrast range as demonstrated by the lack of a significant interaction between group and contrast [$F_{(3, 84)} = .144$, n.s.]. There were no between-group differences found for the N1 component [$F_{(1, 28)} < 1$, n.s.]. A greater effect of high luminance contrast is synesthetes is consistent with enhancement of the parvocellular pathway in this group. There was no significant P2 between-group difference for check stimuli [$t_{(28)} = 0.658$, $P = .424$], although there was a trend towards a group by hemisphere interaction [$t_{(28)} = 3.579$, $P = .068$]. Synesthetes had higher amplitudes to checks in the left hemisphere while controls had higher amplitudes to checks in the right hemisphere. Topographical analyses confirm the increase in the P1 amplitude of the P1 in the synesthesia group (Fig. 6).

Responses to chromatic check patterns

Since the red checks and green background used in the chromatic stimuli were matched for luminance, this stimulus should not activate the magnocellular system but was instead expected to saturate the parvocellular system (as this stimulus uses maximal color contrast).
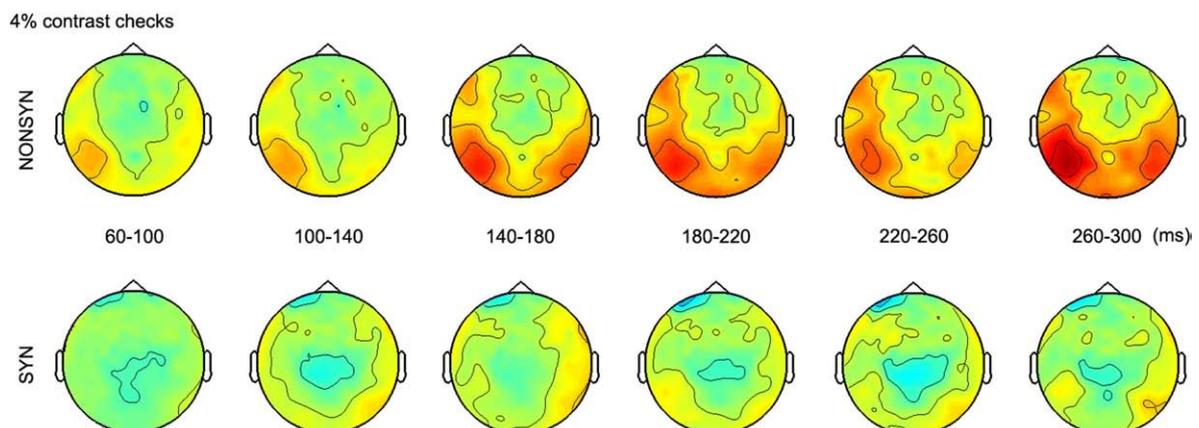

Fig. 4. Check stimuli presented at 4% contrast. Scalp topography map showing amplitude distribution in 40 ms time windows from 60 to 300 ms for controls ($n = 15$) and synesthetes ($n = 15$).

There were no between-group differences in the amplitude of the C1 [$t_{(28)}$=1.266, P=.216] or P1 [$F_{(1, 28)}$=.636, P=.432] responses to this stimulus. There was no difference in the N1 component for chromatic stimuli in either hemisphere [both $F_{(1, 28)}$<1, n.s.]. Visual inspection of the waveform (Fig. 7) however, shows that synesthetes exhibited an average increase in amplitude in response to chromatic checks at
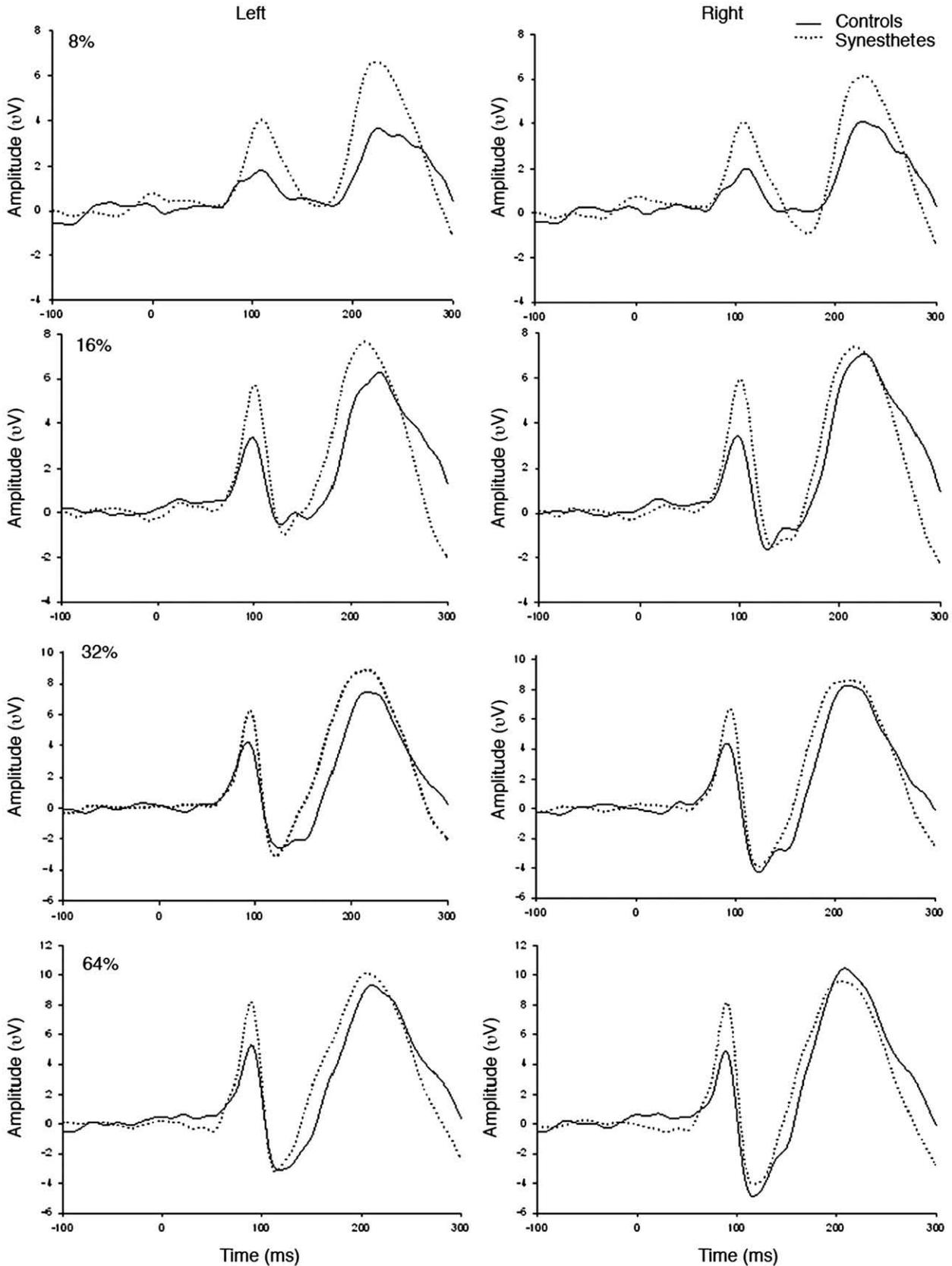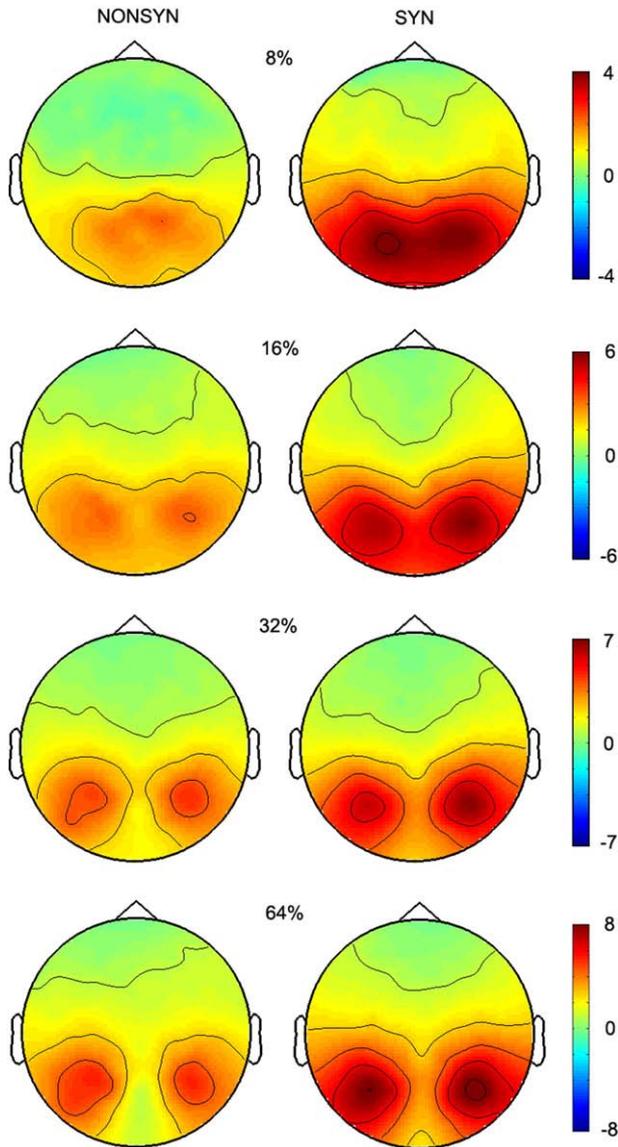

Fig. 5. Grand-average waveforms are shown for controls (n=15) and synesthetes (n=15) in response to check stimuli presented in each contrast condition (8%, 16%, 32%, 64%). Waveforms represent mean amplitude (μV) of the P1 response at seven electrodes sites in the left and right hemispheres respectively.

Fig. 6. Check stimuli presented at 8%, 16%, 32% and 64% contrast. Scalp topography map showing amplitude distribution for the P100 for controls ($n=15$) and synesthetes ($n=15$).

around 190 ms relative to controls. Post hoc analysis of data at 180 to 200 ms showed that this difference was significant in both the left [$F_{(1, 28)}=-2.712$, $P=.011$] and right hemisphere [$F_{(1, 28)}=-2.105$, $P=.044$] (Fig. 7).

Discussion

We report for the first time differences in early sensory-perceptual components of the VEP in linguistic-color synesthetes compared to non-synesthete controls. While synesthete and control groups had identical VEP morphologies, responses from synesthetes were characterized by marked differences in amplitude in early sensory-perceptual components of the VEP in response to simple visual stimuli, that affect both magnocellular and parvocellular pathway responses. Importantly, there were no reports of color experiences elicited in response to any of these simple stimuli, indicating that the effects observed reflect fundamental differences in early visual sensory processing in this fascinating population.

Synesthetes showed an enhanced C1 in response to HSF Gabors that preferentially bias activation of the parvocellular system. This difference was manifested between 65 to 85 ms, suggesting possible hyperactivation of very early sensory processing, with the major generators in the primary and secondary visual cortices (V1 and V2) (see Kelly et al., in press, Martinez et al., 1999). In contrast, LSF Gabor stimuli did not elicit a C1 response in either group, consistent with the notion that the C1 is largely generated by parvocellular inputs (see Schechter et al., 2005). Synesthetes showed a trend towards decreased cortical responsiveness in response to magnocellular-biased check patterns presented at 4% contrast. However, the lack of marked, identifiable peaks in response to the 4% stimuli in either group makes interpretation of this condition difficult. At 8% contrast the parvo-cellular sub-system is recruited (Tootell et al., 1988) and from this level to 64% contrast synesthetes showed a consistent increase in the P1 response to parvocellular-biased check patterns. A simple explanation that is consistent with all these data is that synesthetes have a decrease in magnocellular system responsiveness and a concomitant increase in parvocellular system responsiveness.

Synesthetes showed only a slight but non-significant increase in the P1 in response to a chromatic check of red squares presented against a green background. This stimulus saturates the parvocellular system and may thus occlude any advantage in parvocellular responsiveness in synesthetes in this condition. We also noted a significant increase in the amplitude of the VEP at around 190 ms in a post hoc analysis. The interpretation of this relatively late difference in processing simple color stimuli is not obvious.
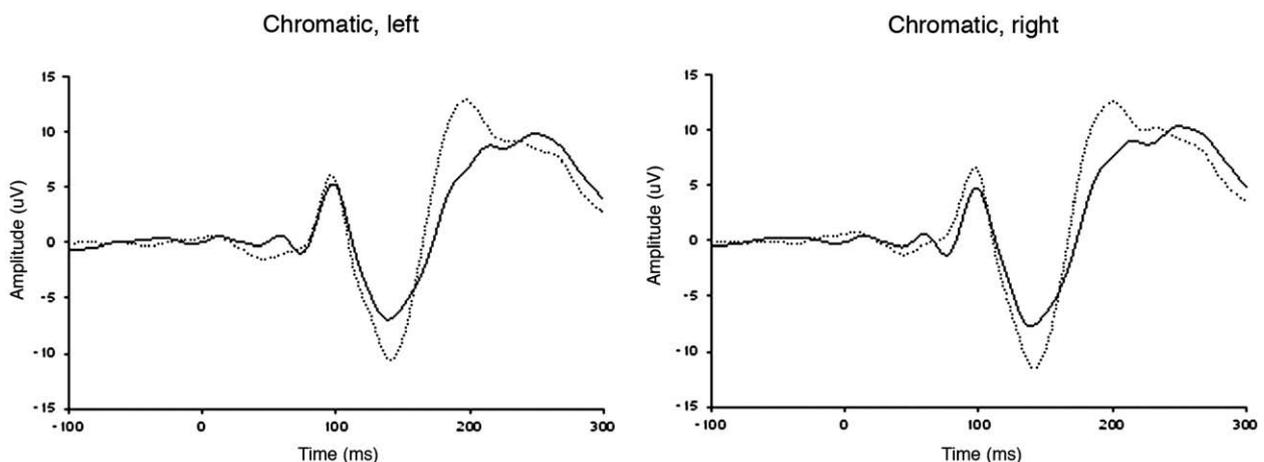
Fig. 7. Grand-average waveforms for controls ($n=15$) and synesthetes ($n=15$) in response to the color stimuli. Waveforms represent mean amplitude (μV) of the P1 response at seven electrodes sites in the left and right hemispheres respectively.

This is the first study to report cortical responses to stimuli that do *not* induce synesthesia in a group of linguistic-color synesthetes. Indeed, the electrophysiological differences we report are manifested earlier than the stimuli that commonly induce synesthesia are recognised: letter strings, for example, are not usually differentiated until approximately 140 to 220 ms (Allison et al., 1999, Nobre et al., 1998, Schendan et al., 1998). The C1 and P1 components of the VEP reflect earlier aspects of visual processing in V1 and extrastriate regions respectively. Both the C1 and P1 are essentially automatic, non-task-specific components that index sensory-perceptual processing in dorsal and ventral regions of extrastriate visual cortex (Foxe and Simpson, 2002). They have both been shown to be largely cognitively impenetrable (see Clark and Hillyard, 1996), especially for central stimulus presentations (Handy and Khoe, 2005). Butler et al. (2007) argue that bottom-up processing deficits in the magnocellular system might be responsible for visuo-perceptual differences in schizophrenia. For future investigations, it would be interesting to determine the behavioral correlates of the effects we observed here. For example, it is likely that synesthetes will show heightened sensitivity in tasks that recruit parvocellular systems such as color discrimination or differences in the resolution of high spatial frequency information. There is already some complementary behavioral evidence to suggest low level sensory differences in synesthesia. Banissy et al. (2008) report that synesthetes who experience touch when watching someone else being touched, have heightened spatial tactile discrimination of gratings. Additionally, linguistic-color synesthetes have been found to perform better on a test color perception (Yaro and Ward, 2007).

There are a number of possible scenarios to explain the relationship of the differences we observe in early visual processing to the overt manifestation of the synesthesia phenotype in these subjects, i.e., the induction of specific color percepts in response to specific linguistic stimuli. First, these phenomena may be caused independently by differences in cortical wiring at several levels and unrelated functionally. Second, differences in early visual processing may indirectly cause a tendency to develop the paired associations of inducing stimuli with color percepts. Perhaps the increased responses to stimuli that are biased towards the parvocellular processing stream reflect an over-elaboration of this pathway that, through the period when graphemes are being learned, alters the normal consolidation of responses to graphemes and manifests as a tendency to co-activate color responses. It is difficult to see why hyperactivation alone would have this result but it cannot be excluded as a possibility, especially as the perceptual consequences of the differences in VEP amplitudes we observe here are unknown. It is also not clear, however, whether this model can be extended to explain other types of synesthesia (Barnett et al., 2008, Bargary and Mitchell, 2008). Third, the experience of synesthesia may, by altering perceptual experience, feed back somehow and result in alterations in early visual circuitry. This seems highly unlikely, especially as early visual processing areas mature much earlier than higher-order areas associated with letter processing, for example (reviewed in Dehaene and Cohen, 2007, Guillery, 2005). The least convoluted interpretation is that the early differences reflect altered circuitry in early visual areas, while the cross-activation that results in the overt perceptual phenotype of synesthesia is the result of altered circuitry between higher perceptual areas (e.g. the grapheme area and V4) (Ramachandran and Hubbard, 2001). The concurrent experience of color predominates in synesthesia. If adjacency (e.g., between grapheme and color regions in the fusiform) influences synesthetic experience we might expect face-color synesthesia to be as common as linguistic-color synesthesia (in fact it is extremely rare). The current data suggest that the balance of spatial frequency and contrast inputs differ in the visual system of synesthetes. This may be a factor in explaining why graphemes might more commonly induce synesthesia, given their high spatial frequency and contrast, whereas face perception relies on low spatial frequency information.

It will be interesting to determine whether similar differences in early visual processing are apparent in other forms of synesthesia, especially those without obvious visual involvement such as tasting words (Ward and Simner, 2003), for example, and also to ask whether such early processing differences extend to other sensory domains. A recent study reported differences in the auditory evoked potential of synesthetes that occurred at around 122 ms (Beeli et al., 2008). This was interpreted as the signature of very early cross-activation of the color area, leading to the synesthetic experience. However, synesthetes in this study reported the induction of color even to the control pseudoword stimuli used, preventing a comparison with stimuli that did not induce synesthesia. Given our findings, an alternative possibility is that the early differences in the auditory evoked potential were not in fact specific to synesthesia-inducing stimuli nor directly linked to synesthetic cross-activation, but rather representative of more general early processing differences in the auditory domain similar to those we observe in the visual domain.

We and others have recently described the co-occurrence in single families of diverse forms of synesthesia (Barnett et al., 2008, Ward and Simner, 2005). We proposed that connectivity differences might be initially widespread in synesthetes but resolved differently through experience-dependent mechanisms or subject to stochastic developmental variation, resulting in an apparently discrete expression of synesthesia in each individual (Barnett et al., 2008, Bargary and Mitchell, 2008). The current data are consistent with this model, as early differences in visual processing may be an independent marker of widespread connectivity differences. They are also consistent with a recent diffusion tensor imaging study which found greater anisotropic diffusion indicating increased structural connectivity in a group of synesthetes (Rouw and Scholte, 2007). Interestingly, differences were not confined to regions of fusiform and inferior temporal cortex, where the grapheme area and V4 are located, but were also present in parietal and frontal regions. Differences in cortical circuitry in synesthetes may be thus far more extensive than the apparently discrete, overt phenomenology of synesthesia would suggest.

Acknowledgments

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