Top–Down Signal Transmission and Global Hyperconnectivity in Auditory-Visual Synesthesia: Evidence From a Functional EEG Resting-State Study

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Abstract: Auditory-visual (AV) synesthesia is a rare phenomenon in which an auditory stimulus induces a “concurrent” color sensation. Current neurophysiological models of synesthesia mainly hypothesize “hyperconnected” and “hyperactivated” brains, but differ in the directionality of signal transmission. The two-stage model proposes bottom–up signal transmission from inducer- to concurrent- to higher-order brain areas, whereas the disinhibited feedback model postulates top–down signal transmission from inducer- to higher-order- to concurrent brain areas. To test the different models of synesthesia, we estimated local current density, directed and undirected connectivity patterns in the intracranial space during 2 min of resting-state (RS) EEG in 11 AV synesthetes and 11 nonsynesthetes. AV synesthetes demonstrated increased parietal theta, alpha, and lower beta current density compared to nonsynesthetes. Furthermore, AV synesthetes were characterized by increased top–down signal transmission from the superior parietal lobe to the left color processing area V4 in the upper beta frequency band. Analyses of undirected connectivity revealed a global, synesthesia-specific hyperconnectivity in the alpha frequency band. The involvement of the superior parietal lobe even during rest is a strong indicator for its key role in AV synesthesia.

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By demonstrating top-down signal transmission in AV synesthetes, we provide direct support for the disinhibited feedback model of synesthesia. Finally, we suggest that synesthesia is a consequence of global hyperconnectivity. *Hum Brain Mapp* 39:522–531, 2018. © 2017 Wiley Periodicals, Inc.

Key words: synesthesia; auditory-visual; resting-state; EEG; connectivity; top-down

INTRODUCTION

Synesthesia is a rare perceptual phenomenon where a sensory or cognitive stimulus (inducer) elicits a concurrent sensory sensation [Cytowic, 2002]. In the case of auditory-visual (AV) and grapheme-color (GC) synesthesia, a concurrent color perception (e.g. indigo blue) is triggered by an auditory stimulus (e.g. a “F sharp”) or a grapheme (e.g. a “B”), respectively. In the domain of GC synesthesia, two distinct types of synesthetic color sensations can be differentiated, namely those that are experienced in the external space (projectors) or experienced “in the mind’s eye” (associators) [Dixon et al., 2004]. While this terminology is reserved for GC synesthesia, the literature on AV synesthesia more likely discriminated between internally and externally experiencing synesthetes [Goller et al., 2009; Jäncke et al., 2012]. Regarding the heterogeneity of synesthesia, manifold neurophysiological models have been suggested. The cross-activation model [Hubbard et al., 2005; Ramachandran and Hubbard, 2001] was inspired by the fact that the grapheme processing visual word form area (VWFA) lies adjacent to the color processing area V4 [Wade et al., 2002]. Thus, synesthetic color sensations in GC synesthesia are thought to arise from direct cross-activation of the concurrent area (V4) by the inducer area (VWFA) due to a lack of pruning of structural connections between the areas during development. This perspective is supported by structural magnetic resonance imaging (sMRI) studies showing increased structural connectivity in the inferior temporal cortex [Rouw and Scholte, 2007] or demonstrating increased grey matter volumes in the vicinity of V4 [Jäncke et al., 2009; Weiss and Fink, 2009]. Also, using functional MRI (fMRI) greater V4 activity in response to graphemes versus nongraphemes in GC synesthetes compared to nonsynesthetes was demonstrated [Hubbard et al., 2005].

The cross-activation model has been extended to a two-stage model [Hubbard, 2007; Hubbard and Ramachandran, 2005]. In addition to cross-activation it proposes the binding of inducing and concurrent sensations by a parietal higher order area. The parietal cortex is known to be involved in perceptual binding mechanisms [Robertson, 2003] and inhibition of this area has been shown to attenuate synesthetic experiences [Esterman et al., 2006].

A competing disinhibited feedback model [Grossenbacher and Lovelace, 2001] states that higher order areas (e.g. the parietal cortex) serve as a multisensory nexus. Neuronal signals emerging from lower sensory areas are thought to propagate in a progressively converging manner through

hierarchically organized modules until they reach this multisensory nexus. In synesthetes, feedback connections from the multisensory nexus to lower sensory areas are thought to be disinhibited. Consequently, the concurrent area V4 is activated by neuronal signals propagating backwards to lower sensory areas, which in turn leads to synesthetic color perceptions. This is supported by an fMRI study reporting increased functional connectivity in GC synesthetes between parietal and primary/secondary visual areas [Sinke et al., 2012]. Also, hallucinogenic drugs were found to induce synesthetic experiences in non-synesthetes [Grossenbacher, 1997] implying that such experiences rely on typically existing adult networks rather than on additional structural connections between inducer and concurrent areas. In addition to these models, it has been argued that synesthesia might be a consequence of globally altered brain network connectivity [Bargary and Mitchell, 2008]. Global hyperconnectivity in GC synesthesia was found in a surface-based morphometry study [Hänggi et al., 2011], consistent with an fMRI resting-state (RS) study showing a global increase of intrinsic internetwork connectivity [Dovern et al., 2012].

Knowledge about the neurophysiological processes in AV synesthesia is relatively sparse due to the small number of accessible subjects. Yet, parietal involvement in AV synesthesia has been demonstrated in multiple functional studies using fMRI [Neufeld et al., 2012a, 2012b] or electroencephalography (EEG) [Jäncke and Langer, 2011]. Moreover, the parietal lobe has turned out to be strongly interconnected to other brain regions, even during RS [Jäncke and Langer, 2011]. We thus argue that synesthetic color perceptions in AV synesthetes do not solely arise from direct cross-activation, but that additional parietal mechanisms play a pivotal role for this kind of synesthesia. Parietal involvement has been interpreted in favor of the two-stage model [Jäncke and Langer, 2011] but also in favor of the disinhibited feedback model [Neufeld et al., 2012b]. These two models can be discriminated according to the proposed directionality of signal transmission. In fact, the two-stage model suggests bottom-up signal transmission from inducer- to concurrent- to higher-order areas, whereas the disinhibited feedback model proposes top-down signal transmission from inducer- to higher-order- to concurrent areas. The correlational nature of the aforementioned studies renders it impossible to draw conclusions about the directionality of signal transmission in AV synesthesia (i.e., bottom-up vs top-down). Therefore, studies investigating directed connectivity patterns are needed to directly test the assumptions made by the different neurophysiological models of synesthesia. So far,

only one fMRI study using dynamic causal modeling has explored directed connectivity patterns in synesthesia [van Leeuwen et al., 2011]. As a main result, the authors found that GC associators rely on top-down signal transmission while GC projectors are more likely characterized by bottom-up signal transmission. Directed connectivity patterns in AV synesthesia have not yet been investigated. Accordingly, in this EEG study, we evaluate directed connectivity in AV synesthetes. Furthermore, only one study has evaluated undirected connectivity patterns in AV synesthesia on a global scale and found a generally altered brain network hyperconnectivity [Jäncke and Langer, 2011]. In our analyses, we hence include a broad evaluation of undirected connectivity patterns. We used a sequential EEG procedure consisting of (1) estimating intracranial current densities, (2) performing analyses of directed connectivity patterns between a priori defined inducer-, concurrent-, and higher-order areas, and of (3) performing analyses of undirected connectivity patterns between globally distributed brain regions.

METHODS

Participants

The analyses in this article are based on RS data collected in the context of a previous mismatch negativity experiment [Jäncke et al., 2012]. In the present study, we evaluated the data of 11 AV synesthetes (mean age 30.7 ± 7.5 , 9 female) who exclusively experienced colors in response to auditory nonlinguistic stimuli and 11 nonsynesthetes (mean age 29.6 ± 8.1 , 9 female). Eight out of 11 AV synesthetes specified that they experience colors internally and only two externally. One synesthete could not explicitly attribute color sensation to the internal or external space. Furthermore, all participants were consistently right-handed with the exception of one ambidextrous person per group, as was revealed by the Edinburgh Handedness Inventory [Oldfield, 1971]. The R statistics package (<https://www.r-project.org/>) was used to test for putative group differences in terms of cognitive capabilities [Lehrl et al., 1995] and musicianship [Gordon, 1989]. All subjects denied taking medication or drugs, had no past or present neurological or psychiatric diseases, and revealed an unremarkable audiological status (Home Audiometer software, <http://www.esseraudio.com/de/home-audiometer-hoertest.html>). The subjects were paid for participation and gave written informed consent. The study was approved by the local ethics committee (Zurich) according to the Helsinki Declaration.

Test of Genuineness Synesthesia

All subjects performed a test of genuineness synesthesia [Eagleman et al., 2007]. In this color-consistency test, subjects are required to choose the color from a color palette of 16.7 million different colors that most closely matches

their synesthetic experience in response to randomly presented piano tones (13 tones, each of them presented three times, f_0 frequency range from 261 to 523 Hz). The induced color sensations were coded by red-green-blue vectors in the range of 0–255. The consistency score for a specific piano tone was mathematically derived from the vector distance between the three randomly presented items. Following from this, the consistency score for each single subject was determined using the averaged tone consistency scores across the 13 piano tones. This test is widely used in synesthesia research [Jäncke and Langer, 2011; Jäncke et al., 2012; Zamm et al., 2013] and has previously been shown to be sensitive for distinguishing between synesthetes and nonsynesthetes [Eagleman et al., 2007].

EEG Recording, Experimental Procedure, and Data Processing

Two minutes of eyes-closed RS EEG was recorded using a 32-channel montage according to the 10–20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, Cz, C4, T8, TP9, TP7, CP3, CPz, CP4, TP8, TP10, P7, P3, Pz, P4, P8, O1, Oz, and O2) with two additional eye channels (BrainAmp System, Germany). The data were collected with a sampling rate of 1000 Hz and a band-pass filter of 0.1–100 Hz. The nose was chosen as an online reference, and the electrode impedance was kept below 10 k Ω by using electro gel. The participants sat comfortably in a chair in a dimly lit sound-shielded Faraday cage and were told that EEG recording would be done while they rested with their eyes closed. The EEG data were processed using the Brain Vision Analyzer software (Version 2.0, Brainproducts, Germany). In particular, the data were filtered by employing infinite impulse response filters (IIR; Butterworth; 48 dB/oct) with a high- and low-pass criteria of 0.5 and 40 Hz and a band-rejection filter of 50 Hz. Eye movement artefacts (i.e., blinks and saccades) were removed by using an independent component analysis (ICA) [Jung et al., 2000]. The eye channels were discarded after ICA correction and the continuous artifact-free data were exported for further analyses with the sLORETA toolbox (Version 20160611; <http://www.uzh.ch/keyinst/loreata.htm>, [Pascual-Marqui, 2002]). Finally, to analyze directed connectivity, the data were additionally downsampled to 256 Hz [Pascual-Marqui et al., 2014a, 2014b].

Source Estimation

To verify the source estimation of sLORETA, we reanalyzed the standard tone A ($f_0 = 440$ Hz) of a mismatch negativity experiment previously performed with the same subjects [Jäncke et al., 2012]. The grand average was calculated as the average of all single-subject event-related potentials evoked by the standard tone A. Considering the whole-brain volume, maximal current density for the peak

of the first negative deflection of the grand average at 115 ms after stimulus onset was estimated in the primary auditory cortex (−45, −30, 15; Montreal Neurological Institute, MNI). We are thus confident that source localization with the sLORETA toolbox works reasonably well.

Current Density Analyses

Current density during RS EEG was estimated for four frequency bands of interest, namely theta (4–7 Hz), alpha (8–12 Hz), lower beta (13–21 Hz), and upper beta (22–30 Hz). We specifically evaluated low- and high-frequency bands as both have been associated with multimodal integration [Kayser and Logothetis, 2009; Von Stein and Sarnthein, 2000], a key feature in AV synesthesia. The R statistics package was used for region-wise comparisons of current density between AV synesthetes and nonsynesthetes. We defined six regions of interest (ROI) according to current models of synesthesia postulating inducer-, concurrent-, and higher-order areas [Grossenbacher and Lovelace, 2001; Hubbard, 2007; Hubbard and Ramachandran, 2005]. The ROIs consisted of single voxels and were located in the left and right primary auditory cortex (inducer areas), the left and right color processing area V4 and the primary visual cortex (concurrent areas) and the superior parietal lobe (higher order area). They are listed in Table I together with the ROIs for the analyses of undirected connectivity. The Juelich Histological and the Harvard–Oxford cortical atlases (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases>; implemented in fMRIB software library: <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL>) were used for a more detailed specification of brain regions. The ROIs for the left and right V4 were derived from an fMRI study performed with AV synesthetes [Neufeld et al., 2012a]. Based on previous work [Esterman et al., 2006; Jäncke and Langer, 2011; Neufeld et al., 2012b] and to increase the power of our analysis, we selected a single medial ROI in the superior parietal lobe showing the highest mean current density across all subjects. All other ROIs consisted of a single centroid voxel of the respective Brodmann areas (BA). sLORETA source estimation is based on the smoothest solution of the inverse problem as the most plausible one [Pascual-Marqui, 2002]. Centroid voxels of BAs are thus highly representative for the overall activity in the corresponding BAs and were also used in other studies of our research group [Elmer et al., 2015; Jäncke and Langer, 2011; Klein et al., 2016].

Directed Connectivity Analyses

RS EEG data were evaluated in four frequency bands (theta, alpha, lower beta, and upper beta) by using the R statistics package. Directed connectivity was computed between the six a-priori defined ROIs that were also used for group comparisons of current density (Table I). Directed connectivity was measured as *isolated effective*

TABLE I. Specification of ROIs

BA	MNI coordinates (x, y, z)	Brain structure
BA5 L ^b	(−15, −45, 60)	SPL
BA5 R ^b	(15, −45, 60)	SPL
BA7 L ^b	(−20, −65, 50)	SPL
BA7 R ^b	(15, −65, 50)	SPL
BA39 L ^b	(−45, −65, 25)	IPL
BA39 R ^b	(45, −65, 25)	IPL
BA40L ^b	(−50, −40, 40)	aIPS
BA40R ^b	(50, −45, 45)	aIPS
BA19 L ^{a,b}	(−30, −70, −15)	VC V4
BA19 R ^{a,b}	(35, −80, −20)	VC V4
BA41 L ^{a,b}	(−45, −30, 10)	A1
BA41 R ^{a,b}	(45, −30, 10)	A1
BA44 L ^b	(−50, 10, 15)	Broca's area
BA44 R ^b	(55, 10, 15)	Broca's area
BA20 L ^b	(−45, −20, −30)	ITG
BA20 R ^b	(45, −20, −30)	ITG
BA21 L ^b	(−60, −20, −15)	MTG
BA21 R ^b	(60, −15, −15)	MTG
BA6 L ^b	(−30, −5, 55)	PreCG
BA6 R ^b	(30, −5, 55)	PreCG
BA8 L ^b	(−20, 30, 50)	SFG
BA8 R ^b	(20, 25, 50)	SFG
BA46 L ^b	(−45, 35, 20)	MFG
BA46 R ^b	(45, 35, 20)	MFG
BA9 L ^b	(−30, 30, 35)	MFG
BA9 R ^b	(30, 30, 35)	MFG
BA11 L ^b	(−20, 40, −15)	FP
BA11 R ^b	(20, 45, −20)	FP
BA17 M ^{a,b}	(0, −90, 0)	VC V1
BA7 M ^a	(0, −65, 50)	SPL

Superior parietal lobule, SPL; inferior parietal lobule, IPL; anterior intra-parietal sulcus, aIPS; visual cortex V4, VC V4; primary auditory cortex, A1; inferior temporal gyrus, ITG; middle temporal gyrus, MTG; precentral gyrus, PreCG; superior frontal gyrus, SFG; middle frontal gyrus, MFG; frontal pole, FP; visual cortex V1, VC V1.

^aUsed for the analyses of current density and directed connectivity

^bUsed for the analyses of undirected connectivity

Coherence (iCoh) [Pascual-Marqui et al., 2014a, 2014b]. The iCoh is an approach for a frequency domain measure for Granger-causality [Granger, 1969]. It is related to the widely used partial directed coherence (PDC) [Baccala and Sameshima, 2001]. The iCoh is defined within the framework of a multivariate autoregressive (MVAR) model. The MVAR model for a time series $X(t)$ with $P \geq 2$ is written as

$$X(t) = \sum_{k=1}^p A(k)X(t-k) + \varepsilon(t) \quad (1)$$

where p is the model order, $A(k)$ are the autoregressive coefficients, $\varepsilon(t)$ is the noise vector, and t denotes the discrete time. The element (i, j) of the matrices $A(k)$ quantifies the direct causal influence for $j \rightarrow i$ which corresponds to

Granger causality. The normalization procedure in the PDC formula has been criticized as the causal interaction between sender ROI j and receiver ROI i is influenced by the number and strength of interactions between j and all other receiver ROIs (Schelter et al., 2009). As a consequence, the PDC (falsely) decreases, if the number and strength of receiver ROI interactions with j is high, even if the relationship between j and i remains unchanged. The iCoh overcomes this pitfall of the PDC by severing all possible connections between j and receiver ROIs that are not of interest:

$$\kappa_{i-j}(\omega) = \frac{[S_e]_{ii}^{-1} |\check{A}(\omega)_{ij}|^2}{[S_e]_{ii}^{-1} |\check{A}(\omega)_{ij}|^2 + [S_e]_{jj}^{-1} |\check{A}(\omega)_{jj}|^2} \quad (2)$$

where $A(\omega)$ is the discrete Fourier transform, ω denotes discrete frequency, and S_e is the noise covariance. Thus, the iCoh can be formulated as the answer to the following question: “Given a dynamic linear system characterized by its autoregressive parameters, what would the equation for the partial coherence be if all connections are severed, except for the single one of interest?” [Pascual-Marqui et al., 2014a, 2014b]. The iCoh takes values between 0 and 1, with a zero value implying no causality. It was further shown that the iCoh comes to very similar results as the PDC when causal interactions between ROIs are simple but that the strength of the interaction between j and i remains unaffected by the number and strength of receiver ROI interactions with j when interactions between ROIs are more complex [Pascual-Marqui et al., 2014a, 2014b].

The statistical procedure used for evaluating group differences was equivalent to a single threshold test [Nichols and Holmes, 2002]. In short, the two-tailed t -statistic between groups was calculated separately for the number of ROIs ($nROI$), number of frequency bands ($nFreq$), and direction of causal influence ($A \rightarrow B$, $B \rightarrow A$). This procedure yielded in a matrix consisting of $nROI \times (nROI - 1) \times nFreq = 120$ statistical tests, serving as the test statistic “ K .” Evaluation of between-group differences was repeated after randomly switching the group labels for a total of $M = 5000$ random permutations. For each permutation, the maximal t -statistic was stored giving the permutation distribution for the maximal statistic. Finally, the family-wise error (FWE) corrected P values of single cells of K were estimated by counting the number of cases where the t -statistic of a random permutation was equal to or greater than the t -statistic of a single cell of K and by dividing this number by M . The BrainNet Viewer was used for the visualization of the results (<https://www.nitrc.org/projects/bnv/>) [Xia et al., 2013].

Undirected Connectivity Analyses

To investigate AV synesthesia on a global scale, we also evaluated undirected connectivity between 29 ROIs (Table I). The selected ROIs were chosen according to previous

studies in AV synesthesia showing the involvement of primary and secondary auditory- [Beeli et al., 2008; Jäncke and Langer, 2011; Jäncke et al., 2012]; primary and secondary visual- [Beeli et al., 2008; Jäncke et al., 2012; Neufeld et al., 2012b]; parietal- [Jäncke and Langer, 2011; Neufeld et al., 2012a, 2012b]; and frontal brain areas [Beeli et al., 2008; Dovern et al., 2012]. As a consequence of sLORETA smoothing parameter [Pascual-Marqui, 2002] and to guarantee that individual ROIs indeed reflected distinct functional areas, we set a minimum of 1.5 cm as inter-ROI distance.

Undirected connectivity was computed on the cross-spectra between EEG epochs for distinct frequency bands. Accordingly, for every single subject, the 2 min of RS EEG were segmented into epochs of one second and undirected connectivity was computed in the following frequency-bands: theta, alpha, lower beta, and upper beta. The undirected connectivity between two ROIs X and Y for a particular frequency (ω) was calculated as *lagged phase synchronization* [Pascual-Marqui, 2007] according to the following formula:

$$\phi_{x \leftrightarrow y}^2(\omega) = \frac{[\text{Im}(s_{xy\omega})]^2}{1 - [\text{Re}(s_{xy\omega})]^2} \quad (3)$$

In this work, we concentrated on a lagged measurement for undirected connectivity between ROIs. This has the major benefit that it is comparable to our analysis of directed connectivity which is—by its nature—lagged. Phase synchronization is quantified as a value between 0 (no synchronization) and 1 (perfect synchronization) and is defined as “the absolute value of the complex valued (hermitian) coherency between the normalized Fourier transforms” [Pascual-Marqui, 2007]. The term “lagged” refers to the process of removing the effect of zero-lag instantaneous interactions on phase synchronization which are contained in the real (Re) part of the Hermitian covariance (i.e., in the denominator of eq. (1)). The normalized Fourier transforms ($X_{j\omega}$) of the phase-information cross-spectra ($S_{XY\omega}$) are defined as

$$\check{X}_{j\omega} = (X_{j\omega}^* X_{j\omega})^{-1/2} X_{j\omega} \quad (4)$$

with j denoting the j -th EEG epoch. As an output of the analysis, we obtained 29×29 square matrices, separately for each single subject and predefined frequency band. ROIs indicate rows and columns, whereas a single element contains the mean lagged phase synchronization between two ROIs during 2 min of RS EEG. These matrices were then submitted to statistical analyses with network-based statistic [Zalesky et al., 2010].

Network-based statistic (NBS)

Between-group differences in undirected connectivity were statistically evaluated by using the network-based statistic (NBS) toolbox [Zalesky et al., 2010] separately for each frequency band (theta, alpha, lower beta, and upper

beta). NBS is based on a nonparametric suprathreshold cluster test which is often used in fMRI analyses [Nichols and Holmes, 2001]. A network or “graph component” is thus defined by “interconnectedness of suprathreshold links in topological space” [Zalesky et al., 2010]. NBS controls the FWE that arises in multiple testing by (1) computing the t -test statistic for each connection. Edges exceeding a specific threshold form a suprathreshold network. The size, that is, the number of edges, of the largest observed suprathreshold network serves as the test statistic “ k .” (2) Run a total of $M = 5,000$ permutations where for each permutation, the group labels of subjects are randomly switched and the size of the largest random suprathreshold network is stored. (3) The FWE-corrected P value of k is estimated by counting the total number of permutations where the size of the largest random suprathreshold is $\geq k$ and by dividing this number by M . In our analyses, only suprathreshold networks exceeding a t value of two ($t = 2.2$ for the alpha frequency band) were considered as functionally meaningful.

RESULTS

Behavioral Data

AV synesthetes and nonsynesthetes did not differ significantly in age ($t(20) = 0.326$, $P = 0.74$), general cognitive capability ($t(20) = 1.391$, $P = 0.18$), nor in the tonal ($t(20) = 1.173$, $P = 0.25$) and rhythmical ($t(20) = 0.568$, $P = 0.57$) part of the test for musical aptitudes (t tests for independent samples, two tailed). The two groups differed significantly in consistency scores, with AV synesthetes demonstrating shorter color distances (i.e., a higher consistency) (mean = 0.82 ± 0.29) than nonsynesthetes (mean = 1.95 ± 0.45) ($t(20) = 7.064$, $P < 0.001$; t test for independent samples, two-tailed).

Current Density

AV synesthetes showed increased current density compared to nonsynesthetes in the parietal lobe: theta ($t(13.46) = -2.15$, $P = 0.050$, two-tailed Welch’s test); alpha ($t(14.86) = -2.26$, $P = 0.039$, two-tailed Welch’s test) and lower beta ($t(10.76) = -2.52$, $P = 0.029$, two-tailed Welch’s test) (uncorrected P values). The two-tailed statistic also yielded a trend toward higher current density in the parietal lobe for the upper beta frequency band in AV synesthetes than in nonsynesthetes: $t(10.47) = -1.82$, $P = 0.098$, two-tailed, uncorrected.

Nonsynesthetes did not demonstrate stronger current density than AV synesthetes.

Directed Connectivity

AV synesthetes demonstrated significantly increased directed connectivity in the upper beta frequency band

from the superior parietal lobe (BA7) to the left color processing area V4 (mean $iCoh = 0.188 \pm 0.110$) compared to nonsynesthetes (mean $iCoh = 0.044 \pm 0.035$ SD) ($t(12.06) = -4.12$, $P = 0.048$, FWE corrected). Compared to AV synesthetes, nonsynesthetes did not reveal increased directed connectivity, irrespective of connection or frequency band. Figure 1 displays the between-group differences in $iCoh$ for the upper beta frequency band.

Undirected Connectivity (NBS)

AV synesthetes showed increased undirected connectivity in the alpha ($P = 0.042$, FWE corrected) frequency band compared to nonsynesthetes. The network in the alpha frequency band consisted of 20 nodes and 45 edges and was characterized by global intra- and interhemispheric connections between auditory, visual, and parietal brain areas. The mean lagged phase synchronization of all edges of the alpha network was $0.168 (\pm 0.036)$ in AV synesthetes, and $0.086 (\pm 0.020)$ in nonsynesthetes. The alpha network is displayed in Figure 2. We did not find significant group differences in the theta, lower beta, or upper beta frequency bands. We also did not identify increased undirected connectivity in nonsynesthetes compared to AV synesthetes.

DISCUSSION

Current neurophysiological models of synesthesia mainly hypothesize hyperconnected and hyperactivated brains. Accordingly, it has previously been argued that synesthesia might be a consequence of a globally altered brain network connectivity [Bargary and Mitchell, 2008; Hänggi et al., 2011; Jäncke and Langer, 2011]. The next section discusses our results in sequential order.

Parietal Involvement

We found higher parietal current density in AV synesthetes compared to nonsynesthetes in a broad frequency range. Although an uncorrected significance level ($P < 0.05$) was employed, our findings are in line with previous studies showing parietal involvement in AV synesthesia [Jäncke and Langer, 2011; Neufeld et al., 2012a, 2012b]. In accordance with a previous EEG study [Jäncke and Langer, 2011], we demonstrated parietal involvement in AV synesthesia even during RS. We suggest that the parietal lobe plays a key role for this specific kind of synesthesia. Accordingly, we believe that direct cross-activation of V4 by inducer areas [Hubbard et al., 2005; Ramachandran and Hubbard, 2001] is not a sufficient explanation for the neurophysiological basis of AV synesthesia.

Top-Down Signal Transmission

We evaluated directed connectivity patterns to directly test the assumptions made by the two-stage and disinhibited

feedback models. The analysis revealed that even during RS, AV synesthetes were characterized by increased top-down signal transmission from a higher-order area in the superior parietal lobe to the concurrent color processing area V4 in the upper beta frequency band. Interestingly, frequencies above 20 Hz have previously been associated with top-down signal transmission during an auditory-visual sensory integration paradigm in rhesus monkeys [Kayser and Logothetis, 2009]. It could thus be that multimodal integration in AV synesthesia is driven by top-down signal transmission in higher frequencies.

An fMRI study performed with AV synesthetes reported stronger connectivity of the parietal cortex with primary auditory and primary visual areas [Neufeld et al., 2012b]. Although this finding is a strong argument for the disinhibited feedback model of synesthesia, the correlational nature of the aforementioned study renders it impossible to draw any conclusions about the directionality of signal transmission between brain areas. By contrast, our results provide direct support for the disinhibited feedback model in AV synesthesia which postulates top-down signal transmission from higher-order areas to concurrent processing areas. On the contrary, as we did not reveal increased directed connectivity in AV synesthetes from primary auditory areas to V4 or from V4 to the superior parietal lobe, our results do not provide evidence for a contribution of bottom-up signal transmission to AV synesthesia, as proposed by the two-stage model.

Different subtypes of synesthetes were found to rely on different signal transmission pathways [van Leeuwen et al., 2011]. Using dynamic causal modeling, this study demonstrated top-down signal transmission in internally perceiving GC associators vs bottom-up signal transmission in externally perceiving GC projectors. As most of the AV synesthetes who participated in this study experience synesthetic colors internally, it is conceivable to assume that increased top-down signal transmission was primarily driven by the majority of internally perceiving subjects.

Global Hyperconnectivity

The undirected connectivity analyses investigated between-group differences in brain networks on a global scale. This approach yielded stronger and globally extended connectivity patterns in AV synesthetes compared to nonsynesthetes in the alpha frequency band. In particular, we revealed increased undirected connectivity between auditory, parietal, and visual brain regions that have previously been shown to differ in a variety of phenotypes of synesthesia [Beeli et al., 2008; Esterman et al., 2006; Hubbard et al., 2005; Jäncke et al., 2012]. Long-range connectivity in the alpha frequency band was specifically associated with the processing of internal mental context, that is, with top-down processing [Von Stein and Sarnthein, 2000]. Therefore, it is plausible to assume that the global hyperconnectivity we revealed in the alpha frequency band might be an indicator for top-down processes in AV synesthesia. Notably, our results are in line with a previous RS

Figure 1.

Directed connectivity differences between auditory-visual synesthetes (A) and nonsynesthetes (B), measured as isolated effective Coherence (iCoh) between parietal- (BA7), primary auditory (BA41), primary visual (V1), and secondary visual (V4) brain areas in the upper beta frequency band. Arrow thickness is weighted by absolute *t* values. (C) Directed connectivity values from the parietal lobe to left color processing area V4 for auditory-visual synesthetes and nonsynesthetes ($P < 0.05$, FWE corrected). A = anterior; L = left hemisphere; R = right hemisphere; AVS = auditory-visual synesthetes; E-AVS = auditory-visual synesthetes experiencing colors externally; NonS = nonsynesthetes. [Color figure can be viewed at wileyonlinelibrary.com]

EEG study investigating AV synesthetes and reporting globally distributed hubs with stronger interconnections in synesthetes compared to nonsynesthetes [Jäncke and Langer, 2011]. Furthermore, an fMRI study targeting at evaluating undirected connectivity in AV synesthesia found stronger connectivity of the parietal cortex with primary auditory and primary visual areas [Neufeld et al., 2012b], which is also a prominent feature in our network of undirected

Figure 2.

Statistical difference in the connectivity profile between auditory-visual synesthetes and nonsynesthetes in the alpha frequency band. Auditory-visual synesthetes showed significantly increased undirected connectivity (depicted in red) ($P < 0.05$,

FWE corrected). A = anterior; L = left hemisphere; R = right hemisphere. Red lines = edges; blue dots = nodes. [Color figure can be viewed at wileyonlinelibrary.com]

connectivities. Yet, the authors used a seed-based approach which results in very large correlation matrices. Therefore, the connectivity of only a single or very few seed regions can be calculated. Here, we overcome this issue by calculating the undirected connectivity between 29 a-priori defined, literature-based and globally distributed nodes.

We find hyperconnected brains of AV synesthetes and suggest that synesthesia per se might be a consequence of global hyperconnectivity. This due to the fact that global hyperconnectivity has previously also been reported in GC synesthesia [Hänggi et al., 2011]. Moreover, different forms of synesthesia are likely to co-occur [Novich et al., 2011]. In our study, synesthetes were recruited by and exclusively tested on the occurrence of AV synesthesia. Although all AV synesthetes reported to experience colors only in response to auditory nonlinguistic stimuli, we cannot rule out the possible co-occurrence of other synesthesia forms in some synesthetes. Future studies could contribute to a more holistic

understanding of the umbrella term “synesthesia” by a more complete description of inducer-concurrent pairings.

LIMITATIONS

The small sample size of this study did not allow for appropriate statistical analyses of subsamples. Whether different subtypes of AV synesthetes rely on different signal transmission pathways (bottom-up vs top-down) remains a matter of research. Future studies should differentiate between subgroups of associator and projector synesthetes, respectively, between internally and externally color experiencing synesthetes.

CONCLUSIONS

The functional involvement of the superior parietal lobe even during rest is a strong indicator for its key role in

AV synesthesia. By demonstrating top-down signal transmission in AV synesthetes, we deliver direct support for the disinhibited feedback model of synesthesia. Finally, we suggest that synesthesia is one consequence of global hyperconnectivity.

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CONFLICT OF INTEREST

None declared.

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