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## **An intracranial EEG study of the neural dynamics of musical valence processing**

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**Running title:** Dynamics of musical valence processing

## **Abstract**

The processing of valence is known to recruit the amygdala, orbitofrontal cortex and relevant sensory areas. However, how these regions interact remains unclear. We recorded cortical electrical activity from 7 epileptic patients implanted with depth electrodes for presurgical evaluation while they listened to positively and negatively valenced musical chords. Time frequency analysis suggested a specific role of the orbitofrontal cortex in the processing of positively valenced stimuli while, most importantly, Granger causality analysis revealed that the amygdala tends to drive both the orbitofrontal cortex and the auditory cortex in theta and alpha frequency bands, during the processing of valenced stimuli. Results from the current study show the amygdala to be a critical hub in the emotion processing network: specifically one that influences not only the higher order areas involved in the evaluation of the stimulus's emotional value but also the sensory cortical areas involved in the processing of its low level acoustic features.

**Key words:** amygdala, consonance, depth electrodes, ERPs, Granger causality.

*Emotional valence* refers to the intrinsic attractiveness (positive emotional valence) or aversiveness (negative emotional valence) of a given object (or event) and applies across sensory domains such that, for instance, unpleasant smells and sad facial expressions are *negatively valenced* while pleasant smells and happy facial expressions are *positively valenced*. However, while functional neuroimaging work has shown that processing of valenced stimuli recruits medial temporal and frontal lobe structures as well as relevant sensory areas, much less is known regarding how these regions interact.

In the auditory domain, the effects on a listener of so called consonant and dissonant musical chords are fairly consistent: in contrast to the former, which tend to be considered *pleasant*, the latter generally evoke a negatively valenced emotion – a feeling of *unpleasantness* (Plomp and Levelt 1965; Wedin 1972; Costa et al. 2000). Music can convey a range of complex and rich emotions, from wonder to nostalgia, and various attempts to examine the neural correlates of such specific aesthetic emotions are emerging (Trost et al. 2011). However, the processing of the simpler *pleasant* versus *unpleasant* dichotomy that consonant and dissonant chords evoke is well established and, critically, the role of regions such as the amygdala and orbitofrontal cortex in such processing has been confirmed (Blood et al, 1999; Gallager and Chiba, 1996; Koelsch et al, 2006).

The fact that processing of consonant and dissonant musical chords recruits both the amygdala and orbitofrontal cortex makes such stimuli relevant in addressing outstanding issues regarding the emotion cerebral network. A number of studies have reported on the latency of processing in the amygdala and orbitofrontal cortex (Oya et al. 2002; Eimer and Holmes 2002; Eger et al. 2003; Streit et al. 2003; Pourtois et al. 2004; Naccacche et al. 2005; Pourtois et al. 2005; Gothard et al. 2007; van Heijnsbergen et al. 2007; James et al. 2008; Mormann et al. 2008). Indeed, some have suggested a dependence of processing latency on factors such as the extent to which the stimulus's valence is attended to (Krolak-Salmon et al.

2004) and the degree of expertise the participant has with the stimulus (James et al, 2008). However, while for instance, Streit and colleagues (2003) suggested a similar onset latency of amygdala and orbitofrontal cortex activity (between 100 and 160 ms) during the processing of visual emotional stimuli, Krolak-Salmon et al (2004) suggested an earlier and more transient response in the amygdala (at around 200ms) relative to that in the orbitofrontal cortex (from around 300ms). Further support for a potentially modulatory effect of the amygdala on the orbitofrontal cortex comes from functional neuroimaging results showing that increased amygdala activation led to increased activation in the ventral prefrontal cortex areas during the processing of emotional stimuli (Lerner et al. 2009). Thus, one key aim of the current study was to examine the directed communication that exists between the amygdala in the medial temporal lobe and the orbitofrontal cortex in the frontal lobe.

Another aim of the current study was to elucidate the nature of the interaction between the amygdala and sensory cortices during the processing of emotional stimuli. Previous studies in the auditory domain have shown the amygdala to respond to aversive sounds (Mirz et al. 2000; Zald and Pardo 2002) and it has been argued that this area plays a modulatory role on activity in early sensory areas (Morris et al. 1998; Vuilleumier et al. 2004). However, the extent to which sensory areas are necessarily implicated in emotional processing is still under discussion with some studies failing to show a modulation of auditory cortical activity by valence (Blood et al, 1999) and at least one neuropsychological study suggesting that the integrity of the auditory cortex is not necessary for emotion recognition (Peretz et al. 2001).

In a single case study reported by our lab (Dellacherie et al. 2009), we took advantage of the high temporal and spatial resolution of intracranial EEG recordings to examine responses to consonant and dissonant sounds in the amygdala, orbitofrontal cortex and auditory cortex. However, while that study provided evidence of valence processing in all three regions, it did not examine how they might interact. Indeed, in this regard, it has been suggested that

oscillations in the theta band bring about integration and synchronisation of long-range activity within the emotion network (Lewis 2005). Support comes from findings in human and animal models showing that theta band activity is modulated by emotional valence (e.g. Aftanas et al. 2001; Knyazev 2007; Maratos et al. 2009; Pourtois et al. 2010; Rutishauser et al. 2010; Meletti et al. 2012) and may increase during emotional arousal (Pare et al. 2002). One prediction that may be made, therefore, is that such low frequency activity should be implicated during musical emotion processing.

The current study sought to provide a better understanding of the way the amygdala, the orbitofrontal cortex and the auditory cortex respond and interact during the processing of emotionally valenced stimuli. Initial analyses, examining oscillatory activity in the amygdala, orbitofrontal cortex and auditory cortex using data from all participants, regardless of whether they had contacts in one, two or all three areas of interest, allowed the identification of any patterns of oscillatory activity that may be specific to the processing of positively and negatively valenced stimuli. However, the main analysis focused on the data from a smaller subset of three participants, all of whom had at least one contact in each of the three areas. Here we investigated the patterns of communication that take place across the three regions, by specifically carrying out analysis of functional connectivity. Spectral Granger causality, a variant of the statistical tool known as Granger causality (Granger, 1969), seeks to predict oscillations in one area from the past history of oscillations in another and in doing so allows the determination of the direction in which oscillations are being propagated. Critically, this analysis technique has proven useful in inferring causality effects within functional networks in non-human and human primates (e.g. Brovelli et al. 2004; Bollimunta et al. 2008; Anderson et al. 2010; Cohen et al. 2012; Cohen and van Gaal 2013). In the current study, it allowed us to examine the transmission of information between structures in the emotion processing network.

We predicted that the current study would confirm processing of musical emotional valence in the amygdala, orbitofrontal and auditory cortex. Specifically, we predicted that time frequency analysis would implicate low frequency rhythms, specifically the theta rhythm, in the processing of these valenced musical stimuli, and most importantly, that the examination of the propagation of low frequency oscillations would reveal a modulatory effect of the amygdala both on the orbitofrontal and the auditory cortex.

## **Materials and Methods**

### *Participants and intracranial recordings*

Data were collected from 11 participants who suffered from severe, pharmacoresistant partial epilepsy and had therefore been implanted with depth electrodes for presurgical evaluation. One participant had to be excluded as a result of unusable data and 3 others were not analyzed as they were not implanted with electrodes in relevant structures, resulting in a final sample of 7 participants (3 males; mean age=  $34.85 \pm 8.9$  years). Experiments were approved by the Ethical Committee for Biomedical Research of Pitié-Salpêtrière Hospital in Paris (agreement 19-07 issued on 26 March 2007). All participants gave informed consent and all clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

The invasive exploration had been planned according to the brain locations expected to be at the origin of epileptic seizures. These localization hypotheses resulted from the analysis of the previously gathered data (clinical examination and history, prolonged continuous surface EEG-video, brain MRI and sometimes FDG Positron Emission Tomography and ictal Single Photon Emission Computed Tomography). Electrodes were composed of 4–10 contacts, 2.3 mm long, 5 to 10 mm apart, mounted on a 1 mm wide flexible plastic probe (Ad-Tech

Medical Instruments, Racine, WI) and were stereotactically inserted using a Leksell frame (Adam et al. 1996). Cartesian co-ordinates were calculated for each recording site after normalizing the anatomical cerebral MRI into Talairach space. Local field potential data were acquired with a Nicolet 6000 (Nicolet-Viasys, Madison, WI, US) at a sampling rate of 400Hz (band-pass: 0.05 to 150 Hz). Data were analyzed with bipolar montage in order to minimize the influence of distant sources. Bipolar derivations were also preferred to monopolar signals since they prevent potentially non-silent references from contaminating the results of granger causality analysis (Bollimunta et al, 2009). Analysis with bipolar montage involved subtracting the signals recorded from adjacent sites. For each bipolar montage, the Cartesian coordinates  $(x, y, z)$  were calculated as the location at mid-distance between the two adjacent recording sites. A skilled anatomist (DH) examined the location of each of the contacts individually in the MRI images in order to verify and confirm their location in the different brain structures. In Figure 1, the distribution of contacts is shown for each participant whose data was used. Table 1 shows the number of contacts in each of the areas of interest in all 7 subjects.

### *Stimuli and task*

Stimuli and task were the same as in Dellacherie et al. (2009). Three-tone consonant and dissonant chords were created using the music computation and notation software, Sibelius. 50% of consonant chords were made of perfect major chords while the other 50% were made of minor chords. Dissonant chords were composed of two minor seconds or a combination of a minor and a major second. The duration of each chord was 1800 ms while the interstimulus interval (time period between the presentation of individual chords) varied between 300 and 700 ms. Participants were presented with the consonant and dissonant chords in 12 blocks of 40 chords each. 50% of each block were consonant chords and the other 50% were dissonant



chords. 80% of each block was comprised of chords of one timbre (piano or organ) while the remaining 20% was presented in the other timbre and constituted 'target chords'. Participants were required to count the number of target chords in each block and report this number at the end of the block. For all analyses, only trials corresponding to non-target chords in each block were considered.

### *Data Preprocessing*

Data were epoched from -1000 ms to 3000 ms relative to the onset of the chords. An automatic artifact removal of epileptic activity was carried out. This excluded 1) trials whose maximum amplitude exceeded the mean amplitude of the trial by at least 5 standard deviations (SD) as well as 2) contacts in which more than 5% of trials were excluded (following the previous criterion). Trials were also checked for spikes and abnormal rhythmic activity.

### *Time frequency analyses*

Estimates of event-related (log) spectral perturbations (ERSPs) were computed using the *newtimef* function from the EEGLAB toolbox (Delorme and Makeig 2004). A fast Fourier transform with Hanning window tapering (EEGLAB's default algorithm) and a padding ratio of 4 was used. ERSPs were computed over a frequency range of 4–30 Hz. A pre-stimulus baseline of 300 ms relative to the onset of the chords was used to compute the differences in log spectral power following the onset of the chord. Trials were collapsed across contacts and across subjects to obtain a set of consonant and dissonant trials for each region. The built-in permutation statistical test with a Bonferroni corrected alpha value of 0.0167 (0.05/3, where 3

is the number of areas being considered) was then used to test for significant differences between consonant and dissonant chord responses within each region of interest.

### *Granger Causality analyses*

Granger causality analysis was performed in three patients who had electrodes implanted in all three regions of interest (the orbitofrontal cortex, the auditory cortex, and the amygdala). In contrast to measures such as synchrony (Engel and Singer 2001) and phase coherence (Nunez et al. 2001), which provide estimates of undirected functional connectivity between signals, Granger causality analysis allows the assessment of directed functional connectivity and therefore the examination of the putative direction of information flow within a system. According to the theory and practice of Granger causality, a variable  $x$  causes  $y$  if information in the past of  $x$  can help to predict the future of  $y$  (in a linear regression model of  $x$  and  $y$ ), with more accuracy than is possible when using only the past of  $y$  itself (Seth 2010). The analyses used here, MultiVariate AutoRegressive (MVAR) modeling, involves the testing of the consistency between data and model by comparing covariance structures estimated from both (Ding et al. 2000).

In the current study, Granger causality analysis based on MVAR modelling was carried out using adapted functions from the Matlab toolbox developed by Anil K. Seth (Seth 2010). Pre-processing steps included the removal of line noise (50Hz) by multitaper filtering (whereby a 50Hz sinusoidal oscillation was fit to the noise and then subtracted), the removal of deterministic linear trends (by subtracting the best straight line fit from each trial), and the removal of the temporal mean (by subtracting the value of the mean of the entire trial from the value at each sample of the trial). Finally, the ensemble mean, the mean value for each variable across trials at each time point, was removed as recommended for meeting the *covariance stationarity* assumption that is required for autoregressive modeling (Brovelli et

al. 2004; Seth 2010). Note, however, that while this step removes iERPs, these may vary on a trial to trial basis both in terms of amplitudes and latencies and indeed it has been demonstrated that time-frequency and granger causality results may, for instance, demonstrate artefactual temporal modulations simply due to the trial-to-trial variability of event-related potentials (Truculo et al, 2002; Wang and Ding, 2011; Wang et al, 2011).

We implemented spectral Granger causality, the frequency domain interpretation of Granger causality obtained by performing a Fourier transform on the time domain MVAR model, as it allowed the examination of causality effects within distinct frequency bands, in this case the theta, alpha and beta bands. As spectral Granger causality measures lack a known statistical distribution, bootstrap confidence intervals were constructed to identify Granger causality values that were significantly greater from zero. The model order parameter required for the MVAR model is sometimes estimable using the ‘Akaike information criterion’ or ‘Bayesian Information criterion’. However, in the event that these methods are not able to provide an optimal model order, a range of model orders may be tested (Seth 2010). Thus, we carried out analysis using model orders of 20 and 10, downsampling the data for the theta band analysis to 200Hz and keeping the sampling rate at 400Hz for the alpha and beta band. For both types of analysis, we report results using a model order of 20 (at a sampling rate of 200 Hz for the theta band and 400Hz for the alpha and beta band, this is the equivalent of a 100 ms and 50ms lag respectively) since other models produced similar results. These time lags of 100ms and 50ms for theta and alpha-beta, respectively, were also favoured as they are in line with the previous literature (Brovelli et al. 2004; Bressler et al. 2007; Bollimunta et al. 2008; Zhang et al. 2008; Andersen et al. 2010; Hoerzer et al, 2010; Bollimunta et al. 2011).

To avoid the complication of cross hemisphere effects that would vary across participants by virtue of varying implantation distributions, the contacts from only one hemisphere were considered for each participant: this was the right hemisphere in subject 3 and the left

hemispheres in subjects 5 and 6. Importantly, this resulted in data from only 3 out of 21 contacts being discarded (2 orbitofrontal cortex contacts from patient 5, and 1 amygdala contact from patient 6) due to the general tendency for patients to have greater coverage in one hemisphere than the other. Table 1 shows the resulting number of contacts in each of the three areas for each of the three subjects of interest. For pairwise computation of Granger causality values, three area pairs are possible (amygdala and orbitofrontal cortex, auditory cortex and orbitofrontal cortex, and auditory cortex and amygdala). Thus for each subject, each contact from each area was pairwise combined with each of the contacts from a given other area (Anderson et al. 2010). Table 1 shows the number of such contact pairs for each area pair for each subject. In the results, we report the mean Granger causality values across contact pairs to obtain a single causality profile per area pair (in each direction) per subject.

-----Insert Table 1 Here-----

In addition to seeking to observe causality effects as they change over time, the choice of the size of the analysis time window on which to compute Granger causality values was governed by methodological considerations. The Granger causality analysis approach assumes that all variables concerned have an unchanging mean and variance over time; i.e. that the variables are *covariance stationary*. With the current data, it was necessary to carry out analysis on windows as small as 125 ms (0-125 ms, 125-250 ms, etc.) to achieve perfect stationarity (100% performance on the KPSS test of non-stationarity which tests the null hypothesis of no unit roots). However, although allowing the MVAR model to meet the covariance stationarity criterion to somewhat lesser extent (approximately 90% covariance stationarity), time windows of 250 ms (0-250 ms, 250-500 ms, 500–750 ms) were necessary to obtain meaningful estimates of causality in the theta range: 250 ms corresponds to one full cycle oscillation of the lowest frequency of interest in the theta band, 4Hz. Given these considerations, we used the 250 ms windows for the examination of Granger causality in the

theta band (4-7Hz) and the more reliable and greater temporally resolved 125 ms analysis windows for the examination of Granger causality in the alpha (8-12 Hz) and beta bands (13-30Hz). The power spectra of the data used in these analyses are shown in Supplementary Figure 1 and the peaks in power for the 250 ms and 125 ms analysis windows at approximately 7 (yellow and green lines) and 10Hz (blue and red lines) respectively demonstrate the effect of the analysis window size parameter on the amount of theta power that could be estimated. Importantly, the peaks observed in the power spectrum can be seen to correspond with the peaks of the granger causality values. Finally, inferences using the Granger causality method may be considered valid only if the estimated MVAR model adequately captures the correlation structure in the data and it was therefore ensured that all models considered had an appropriately high model consistency (a measure of the variance accounted for by an MVAR model) of no less than 90%.

## **Results**

### *Time-frequency*

To examine, for each region, whether either consonant or dissonant chords were associated with relatively disproportionate changes in power, trials across all contacts across relevant participants in each region were aggregated to obtain two sets of trials (one ‘consonant’ and the other ‘dissonant’), which were then compared. Figure 2 plots, for each region, time-frequency representations of the output of event-related (log) spectral perturbation (ERSP) analysis carried out on all trials from all subjects (upper nine plots) as well as on all trials from contacts in the three-subject subsample (bottom nine plots).

The figure shows a large-band transient increase in power in auditory cortex peaking at a latency of approximately 100 ms after sound onset and a more gradual increase in theta and

alpha power over time, reaching a peak between 200 and 600 ms, in the amygdala and orbitofrontal cortex. In the orbitofrontal cortex, results from data of the three subjects alone indicated greater theta, alpha and low beta power (between 13 and 20 Hz) for consonant relative to dissonant sounds that were centered at approximately 250 ms, 400 ms and 150 ms respectively. Also observed in this region was a drop in high beta power (between 21 and 30 Hz) for consonant relative to dissonant chords between 100 and 400ms. Results of analysis considering data from all subjects indicated a similar pattern of results although the lower beta power difference previously observed was absent. In the auditory cortex, both types of analysis (all subjects, and the three subjects alone) revealed a drop in low beta power from consonance to dissonance centered at approximately 800 ms and another late drop in high beta power from consonance to dissonance centered at approximately 1300 ms. In contrast to the orbitofrontal cortex and auditory cortex, no consistent significant power differences between the consonant and dissonant conditions were observed in the amygdala.

### *Granger causality*

This analysis sought to determine whether there was any evidence of directed functional connectivity amongst the three regions of interest with a focus on the theta, alpha and beta frequency bands, given that frequencies in this range are held to be involved in long-range neural communication during emotional processing (Lewis 2005). Figure 3 shows, for each subject, how the mean significant Granger causality values computed for each of the 6 different directions (amygdala to orbitofrontal cortex, orbitofrontal cortex to amygdala, auditory cortex to orbitofrontal cortex, orbitofrontal cortex to auditory cortex, auditory cortex to amygdala and amygdala to auditory cortex) evolved over time from sound onset in windows of 250ms for the theta band (0-250 ms; 250-500 ms ... 1500-1750ms) and 125 ms

for the alpha and beta bands (0-125 ms; 125-250 ms ... 1625-1750ms). The value at time 0 indicates the significant causality observable for the given directed connection in the 250ms preceding the onset of the sound. Examination of the patterns of causal flow in the six possible directions, for each frequency band separately, revealed a number of interesting patterns. With regard to the theta band, when considering the 6 directed connections for which granger causality was calculated, significant flow was observed from the amygdala to the orbito-frontal cortex (Amyg→ Orb). While one subject did not show any flow either in this direction or the opposite (Orb → Amyg, subject 3), another participant (subject 5) showed much larger flow from the amygdala to orbitofrontal cortex relative to the opposite direction (Orb → Amyg), while the third also showed an asymmetry, especially for consonant sounds, despite a higher baseline activity in the direction from amygdala to orbitofrontal cortex. Comparable to the flow between amygdala and orbitofrontal cortex, with regard to magnitude, was the flow from the amygdala to the auditory cortex (Amyg → Aud). Causal flow between the amygdala and auditory cortex showed even higher consistency here with all three subjects showing greater flow in this direction than in the reverse (Aud→Amyg). A final observation was that there was only little flow between the auditory cortex and the orbitofrontal cortex and this flow tended to be from the latter to the former (Orb→Aud) with 3 participants showing flow in this direction and 2 showing flow in the reverse direction.

With regard to the alpha band, once again the greatest causal flow observable was from the amygdala to the orbitofrontal cortex (Amyg → Orb). All three participants showed greater flow in this direction than in the reverse (Orb → Amyg). Further, the peak of causal flow was fairly consistent at around 500 ms in all subjects. As for the flow to and from the auditory cortex, there was bidirectional flow between the auditory cortex and amygdala: with all three subjects showing significant flow from auditory cortex to amygdala (Aud→Amyg) and two out of the three participants showing flow from amygdala to auditory cortex (Amyg → Aud).

Bidirectional flow was also observed between auditory cortex and orbitofrontal cortex (with three subjects showing significant flow from Orb to Aud (Orb→Aud) and 2 showing flow in the reverse (Aud→Orb)). A potential effect of valence could be observed with amount of causal flow for all three directions being generally greater for consonant than dissonant sounds. Finally, with regard to the beta band, the greatest causal flow was once again observed from amygdala to orbitofrontal cortex, although this was not as consistently large or as time locked across participants as in the alpha band. Significant causal flows in the five other directions were generally lower than that which was observable in the theta and alpha bands.

To summarise the patterns of causal flow between the three different structures making up the distributed network considered here, Figure 4 shows the total causality over the duration of the stimuli in each of the 6 possible directions, averaged across consonant and dissonant sounds and across the three subjects. This highlights two noteworthy findings: First, a tendency for the causal flow from the amygdala to the orbitofrontal cortex to be greater than in the reverse direction in all three bands (although with greater consistency across subjects in the alpha band) and second, a considerable and reliable causal flow from amygdala to auditory cortex, specifically in the theta band. Supplementary Figure 2, showing the results when the causal flow in the 250 ms preceding sound onset are subtracted from significant granger causality values in each time window, confirm these main findings to be robust to any variation in baseline levels of connectivity.

## **Discussion**

By examining intracranial depth electrode recordings collected while participants were presented with consonant and dissonant chords, the current study was able to elaborate on the



neural dynamics of emotional valence processing in three areas of interest: the amygdala, the orbitofrontal cortex and the auditory cortex. We initially analyzed the data of all patients from whom data were collected in these regions (regardless of whether they had contacts in one, two or all three areas of interest), before focusing on the data from a subset of three participants, all of whom had at least one contact in each of the three areas. Our approach allowed us to fully exploit the data available while addressing the dual objectives of characterizing the patterns of neural responses within each region separately and the patterns of communication that take place across the three regions.

Initial time-frequency analysis suggested a special role of the orbitofrontal cortex in the processing of positively valenced stimuli. Specifically, greater power in the theta and alpha frequency bands was observed during the processing of consonant stimuli relative to dissonant stimuli, while no such trends (i.e. greater oscillatory activity in response to either positive or negatively valenced stimuli) were seen in the amygdala. This finding replicates results in a previous non-invasive EEG study (Sammler et al 2007), showing in response to consonant sounds, increases in frontal midline theta, held to arise from the medial pre-frontal cortex (Asada 1999). Thus, perhaps the most novel contribution of the study was its demonstration of directed communication within the emotional processing network: firstly, from the amygdala to the orbitofrontal cortex and secondly, from the amygdala to the auditory cortex, suggesting that orbitofrontal and auditory cortex responses are modulated by the amygdala.

Indeed, our main finding was that in contrast to causal flow in the reverse directions, the causal flow from the amygdala to the orbitofrontal cortex and from the amygdala to the auditory cortex was considerable and reliable across subjects. Various previous fMRI and PET studies have been able to identify the amygdala and orbitofrontal cortex as key players in the processing of emotionally valenced sounds (Blood et al. 1999; Blood et al. 2001; Koelsch

et al. 2006). However, these haemodynamic studies had not been able to elaborate either on the time course of processing in these areas or the degree of influence that they have on each other. The current study, which along with our previous case study is the first to examine intracranial EEG data in these areas during the processing of emotional musical stimuli, was well placed to address such questions. For one, while the ability to record from intracranial electrodes provided the necessary spatial resolution for describing the activity in the specific areas, the method's high temporal resolution allowed the inference of functional connectivity using Granger causality analysis. This analysis is dependent on there being an invariable (if any) response delay across the different structures being considered, and is therefore more reliable for electrophysiological than, for instance, fMRI data, where a difference in haemodynamics in different areas can present a severe confound.

While the classical view of the amygdala associates it chiefly with the processing of negative stimuli (LeDoux 1993; Morris, 1998), we demonstrate here that the amygdala is a critical hub in the musical emotion processing network and may have a rather more valence-general role (Lane et al. 1999; Taylor et al. 2000; Davis and Whalen 2001; Garavan et al. 2001; Zald 2003). One part of this role, as indexed by the flow from this region to the orbitofrontal cortex, might be to influence higher order areas, which are involved in the evaluation of a stimulus' value. Another might be to influence the sensory cortices, which are involved in the processing of stimuli's low level features. Indeed, adaptive behaviour necessitates that emotionally salient information is processed particularly efficiently, and our results here suggesting a modulation of the auditory cortex by the amygdala alludes to this potential tendency for sensory level processing of a stimulus to be influenced by classical emotion processing areas.

The notion of a modulatory role of the amygdala on sensory cortical processing is in agreement with the extensive anatomical connections between the amygdala and auditory

cortex (Amaral and Price 1984; Iwai and Yuki 1987) as well as previous neuroimaging studies. Several authors have suggested that the amygdala may be responsible for the modulation of activity observable in the visual and auditory cortices when participants are presented with emotional stimuli (Lang et al. 1998; Morris et al, 1998; Plichta et al. 2011; Viinikainen et al. 2011). In the auditory domain, the idea of a modulatory role of the amygdala has been supported by an fMRI study (Kumar et al. 2012), which examined the specific effect of acoustic features and emotional valence on the coupling between amygdala and the auditory cortex. Using dynamic causal modeling, a tool for inferring effective connectivity, the authors showed that while acoustic features of aversive sounds modulated the connectivity from the auditory cortex to the amygdala, it was the sounds' valence that modulated connectivity from the amygdala to the auditory cortex. Our findings extend those from Kumar and colleagues in demonstrating connectivity from the amygdala to the auditory cortex during processing of positively valenced stimuli and in doing so support the notion of the amygdala being involved in the processing of positive as well as negative stimuli (Davis and Whalen, 2001; Garavan et al. 2001; Zald 2003; Lane et al. 1999; Taylor et al. 2000). Our results also extend the notion of a modulatory role of the amygdala on sensory cortices to the musical domain and calls for further investigation into the previously suggested dissociation between perceptual and emotional processing in the auditory cortex (Peretz et al. 2001).

Strong anatomical connections are known to exist between the amygdala, orbitofrontal cortex and auditory cortex (Amaral and Price 1984; Iwai and Yuki 1987; Ebeling et al. 1992; Petrides et al. 2007; Thiebaut de Schotten et al. 2012) and the current study contributes to the literature by showing that communication between these areas is underlied by low frequency oscillations. The notion that low frequency oscillations may allow long-range synchronization of distributed brain regions (Varela, 2001; Fries 2005; Buzsaki 2006) has been supported by studies showing theta coherence between frontal and posterior areas during cognitive tasks

(Sarnthein et al 1998; Sauseng et al 2005; Summerfield and Mangels 2005). It had also been suggested that theta might play a specific role in the synchronization of medial temporal and prefrontal lobe structures during the processing of emotional stimuli (Lewis 2005). The current work supports such a notion further in showing that in addition to the theta band, such synchronized activity during emotion processing may also occur in the alpha frequency band in line with an increasing number of studies associating this frequency band with the processing of emotional stimuli (Knyazev et al. 2008; Parvaz et al. 2012).

In summary, our work confirms previous studies, both in the visual and auditory domain, that demonstrate processing of emotional valence in the amygdala, orbitofrontal cortex and auditory cortex. It demonstrates that activity in both the theta and alpha frequency bands play an important role in the processing of emotional stimuli. Moreover, it makes a particularly significant contribution in its clarification of the nature of the directed communications that exists in the emotion network during the processing of valenced stimuli. However, there are some limitations in the current study, notably regarding the consistency of the granger causality analysis results across patients. Indeed while we emphasise certain trends, namely for amygdala to drive orbitofrontal cortex and auditory cortex, the timing and size of causal flows vary considerably across participants. One possibility is that the sources of this variation are on a cognitive and behavioural level. The stimuli used in the experiments were fairly long at 1800ms and indeed it is possible that participants might have varied in how they considered the stimuli over time. For example, some perhaps might have focused on the sounds for the whole duration while others may have focused during just the first few hundred milliseconds. Also while some participants might have tended to make evaluative judgments (even if not asked to), others may have been less inclined to do so, resulting in differential moderation of the network. Another source of inconsistencies across subjects may be in the variability in terms of where contacts were situated in each participant. Indeed, while we carry

out analysis on a region level, due to a limited number of contacts and therefore a limited ability to differentiate between subregions (e.g. amygdala subnuclei), it is possible that the contacts considered varied across participants in terms of location and possibly function and resulted in the differences in timing as well as sensitivity to positive and negative valence that is seen across subjects.

Finally, while the current paper throws some new light on the processing of valenced stimuli, a few points are worth considering in the future. Firstly, given that previous studies have shown enhanced processing in the amygdala when explicit emotion judgments are being made (e.g. Krolak-Salmon et al. 2004), it would be interesting to observe how the effects seen here are modulated by task, in other words, to what extent explicit assessment of pleasantness (in contrast to the timbral deviant counting task used here) may influence the system's behaviour. Secondly, while Granger causality analysis is proving a useful tool in inferring causality in neural systems, it remains simply a statistical approach and, indeed, as argued by Pearl (1999), causality effects can be proven only by observing the consequences of disturbing the system. One way to confirm the source of modulatory influences on particular regions in a network may be to combine neuroimaging and lesion patient approaches. Using this method, Vuilleumier et al. (2004) were able to show a parametric relationship between the extent of damage of the amygdala and the level of activation in the visual areas involved in face processing. A similar approach taken here would allow further verification of the extent to which processing in the amygdala does influence activity in both the orbitofrontal cortex and auditory cortex.

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## Tables

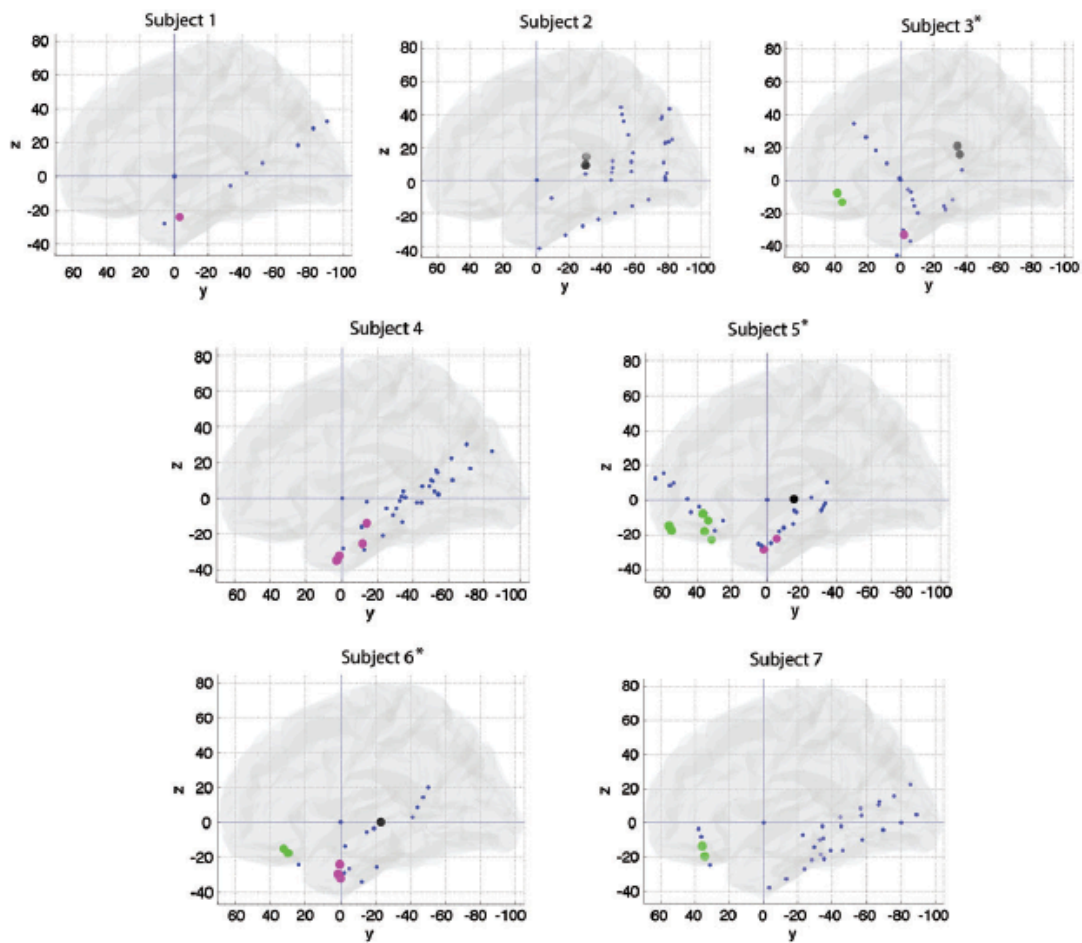
**Table 1.** Total number of bipolar contacts in each area for each subject and total number of pairwise combinations of contact signals in the three subject subsample.<sup>1</sup>

	Subject	Number of bipolar contacts per area			Number of connections per area pair		
		Amyg	Orb	Aud			
	1	1	0	0			
	2	0	0	2			
	4	4	0	0			
	7	0	2	0			
Three-	3	2	2	2	4	4	4
subject	5	2	6(4)	1	8	4	2
subsample	6	3(2)	2	1	4	2	2

<sup>1</sup>*Amyg, Orb and Aud short for amygdala, orbitofrontal cortex and auditory cortex respectively. In parentheses are presented the number of contacts in the dominant hemisphere for the subsample of three subjects. Granger causality analysis was carried out only on the contacts in this hemisphere.*

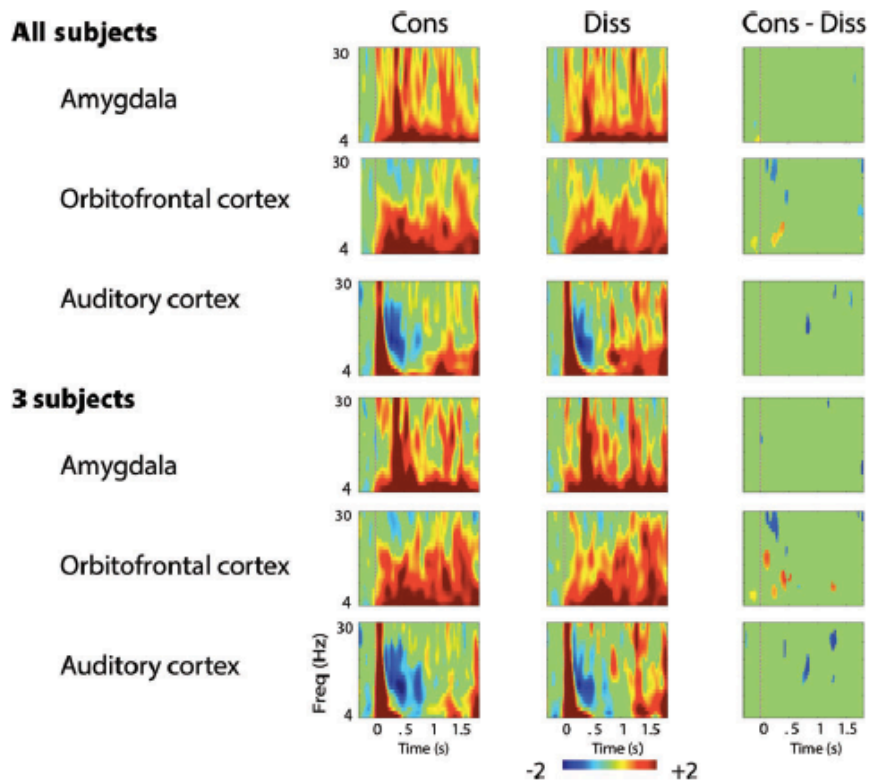
### **Figure captions**

**Figure 1.** The distribution of all the contacts in each of the 7 patients whose data are considered. Amygdala (pink), orbitofrontal cortex (green) and auditory cortex (black) contacts used in the analysis are indicated in colour. The three subjects with contacts in the amygdala, orbitofrontal and auditory cortex, whose data are therefore most extensively reported, are indicated with asterisks.



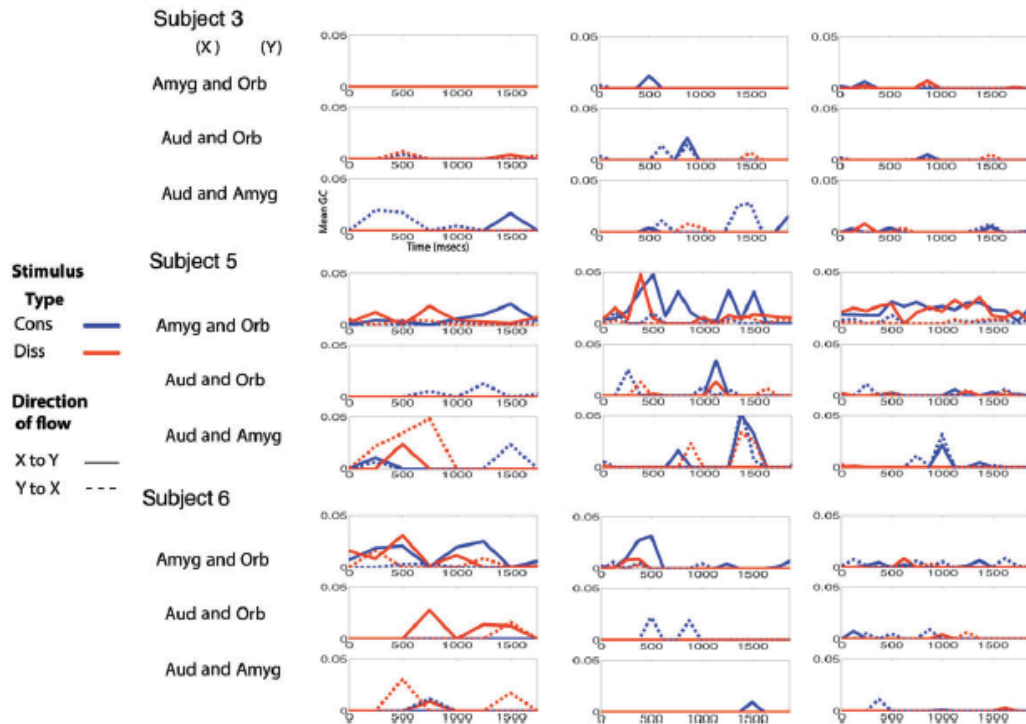
**Figure 2.** Grand average time frequency diagrams power in response to consonant and dissonant chords and the significant difference between these responses. Colour in the columns showing responses to consonant and dissonant chords (first two columns) indicate the log increase or decrease in power relative to a baseline of the 300 ms preceding the sound onset. Colour in the third column indicates the presence and strength of significant differences between spectral perturbations in response to the two types of sounds as evaluated

using permutation statistical testing with a Bonferroni corrected alpha value of 0.0167 (0.05/3).



**Figure 3.** Plots showing the evolution over time of significant causal flow for consonant (blue) and dissonant (red) chords in the theta, alpha and beta bands for the three-subject subsample. For all curves, solid lines indicate the forward direction of Granger causality within the pair (thus Amygdala  $\rightarrow$  Orbitofrontal cortex, Auditory Cortex  $\rightarrow$  Orbitofrontal cortex, Auditory Cortex  $\rightarrow$  Amygdala) while broken lines indicate causality in the reverse direction (Orbitofrontal cortex  $\rightarrow$  Amygdala, Orbitofrontal cortex  $\rightarrow$  Auditory Cortex,

Amygdala → Auditory Cortex). The value at time 0 indicates the significant causality observable in the 250 ms preceding the onset of the sound.



**Figure 4:** Barplots showing mean significant causal flow in each of the 6 possible directions averaged across consonant and dissonant sounds and across the three subjects. The number of participants showing causal flow in each given direction is indicated.

