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Distinct iEEG activity patterns in temporal-limbic and prefrontal sites induced by emotional intentionality

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Abstract

Our emotions tend to be directed towards someone or something. Such emotional intentionality calls for the integration between two streams of information; abstract hedonic value and its associated concrete content. In a previous functional magnetic resonance imaging (fMRI) study we found that the combination of these two streams, as modeled by short emotional music excerpts and neutral film clips, was associated with synergistic activation in both temporal-limbic (TL) and ventral-lateral PFC (vLPFC) regions. This additive effect implies the integration of domain-specific ‘affective’ and ‘cognitive’ processes. Yet, the low temporal resolution of the fMRI limits the characterization of such cross-domain integration. To this end, we complemented the fMRI data with intracranial electroencephalogram (iEEG) recordings from twelve patients with intractable epilepsy. As expected, the additive fMRI activation in the amygdala and vLPFC was associated with distinct spatio-temporal iEEG patterns among electrodes situated within the vicinity of the fMRI activation foci. On the one hand, TL channels exhibited a transient (0–500 msec) increase in gamma power (61–69 Hz), possibly reflecting initial relevance detection or hedonic value tagging. On the other hand, vLPFC channels showed sustained (1–12 sec) suppression of low frequency power (2.3–24 Hz), possibly mediating changes in gating, enabling an on-going readiness for content-based processing of emotionally tagged signals. Moreover, an additive effect in delta-gamma phase-amplitude coupling (PAC) was found among the TL

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channels, possibly reflecting the integration between distinct domain specific processes. Together, this study provides a multi-faceted neurophysiological signature for computations that possibly underlie emotional intentionality in humans.

Keywords

Emotional dynamics; iEEG and fMRI; High- and low; frequency oscillations; Gamma power; Phase-amplitude-coupling

1. Introduction

Emotions serve as an adaptive guide to our behavior, affecting our actions, thoughts, and the way we perceive the world. To support such behaviors, emotions need to be related to concrete information regarding relevant events or cues in the environment. This concept of the intentionality of emotions -pointing to objects beyond themselves – is considered a central aspect in philosophical (Deonna & Teroni, 2012) and psychological (Barrett, Mesquita, Ochsner, & Gross, 2007; Clore & Ortony, 2000; Frijda, 2005; Russell, 2003) definitions of emotions.

In a previous fMRI study we examined the neural correlates of emotional intentionality using a naturalistic multi-modal paradigm composed of short emotional music excerpts that provided abstract hedonic signals and short neutral film clips that provided non-emotional perceptual content. These stimuli were presented separately and in combination, allowing the examination of the effects arising from the synergy between abstract emotional cue and its associated content (herby termed the *additive effect*; Eldar, Ganor, Admon, Bleich, & Hendler, 2007). Surprisingly, additive effects were observed in both core limbic regions areas, such as the amygdala and hippocampus, as well as in cognitive areas in the ventral-lateral frontal cortex, such as the inferior frontal gyrus and ventral-lateral prefrontal cortex (vLPFC). To note, this investigation of the additive effects that arise by binding two distinct channels of information relative to their separate presentation differs in principle from other studies that have looked at cross-modal affective processing, generally using congruent affective stimuli (e.g. facial and vocal expressions of a specific emotion). Consequently, these studies have mainly highlighted converging activation in typical cross-modal areas such as the superior temporal gyrus and sulcus, as well as limbic and para-limbic regions (Brück, Kreifelts, & Wildgruber, 2011; Klasen, Chen, & Mathiak, 2012; Kreifelts, Ethofer, Grodd, Erb, & Wildgruber, 2007; Park et al., 2010; Pourtois, de Gelder, Bol, & Crommelinck, 2005).

The identification of the main brain areas involved in emotional intentionality is only the first step to understand this complex and multi-domain process. In consideration of existing models of emotion, the additive activation within the temporal-limbic (TL) area and vLPFC can be seen as reflecting two distinct domain-specific computations. More specifically, while the TL may be rapidly recruited due to the enhanced relevance or hedonic value of the affective information in the presence of concrete content (Brosch & Sander, 2013; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Sander, Grafman, & Zalla, 2003), the vLPFC may then support more flexible cognitive evaluations or the elaboration of this multifaceted

scene (Brosch & Sander, 2013; Lindquist et al., 2012). To distinguish between these different processes, improved temporal resolution of neural recordings is needed (Adolphs, 2002; Grandjean & Scherer, 2008). To this end, in the current study we finely tracked the processes underlying the additive fMRI effect using intracranial electroencephalogram (iEEG), an invasive method of electrical recording in the human brain that provides both superior spatial and temporal resolution. It was assumed that this approach will allow the pinpointing of various domain-specific neural processes underlying the intentional aspect of emotional experiences, which may consist of different time scales and spectral profiles (Adolphs, 2002; Glauser & Scherer, 2008; Grandjean & Scherer, 2008; Krolak-Salmon, Hénaff, Vighetto, Bertrand, & Mauguière, 2004).

Previous iEEG investigations that used unimodal exposure to static affective pictures have shown that emotional-selective responses occur at different latencies among various regions. While selectivity for briefly presented emotion-provoking pictures in the amygdala begins as early as 50–200 msec after stimulus presentation (Krolak-Salmon et al., 2004; Meletti et al., 2012; Oya, Kawasaki, Howard, & Adolphs, 2002; Sato et al., 2011a, 2011b), even under pre-attentive viewing conditions (Pourtois, Spinelli, Seeck, & Vuilleumier, 2010), it arises later, around 500 msec from stimulus onset, in the insula (Krolak-Salmon et al., 2003) and orbital-prefrontal cortex (Krolak-Salmon et al., 2004; But see Kawasaki et al., 2001 for earlier response in the PFC). Nevertheless, as these experiments used briefly presented static stimuli (.4–4 sec), it is yet unknown whether these processes persist or abruptly decay when using longer and more naturalistic viewing conditions. The advantage of using naturalistic stimuli for studying the temporal dynamics of cognitive processing in humans has been previously demonstrated (Hasson, Yang, Vallines, Heeger, & Rubin, 2008). However, the issue of the specific dynamics in emotional processing has yet to be fully addressed. This is especially important when considering contemporary theories of emotions that emphasize the dynamic and recursive nature of emotional processing, extending far beyond brief controlled moments (Barrett et al., 2007; Lewis, 2005; Scherer, 2009).

An additional possible route for probing distinct processing types via neural dynamics is the examination of brain oscillations – a phenomenon that has been explored extensively within the field neurophysiology, leading to advances in proposed theoretical frameworks that assign high and low frequency rhythms to encoding “bottom-up” and integrative “top-down” processes, respectively (Buschman & Miller, 2007; Donner & Siegel, 2011; Lee, Whittington, & Kopell, 2013; von Stein, Chiang, & Konig, 2000; von Stein & Sarnthein, 2000). Pioneering studies using invasive intra-cerebral recordings from the amygdala have identified emotion-induced local enhancement of gamma-power (Oya et al., 2002; Sato et al., 2011a, 2011b). Less spatially localized gamma power augmentation in response to emotional stimuli has also been found using magnetoencephalography (MEG; Luo, Holroyd, Jones, Hendler, & Blair, 2007; Luo et al., 2009) and EEG (Grandjean & Scherer, 2008; Keil et al., 2001; Müller, Keil, Gruber, & Elbert, 1999). Emotion related EEG power modulations have been additionally reported for lower frequency bands, such as theta (Maratos, Mogg, Bradley, Rippon, & Senior, 2009; Meletti et al., 2012; Sammler, Grigutsch, Fritz, & Koelsch, 2007), alpha (Baumgartner, Esslen, & Jancke, 2006; Kuhn et al., 2005; Popov, Steffen, Weisz, Miller, & Rockstroh, 2012) and beta (Glauser & Scherer, 2008) over a broad range of regions, including the PFC (Baumgartner et al., 2006; Maratos et al., 2009; Popov et al.,

2012; Sammler et al., 2007), amygdala (Maratos et al., 2009; Meletti et al., 2012) or sub thalamic nucleus (Kuhn et al., 2005).

Overall, the findings of induced gamma changes within the amygdala along with less localized changes in low frequency bands may imply the engagement of different regions for different types of processing. Nevertheless, it is yet unclear how these neural processing markers relate to emotional intentionality. To this end, we used fMRI and iEEG recordings among patients with epilepsy and examined the neural signature of emotional intentionality, modeled as the additive effects in response to the combination of abstract musical emotion and neutral perceptual content (Eldar et al., 2007). Progressing from the static “emotional brain” to its dynamic manifestation, we inspected TL- and vLPFC- additive power changes in transient and sustained time frames (0–500 msec and 1–12 sec, respectively) and in low and high frequency bands. In line with our previous findings (Eldar et al., 2007), we hypothesized that vLPFC and TL regions will show additive effect – enhanced fMRI activation during the emotional combined condition relative to the presentation of film or emotional music alone. Additionally, we speculated that significant additive band-limited power effects would be evident among iEEG electrodes within the vicinity of the fMRI activity in the TL and vLPFC. In accordance with electrophysiological studies, demonstrating the early effects of affective audiovisual binding (de Gelder et al., 1999; Hagan et al., 2009; Jessen and Kotz, 2011; Pourtois et al., 2000), we predicted that the additive effect should already be evident close to stimulus onset (a few hundreds of msec; Hagan et al., 2009). Based on evidence from iEEG recordings for rapid (e.g., Krolak-Salmon et al., 2004) and brief (e.g., Sato et al., 2011b) responses to emotionally charged stimuli within the amygdala, we expected relatively fast and transient responses within the TL channels. Finally, we hypothesized that the spectral profile of power perturbations would differ between TL and vLPFC channels. Specifically, we expected additive gamma power changes to be found in the TL- (Oya et al., 2002; Sato et al., 2011a, 2011b), and additive low-frequency power changes in the vLPFC-channels (Baumgartner et al., 2006; Maratos et al., 2009; Popov et al., 2012).

Indeed, the current multi-modal procedure extended our previous findings by showing that the additive fMRI activity patterns in vLPFC and TL regions could be dissected into distinct spectral and temporal profiles when examining iEEG recordings from channels in the vicinity of these areas. This distinction pointed to a transient gamma enhancement in the TL channels and sustained suppression among low-frequencies in the vLPFC channels.

2. Materials and methods

2.1. Participants

Recordings were obtained from 13 neurosurgical patients suffering from medically intractable epilepsy, who were evaluated for possible surgery ($M_{age} 32 \pm 7.5$ years, 6 males; see Table 1a for more details). The patients were recruited from the Neurosurgery Department at the Tel-Aviv Sourasky Medical Center following their clinical assignment for subdural electrode implantation (for approximately 1 week). All patients provided written informed consent according to the Tel Aviv Sourasky Medical Center Institutional Review Board (IRB) committee guidelines prior to the experiment. One of the patients (P09)

underwent a second intracranial electrode implantation a year after the first implantation since the focus of the seizures was not sufficiently localized; both recordings were used. Data from 3 patients were excluded from analysis due to: evidence of a vast right parietal-temporal-occipital dysplasia and heterotrophy (P03, age 25 y, female); evidence for vast noisy activity stemming either from equipment failure or from abnormal activity (P05, age 38, male; P13, age 37, female). The final study cohort of ECoG recordings comprised 10 patients, implanted with a total of 600 channels during 11 different implantation procedures ($M_{\text{age}} 31.6 \pm 7.9$ years, 5 males).

2.2. Experimental design and procedure

The paradigm that we used was described previously (Eldar et al., 2007). Briefly, it consisted of 12 emotionally-neutral film clips (e.g., a car driving), 12 music clips, which were of positive (joyful), negative (scary), or neutral (simple and monotonic) emotional tones (4 clips of each type) and 12 combinations of the same music and film clips. The stimuli were presented as 12 sec epochs separated by 9 sec blank epochs (gray screen). All conditions were order-balanced and pseudo-randomly distributed both within and between subjects. Please note that by using this paradigm (same stimuli for the unimodal and multimodal exposures) we were able to control for differences between low-level features across contrasted conditions. The joint pool of positive and negative music clips and their combinations with the film will be referred from here on as emotional music or emotional combined, respectively. Further details about the procedure, can be found in our previous paper (Esposito et al., 2012) and in the Supplementary materials.

2.3. Data acquisition

2.3.1. iEEG—Each patient was implanted with subdural electrode arrays containing between 32 and 74 contact electrodes (Ad-tech, Racine, WI, USA; 2 mm diameter, 8 mm spacing). The electrodes were arranged in one-dimensional strips or in two dimensional grids placed directly on the cortical surface. IEEG recordings in all patients except patients 09 and 10 were sampled at 200 Hz and digitally filtered between 1 and 70 Hz using a 32 channel Telefactor EEG system (Grass Technologies, West Warwick, RI, USA). In patients 09 and 10 recordings were sampled at 256 Hz using a 64 channels Nicolet system (Care-Fusion, Middleton, WI, USA) and digitally filtered between 1 and 70 Hz, these data sets were down sampled to 200 Hz. During the second pre-surgical evaluation procedure of patient 09 (will be referred to as 09b) an eight contact depth electrode was implanted to the medial temporal lobe (Adtech, platinum contacts, 2.4/1.1 mm length/diameter, 5 mm spacing) in addition to the regular cortical electrode grids (see Fig. S3). Recordings were monopolar and were referenced to an extra-cranial scalp electrode. The choice of implant sites was based purely on clinical considerations about the suspected locations of seizure origin.

The electrode contacts were identified on each individual stereotactic scheme. In addition, computer-assisted co-registration of a post-implantation CT-scan with a pre-implantation 3-D MRI provided direct visualization of electrode contacts with respect to each patient's brain anatomy. The MRI and CT 3-D images were co-registered using Brain-Voyager QX software package (Brain Innovation, Maastricht, The Netherlands) and were then normalized

into Talairach space. iEEG recording sites were marked on the co-registered anatomical MRI and their Talairach coordinates were extracted for further processing. The spatial coverage of the electrodes is generally summarized in Table 1 and Fig. 1b and specifically depicted per patient in the Supplementary materials and in Fig. S1. Overall, 52% of the electrodes were located in the temporal lobe, 24% in the frontal, 11% in the occipital and 13% in the parietal lobes.

2.3.2. MRI—Prior to the implantation of iEEG channels, 10 of the 13 participants underwent an fMRI scan, which was performed on a 3-T scanner (GE, Milwaukee, WI, USA) equipped with echo-planar imaging (EPI) acquisition. Acquisition parameters were identical to those reported in our previous work (Esposito et al., 2012), and are detailed in the Supplementary materials. Data from three patients were excluded from analysis due to: evidence of a vast dysplasia and heterotrophy (P03, age 25 y, female); evidence for vast abnormal activity in iEEG data (P05, age 38, male) and excessive head movements during the fMRI scan (>2 mm, P04, age 19, female).

2.4. Data analysis

2.4.1. fMRI—Imaging data were analyzed using BrainVoyager QX software package, similarly to our previous fMRI work using this multimodal paradigm (Eldar et al., 2007; Esposito et al., 2012; for more details, see Supplementary materials). The GLM consisted of 6 conditions: three modality types (film, music, combination) times two musical valence types (emotional and neutral). Fixed effects t-tests were calculated to compare between experimental conditions and baseline. Additionally, combination specific activations were highlighted as the overlapping voxels that were significantly activated by both contrasts of [combination > film] and [combination > music]. Results are reported at a threshold of $p = .05$, corrected for multiple comparisons using a false-discovery-rate (FDR) approach (Benjamini & Yekutieli, 2001).

2.4.2. iEEG preprocessing—Channel-level iEEG data preparation and preprocessing was performed in EEGLAB 9 (Delorme & Makeig, 2004), running on Matlab 2008a or later (www.mathworks.com). Preprocessing included: 1) Removal of electrodes that were either disconnected (as identified by visual inspection) or presented propagating ictal or inter-ictal epileptiform activity (as decided by a professional neurologist). This procedure resulted in the removal of a total of 239 iEEG channels from the analysis, leaving data from 361 channels gathered from 11 different iEEG recordings. 2) Application of global noise filtering by subtraction of the mean signal across all electrodes from each electrode. The continuous channel time-series were then segmented into single trials, separately per condition, extending from 5 sec before to 15 sec after the onset of each interval of stimulation. All subsequent iEEG analyses were carried out using the EEGLAB toolbox and the EEG-MEG module of BrainVoyager QX software and were further adapted using in house Matlab scripts.

2.4.3. fMR-based channel selection for region-restricted iEEG analysis—The selection of the iEEG channels within a given region of interest (ROI) was guided by our interest in sampling the channels that are sufficiently close to the peak of fMRI activation

from as many different data sets as possible in a minimally biased fashion. Accordingly, our selection was based on the following rational: 1) The Euclidean distance between the Talairach coordinates of each electrode and the Talairach coordinates of the peak of fMRI activation in vLPFC or TL (i.e., amygdala) that showed significant emotional-combination-specific group effect was calculated. 2) To avoid bias in selection while assuring sufficient coverage per each ROI, the distance threshold for channel selection in each ROI was determined in a data driven fashion. This was done by averaging, across patients, the distances of the three closest channels for each patient (within 50 mm from the peak fMRI activation). 3) To avoid over-sampling of electrodes from one patient with high number of electrodes within the distance threshold we limited the selection of electrode to five per ROI in each hemisphere. A total of 27 channels from 9 different pre-surgical evaluation procedures met this distance criterion for the vLPFC activation (20 mm) and 16 channels from 6 different pre-surgical procedures met this distance criterion for the TL activation (36 mm; see Fig. 1a, Fig. S3 and Tables S2 and S4 for a description of the selected channels and validation of channel selection strategy). We additionally selected in a similar fashion auditory and visual channels that were within 14 and 24 mm distance from bilateral fMRI peak of activations in response to the combined condition relative to baseline in auditory and ventral visual regions, resulting in a total of 23 channels from 9 different iEEG sets and 16 channels from 6 different iEEG sets, respectively (see Fig. 1a and Tables S3 and S4 for a description of the selected channels). From here on, these groups of electrodes will be referred to as vLPFC, TL, auditory or visual channels, respectively.

To avoid noise contamination of the data in all selected channels, these channels underwent a noise rejection procedure where any epoch with an amplitude deviation greater than $|350|$ μV was rejected as an artifact. We additionally refined the rejection criteria for transient response at stimulus onset and discarded any epoch in which the amplitude during the period between -500 and 1000 msec exceeded 5SD from the mean of each electrode (Sato et al., 2011b). This elimination procedure resulted in the rejection of 12% of the epochs, with no significant difference in rejection ratio across conditions ($\chi^2_{(5)} = 8.8$, $p = .12$).

The procedure of channel selection was validated by examining the time-frequency activity in the auditory and visual channels. As anticipated, robust increased gamma along with low-frequency power suppression was seen during the film alone condition in the visual channels ($n_{\text{ch}} = 16$), and during the music alone condition in the auditory channels ($n_{\text{ch}} = 23$), while the combined condition demonstrated similar patterns of power changes in both auditory and visual channels (Fig. 3a, b; $p < .001$, FDR corrected). This validation procedure clearly shows modality specific modulations in sensory regions. However, further investigation of these effects is beyond the scope of this paper.

2.4.4. iEEG channel restricted band limited power analysis—For each channel and trial, time frequency decomposition via a short-time Fourier transformation (FFT) approach was calculated for frequencies between 2.3 and 70 Hz in 136 logarithmically spaced steps over 200 sliding latency windows that were averaged across trials (window size 2560 msec long, mean step size 87.5 msec) using the *newtimef.m* function from EEGLAB (Delorme & Makeig, 2004). To allow for a direct comparison of effects across patients and frequency

bands, these calculated event-related spectral perturbations were normalized to baseline (–5 to 0 sec) and converted to dB scale ($10 \cdot \log_{10}[\text{power}/\text{baseline}]$).

2.4.5. iEEG “AH channels” group analysis – cortex-based distributed analysis

—Effects that were found significant at the channel level were further examined in a wider spatial context by assessing the mapping of responsive channels at the group level. To optimally group subdural iEEG data from multiple subjects in the same cortical regions of a common brain space, we applied a recently developed technique that is described in details in our previous paper (Esposito et al., 2012) and schematically depicted in Fig. 1b. Briefly, this approach utilized a cortex-based alignment (CBA) procedure for optimizing the anatomical correspondence across the different patients along with the application of an activity spread model around each channel that assumes that the signal decays with distance (see Supplementary materials for further details). The depiction of the electrode spread density across patients in Fig. 1b directly demonstrates the variation in spatial coverage of the electrodes. This depiction may further serve as a reference when inspecting the spatial distribution of the “all channels” analysis, revealing cortical areas densely or sparsely covered. As can be seen, despite exclusion there is still a high density of electrodes in the major areas of interest. Time frequency representations for this analysis were obtained for each channel and trial using short-time-FFT approach (time resolution 200 msec, time window 2 sec, frequency resolution .39 Hz). This procedure was carried out using Brain Voyager QX software.

2.4.6. Phase amplitude coupling (PAC)—Calculation of PAC was performed per condition in each channel separately using the approach of Voytek et al. (2010). Briefly, we initially band-pass filtered the concatenated epochs of iEEG data into low-frequency (calculated in 22 bins of 2 Hz between 2 and 23 Hz) and gamma (calculated in 29 bins of 6 Hz between 41 and 69 Hz) bands using a linear finite impulse response filter (*eegfilt.m* in EEGLAB toolbox, Delorme & Makeig, 2004). The filtered data were then decomposed using a Hilbert transformation and the low-frequency phase and gamma amplitude were calculated from the resulting complex signals. We then calculated the phase locking between the instantaneous low-frequency-phase and the phase of the instantaneous low-frequency-filtered gamma amplitude envelope by assessing the length of the mean vector between these phases (Penny, Duzel, Miller, & Ojemann, 2008). Finally, the resulting PAC indices were z-scored using the mean and standard deviation of 200 surrogate values (generated by randomly shuffling the amplitude time series) to account for the difference in amplitudes and to allow for parametric statistics on these data (Allen et al., 2011). The resulting PAC values were then averaged across the gamma frequency band separately for the different low-frequency bands (delta: 2–3 Hz, theta: 4–8 Hz, alpha: 9–13 Hz, beta: 14–23 Hz). Time frequency plots time locked to the trough of delta phase, were obtained using a similar approach to Canolty et al. (2006). Troughs were identified as the local minima of the low-frequency phase, which was lower than $-\pi + .24$.

2.5. Statistical analysis

The data used in the group statistics were extracted by averaging the power in each frequency band (delta: 2.3–2.9 Hz; theta: 4–8 Hz; alpha: 9–13 Hz; beta: 15–24 Hz; gamma: 41–69 Hz).

41–49 Hz; gamma2: 51–59 Hz; gamma3: 61–69 Hz) and time window of interest (transient: 0–500 msec; sustained: 1–12 sec), separately per condition (film, music and combination). The determination of 0–500 msec as the time frame for transient processing was done in order to ensure that beyond the early response, meaning or concept related neural processes would be additionally included. Such high level processes are considered to emerge between 250 and 500 msec (Adolphs, 2002; Kutas & Federmeier, 2011). To further ensure clear distinction between transient and sustained effects, the period between 500 and 1000 msec was not included in the sustained time frames. Notice, that power changes were separately estimated in three different sub-bands of the high frequency range. This division into sub bands was guided by our goal to distinctly probe low (~ 35 –50 Hz) and high gamma (>60 Hz) bands, which have been highlighted as reflecting separate processes (Edwards, Soltani, Deouell, Berger, & Knight, 2005) and underlying physiological mechanisms (Neuenschwander & Singer, 1996). Under the restriction of a maximum frequency of 70 Hz and given that high gamma is defined as >60 Hz we were left with a band width of 10 Hz (i.e. 61–69). This determined our frequency bins also for the low gamma (i.e. 41–49 and 51–59). We additionally avoided using the edges of each frequency band to minimize cross talk. These values were used to initially highlight the conditions and frequency bands in which significant activity changes relative to the null distribution were observed (i.e., simple effects) and for further assessing whether these simple effects are modulated by the different stimulation conditions (i.e., additive effect). Given that we had no a-priori hypotheses regarding functional differences between sub-bands, beyond their distinction as belonging to either low or high ranges – for the subsequent additive effect analysis we thus collapsed across sub-bands in cases where simple effects were evident for the entire range of either low or high frequencies. For the *simple effect analyses*, we constructed surrogate activity distribution per each frequency by computing 10,000 trial-averaged activity estimates in randomly selected windows in the baseline period (–5 to 0 sec, Delorme & Makeig, 2004). Single sample t-tests were then performed per frequency band and condition to compare the condition-dependent-band-limited activity to the mean of the null distributions across all channels. Finally, Bonferroni correction for the 21 comparisons across conditions and bands was applied. *Additive effect* was assessed using Friedman's non-parametric test, followed by post-hoc Wilcoxon's non-parametric paired comparisons once a significant difference across conditions was found. To avoid biasing of the comparisons by outliers, in each frequency band and condition, we removed any entry that was higher than $2 \times$ inter-quartile range (IQR) above the third quartile or lower than $2 \times$ IQR below the first quartile (See Table S4 for more details about the number of electrodes analyzed per analysis). The group's time frequency plots were obtained by averaging the time frequency data from all channels at each time-frequency point. The statistical significance at each point was determined by assessing its percentile location in the group null distribution (see above, $N_{\text{rand}} = 10,000$) and further correcting for multiple comparisons using an FDR approach (Benjamini & Yekutieli, 2001).

“All-channels” analysis to assess the spatial distribution of the region-restricted effects was performed using our previously described approach (Esposito et al., 2012). Briefly, single-sample and paired-sample t-tests with a spatially varying number of degrees of freedom, reflecting the number of subjects contributing to each vertex, were applied on the projected band limited power data from all patients' channels. The resulting t-maps expressing the

iEEG power modulation for each condition versus baseline were converted to z-score maps for display. Combination specific activations were highlighted as the overlapping vertices that were significantly activated by both comparisons of [combination us film] and [combination us music]. Given the exploratory nature of this all-channel analysis and the relatively low number of participants, thresholding of the cortical maps was performed without correction for multiple comparisons.

The statistical significance of the z-scored PAC in each group of channels was determined using a single-sample t-test in comparison to null hypothesis – zero. Since Kolmogorov-Smirnov Tests revealed that the z-scored PAC values were normally distributed ($p > .1$ for all conditions and low-frequency bands), we used 4×3 repeated measures analysis of variance (ANOVA, with frequency band and condition as within subjects variables) to compare the PAC values across frequency and condition.

Unless otherwise mentioned, two sided statistical tests were performed for all analyses. The values in figures are expressed as mean $\pm$ SEM. N_{ch} referred to the number of channels in the analysis and $N_{patient}$ to the number of patients.

2.6. Depth iEEG recordings

We recorded from two additional patients with medically intractable epilepsy, who were implanted with intracranial macro depth electrodes (Ad-tech, 7 platinum contacts, 1.57/ 1.28 mm length/diameter, 3.14 mm spacing), to identify seizure foci for possible surgical treatment (see Table 1b for further details). Prior to the experiment, the patients provided written informed consent according to the Tel Aviv Sourasky Medical Center IRB committee guidelines. Patient 14, a 32 years old male, was implanted with 6 different macro electrodes (each containing 7 contacts) targeting the R + L amygdala, R + L middle hippocampus and R + L Parahippocampal gyrus. Patient 15, a 29 years old female, was implanted with 8 different macro electrodes targeting the R + L amygdala, R + L middle hippocampus, R + L Orbital frontal cortex and R + L supplementary motor area. The recordings were sampled at 256 Hz using a 64 channels Nicolet system, digitally filtered between 1 and 70 Hz and down sampled to 200 Hz. Recordings were monopolar and were referenced to an extra-cranial scalp electrode. The preparation of data and the subsequent band-limited power analysis was performed in a similar fashion as described above. The statistical analyses were performed separately for each patient based on single trials' data and were focused on the transient perturbations in gamma power (61-69 Hz). Specifically, analyses included the estimation of the *simple effects* using single sample t-tests (in comparison to the mean of 10,000 surrogate values) and the estimation of their further *additive effect* using Kruskal-Wallis and Mann-Whitney U non-parametric tests.

3. Results

3.1. fMRI activation related to emotional intentionality

Fig. 2 shows the fMRI group-level statistical parametric maps of activations during the combined and separate film and emotional music clips relative to baseline. As expected, the combined condition recruited the PFC and TL areas, centered on the vLPFC (i.e. ventral pre-

motor and IFG) and amygdala, respectively. Estimation of the overlap between the contrasts (emotional combined > film & emotional combined > emotional music) revealed that activity changes in the vLPFC and in the right amygdala were selectively enhanced with increased emotional intentionality ($n = 7$, FFX, $p = .05$, FDR corrected, see also Table S1a). The increased combined effect within these regions cannot be simply assigned to the binding of the two modalities since the conjunction effect for the combination of neutral music and film highlighted clusters in areas distinct from those found for the emotional combination (Table S1b) and included neither the TL nor vLPFC regions.

3.2. Local iEEG band limited power changes related to emotional intentionality

Based on the fMRI results, subsequent analyses focused on the iEEG channels closest to the fMRI activation in the posterior aspect of the vLPFC (i.e. ventral pre-motor) and TL (the amygdala) areas (see methods and Fig. 1 for the analysis scheme). We initially examined the local band-limited activity profile in the TL and vLPFC channels and whether they corresponded to changes in the emotional conditions. To depict the neural dynamics, we assessed transient (i.e. 0–500 msec) and sustained (i.e. 1–12 sec) band-limited power changes in low (delta: 2.3–2.9; theta: 4–8; alpha: 9–13; beta: 15–24 Hz) and high (gamma1: 41–49; gamma2: 51–59, gamma3: 61–69 Hz) frequency bands within each pre-defined ROI (i.e. TL and vLPFC), per condition, within each channel.

Among the vLPFC channel group, a significant sustained power suppression, relative to the null distribution, was revealed in all of the low frequency bands but only during the emotional combined condition [delta: $t(26) = -5.58$, $p < .0001$; theta: $t(26) = -4.55$, $p < .001$; alpha: $t(26) = -5.82$, $p < .0001$; beta: $t(26) = -3.93$, $p < .001$]. Given this overall simple suppression effect across the low frequency bands, we used this entire range of frequencies as a probe for additive effect estimation. Subsequent evaluation of average sustained low-frequency power changes, ranging from 2.3 to 24 Hz, revealed an overall significant difference across conditions [Freidman's non-parametric test with mean db scaled power values as the dependent variable and condition [i.e. film, music, combined] as the within subject variable, $\chi^2_{(5)} = 9.77$, $P = .008$, $n_{ch} = 26$]. This difference was accounted for by greater sustained suppression during the emotional combined condition relative to the separate neutral film and emotional music conditions [post hoc Wilcoxon's paired tests, $z = 3.14$, $p = .002$; $z = 2.7$, $p = .007$, respectively, Fig. 4a,b]. We further extracted time frequency plots for each condition and calculated the significance at each point using bootstrapping techniques. As expected, this revealed robust low frequency suppression during the combined condition ($p < .001$, FDR corrected, Fig. 3c). The individual time courses of low frequency power changes were also depicted in each vLPFC channel per condition (Fig. S2a). To further investigate the spatial distribution of this additive effect we performed an “all channels” group analysis using data from all iEEG channels (Esposito et al., 2012; see methods and Supplemental materials for details). Fig. 4c shows that in addition to the vLPFC, additive modulation during the emotional combined condition was associated with relatively widespread low-frequency power (2.3–24 Hz) suppression, including the right posterior peri-sylvian region, temporal-parietal junction and anterior temporal areas ($p < .05$, one tailed).

In contrast to the vLPFC, among TL channels a transient increase in gamma3 power (61–69 Hz; will be termed from here on as gamma), relative to the null distribution, was evident during the combined condition [$t(15) = 4$, $p = .001$]. Subsequent analysis revealed a significant difference across conditions in this transient gamma power [Freidman's non-parametric test with the mean db scaled gamma power values as the dependent variable and condition as the within subject variable, $\chi^2_{(5)} = 8.375$, $p = .015$; $n_{ch} = 16$], which was further shown as enhanced gamma power for the combined condition relative to the separate film condition and marginally relative to the separate music condition [post hoc Wilcoxon's Paired tests, $z = 2.69$, $p = .008$; $z = 2.01$, $p = .04$ respectively; Fig. 5a,b]. The transient and narrow band nature of this simple effect was also evident within a whole-spectrum context in the time frequency plots, averaged across TL channels for each condition ($p < .001$, FDR corrected, Fig. 3d). The time courses of gamma power in each TL channel were also depicted per condition at the individual channel level (Fig. S2b). We performed a post-hoc “all channels” analysis to further explore the spatial distribution of the obtained transient gamma effect. As the combined condition was only significantly different from the film condition in the TL channels (Fig. 5a), additive effect were examined here by comparing the emotional combined and the film conditions only. This analysis revealed transient gamma power modulation in bilateral anterior temporal areas, as well as in other temporal regions such as the right primary and secondary auditory areas and in the right vLPFC. Finally, a simple effect was observed in auditory regions during the music condition, in visual regions during the film condition, and in both auditory and visual regions, as well as right posterior perisylvian region and the vLPFC during the combined condition (Fig. 5c).

In summary, local spectral analyses revealed that the additive effect of combining emotional music and neutral film is associated with distinct power changes in vLPFC and TL channels, namely sustained low frequency suppression for the former and a transient gamma increase for the later. Interestingly, examination of the combined condition under the context of neutral music did not reveal significant differences across the neutral conditions for neither sustained low frequency power in the vLPFC channels [$\chi^2_{(2)} = .96$, $p = .62$; $n_{ch} = 25$] nor for transient gamma power in the TL channels [$\chi^2_{(2)} = 3$, $p = .22$; $n_{ch} = 14$]. This finding may point to the specificity of the effect for emotional contexts; the combination of film with emotional music. Nevertheless, as the study was not designed to directly compare neutral and affective contexts, the interaction between presentation modality and affect type remains to be explored.

3.3. Validation of gamma transient power changes via depth electrodes in the amygdala

To validate the localization of the transient gamma effect observed in the TL channels, we examined data obtained from two additional patients with epilepsy, implanted with bilateral depth electrodes within the amygdala and hippocampus and who underwent identical experimental procedures. Remarkably, a significant enhancement of transient gamma power (61–69 Hz) during the combined condition, relative to the null distribution, was evident in the channels located within the right amygdala in patient 14 and the left amygdala in patient 15 (see Fig. 6a,b); [$t(12) = 3.12$, $p = .009$; $t(7) = 4.15$, $p = .004$, respectively]. Subsequent analysis within these channels revealed a significant difference across conditions [non

parametric Kruskal-Wallis tests, $H(2) = 8.62, p = .01, n_{\text{trials}} = 36$; $H(2) = 9.52, p = .009, n_{\text{trials}} = 20$, respectively], depicting enhanced gamma power during the combined condition relative to the music or film conditions alone [non parametric Mann-Whitney U post-hoc tests; combined vs film: $Z = 2.56, p = .01, Z = 2.93, p = .003$; combined vs music: $Z = 2.4, p = .02, Z = 2.31, p = .02$]. Similar less robust effects were evident in two neighboring channels within the right amygdala for patient 14 and in an additional channel within the left amygdala for patient 15 (see bottom panel in Fig. 6a,b for more details).

To assess the spatial specificity of this effect we looked for additional channels presenting both simple (enhanced activity relative to the null hypothesis) and additive effects. Out of the 39 channels examined in patient 14, a similar combined effect was only evident in a single channel in the right Para-hippocampal gyrus [simple effect: $t(14) = 2.7, p = .02$; additive effect: $H(2) = 10.06, p = .0065, n_{\text{trials}} = 36$; Fig. 6a]. In patient 15, out of the 50 channels examined no additional channels presented an effect. Hence, the data from these two patients enabled better localization of the transient gamma power effect within the amygdala. This effect found within the amygdala provides further support of the marginal gamma effect obtained from the comparison between the combined and music conditions among the cortical TL channels (Fig. 5a).

3.4. Cross frequency coupling related to emotional intentionality

Our analyses suggest that emotional intentionality is processed differently in the TL and vLPFC areas, as probed by effects in gamma power in the TL and in low frequency power in the vLPFC. We next used cross-frequency coupling measures to examine whether there was a relation between the two processing levels and inspected the extent of condition-dependent modulation of gamma power by the lower frequency phase (Canolty et al., 2006; Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008). We thus calculated a z-scored PAC index (Voytek et al., 2010) between the phase of low frequency bands (delta: 2–3 Hz, theta: 4–8 Hz, alpha: 9–13 Hz, beta: 15–23 Hz) and gamma power (41–69 Hz) in the TL and vLPFC channels and compared these band-limited values across conditions (repeated measures-ANOVA with frequency band and condition as the within subject measures). Within the TL channels PAC was modulated by condition as a function of the frequency band for phase [frequency band * condition interaction, $F(6,72) = 2.57, p = .03, N_{\text{ch}} = 13$]. This condition dependent modulation was explained by greater delta-gamma PAC during the combined condition relative to the separate film and music conditions [i.e., additive effect; post hoc within band TukeyHSD tests, $p = .03, p = .04$, respectively, see Fig. 7 a, c, e]. In the vLPFC channels, on the other hand, there was no condition-dependent modulation. Nevertheless, there was a strong modulation by the frequency band for phase [main effect for frequency band, $F(3,72) = 12.47, p < .0001, N_{\text{ch}} = 25$] that was further explained as an enhanced beta-gamma coupling during all types of stimulus presentations relative to the coupling with the other low frequency bands [post hoc Tukey tests, $p < .005$ for all comparisons, see Fig. 7b,d,f].

4. Discussion

In this study we extended the fMRI finding regarding emotional intentionality processing in the TL and vLPFC by using iEEG to provide neurophysiological indications of the related functional dynamics within these regions. According to our expectations, the iEEG signals from these regions were characterized by distinct profiles of additive effects in response to the relatively abstract hedonic value when paired with concrete perceptual information. Specifically, additive sustained suppression of low-frequency (2.3–24 Hz) power was observed in the vLPFC channels, while a transient enhancement of gamma power (61–69 Hz) was observed in the TL channels. We further demonstrated that during the emotional combined condition local gamma power couples with the delta phase in the TL channels, providing evidence of the possible integration of domain-specific processes.

4.1. The spectral profiles of local rhythms during emotional intentionality processing

The transient additive increased gamma power found among the TL channels along with the sustained additive suppression of low-frequency power in the vLPFC channels are generally consistent with previous demonstrations of emotion-selective enhancement in gamma (Grandjean & Scherer, 2008; Keil et al., 2001; Luo et al., 2007, 2009; Müller et al., 1999; Oya et al., 2002; Sato et al., 2011a, 2011b), and reduction in theta (Maratos et al., 2009), alpha (Baumgartner et al., 2006; Popov et al., 2012) and beta (Glauser & Scherer, 2008) power, observed by using either invasive (Oya et al., 2002; Sato et al., 2011a, 2011b) or non-invasive recording techniques (Glauser & Scherer, 2008; Grandjean & Scherer, 2008; Keil et al., 2001; Luo et al., 2007, 2009; Maratos et al., 2009; Müller et al., 1999; Popov et al., 2012). Our findings in the low frequency range particularly correspond with an EEG study that found that alpha power diminishes as affective information becomes increasingly more explicit and accurate, from affective music, to affective pictures, to their combination (Baumgartner et al., 2006).

These various manifestations can be related to distinct stages in affective processing. For example, a previous EEG study that specifically tested the different stages of affective processing based on predictions of the component process model, associated induced gamma power with the evaluation stage of goal conduciveness (Grandjean & Scherer, 2008). Along that line, the observed difference in the spectral profiles of the additive effects in TL and vLPFC sites may point to distinct domain-specific processes within these regions during emotional intentionality processing. This suggestion relies on a recent theory by Donner and Siegel (2011), proposing that high and low frequency rhythms are not only associated with different extents of spatial integration, known as local and long-range respectively (Kopell, Ermentrout, Whittington, & Traub, 2000; von Stein & Sarnthein, 2000), but also with different classes of local functional processes. According to this framework, local encoding functions such as sensory representations have been associated with local cortical interactions that give rise to gamma rhythms, whereas more integrative functions such as decision making have been associated with long range interactions that produce local low-frequency rhythms.

The additive gamma effect observed for the combined condition – an emotionally meaningful whole that emerges when binding two distinct streams of information – is also

consistent with the well-known “binding by synchronization hypothesis”, suggesting the significant role gamma synchronization plays on perceptual grouping (Singer, 1999). The finding of additive effect in low-frequency band in the vLPFC can be further considered in light of recent theoretical claims that the suppression of low-frequency power may provide a release from the “status-quo”- (Engel & Fries, 2010) or an internally oriented (Hanslmayr, Gross, Klimesch, & Shapiro, 2011) gating processing mode that enables online externally oriented processing (Lakatos et al., 2008). Consistent with this view, EEG (e.g., Thut, Nietzel, Brandt, & Pascual-Leone, 2006) and iEEG studies (Canolty et al., 2007) have associated low-frequency suppression with an enhanced readiness to act upon changes in the environment. With regards to affective processing, a recent MEG study demonstrated alpha power suppression in the vLPFC during the cognitive reappraisal of emotional pictures and even in the preparatory stages for such a regulatory task (Popov et al., 2012). In another EEG study, a decrease in beta power corresponded with the emergence of conscious subjective emotional experiences induced by pictures (Glauser & Scherer, 2008).

The temporal distinction between transient and sustained additive effects is in accordance with previous indications from invasive human electrophysiological studies, pointing to fast affect-related responses within the amygdala (e.g., Krolak-Salmon et al., 2004; Pourtois et al., 2010), and delayed orbital PFC responses (Krolak-Salmon et al., 2004). A recent fMRI study has further demonstrated this distinction, revealing fairly transient responses in the amygdala along with sustained responses within the ventral basal forebrain and insula in response to emotional stimuli (Somerville et al., 2013). This spectro-temporal distinction has also been reported in a recent MEG study in the context of motor actions, where transient enhanced gamma power and sustained decreased alpha and beta power were evident in the motor cortex prior to button pressing, indicating an internally driven perceptual choice (Donner, Siegel, Fries, & Engel, 2009).

The segregation into distinct processes in the TL and vLPFC channels can be viewed within a wider context of contemporary theories, suggesting that the emotional experience is constructed from more basic psychological domains (Barrett et al., 2007; Brosch, 2013; Clore & Ortony, 2000; Russell, 2003; Scherer, 2009). More specifically, although the timing and precedence of these processes are still under debate, there is consensus that emotional processing consists of both fairly low-level detection of affective relevance centered in limbic areas and high-level elaboration and exertion of control, rooted in prefrontal regions (Brosch & Sander, 2013; Klavir, Genuit-Gabai, & Paz, 2013; LeDoux, 1998; Lindquist et al., 2012; Pessoa, 2008). Similar notions were recently introduced in a neurobiological model of multi modal affective processing, proposing that the amygdala and LPFC are respectively responsible for the implicit and explicit decoding of audiovisual emotional information (Brück et al., 2011). Thus, we suggest that the additive transient gamma power increase within the TL sites may be associated with the rapid evaluation of stimulus relevance and/or hedonic value, likely to be operated once new information is encountered by limbic areas. Following this initial processing stage, the ongoing content-based evaluation of incoming information may be supported by the continuous readiness of the vLPFC, shown as sustained suppression in low-frequency power.

4.2. Condition selective PAC

The significant delta-gamma PAC in TL channels and beta-gamma PAC in vLPFC channels further expanded our initial hypothesis regarding local power modulations during emotional intentionality processing. Phase-amplitude cross frequency coupling has increasingly been observed among both animals and humans, in multiple regions and under various cognitive-perceptual tasks (for a review, see Canolty & Knight, 2010; Jensen & Colgin, 2007; Lakatos et al., 2008). This statistical dependency between the phase of low frequency and the amplitude of a higher frequency has been suggested to play a role in the organization and communication of functional systems by coordinating fast and local computations with slower and distributed neuronal processes (Canolty & Knight, 2010; Lakatos et al., 2008). Hence, the modulation of PAC in our study may generally be viewed as evidence for such local interactions between processing domains in the context of emotional intentionality processing. The difference in the PAC profile between TL and vLPFC regions is consistent with recent studies that demonstrated that PAC occurs between different frequencies in different regions (van der Meij, Kahana, & Maris, 2012; Voytek et al., 2010). This spatial variability in PAC frequencies may point to different processes that distinctly dominated the vLPFC and TL regions. As such, diversity in PAC has been suggested as a possible mechanism for parallel selective routing of information through different neuronal networks (van der Meij et al., 2012; Voytek et al., 2010). Interestingly, the additive effect of delta-gamma coupling in the TL channels was more pronounced during the emotional combined condition (Fig. 7). This finding joins previous studies that have demonstrated affect-related cross-frequency coupling between alpha-phase and gamma-power in the nucleus accumbens (Cohen et al., 2009) and LPFC (Popov et al., 2012). Furthermore, a series of EEG studies has associated beta-delta amplitude-amplitude coupling with affective processing by showing that individual differences in trait anxiety, Cortisol levels and attentional bias towards threat were positively correlated with such coupling (Knyazev, Schutter, & Van Honk, 2006; Putman, 2011). Nevertheless, as the specific functional role of cross frequency coupling is still unclear, and has been associated with different operations (Arnal & Giraud, 2012; Canolty & Knight, 2010; Jensen & Colgin, 2007; Lakatos et al., 2008; Voytek et al., 2010), further investigation into the role of cross frequency coupling in the context of affective processing is needed.

4.3. Limitations

It may be argued that given the epileptic pathology of our participants the results of this study do not necessarily reflect the normal brain (Jerbi, Ossandon, et al., 2009). First, we demonstrated that the patient group presented similar fMRI activation patterns as found in our previous fMRI study with healthy participants (Eldar et al., 2007; see Fig. 2). In addition, we used a stringent criteria for removing channels identified as being associated with either ictal or inter-ictal activity from the analysis, resulting in exclusion of ~40% of the channels. Note that the excluded electrodes were widely distributed among patients' brains (see Fig. S1).

Although subdural iEEG recordings have far superior spatial resolution than non-invasive electrophysiological recordings, our findings still lack fine-scale localization (within the mm range). Slight shifts in channel localization may have occurred given that electrode

localization in our study consisted of co-registrating pre-operative MRI with postoperative CT, which may have introduced inaccuracies. In addition, shifts may have occurred in the brain tissue due to the invasive nature of the surgical procedure, known as the brain-shift problem (Hermes, Miller, Noordmans, Vansteensel, & Ramsey, 2010). To minimize such inaccuracies we used manual verification of electrode positioning in relation to the cortical surface. Additionally, since the channels that were included in the region-restricted analysis were within the range of ~2–3 cm from the areas of interest, the results should be regarded as revealing the activity profile of fairly large brain areas. Nonetheless, the rare opportunity to obtain depth electrode recordings from two additional patients allowed confirming that the additive transient gamma effect occurs within the amygdala. Although this nicely supports the findings among TL electrodes (Fig. 5a), the data from depth electrodes also points to the inherent variability in band limited power changes across patients and electrode positions and highlights the benefits of applying group statistics; while there was a fairly broad-band and sustained gamma power enhancement in the response to the combined condition for patient 14, for patient 15 this effect was slightly limited in time and frequency (Fig. 6).

To note, it may additionally be argued that the transient gamma effects in the TL observed in our study originated in non-neural ocular and myogenic artifacts derived from differences in stimulus locked eye movements across the experimental conditions (Jerbi, Freyermuth, et al., 2009; Nagasawa et al., 2011; Yuval-Greenberg, Tomer, Keren, Nelken, & Deouell, 2008). However, the use of a cross modal design, whereby the only difference across conditions is the mode of presentation – either separately or in combination, renders the possibility of eye movements confounds unlikely as the unique low-level visual or auditory features during the combined condition were identical. Still, it may be argued that the combination of auditory and visual information is associated with a pattern of eye movements that is distinct from the presentation of visual or auditory stimuli alone. Such an explanation, however, is not concurrent with the lack of transient gamma effect for the combination of the neutral music excerpts with the film. Lastly, while the studies reporting ocular movement confounds point to a fairly broadband phenomenon (Yuval-Greenberg et al., 2008), our findings point to a narrow band effect, limited to 61–69 Hz. However, in future studies, to completely rule out this possible confound, eye movements should be directly monitored via eye tracking.

Finally, the use of monopolar rather than bipolar referencing in our analyses may have hampered the ability to distinguish between common and selective activity among electrodes. Still, our demonstration of distinct activation profiles among different regions in the ECoG data, and the relatively localized effects in the depth electrode recordings, suggest that the spatial specificity of the recordings was indeed preserved when using this referencing approach.

4.4. Conclusions

Our multi-scale fMRI-iEEG approach, along with the use of multi-modal and domain specific stimuli, enabled the dissection of the neural processes that underlie emotional intentionality. The transient increase in TL gamma power in the combined condition may be

associated with initial relevance detection or hedonic value encoding. In addition, the sustained low-frequency power suppression in vLPFC may underlie gating changes, facilitating subsequent content-based evaluations of the tagged stimulus. Such multi-domain depiction supports current models of emotion, in which both hierarchy and the dynamics of processing are emphasized (Barrett et al., 2007; Scherer, 2009). This detailed neurophysiological profile obtained by localized iEEG measurements may further highlight potential neuro-markers for distinct emotional processing domains in humans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Overview of analysis approach

a. Initial analysis focused on selected groups of iEEG channels, chosen based on their proximity to the fMRI activation in vLPFC, TL, auditory and visual areas. b. Follow-up group analysis of data from all channels employed analytical approach that allows for optimal correspondence of iEEG data across different patients. This approach was based on the application of an activity spread model around each iEEG channel, group-cortex-based-alignment of the obtained activity patches and projection of the resulting patches onto on the average of the group reconstructed aligned brains. The correspondence across the iEEG data sets is depicted as the density of the resulting maps of aligned activity spread. c. To obtain a comprehensive neural characterization of processing, different parameters of the activity were taken into account.

fMRI results $N=7$, FFX**a. Simple effects** **b. Modulation effect:**
Combined >
[Film & Music] **Fig. 2.**

fMRI results obtained from 7 patients with intractable epilepsy prior to the surgery. a. simple effects of activity changes are demonstrated for the comparison of film, emotional music or the combined emotional condition with baseline in sagittal (upper) and coronal (lower) views. b. emotional additive effect is demonstrated by the conjunction of maps obtained by the contrasts: [emotional combined > film] & [emotional combined > emotional music] and is shown on sagittal view (left) and coronal (right) views.

Fig. 3. Time frequency plots of activity in the fMRI-based selected groups of channels

Time-frequency plots of the grand average of power changes obtained from the iEEG channels that were located in vicinity of a. visual cortex, b. auditory cortex, c. vLPFC region and d. TL region. The locations of the channels' group are depicted, correspondingly, on the left panel and the different color tones denote different patients. Plots are time locked to the onset of stimuli and colors represent changes in frequency power relative to a pre-stimulus baseline (-5000-0 msec). The contour indicates statistical significance relative to the null distribution ($N_{\text{rand}} = 10,000$, $p < .001$, FDR corrected).

Fig. 4. Sustained iEEG low frequency power changes

a. mean low-frequency power changes in the vLPFC channels, averaged from 2.3 to 24 Hz, between 1 and 12 sec of stimulus presentation (i.e. sustained), per condition; b. time series of the low-frequency power, locked to the onset of stimulus presentation are shown per condition. Dotted lines indicate stimulus onset and offset, and thickness of shading represents 1 deviation from the mean (SEM), red vertical line marks the sustained time window. c. *All channels analysis for sustained low-frequency power suppression.* Group-level random-effects z-maps of CBA-aligned distributed sustained LF power on the target cortex mesh. Simple effects are demonstrated for each condition as the regions where LF power significantly diminished relative to baseline ($p = .01$, one tailed). Emotional additive effect is indicated by the overlap of maps obtained by the contrasts [emotional combined > film] & [emotional combined > emotional music] ($p = .05$, one tailed). Stars represent significant simple effects (i.e., change in relation to the null distribution, $N_{\text{rand}} = 10,000$), asterisks represent significant additive effects as follows: * $p < .05$, ** $p < .01$, *** $p < .005$ vLPFC = lateral prefrontal cortex.

Fig. 5. Transient iEEG gamma power changes

a. Mean gamma power changes in the TL channels, averaged from 61 to 69 Hz, between 0 and 500 msec of stimulus presentation for each condition b. Time series of the mean gamma power, locked to the onset of stimulus presentation are shown per condition. Dotted lines indicate stimulus onset and offset, and thickness of shading represents 1 deviation from the mean (SEM), red vertical line marks the sustained time window. c. *All channels analysis for transient gamma power enhancement.* Group-level random-effects z-maps of CBA-aligned distributed transient gamma power on the target cortex mesh. Simple effects are demonstrated for each condition as the regions where gamma power significantly increased relative to baseline ($p = .01$, one tailed). Emotional additive effect is indicated by the contrast [emotional combined > film] ($p = .05$, one tailed). Stars represent significant simple effects (i.e., change in relation to the null distribution, $N_{\text{rand}} = 10,000$), asterisks represent significant additive effects as follows: * $p < .05$, ** $p < .01$, *** $p < .005$; TL = temporal-limbic. Grey coloring of asterisk indicate effect that was not corrected for multiple comparisons.

Fig. 6. *Single subjects transient gamma power changes in depth iEEG recordings* depicted for patient 14 (a.) and 15 (b.) **Left Panel.** Coronal and axial MRI images showing the anatomical localization of selected iEEG depth electrodes. Yellow circles mark the channels where enhanced activation relative to baseline was found, as well as significant difference across conditions ($p < .05$, FDR corrected). **Right Panel.** Time-frequency plots of power changes obtained from the extreme medial contact within a. the right amygdala (patient 14); b. left amygdala (patient 15). Plots are time locked to the onset of stimuli, and colors represent strength of change in frequency power relative to a pre-stimulus baseline ($-5000-0$ msec). The contour indicates statistical significance relative to the null distribution ($N_{\text{rand}} = 10,000$, $p < .005$, FDR corrected). The mean transient gamma power changes (averaged across trials from 61 to 69 Hz, between 0 and 500 msec of stimulus presentation) and the time series of

the mean gamma power, locked to the onset of stimulus presentation, are additionally depicted per condition in the lower panel. Dotted lines indicate stimulus onset and offset, and thickness of shading represents 1 deviation from the mean (SEM), the red vertical line marks the sustained time window. Stars represent significant simple effects (i.e., changes in relation to the null distribution, $N_{\text{rand}} = 10,000$), asterisks represent significant additive effects as follows: $*p < .05$, $**p < .01$, $***p < .005$, $*p = .06$.

Fig. 7. Phase Amplitude Coupling (PAC) in TL and vLPFC channels

The z-scored group-averaged PAC indices for the (a.) TL and (b.) vLPFC channels as a function of analytic amplitude (center frequency 41–69 Hz), and analytic phase (center frequency 2–23 Hz) are depicted for each of the stimulation conditions. Larger values indicate stronger cross frequency coupling; The mean band limited PAC, as assessed between delta (2–3 Hz), theta (4–8 Hz), alpha (9–13 Hz) or beta (14–23 Hz) phase, and gamma (41–69 Hz) power during the entire epoch of stimulus presentation is depicted per condition in TL channels (c.) and collapsed across conditions in vLPFC channels (d.). The mean delta-phase-locked gamma power across TL channels (e.) and the mean beta-phase-locked gamma power across vLPFC channels (f.) are depicted for the emotional combined condition. Upper row shows the average normalized power modulation that is time-locked to delta or beta trough, respectively. The lower row indicates the time-locked averaged delta or beta trough of the raw iEEG data. Asterisks represent significant effects as follows: * $p < .05$, ** $p < .01$.

Table 1a

Patients information and recording details. Subdural iEEG recordings (ECoG).

Patient	Age	Gender	Handedness	#Chan. general	Chan. location (hemisphere)	Distribution of channel location per lobe (%)				# Chan. In analysis	# session used	fMRI scan	Seizure onset	Resection	MRI evidence for lesion	General cognitive functioning
						T	Fr	O	P							
01	23	M	R	62	R	40%	0%	47%	13%	29	1	V	R OP	R OP	–	“Average”
02	35	M	R	32	L	50%	41%	0%	9%	7	2	V	L Fr,T	–	L T	“Average”
03	25	F	R	47	R + L	26%	34%	23%	17%	–	–	V	Diffusive;	–	R PTO	“Borderline”
04	18	F	L	74	R	54%	11%	20%	15%	45	2	V	R OP	R OP	R T, L med. T	“Average”
05	38	M	R	48	R + L	75%	17%	0%	8%	–	–	V	Diffusive; R Fr. T	–	–	“Low-average”
06	39	F	R	44	R	70%	14%	0%	16%	27	2	V	R T	R T	–	“Average”
07	27	F	R	56	R + L	66%	9%	21%	4%	38	2	V	R T	–	–	“Average”
08	35	F	L	47	R + L	13%	79%	0%	9%	34	1	V	L mes.Fr	L mes.Fr	–	“Average”
09	33	F	R	60	R + L	55%	20%	20%	5%	43	1	V	R med. T	R med. T	R MTS	“High-average”
09b ^a	“	“	“	53	R	26%	53%	0%	6%	38	2	“	“	“	“	“
10	36	M	R	68	R	56%	10%	9%	25%	44	2	V	R Fr,T	–	–	“Average”
11	26	M	R	56	R + L	71%	16%	5%	7%	18	2	–	Diffusive; R + LT	–	–	“Low-average”
12	44	M	R	48	R + L	65%	12%	4%	19%	38	2	–	RTP	–	–	“Average”
13	37	F	R	54	R	61%	13%	0%	26%	–	–	–	R TPO	R TPO	R O	“High-average”
Average	32			53.5		52%	24%	11%	13%	32.8						
S.E.M	2.08			2.83		.05	.06	.04	.02	3.56						
Total		6M; 7F		749		392	162	90	97	8						

^a09b → 2nd electrodes' implantation procedure of patient 09.

Table 1b

Patients information and recording details. Depth iEEG recordings (intracerebral).

Patient	Age	Gender	Handedness	#Chan. General	Chan. Location (hemisphere)	Channel locations				# chan. In analysis	# session used	fMRI scan	Seizure onset	Resection	MRI evidence for lesion	General cognitive functioning
						Amygdala	Hip.	PHG	SMA	OFC						
14	32	M	R	42	R + L	V	V	V	-	-	2	-	R Hip.	-	R Mes.T	“Low-average”
15	29	F	R	56	R + L	V	V	-	V	V	1	-	L(+R)	-	-	“Low-average”
SMA																

M = male, **F** = female, **R** = Right; **L** = left; **T**- temporal; **Fr** = frontal, **O** = occipital, **P** = parietal, **MTS** = mesial temporal sclerosis, **med.** = medial, **mes.** = mesial; **Hip.** = Hippocampus, **SMA** = Supplementary Motor Area, **OFC** = Orbital Frontal Cortex, **PHG** = ParaHippocampal Gyrus, **chan.** = channels.