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Time Course of Neural Activity Correlated with Colored-Hearing Synesthesia

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Synesthesia is defined as the involuntary and automatic perception of a stimulus in 2 or more sensory modalities (i.e., cross-modal linkage). Colored-hearing synesthetes experience colors when hearing tones or spoken utterances. Based on event-related potentials we employed electric brain tomography with high temporal resolution in colored-hearing synesthetes and nonsynesthetic controls during auditory verbal stimulation. The auditory-evoked potentials to words and letters were different between synesthetes and controls at the N1 and P2 components, showing longer latencies and lower amplitudes in synesthetes. The intracerebral sources of these components were estimated with low-resolution brain electromagnetic tomography and revealed stronger activation in synesthetes in left posterior inferior temporal regions, within the color area in the fusiform gyrus (V4), and in orbitofrontal brain regions (ventromedial and lateral). The differences occurred as early as 122 ms after stimulus onset. Our findings replicate and extend earlier reports with functional magnetic resonance imaging and positron emission tomography in colored-hearing synesthesia and contribute new information on the time course in synesthesia demonstrating the fast and possibly automatic processing of this unusual and remarkable phenomenon.

Keywords: colored-hearing, colored-perception, cross-modal, EEG, LORETA, synesthesia

Introduction

Synesthesia is a fascinating perceptual phenomenon in which certain stimuli lead to a sensation in 2 or more sensory modalities. For example, hearing a tone (inducing stimulus) leads to the experience of a color (concurrent perception) in so-called colored-hearing synesthetes. Thus, auditory stimulation leads to a visual perception. The most common form is grapheme-color synesthesia in which visual perception of a character in black ink induces its perception in color (Rich et al. 2005). In a strict sense only one sensory modality (here vision) is involved. Basically, any combination of 2 modalities is possible, even rare combinations such as music-to-taste synesthesia have been reported (Beeli et al. 2005). Synesthetes usually report lifelong experience of their synesthetic perceptions and describe them as automatic and involuntary, even if they wanted to suppress them (see Rich and Mattingley 2002). The high degree of automaticity and the strength of synesthetic perception have recently been supported by behavioral data (Dixon et al. 2000; Mattingley et al. 2001; Elias et al. 2003; Beeli et al. 2005).

Recently, modern brain imaging methods have been used to uncover the possible neural underpinnings of synesthesia. Six brain imaging studies have been published so far examining neural activations in groups of synesthetes. In these studies, the color perception in the synesthetes was either induced by auditory (tones and words) or visual (graphemes and words) stimuli. Most studies uncovered activations within the color area V4 and/or in the posterior temporo-occipital area (PIT, posterior inferior temporal gyrus) in response to the inducing stimuli irrespective of stimulus modality. Thus, these studies clearly demonstrate that the subjective synesthetic perception of color is inevitably linked to activations in brain areas typically involved in color and object perception (Paulesu et al. 1995; Nunn et al. 2002; Hubbard et al. 2005; Rich et al. 2006; Sperling et al. 2006). However, one study (Weiss et al. 2005) uncovered induced activations in left-sided IPS emphasizing the role of the IPS in synesthetic experience. Although these studies clearly demonstrate which brain areas are involved in the generation of the induced color perception in synesthetes, there is currently no information available about the time course of the activation in these brain areas. In case of knowing the time course of activation one would be able to generate more sophisticated theories about synesthetic experiences. For example, we do not know so far whether the activation in V4 or PIT occurs early or late within the sequence of information processing. If these activations occur early in the course of information processing (e.g., 100 ms after onset of the inducing stimulus), one might argue for more automatic processes driving the synesthetic color perception. However, if these activations occur later (e.g., 300–800 ms after stimulus onset) this might support top-down processes controlling color synesthesia.

In order to unravel the sequence of cortical activations during synesthetic perceptions we used event-related potentials (ERP) to words and letters in combination with an established method to estimate the intracortical activations from the ERPs in the millisecond range (low-resolution brain electromagnetic tomography: LORETA; Pascual-Marqui et al. 1994, 1999). The only previously published ERP study on synesthesia (Schiltz et al. 1999), demonstrated differences between synesthetes and controls at approximately 200 ms after stimulus onset at frontal and central electrodes, but without the identification of the intracerebral sources of the electrical fields measured on the scalp.

The previously conducted brain imaging experiments on color synesthetes have used experimental conditions (e.g., word-presentation), which were compared with a control condition. Studies using auditory input employed tone-presentation as baseline condition (Paulesu et al. 1995; Nunn et al. 2002). The logic of these designs was to induce the color synesthesia by presenting words, which are used as inducing stimuli. Tones on the other hand were treated as if they did not induce color synesthesia. However, to our knowledge many synesthetes report beside a grapheme-color-synesthesia some kind of synesthetic visual perception when exposed to tones (tone-form- or tone-color-synesthesia), thus, we hypothesize that some basic processes of synesthesia might have been subtracted in these studies. In the present study we therefore avoided this problem by comparing synesthetes with carefully matched nonsynesthetic controls.

In summary, the present study has 2 aims: 1) to localize intracortical activations (on the basis of auditory evoked potentials) related to synesthetic color perception induced by auditorily presented words or letters, and 2) to determine the time course of these intracortical activations during synesthetic processing on a millisecond basis.

Materials and Methods

Subjects

We tested 16 so-called "color-hearing" synesthetes, that is, persons who see colors when hearing words or sounds. All synesthetes reported also synesthesia for visually presented words and letters. Some could indicate a slightly stronger synesthetic sensation for one modality. All synesthetes reported lifelong history of "color-hearing" synesthetic perception (i.e., as long as they could remember) and were tested carefully for their color perception to letters (A–Z) and numbers (0–9). They were asked to produce their synesthetic colors elicited by letters and digits as accurately as possible using a digital image-editing software (Adobe Photoshop 7.0). All synesthetes had to repeat this task (on average 55 days later), and all of them demonstrated constant and consistent reproduction (findings of these tests will be reported elsewhere; Beeli et al. forthcoming). This procedure is based on the established "test of genuineness" that is typically used for diagnosis of synesthesia (Baron-Cohen et al. 1987). Three subjects were excluded from further analysis because of left-handedness resulting in a total of 13 synesthetes included in the ERP study. These subjects were matched with nonsynesthetes according to age, education, and sex (mean age ± standard deviation: synesthetes 25.6 ± 9.3, controls 26.1 ± 6.4; mean years of education: synesthetes 15.3 ± 1.8, controls 14.3 ± 0.9; groups did not differ significantly: $P = 0.88$ for age, and $P = 0.13$ for education). All subjects were consistently right-handed according to the Annett-Handedness-Questionnaire (Annett 1970) and each group comprised 8 women and 5 men.

Stimuli

Three categories of auditory stimuli were used: words, pseudowords, and letters. Words and pseudowords consisted of 2 syllables and had a duration of 1000 ms. Words were selected from a previous study (Gianotti et al. 2006) where they had been rated as emotionally neutral. The following words were used: Ecke (corner), Format, Forum, Gebiet (area), Kugel (sphere), Länge (length), Pfeife (pipe), Phase, Regel (rule), Sitte (conventions), Umbau (alteration), Waage (balance), Woche (week), Zitat (citation). Pseudowords were kasi, dale, dipu, tifa, peto, dusa, sepa, kobi, soki, bufe, dosu, betu, pofi, kelu. Letters (a, e, i, o, u, b, c, d, f, g, l, p, r, t) had a shorter duration (500 ms), were randomly selected and were pronounced in German articulation, for example, "t" pronounced as [te]. Three hundred items were presented (100 per category) with an interstimulus interval of 1500 ms. All stimuli were vocalized by a female speaker and digitally recorded. To ensure that the subject concentrated on the stimuli, 10% of the stimuli were followed by a piano tone after which the subject had to repeat aloud the previously heard stimulus (1-back-task). Originally, pseudowords were chosen because we hypothesized that they should elicit different synesthetic perceptions compared with regular words. However, all synesthetes reported synesthetic perceptions for all stimuli. Therefore, pseudowords were not analyzed separately, but combined with regular words in order to enhance statistical power. All auditory stimuli were presented via high-fidelity stereo earphones with an average intensity level of 75 dB (sound pressure level).

Electroencephalography Recordings and Preprocessing

A 30-channel electroencephalography (EEG) was recorded according to the 10-10 system (Fp1/2, F3/4, F7/8, Fz, FT7/8, FC3/4, FCz, T7/8, C3/4, Cz, TP7/8, CP3/4, CPz, P7/8, P3/4, Pz, O1/2, Oz) with the BrainAmp system of BrainProducts, Munich, Germany. Additionally, 2 EOG channels were corecorded, located below the left and right outer canthi of the eyes. Recording reference was at FCz, with off-line rereferencing to average reference. Digital sampling rate was 500 Hz, on-line filtering 0.1–100 Hz, off-line filtering 0.5–30 Hz, impedance was kept below 10 kOhm. Subjects were sitting comfortably in a chair while hearing the stimuli. In order to impede any direct stimulation of visual brain areas subjects were told to keep their eyes closed.

ERP Analysis

After recording, trials with muscle-artifacts were excluded after visual inspection of each EEG sweep. Thus, ERPs were calculated for each condition and subject on the basis of artifact-free EEG sweeps. ERPs of different conditions were statistically compared between both groups using the amplitudes and latencies of the P1, N1, and P2 taken from the Cz position. Cz was used because auditory evoked potentials usually reveal the most prominent peaks at this electrode lead. Latencies and amplitudes of these components were automatically detected in every subject. The statistical between-groups test was done on the basis of a *t*-test for independent samples.

Low-Resolution Brain Electromagnetic Tomography

The 3D distribution of electric neuronal activity was computed with the LORETA method (Pascual-Marqui et al. 1994, 1999). This distributed source localization technique has recently received important validation from studies combining LORETA with functional magnetic resonance imaging (fMRI) (Vitacco et al. 2002; Mulert et al. 2004, 2005), with structural MRI (Worrell et al. 2000), and with positron emission tomography (PET) (Pizzagalli et al. 2004; Zumsteg et al. 2005). LORETA computes electrical activity by assuming similar activation among neighboring neuronal clusters. A 3-shell spherical head model and EEG electrode coordinates derived from cross-registrations between spherical and realistic head geometry were utilized, which were both registered to the digitized MRI available from the Brain Imaging Centre, Montreal Neurologic Institute (MNI) (Evans et al. 1993). Computations are performed on a regular cubic grid at 7-mm resolution, producing a total of 2394 cortical gray matter voxels. Anatomical labels such as Brodmann areas are reported using an appropriate correction (Brett et al. 2002) from MNI to Talairach–Tornoux space.

Results

All subjects showed perfect accuracy in the 1-back-task (99–100% correct answers), which proves that they were attentively listening to the stimuli. The average auditory ERP computed across all conditions for both groups shows the typical components (P1, N1, P2) (see Fig. 1*A*) and the typical scalp distribution of N1 (Fig. 1*B*). As expected, LORETA reveals intracerebral sources of electric activity for the N1 component in left and right auditory cortices (Pratt et al. 2002; Jaaskelainen et al. 2004; Meyer et al. 2006) with enhanced activation in the left hemisphere as a result of stimulation with verbal material (Fig. 1*C*).

The differences between latencies and amplitudes of the 2 conditions (words and letters) are illustrated in Figure 2. Synesthetes show longer latencies and lower amplitudes in all conditions. Statistically significant differences were found for latencies of the N1 and P2 components and for amplitudes of the P2. The ERPs at Cz for the conditions with significant differences (words and letters) are illustrated in Figure 3.

Based on the scalp distribution of the auditory ERP potentials LORETA images (3D estimates of current densities) were computed for both groups and the different conditions within a time interval of 20 ms around the peaks of the N1 and P2 components (peak latency ± 10 ms identified at Cz). For this statistical test, the current densities estimated by LORETA for each voxel were subjected to a voxel-based whole brain

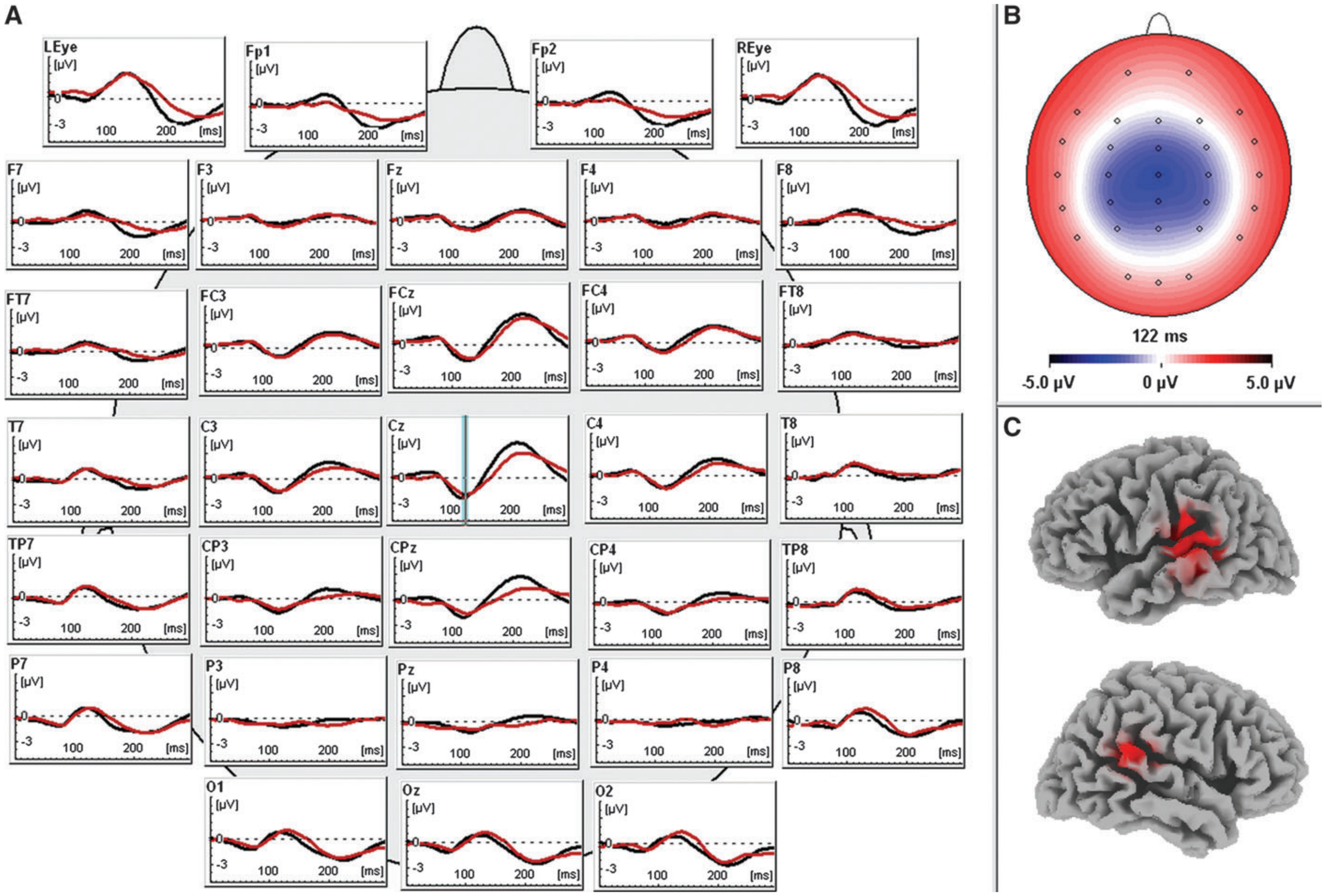


Figure 1. (*A*) Auditory ERP over all conditions for both groups (synesthetes = red, control = black); blue line indicates the N1 component at Cz. (*B*) Right side shows the scalp potential topography of the N1 (122 ms after stimulus onset); blue color corresponds to negative potential values, red to positive potential values, small circles indicate electrode sites. (*C*) Cortical activation in primary and secondary auditory areas estimated with LORETA at N1 (122 ms) displayed in red. Enhanced activation in the left hemisphere corresponds to left-sided language processing. Upper image shows the left hemisphere; lower image shows the right hemisphere.

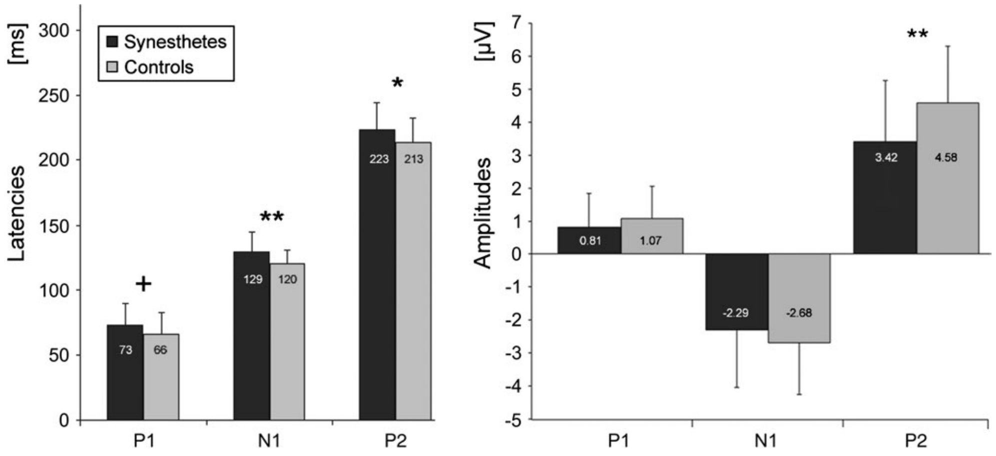


Figure 2. Latencies (left side) and amplitudes (right side) of the 3 grand-mean ERP components (P1, N1, P2) for synesthetes and controls. Synesthetes show longer latencies and smaller amplitudes than controls in all 3 components; significant differences were found in N1 and P2 for latencies, and in P2 for amplitudes ($+P < 0.1$, $*P < 0.05$, $**P < 0.01$).

statistical between-groups *t*-test. Because 2394 *t*-tests were conducted we employed a statistical correction for multiple tests (Bonferoni correction). Thus, only between-group differences passing this corrected threshold were considered as significant. This test identified a between-group difference at the N1 component ($t = 4.38$, $P < 0.01$) for letters at 122 ms (Fig. 4), with synesthetes showing increased activation in left PIT gyrus (local maxima in the Talairach–Tornoux space at: $x = -59$, $y = -25$, $z = -27$), whereas only a tendency for enhanced activation ($t = 3.28$, $P < 0.10$, corrected for multiple comparisons)

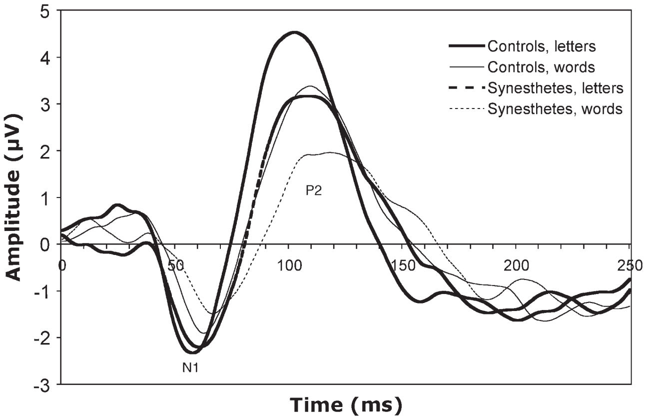


Figure 3. ERPs of letter and words conditions at Cz electrode show delayed reaction and reduced amplitudes for synesthetes (green and blue line), as compared with nonsynesthetes (black and red line). N1 = negative ERP components between 116–137 ms after stimulus onset, P2 = positive ERP components between 206–233 ms after stimulus onset. Significant latency delay at N1 ($P < 0.01$), P2 ($P < 0.05$), significant amplitude reduction at P2 ($P < 0.01$).

was found in the words condition in similar areas as illustrated in Figure 4 (local maxima at: $x = -52$, $y = -53$, $z = -13$) . There was also a significant activation difference in the letter condition within the ventromedial orbitofrontal cortex (OFC) with synesthetes showing stronger intracerebral activations in this area than control subjects (local maxima at: $x = 18$, $y = 31$, $z = -20$).

At the P2 component (around 218 ms latency), synesthetes showed significantly ($t = 3.67$, $P < 0.05$) enhanced activation for words in ventromedial orbitofrontal areas and within the PIT as illustrated in Figure 4 (local maxima at: $x = 4$, $y = 45$, $z = -13$ for OFC and $x = -59$, $y = -46$, $z = -20$ for PIT). The letters-condition at P2 revealed significantly ($t = 4.40$, $P < 0.05$) activated brain areas for synesthetes in several brain areas. We found activation in the left superior frontal gyrus (lSFG, local maxima at: $x = -17$, $y = 52$, $z = 36$), left precuneus (lPre, local maxima at: $x = -24$, $y = -74$, $z = 36$), and right intraparietal sulcus (rIPS, local maxima at: $x = 32$, $y = -53$, $z = 57$).

In order to determine whether the orbitofrontal activation differences might be caused by visually barely noticeable small eye movements, we statistically compared the averaged electrical signals obtained at the eye channels and found no significant differences at the time points of interest (N1: $P = 0.51$; P2: $P = 0.56$).

As an additional step, we computed the average intracerebral activity obtained for words and letters in a time interval over 2000-ms poststimulus onset, in order to compare our ERP-LORETA results to findings obtained by fMRI and PET with lower time resolution (Paulesu et al. 1995; Nunn et al. 2002). Statistical comparison (t-test for independent samples) between both groups showed increased activation in synesthetes within several brain areas (Fig. 4). Local maxima of average activation differences over 0–2000 ms after stimulus onset are located in left V4 (for words at: $x = -52$, $y = -46$, $z = -13$; $t = 3.62$, $P < 0.01$; and for letters at: $x = -52$, $y = -32$, $z = -27$; $t = 3.74$, $P < 0.01$). Furthermore, we found significantly enhanced activation in both conditions and components for synesthetes in mesial and lateral orbitofrontal areas, mainly in the left hemisphere (local maxima for words at $x = -17$, $y = 17$, $z = -20$ and for letters at $x = 11$, $y = 3$, $z = -13$).

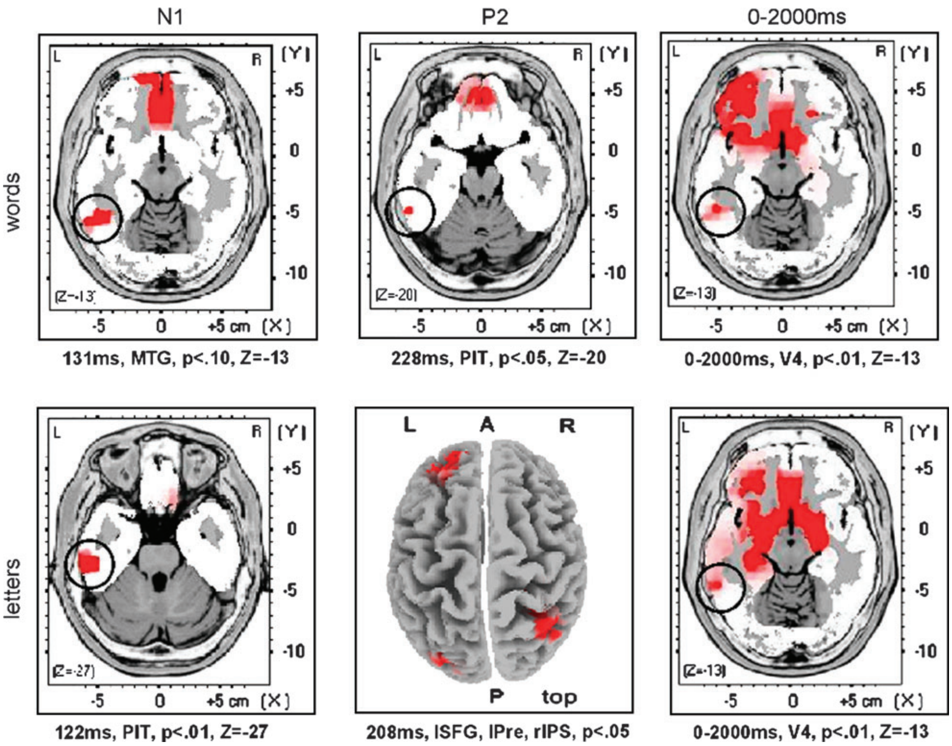
A comparison of our data with previous brain imaging studies (Table 1) shows that the localization with EEG/LORETA is in line with results obtained by fMRI or PET.

Discussion

This study replicates the findings of the few previously published fMRI and PET studies (Paulesu et al. 1995; Nunn et al. 2002; Hubbard et al. 2005; Rich et al. 2006; Sperling et al. 2006) in showing that V4 and PIT are active during color perception elicited by inducing stimuli in color synesthetes. Exploiting the superior time resolution of ERPs we uncovered that these areas are activated very early 122 ms after onset of the inducing auditory stimulus. Even when the average intracortical activation was computed across 2000 ms after onset of the inducing stimulus (thus roughly simulation the time resolution of fMRI), the intracerebral activation pattern remains the same as in the previously mentioned brain imaging experiments. Thus, our study partly uncovers similar results, which are extended by the new finding of the astonishingly very early activation in these areas. Thus, both study questions that have been the motivation of our study have been answered. However, the early activation in V4 and PIT warrants further clarification and interpretation.

This early activation at 122 ms supports the idea of synesthesia as being driven by an automatic process and also supports the reports of synesthetes mentioning that their synesthetic perceptions are automatic and fast. According to the theory of Ramachandran and Hubbard (2001), an increased neuronal wiring between the left PIT and the left V4 might serve as the neuronal basis of “color-hearing” synesthesia. Similarly, Smilek et al. (2001) emphasize re-entry mechanisms interconnecting V4 and PIT. Thus, our findings are in line with both models. However, further explanations are also possible. As reported by Jaaskelainen et al. (2004) there are very early activations (about 60 ms after stimulus onset) in primary auditory cortex (A1) making it possible that multimodal areas in occipito-temporal cortex are activated early via A1. Because we found simultaneous and relatively early (122 ms) activation in auditory and color processing areas one might also hypothesize a simultaneous bottom-up driven activation from lower level structures like the medial geniculate nucleus (MGN). If this is the case there would be an unusual wiring from the MGN to the color processing areas. A further possibility would be that attentional processes might yield to increased activations in V4 or PIT (similarly as it has been shown by Noesselt et al. 2002 in the visual domain for normal subjects). However, these ideas cannot directly account for the specificity of colored-hearing synesthesia and thus needs more research.

The longer latencies for N1 and P2 amplitudes as well as the reduced amplitudes in synesthetes might depend on different sources ranging from different cognitive strategies evoked during synesthesia to a different interconnection between neural networks. Which of these causes are operative is difficult to decide on the basis of current knowledge. A further finding which is difficult to explain is the activation within the OFC. That synesthetes demonstrate stronger OFC and ventromedial cortex activation than nonsynesthetes is somewhat unexpected. These activation increases were found in mesial areas (already at early time points approximately at 122- to 220-ms poststimulus) but also more laterally at later time points. To our best knowledge up to now no one has suggested that these



131ms, MTG, p<.10, Z=-13

228ms, PIT, p<.05, Z=-20

0-2000ms, V4, p<.01, Z=-13

122ms, PIT, p<.01, Z=-27

208ms, lSFG, lPre, rIPS, p<.05

0-2000ms, V4, p<.01, Z=-13

Figure 4. Significantly increased activation for synesthetes as compared with controls displayed in red, predominantly found in orbitofrontal areas and in the left temporo-occipital junction. L = left, R = right, A = anterior, P = posterior, MTG = medial temporal gyrus, V4 = visual association area in the fusiform gyrus. Enhanced brain activity in synesthetes when exposed to words and letters at N1 (first column) and P2 (second column) ERP components, and average activation in synesthetes as compared with controls over a 2000-ms time interval (third column) starting at stimulus presentation onset. *Z* values of axial slices are indicated under each figure, except for P2/letters, where a top view was chosen for best illustration of the results. In all axial slices, the location with maximal activation in temporo-occipital junction (encircled) is specified. Significance levels are indicated under each image.

regions and the functions located herein are important for synesthetes (with the exception of the early frontal scalp EEG differences found in the study of Schiltz et al. 1999). Thus, we can only speculate about the possible reasons of this activation difference. Recent studies exploring the functional neuroanatomy of the OFC and adjacent brain areas have uncovered that several psychological functions are controlled by these regions. Among them are functions associated with reward processing including monitoring, learning, and memory of the reward value of reinforcers. The lateral part of OFC activity is related to the evaluation of punishers that can lead to a change in behavior (Kringelbach 2005; Pizzagalli et al. 2005). The more rostral part of the ventromedial OFC (which is also activated to a stronger degree in synesthetes) appears to be recruited in situations when individuals have to refer to their own mental states or to mental states of others particularly those charged with emotional significance. Others believe on the basis of volumetric brain morphometry data that this area is involved in controlling or modulating fluid intelligence in relation to self-referencing. Beside these studies, there is an increasing amount of literature discussing connections between auditory cortex and orbitofrontal gyrus as well as the involvement of the OFC in auditory information processing (Hackett et al. 1999; Cavada et al. 2000). For example, Frey et al. (Frey et al. 2000, 2004) observed a correlation between activity in the OFC and the superior temporal gyrus and suggest that the OFC is involved in the encoding of nonverbal auditory information. In addition, several studies have uncovered reciprocal connections between the orbitofrontal and parahippocampal regions (Deacon et al. 1983) supporting the idea that the OFC is strongly involved in auditory learning and memory processes.

Table 1
Summary of the most important studies investigating the neuronal basis of grapheme-color-synesthetes

Publication	Method	Modality of presentation	Areas correlated with synesthesia				
			Left V4	Left PIT	Frontal cortex	Lingual gyrus	IPS
Nunn et al. (2002)	fMRI	Auditory	X				
Paulesu et al. (1995)	PET	Auditory		X			
Hubbard et al. (2005)	fMRI	Visual	X (also right)				
Sperling et al. (2006)	fMRI	Visual	X (also right)		X		
Schiltz et al. (1999)	EEG	Visual			X		
Weiss et al. (2005)	fMRI	Visual					X
Esterman et al. (2006)	TMS	Visual					X
Rich et al. (2006)	fMRI	Visual				X	
Present study	EEG/LORETA	Auditory	X	X	X		X

Note: X indicates findings of activation in the corresponding areas. In some studies, stimuli were presented visually, in others auditorily. Note that some anatomical areas as for example left PIT and lingual gyrus are adjacent brain areas. The coordinates of activation indicate that the activation might also derive from similar brain areas.

Whether the above-mentioned functions are indeed operative in synesthetes has to be demonstrated. To our knowledge most synesthetes report no emotional or reward related experience during their synesthetic experience. Similarly, the synesthetes participating in our study mention that their particular perception and experience is simply there without any additional emotional content. Thus, it is unlikely that the synesthetes experienced some kind of reward during their synesthetic experience. However, it might be that during presentation of auditory stimuli the auditory memory system is activated with the OFC as one part of this system possibly coding emotional aspects of the auditory stimulus. Whether this reactivation of the auditory memory system might be important for synesthesia has to be shown in future experiments.

During the letter condition, enhanced activation at the P2 component was found for the synesthetes in the lSFG, lPre, and rIPS. Activation in SFG is also found during attention processing (Voisin et al. 2006), whereas precuneus is related to mental imagery (Cavanna and Trimble 2006), and the IPS in spatial cognition as well as attention (Culham and Kanwisher 2001). The subjects' task was to listen to the verbal stimuli and to repeat them when demanded. In order to solve this task, they had to keep the stimuli in working memory. Although the nonsynesthetic controls could perform auditory rehearsal to keep the acoustic component in mind, the synesthetes automatically experienced an additional visual, "inner" picture in color, and thus had to perform extra working memory processing. This extra processing might be related to significantly enhanced attention processes, mental imagery and spatial cognition. The IPS activation during induced color perception in synesthetes found in our study roughly corresponds to 2 recent findings in which the involvement of the IPS in grapheme-color synesthetes has been emphasized (Weiss et al. 2005; Esterman et al. 2006). However, the precise role of the IPS in synesthetic perception is still a matter of dispute. For example, it is not entirely clear whether the right- or left-sided IPS is crucially involved. Although our study and the transcranial magnetic stimulation (TMS) experiment of Esterman et al. (2006) found that the right-sided IPS is activated during synesthetic experience, Weiss et al. (2005) identified the left-sided IPS as being important for synesthetic experience.

Conclusion

Our findings answer several questions about neuronal processing of "color-hearing" synesthesia. Although we replicated previous findings on brain structures involved in synesthetic color processing (showing simultaneous activation of auditory and color processing areas), we additionally delineated the time course of colored-hearing synesthesia, demonstrating its fast and possibly automatic nature.

Notes

Conflict of Interest: None declared.

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