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RESEARCH ARTICLE

Multisensory processing and oscillatory activity: analyzing non-linear electrophysiological measures in humans and simians

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Abstract Stimulus-related oscillations are known to be closely linked to integrative processing in the brain. One research domain within which there has been tremendous interest in oscillatory mechanisms is in the integration of inputs across the widely separated sensory systems. Under the standard approach of assessing multisensory interactions in electrophysiological datasets, the event-related response to a multisensory stimulus is directly compared with the sum of the responses to its unisensory constituents when presented alone. When using methods like wavelet transformation or fast Fourier transformation to derive induced oscillatory signals, however, such linear operations are not appropriate. Here we introduce a simple bootstrapping procedure wherein the linear summation of single unisensory trials forms a distribution against which multisensory trials may be statistically compared, an approach that circumvents the issue of non-linearity when combining unisensory oscillatory responses. To test this approach we applied it to datasets from intracranial recordings in non-human primates and human scalp-recorded EEG, both derived from a simple audio-visual integration paradigm. Significant multisensory interactions were revealed in oscillatory activity centered at 15 and 20 Hz (the so-called beta band). Simulations of different levels of background noise further validated the results obtained by this method. By demonstrating super- and sub-additive effects, our analyses showed that this approach is a valuable metric for studying multisensory interactions reflected in induced oscillatory responses.

Keywords Cross-modal · Bimodal · EEG · ERP · Binding · Oscillation · Beta Gamma

In 1989, Gray, Singer, and colleagues published groundbreaking work on the association between gamma oscillations and stimulus feature integration processes in the cat visual cortex (Gray et al. 1989). Further animal studies have shown that oscillatory responses in the gamma band (30–80 Hz) are associated with short and long-range synchronizations in visual cortical areas (Castelo-Branco et al. 1998; Engel et al. 1991; Konig et al. 1995). Subsequent human studies using electroencephalography (EEG) and magnetoencephalography (MEG) have demonstrated similar oscillatory phenomena (e.g., Kaiser et al. 2004; Tallon-Baudry and Bertrand 1999; Muller et al. 1996). Feature integration processing has also been linked to oscillatory activity in other frequencies such as alpha (8–12 Hz) or beta band activity (12–30 Hz) (e.g., Alegre et al. 2004; Brovelli et al. 2004; Busch et al. 2003; Classen et al. 1998; Herrmann et al. 2004; Klimesch 1999; Liang et al. 2002).

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This association between oscillatory activity and feature integration raises the strong likelihood that similar oscillatory mechanisms are involved in multisensory processing, for example, when auditory speech is integrated with visual lip movements. Recent work has also shown that the different sensory features of a multisensory object are integrated not only in the classical ‘‘multisensory areas’’ but also in low level cortical structures that were traditionally believed to be purely unisensory in function (e.g., Foxe et al. 2000; Foxe and Schroeder 2005; Fort et al. 2002a; Giard and Perronet 1999; Gonzalez Andino et al. 2005; Molholm et al. 2004; Murray et al. 2005a, b Schroeder et al. 2001; Schroeder and Foxe 2002, 2004, 2005). It is likely that oscillatory synchronization in these structures plays an important role in the integration of the multiple sensory inputs of a multisensory event (Kaiser et al. 2005; Sakowitz et al. 2005; Senkowski et al. 2005). Moreover, recent observations indicate that oscillatory responses may even be more sensitive to some experimental manipulations than the broad-band event-related potential (ERP) (Bertrand and Tallon-Baudry 2000; Herrmann and Mecklinger 2001; Senkowski and Herrmann 2002; Tallon-Baudry et al. 1996, 1998), emphasizing the importance of examining multisensory interactions in oscillatory responses.

The standard approach for assessing multisensory interactions in the ERP and functional magnetic resonance imaging (fMRI) literature is to compare the responses evoked by multisensory stimuli (e.g., multisensory audio-visual) with the linear summation of the responses to the respective unisensory constituents (e.g., unisensory-auditory plus unisensory-visual) (Calvert 2001a, b; Fort et al. 2002b; Foxe et al. 2002; Giard and Peronnet 1999; Molholm et al. 2002; Talsma and Woldorff 2005).[1] This approach is warranted and appropriate when assessing ERPs since voltage measures sum linearly. However, the property of linearity does not hold for induced oscillatory responses when they are computed using the standard methods such as the wavelet transformation (WT) or fast Fourier transformations (FFTs). For this reason, it is not valid to use the standard approach to study multisensory interactions in induced oscillatory responses (Fig. 1), although it has been certainly applied already in the literature (e.g., Bhattacharya et al. 2002).

Here we present an approach for studying multisensory interactions in induced oscillatory brain responses. The approach is based on the linear summation of the raw data of all single trials from two separately presented unisensory modalities (e.g., all single unisensory-auditory trials are combined with all single unisensory-visual trials). The unisensory trial combinations are bootstrapped to provide a distribution against which the responses to multisensory stimuli are compared.

The method was tested in monkey intracranial local field potential data and in human EEG recordings exploring multisensory audiovisual interactions in the induced beta band (13–30 Hz). Although both datasets were collected for audiovisual interactions, there were substantial differences in the location of recording sites and the paradigms used between species. As such, it should be stated that our purpose here was not to directly compare and contrast these datasets but rather, to test the approach on different types of recordings (i.e., different species and different recording techniques). The beta frequency band was chosen because we have recently found multisensory interactions in the evoked responses in this frequency range (Senkowski et al. 2006a). Evoked and induced oscillatory activity differ in that the former is strictly phase and time locked to the onset of a stimulus, whereas the latter does not have to be strictly phase and time locked to the onset of each trial. In Senkowski et al. (2006a), we have explicitly described how multisensory interactions can be examined for evoked oscillations. The issue of non-linearity mentioned above, however, prevents the application of the previously described approach for the analysis of induced oscillations. For this reason, we present a more appropriate non-linear approach to study multisensory interactions in induced oscillations here.

Since the approach is based on the linear summation of single trials from two different sensory modalities, it is possible that background noise in the data affects the output of the method. That is, background noise is only represented once in the multisensory audiovisual trials whereas during linear summation of unisensory-auditory and unisensory-visual trials two sources of background noise activities are summated. To rule out the possibility that some of the multisensory oscillatory effects we observe with this method are a result of this background noise issue, we performed a noise simulation where we added artificial noise to the continuous raw data. This simulation shows that background noise is not the source of our multisensory effects.

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[1] By convention, multisensory responses that are smaller than the sum of the unisensory responses are referred to as sub-additive while multisensory responses that are larger than the sum are referred to as super-additive (e.g., Calvert 2001a, b). However, it should be noted that a multisensory AV stimulus could evoke larger responses than either of the respective unisensory responses while still being classified as sub-additive relative to the summed unisensory responses.

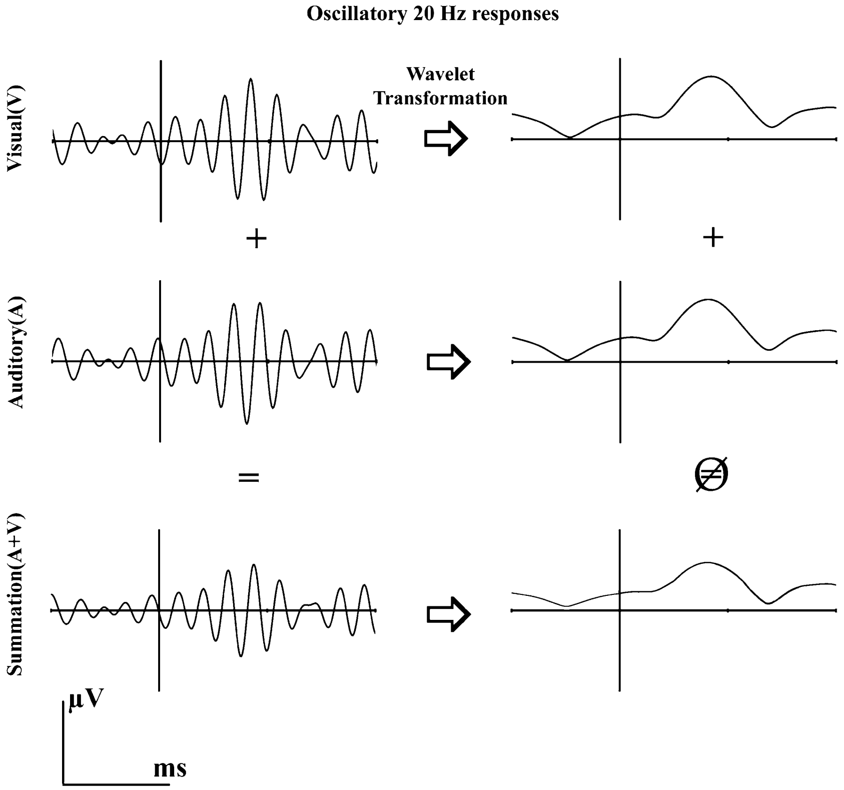

Fig. 1 The figure illustrates the differences between the linear summation of oscillatory 20 Hz responses to unisensory-visual and unisensory-auditory stimuli (*left panel*) and the linear summation of the same responses after wavelet transformation (*WT*) (*right panel*) for simulated data. Here we show a case where there is no multisensory interaction (i.e., A + V = AV). Due to phase variability, the summation of unisensory oscillatory responses in the time domain, in nearly all cases, results in amplitude that is less than the sum of the amplitudes of these responses after WT. For this reason, the wavelet-transformed responses to unisensory stimuli (*right panel*) cannot simply be summated and compared with wavelet-transformed responses to multisensory stimuli

Methods and results

Multisensory audiovisual interactions in induced oscillatory beta responses were investigated in monkey intracranial local field potential data and in human EEG data from a simple audio-visual integration paradigm (The materials and paradigms of the data analyzed here are described in the Appendix.). First, a target frequency and a time interval were defined for the analysis. Then a five-step analysis was performed for the selected target frequency and time interval.

Definition of a frequency and time interval for the analysis of multisensory interactions

The five-step analysis of multisensory interactions is described here in detail for the intracranial monkey data shown in Fig. 2.

Before analysis begins, a time window and a specific frequency-band must be first defined. We recommend computing time–frequency (TF) planes to define these parameters (e.g., Herrmann et al. 1999; Senkowski and Herrmann 2002). Figure 2a shows TF planes of induced oscillatory beta responses measured from intracranial local field potentials in auditory cortex. Responses are shown for unisensory-auditory, unisensory-visual, and multisensory audiovisual stimulation. The TFs showed a post-stimulus induced beta band activity (at about 15 Hz) for auditory and audiovisual stimuli after about 60 ms. A smaller but visible beta activity was also observed for unisensory-visual stimuli. The analysis of multisensory interactions in the beta frequency was performed for a time interval between 10 and 110 ms. The five step analysis on these data then addressed whether induced oscillatory responses to multisensory stimuli shown in Fig. 2b differed from oscillatory responses to combined unisensory-auditory and unisensory-visual trials in this time interval.

Five step analysis of multisensory interactions

First, epochs for all unisensory and all multisensory trials are computed (Fig. 3a). Second, each single epoch from one unisensory modality (e.g., auditory) is

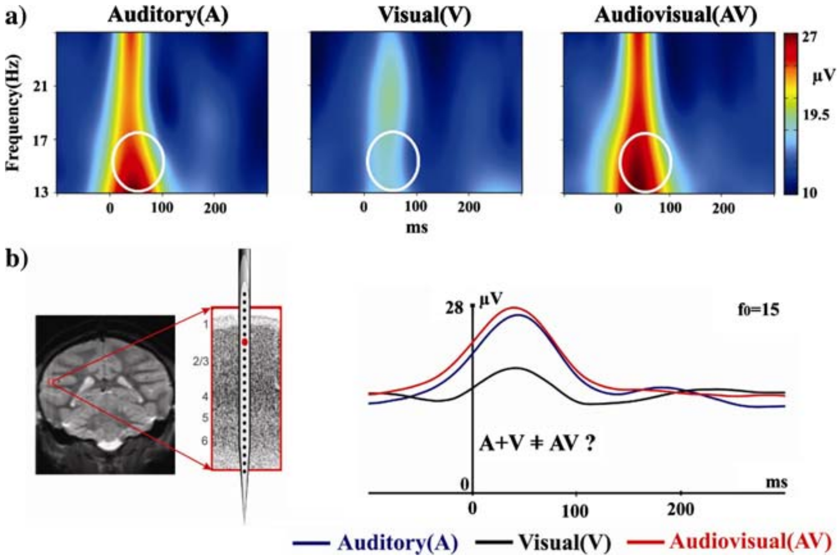

Fig. 2 Induced oscillatory beta responses recorded from auditory cortex in monkey intracranial local field potentials. **a** Time–frequency planes for unisensory-auditory, unisensory-visual, and multisensory audiovisual trials. The *white oval* denotes the analyzed frequency range and time window. **b** *Left panel* illustration of the intracranial recording procedure. *Right panel* wavelet transformed (f_0 = 15 Hz) beta responses to auditory, visual and multisensory stimuli

linearly summed with each single epoch from the other sensory modality (e.g., visual). The number of combinations equals the number of auditory epochs multiplied by the number of visual epochs (Fig. 3b). Third, the Morlet WT is applied to all combined A + V epochs (Fig. 4a) and all multisensory AV epochs (e.g., Herrmann et al. 1999). Baseline activity is then subtracted from each wavelet-transformed epoch. The baseline here was defined as the pre-stimulus time interval between –300 and –100 ms. A single-dependent variable is computed for each WT of the combined A + V epochs and for each WT of the multisensory AV epochs. In accordance with the observed activity pattern in the TF planes for monkey intracranial data, the dependent variable for the present analysis was the maximum amplitude of 15 Hz wavelet transformed beta responses in the 10–110 ms time interval[2].

The fourth step is the bootstrap procedure. Wavelet transformed A + V epochs are randomly selected from all epoch combinations (Fig. 4b). It is important that the number of epochs selected for one A + V bootstrap sample corresponds to the number of multisensory AV epochs. The bootstrap procedure is repeated 10,000 times, resulting in 10,000 A + V bootstrap samples. For these bootstrap samples the mean of the dependent variable is computed separately, giving the sample mean. In addition, the mean of the dependent variable of wavelet transformed multisensory AV epochs is computed.

In the final step the mean of the dependent variable of multisensory AV epochs is compared with the distribution of the bootstrap sample means. Figure 4c shows the distribution of the A + V bootstrap sample means and the mean of the dependent variable of wavelet transformed multisensory AV epochs, both plotted on the same histogram. The figure demonstrates that the multisensory AV activity was found to be in the lower 1% compared to the bootstrap sample mean distribution. Thus, the percentile of multisensory AV responses relative to the bootstrap sample means was 1%. A percentile below 2.5% or above 97.5% can be called significant at a 2-tailed significance level of 5%. Sub-additive multisensory integration effects (i.e., A + V > AV) are expressed by a percentile below 2.5% and super-additive effects (i.e., A + V < AV) are expressed by a percentile above 97.5%. Thus, the observed percentile of 1% indicates a sub-additive multisensory integration effect (A + V > AV) (Fig. 4c, left panel).

Noise simulation

In the bootstrap samples, two sources of background noise are summed and compared with one single source of background noise in the multisensory epochs. Thus, it might be that the sub-additive effect (A + V > AV) on induced beta responses reported here for intracranial local field potential data is contaminated by differences in background noise between the bootstrap samples and the multisensory epochs. For this reason, a simulation was performed to study the effects of background noise on the results obtained by the approach.

For the noise simulation, FFTs were performed in a pre-stimulus and a post-stimulus time interval

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[2] If a decrease in oscillatory responses relative to baseline is observed, then the dependent variable may be taken as the most negative value in the selected time interval.

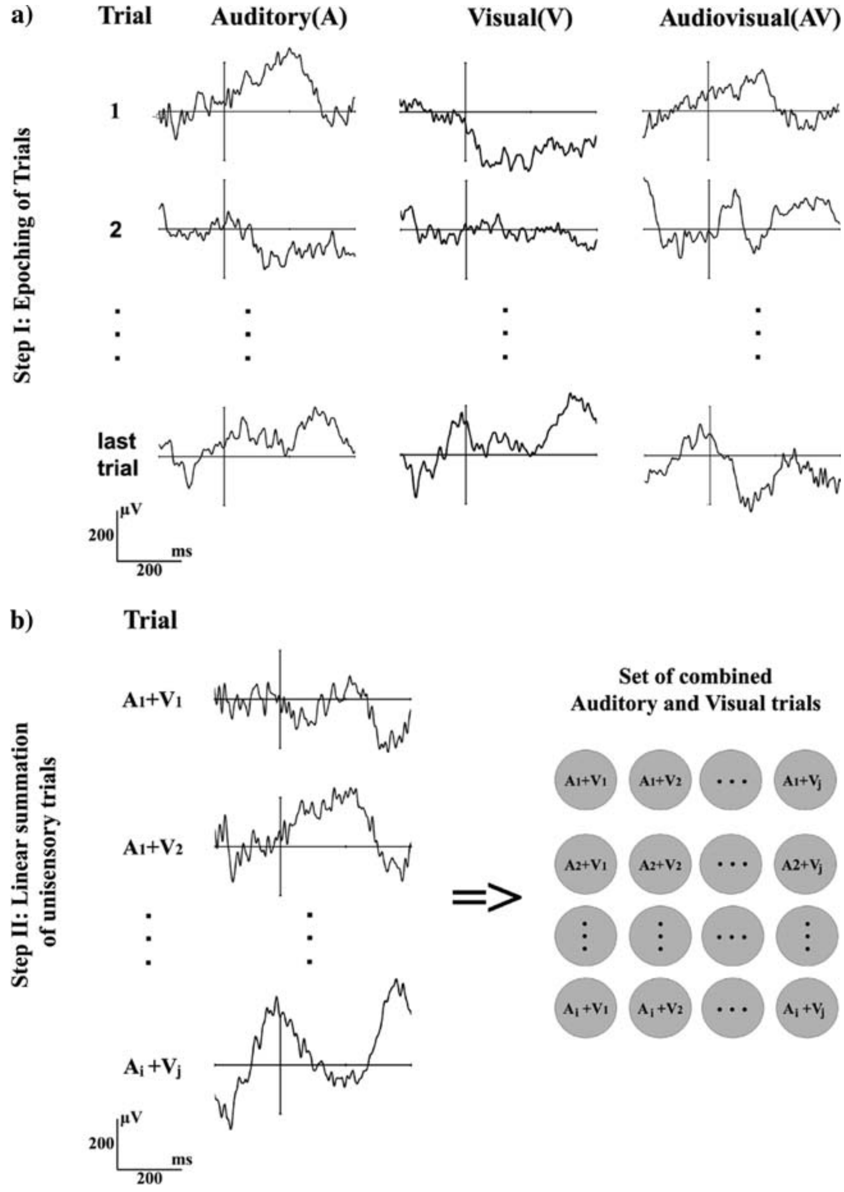

Fig. 3 The figure illustrates the first two steps of the five step analysis of multisensory interactions in induced oscillatory responses. Trials are baseline corrected for visualization purpose

(10–110 ms pre- and post-stimulus activity) for a frequency of 15 Hz. The signal-to-background noise $[(S + N)/N]$ ratio in the data was calculated by dividing the post-stimulus activity [i.e., the signal plus background noise $(S + N)$] by the pre-stimulus activity [i.e., the background noise (N)]. The $(S + N)/N$ ratio for multisensory stimuli of the intracranial data here was 1.6. For the noise simulation, pink noise similar in its frequency characteristics to the typically observed EEG background noise was added to the original continuous data. The amount of pink noise added to the continuous data here led to a reduction of the $(S + N)/N$ ratio to about 25% of its original value [e.g., the $(S + N)/N$ ratio for multisensory stimuli was reduced to 1.15]. Importantly, the same amount of pink noise was added to each multisensory and each unisensory epoch. The examination of multisensory interactions for the noise-simulated data using the five-step analysis revealed a significant sub-additive effect as expressed by a percentile of 2% (Fig. 4c, right panel). For the noise-simulated as compared to the original data, a flattening of the distribution of the bootstrap sample means was observed. This flattening has the effect of an increased probability of Type II statistical error. The Type II error describes the situation that the experimental null hypothesis (i.e., multisensory activity is equal to combined unisensory activities) is accepted, when in reality there are multisensory interactions in the data. In addition, the bootstrap sample mean distribution was shifted in the positive direction (compare left and right panel of Fig. 4c). This shift in the positive direction could lead

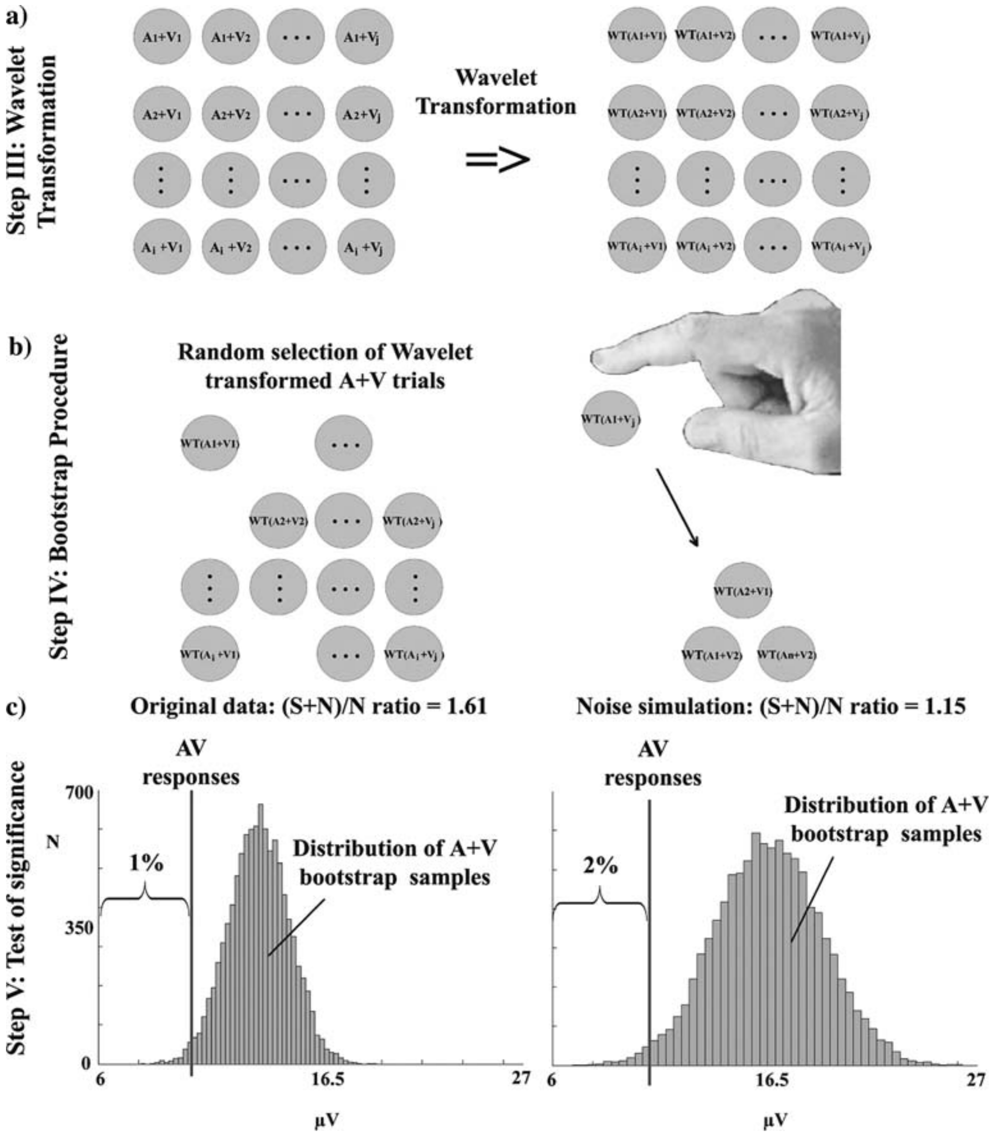

Fig. 4 The figure illustrates steps three to five of the five step analysis. In addition, the results of the noise simulation are shown (Step **c**, *right panel*)

to an increase in the probability of Type I statistical error (i.e., the null hypothesis is falsy rejected). The reduction of statistical significance of the noise-simulated data compared to the original data (2 vs. 1%, respectively), however, demonstrates that noise mainly increases the probability of Type II statistical errors (i.e., the null hypothesis is falsely accepted). Thus, it is very unlikely that background noise accounts for the multisensory sub-additive effect observed in the intracranial data.

Multisensory interactions in scalp recorded human EEG recordings

Figure 5a shows time–frequency (TF) representations for wavelet transformed induced beta responses to unisensory-auditory, unisensory-visual, and multisensory audiovisual stimuli for one right-frontal channel. The figure illustrates a strong increase in beta activity after about 150 ms, primarily for multisensory stimuli. Thus, based on our observations from the TF, the maximum amplitude of the 20 Hz wavelet transform in the time interval 80–170 ms was defined as the dependent variable to analyze for multisensory interactions (Fig. 5b). Figure 5c (left panel) shows the distribution of the bootstrap sample means and the mean of the dependent variable of multisensory epochs. A percentile of 99.9 % was observed for the mean of the dependent variable of multisensory epochs compared to the distribution of the bootstrap sample means, suggesting a multisensory super-additive effect [(A + V) < AV)]. As detailed above, the effects of background noise this super-additive effect were then explored. The $(S + N)/N$ ratio was computed by cal-

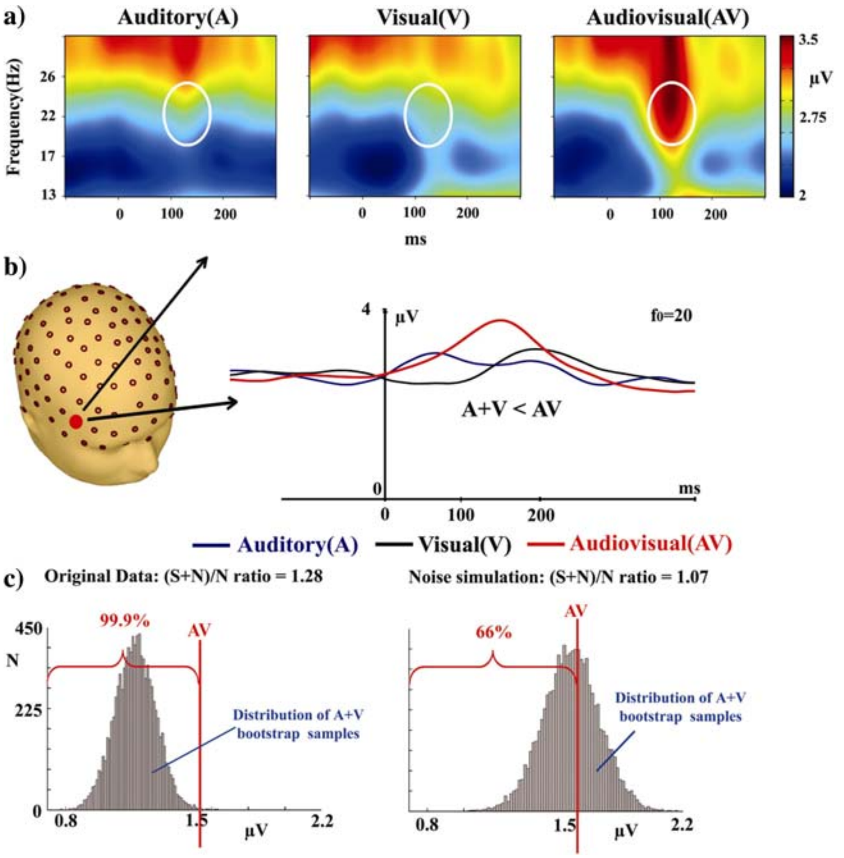

Fig. 5 Induced oscillatory beta responses recorded from one right-frontal scalp site in human EEG. **a** Time–frequency planes for unisensory-auditory, unisensory-visual, and multisensory audiovisual trials. The *white oval* denotes the analyzed frequency range and time window. **b** *Left panel* scalp location of the EEG channel. *Right panel* wavelet transformed ($f0 = 20$ Hz) beta responses to unisensory-auditory, unisensory-visual and multisensory audiovisual stimuli. **c** *Left panel* distribution bootstrapped samples compared with the mean of the dependent variable of wavelet transformed multisensory AV stimuli. The figure shows a multisensory super-additive ($A + V < AV$) effect. *Right panel* adding noise to the original data causes a flattening of the distribution and a shifting to the right. This results in reduced percentile values. Thus, noise cannot account for the significant results obtained by the approach

culating FFTs for a 80–170 ms pre-stimulus and post-stimulus interval for a frequency of 20 Hz. The $(S + N)/N$ ratio for multisensory stimuli was 1.28 in the original data and 1.07 in the noise simulated data, effectively reducing the $(S + N)/N$ ratio to 25% of its original value. For the noise simulated data a percentile of 67% was observed (Fig. 5a, right panel). The reduced statistical significance of the noise-simulated data (67% compared to 99.9% in the original data) demonstrates that noise cannot explain the super-additive effect observed here. The differences in findings of monkey intracranial (i.e., multisensory sub-additive effect) and human EEG data (multisensory super-additive effect) could be explained by the differences in the paradigms and/or by the fact that these responses were measured from different brain areas and were observed at different latencies.

Previous studies have revealed an association between a decrease in beta amplitude power and motor preparation (e.g., Pfurtscheller 1992). To examine whether the induced oscillatory beta responses to multisensory stimuli might be related to motor processing in the present data set, a correlation analysis between beta responses and reactions times was performed on a single trial level ($N = 530$ trials). In line with our previous observations (Senkowski et al. 2006a), we did not find a significant association between RTs (mean 286 ± 61 ms) and induced beta oscillations ($r = 0.01$, $P < 1$). This supports the notion that right-frontal induced beta responses (80–170 after stimulus onset) are not directly linked to motor processing in a multisensory context.

Finally, we would like to emphasize that we also observed non-significant results (i.e., there was no difference between the induced oscillatory responses to multisensory and combined unisensory trials) during exploratory testing of other EEG electrode sites (e.g., left-frontal). Since it is difficult to interpret non-significant statistical results, however, these findings are not presented in further detail here.

Protocol for the five-step analysis

The five-step analysis can be reiterated briefly as follows:

1. Segmentation of each unisensory-auditory (X_{A}), unisensory visual (Xv), and multisensory (X_{AV}) epochs.
2. Linear summation of unisensory epochs: $X^{i,j}_{\mathrm{A+V}} = X^{j}_{\mathrm{V}}$, for $i = 1, \ldots, N_{\mathrm{A}}$ and $j = 1, \ldots, N_{\mathrm{V}}$, where N denotes the number of epochs.
3. Wavelet transformation of each combined unisensory epoch

$$\mathrm{WT}^{i,j}_{\mathrm{A+V}}(a,b) = \left|\frac{1}{\sqrt{a}}\overline{\Psi}\left(\frac{t-b}{a}\right)X^{i,j}_{\mathrm{A+V}}(t)\mathrm{d}t\right|,$$
$$\text{for } i = 1, \ldots, N_{\mathrm{A}} \text{ and } j = 1, \ldots, N_{\mathrm{v}},$$

   and each multisensory epoch

$$\mathrm{WT}^{k}_{\mathrm{AV}}(a,b) = \left|\frac{1}{\sqrt{a}}\overline{\Psi}\left(\frac{t-b}{a}\right)X^{k}_{\mathrm{AV}}(t)\mathrm{d}t\right|,$$
$$\text{for } k = 1, \ \ldots, \ N_{\mathrm{AV}}.$$

   The complex morlet WT is represented by $\Psi(t) = \mathrm{e}^{j\omega t} \cdot \mathrm{e}^{-t^2/2}$, where $\mathrm{e}^{j\omega \mathrm{t}}$ represents a sinusoidal function which is multiplied with the envelope function $\mathrm{e}^{-t^2/2}$. $\bar{\psi}$ is the conjugate of the complex wavelet. The term a represents scale and b the time shift. The maxima or minima within a chosen interval at a chosen scale are defined as the dependent variable for the analysis.
4. Bootstrapping the dependent variables from the set of combined $\mathrm{WT}_{\mathrm{A+V}}$ epochs and calculating the mean of the dependent variable over epochs for each bootstrap sample. The number of combined $\mathrm{WT}_{\mathrm{A+V}}$ epochs in each bootstrap sample should correspond to the number of multisensory $\mathrm{WT}_{\mathrm{AV}}$ epochs (i.e., N_{AV}). We recommend repeating the bootstrap procedure 10,000 times, resulting in 10,000 bootstrap samples.
5. Comparison of the mean of the dependent variable for $\mathrm{WT}_{\mathrm{AV}}$ with the distribution of bootstrap sample means.

From single subject data to group level statistics

To explore whether statistical findings on a single subject level are significant on a group level, it seems to be useful to test whether the percentile values over subjects differ from that expected by chance. One possible approach is the application of chi-square-tests. To perform chi-square-tests, the percentiles obtained from different subjects would have to be categorized first. For instance, percentiles might be categorized in three groups (Group A: percentile < 0.025, Group B: $0.025 \leq$ percentile ≥ 0.975, and Group C: percentile > 0.025). For a given sample of $N = 40$, one would on average expect to find one subject in group A, 38 subjects in group B, and one subject in group C. The Chi-Square-test computes the goodness-of-fit between the distribution expected simply by chance and the actual distribution, providing a statistic that indicates whether they differ significantly.

Discussion

Here we present a simple approach for the analysis of induced oscillatory responses in multisensory studies. Induced oscillatory responses are believed to be a sensitive marker of feature integration processes in the visual and the auditory domains (Gray 1999; Kaiser and Lutzenberger 2003; Konig et al. 1995; von Stein et al. 2000), and there is reason to believe that they also play a role in integration of multisensory inputs. For example, electrophysiological studies have revealed multisensory oscillatory interactions during the early phases of the evoked response (Sakowitz et al. 2001, 2005; Senkowski et al. 2005, 2006b). The role of induced oscillatory activity in cortical binding and findings of multisensory processing in evoked oscillatory activity, suggests that the analysis of induced oscillatory responses will reveal important information about the mechanisms underlying multisensory interactions in the brain.

Possible applications

This approach provides a reliable metric for detecting multisensory interactions (both sub- and super-additive) in human and non-human primate electrophysiological data. A particular advantage of the approach is the statistical testing of multisensory interactions at the single subject level. This offers the opportunity of reliable application in research fields that often rely on the analysis of small sample sizes (e.g., non-human primate research or human intracranial studies).

In principle, the approach can be applied to diverse multisensory datasets. For example, it has been shown that induced alpha and theta activity play an important role in memory processing (Herrmann et al. 2004; Klimesch 1999; Sauseng et al. 2004) and oscillatory responses may also be important during audiovisual speech processing, where both ERP and fMRI studies have demonstrated clear multisensory interactions (Besle et al. 2004; Calvert et al. 1999, 2000). Indeed, a more recent study of audio-visual speech processing has uncovered multisensory effects in the gamma band (Kaiser et al. 2005).

Finally, we would like to emphasize that the linear summation of unisensory oscillatory responses does not artificially cause a reduction in frequency amplitude compared to the respective multisensory responses. One could argue that the frequency amplitude of two summated unisensory responses is likely to be lower than the amplitude of multisensory responses simply due to differences in phases between the two oscillatory unisensory responses. However, the same differences in oscillatory phases can be expected for the responses to the different sensory inputs of multisensory stimuli (i.e., the oscillations in responses to auditory and visual inputs of a multisensory audiovisual stimulus). Thus, possible differences between the amplitude of summed unisensory responses and the amplitude of multisensory responses obtained by this modified approach can be indeed attributed to interactions between the two sensory modalities when these stimuli are presented in a multisensory context.

Effects of noise

Like almost all other electrophysiological approaches, the signal-to-noise level in the data affects the reliability of the approach. Here, noise simulations showed that the $(S + N)/N$ ratio in the data does not account for statistically significant results obtained by the approach. The noise simulation showed that noise has mainly the effect of an increase of the probability of Type II statistical errors (i.e., the null hypothesis is falsely accepted). This was demonstrated for both sub-additive effects and super-additive effects. For this reason, it is advisable to first quantify the signal-to-noise level before applying the approach. Results from the present simulations suggest that the $(S + N)/N$ ratio for multisensory stimuli should be at least 1.15 in the beta frequency range.

Issues to be considered when analyzing multisensory interactions in induced oscillatory responses

Induced oscillatory responses to unisensory stimuli have frequently been observed at relatively late latencies, during timeframes that are likely to reflect higher cognitive processing (Gruber and Muller 2002; Gruber et al. 1999; Tallon-Baudry et al. 1996, 1998). For some cognitive functions, however, great care needs to be taken if applying the standard technique. In some cases it is clearly not valid to combine the activity to two unisensory stimuli. For example, during target processing, the classical P3 component is observed (Polich et al. 1997; Comerchero and Polich 1999) and this P3 is induced by targets in all sensory modalities. If one were to simply add the responses to two unisensory targets and compare this summed response to that to a single multisensory target, the modality-independent target P3 would be represented twice in the summed response and only once in the multisensory response. A sub-additive effect ($A + V > AV$) would certainly be seen but this effect would be observed without necessitating any direct interactions between the constituent unisensory systems. Care must also be taken to ensure that similar modality non-specific mechanisms are not being represented twice in the induced oscillatory responses. In a similar vein, the comparison of combined unisensory oscillations with multisensory oscillatory activity should be handled with care if subjects are performing a motor response in the selected analysis time window. In this case the unisensory stimuli, when combined, would contain two motor responses whereas the multisensory stimuli contain only a single motor response.

Conclusion

We present a simple bootstrapping approach for the analysis of induced oscillatory responses in multisensory studies. This approach circumvents a limitation of the standard linear approach used for analyzing multisensory interactions, a approach that is not appropriate for oscillatory signals that have been derived using non-linear methods such as the wavelet transform. The study of induced oscillations is important since recent data links them to integrative processing in the brain, processing which must surely underlie integration of inputs across the senses. This approach is the first tool, to our knowledge, that permits the direct comparison of oscillatory responses to multisensory stimuli with the combined oscillatory responses to the respective unisensory stimuli.

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Appendix: Materials and paradigm

Intracranial field potentials in macaques

To evaluate the application of this technique to intracranial field potential data, we used data recorded during the course of a multisensory investigation in auditory cortex of an awake behaving macaque monkey (see Lakatos et al. 2005a). All procedures were approved in advance by the Animal Care and Use Committee of the Nathan Kline Institute. The subject, a Rhesus monkey (Maccaca mulatta) was adapted to a custom fitted primate chair and to the recording chamber and then surgically prepared for chronic awake electrophysiological recording. Surgery was performed under anesthesia (1–2% isoflourane), using standard aseptic surgical methods (see Schroeder et al. 2001). To allow electrode access to the brain, and to promote an orderly pattern of sampling across the surface of the auditory cortices, matrices of 18 gauge stainless steel guide tubes were placed over auditory cortex. These matrices were angled so that the electrode track would be perpendicular to the plane of auditory cortex, as determined by pre-implant MRI (Schroeder et al. 1998). They were placed within small, appropriately shaped craniotomies, to rest against the intact dura. The matrices, along with a titanium head post (permitting painless head restraint), were embedded in dental acrylic and secured to the skull with titanium orthopaedic screws.

Recordings were made in an electrically shielded, sound-attenuated chamber with SONEX ProSPEC Composite^{TM} sound absorbing foam. Laminar profiles of field potentials (EEG) were recorded using a linear array multi-contact electrode (24 contacts, 100 μm intercontact spacing) positioned to sample from all the layers simultaneously (Lakatos et al. 2005b). Signals were impedance matched with a pre-amplifier (10× gain, bandpass dc-10 kHz) situated on the electrode, and after further amplification (500×) the signal was band pass filtered by analogue filtering (0.1–500 Hz) to extract the field potential sampled at 2 kHz/16 bit precision.

Eye position was monitored using an ISCAN ETL-200 eye tracking system, and stimuli were presented only when the monkey's gaze was held within a 10° degree window surrounding the fixation point in the middle of the monitor. Auditory stimuli consisted of broadband Gaussian noise bursts (16 ms duration; 70 dB SPL, 1 ms rise/fall times). The visual stimuli consisted of a bright white monitor flash (16 ms duration). Unisensory-auditory, unisensory-visual, and multisensory audiovisual stimuli were presented in separate blocks (SOA = 767 ms), each consisting of 100 stimuli. Trial blocks were separated by brief breaks in which the monkey was checked and fed dried fruits and other preferred treats.

In accordance with the time–frequency representations (Fig. 2), for the analysis of multisensory interactions a 15 Hz WT was performed. The wavelet had a duration ($2\sigma_t$) of 67 ms and a spectral bandwidth ($2\sigma_f$) of 4.8 Hz. As a measure of 15 Hz activity, the maximum value of the modulus of the complex transform coefficient was computed in a time interval between 10 and 110 ms for each epoch.

Human EEG recordings

Induced oscillatory beta responses for one subject (female, 27 years, right handed) from one right-frontal channel were analyzed (Fig. 5). This channel was selected because a right-frontal maximum was found at this electrode site. The nearest neighboring site within the 10–20 system of this electrode is the F4 electrode. The EEG was recorded in an electrically shielded chamber from 2 EOG and 128 scalp electrodes (impedances < 5 kΩ), referenced to the nose at a sample rate of 500 Hz. Epochs for EEG beta activity lasted from 500 ms before to 1000 ms after stimulus onset. Baselines were computed from –300 to –100 ms pre-stimulus. For artifact suppression, trials were automatically excluded from averaging if the standard deviation within a moving 200 ms time interval exceeded 30 μV in any one of the EEG channels and 40 μV at the EOG channels in a time interval between –300 and 500 ms.

Auditory stimuli in the experiment consisted of a 1,000 Hz tone (60 ms duration; 75 dB SPL) presented from a single speaker located atop the monitor on which the visual stimuli were presented. The visual stimulus consisted of a red circular disk subtending 1.2° in diameter presented on a black background. Visual stimuli were presented 1.56° lateral left above a central fixation cross for 60 ms. Unisensory-auditory (A), unisensory-visual (V), and multisensory audiovisual (AV) were presented at inter-stimulus-intervals ranging between 750 and 3,000 ms. The subject was instructed to maintain central fixation at all times and to make a speeded button response with their right index finger when a stimulus in either modality was detected. A total number of 533 auditory, 547 auditory and 530 audiovisual trials were submitted to the analysis.

For the analysis of beta responses, the maximum value of the modulus of the complex 20 Hz transformed coefficient was computed in a time interval between 80 and 170 ms for each epoch. The duration

($2\sigma_t$) of the wavelet was 100 ms with a spectral bandwidth ($2\sigma_f$) of 6.4 Hz. The subject gave written informed consent to participate in the study.

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