Prestimulus Oscillatory Alpha Power and Connectivity Patterns Predispose Perceptual Integration of an Audio and a Tactile Stimulus

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Abstract: To efficiently perceive and respond to the external environment, our brain has to perceptually integrate or segregate stimuli of different modalities. The temporal relationship between the different sensory modalities is therefore essential for the formation of different multisensory percepts. In this magnetoencephalography study, we created a paradigm where an audio and a tactile stimulus were presented by an ambiguous temporal relationship so that perception of physically identical audiotactile stimuli could vary between integrated (emanating from the same source) and segregated. This bistable paradigm allowed us to compare identical bimodal stimuli that elicited different percepts, providing a possibility to directly infer multisensory interaction effects. Local differences in alpha power over bilateral inferior parietal lobules (IPLs) and superior parietal lobules (SPLs) preceded integrated versus segregated percepts of the two stimuli (audio and tactile). Furthermore, differences in long-range cortical functional connectivity seeded in rIPL (region of maximum difference) revealed differential patterns that predisposed integrated or segregated percepts encompassing secondary areas of all different modalities and prefrontal cortex. We showed that the prestimulus brain states predispose the perception of the audiotactile stimulus both in a global and a local manner. Our findings are in line with a recent consistent body of findings on the importance of prestimulus brain states for perception of an upcoming stimulus. This new perspective on how stimuli originating from different modalities are integrated suggests a non-modality specific network predisposing multisensory perception. *Hum Brain Mapp* 36:3486–3498, 2015. © 2015 Wiley Periodicals, Inc.

Key words: audiotactile; multisensory interactions; magnetoencephalography; functional connectivity; prestimulus

INTRODUCTION

Inputs through multiple senses are continuously processed in our brain, resulting in a unique and coherent perception of the world. Using data recorded from single neurons in the cat's superior colliculus, Stein and Meredith [1993] were the first to propose specific principles of multisensory interactions. They showed that, rather than being independent, processing of stimuli of different modalities depends on their relative spatiotemporal properties and salience. However, the mechanism of cross-modal interactions in the human brain remains largely unknown. Specifically, audio-tactile (AT) interactions have been far less investigated than those of other sensory modalities (e.g., audio-visual or visuo-tactile), despite their frequent occurrence in everyday life (knocking at a door, playing instruments, walking, shaving, perceiving the buzzing, and the sting of a mosquito).

To date, neurons responsive to both audio and tactile stimuli have been found in primates in the ventral premotor cortex, the ventral intraparietal region and the superior temporal sulcus [e.g., Bruce et al., 1981; Graziano et al., 1999; Schlack et al., 2005]. Further evidence suggests that AT interactions may occur already at early latencies of the sensory processing in brain regions close to or within primary sensory areas. More specifically, somatosensory stimulation was found to evoke rapid activations in belt areas of the auditory cortex [e.g., Schroeder and Foxe, 2002; Fu et al., 2003] and tactile stimuli modulated the activity of primary auditory cortex [Lakatos et al., 2007].

In human neuroimaging studies, AT multisensory interactions have been identified in secondary somatosensory cortex, the auditory belt area, and the posterior parietal cortex also before 100 ms [Beauchamp et al., 2008; Foxe et al., 2000; Foxe et al., 2002; Gobbelé et al., 2003; Hoefer et al., 2013; Kassuba et al., 2013; Lütkenhöner et al., 2002; Murray et al., 2005; Schürmann et al., 2006].

In this study, we aimed to elucidate the mechanism of perceptual integration/segregation of AT stimuli. It is well known that to create a coherent and correct representation of the external world, stimuli emanating from the same object or event are perceptually integrated, while stimuli independently generated are perceptually segregated [Ghazanfar and Schroeder, 2006]. To investigate this process, we created a bistable paradigm that allowed direct comparison of identical bimodal stimuli that however could elicit different (integrated or segregated) percepts. A sound of 1 s, simulating a looming mosquito approaching the head, was utilized as the auditory stimulus. A short touch, delivered on the face and resembling the mosquito landing, was the tactile stimulus. As the timing between the different modalities is critical for perceptually merging two stimuli [Calvert et al., 2004; Welch, 1999], we manipulated the stimulus onset asynchronies (SOAs) between the stimuli, rendering their temporal relation "ambiguous": that is, the perception of the physically identical AT stimuli could vary from integrated (condition INT) (audio and tactile stimuli perceived as the approaching mosquito and its landing) to segregated (condition SEG) (audio and tactile perceived as independent events) from trial to trial. These stimuli were selected because of their ecological relevance, and because approaching sounds [Canzoneri et al., 2012] and the space around the head [e.g., Kitagawa et al., 2005] have been shown to evoke stronger AT interactions.

As with our paradigm we can exclude the fact that integrated and segregated percepts are due to physical differences between stimuli, we hypothesize that different brain-states prior to the upcoming tactile stimulus predispose different multisensory percepts. Indeed, an increasing body of evidence is showing an influence of prestimulus activity on subsequent perception, especially in the case of near-threshold (NT) stimuli [Ruhnau et al., 2014] and in multisensory perception [Hipp et al., 2011; Keil et al., 2012]. We focused our analysis on the prestimulus time-window and characterized the multimodal AT interaction by local measures of power and global measures of inter-areal coupling [Weisz et al., 2014].

MATERIALS AND METHODS

Participants

Sixteen participants (5 females, mean age ± SD, 26 ± 7 years, all right-handed) were recruited from a participant database of the Center for Mind/Brain Sciences at the University of Trento. Visual acuity was normal or corrected-to-normal and all participants reported a normal sense of hearing and touch. The study was approved by the Ethical Committee of the University of Trento and was conducted in accordance with the Declaration of Helsinki as revised in October 2008. All participants gave written informed consent prior to participation and received monetary compensation for their time. The approximate duration of the study including preparation was 90 min.

Stimuli and Experimental Instrumentation

The auditory stimuli consisted of a sound simulating a flying mosquito (44,100 Hz sample rate, 16 bits resolution). The original stimulus length (see http://www.acoustics. org/press/132nd/3pab10.html) was truncated to 1 s and its intensity was modulated with an exponential envelope increasing of 35 dB (from 25 to 60 dB) over the duration of the sound to create the impression of a looming sound approaching the participant's head. Stimuli were presented binaurally via tubal insert headphones compatible with MEG. The sound was filtered with the head related transfer function (HRTF) of a KEMAR dummy head. The function was selected from the CIPIC HRTF Database [Algazi et al., 2001, dataset freely downloadable at http:// interface.cipic.ucdavis.edu/sound/hrtf.html]. The simulated sound source appeared in the horizontal plane, at an azimuth angle of 30° left of the direction of the

participant's gaze and was in accordance with the spatial position of the tactile stimulus. The tactile stimulation consisted of a light touch (diameter = 3 mm) at the participant's left perioral area. The tactile stimulation was delivered via a custom-built apparatus. A plastic filament was attached to a piston that could be moved back and forth by a double-acting pneumatic cylinder that was driven by compressed air with a pressure of 0.7 bars. The system was controlled electrically by a valve via a custom-built relay box. The final part of the stimulation equipment was mounted on a wooden MEG-compatible pedestal (that had no direct contact with the participant). The pneumatic system was placed outside the magnetically shielded room, so the noise produced by the device was not audible inside. The plastic filament was the terminal part of a fiber optic system (Keyence series FS-N, Neu-Isenburg, Germany). One fiber of the system was connected to an infra-red light and the other to a light sensor installed outside the magnetically shielded room. The fiber approaching the skin during stimulation resulted in an increase of reflected light until the fiber reached the skin. It was, therefore, possible to measure the precise timing of the delivery of the tactile stimulation. Participants' view of the tactile stimulation apparatus was obstructed to avoid them performing the task using visual cues provided by the movement of the apparatus.

Procedure

In each trial, the participants listened to the one second mosquito sound and felt the tactile stimulus described above (see Fig. 1A). While the individual stimuli were always the same, their relative timing, that is, SOA, could vary from trial to trial.

The SOAs were individually determined prior to recording in a pilot run. Aim of this pilot was to determine the individual psychophysical curve (Fig. 1B) that describes how, in function of their SOAs, perception of the auditory and the tactile stimuli varies between integrated (i.e., the touch being judged as caused by the approaching mosquito) and segregated (i.e., the touch being judged as unrelated to the approaching mosquito). In particular, we were interested in the two "transition" SOAs, one before and one after the end of the sound, at which the occurrence of the touch elicited 50% of time an integrated and 50% of the time a segregated percept. Each one of these two SOAs was determined by staircase procedures conducted using a staircase toolbox for MATLAB (https://code.google.com/p/matlabstaircase/). Four (i.e., two for each of the two SOAs) independent staircase procedures were randomly interleaved during the same pilot run. For each of the two SOAs one staircase started from a clearly integrated percept (touch occurring at the sound offset) and one from a clearly segregated percept (touch occurring at the sound onset or 1 s after sound offset) and they moved toward the ambiguity threshold with a one-up/one-down
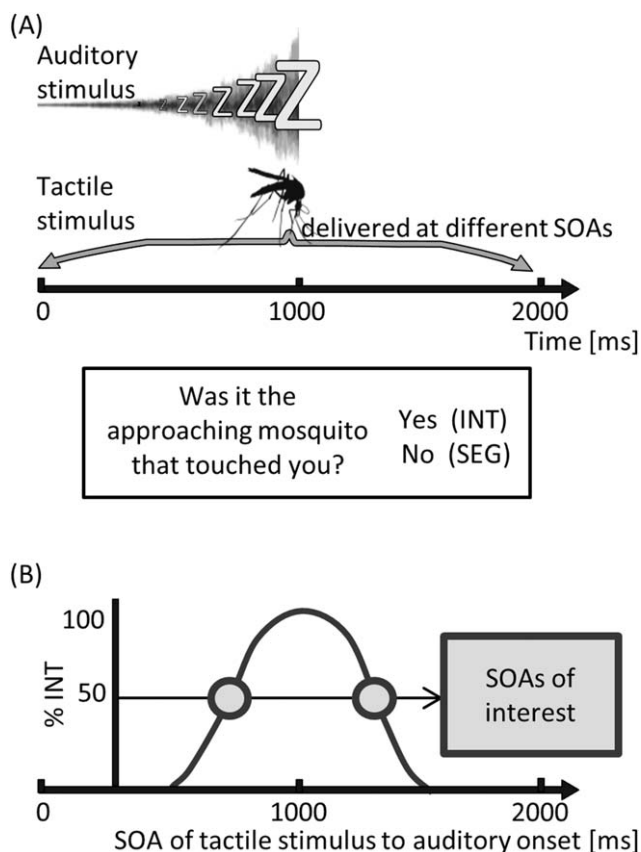

Figure 1.
(A) Each trial consisted of an auditory stimulus, a one-second sound of a mosquito approaching the participant's head from the left side, and a spatially correlated tactile stimulus that was intended to simulate the bite of a mosquito. Different (SOAs) between audio and tactile stimuli yielded different percepts: integrated, that is, the approaching mosquito and the touch belonged to the same event (condition INT, the impression that it was the approaching mosquito that touched them) or segregated (condition SEG, audio and tactile stimuli were unrelated events). SOAs could vary from trial to trial. Participants were asked to report their percept after each trial. (B) Schematic psychophysical function describing the relationship between different SOAs and an integrated percept. SOAs of interest (prior and following sound offset) were those in which integrated and segregated percepts were equally probable.

step procedure. To quickly approach the ambiguity region, the step-sizes at the beginning were bigger (80 ms) and progressively diminished until (after 7 reversals) becoming stable with a step-size of 16 ms. Each staircase procedure stopped when a defined number of trials (40) or of reversals (30), or of boundaries-hits (5) was reached. At this point the SOA was determined by averaging the two thresholds obtained.

In the recording session, according to previously individually estimated SOAs, two types of trials were

presented. In the first type of trials, the touch occurred before the end of the sound and the SOA matched the 50% rate of integration/segregation as previously determined. In the second type of trials, the tactile stimulation was delivered after the end of the sound and matched the previously determined 50% rate of integration/segregation (Fig. 1B). Additionally, a third type of trials was presented where SOAs between audio and tactile stimuli were randomly chosen from a uniform distribution of SOA ranging from sound onset (1,000 ms prior to the end of the sound) to 1,000 ms after the sound offset. The latter trials were presented to increase the difficulty level of the perception evaluation task and were discarded from further analyses.

The three types of trials were randomly presented within a block. Each block consisted of 78 trials with 26 trials of each trial type. Each participant underwent nine blocks. The participants' task was to report after each trial whether the two sensory inputs belonged to the same event or were distinct events. Henceforth, INT response refers to the perception of the auditory and the tactile stimuli being perceived as a single event (i.e., the touch being judged as caused by the approaching mosquito); SEG response refers to the perception of the auditory and the tactile stimuli as distinct events (i.e., the touch being judged as unrelated to the approaching mosquito).

The experiment design allowed direct comparison of physically identical stimuli that produced either the percept of integrated or segregated AT stimuli. During the trial, participants were instructed to fixate on a cross on the display screen. After a period of 2,000 ± 400 ms (uniform distribution) following the sound onset, participants were asked to report their perception by answering the question "Do the auditory and the tactile stimuli belong together?" Responses were delivered via button presses within the given time limit of 2,000 ms using the left and right index fingers to respond "yes" or "no" respectively. The buttons corresponding to positive and negative were changed randomly on a trial-by-trial basis, to avoid possible confounds due to motor-response mapping preparation. Trials were eliminated if participants responded prior to the onset of the tactile stimulus or failed to make a response within the limit. Such responses accounted for less than 1% of trials overall and were not further analyzed.

Data Acquisition

MEG data were recorded at a sampling rate of 5 kHz using a 306-channel (204 first order planar gradiometers, 102 magnetometers) VectorView MEG system (Elekta-Neuromag Ltd., Helsinki, Finland) in a magnetically shielded room (AK3B, Vakuum Schmelze, Hanau, Germany). Hardware filters were adjusted to band-pass the MEG signal in the frequency range of 0.01–1,000 Hz. Prior to the MEG recording, 3 localization coils were placed on the forehead and 2 behind the ears. The position of the coils and the participants' head shapes were digitized with a Fastrak 3D digitizer (Polhemus, Colchester, VT, http://www.polhemus.com). Prior to each experimental block, participants' head positions with respect to the MEG sensors were estimated. The neurophysiological MEG data were analyzed offline using Fieldtrip [Oostenveld et al., 2011], an open source toolbox for Matlab (www.mathworks.com).

Data Preprocessing

As we were interested in the integration of a tactile stimulus with an ongoing auditory stimulus, epochs of 4 s (2.5 s pre and 1.5 s post) were centered on the tactile stimulus onset; onsets were obtained from the optical fiber device (see Stimuli and experimental instrumentation). Zero seconds therefore represents the onset of the tactile stimulus. Epochs were high-pass filtered at 1 Hz to remove very slow frequencies (DC offset) and filtered for line noise removal, then down-sampled to 400 Hz. Trials were visually inspected for possible artefacts and contaminated trials were excluded from further processing. As mentioned in the Procedure section, we are interested only in trials where the auditory and the tactile stimulus are related by a certain SOA that produced a rate of INT/SEG responses as close as possible to 50%, while the other trials (i.e., trials with random SOA) were discarded. Remaining trials were divided into two conditions based on participant responses: SEG and INT conditions. As the rate of integrated/segregated percepts was not always 50%, we equalized the trial number by randomly discarding trials from the condition having a larger number of trials for each subject. This procedure was conducted separately for the case of touch occurring prior to the end of the sound and after the end of the sound. Equalization of trial number ensured comparable signal-to-noise ratios and ensured that any other common activation, including activity due to the auditory stimulus in the condition where touch arrives prior to the end of the sound, was cancelled when contrasting SEG and INT. Since we were interested in the neural mechanism underlying perceptual integration, trials in which touch occurred prior and after sound offset were collapsed.

Event Related Fields Analysis in Sensor Space

For each participant, for condition INT and SEG, we averaged the preprocessed data over trials to obtain the event related fields (ERF) waveforms. Since we were interested in the perception of a tactile stimulus with an ongoing auditory stimulus, statistical analysis was performed on the poststimulus time after the tactile stimulus was delivered. A nonparametric cluster-based dependent-samples t-test with Monte-Carlo randomization [Maris and Oostenveld, 2007] was conducted on the time window 0–200 ms (0 ms refers to the tactile stimulus onset). The time window was selected to encompass the first peak of activation following tactile stimulation.

Time-Frequency Analysis in Sensors Space

For each participant, time-frequency analysis was performed on single trials between 1 and 40 Hz. We applied an adaptive sliding time window with a length (Δt) of 5 cycles of the respective frequency and shifted in steps of 50 ms between −1.2 and 0.9s. A Hanning taper was applied yielding a spectral smoothing of $1/\Delta t$. For the gradiometers, orthogonal gradients of the magnetic field were calculated separately at each position. The sum of both directions was computed to obtain the power at each sensor irrespective of the orientation of the gradients [Medendorp et al., 2007]. To statistically examine sensor level differences between the condition SEG and INT, we performed two nonparametric cluster-based dependent-samples t-tests with Monte-Carlo randomization for gradiometer recordings [Maris and Oostenveld, 2007]. A first statistical test of this type was run on a time-frequency window that encompassed the pre-(tactile) stimulus period (−450 to 50 ms and 1–40 Hz), while the second test was run for the post-(tactile) stimulus time-window (0–500 ms and 1–40 Hz). This type of statistical test was used because it controls for the multiple comparisons problem (type I error rate). In particular, a t-test for each sensor-time- frequency pair is performed. Subsequently, t-values exceeding a certain threshold (here 0.05) are considered and, based on spatial, temporal and frequency adjacencies, clusters of significant differences over space, time, and frequency are identified. Finally, cluster-level statistics, that is, the sum of t-values within each identified cluster, are evaluated under the permutation distribution of the maximum cluster-level statistic. This permutation distribution is obtained from a random draw of the observed data (random partition) repeated a high number of times (here 1,000). Thus, the proportion of random partitions that resulted in a larger value than the true observed one (maximum cluster-level statistics) is calculated and represents significance probability (P-value) under which cluster-level statistics are evaluated. Since a significant positive cluster of condition INT versus SEG was revealed in the time window from −300 ms to 50 ms in the alpha range (peak at 9Hz), further investigation in the prestimulus window was focused on this frequency band and time window.

Localization of the Time-Frequency Findings in Source Space

The individual head shapes obtained with Polhemus were coregistered with the individual structural MRI (4T Bruker MedSpec, Siemens). First, a course alignment was performed on the three fiducials, as collected with Polhemus prior to the MEG measurement, to the corresponding points on the individual MRI. Second, a rigid body transformation fitted the digitized head shape points of the individual to the head surface as extracted from the structural MRI. For two participants for whom individual MRIs were not available, a Montreal Neurological Institute (MNI) brain was morphed to fit the individual head shape. To compare the source activity across participants on a group level, a grid (1 cm spacing, 2,982 points inside the brain) fitted to a template MNI brain was warped to individual headspace for each participant. Resulting grid points were not regularly spaced but they were located in the same area with respect to the MNI template across participants [Larson-Prior et al., 2013]. An analytical single shell model was fitted to the individual segmented MRI [Nolte, 2003] and the leadfield was calculated for each grid point.

Both magnetometers and gradiometers were taken into account for source estimation after appropriate adjustment of the balancing matrix based on the distance of the gradiometers (17 mm), applied to take into account the different measurement units of magnetometer [T] and gradiometers [T/m] sensors. We projected the preprocessed data, that is, each trial, into source space, that is, on the points of the grid, using the linearly constrained minimum variance (LCMV) spatial filter [Van Veen et al., 1997]: first, for each participant, a LCMV filter was estimated on the combined conditions SEG and INT on the time interval −0.8 to +0.8 ms with respect to touch onset; then, the time-series of each trial was multiplied with this common filter. This allowed time-frequency analysis with the same parameters utilized at the sensor level for conditions INT and SEG. The grand average of the difference between the two conditions for the significant time interval (from −291 to +42 ms) at the significant frequency (9 Hz) was then plotted on an MNI brain.

Connectivity Analysis in Source Space

The spectral analysis suggested strong pretouch alpha power differences (see Results). To investigate potential connectivity patterns that predispose different percepts, we examined brain functional connectivity to and from the voxel with the maximum power effect (MNI coordinates: [60 −40 40]; corresponding to BA40). As a connectivity metrics we used phase locking values (PLV) [Lachaux et al., 1999]. The frequency of interest was the peak frequency in the time-frequency results (9 Hz) in the time window chosen for the source analysis (−291 ms +42 ms). We used the fast Fourier transform (FFT) algorithm on the sensor data (multitaper analysis, Hanning window) and projected the complex Fourier coefficients into source space by multiplying them with the respective spatial filters. Spatial filters were constructed using Dynamic Imaging of Coherent Sources beamformer [Gross et al., 2001] from the cross-spectral density matrix, calculated using a multitaper FFT transformation over the time window and frequency of interest resulting from the analysis on sensor level (−0.291 0.042 ms, 9 Hz, temporal interval centered at the maximum effect found in the time frequency analysis, length of 3 cycles/9 Hz = 333 ms) and the respective

leadfields. We then calculated PLV between the reference voxel and all other voxels.

To perform the statistical analysis, we used a nonparametric cluster-based dependent-samples *t*-test with Monte-Carlo randomization for condition INT versus SEG. Neighboring voxels above a given threshold with a minimum cluster size were considered as significant. The minimum size required for a cluster to be considered significant was defined according to a cluster-based approach common in fMRI research and implemented as 3DClustSim within the AFNI suite [Cox, 1996; Cox and Hyde, 1997]. The program simulates random *t*-values on a grid provided by the user, thresholds them according to a *P*-value and records the size of remaining clusters. This process is repeated 10,000 times and calculates the probability that this purely random activity will produce a significant cluster of a given size. To account for correlation between neighboring voxels, we applied a smoothing to the random activity. We used a smoothing factor of 1 cm on the random data prior to cluster identification. The value of 1 cm was chosen as it coincides to the estimated spatial resolution of MEG [Hansen et al., 2010]. This leads to a minimum cluster size of 15 voxels to be significant, for an alpha threshold of $P <= 0.05$.

RESULTS

In each trial in the experimental paradigm, an audio and a tactile stimulus were presented in a way that, although physically identical, could be perceived either as integrated, that is, as emanating from the same source, or as segregated, that is, they were independently generated. The perception fluctuated on a trial-by-trial basis. As the stimuli were physically identical, it is expected that any differences between conditions INT and SEG will arise from intrinsic neural dynamics and reflect only the differences related to perception.

Behavior

In a first pilot run, we studied for each participant the individual psychophysical function that links perception of integration/segregation to SOAs, so as to determine the two "transition" SOAs at which stimuli are ambiguously related and the rate of INT/SEG is 50. For touch occurring before the end of the sound, mean "transition" SOA is at 665 ms (±238 ms SD, 0 ms refers to the onset of sound). Exploration of the "right" part of the psychophysical function, that is, for touch occurring after the end of the sound, resulted in a mean "transition" SOAs of 1,338 ms (±188 ms SD, 0 ms refers to the onset of sound). In the subsequent part of the experiment, stimulation at these "transition" SOAs resulted in a percentage of INT of 44 ± 14% trials (mean ± SD) for the touch occurring before the end of the sound, and 46 ± 15% trials for the other case. For three participants, we were unable to elicit an
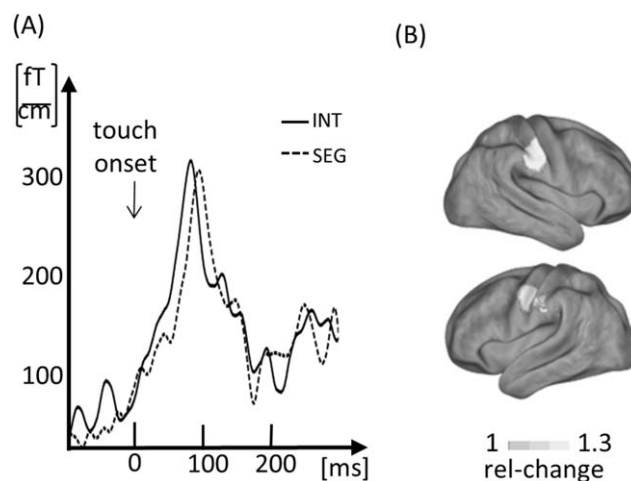

Figure 2.
(**A**) The event-related field for the combined gradiometers for condition INT (black line) and SEG (dotted line). A nonparametric cluster-based dependent-samples *t*-test with Monte-Carlo randomization was conducted on the time window 0 to 200 ms and failed to reveal any statistically significant difference between the two conditions. (**B**) Source analysis shows the localization of touch-related evoked responses - independent of condition - in primary somatosensory cortex. These results are shown as a sanity check of our data

ambiguous percept for touch before the end of the sound. For these participants only trials belonging to "transition" SOAs for touch after the end of the sound were used in the analysis.

Event Related Fields Analysis

Touch elicited strong responses in both conditions, with the evoked response showing the most pronounced peak ~85 ms. Source analysis of the 0–200 ms time window versus prestimulus baseline revealed pronounced generators in left and right primary somatosensory regions. Bilateral activation for lip/face tactile stimulation is in accordance with the literature [e.g., Schulz et al., 2004]. Interestingly, the ERF following the tactile stimulus did not differ between INT and SEG (Fig. 2A). In the following analysis we focused on the period before the upcoming tactile stimulus.

Time-Frequency Analysis

We statistically compared the time-frequency representations of INT trials versus SEG trials at sensor level. This comparison yielded a positive cluster ($P < 0.05$) starting from approximately 290 ms prior to touch onset and lasting until 40 ms after touch onset. The effect was in the alpha range (Fig. 3A), clearly peaking at 9 Hz and was
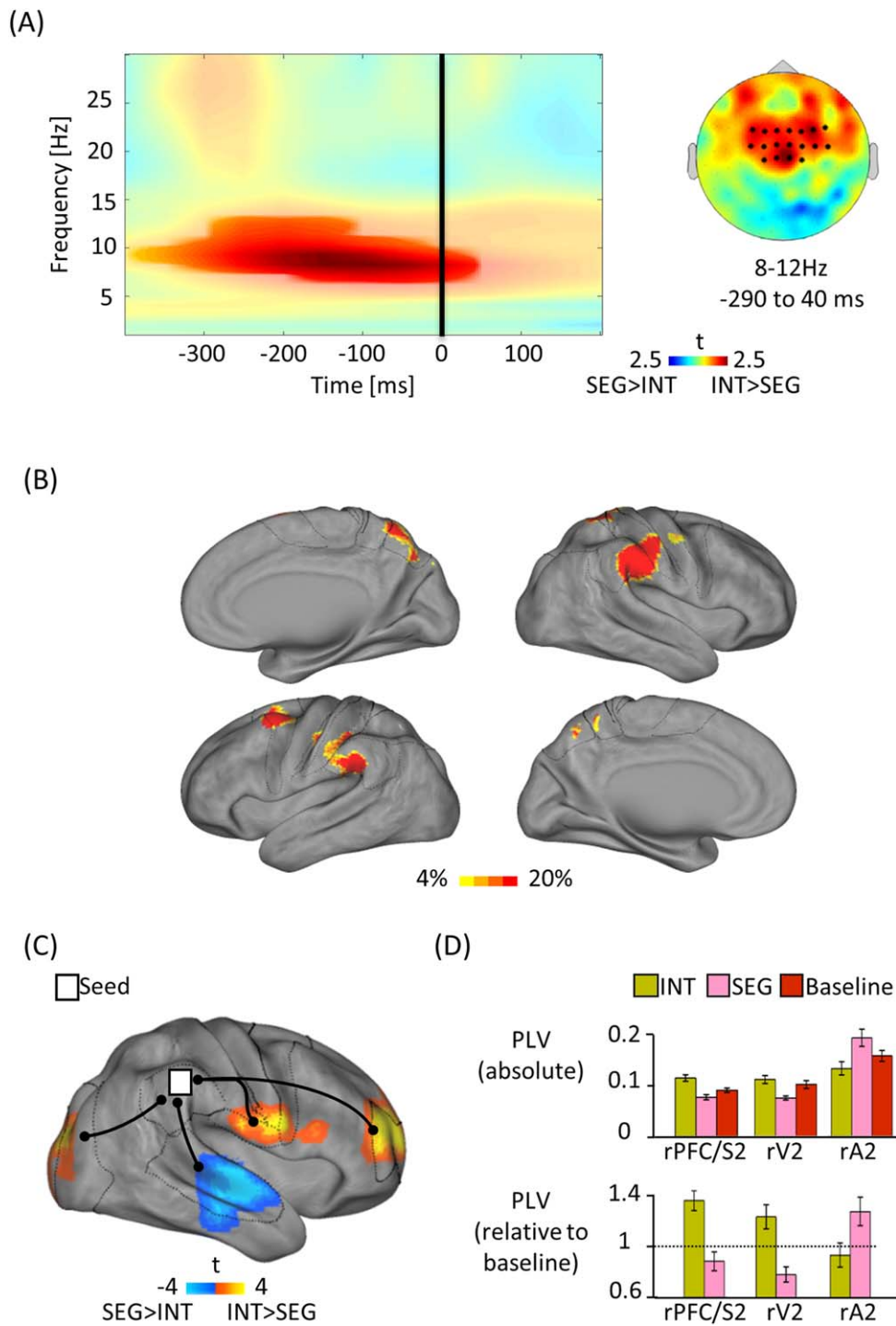
Figure 3.

dominant at central and frontal sensors bilaterally. We consider the time-window of the significant effect as prestimulus (prior to the tactile stimulus) even if it exceeds the presentation of the tactile stimulus, since the ERF of the tactile stimulus had its first peak only at 85 ms on primary somatosensory cortex (Fig. 2A). The spatial pattern of the sensor topography is also reflected at source level (Fig. 3B). The main cortical generator of the difference between

INT and SEG is localized in the right hemisphere (contralateral to tactile stimulus) in the inferior parietal lobule (rIPL) (BA 40, max: [60, −40, 40] MNI coordinates). This cluster propagates toward sensorimotor cortices (BA 2, 3, 4). Another cluster of activation is localized centrally over SPLs (BA7). Finally, ipsilateral (with respect to touch) activation is localized in lIPL and similarly to contralateral activation, this cluster expands toward sensorimotor cortices (BA 2 and 3) reaching the frontal cortex (BA6).

Functional Connectivity Analysis

The maximum grid point of the right IPL cluster described above (MNI coordinates [60 −40 40]) was chosen as a seed and functional connectivity between the seed and the rest of the brain was conducted in the time-window of interest (−290 until 40 ms) for the frequency of interest (9 Hz). As shown in Figure 3C, three brain regions—all located in the right hemisphere and contralateral to the upcoming tactile stimulus - showed altered functional connectivity to rIPL during INT with respect to SEG. In particular, rIPL showed more coupling with the right prefrontal cortex (BA 10) and motor-sensory regions (size: 35 voxels, max at MNI [30 50 20]) for condition INT (0.112 ± 0.007, PLV absolute value of the cluster ± SEM.) than for condition SEG (0.075 ± 0.0051). RIPL showed increased coupling as well with the right visual cortex (BA 18, BA 19) (size: 16 voxels, max at MNI [40 −90 20]) prior to the INT (0.1078 ± 0.008) with respect to SEG condition (0.0724 ± 0.004). Interestingly, the coupling between rIPL and the right auditory belt area (BA 20, size: 20 voxels, max at MNI [60, −10, 10]) was reduced in INT (0.133 ± 0.01) with respect to SEG condition (0.1929 ± 0.02). For each of these three clusters we calculated the mean PLV value across voxels and normalized it to the

values of the baseline, that is, prior to the sound onset, as shown in Figure 3D. A coupling in condition SEG drives the effect in auditory belt area, while a decoupling in condition SEG and a coupling in condition INT drive the other effects. Results are shown in Figure 3D.

DISCUSSION

In the present MEG study, we investigated how prestimulus brain-states predispose integrated or segregated percepts of an ongoing audio and an upcoming tactile stimulus. Since the temporal relationship between stimuli of different modalities is a critical factor for their perceptual integration [Calvert et al., 2004; Welch, 1999], we manipulated the temporal relation between the offset of a dynamic (approaching) sound of a mosquito and the onset of a touch (resembling the landing of the mosquito). By stimulating around the threshold SOA at which stimuli were perceived as either emanating from the same source (i.e., the mosquito approaching the head and landing on it; condition INT) or as two distinct events (condition SEG) perception of physically identical multisensory stimuli fluctuated between trials from integrated to segregated and vice versa. This approach allows direct comparison of physically identical but differently perceived stimuli.

We hypothesized that differences in brain-states prior to upcoming tactile stimulus can predispose different multisensory percepts. Alpha power was relatively increased in a pretactile stimulus time-window of about 330 ms for subsequent perceptions of integrated versus segregated. The difference was localized in IPLs and SPLs bilaterally. Moreover, the functional connectivity pattern was modulated by different percepts in the same time window. Prior to integrated percept, rIPL was more coupled with the

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Figure 3.

(**A**) Results of the statistical comparison at sensor level for condition INT versus condition SEG. Red color indicates relatively more power during condition INT. Time 0 ms indicates the onset of touch. Left: time-frequency representation (TFR) of the statistically significant sensors (cluster-$P<0.05$) for the interval pre- and post- tactile stimulus. Nonsignificant values have been reduced to 40% opacity. Right: Topographical representation of the statistical results for the time-window −290 to 40 ms in the frequency band 8–12 Hz. Black dots represent the sensors that gave statistically significant results at sensor level and whose TFR are plotted on the left side of the figure. (**B**) Projection in source space of the grand average of INT versus SEG for the time-frequency window and frequency of the significant results at sensors level. (**C**) Phase synchrony between the seed region, rIPL ([60 −40 40], MNI coordinates), and the whole-brain volume. *T*-values of INT versus SEG percept masked for statistical significance are displayed. Dashed lines represent the borders of Brodmann areas of interest. rA2 exhibited significant decoupling with the rIPL, while rPFC/rS2 and rV2 showed increased

coupling with rIPL during integrated compared to segregated percept. (**D**) We calculated PLV of each significant cluster showed in (C). In the upper part, we show the absolute PLV values (absolute values are reported in the results section). The lowest part shows PLV values normalized to the baseline prior to the sound onset. This is calculated to evaluate if the differences reported in (C), originate by, respectively, a coupling and a decoupling in both conditions with respect to baseline or, on the contrary, the effect is driven only by a coupling (or decoupling) in one condition. PLV greater than 1, indicated by the dashed line, indicates higher coupling with respect to baseline and vice versa. It shows how differences of PLV in the rPFC/rS2 originate from an increase of coupling for INT (1.32 ± 0.08, mean ± SEM) and a decrease of coupling for SEG (0.86 ± 0.07) with respect to the baseline. The same pattern is observed in rV2 (INT: 1.19 ± 0.09; SEG: 0.77 ± 0.06). For the rA2, the difference is primarily driven by an increase of coupling for the SEG percept (INT: 0.92 ± 0.09; SEG: 1.25 ± 1.1).

right secondary somatosensory and visual cortices and more decoupled from secondary auditory cortex as compared to the period prior to segregated percept.

IPLs and SPLs in Multisensory Interactions

Comparisons between the human and primate auditory cortices [Galaburda and Sanides, 1980; Hackett et al., 2001; Sweet et al., 2005] reveal that human IPL seems to be a close homologue of the caudomedial (CM) belt area of primates' auditory association cortex, which consistently shows auditory and somatosensory stimuli convergence with a bias for the skin surfaces of the head and neck [Brosch et al., 2005; Fu et al., 2003; Giard and Peronnet, 1999; Kayser et al., 2005; Schroeder et al., 2001; Schroeder and Foxe, 2002]. Moreover, in humans AT interactions have been localized in IPL or in its vicinity [e.g., Foxe et al., 2002; Gobbelé et al., 2003; Lütkenhöner et al., 2002; Murray et al., 2005]. Our findings are consistent with the IPL being an AT multisensory area and possibly the human homologue of the multisensory area CM in monkeys [Calvert et al., 2004; Hackett et al., 2007], since the integrated percept of the looming sound and the touch were preceded by higher alpha power exactly in bilateral IPLs.

In previous literature, IPLs and SPLs have been described as being activated during a localization task for both auditory and tactile stimuli [Renier et al., 2009], and relevant in localization tasks for stimuli of all modalities [e.g., Bushara et al., 1999; Reed et al., 2005]. Furthermore, rIPL appears to be involved in perception of time [e.g., Harrington et al., 1998; Rao et al., 2001] and the detection of temporal synchrony between auditory and visual stimuli [Adhikari et al., 2013; Bushara et al., 1999; Dhamala et al., 2007], and in tasks where multisensory temporal and spatial information need to be evaluated together [Assmus et al., 2003; Assmus et al., 2005]. In our paradigm, we manipulated the temporal relationship between the two stimuli. Given that the sound is looming, time is translated into the location of the sound source so that the integration/segregation task also had a spatial component, that is, the localization of the flying mosquito, based on the loudness of its buzzing sound, at the time the tactile stimulus is delivered. Although the role of IPLs and SPLs described above has been determined based on poststimulus activities, in our experiment the difference in IPLs and SPLs prior to the application of the tactile stimulus between conditions INT and SEG suggests that the ongoing brain state affects upcoming computations of spatiotemporal relations between stimuli of different modalities (here, audio and tactile).

Differently to previous AT neuroimaging studies in humans [e.g., Foxe et al., 2000; Gobbelé et al., 2003; Lütkenhöner et al., 2002; Murray et al., 2005], we lack a statistically significant difference in the poststimulus phase suggesting that, at least initially, both conditions elicit the same pattern of activation. This might be due to the fact that in previous studies AT interaction was defined as the difference between responses to bimodal stimuli and the sum of the activity evoked by the two stimuli when presented in isolation, while here we compared brain activity of identical bimodal stimuli (that were differently perceived). However we cannot exclude that the lack of significance is due to insufficient power or too conservative statistical methods or blindness of MEG to certain processes.

Our results propose for the first time that local and interareal synchronization properties of IPL prior to the stimuli crucially determine whether an AT stimulus will be perceived as integrated or not.

The Role of Alpha Band Activity

Local fluctuations of alpha activity in the prestimulus period over task-relevant areas, modulate the perception of NT stimuli, namely low levels of alpha power preceded "hits" (the NT stimulus is perceived), while high levels of alpha power preceded misses (the NT stimulus is not perceived) [e.g., Ergenoglu et al., 2004; Linkenkaer-Hansen et al., 2004; Hanslmayr et al., 2007; Van Dijk et al., 2008; Weisz et al., 2014]. Interestingly, recent studies show that low prestimulus alpha is related not only to higher probability of NT stimuli detection, but also to identification of more than one suprathreshold stimuli of the same modality presented with very close temporal proximity, that is, low prestimulus alpha over somatosensory and occipital predicted perception of two tactile stimuli [Baumgarten et al., 2014] or, in the context of visual illusions, low alpha over occipital areas predicted perception of two stimuli in the double flash illusion and in the fusion effect [Lange et al., 2013]. In our paradigm, perception of the very same audio and tactile stimuli as integrated or segregated fluctuates across repeated presentations. Our results are nicely in line with the previous results [Baumgarten et al., 2014, Lange et al., 2013] since low prestimulus levels of alpha predispose perception of two events (segregation; i.e., auditory and tactile stimuli being judged as unrelated) and high levels of alpha predisposing perception of one integrated AT event (i.e., the touch being judged as caused by the approaching mosquito).

Prestimulus alpha power fluctuations have been associated also to modulations of expectation and attention [Anderson and Ding, 2011; Foxe et al., 1998; Haegens et al., 2012; Jones et al., 2010; Worden et al., 2000]. So, one might argue that our findings indicate the expectation of a touch following a sound stimulus rather than a mechanism for perceptual integration in the brain. However, the tactile stimulus was expected in all trials in both conditions. Moreover, the SOAs of trials were randomized for each run and an equal number of trials of both conditions was used in our analysis. Therefore we are convinced that expectation is not the source of our differences.

We cannot exclude though that AT integration and segregation depend on participants' attention. In our study

variations of prestimulus alpha power could reflect ongoing intrinsic attentional fluctuations that influence subsequent percept, given that we did not explicitly modulate attention. In the literature, higher alpha levels have been found associated to less attentional demanding tasks [e.g., Foxe et al. 1998; Haegens et al. 2012]. Thus, if we consider attentional fluctuations as the origin of our effect, the perception of two distinct auditory and tactile stimuli (segregated) is more attentional demanding than the perception of two stimuli as emanating from the same event. Interestingly however, lower prestimulus alpha was localized in areas characterized as multisensory in the literature (see first section of the Discussion). Moreover, our results are in line with the aforementioned findings [Baumgarten et al. 2014; Lange et al. 2013], that is, indicating that high excitability of these multisensory areas (low alpha) predisposes perceptual segregation of two stimuli independent of the "cognitive" nature of the effect (e.g., attention). Finally, it should be noted that previous studies that have shown a role of alpha activity in shaping the allocation of attentional resources [e.g., Foxe et al. 1998; Haegens et al. 2012] have adopted cueing paradigms. Therefore, to investigate a possible role of attention allocation mechanisms a future study could include additional cues informing about the appearance of the tactile stimulus with respect to the auditory stimulus to manipulate attention.

Concluding, we argue first that IPLs and SPLs are critical for perceptual binding, and second, that alpha, and cortical excitability, plays a role in cross-modal perception on relevant areas.

Engagement/Disengagement of Relevant Brain Areas into a Distributed Network Predispose Distinct Multisensory Percepts

The brain connectivity analysis revealed a specific pattern of functional connections between distant cortical areas preceding different multisensory percepts. For the connectivity analysis, we used rIPL as a seed from which we computed connectivity to all other voxels of the brain. rIPL was chosen because it yielded the maximum difference between INT and SEG in the prestimulus time window and was therefore assumed to reveal major differences in a network level. rIPL exhibited increased coupling with rPFC, right secondary somatosensory and visual cortices, and decreased coupling with secondary auditory cortex, prior to the integrated percept with respect to the segregated percept.

The relationship between prestimulus activity patterns and perception has been recently investigated [Hanslmayr et al., 2007; Keil et al., 2012; Ploner et al., 2010]. These studies not only showed local power differences over relevant regions, but also that the inclusion or exclusion of these regions into a globally distributed functional network critically influences subsequent perception [Weisz et al., 2014]. Our data essentially confirm the relevance of both local and global aspects of brain-states in the prestimulus for subsequent perception: local alpha power levels as well as long-range connections appear to predispose whether subsequent AT stimuli are integrated or not.

The absence of poststimulus effects suggests that, rather than a specific multisensory area, integrated/segregated perception is predisposed by a network comprising "multisensory integration" areas with unisensory areas. The precise network configuration is possibly modulated by local inhibitory/excitatory balance. Indeed, inhibition is believed to be essential for the establishment of long-range networks [Jonas and Buzsaki, 2007] and one might hypothesize that the higher alpha power observed in IPLs and SPLs in our study for the integrated condition reflect the formation of the network relevant for multisensory integration.

The notion of a network that predisposes integrated or segregated percepts offers advantages and proposes a complementary mechanism to the traditional hierarchical model. The latter assumes that each sense is first processed in isolation and interaction takes place in multisensory "heteromodal" brain regions where feedforward convergence from the sensory-specific cortices occurs [Stein and Meredith, 1993]. However, this fails to explain interactions already at early latencies and in areas close to primary cortices [e.g., Foxe et al., 2000], and multisensory interactions that create novel percepts such as the "Hearing Hands Effect" in which gently touching a vibrating probe dramatically changes the perception of the sound intensity of a probe tone [Schürmann et al., 2004], or the "Parchment-Skin Illusion" [Jousmäki and Hari, 1998]. Contrary to the hierarchical model, large-scale interactions provide flexibility and efficiency in a network [Varela et al., 2001], which, when it comes to the brain, is fundamental to the efficient integration of inputs from a dynamic and multifaceted world along with endogenous activity. Thus, functional dynamic long-scale interactions seem to be a plausible mechanism to be added to the way multisensory interactions are thought about, using the hierarchical model which is primarily based on unchanged anatomical pathways.

The fact that the differentiated network comprised even visual areas despite the presentation of AT stimuli, suggests a nonmodality specific integration/segregation network. Indeed, vision plays a dominant role in localization tasks [Eimer, 2004]. For example, in the famous Ventriloquist Effect, auditory [Alais and Burr, 2004] and tactile [Caclin et al., 2002] stimuli were wrongly detected toward a simultaneous visual stimulus at a different location. Interestingly, it has also been shown that by blurring the visual stimulus, the effect is reversed with vision being captured by audition thus showing how multisensory perception must rely on a flexible mechanism. In our experiment, participants had no visual information that could bias their percept and no poststimulus effects were found in visual areas. It seems that visual cortices form part of a distributed cortical network that predisposes integration/segregation possibly for exploiting any upcoming visual information.

CONCLUSION

Previous research has already pointed out the role of prestimulus brain-states and cortical networks in multisensory processing [Hipp et al., 2011; Keil et al., 2012; Senkowski et al., 2008]. In the present MEG study, we investigated the neural correlates of multisensory percepts. We enhanced our results by exploiting a paradigm that allowed direct comparison of physically identical AT stimuli that elicited different percepts. Locally, our results showed how relative inhibition prior to the upcoming tactile stimulus of areas involved in temporal and localization tasks across different modalities leads to an AT integrated percept. The results suggest a functional role of these areas in comparing and separating stimuli of different modalities. Globally, we observed prestimulus differences in a cortical network that encompasses secondary areas of different modalities and prefrontal cortex suggesting a non-modality specific integration/segregation network.

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