

FUNCTIONAL NEUROIMAGING OF EMOTIONAL PERCEPTION: STABILITY, TIMING,
AND DIRECTIONAL CONNECTIVITY

by

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(Under the Direction of DEAN SABATINELLI)

ABSTRACT

The brain's ventral visual processing network includes the fusiform gyrus (FG) and lateral occipital cortex (LOC) that, in concert with the amygdala, show enhanced activation during the perception of emotionally arousing scenes. The orbitofrontal cortex shares dense interconnections with amygdala, and has been implicated in naturalistic scene processing in humans, but our understanding of the contributions of this region to emotional perception is poorly defined. Here we present rapid functional imaging data acquired from these ventral brain regions as a group of participants viewed pleasant, neutral, and unpleasant scenes over multiple scanning sessions across three days. Amygdala, FG, and LOC all exhibited enhanced activation in response to emotionally arousing, compared to neutral scenes, while OFC activity showed a marginally significant enhancement by scene arousal. Additionally, the amygdala and FG discriminated arousing scenes prior to such discrimination in LOC, consistent with past work. We also identified bidirectional directional connectivity between the amygdala and both OFC and FG. We found no significant influence of scanning session on the amplitude of affective neural enhancement by essentially novel scenes, thus, activity of the brain regions examined here appears to be resistant to emotional scene habituation. In sum, these data support a perspective in

which amygdala and rostral visual regions initiate the discrimination of emotional scenes. This process involves contributions from the orbitofrontal and lateral occipital cortex, and shows a pattern of persistent reactivity that may reflect an evolved adaptation toward sensitivity to survival relevant cues.

INDEX WORDS: Emotional perception, neural timing, directional connectivity, habituation, fMRI

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CHAPTER 1

INTRODUCTION

Exposure to emotionally arousing cues in the environment often results in enhanced neural and behavioral processing. For instance, highly arousing unconditioned stimuli promote learning via classical conditioning (Davis, 1992; McAllister & McAllister, 1962), enhance memory (Bradley et al., 1992; Phelps, 2004), and increase the speed of attentional orienting (Bar-Haim et al., 2007; Mohanty et al., 2008; Öhman et al., 2001).

The neural orchestration of this enhanced processing is poorly understood, especially regarding the timing and directional connectivity across brain structures. Following a general review of the neural basis of emotional scene perception, we will describe a human neuroimaging experiment with which our understanding of emotional perception may be refined. Rapid functional imaging data was collected in ten humans as they each viewed emotional and neutral natural scenes over 18 individual sessions, each including 60 scenes. This extended data collection paradigm will allow us to outline the extent to which emotional cues modulate the amplitude, timing, and directional connectivity of activity in ventral visual, amygdalar, and ventral frontal cortex. Moreover, the extended nature of the data collection scheme will enable an examination of stimulus and experimental habituation across sessions.

Emotional perception

Visual processing cortically originates in striate occipital cortex and spreads anteriorly along dorsal and ventral cortical paths (Grill-Spector & Malach, 2004), while also feeding back

posteriorly in a recurrent fashion (de Graaf et al., 2011; Hegde & Felleman, 2007; Lamme & Roelfsema, 2000). In the occipital cortex, pleasant and unpleasant arousing images elicit enhanced blood oxygenation level dependent (BOLD) activation relative to neutral or weakly arousing images, with no difference in emotional modulation between colored and grayscale images (Bradley et al., 2003; Lang et al., 1998a). Information from occipital cortex feeds into the inferior temporal (IT) cortex, which is also emotionally modulated. The fusiform gyrus (FG), residing within IT, seems particularly involved in the processing of emotional faces (Breiter et al., 1996; Sprengelmeyer et al., 1998) and scenes (Bradley et al., 2003; Lang et al., 1998a; Norris et al., 2004), irrespective of valence, and is sensitive to motivationally relevant hunger states (LaBar et al., 2001). The visual stream proceeds from FG to amygdala, which plays a critical role in processing emotionally evocative stimuli and projects to multiple brain regions, modulating neural and peripheral physiological responses to emotional stimuli (Everitt et al., 2003; Zald, 2003). The amygdala also appears to be crucially involved in fear learning by forming connections with thalamus and hippocampus for sensory and contextual conditioning, respectively (Davis, 1992; LeDoux, 1993). Using intracranial recordings, researchers have demonstrated emotional discrimination of visual stimuli in the amygdalae of monkeys approximately 150ms after onset (Kuraoka & Nakamura, 2007; Nakamura et al., 1992). Research using intracranial recording in human clinical patients has also found amygdala activation in response to fearful faces and unpleasant scenes approximately 150ms after stimulus onset (Krolak-Salmon et al., 2004; Oya et al., 2002; Pourtois et al., 2010), supporting a rapid yet cortically mediated affective assessment of the visual environment.

Emotion modulation in occipital and inferotemporal regions appears to be facilitated, at least in part, through recurrent feedback from the amygdala, potentially via the inferior

longitudinal fasciculus (Amaral et al., 2003; Amaral & Price, 1984; Catani et al., 2003; Spiegler & Mishkin, 1981). Support for this re-entrant model in humans is found from parallel amygdala and FG blood oxygen level dependent (BOLD) modulation by arousing scenes (Morris et al., 1998; Sabatinelli et al., 2005; Vuilleumier et al., 2004). Per the re-entrant perspective, scene processing undergoes an initial feed forward sweep through the ventral pathway where highly processed visual information reaches the amygdala. The amygdala, in concert with fusiform gyrus, may then discriminate the motivational relevance of the image and feed back to occipital visual structures along the ventral visual pathway. In line with this, Sabatinelli and colleagues (2009) investigated the timing of affectively modulated BOLD signal response in the amygdala, FG, secondary occipital cortex, and primary visual cortex using rapidly sampled fMRI. Results indicated that the amygdala and FG differentiated emotional from non-emotional scenes earlier than secondary occipital cortex, while primary visual areas exhibited no differentiation. These data are consistent with a reentrant model of emotional discrimination.

The amygdala also maintains structural and functional connections to emotionally sensitive frontal cortical structures such as the orbitofrontal cortex (OFC; Cavada et al., 2000; Ghashghaei et al., 2007). The OFC incorporates affective information to assess appetitive or aversive outcomes across all sensory modalities (Cardinal et al., 2002b; Rolls, 2004). Since this region may also allow for environmental context and memory to facilitate the perceptual categorization of visual scenes (Ahlfors et al., 2015; Bar et al., 2006; Trapp & Bar, 2015), together with its role in processing emotional outcomes (Cardinal et al., 2002a), the amygdala and OFC may therefore constitute a network instrumental for the general evaluation of emotional stimuli. Thus, together with the amygdala, caudal occipito-temporal structures and rostral

prefrontal regions form two major ventral cortical networks involved in discriminating the potential motivational value of visual scenes.

BOLD signal timing and connectivity

The relative timing of BOLD signal modulation by classes of naturalistic scenes can be used to address research questions regarding the mechanisms of emotional perception. The BOLD signal is a hemodynamic response that is delayed and smoothed relative to neuronal activity, and occurs on the order of milliseconds. However, Aguirre and colleagues (1998), among others, have demonstrated the consistency of the hemodynamic response function (HRF) within and across subjects. These authors recorded BOLD signal in the central sulcus among individuals performing a reaction time task, and while the profile of the HRF varied between participants, it remained consistent within participants across multiple scanning sessions. The shape was most stable within multiple sessions within a single day, with decreased reliability across day. There is also evidence that the HRF onset remains consistent relative to the timing of stimulus onset (Menon et al., 1998). This was demonstrated by measuring BOLD signal in primary visual cortex (V1) while visual stimuli were presented to each visual hemifield, with a variable offset between them ranging from 125ms to 1000ms. Although delayed by the HRF, the peak of BOLD signal change demonstrated a consistent offset between left and right hemisphere that matched the stimulus offset very strongly ($r=.98$). These parametric studies provide support for the interpretation of BOLD signal timing within structure across stimulus conditions. For example, the time at which BOLD signal from amygdala and ventral visual structures differentiates emotional from neutral stimuli can be reliably resolved (Sabatinelli et al., 2014; Sabatinelli et al., 2009). Thus, information gained from establishing the temporal order of neural

discrimination can be used to test hypothetical directional influences within implicated structures involved in emotional perception.

The directional relationships among nodes within the affective network may also be tested using techniques such as Granger Causality Analysis (GCA; Barnett & Seth, 2014; Seth, 2005; Seth, 2011). GCA is an analytical technique that tests if signal variation from one region (e.g., amygdala) at time point A can enhance the prediction of signal variation in a second region (e.g., fusiform gyrus) at time point B, over and above that which can be predicted from the past of B (and any additional nodes in the network) alone. If two regions are directionally connected, then the activation of one area will predict, to a quantifiable degree, activation in the second area later in time, resulting in a potentiated GC measure. Conversely, two unrelated regions will yield a diminished GC measure. Since Granger Causality is not based on multiple a priori models it can be applied to a wide range of data scales, from millisecond-based electrophysiological to year-based economic data. This differs from Dynamic Causal Modeling (DCM) which incorporates prior assumptions and vascular models to determine the simplest circuit that best represents the sampled data (Friston et al., 2003). Therefore, DCM is more specifically tailored to BOLD data, though it is perhaps limited to the testing of specific research questions while GC may be more appropriate for exploratory analysis (for comparisons, see Friston et al., 2013).

To test directional prediction, GCA implements autoregressive models that depend on stationary data, such that the variance and mean of each time series remains constant over time. If this assumption is violated, the data may be divided into shorter windows to improve the likelihood of stationarity, although this will sacrifice GCA accuracy. Procedures such as linear de-trending may also help resolve non-stationarity. Granger analysis also tests multiple time lags to determine the best predictive model. For example, the activity in region A may predict

activation in region B two seconds into the future, but not five seconds into the future. Criteria, such as the Bayes Information Criterion (BIC) and Akaike Information Criterion (AIC), are thus employed to select the best model and to prevent overfitting by imposing a penalty for each added parameter (Akaike, 1974; Schwarz, 1978).

In some respects, GCA is ill-suited for fMRI analysis. First, the BOLD signal may have poor signal to noise ratio, especially around regions that experience susceptibility artifacts (Glover & Thomason, 2004), which can hinder the detection of predictive causality (Nalatore et al., 2007). Second, the typical sampling rate of the BOLD signal is slow compared to real time recording methodologies, such as EEG, which results in a considerable loss of data that contribute to GCA predictions (Deshpande et al., 2010; Witt & Meyerand, 2009). Third, the onset of the HRF can vary across regions and, since GCA relies on temporal precedence, may lead to spurious causality results (Aguirre et al., 1998; David et al., 2008; Deshpande et al., 2010). However, when sampled adequately, GCA has been shown to effectively incorporate BOLD activation in fMRI analysis to draw accurate directional results (Bressler & Seth, 2011; Roebroek et al., 2005; Seth et al., 2013; Wen et al., 2012). In one particular study, Wen and colleagues (2013) artificially modeled two neural signals and then deconvolved them to create two “BOLD” responses, manipulating sampling rate (TR), background noise (SNR), and onset variability, in an effort to investigate the relationship between GC values derived from hemodynamic and neural data. The authors found that, with an SNR of 5 and TR of 2s, fMRI and neural GC values were linearly correlated ($r=.95$). Furthermore, across 100 experiments, 50% of true bidirectional connections were identified with only 0.5% of false connections endorsed ($p<.01$). True GC detection rate (not correlation) also remained stable at approximately 70% when TR was at, or below, one second. With longer TRs, starting at two seconds, the true

detection rate progressively diminished. Additionally, GC detection was maintained, between 50% and 70%, as the SNR was reduced to 2.5. Onset variability appeared to be the most potent factor influencing GC detection, such that true detection dropped to 27.5% with a latency difference of 0.4s. However, the false detection rate was also low, resulting in a 77% chance to detect a true connection, which remained stable up to a one second latency differential.

Therefore, this study suggests that the major problems involved in using GCA with fMRI data may be reasonably overcome with high SNR and a fast sampling rate. While GC detectability remains challenging diminished among regions with significant HRF onset variability, the GC influences that are identified are likely accurate. The HRF latency issue may also be ameliorated with mathematical correction procedures (Chang et al., 2008). The interpretation of GC results with fMRI data may further be strengthened with reasonable a priori hypotheses and by comparing GC value changes between experimental groups or correlating them with other neural metrics. Thus, the use of GCA on fMRI data, along with timing discrimination discussed above, can inform the directional nature of neural processing among regions involved in affective discrimination, such as amygdala, fusiform gyrus, intraparietal sulcus, and frontal eye fields (Sabatinelli et al., 2014).

Repetition

It is well established that repetition of the same stimulus can result in neural habituation throughout multiple brain regions (Grill-Spector et al., 1999; Naccache & Dehaene, 2001; Sawamura et al., 2006). While our focus is on habituation of the BOLD signal, the specific neural mechanisms that underlie this process are elusive, though several potential models describing these mechanisms, including Fatigue and Sharpening, have been hypothesized (Gotts

et al., 2012; Grill-Spector et al., 2006). Per the Fatigue model, repetition results in firing rate attenuation of the most stimulus selective neurons, which may increase synchrony among neurons. This increased synchrony allows for efficient neural processing at a reduced metabolic cost. Alternatively, in line with the Sharpening model, only the most stimulus selective neurons remain active while the least selective neurons are attenuated, resulting in a more efficient response of the neural group. Regardless of mechanism, habituation has been revealed in seminal studies using single electrode recordings of neurons in the inferotemporal visual cortex of monkeys (Brown et al., 1987; Miller & Desimone, 1994). Not only can a contiguous repeated stimulus lower the firing rate of a given neuron, but activity of IT neurons may also be reduced regardless of intervening novel items between repetitions (Desimone, 1996; Miller et al., 1991). Over time IT neurons will also habituate as initially novel stimuli become more familiar to the monkey (Li et al., 1993). Furthermore, Lueschow and colleagues (1994) were able to manipulate the spatial qualities of repeated stimuli to identify neuronal selectivity in the IT, such that when the size or location of a repeated object was changed, the same level of habituation occurred as if its size or location were unchanged. This allowed the authors to infer that these IT cells were part of a spatially invariant circuit selective for the stimulus object in a holistic fashion. Habituation paradigms have also been employed to explore brain mechanisms in humans, using noninvasive neuroimaging.

Neuronal habituation can be exploited by researchers as a useful fMRI technique to identify stimulus selective neuronal activity. To leverage the adaptation effect, researchers present a stimulus repeatedly to reduce BOLD signal activation and then alter specific properties of the repeated stimulus. If the BOLD signal is released from suppression, one may interpret that area of the brain to be involved in processing the manipulated stimulus characteristics (Grill-

Spector et al., 2006; Grill-Spector & Malach, 2001). Habituation is a beneficial tool in functional imaging because it can provide information about subpopulations of voxels in the brain, such that the level of habituation in individual voxels may be experimentally influenced and recorded. Researchers have used this method to identify brain regions implicated in facial recognition and familiarity (Henson et al., 2000; Jiang et al., 2000), numerical encoding (Naccache & Dehaene, 2001), memory encoding (Stern et al., 1996), and semantic encoding (Demb et al., 1995), in addition to subdividing distinct object processing regions in the visual cortex (Grill-Spector et al., 1999). Neural habituation may also be applied to studies examining emotional processing.

Affective habituation

Since highly arousing affective stimuli play an important role in survival, several researchers have examined if repetition of these stimuli differentially modulate neuronal habituation. Several visual studies involving repetition of either affective faces or natural scenes have concluded that there are no differential habituation effects across emotional or neutral stimuli in amygdala (Bradley et al., 2015; Denny et al., 2014; Fischer et al., 2003; Johnstone et al., 2005; Luan Phan et al., 2003) or FG (Bradley et al., 2015; Breiter et al., 1996; Fischer et al., 2003). However, Breiter and colleagues (1996) found amygdala habituation in response to fearful and neutral, but not happy faces. Other contradictory evidence illustrates amygdala habituation to sad and neutral, but not fearful faces (Swartz et al., 2013). In the occipital cortex, emotional stimuli may habituate to a lesser extent, or rate, than neutral stimuli (Bradley et al., 2015; Codispoti et al., 2007; Gerlicher et al., 2014; Liu et al., 2012), although inconsistent results exist for this finding as well. For instance, Schupp and colleagues (2006) illustrated that arousal discrimination was maintained over time, as indexed by the early posterior negativity (EPN)

averaged across posterior occipital electrodes. Thus, it is unclear if an extended series of emotional cue presentations results in differential neural habituation without consistent experimental paradigms to compare.

There is little support for differences in habituation based on the elapsed time between stimulus presentations within amygdala and FG. However, it appears that the OFC and occipital cortex may habituate to affective scenes presented seconds apart, but recover after several minutes without stimulation (Bradley et al., 2015; Codispoti et al., 2007). There is also limited evidence for differences in habituation to identical stimuli, compared to unique emotionally evocative stimuli, in the amygdala or OFC. In the FG some researchers have observed habituation to identical, but not to novel emotional faces (Kadosh et al., 2010; Winston et al., 2004). Another study suggests an emotional arousal effect in the occipital cortex wherein identical neutral images result in greater habituation, compared to novel images, while identical emotional images do not result in differential habituation (Gerlicher et al., 2014).

Specific categories of emotional scenes (e.g., erotica, attacking animals) may uniquely modulate habituation. Unpleasant stimuli, such as images depicting fearful and abused people, appear to result in less BOLD signal reduction in the amygdala than pleasant stimuli, such as romantic people and images depicting sports (Hazlett et al., 2012; Swartz et al., 2013), though the magnitude of emotional arousal is often weakly balanced in these designs. These differential habituation effects may be specific to the sensory modality in which the cues are presented, because habituation of a specific affective category can differ depending on if the stimuli were heard (Wiethoff et al., 2009), viewed as facial expressions (Swartz et al., 2013), or viewed as natural scenes (Hazlett et al., 2012). Additionally, it is unclear if the occipital cortex differentially habituates to stimuli based on the semantic category of the scene. Carretié and

colleagues (2003) used EEG to illustrate that unpleasant scenes result in reduced visual cortical activation, compared to neutral and pleasant stimuli, while Codispoti and colleagues (2007) show that pleasant images result in diminished visual cortical activation, compared to neutral and unpleasant stimuli. Conversely, EEG results indicating no categorical differences (Gerlicher et al., 2014), or even any visual cortical habituation at all (Schupp et al., 2006), have been reported. Thus, there is no clear consensus as to the effects of repeated scenes within semantic categories on visual system activity.

Affective information presented in habituation paradigms also appear to modulate the connectivity between the amygdala and other brain regions. Recent studies indicate that repeated unpleasant stimuli result in increased directional connectivity between amygdala and vmPFC (Swartz et al., 2013). The positive correlation between these two measures suggests that at least these two pathways may be involved in the process of reducing neural activity in response to repeated emotional stimuli. Thus, few studies have attempted to define the long-term stability of functional relationships within emotional networks of the brain.

Aims and hypotheses

The results of affective habituation studies are often contradictory based on the variable nature of the task paradigms and the specific research questions addressed. When reviewing these studies at least two major questions arise: (1) Do affectively arousing stimuli cause differential neuronal habituation? (2) Do specific emotional semantic categories (e.g. animal threat, happy children, etc.) differentially alter neuronal habituation? Several brain regions merit investigation, such as those within the ventral visual pathway that rapidly discriminate emotional stimuli. Since this pathway impacts much of the visual system, we are particularly interested in

the amygdala, FG, and occipital cortex, while additionally evaluating ventral brain regions previously implicated in enhanced emotional processing such as OFC (Frank et al., 2014; Frank & Sabatinelli, 2014; Sabatinelli et al., 2015). Using rapid fMRI, we may investigate components of this ventral visual system.

By using rapid sampling (2Hz; 500ms) fMRI the relative timing of emotional discrimination may be more effectively analyzed (Sabatinelli et al., 2009), which is typically only possible through high temporal resolution techniques such as EEG (Liu et al., 2012). To achieve this temporal resolution, we must limit sampling to ventral brain areas. This also allows us the opportunity to replicate previous findings regarding affective discrimination timing in amygdala, FG, LOC, and calcarine fissure (Frank & Sabatinelli, 2014; Sabatinelli et al., 2015), while providing new information about timing in the OFC. A relatively high sampling rate will also permit more robust directional connectivity analyses across structures (Sabatinelli et al., 2014; Sabatinelli et al., 2015). Finally, the use of 720 picture presentations of three picture categories across three days of scanning with 10 participants will provide more within-subject statistical power than is available in typical habituation paradigms. Unlike previous studies examining the repetition of identical pictures, here we focus on semantic categorical effects over time, both within and between scanning days. This allows us to depict the temporal dynamics of emotional perception of classes of natural scenes (e.g., erotica, threat) as opposed to responses to specific scenes. However, this does preclude us from identifying habituation effects resulting from specific stimulus exemplars, as is typically done in studies focused on habituation.

In this study, we will track the activity of the lateral OFC, amygdala, FG, LOC, and calcarine fissure (Fig. 1). These structures of interest will fall within a slab of tissue (10 slices) that can be sampled at 2 Hz. Based on prior imaging and EEG work, we hypothesize that the

amygdala and FG activity will reflect no differential habituation between repeated emotional and neutral stimuli; both stimulus categories should cause the BOLD signal to diminish at equal rates, if they habituate at all. However, in the occipital cortex emotional stimuli may cause activity to habituate less than neutral stimuli. We also expect that amygdala and FG will discriminate arousing images earlier than occipital regions, as has been shown in past studies. We suspect that the OFC will contribute to the early discrimination of emotional scenes, as suggested in MEG studies (Luo et al., 2007; Rudrauf et al., 2008). Finally, we predict bidirectional connectivity between the amygdala and the OFC, and between the amygdala and FG.

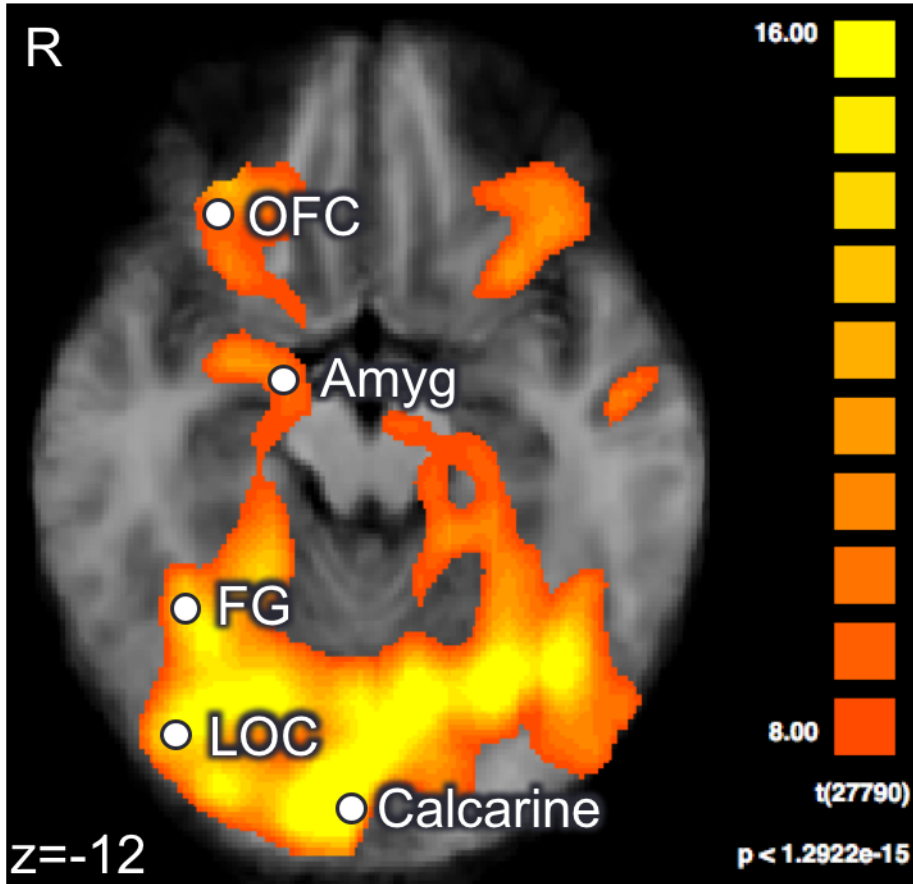


Figure 1: Regions of interest. Picture driven BOLD activation GLM from a representative subject overlaid onto a Talairach transformed anatomical image. Labeled are the locations of orbitofrontal cortex (OFC), amygdala, fusiform gyrus (FG), lateral occipital cortex (LOC), and calcarine fissure. Image is in radiological view with the right hemisphere presented on the left side.

CHAPTER 2

METHODS

Participants and procedure

A total of 10 healthy subjects (5 female, 5 male, mean age 25.8 ± 5.7 SD, 3 African-American, 3 Asian, and 4 White Non-Hispanic) participated in our study. However, due to missing data and poor data quality, one participant was removed from analysis, yielding a total of 9 individuals (5f). All subjects were right handed, had normal or corrected-to-normal vision, and were in good health with no past neurological or psychiatric history. All participants gave informed consent according to a protocol approved by the Institutional Review Board of the National Institute of Mental Health. These individuals were recruited from a database of volunteers that initially responded to flyers and advertisements placed around the metropolitan Washington, DC area, and were paid \$100 per hour (maximum of 2 hours) per day, totaling three separate days of scanning. The participants consisted of post-baccalaureate students or research assistants at NIH who had previously participated in other experiments. On average, each participant was scanned every nine days. One day constituted 4-8 scanning runs consisting of 60 pictures, each with an average of 360 picture presentations per day. Once situated in the scanner, participants viewed pictures while focusing on a centrally depicted crosshair. On 10% of the trials the crosshair changed color, at which time participants pressed a button acknowledging the change (Fig. 2). This task was employed to ensure central picture fixation and avoid excessive eye movements, as this can result in increased activation in canonical visual regions, such as occipital cortex (Petit & Haxby, 1999). It is also possible that OFC may be influenced due its,

potentially indirect, role in action preparation (Rudebeck & Murray, 2014). Instructing participants to maintain focus on a central fixation cross confirmed that any potential arousal effects would not be a result of increased ocular scanning of emotional scenes, although this issue may be overstated (Lang et al., 1998b), while also equating the level of spectral input across participants. All response trials were excluded from the analysis to avoid action confounds.

Stimuli and Procedure

The picture set consisted of 720 scenes presented in color, drawn from the International Affective Picture System (IAPS; Lang et al., 2008) and pictures from the internet meeting the same basic features of the IAPS. A subset of 94% of the scenes fell into homogenous categories including erotica, romantic couples, complex neutral people, neutral individuals (neutral picture complexity was determined by differentiating groups of people from single individuals), human threat, and graphic bodily injury (mutilations). An additional 6% of scenes depicted contents outside these categories, and were excluded from the analysis. This resulted in a final picture set consisting of 681 images that were presented 1-5 times across all sessions. Each scan run for each day consisted of a random sample of the entire picture set, resulting in unique picture orders and identities for every scan run in every participant. Scans began with a single scrambled image presented for 2s followed by a series of IAPS images presented for 2s every 10-12s. Each run lasted approximately 13min. The BOLD signal change was measured as peak signal activation from 4-8s relative to a 500ms pre-stimulus baseline.

Image acquisition, processing, and analysis

On each day, once participants were comfortable in GE MR 750 3T scanner, a T1 structural image was collected consisting of 124 slices, a 256x256 matrix, with 1.2x9.4x.94mm voxels. This was followed by 4-8, 1385 volume, functional scans. Each functional scan was rapidly sampled (500ms TR), comprising 10 oblique axial slices oriented to cover ventral brain regions, including the calcarine fissure, inferior temporal cortex, amygdala, and orbitofrontal cortex (72x72 T2* weighted gradient echo EPI, 3x3x4.5mm voxels, 1mm gap, 34ms TE, 60° FA). Slices were centered over the amygdala and then manually tilted to equalize coverage of the anterior and posterior poles.

Each participant's functional time series was spatially smoothed across two voxels (6mm FWHM) and linearly de-trended using BrainVoyager QX 2.8 (Brain Innovation; brainvoyager.com). In post-processing, trials with residual head motion were removed manually by identifying large (greater than 4 times the background variation) and brief spikes in the time series that are indicative of motion artifact. These spikes were located by examining the average signal intensity, per subject, across most the voxels in a slice (rectangular region larger than half the total voxels within the brain). This resulted in the removal of fewer than 1.2% of total trials, and no more than 3.7% of trials from any subject.

All structural and functional data were spatially standardized to Talairach coordinate space and entered into a random-effects ANOVA, with scene contents (erotica, romance, neutral groups of people, neutral individuals, threat, and mutilations) entered as predictors, convolved with a standard 2-gamma hemodynamic response function. Single subject ANOVAs were then performed to identify BOLD signal associated with all picture presentations. Using individual data with an FDR threshold of $p < 0.05$, 10mm³ samples of BOLD signal were bilaterally

sampled from a priori regions of interest (ROI), including lateral orbitofrontal cortex (OFC), amygdala, fusiform gyrus (FG), lateral occipital cortex (LOC), and calcarine fissure. Therefore, each ROI was represented by a sampling region of the same size and shape. The locations of these regions were guided by picture-driven group ANOVA data, and by previous research in emotional picture perception (Frank & Sabatinelli, 2014; Sabatinelli et al., 2011; Sabatinelli et al., 2014; Sabatinelli et al., 2013). Specifically, for each subject we started with coordinates from a previously published Talairach region (e.g. amygdala) and sampled from the area with the greatest picture-driven signal within 5mm of the initial landmark. We additionally checked to confirm that each region corresponded with labels in the Talairach Daemon atlas (Lancaster et al., 2000).

To assess overall emotion and hemisphere effects, we sampled from functional maps consisting of BOLD signal averaged across all days for each participant. To assess repetition effects, we sampled from functional maps consisting of BOLD signal acquired from each day (3 total) for each participant. While each participant did not always contribute statistically reliable activation in every region for every scanning run, each subject retained at least 94% of all BOLD signal measurements and each structure retained at least 84% of all BOLD signal measurements.

Granger causality analysis

We estimated the directional contributions among our regions of interest using the Granger Causal Connectivity Analysis MATLAB toolbox (Barnett & Seth, 2014). Here, we ensured our data were free of autocorrelations and were linear de-trended, thus representing a stable state, as a necessary assumption of the GC analysis. We limited our GC analysis to amygdala, FG, and OFC, using the minimum model order (temporal lag) of two points (1

second), corrected with an FDR of .05, across all scan runs. These regions were chosen based on our previous work investigating amygdala connectivity with ventral visual and prefrontal emotionally modulated regions, and their roles in affectively modulated scene perception (Sabatinelli et al., 2014; Sabatinelli et al., 2015).

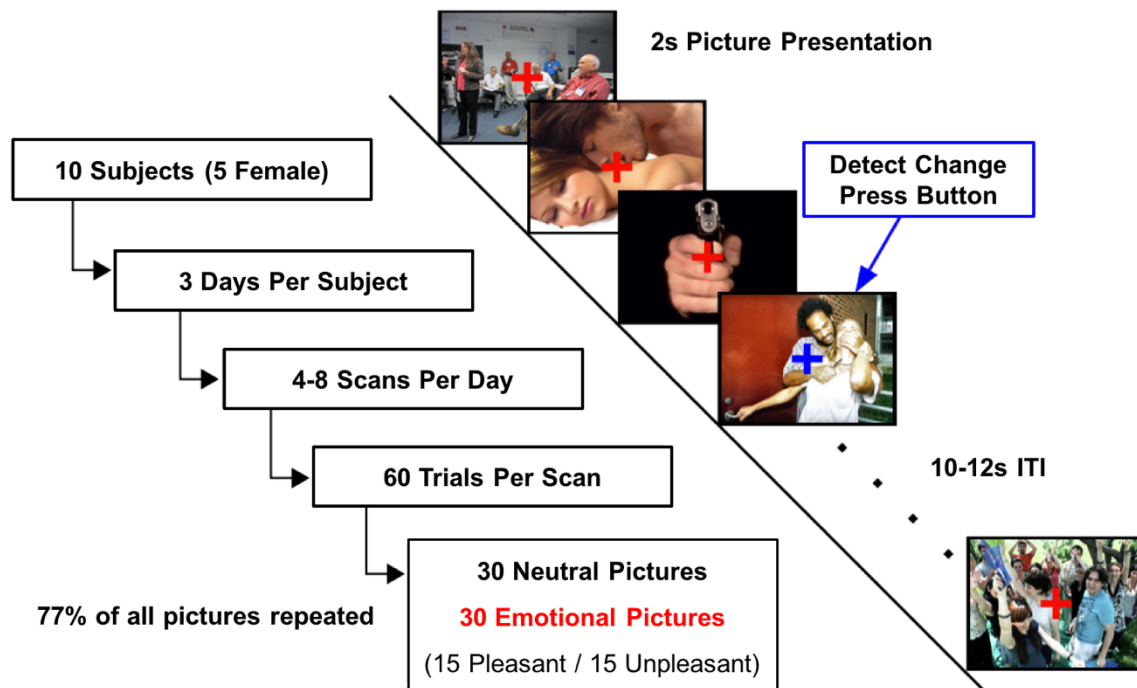


Figure 2: Task paradigm. Individuals were shown a series of emotional pleasant, neutral, and unpleasant scenes in random order for 2s, every 10-12s. To maintain attention to the center of each picture, each participant engaged in an attention task in which they pressed a button any time the central fixation cross changed color. A total of 10 participants were scanned 4-8 times per day for 3 days. A total of 77% of the pictures were repeated.

CHAPTER 3

RESULTS

Stimulus Ratings

Scene pleasantness ratings differed reliably across valence ($F_{(2,138)}=314.1, p<.01$), as indicated by 48 independent reviewers (21 male, 26 female, 1 undeclared), with pleasant scenes (erotic couples, romance scenes) rated as more pleasant than neutral (complex and simple people) scenes ($t_{(138)}=5.9, p<.01$), that were in turn rated as more pleasant than unpleasant (threat and mutilation) scenes ($t_{(138)}=18.1, p<.01$). Arousal ratings were also significantly higher for pleasant and unpleasant compared to neutral scenes ($F_{(2,138)}=103.4, p<.01$), with unpleasant rated as more arousing than pleasant scenes ($t_{(138)}=3.1, p<.01$), and pleasant rated as more arousing than neutral scenes ($t_{(138)}=10.6, p<.01$). Each reviewer rated a random 60 picture subset of the entire collection. Participants also accurately identified the fixation cross change 96% of the time, with no single participant missing more than 5% of the changes. No interaction of emotional modulation and reaction time was found.

Functional Imaging Amplitude, Timing, and Habituation

Table 1 presents ROI coordinates and results from a multivariate analysis of variance (MANOVA) for each ROI collapsed across days. The amygdala, FG, and LOC exhibited enhanced activation for both pleasant and unpleasant scenes compared to neutral scenes (Fig. 3). This pattern of activation was marginally significant in OFC ($p=.08$). The calcarine fissure also exhibited semantic modulation, but in the opposite direction, with heightened processing of

neutral over unpleasant scenes. We used non-parametric permutation tests (Maris, 2004; Maris & Oostenveld, 2007) to determine the time point at which BOLD signal discrimination of semantic scene content occurred, represented by arrows on the x-axis illustrated in Figure 3. This analysis revealed emotional discrimination in amygdala, FG, and calcarine fissure at 3s, LOC at 4s, and OFC at 6s post-stimulus onset. No effect of hemisphere was found (Table 2; Fig. 4), however there did exist a valence by hemisphere interaction in the LOC, where reliable emotional modulation occurred only in the left hemisphere (Table 2; Fig. 4).

We conducted a repeated measures MANOVA to investigate semantic habituation of pleasant, neutral, and unpleasant scenes across the three days of scanning. The amygdala, LOC, and OFC showed enhanced emotional modulation across days, in addition to enhancement by neutral scenes in calcarine fissure, while no BOLD signal change across days, nor a day by scene category interaction, was found (Table 3; Fig. 5). To determine the consistency of affective modulation within participants across days, we conducted a correlation analysis comparing days 1 to 2, 2 to 3, and 1 to 3 with everyone contributing 3 BOLD signal measurements (pleasant, neutral, and unpleasant) to each day (totaling 27 points per correlation). This analysis illustrated that BOLD signal variability among participants across scanning days was highest in the OFC and lowest, on average, in the amygdala (Table 4). A second repeated measures MANOVA revealed that the amygdala, LOC, and OFC retained their enhanced emotional modulation across scan runs ($p < .05$), collapsed across day, but evoked neither repetition enhancement nor habituation. We also compared the first and second presentation of all repeated scenes, finding no difference in average BOLD signal. This result did not change when including affective content categories into the analysis.

Directional Connectivity

Granger causality analysis was used to assess the strength of three directional connectivity relationships among the amygdala, OFC, and LOC, using an average of the time series across the last 8.3 minutes of the ~10-minute scene series (1001 volumes), to maximize stationarity of the estimate. The amygdala exhibited a bidirectional relationship with both OFC and FG (Fig. 6). Furthermore, each directional connection was found in most individuals tested, as listed in Table 5. As an exploratory measure, we conducted a GCA on all five ROIs across the three days. In this analysis, the amygdala exhibited a unidirectional influence on OFC, FG, and calcarine fissure. Information from the OFC also projected to calcarine fissure while the calcarine fissure maintained a directional connection to FG and LOC. We did not find projections from either the FG or LOC to any other ROI (Table 6; Fig. 7).

Table 1. Talairach coordinates and picture valence modulation by region. Analysis was based on comparisons among 4-8s peak averages. Participants viewed pleasant, unpleasant, and neutral natural scenes. Affective category scores represent average percent signal change and standard error (in parentheses). OFC: lateral Orbitofrontal Cortex, FG: Fusiform Gyrus, LOC: Lateral Occipital Cortex.

ROI	X	Y	Z	Pleasant	Neutral	Unpleasant	F	p
OFC	±30	33	-9	.24 (.03)	.18 (.02)	.23 (.03)	3.69	.08
Amygdala	±20	-3	-15	.17 (.03)	.09 (.02)	.13 (.04)	10.04	<.01
FG	±41	-50	-16	.42 (.06)	.29 (.04)	.35 (.05)	5.32	<.05
LOC	±42	-80	-10	.52 (.07)	.37 (.06)	.39 (.06)	17.38	<.01
Calcarine	4	-90	-8	.78 (.09)	.90 (.10)	.65 (.09)	9.38	<.05

Table 2. Affective modulation, hemispheric modulation, and the interactions among ROIs.

Participants viewed three picture categories while all bilateral ROIs were measured. OFC: lateral Orbitofrontal Cortex, FG: Fusiform Gyrus, LOC: Lateral Occipital Cortex.

ROI	Valence		Hemisphere		Valence x Hemisphere	
	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
OFC	3.69	.08	3.27	.11	2.41	.16
Amygdala	10.04	<.01	<.01	.97	.38	.70
FG	5.32	<.05	.34	.58	.31	.74
LOC	17.38	<.01	.73	.42	5.73	<.05

Table 3. Effect of picture valence, scanning days, and their interaction within each ROI.

Participants viewed three different picture categories on three separate days. OFC: lateral

Orbitofrontal Cortex, FG: Fusiform Gyrus, LOC: Lateral Occipital Cortex.

ROI	Valence		Days		Valence x Day	
	F	p	F	p	F	p
OFC	9.99	<.01	.78	.49	2.77	.15
Amygdala	8.83	<.05	.17	.85	1.17	.44
FG	3.22	.10	.82	.48	.18	.94
LOC	4.16	<.05	1.12	.38	2.52	.17
Calcarine	5.28	<.05	.82	.48	1.86	.26

Table 4. Consistency of BOLD signal reactivity across days. Correlations, depicted as r values,

are presented between days 1 to 2, 2 to 3, and 1 to 3. Each participant contributed 3 average

BOLD signal measures (pleasant, neutral, and unpleasant) to each region for each day, totaling

27 points per correlation (n=9). All results in bold are statistically significant at p<.05. OFC:

lateral Orbitofrontal Cortex, FG: Fusiform Gyrus, LOC: Lateral Occipital Cortex.

Region	Days 1-2 (r)	Days 2-3 (r)	Days 1-3 (r)
OFC	0.45	0.28	0.09
Amygdala	0.61	0.68	0.42
FG	0.50	0.53	0.79
LOC	0.29	0.53	0.29
Calcarine	0.53	0.68	0.52

Table 5. Directional Granger Causality measures among three ROIs. The GC value is an absolute measure of the amount of information transferred from one region to another. Also presented are the number of participants who exhibited significant GC connectivity for each pair of regions out of 9 total participants. OFC: lateral Orbitofrontal Cortex, FG: Fusiform Gyrus, LOC: Lateral Occipital Cortex.

GC direction	GC value	p	# subs connected	total # subs
Amyg → FG	0.024	<.05	7	9
FG → Amyg	0.013	<.05	5	9
Amyg → OFC	0.019	<.05	8	9
OFC → Amyg	0.011	<.05	7	9

Table 6. Directional Granger Causality measures among five ROIs. The GC value is an absolute measure of the amount of information transferred from one region to another. OFC: lateral Orbitofrontal Cortex, FG: Fusiform Gyrus, LOC: Lateral Occipital Cortex.

GC connection	GC value	p
Amyg → Calc	0.023	<.01
Amyg → FG	0.018	<.01
Amyg → OFC	0.015	<.01
Calc → FG	0.021	<.01
Calc → LOC	0.045	<.01
OFC → Calc	0.031	<.01

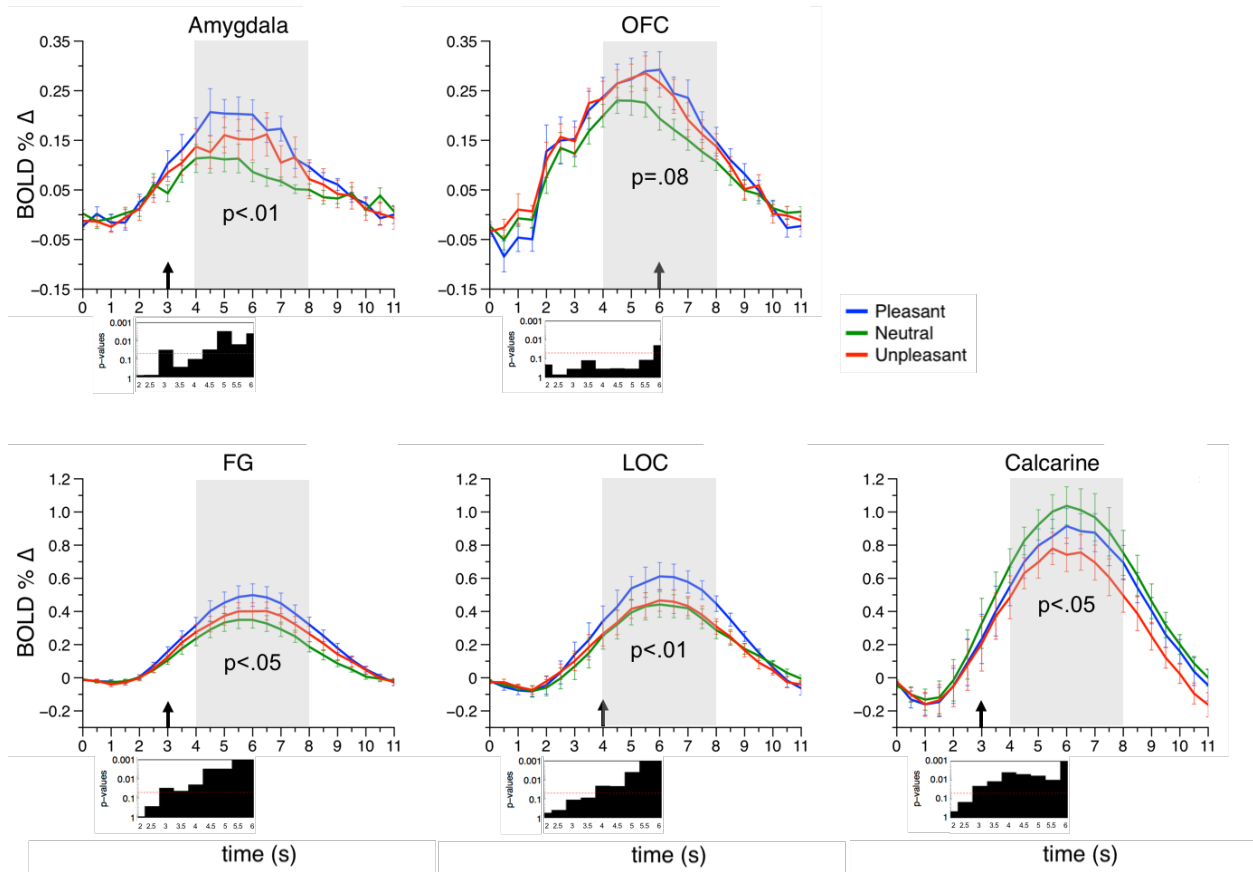


Figure 3: Average BOLD signal change time series for each ROI. The arrows indicate the time point (seconds post picture onset) in which the semantic categories reliably diverge. Gray boxes represent the 4-8 seconds that were averaged to determine affective discrimination, with corresponding p values denoted. The bar plots below the time series axes represent this divergence point for each time point. If the bar passes above the red line, which represents a $p = .05$ threshold, then the 3 categories are reliably discriminated at that moment. Error bars represent the standard error of the mean. OFC: lateral Orbitofrontal Cortex, FG: Fusiform Gyrus, LOC: Lateral Occipital Cortex.

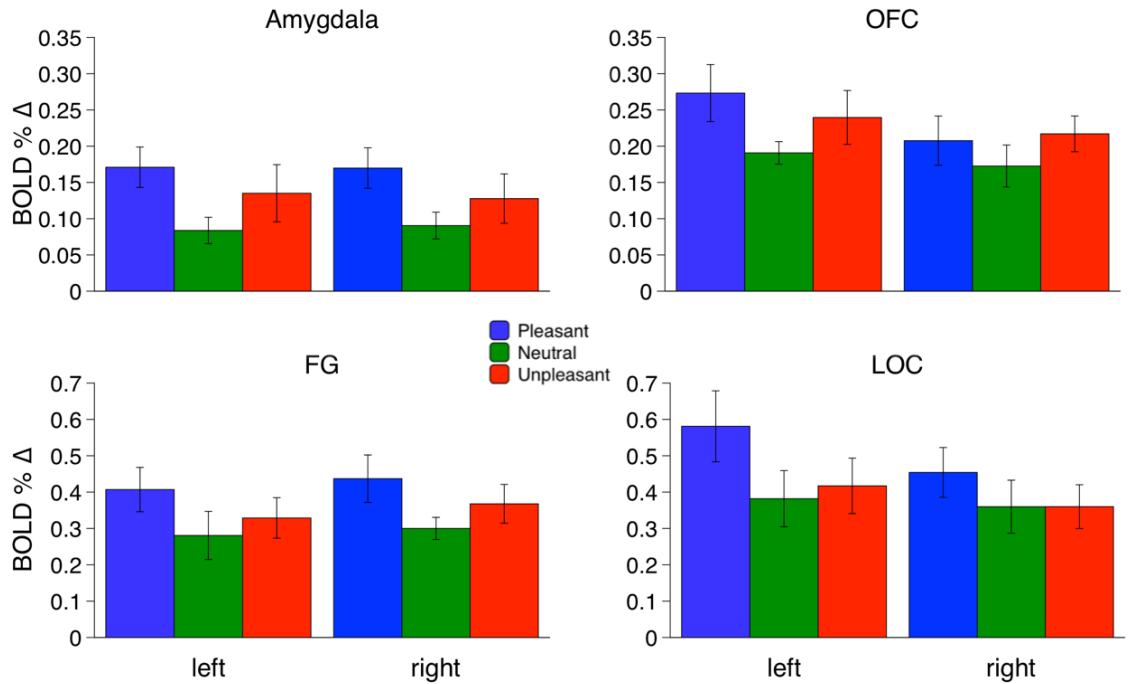


Figure 4: Hemisphere and valence modulation for each ROI. Error bars represent the standard error of the mean. OFC: lateral Orbitofrontal Cortex, FG: Fusiform Gyrus, LOC: Lateral Occipital Cortex.

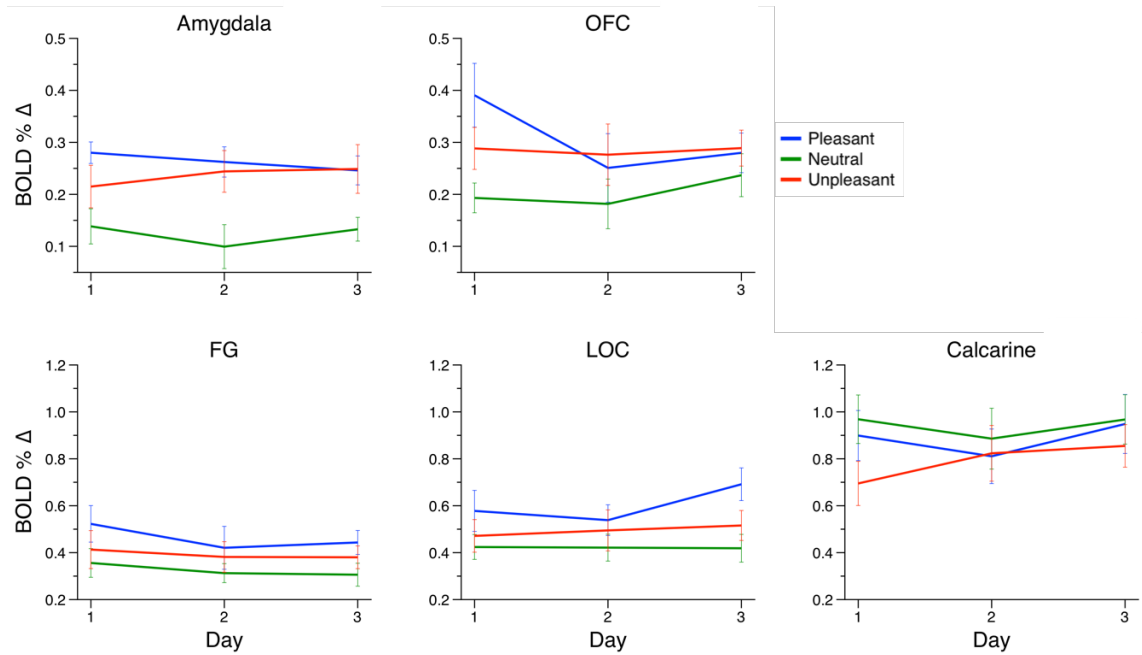


Figure 5: Valence modulation across days for each ROI. Error bars represent the standard error of the mean. OFC: lateral Orbitofrontal Cortex, FG: Fusiform Gyrus, LOC: Lateral Occipital Cortex.

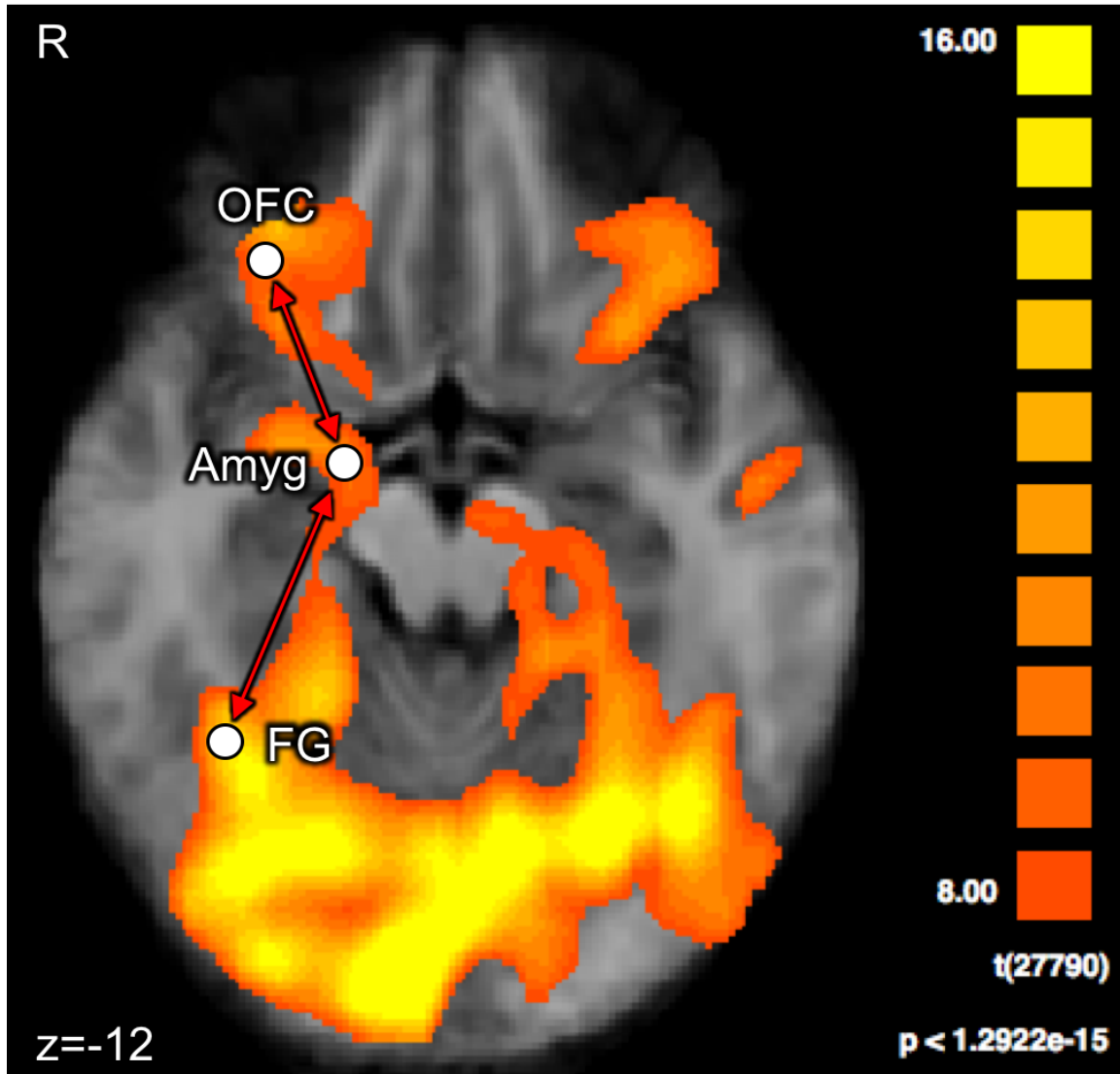


Figure 6: Granger causality influences mapped onto a representative brain (3 ROI). Red arrows denote bidirectional influences. All GC measures are significant at $p < .05$, FDR corrected. OFC: lateral Orbitofrontal Cortex, FG: Fusiform Gyrus.

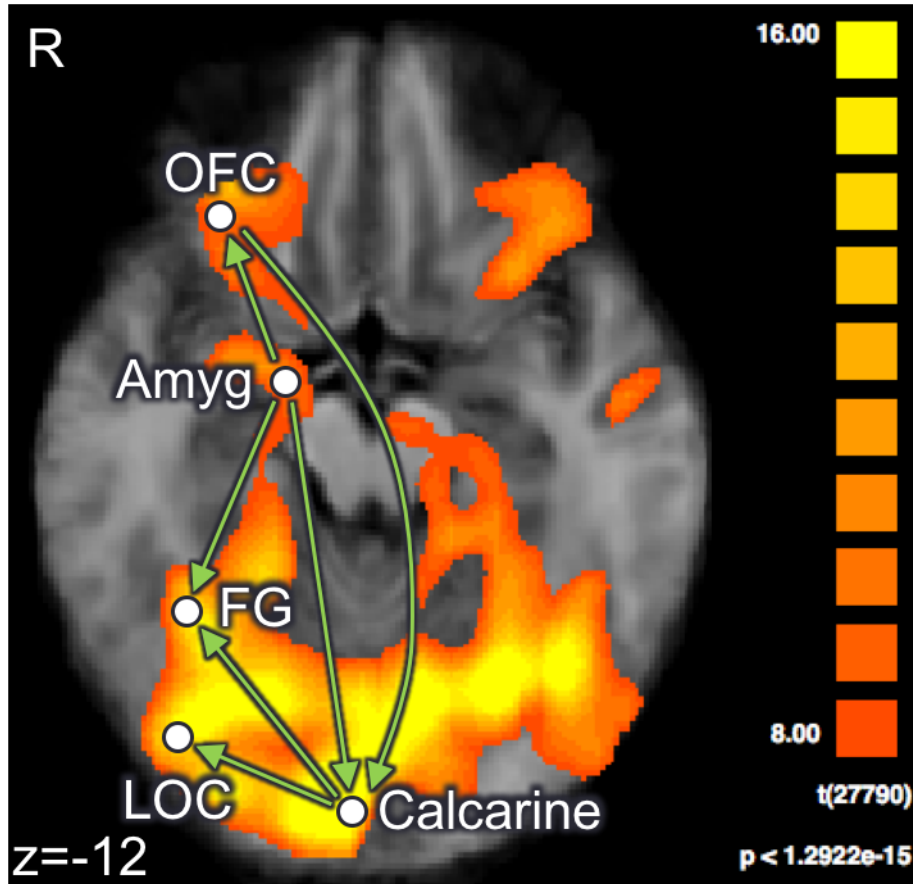


Figure 7: Granger causality influences mapped onto a representative brain (5 ROI). Green arrows denote unidirectional influences while red arrows denote bidirectional influences. All GC measures are significant at $p < .01$, FDR corrected. OFC: lateral Orbitofrontal Cortex, FG: Fusiform Gyrus, LOC: Lateral Occipital Cortex.

CHAPTER 4

DISCUSSION

Consistent with prior studies, we identified enhanced peak BOLD signal (4-8 s after scene onset) during emotional versus neutral scene perception across structures in the ventral visual network including the amygdala, FG, and LOC (Frank & Sabatinelli, 2014; Sabatinelli et al., 2015). The LOC endorsed a pleasantness bias, as activity evoked by neutral and unpleasant scenes were statistically equivalent (Tukey HSD test; $p=.79$), but enhanced during pleasant scenes (Tukey HSD test; $p<.01$). This pleasantness bias in LOC has been reported previously (Sabatinelli & Frank, under review; Sabatinelli et al., 2013). The OFC showed marginal ($p = .08$) BOLD signal enhancement during emotionally arousing scenes in the current study. This may reflect a small role for the OFC in emotional scene processing, as this structure has most clearly been tied to human reward and punishment processing (Cardinal et al., 2002b; Rolls, 2004). Another potential reason for the marginal effect of emotional scenes on OFC modulation may be a result of poor MR signal quality in this area of the brain, which it is prone to susceptibility artifact ("blowout") due to its proximity to the nasal sinus cavity, especially at higher sampling rates. However, the average SNR in this region was 95 (Mean/SD signal), so this is unlikely the case in the present study. Future studies may still employ alternate imaging methods that minimize susceptibility losses, such as spiral EPI (Glover & Thomason, 2004) to further enhance signal from this area, and re-examine the role of OFC in emotional scene perception.

Previous work in which scene brightness and perceptual complexity are balanced have reported no effect of emotional scene content on modulation of calcarine fissure BOLD signal

(Sabatinelli et al., 2014; Sabatinelli et al., 2009). In the current dataset, we did find an effect of scene content on calcarine fissure activity, however the modulation effect was opposite from what is found in canonical emotional processing regions, with weaker BOLD signal during unpleasant and pleasant scenes, relative to neutral scenes. Thus, the pattern of modulation suggests that the differences in brightness and complexity between the pleasant, neutral, and unpleasant scenes are unlikely to have contributed to the enhanced signal in later stage visual regions and the amygdala.

Neural signaling occurs on the order of milliseconds, and therefore real time communication cannot be measured using the hemodynamic BOLD signal response recorded using fMRI. However, we can compare differences in BOLD signal timing within structure to infer the order in which neural processing occurs. In the current study, recorded at 500ms resolution, permutation tests indicated initial emotional discrimination in amygdala and FG, identified at three seconds after stimulus onset. This was soon followed by LOC measured at four seconds, and OFC at six seconds. In OFC, this individual time point was significant, while the peak average from 4-8 s post scene onset was not. We predicted a comparatively early discrimination in amygdala and FG, which we have identified in prior studies (Sabatinelli et al., 2014; Sabatinelli et al., 2009), and is consistent with a reentrant feedback model of emotional perception (Amaral et al., 2003; Amaral & Price, 1984; Catani et al., 2003; Spiegler & Mishkin, 1981). Also, consistent with this reentrant perspective is a later discrimination point in lateral occipital areas. The relative delay in OFC emotional discrimination should be interpreted with caution, as we are less confident in the quality of our BOLD signal estimate.

Habituation Effects

Here we found no evidence for habituation of neural activity during emotional scene perception, neither across scan runs within day, nor across days. This study was designed such that many scene stimuli were presented to subjects over the course of multiple days, and multiple scan runs within days. Within each session, the category of scene was consistent (e.g., erotica, threat), but the specific exemplar was left to vary, such that any individual scene was only presented a few times over the course of the entire experiment. Thus, the experience of the subject was that of a long, mixed series of distinct scenes, falling into a few homogenous categories of content. This paradigm is distinct from many prior studies of neural habituation, in which the same stimulus is repeated many times within a single session. These previous studies, employing paradigms that repeated stimuli after seconds or minutes, have found habituation of activity in many brain regions, such as the amygdala (Bradley et al., 2015; Breiter et al., 1996; Denny et al., 2014; Swartz et al., 2013). In an experiment more similar to the current design, Johnstone and colleagues (2005) performed a multi-session investigation of amygdala activity, and found no evidence for amygdala habituation, consistent with our results. Thus, these results suggest that while activity within affective processing regions may habituate to repeated stimuli within a short time, they reserve the ability to recover and remain stable over more extended time periods.

Directional Connectivity Analyses

To address our hypotheses regarding directional connectivity between amygdala, FG, and OFC, we employed temporal GCA on the average time series across all experimental sessions. The GCA results yielded significant bidirectional connectivity between amygdala and both OFC

and FG, consistent with our predictions. Directional connectivity was not identified between OFC and FG. These analyses suggest that the amygdala may serve as a hub of scene processing involving mutual transaction with both FG and OFC (Ghashghaei & Barbas, 2002; Salzman & Fusi, 2010).

As an exploratory analysis, we also conducted GCA across the entire set of ROIs. This analysis revealed influences from the calcarine fissure to LOC and FG, in addition to projections from the amygdala to FG and calcarine fissure. This is in line with hierarchical and recurrent visual processing theories demonstrating a flow of information anteriorly along the lateral occipital and inferotemporal cortices (Grill-Spector & Malach, 2004), along with feedback for rapid updating (de Graaf et al., 2011; Hegde & Felleman, 2007; Lamme & Roelfsema, 2000). Additionally, activity of the OFC predicted activation in the calcarine fissure, which may be achieved via the inferior longitudinal fasciculus and the inferior frontal occipital fasciculus (Gschwind et al., 2012).

As this analysis is based on statistical assessment of predictive information between regions, we are unable to conclude which anatomical pathways were incorporated during our scene viewing paradigm. While it is likely that the inferior longitudinal and the inferior frontal occipital fasciculi are involved in affective visual processing, there are other paths that may facilitate neural communication. For instance, the thalamus supports connections with OFC, amygdala, FG, and LOC (Padmala et al., 2010; Pessoa & Adolphs, 2010; Shipp, 2003). Furthermore, there is evidence to suggest that the medial dorsal and pulvinar nuclei are modulated by both pleasant and unpleasant affective scenes (Frank & Sabatinelli, 2014). These authors have also reported that the thalamus discriminates emotional stimuli at a similar time

point as FG. Thus, it is possible that affective information is spread to anterior and posterior cortex from amygdala directly, through the thalamus, or both.

Study limitations and summary

This study was designed to collect many trials as a means of maximizing statistical power to investigate subtle effects associated with neural reactivity during emotional scene perception. This was accomplished by sampling a comparatively small group of participants (here nine individuals were included in the final sample) over many sessions. Another approach would be to sample a larger number of participants over fewer sessions. Considering the essentially modest effect sizes found in amygdala and fusiform gyrus, roughly equivalent to past work in which only 60-80 trials were collected (Sabatinelli et al., 2005; Sabatinelli et al., 2009), this latter approach may provide a more reliable estimate for future studies of this kind.

Other design limitations include the fact that not all participants underwent the same number of scan runs per day. Therefore, if differences had been found between days, they may have been confounded with unequal picture presentations. Finally, though not strictly a limitation, each unique image is only repeated a few times throughout the entire 3 days, and the interval between repetitions varied randomly. Because of this, we were unable to satisfactorily evaluate the difference between semantic category repetition and repetition of discrete pictures. Future studies may include more repetitions of identical exemplars and pseudo-randomize all picture sequences across participants to equate the number of repetitions, and time elapsed between repetitions. This would allow meaningful investigation of both semantic and picture habituation effects within and across days.

In summary, here we show reliable emotion driven modulation of the amygdala, lateral occipital gyrus, and fusiform gyrus, with a marginal effect for the lateral orbitofrontal cortex. Granger causality indicates that these regions are connected such that the amygdala communicates bilaterally with both fusiform gyrus and orbitofrontal cortex, while calcarine fissure projects to neighboring visual areas LOC, and FG. Furthermore, temporal discrimination analyses suggest that emotional modulation occurs first in amygdala and FG, followed by LOC, consistent with past work. Both the timing and Granger analysis supports a perspective in which amygdalar feedback to ventral visual structures and the OFC may serve to integrate emotional relevance with object identification and contingency learning, respectively. Finally, the effect of emotional BOLD signal enhancement appears resistant to habituation across scanning days among all regions investigated here. Thus, while habituation may occur on the order of seconds or minutes, affective discrimination appears resistant to habituation over longer time scales, consistent with an evolved need for persistent emotional sensitivity across the lifespan. While researchers have investigated neural habituation using repeated same-identity stimuli, information about general hedonic habituation is limited. This study provides some of the first evidence in support of stable affective modulation of human brain structures. Additional investigation of semantic habituation over various timescales comparing both identical and unique emotional exemplars will further refine our understanding of the affective visual system. Several cognitive processes, such as the possible differential habituation rate of identical compared to unique exemplars, remain to be explored.

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