

Disinhibited feedback as a cause of synesthesia: Evidence from a functional connectivity study on auditory-visual synesthetes

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ABSTRACT

In synesthesia, certain stimuli to one sensory modality lead to sensory perception in another unstimulated modality. In addition to other models, a two-stage model is discussed to explain this phenomenon, which combines two previously formulated hypotheses regarding synesthesia: direct cross-activation and hyperbinding. The direct cross-activation model postulates that direct connections between sensory-specific areas are responsible for co-activation and synesthetic perception. The hyperbinding hypothesis suggests that the inducing stimulus and the synesthetic sensation are coupled by a sensory nexus area, which may be located in the parietal cortex. This latter hypothesis is compatible with the disinhibited feedback model, which suggests unusual feedback from multimodal convergence areas as the cause of synesthesia. In this study, the relevance of these models was tested in a group ($n = 14$) of auditory-visual synesthetes by performing a functional connectivity analysis on functional magnetic resonance imaging (fMRI) data. Different simple and complex sounds were used as stimuli, and functionally defined seed areas in the bilateral auditory cortex (AC) and the left inferior parietal cortex (IPC) were used for the connectivity calculations. We found no differences in the connectivity of the AC and the visual areas between synesthetes and controls. The main finding of the study was stronger connectivity of the left IPC with the left primary auditory and right primary visual cortex in the group of auditory-visual synesthetes. The results support the model of disinhibited feedback as a cause of synesthetic perception but do not suggest direct cross-activation.

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1. Introduction

In synesthesia, the perception of a certain stimulus, called an inducer, leads automatically and involuntarily to an additional internally generated sensation (Lupianez & Callejas, 2006; Mills, Metzger, Foster, Valentine-Gresko, & Ricketts, 2009), called a concurrent. Inducer-concurrent pairings remain stable over long time periods (Simner & Logie, 2007). Three main classes of neuropsychological theories of synesthesia have been discussed: the cross activation model (Ramachandran & Hubbard, 2001), the re-entrant feedback model (Smilek, Dixon, Cudahy, & Merikle, 2001), and the disinhibited feedback model (Grossenbacher & Lovelace, 2001). The cross activation model proposes a direct linkage between the areas of inducer and concurrent representation. The re-entrant feedback model suggests crosstalk between the inducer and concurrent

brain areas along with additional feedback from higher-level areas. The disinhibited feedback model proposes an unusual activation of the concurrent-related brain areas caused by the disinhibition of feedback to these areas from a “multisensory nexus” area, e.g., the parietal cortex. Recently, new models of synesthesia have been introduced based on research on grapheme-color synesthetes. These models represent extensions of the cross activation theory in the form of the so-called two-stage model (Hubbard, 2007) and the new cascaded cross-tuning model of synesthesia (Hubbard, Brang, & Ramachandran, 2011).

The majority of the knowledge about synesthesia comes from the most commonly investigated type, namely grapheme-color synesthesia (Simner et al., 2006). There is evidence that this type of synesthesia involves spatially adjacent brain areas responsible for color processing (area V4) and grapheme representation (Brang, Hubbard, Coulson, Huang, & Ramachandran, 2010; Hubbard, Arman, Ramachandran, & Boynton, 2005; Nunn et al., 2002), although a recent functional neuroimaging study in which color processing centers were identified individually in each participant challenges this view (Hupe, Bordier, & Dojat, 2011). The spatial proximity of the two areas suggests direct cross-activation as the mechanism responsible for grapheme-color

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synesthesia (Ramachandran & Hubbard, 2001). Evidence for this model has been provided by imaging research focusing on neuroanatomical alterations (Jäncke, Beeli, Eulig, & Hanggi, 2009) or effective connectivity analyses (van Leeuwen, den Ouden, & Hagoort, 2011). However, there is also growing evidence from several neuroimaging studies supporting the additional involvement of the parietal cortex (Rouw & Scholte, 2007, 2010; van Leeuwen, Petersson, & Hagoort, 2010; Weiss & Fink, 2009; Weiss, Zilles, & Fink, 2005) in grapheme-color synesthesia. This involvement of the parietal cortex speaks against cross-activation as the only mechanism in synesthesia. Furthermore, other forms of synesthesia combine modalities with more spatial distance between the involved brain areas, e.g., auditory-visual synesthesia, in which acoustic stimulation leads to a visual experience, indicating that additional mechanisms, apart from cross-activation, could be responsible for this phenomenon (Goller, Otten, & Ward, 2009). Currently, a combined model of cross-activation together with a parietal ‘hyperbinding’ mechanism (Esterman, Verstynen, Ivry, & Robertson, 2006) is presented as an adequate explanation for synesthetic perception. This two-stage model proposes that activation of concurrent areas is evoked directly by the activation of areas that process the inducing stimuli, but the inducer and concurrent sensations are bound together to form a holistic experience by parietal modulating mechanisms in a second step (Hubbard, 2007). The recently introduced cascaded cross-tuning model of grapheme-color synesthesia (Hubbard et al., 2011) incorporates both early direct cross activation and top-down influences. Furthermore, the model suggests that some of the form-related features of the grapheme, rather than entire letters, may lead to partial activation of color area V4. Support for the two-stage model comes from a recent resting-state EEG study on subjects manifesting visual concurrents evoked by auditorily presented words and letters (Jäncke & Langer, 2011). In this study, in addition to the auditory, visual, frontal and limbic brain regions, the left parietal cortex was identified as a major hub region, which was more functionally interconnected in synesthetes than in non-synesthetes. Structural aberrations in brain connectivity have also been shown in a single case study on a subject with tone-color and interval-taste synesthesia (Hanggi, Beeli, Oechslin, & Jancke, 2008) and in a group study on grapheme-color synesthetes, which indicated structural connectivity changes in the fusiform gyrus and intraparietal sulcus (Hanggi, Wotruba, & Jancke, 2011). These latter studies suggest a well-distributed network, rather than only color-related areas (visual cortex), as relevant for synesthetic color perception. The detected functional and structural connectivity aberrations in the fusiform gyrus can explain the synesthetic perceptions for couplings affecting spatially adjacent inducer and concurrent brain areas (as in grapheme-color synesthesia) based on the “small-world” properties of cortical connectivity (Bargary & Mitchell, 2008). It follows that synesthesia could be a result of direct, feedforward connections between adjacent areas, especially for “within-modality” couplings. For other kinds of synesthesia (e.g., between-modality), it is conceivable that the underlying mechanism is different and that sound-color (without speech relation) synesthesia, for example, has a different principal mechanism (e.g., disinhibition) than “within modality” synesthesia (Cohen Kadosh & Walsh, 2008). Furthermore, many multisensory phenomena (also unrelated to synesthesia) reflect feedback influences on sensory-specific areas coming from spatial distant multimodal convergence zones (Driver & Noesselt, 2008).

Until now, knowledge regarding the perception processes in synesthesia has been largely based on research regarding the “within modality” grapheme-color synesthesia. Knowledge about other forms of synesthesia, although important for a global understanding of perceptual processes, has been unfortunately sparse due to the relatively small number of available subjects. The aim

of the current study was to investigate the connectivity of a priori functionally defined brain regions in synesthesia. We decided to use a functional connectivity analysis of functional magnetic resonance imaging (fMRI) data from auditory-visual synesthetes and controls recorded during the perception of synesthesia induced by stimuli unrelated to speech (tones and chords). In this form of synesthesia, hearing a sound leads to the perception of color or (mostly three-dimensional) colored shapes moving in space (Fig. 1). We focused the analysis on three seeds of interest to calculate the connectivity: the left inferior parietal cortex (IPC) and the bilateral auditory cortex (AC). The areas of interest were defined functionally in our previous study using a standard GLM (general linear model) analysis (Neufeld et al., 2012). The analysis method employed here was introduced previously by Rissman, Gazzaley, and D’Esposito (2004) and allows analysis of the functional connectivity of predefined brain areas in relation to a specific cognitive process in the whole brain. Thus, it is particularly suitable for examining the two-stage synesthesia model. The advantage of this method compared to resting-state connectivity analysis lies in the ability to identify brain connectivity related to the perception of synesthesia-inducing sounds. In contrast to dynamic causal modeling, our method is free of the necessity to predefine networks and thereby also has an explorative quality. With respect to the two-stage model of synesthesia, we hypothesized that if synesthesia was mediated by direct cross-activation, increased connectivity between the AC and at least one area of concurrent representation (e.g., the visual cortex) would be expected. If disinhibited feedback from the IPC leads to synesthesia, such an increased connectivity should not be found. In contrast, one would expect increased connectivity between the IPC and at least one area of concurrent representation and perhaps also to areas representing the inducer.

2. Methods

All procedures were approved by the local Ethics Committee. The participants gave informed consent and received a minimal monetary compensation in this study.

2.1. Subjects

Fourteen auditory-visual synesthetes and fourteen control subjects, who did not report synesthesia, participated in the study. Participants were matched for age, sex, handedness (self-reported), IQ, as measured by the MWT-B (Mehrfach-Wortschatz-Intelligenztest B) (Lehrl, Triebig, & Fischer, 1995) and musical expertise, as determined by the Ollen Musical Sophistication Index (OMSI) (Ollen, 2006) and years of music lessons (Table 1).

Each participant was subjected to a consistency test for synesthesia with 36 different tones, which was a modified offline version of the synesthesia battery (Eagleman, Kagan, Nelson, Sagaram, & Sarma, 2007). In this test, the subjects were instructed to indicate a color related to the tones presented from different instruments and with different pitches. The synesthetes were asked to choose the color that best matched the synesthetic color induced by the tone; the non-synesthetes were asked to select the color that they believed fit the tone best. After three presentations of the stimuli in a randomized order, the geometric distance in the RGB (red, green, blue) color space of the color choices indicated by the subjects for each item during the three runs was calculated. The mean values were then compared between groups. The synesthetes were significantly more consistent in their responses (Table 1). Furthermore, we conducted an intensive interview with the synesthetes regarding the type of synesthetic perception. All of the synesthetes could be identified as so-called “associators”, or subjects who experience synesthesia “in their minds’ eye”. In contrast, synesthesia “projectors” experience concurrents externally, colocalized with a presented inducer.

2.2. Stimuli and paradigm

To elicit visual synesthetic perceptions, we presented different auditory stimuli during the acquisition of the fMRI data (see Fig. 1 for examples of the induced concurrents). We used 6 different sound classes (major, minor and dissonant piano chords and pure piano, sine and bassoon tones) presented in pseudo-randomized order. The stimuli were presented via pneumatic headphones in an event-related design composed of three sessions and 48 stimuli per session (8 stimuli per condition per block; 24 stimuli per condition in total) with a stimulus duration of 2 s and an inter-stimulus interval of 13 s. Between the sessions, the participants had

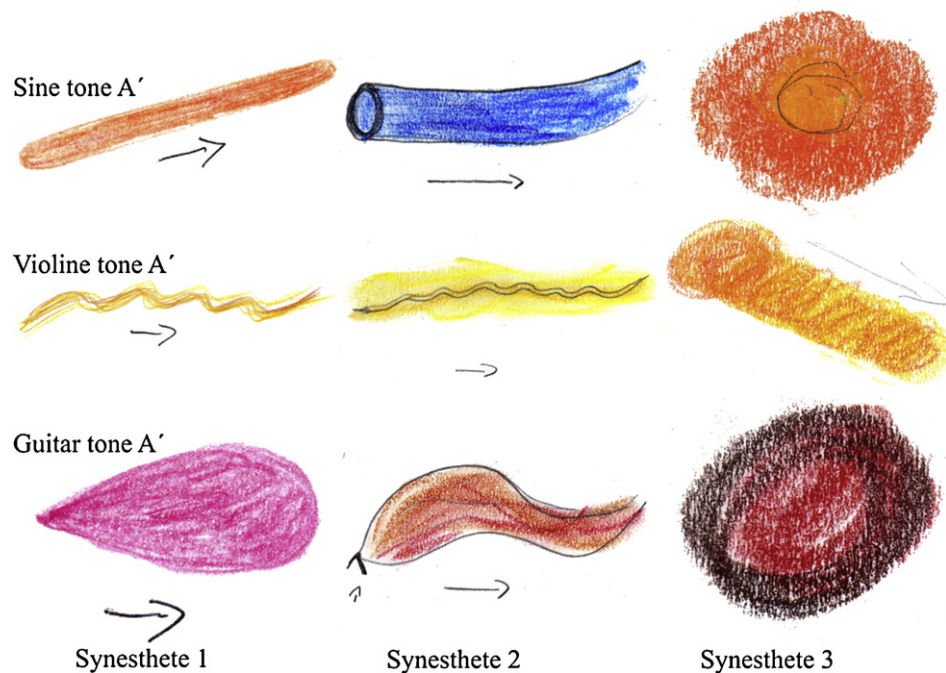


Fig. 1. Acoustically induced synesthetic photisms. The photisms induced by single tones (sine, violin and guitar) in A, which were painted by three different synesthetes, are shown exemplarily. The photisms were perceived in 3D, and the forms changed according to the mounting and fading of the tone. The arrows indicate the direction of movement.

an opportunity to relax to avoid tiring and attention diminishment. To reduce the general noise load on our subjects, all of the subjects used ear plugs during the fMRI data acquisition. Additionally, to achieve a better signal to noise ratio of the acoustic stimuli against the scanner noise, the sound level was adjusted individually for each subject during a test scan in which some of the stimuli were presented and the sound level was adjusted until the stimuli were clearly audible and the tones and chords were clearly discriminable for the subject. Directly following the scanning procedure, we asked all participants about the synesthetic sensations induced by the stimuli and the scanner noise. All of the control participants denied having perceived any synesthetic sensations. All synesthetes reported strong synesthesia induced by the stimuli. The majority of the synesthetes also reported synesthetic sensations induced by the scanner noise, which were of a different quality than the synesthetic sensations induced by the stimuli (e.g., “more in the background”). All participants held a response device in their right hand and performed a task during measurement to guarantee that they fully attended the stimuli. They were asked to press the right button (with their right middle finger) when hearing a chord and the left one (with their right index finger) when hearing a tone. The subjects were instructed to keep their eyes closed during the sessions to avoid visual deflection. All synesthetes reported that they perceive synesthesia with open and closed eyes.

2.3. Image acquisition

Functional images were acquired on a 1.5 T General Electric scanner (Signa Horizon; GE Medical Systems, Milwaukee, WI) equipped with a standard head coil. T2* functional scans covering the whole brain were acquired using a multislice two-dimensional echo-planar imaging (EPI) sequence (acquisition matrix 64×64 pixels, 26 axial slices, TR = 3000 ms, echo-time (TE) = 40 ms, field of view (FOV) = 26 cm, slice

thickness = 5 mm, flip angle = 90°). The measurements were acquired in three sessions of 12 min each. Each fMRI time series consisted of 244 images; the first 4 were discarded to allow the scanner to reach a steady state.

2.4. Data analysis

Data were analyzed with SPM5 (<http://www.fil.ion.ucl.ac.uk/spm>). We realigned the images to the 1st volume to correct for inter-scan movements with a least squares approach and a rigid body spatial transformation to remove artifacts. The realigned images were normalized to the EPI-derived MNI template (ICBM 152, Montreal Neurological Institute), resulting in a voxel size of $2 \text{ mm} \times 2 \text{ mm} \times 2 \text{ mm}$. The normalized images were finally smoothed with an 8-mm full-width half-maximum Gaussian kernel and filtered with a high-pass filter of 128 s.

The functional connectivity analysis was performed to examine how different brain areas work together during the perception of auditory stimuli in synesthesia. This approach was based on the hypothesis that if two regions interact within a network, their activity patterns should be strongly correlated (Rissman et al., 2004). This analysis was implemented on the basis of a specific general linear model (GLM) using separate covariates to model the hemodynamic responses of each single trial (for each separate stimulus and individual subject). The estimated movement parameters were incorporated into the model to minimize the signal-correlated motion effect. For each participant in both experimental groups and each presented stimulus, parameter estimates (beta values) were extracted to form a set of condition- and group-specific beta series. We functionally defined three seeds by calculating an analysis of variance (ANOVA) model on spatially normalized data including two main effects: between the main effect “group” (2 levels, synesthetes and controls) and within the main effect “stimulation” (6 levels, different sound conditions). This

Table 1

Mean values, standard deviations (SD) and *T*-statistics of demographic data.

	Synaesthetes	Controls	Statistics
<i>N</i> (male)	14 (5)	14 (5)	
Age (SD)	38.00 (13.77)	36.79 (12.64)	$t = 0.215$; $p = 0.832$
MWT-B ^a right answers (SD)	30.79 (3.87)	30.00 (4.13)	$t = 0.519$; $p = 0.608$
OMSI ^b probability in % (SD)	43.45 (27.66)	36.54 (26.76)	$t = 0.671$; $p = 0.508$
Years of music lessons (SD)	7.64 (5.92)	8.36 (8.85)	$t = 0.251$; $p = 0.804$
Years of instrumental training (SD)	8.21 (10.53)	7.36 (9.46)	$t = 0.227$; $p = 0.822$
Handedness: right (left)	13 (1)	13 (1)	
Dimensionless consistency score ^c (SD)	1.26 (0.55)	1.85 (0.50)	$t = 2.981$; $p = 0.006^{**}$

^a Mehrfach Wortschatz Test B according to Lehl et al. (1995).

^b Ollen Musical Sophistication Index according to Ollen (2006).

^c Tone-color consistency test: smaller scores indicate a higher tone-color consistency.

^{**} Significant at 0.01 level.

Table 2

Areas showing increased functional connectivity in synaesthetes compared to controls.

Seed area	Area showing increased connectivity	MNI coordinates (xyz)	Talairach coordinates (xyz)	Cluster size
Right A1	Left motor cortex (BA 6)	–16, –4, 60	–14, –1, 55	209
	Right motor cortex (BA 6)	26, 12, 56	26, 14, 51	68
Left IPC	Primary auditory cortex (BA 41)	–40, –26, 8	–40, –25, 9	113
	Primary visual cortex (BA 17)	12, –94, –6	12, –91, –1	53

Areas showing significantly increased functional connectivity to the investigated seed areas, their coordinates and their size (in voxels) are listed. The areas were identified using the Talairach demon tool.

analysis revealed one significant cluster in the inferior parietal cortex (IPC) for the main effect “group” (this area exhibited stronger activation for auditory stimulation in synesthetes compared to the controls) and two clusters in the right and left auditory cortex (AC) for the main effect “stimulation”. The results of this analysis are presented and discussed extensively in Neufeld et al. (2012). The seed areas were defined for the whole group of subjects as a sphere with a 5 mm radius around the center of mass of the previously detected clusters: the left and right AC (IAC, xyz [–50; –24; –2], rAC [58; –16; –4]) and the left IPC (xyz [–46; –54; 58]). The beta series of each seed were averaged across the voxels within the critical region and correlated with the beta series of every other voxel in the whole brain. For each participant, maps of the correlation coefficients were calculated for each condition (first level analysis) and normalized using an arc-hyperbolic tangent transform for further statistical inference.

In the second step of the analysis, we focused on testing our hypotheses regarding the connectivity pattern underlying synesthesia. Thus, we conducted two-sample *t* tests to examine connectivity differences between the controls and synesthetes during the perception of auditory stimulation. The resulting maps were considered at $p < 0.001$ at the voxel level and $p < 0.05$ at the cluster level threshold. Here, we used a cluster level threshold correction technique based on permutation analyses of sub-samples of a large dataset (Slotnick, Moo, Segal, & Hart, 2003). The cluster threshold correction technique for multiple comparisons used here controls for false positives, with a relative sparing of statistical power (Forman et al., 1995; Thirion et al., 2007), and solves the problem of multiple comparisons with voxel-wise *p*-values in combination with a specific cluster size threshold. The identified minimal cluster size calculated for our data amounts to 41 resampled voxels. All of the brain sites meeting this criterion were considered. The anatomical identification of the resulting brain sites was conducted using the SPM Anatomy toolbox version 1.7 (Eickhoff et al., 2005).

3. Results

No significant differences were found between the synesthetes and controls in the number of correctly identified stimuli ($p = 0.312$)

or reaction times ($p = 0.793$) in the tone-chord discrimination task conducted during fMRI.

No increased connectivity in the controls compared to the synesthetes was found in any region for any of the seed areas.

To test the direct cross-activation model of synesthesia, the functional connectivity of the bilateral auditory cortex (AC) for auditory stimulation was calculated. Based on this model, we hypothesized that there would be a stronger connectivity between the AC and the visual cortex in the synesthesia group, but we did not observe this effect. The right AC merely exhibited increased connectivity to areas in the left and right motor cortex in synesthetes compared to controls (Table 2). The left AC showed no differences in connectivity between the groups.

The main result of this study (Table 2, Fig. 2) is the finding of a stronger connectivity of the left IPC to both the left primary auditory cortex (BA 41, SPM Anatomy toolbox: probability of maximum = 60–90% of cluster in Te 1.1; 10–60% of cluster in Te 1.0, 51% of cluster in Te 1.1; 13.3% of cluster in Te 1.0, 12.6% of cluster in OP 2, 11.3% of cluster in insula) and the right primary visual cortex (BA17, SPM Anatomy toolbox: probability of maximum = 70–100% of cluster in area 17; 81.1% of cluster in area 17, 1.3% of cluster in area 18) in the synesthetes. Thus, the processing of auditory stimuli in auditory-visual synesthetes is accompanied by a stronger interaction between these areas.

4. Discussion

The main finding of this study is the increased connectivity between the left IPC and primary auditory (A1) and visual (V1)

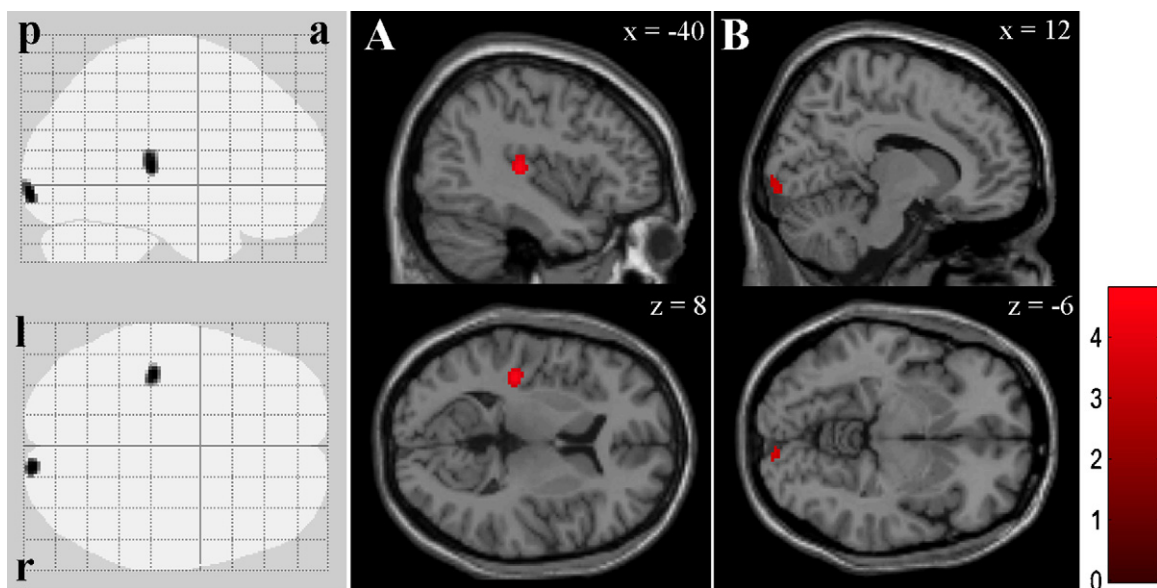


Fig. 2. Significant group differences in functional connectivity of the IPC. The connectivity analysis revealed two brain areas exhibiting significantly more connectivity to the inferior parietal cortex (IPC) in synesthetes compared to controls ($p < 0.05$, corrected for multiple comparisons): (A) a cluster in the left temporal cortex (center of mass at MNI coordinates xyz = –40, –26, 8), identified as the primary auditory cortex (BA 41) and (B) a cluster in the left occipital cortex (center of mass at MNI coordinates xyz = 12, –94, –6), identified as the primary visual cortex (BA 17). p = posterior, a = anterior, r = right, l = left, color bars indicate the strength of activation.

areas in synesthesia. This finding supports the disinhibited feedback model of synesthesia, which proposes increased feedback projections to the sensory areas in synesthetes from multimodal (e.g., parietal) brain sites (Grossenbacher & Lovelace, 2001). Interestingly, the target feedback regions are primary sensory areas and not secondary or later sensory areas (e.g., V4). Furthermore we did not find evidence to support the cross-activation model in the investigated brain sites, as there was no increase in the direct connectivity between the auditory and visual brain areas.

As a higher-order cortical area, the left IPC plays a role in a variety of cognitive functions. Recent research underlines the importance of this area in multimodal sensory perception (Bushara, Grafman, & Hallett, 2001; Calvert, 2001; Macaluso, George, Dolan, Spence, & Driver, 2004; Szycik, Jansma, & Münte, 2009). Furthermore, it has also been identified as a major hub for processing synesthetic perception (Neufeld et al., 2012; Rouw & Scholte, 2007, 2010; van Leeuwen et al., 2010; Weiss & Fink, 2009; Weiss et al., 2005). Thus, in accordance with the disinhibited feedback model of synesthesia (Grossenbacher & Lovelace, 2001), this area may play a crucial role as a “pathway convergence site” in synesthesia and as the origin of the disinhibited feedback. In this model, the processing of the inducing stimuli follows the inducer pathway hierarchically from the sensory-specific areas toward the areas receiving signals from multiple pathways. It is known that auditory stimuli enter the system in the sensory-specific auditory cortex of the temporal lobe and, after some processing stations, reach multimodal areas in the parietal cortex (Campbell, 2008; Vigneau et al., 2006). Functional connections between A1 and the IPC have also been reported in a brain imaging study using structural equation modeling (Caclin & Fonlupt, 2006). Our data indicate that in synesthetes, these connections are stronger compared to the controls during tone perception. However, our results also indicate that the connections from the IPC to sensory-specific areas of the concurrent (primary visual cortex) are stronger in synesthetes. Structural connectivity changes to the IPC have recently been demonstrated, as revealed by the analysis of magnetic resonance surface-based morphometry data (Hanggi et al., 2011). Although in this latter study, the connectivity differences exhibited only a low specificity (suggesting global connectivity differences), this effect of altered connectivity between the IPC and sensory-specific areas may be responsible for the synesthetic visual experience concurrent to auditory stimulation. More precisely, as proposed by the disinhibited feedback model, the information entering such a convergence area through the inducer pathway could propagate down the concurrent pathway. Furthermore, the current results suggest that the influence of the parietal cortex (for example, via disinhibited feedback) impacts the sensory system at low-level stages of processing, namely at the stage of the primary sensory areas. Support for low-level effects in synesthesia comes from a recent EEG study on auditory-visual synesthetes with tones as stimuli (Goller et al., 2009). In this study, effects on different EEG components at early stages (approximately 100 ms after the stimulus onset) were found. Many previous investigations of grapheme-color synesthesia (Brang et al., 2010; Hubbard et al., 2005; Nunn et al., 2002; Ramachandran & Hubbard, 2001) and auditory-visual synesthesia using auditory verbal stimuli (Beeli, Esslen, & Jancke, 2008) identified more associative visual areas as important for concurrent perception, especially area V4 in the fusiform gyrus. Therefore, increased functional connectivity between the IPC and V4 could have been expected. The lack of this finding in the current study may be explained by the different form of synesthesia analyzed here. It is likely that there are different mechanisms underlying grapheme-color and auditory-visual synesthesia. Moreover, within one form of synesthesia, individual synesthetes might perceive their synesthetic sensations differently, for example, at different spatial locations (Dixon, Smilek, & Merikle, 2004). Evidence for the

involvement of different mechanisms in different types of synesthetes has been found in synesthetes divided into projectors and associators (van Leeuwen et al., 2011). Our results are in line with the results of the study by van Leeuwen et al. because all our subjects could be identified as “associators”.

Increased activation of the auditory cortex in synesthesia has been observed previously in two studies investigating grapheme-color synesthesia with acoustically induced stimuli (Gaschler-Markefski et al., 2011; Sperling, Prvulovic, Linden, Singer, & Stirn, 2006). Furthermore, increased gray matter volumes in the right A1 have been detected in projector synesthetes (Rouw & Scholte, 2010). Structural peculiarities in sensory areas related to the inducer-concurrent coupling revealed by a single subject study on the auditory-taste synesthete E.S. suggest the involvement of the auditory cortex in audition-related synesthesia (Hanggi et al., 2008). Furthermore the involvement of the right auditory cortex as a strong hub in auditory-visual synesthesia was recently demonstrated by means of resting state EEG connectivity analysis (Jäncke & Langer, 2011). In addition, V1 activation induced by acoustically presented inducers has been found in single cases of synesthesia (Aleman, Rutten, Sitskoorn, Dautzenberg, & Ramsey, 2001; Steven, Hansen, & Blakemore, 2006), providing evidence for the involvement of this area in synesthesia. Furthermore, recent group studies with grapheme-color synesthetes have revealed increased gray matter volumes in low-level visual areas in projector synesthetes (Rouw & Scholte, 2010) and increased structural connectivity, as measured by Fractional Anisotropy, in synesthetes in low-level and associative visual areas (Jäncke et al., 2009). In addition, color processing is not limited to V4: in non-synesthetes, V1 activation has been observed to be most sensitive to isoluminant chromatic stimulation and red-green/blue-yellow stimuli (Engel, Zhang, & Wandell, 1997; Kleinschmidt, Lee, Requardt, & Frahm, 1996). Therefore, V1 might serve as a concurrent representation area, although it does not appear to be the only visual area involved in concurrent processing.

One important limitation of this study is the fact that we have calculated the connectivity of only one auditory area. The human auditory cortex can be divided into a considerable number of sub-areas, each a potential candidate as a seed for the cross activation model of synesthesia (Ramachandran & Hubbard, 2001). Thus, further examination of the connectivity over the entire auditory cortex may be required, e.g., oriented on anatomical or functional parcellations (Brechmann, Baumgart, & Scheich, 2002; Morosan et al., 2001; Pandya, 1995). Another important limitation of the method used in this study is the lack of the ability to estimate the direction of the observed connections. A directional analysis would be interesting, for example, in relation to the question of whether synesthesia is uni- or bi-directional. In fact, there are descriptions of synesthetic subjects with only unidirectional inducer-concurrent couplings (Beeli, Esslen, & Jancke, 2005) as well as with bidirectional couplings (Goller et al., 2009).

Thus, although our data fit well with the model of disinhibited feedback, there is also another possible explanation for the induction of concurrents in synesthesia. Alternatively to the information flow from A1 through the IPC toward V1, we can hypothesize from recent data that there is increased concomitant feedback from the IPC to A1 and V1. Besides its involvement in auditory-visual synesthesia, the IPC has proved to also be involved in grapheme-color and number-form synesthesia (Rouw & Scholte, 2010; Tang, Ward, & Butterworth, 2008; van Leeuwen et al., 2010; Weiss et al., 2005). Furthermore, this area plays an important role in the control of attention shifts to a certain sensory modality (Macaluso, Frith, & Driver, 2000). Thus, the IPC may influence signal processing in sensory regions by modulating attentional processes. Further research is required to elucidate the mechanisms underlying synesthesia, particularly because there are earlier audio-visual convergence

sites than the IPC involved in multimodal processing, which may also serve as the origin of disinhibited feedback, e.g., the posterior region of the superior temporal sulcus area (Beauchamp, Argall, Bodurka, Duyn, & Martin, 2004; Reale et al., 2007; Szyck, Tausche, & Münte, 2008). The involvement of this area in auditory-visual synesthesia has already been suggested by Goller et al. (2009), who investigated this form of synesthesia using electrophysiology and also did not find evidence supporting the cross-activation model.

5. Conclusions

In this study, we used a functional connectivity analysis method in combination with fMRI to examine the importance of different models of synesthesia in auditory-visual synesthetes. The results suggest an increased communication between the IPC and the sensory-specific primary areas of the inducer (A1) and the concurrent (V1) representation. Therefore, the present study provides evidence for a disinhibited feedback mechanism in auditory-visual synesthesia, mediated by the IPC as a sensory nexus area, rather than a direct linkage between the auditory and visual areas.

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