ELECTROCORTICAL AND HEMODYNAMIC MEASURES OF EMOTIONAL AND REWARD RELEVANT SCENE PERCEPTION

by

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(Under the Direction of DEAN SABATINELLI)

ABSTRACT

The origins of emotional and reward disorders, which are increasing in prevalence, can be associated with dysfunction of neural circuitry involved in emotional cue perception. By identifying the specific brain mechanisms involved in disorders of emotion and addiction, treatments such as neuromodulation can be better understood and refined. Here, we use recent developments in neuroimaging techniques, including steady state evoked potentials (ssVEP) and rapidly sampled functional magnetic resonance imaging (fMRI) to investigate the modulation of, and causal connectivity among brain regions involved in emotional and rewarding scene processing. Specifically, we were interested in individual differences in evaluative and neural responses to naturalistic scenes of cigarette smoking in nicotine users, and acceleration-relevant scenes in thrill seekers. While event-related and steady-state evoked potential amplitudes were enhanced during arousing (pleasant and unpleasant), relative to neutral scenes, no interactions were found between nicotine users, thrill-seekers, and controls. Whole brain fMRI analysis revealed increased activation in nicotine users relative to controls in response to smoking cues in
multiple brain regions including visual association cortex and reward-related medial prefrontal cortex. Granger causality analyses of rapidly sampled fMRI data found significant bidirectional connectivity between amygdala, fusiform gyrus, and orbitofrontal cortex, with variable connectivity patterns between groups in response to reward-relevant scene contents. The interpretation of patterns of EEG and fMRI reactivity and connectivity are discussed with respect to selective and evolved attention mechanisms.

INDEX WORDS: Emotional perception, reward, EEG, fMRI, connectivity
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CHAPTER 1
INTRODUCTION

The origins of emotional and addiction disorders, which are increasing in prevalence (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012) are likely to be associated with a dysfunction of neural circuitry within the human brain. For example, major depressive disorder is associated with regional cortical and subcortical dysfunction, which may be ameliorated using research driven techniques such as deep brain stimulation (Holtzheimer et al., 2012; Mayberg et al., 2005), vagus nerve stimulation (Nahas et al., 2005; Nemeroff et al., 2006), or transcranial magnetic stimulation (Holtzheimer, Russo, & Avery, 2001; O’Reardon et al., 2007). How such treatments work is incompletely understood, however, rather than simply creating reversible lesions, research suggests that neuromodulatory treatments affect extensive neural circuits (Choi, Riva-Posse, Gross, & Mayberg, 2015). In order to understand the mechanisms behind currently available treatments, such as DBS, we must first identify the operation of the specific brain networks involved.

Following a general review of the neural basis of emotional and rewarding scene processing, we will describe a human neuroimaging experiment with which our understanding of the neural networks involved in emotion and reward-related perception may be better understood. The current research draws upon recent innovations in noninvasive human neuroimaging that may advance our mechanistic understanding of the neural circuitry and relationships between electrocortical (electroencephalography; EEG) and hemodynamic (functional magnetic resonance imaging; fMRI) measures of the brain during the processing of
emotional and reward related scenes. More specifically, it seeks to determine the temporal and causal relationships between visual cortical and non-visual subcortical regions as participants view naturalistic scenes that vary in emotional and reward-relevant content. Functional MRI (N40) and electroencephalography (EEG) (N96) data was collected as subjects viewed a series of emotional, rewarding, and neutral natural scenes. By combining new variants of these complementary techniques, the current research exploits the convergent aspects of each technique to address questions relevant to the underlying mechanisms of emotional and reward scene perception, such as the ability to differentiate neural responses and directional connectivity to secondary reward cues based on individuals differences in reward preferences. To address the research questions, the scope of the present study expands upon previous research (Sabatinelli, Keil, Frank, & Lang, 2013; Sabatinelli, Lang, Keil, & Bradley, 2007) by collecting traditional event related potential (ERP) data along with steady-state visually evoked potentials (ssVEP), in parallel with rapidly sampled and whole brain fMRI data collected within the same sample.

*Emotional scene perception.*

Our ability to quickly and efficiently scan the environment to avoid danger is highly evolved and engages neural circuits involved in motivation and attention (Lang & Bradley, 2010). When engaging with your environment, specific brain networks are activated based upon the context of a given scene and visual features relating to motivational relevance, such as emotional arousal and pleasantness (Bradley et al., 2003; Vuilleumier, 2005). Once activated, these networks, which include cortical and subcortical nodes, prompt a cascade of effects that facilitate action preparation and natural selective attention (Bradley 2009, Bradley, Keil & Lang, 2012; (Freese &
Amaral, 2005; Hegde & Felleman, 2007; Vuilleumier, 2005). In the laboratory, naturalistic scenes depicting emotional content are employed to engage these same networks.

When processing emotional relative to neutral scenes, electrocortical and hemodynamic methods consistently identify enhanced activity in ventral and dorsal visual cortices (Pastor et al., 2008; Pourtois, Schettino, & Vuilleumier, 2013; Sabatinelli et al., 2014; Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005; Sabatinelli et al., 2013; Sabatinelli, Lang, et al., 2007). Specifically, the fusiform gyrus (FUS) and lateral occipital cortex (LOC), regions of the ventral visual processing network, exhibit increased activation in response to emotional scenes. The fronto-parietal attention network (FP) including frontal eye fields (FEF) and intraparietal sulcus (IPS) as well as subcortical regions such as amygdala (AMG), and ventral regions of prefrontal cortex such as the medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC) are also implicated in emotional scene perception (Bradley et al., 2003; Britton, Taylor, Sudheimer, & Liberzon, 2006; Hariri, Bookheimer, & Mazziotta, 2000; Sabatinelli et al., 2005; Sabatinelli, Bradley, Lang, Costa, & Versace, 2007; Sabatinelli, Lang, Bradley, Costa, & Keil, 2009). Highly arousing scenes such as erotica and mutilations are particularly evocative and result in widespread increases in neural activation relative to both neutral scenes and moderately arousing scenes such as romantic couples or happy families (Bradley et al., 2003; Keil et al., 2003).

Enhanced activity is thought to occur because arousing scenes evoke extended and oriented perceptual processing in secondary visual areas via reentrant feedback from subcortical AMG (Amaral & Price, 1984). This reentrant model of emotional perception posits that visual information is initially fed forward through the ventral visual pathway, after which highly processed information reaches the AMG where in concert with the FUS, emotional scene discrimination is performed. The AMG then feeds information back to inferior temporal and
occipital visual structures along the ventral pathway (Armony & Dolan, 2002; Keil et al., 2009; Sabatinelli et al., 2005; Sabatinelli et al., 2009; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). Though not integrated in the reentrant model, feedback could also arise from the FP network including the FEF and IPS, which interact with ventral regions such as the temporoparietal junction and inferior frontal gyrus, and are associated with stimulus driven top-down attention (Asplund, Todd, Snyder, & Marois, 2010; Carretie, 2014; Corbetta & Shulman, 2002; Szczepanski, Konen, & Kastner, 2010). Sabatinelli et al. (2014) investigated the timing of both ventral and FP networks during emotional scene processing using rapid fMRI and demonstrated that emotional information is initially discriminated in the ventral visual network (FUS and AMG) roughly 2.25 sec after scene onset. In contrast, dorsal regions including the FEF and IPS did not discriminate emotional from neutral content until 4.25 seconds after scene onset, indicating that emotional enhancement of the dorsal visual network is unlikely to precede such discrimination in the AMG and ventral visual network. Directional connectivity analyses demonstrated stronger connectivity from the AMG to FUS than the reverse, possibly via the inferior longitudinal fasciculus (Catani, Jones, & Donato, 2003), which further supports the reentrant perspective. Together these latency and connectivity analyses suggest that discrimination of emotional scenes occurs initially in the amygdala and ventral regions, which then may distribute this categorization to other brain networks (Sabatinelli et al., 2014).

**Reward Processing**

In addition to activating emotional networks, emotional scenes such as erotica and appetizing food also activate networks associated specifically with reward processing. Generally, stimuli are considered rewarding if pleasant emotions are elicited and associated with increased motivation
to approach or consume the stimulus (Berridge & Kringelbach, 2008). Two types of rewarding stimuli, primary and secondary rewards, differ in that primary rewards are basic instinctual rewards such as food and sex, whereas secondary rewards must be learned, for example, money (Schultz, 2000; Sescousse, Caldú, Segura, & Dreher, 2013). Visual stimuli depicting rewards are thought to act as conditioned incentives and can acquire motivating and hedonic properties (Cardinal, Parkinson, Hall, & Everitt, 2002). Furthermore, previous research suggests neural activation in response to reward cues may predict future outcomes such as risk of obesity or weight gain (Polivy, Herman, & Coelho, 2008; Stice, Yokum, Burger, Epstein, & Small, 2011) and abstinence from smoking (Versace et al., 2014; Versace et al., 2012). Given the overlapping aspects of emotion and reward, it is not surprising that both engage shared brain regions, and links between these networks and the properties of the rewarding stimuli may provide insights into emotional, addiction and obesity related disorders (Kringelbach, 2005).

Extensive literature on reward processing highlights a core network of regions including the OFC, ACC, ventral striatum, AMG, insula, and mediodorsal nucleus of the thalamus (MDN) (Haber & Knutson, 2010; Liu, Hairston, Schrier, & Fan, 2011; Richards, Plate, & Ernst, 2013; Sescousse et al., 2013; Tang, Fellows, Small, & Dagher, 2012). Furthermore, primary versus secondary rewards elicit both overlapping and distinct activation (Beck, Locke, Savine, Jimura, & Braver, 2010; Sescousse et al., 2013). A recent meta-analysis (Sescousse et al., 2013) investigating differences between reward type and brain activity found that while rewarding stimuli in general resulted in activation in ventral striatum, OFC, AMG, insula, and MDN, erotica more reliably engaged the hypothalamus, extrastriate body area, and AMG. Erotica reliably engaged the insula and was specifically associated with increased reactivity in ventral anterior insula and lateral posterior OFC.
Rewarding stimuli, particularly secondary learned rewards, are abundant, and much neuroimaging research has focused on monetary rewards through a variety of gambling paradigms. Other secondary rewards that may lead to risky behaviors such as drug use are also widely studied. For example, scenes of individuals smoking can activate emotion and attention networks in both smokers and non-smokers. Smokers are reported to process cigarette cues similarly to pleasant stimuli (Dempsey, Cohen, Hobson, & Randall, 2007; Geier, Pauli, & Mucha, 2000) with activation in the extended visual system including the lingual gyrus, cuneus, precuneus, and FUS in addition to the ACC, mPFC, insula and subcortical structures such as the striatum (Engelmann et al., 2012; Robinson et al., 2014; Versace et al., 2011). Those who have never used nicotine products (never-smokers) also exhibit increased neuronal activity as assessed with EEG, specifically an increased late positive potential (LPP) ERP, in response to smoking cues as compared to neutral stimuli (Deweese, Robinson, Cinciripini, & Versace, 2016; Geier et al., 2000; Robinson et al., 2014). It is believed that drug cues such as scenes of individuals smoking may engage neural networks involved in both emotion and reward processing relevant to survival (Everitt, Dickinson, & Robbins, 2001; Hyman, 2005; Robinson & Berridge, 2003).

Response to reward cues may be based on personal preference as previous research suggests individual differences in reward sensitivity (Gray, 1987), and these differences are suggested to predict cravings, hyperphagia, and relative body weight (Beaver et al., 2006; Davis, Strachan, & Berkson, 2004; Franken & Muris, 2005). Secondary cues, such as smoking scenes, may also result in differential neural response based on personal preference. For instance, smoking cues may be associated with pleasant experiences (e.g. parties/bars/friends) or unpleasant experiences (e.g. second hand smoke or cancer/death of a loved one) (Robinson et al., 2014), which then elevate smoking cues to particularly salient stimuli. Other secondary rewards
such as the enjoyment of fast acceleration from rollercoasters, sports cars, and skydiving may also rely on preference or personality traits such as sensation seeking.

Sensation seeking is a personality trait that is characterized by the active seeking of novel and intense sensations or experiences with the acceptance of physical, social, and legal risks associated with those experiences (Zuckerman, 1994). Individuals self-reporting as high sensation seekers are at increased risk for dangerous behaviors such as risky driving and other activities such as promiscuity, gambling and substance abuse (Bardo, Donohew, & Harrington, 1996; Roberti, 2004; Zuckerman, 2007). High sensation seeking individuals are reported to exhibit stronger orienting responses to new stimuli and stronger cortical arousal to intense visual stimuli while low sensation seeking individuals exhibit the opposite response patterns (Zuckerman, 2005). Sensation seeking has been associated with brain structure (Martin et al., 2007) and function, such that high sensation seekers exhibiting neural differences during EEG and fMRI studies involving novelty, stimulus repetition, reward processing, and emotion processing (Abler, Walter, Erk, Kammerer, & Spitzer, 2006; Jiang et al., 2009; Joseph, Liu, Jiang, Lynam, & Kelly, 2009; Lawson et al., 2012; Zheng et al., 2011). These studies suggest that high versus low sensation seekers differentially process arousing and novel stimuli. A common interpretation suggests that these differences are a result of different degrees of arousability in each group. While both groups are thought to experience equivalent base levels of arousal, high sensation seekers are believed to react less to stimulation and require more intense stimuli to reach the same level of arousal as low sensation seekers (Zuckerman, 1997). Most research examining high sensation seeking has focused on the overall score from the sensation seeking scale, but sensation seeking is comprised of several components including experience seeking, thrill and adventure seeking, boredom susceptibility, and disinhibition. The thrill-
seeking dimension, specifically, is reported to be the best indicator of a more narrowly defined sensation seeking construct (Miller, 2007) and can lead to an increase in risky behaviors, but there is a dearth of research investigating the neural implications of this construct.

**Neuroimaging methods**

Two of the most common noninvasive methods of assessing human brain activity are ERPs derived from the EEG and blood oxygen level-dependent (BOLD) contrast from fMRI. The LPP, a slow centro-parietal voltage-positive ERP that occurs between 400-900 ms after stimulus onset (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Schupp et al., 2000) is modulated by arousing content (pleasant and unpleasant) (Cuthbert et al., 2000; Keil, Muller, et al., 2001; Schupp, Junghöfer, Weike, & Hamm, 2004). Consistent with its latency and duration, the neural generators of the LPP are thought to include a network of distributed cortical and subcortical structures that encompass areas beyond the conventional sensory regions (Liu, Huang, McGinnis-Deweese, Keil, & Ding, 2012; Sabatinelli et al., 2013; Sabatinelli, Lang, et al., 2007). Given its modulation by arousing stimuli, the LPP is interpreted as a measure of increased attention to or facilitated processing of motivationally relevant or emotional stimuli (Hajcak, MacNamara, & Olvet, 2010; Lang & Bradley, 2010; Schupp et al., 2000). ERPs such as the LPP have the potential to track brain activity in real time, but are difficult to localize with precision due to difficulties in source localization. As a result, capturing reliable activity from deeper cortical structures is limited, and impractical in subcortical regions that form electrically closed units (Russell, Srinivasan, & Tucker, 1998; Schoffelen & Gross, 2009).

The BOLD contrast, obtained through fMRI, overcomes the limitation in spatial resolution inherent in EEG. As neuronal activity increases, the demand for oxygenated blood
also increases, and BOLD contrast (and functional image intensity) is linearly related to the ratio of oxygenated to deoxygenated hemoglobin. Due to the inherently slow changes in hemodynamic response over time, the BOLD signal is delayed and smoothed relative to neural activity. While an indirect measure of neuronal activity, previous research supports the association between intracranially recorded local field potentials (LFPs) and the BOLD signal in non-human primates (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Logothetis & Wandell, 2004). In addition, the timing of BOLD signal change within active clusters is highly reliable (Kim, Richter, & Ügurbil, 1997; Lin et al., 2013) and several ERP components such as P1/N1 covary with the BOLD signal (Hesselmann, Flandin, & Dehaene, 2011; Novitskiy et al., 2011). Taken together these studies support that, although delayed temporally, the BOLD signal can be interpreted as representing equivalent neural activity if sampled from the same structure and person, otherwise the signal can be confounded by the regional variability in the timing of the hemodynamic response (Aguirre, Zarahn, & D'esposito, 1998). fMRI can significantly inform our understanding of how we process emotional scenes, but like EEG, has limitations. Specifically, while fMRI offers excellent spatial resolution, it is an indirect measure of brain activity mediated by neurovascular coupling and requires more time between samples, due to the nature of the image creation process. Therefore, fMRI cannot track real-time neural dynamics. Recent developments in both ERP and fMRI methodology can overcome some limitations of electrocortical and hemodynamic methods and potentially provide converging information regarding the dynamics of neural networks involved in the perception of emotional and reward related scenes.
Rapid sampling function magnetic resonance imaging

Another way to investigate ventromedial and subcortical neural activity that are difficult to measure via EEG is to track the timing of the BOLD signal during the presentation of emotional and neutral stimuli using rapid sampling techniques (Sabatinelli et al., 2015). To increase the sampling rate of fMRI, a targeted sampling approach is employed to allow rapid sampling rates of 100-500 ms of specific regions or slabs of interest, thus enabling an investigation of the relative timing of BOLD signal change within structures across experimental conditions. Rapid fMRI allows for simultaneously sampling from a set of pre-determined brain regions, which can be used to assess how brain regions are functionally connected and allow explicit testing of the hypothesized hierarchies of control during emotional and neutral scene perception. Recent studies using rapid sampling techniques have elucidated the connectivity and timing of emotional discrimination in ventral and dorsal attention networks, specifically AMG, FEF, FUS, and IPS (Sabatinelli et al., 2014; Sabatinelli et al., 2009). Furthermore, the data obtained using this technique are well suited for performing directed functional connectivity analyses across structures such as Granger Causality Analysis (GCA) as the data consist of significantly more sampling points within the same time period (Sabatinelli et al., 2014; Sabatinelli et al., 2015).

Granger causality analysis is an increasingly employed technique to evaluate the directional connectivity in neural times series data (Bressler & Seth, 2011). In GCA, a region is said to “Granger cause” another if signal variation from region X can predict the signal variation of a region Y over and above that which can be predicted from the history of region Y alone. Therefore, if two or more regions are directionally connected, activity in one area should be able to predict the subsequent activity of another area/s. Using GCA in typical fMRI studies is controversial due to the slow pace of the hemodynamic response function (HRF), measurement
noise, and downsampling with sample intervals from 1-3 seconds used in standard scanning parameters, which is significantly longer than inter-neuron delays (Barnett & Seth, 2014). By significantly reducing the sampling rate, examining directional connectivity between conditions, and correlating changes in causality magnitude, these limitations can be overcome. Using this method, in tandem with rapid fMRI, recent research differentiated directionally connected regions of the ventral visual and FP networks as well as reward structures during emotion discrimination (Sabatinelli et al., 2014) as discussed above.

Steady-state visually evoked potentials

A variant of ERP measurement, steady-state visually evoked potentials (ssVEPs) involves the presentation of flickering visual stimuli at a rapid rate ("steady-state") defined by the experimenter. The ssVEP response, recorded as an oscillatory waveform, depicts the synchronization of neuronal activity at the driven frequency of the flickering stimulus (Regan, 1989; Spekreijse, Dagnelie, Maier, & Regan, 1985). This methodology promotes better localization of neuronal generator origin, and the evaluation of neural activation amplitude on a trial-by-trial basis, a difficult prospect with standard ERP methods (Wang, Clementz, & Keil, 2007; Wieser, Miskovic, & Keil, 2016). In addition, ssVEPs have excellent signal-to-noise ratio characteristics compared with traditional ERP components (Nunez and Srinivasan, 2005). The neural generators of the ssVEP signal have been localized to the extended visual cortex with strong contributions from primary visual cortex (V1), extrastriate cortex, and higher-order cortices such as mid-temporal regions and IPS (Di Russo et al., 2007; Müller, Teder, & Hillyard, 1997; Pastor et al., 2008).
While ssVEPs generally reflect sensory responses, ssVEPs are also sensitive to affective and attentional features of experimental tasks allowing investigation of various aspects of emotional content, selective attention, and learned motivational relevance (Keil et al., 2012; Keil et al., 2003; Keil et al., 2009; Andreas Keil et al., 2008; Moratti & Keil, 2009; Muller, Malinowski, Gruber, & Hillyard, 2003). When a flickering emotional stimulus such as a scene depicting mutilation or erotica is presented, increased ssVEP amplitude for emotional relative to neutral scenes is observed (Bradley, Keil, & Lang, 2012; Keil et al., 2003; Keil et al., 2009; A. Keil et al., 2008). Research using a modified paradigm involving the incorporation of an additional element, flickering dots superimposed on a static emotional or neutral image, report the opposite modulatory effect, with decreased ssVEP amplitude in response to emotional scenes relative to neutral scenes (Kemp, Gray, Eide, Silberstein, & Nathan, 2002; Kemp, Gray, Silberstein, Armstrong, & Nathan, 2004). This reverse response is interpreted as attentional interference between heightened attention drawn to the scene and away from the overlaid flickering dots. Steady-state potentials provide unique information regarding neurophysiological aspects of emotion processing and attention as ssVEPs are reported to be loosely or uncorrelated with other ERP measures such as the LPP (Hajcak, MacNamara, Foti, Ferri, & Keil, 2013; Miskovic et al., 2015). It is unclear whether a correlation between ssVEPs and the BOLD signal exists, however, preliminary studies suggest covariation between the two measures in visual cortex (Keil et al. unpublished data).

Aims and hypotheses

It is predicted that modulation of ERPs and BOLD signal will be enhanced in response to emotional and reward related relative to neutral scenes, with a correlation between both measures
in cortical and subcortical brain regions associated with visual, emotion, and reward processing. By increased temporal resolution and examining additional distinct ERP measurements, the development of rapid sampling fMRI and ssVEPs techniques provide a multimodal assessment of scene perception, and may further our understanding of emotional and reward activity in addiction. Steady-state potentials, which are distinct from scene onset ERPs, may provide additional information on emotion processing; however, there are several unanswered questions; 1) Do individuals with specific reward sensitivities show enhanced EEG or fMRI reactivity during primary (emotional) and secondary (reward-relevant) scene perception? 2) Do these electrocortical and hemodynamic measures differentially reflect emotional and reward-relevant scene processing? and 3) Do individuals with specific reward sensitivities show differential patterns of causal influence in implicated brain regions associated with emotion and reward?

In this study, the activity of the extended visual system including the FUS, LOC, and middle occipital gyrus (MOG), regions associated with the reward system including AMG and lateral OFC as well as regions of the dorsal attention network during the processing of emotional and reward-related stimuli is examined. Based on prior electrocortical and hemodynamic research, we hypothesize ssVEP response will be attenuated (Keil, Bradley, Rockstroh, & Lang, 2001; Keil et al., 2003; Kemp et al., 2002; Kemp et al., 2004), and the EPN and LPP will be modulated by emotionally arousing stimuli relative to neutral stimuli. To obtain both the standard ERPs (EPN/LPP) unadulterated by the dot flicker, and ssVEPs in the same trial, this study will modify the standard ssVEP paradigm in which scenes and flickering dots are presented simultaneously, and instead present each scene alone for 2000ms before overlay of the flickering dots. The ssVEP and LPP response are hypothesized to be uncorrelated as previously reported (Hajcak et al., 2010; Miskovic et al., 2015). BOLD response is hypothesized to increase
relative to neutral in OFC, AMG, FUS, and IPS when viewing emotionally arousing pictures regardless of valence. Given preliminary data suggesting a relationship between the ssVEP and BOLD signal using a modified paradigm, we expect that ssVEP will be positively correlated with the regional BOLD signal data obtained from rapidly sampled fMRI. Reward stimuli may be associated with increased LPP and BOLD response relative to neutral stimuli; however, the response is expected to differ for secondary reward stimuli depicting scenes of fast acceleration and smoking cues based on individual differences in thrill-seeking traits and nicotine use.
CHAPTER 2
METHODS

Participants and procedure

All procedures were approved by The University of Georgia Institutional Review Board. The study consisted of two separate sessions: an EEG session and a fMRI session. For the both sessions, participants self-referred in response to fliers and through the University of Georgia undergraduate research pool website. Eligible participants were then scheduled for the EEG session, where a trained research assistant explained the study procedures to potential participants, and collected written, informed consent. For the fMRI portion of the study, participants of the EEG session who indicated interest in participating in the follow up fMRI study were contacted. Interested participants were screened to establish initial eligibility for the study. Participants were included if they were between the ages of 18-28, right-handed, a University of Georgia student. Participants with a history of psychiatric or neurological diagnoses or contraindications to MRI were excluded from the study.

After obtaining informed consent, participants rated each picture to be presented during the experiment using the Self-Assessment Manikin (Lang, 1980), a language-free instrument for rating hedonic valence and arousal evoked by scene stimuli, which uses graphic figures to represent nine levels of pleasure and arousal. Following experimental session, participants were asked about their awareness and ability to detect overlaid stimulus features present in some trials (see below). Participants completed a post-experiment questionnaire, which contained questions regarding demographic information, smoking status, and preference for visceral acceleration
after which subjects were debriefed on the nature of the experiment. For the EEG portion of the study, thrill seekers (TS) were defined as individuals rated themselves as a 5 (“I love it”) on their preference for acceleration. All other responses were classified as healthy control subjects (HC). Individuals who endorsed being a current cigarette smoker or nicotine vaporizer user were classified as nicotine users (NU).

Participants in the fMRI portion of the study also completed two additional rating scales to measure nicotine dependency and sensation seeking. The Fagerstrom Test of Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) is a 6-item scale designed to measure the degree to which participants are dependent on nicotine. To better assess thrill seeking behavior, a standardized and validated scale was completed by participants completing the fMRI portion of the study. The Brief Sensation Seeking Scale (B-SSS) (Hoyle, Stephenson, Palmgreen, Lorch, & Donohew, 2002) evaluates 4 different subtypes of sensation seeking including experience seeking, boredom susceptibility, disinhibition, and adventure or thrill seeking. The thrill seeking sub-score from the B-SSS is used to categorize individuals as a low (2-4), medium (5-7), or high (8-10) sensation seeking. Non-smoking participants who scored in the high range were classified as TS.

*Stimuli*

Two grayscale picture sets were created by selecting pictures from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2008), cigarette-related pictures from other laboratories (Versace et al., 2012), and scenes similar to the IAPS assembled in our laboratory. Each set included 5 picture categories: mutilations [MUTI], neutral [NEUT], erotica [EROT], acceleration [ACCL], and carcinogenic [CARC]) with 15 pictures each repeated once (75 total
pictures per set). All scenes depicted human beings as previous research suggests that stimuli with people, regardless of valence, are rated as more arousing and evoke higher LPPs than those without people (Schupp et al., 2004; Weinberg & Hajcak, 2010). Scenes, presented at 800x600 resolution, were balanced by category to be statistically equivalent in luminance and 90% quality JPEG files size using GIMP 2.8 (www.gimp.org). Scene sets were presented in a pseudo-random sequence with no more than two scenes of the same category presented consecutively using Psychophysics Toolbox (Brainard, 1997), implemented in MATLAB (R2007b; Mathworks, Inc., Natick, MA, USA).

**ERP acquisition, processing, and analysis**

Participants were seated in a dimly lit room approximately 60 inches from a 32” Westinghouse monitor resulting in a 26° viewing angle. As depicted in Figure 1, each picture was initially presented for 2000ms and contained a central red fixation dot. To evoke the steady-state, a series of yellow dots, flickering at 7.5 Hz, was then overlaid on top of the picture for 4000ms followed by a variable inter-trial interval (ITI) of 3500-5500ms that contained a black background with a white question mark. To maintain participant attention during the presentation, during the presentation of specific pictures (2 pictures from each category, N=10), the randomly moving dots briefly began moving coherently. During the ITI, participants were instructed to respond with a mouse click whether the randomly moving dots moved coherently at any point during the presentation of the picture. To improve the signal-to-noise ratio, each picture was presented twice during the session. Prior research has shown that brain reactivity is highly consistent across repeated scene series, and thus habituation was not a concern (Schupp et al., 2006). The stimuli were presented the second time in a different pseudo-random order after the completion of the
initial presentation cycle. Trials that contained coherent motion were discarded prior to ssVEP analysis (N=20). The entire picture-viewing session lasted approximately 35 min.

Electrocortical activity was recorded continuously from 64 electrodes using a Biosemi EEG system (Biosemi B.V. Amsterdam, Netherlands; www.biosemi.com) and sampled at a rate of 512Hz, using midline CMS/DRL as a recording reference. Impedances were kept below 50kΩ, as recommended. For EPN/LPP analysis, trial epochs (approximately 2200ms before and 0ms after onset of the flickers dots) were analyzed with EMEGS 2.6 (Peyk, De Cesarei, & Junghöfer, 2011), eye-blink correction and interpolation was applied and trials with excessive noise (< 2% of total) were excluded. Data were first low-pass filtered with a 19th order Butterworth filter with a stopband of at least 45dB and passband of 30Hz. A high-pass filter was also applied with a stopband of .01dB and passband of .05Hz. The LPP signal was extracted between 400-900ms (channels: CP1, P7, Pz, CPz, Cz, CP2) and the EPN signal was extracted between 200-350ms (channels: P7, PO7, O1, P8, PO8, O2).

For ssVEP analyses, trial epochs (190ms before and 4940ms after dot onset) were corrected for eye-blinks and trials with excessive (< 2%) noise were excluded. Data were first low-pass filtered with a 19th order Butterworth filter with a stopband of at least 45dB and passband of 30Hz. A high-pass filter was also applied with a stopband of 1dB and passband of 3Hz. A phase-shifted version (the analytic signal) of the empirical signal was then generated using the native Hilbert function implemented in MATLAB, and the time-varying amplitude was extracted as the modulus of the empirical and analytic signal. This process finds the driven frequency of the ssVEP signal and smooths the overall signal into an interpretable waveform. The Hilbert transformation possesses high oscillatory visuocortical response at the driving frequency (7.5 Hz) and its frequency spectrum as derived from FFT. The ssVEP signal was
fMRI acquisition, processing, and analysis

Prior to entering the bore of the scanner, participants were fitted with earplugs, headphones, fiber-optic goggles (Resonance Technology, Inc., San Diego, CA, United States), and given a patient-alarm squeeze ball. Padding inside the head coil and explicit verbal instruction were used to limit head motion. Each participant spent approximately 40 minutes inside the scanner, during which they received a structural scan and two functional scans, one rapid sampling prescription and one whole brain prescription. During the functional scans, participants were instructed to attend to each picture and maintain fixation on a red point at the center of the screen throughout the picture series. As depicted in Figure 2, pictures were presented for 2000ms followed by a variable ITI of 10000-12000ms. Scenes consisted of the same 75 pictures presented during the EEG session. Each scene was presented once during each functional scan in a different pseudorandomized order. Orders of presentation were counterbalanced across subjects. The task duration for each fMRI session was approximately 16.25 minutes.

Once participants were comfortable inside the magnet, a T1-weighted structural volume was collected consisting of 144 sagittal slices with a 256x256 matrix and 1-mm isotropic voxels. The functional prescription for the rapid sampling scan was comprised of eight oblique axial slices (64 x 64 gradient echo planar imaging (EPI), 192mm field of view (FOV), 4mm thickness, 0.5-mm gap, 25° flip angle, 30-ms echo time (TE), 500-ms repeat time (TR)) positioned over the brain to enable coverage of the OFC, AMG, FUS, LOC, and MOG in one slab. The whole brain
functional prescription consisted of 30 interleaved axial slices (64 x 64 gradient echo planar imaging (EPI), 224mm FOV, 3.5mm thickness, no gap, 90° flip angle, 30-ms TE, 2000-ms TR).

Each participant’s whole brain time series was motion corrected using trilinear interpolation, spatially smoothed across two voxels (5.625mm FWHM), linearly de-trended, filtered at 0.02-Hz high pass, and temporally smoothed with a 3 sec Gaussian filter using BrainVoyager QX 2.8 (Brain Innovation; brainvoyager.com). Rapidly sampled functional time series was motion corrected using trilinear interpolation, spatially smoothed across two voxels (5.625mm FWHM) and linearly de-trended and filtered at 0.02-Hz high pass, and temporally smoothed with a 3-point (750ms) Gaussian filter. 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).

All structural and whole brain data were spatially standardized to Talairach coordinate space and entered into a random-effects (RFX) ANOVA, with scene content (EROT, ACCL, NEUT, CARC, and MUTI) convolved with a standard 2-gamma hemodynamic response function, a 4-voxel threshold, corrected for serial correlations, and limited to voxels within the brain. An RFX-ANOVA analysis examining the interaction between group (TS-HC, and NU-HC) and a priori scene categories of interest (ACCL, CARC, NEUT) was conducted using an alpha of .01, corrected for multiple comparisons with a 28-voxel threshold, and brain mask.

Furthermore, t-tests were conducted to evaluate BOLD signal differences in each group relative to HC for the scenes of interest (ACCL or CARC) relative to NEUT.
**Granger Causality Analysis**

Granger causality analysis (GCA) assesses the degree of directional connectivity between regions of interest (nodes in a connected network) based on the predictive value of one region's time series on the activity in another. For example, in the context of the current study, if BOLD signal variation of FUS can be predicted by past activity in AMG, over and above what previous activity in FUS can predict of itself, then the amygdala can be said to "Granger cause" or show directional connectivity with FUS. Because GCA can account for conditional probabilities among multiple regions of interest, here we are specifically interested in the causal relationships among AMG, FUS, and lateral OFC during emotional scene perception.

We estimated directional connectivity among our regions of interest using the Multivariate Granger Causality (MVGC) Analysis MATLAB toolbox (for a full description of the method, see Barnett & Seth, 2014). While GCA is most often implemented on electrophysiology data recorded at high temporal resolution, it has also been shown to be valid and reliable in the analyses of BOLD signal time series, given sufficient sampling rates, as collected in the current study (Bressler & Seth, 2011; Deshpande, Sathian, & Hu, 2010b; Friston, Moran, & Seth, 2013; Wen, Rangarajan, & Ding, 2013). Although temporal smoothing, commonly employed in fMRI preprocess, can lead to zero-lag correlation that can bleed into estimates of time-lagged causality, previous work indicates that this has minimal effect on connectivity results (Deshpande, Sathian, & Hu, 2010a).

Results from random-effects ANOVA with a false discovery rate (FDR) threshold of $p < 0.05$ were used to bilaterally sample BOLD signal from regions of interest (ROI), including AMG, FUS, and lateral OFC with a cluster size of 10 mm$^3$ resulting in ROIs of the same size and shape. These regions were chosen based on our previous work investigating subcortical
connectivity with ventral visual and prefrontal regions, and their roles in emotion and rewarding scene perception (Sabatinelli et al., 2014; Sabatinelli et al., 2009; Sabatinelli et al., 2015).

Coordinates for each ROI were chosen by a combination of previous work, visual inspection, and verification by the Talairach Daemon. These directional connectivity estimates reflect the reliability of influence between the 3 regions during the scene series, thus exploiting the temporal resolution of our MR acquisition design to identify potential differences in the pattern of causality among these regions that may be specific to our subject groups.
Figure 1. EEG paradigm. Participants (N96) first viewed an emotional, rewarding, or neutral scene for 2 seconds. This was followed by an overlay of flickering dots (7.5Hz) to evoke the steady-state response for 4 seconds. Trials were followed by a variable inter-trial interval of 3.5-5.5 seconds. 20 of the 150 trials included coherent motion during which time the dots moved together. During the inter-trial interval, participants indicated if they noticed the coherent motion (yes/no).
Figure 2. fMRI paradigm. Participants (N40) viewed the same series of 75 emotional, rewarding, or neutral scenes. Each scene was presented for 2 seconds followed by a variable inter-trial interval of 10-12 seconds. Participants were instructed to maintain gaze on the red dot at the center of each picture.
CHAPTER 3

RESULTS

Participants

EEG Session

96 individuals participated in the EEG portion of the study (48 female) with an average age of 19.36 years (SD=1.52 years). Across subjects, males and females did not significantly differ in age (mean males: 19.44 ± 1.79 years, females: 19.29±1.22 years, \(t(94)= -.467, p=.641\)).

The sample consisted of 21 nicotine users (6 female). Of the non-smoking sample, 32 participants (15 female) were classified as “thrill seekers” (TS) as defined by post-experimental self-report and 39 (26 female) were classified as HCs. Of the smoking sample, 9 subjects also classified as TS, but were only included in the smoking category for data analysis. Four subjects (1 female) did not complete the post-experimental questionnaire therefore, smoking status and acceleration preference was unavailable for those participants. Age did not differ between any of the groups (mean HCs: 19.36 ± 1.22 years, mean NU: 19.19 ± 1.33 years, mean TS: 19.59 ± 1.98 years). Sex distribution for the NU and HC groups was uneven with NUs more likely to be male (\(\chi^2 = 5.520, p=.017\)) and HCs more likely to be female (\(\chi^2 = 4.423\ p=.031\)).
fMRI Session

40 participants (18 female) participated in the fMRI portion of the study. One NU participant fell asleep during the MRI session and was excluded resulting in 13 HC (8 female) (mean age: 19.23 ± 1.01 years), 13 TS (6 female) (mean age: 19.38 ± 1.66 years) as classified by the B-SSS, and 13 NU (4 female) (mean age: 19.38 ± 1.39 years). 7 NUs classified as TS but were only included in the NU group for data analysis. NUs reported an average Fagerstrom score of 2.62 ± 2.33 resulting in a low overall nicotine dependence across the sample. There were no differences between the fMRI group and whole group regarding scene ratings or EEG results as discussed below.

Scene Stimulus Ratings

Arousal and pleasantness ratings of the scenes are shown in Figure 3. ACCL scenes were rated the most pleasant and MUTI the least pleasant. As designed, both pleasantness and arousal differed as a function of category (pleasantness: $F(4)=169.57$, p<.001; arousal: $(F(4)=143.83$, p<.001). For pleasantness, each category significantly differed from the others. For arousal, all categories significantly differed from one another except for EROT and ACCL and EROT and MUTI.

Group Differences

Across the entire sample (N96), there was a category by group interaction for pleasantness ratings ($F(8)=3.70$, p<.001) (Figure 4). This interaction was driven by the NU group; with higher pleasantness ratings for CARC scenes relative to both HC and TS (NU>HC: mean diff=1.60, $t(89): 4.60$, p<.001; NU>TS: mean diff=1.53, $t(89)=4.96$,
p<.001). There was no group by category interaction or effect of group for arousal ratings (Figure 4).

**ERP Results**

EPN, LPP, and ssVEP waveforms across participants (N96) and scene category are shown in Figure 5. LPP and EPN amplitudes were the most sensitive to EROT scenes. ssVEP amplitude was more sensitive to MUTI scenes (Figure 5). Each ERP measure significantly differed as a function of scenes category (LPP: F(4)=63.57, p<.001; EPN: F(4)=29.41, p<.001; ssVEP: F(4): 19.37, p<.001). Significant LPP amplitude differences were found between each category except CARC vs. ACCL and CARC vs. NEUT. The EPN for EROT scenes elicited significantly enhanced negativity (less positivity) compared to all scenes categories, and ACCL scenes elicited enhanced negativity relative to CARC scenes. As a potential result of the delayed onset of the flickering dots, all scenes categories except ACCL evoked a significantly higher ssVEP amplitude as compared to NEUT scenes (EROT mean: 1.11± 0.47, t(95)=2.721, p=.008; CARC mean: 1.10 ± .50, t(95)=2.35, p=.021; MUTI mean: 1.16±.51, t(95)=3.52, p=.001) (Figure 6 & 7).

Correlational analyses constructed using the average BOLD signal (6-8s) extracted from rapidly sampled fMRI in response regardless of category in each subject and found a negative correlation between the LPP and EPN (\(R^2=.41, F(1)=43.16, p<.001\)) as well as a weak positive correlation between the ssVEP and LPP (\(R^2=.07, F(1)=4.74, p=0.03\)). There was no relationship between average peak BOLD signal from visual regions and any ERP measure.
ERP Group Differences

There was no effect of group on EPN, LPP, or ssVEP amplitudes, nor was there a group by category interaction (Figure 8). When exploring potential differences scene by scene within each category, no differences were found between groups, and there was no correlation between ERP response and scene valence or arousal ratings.

Whole Brain fMRI Results

BOLD activation across category relative to fixation is depicted in Figure 9 and results from the random-effects ANOVA across category in Figure 10. When examining 2x2 ANOVAs (NU or TS vs. HC and ACCL or CARC and NEUT), there was a group by category interaction for NU and HC in multiple regions including mPFC, insula, IFG, MOG, and IOG (Figure 11 and Table 1). T-tests revealed that the NU group exhibited more reactivity relative to HC to CARC scenes (Figure 12 & Table 2). The NU group also exhibited increased activation in left cerebellum to NEUT scenes (Table 2) compared to the HC group. This cluster was adjacent to but not overlapping with CARC clusters (Figure 13). There was no category by group interaction between TS and HC and ACCL/NEUT scenes.

Granger Causality Analyses

fMRI rapid sampling RFX-ANOVA results are depicted in Figure 14, and GCA results across category and group are depicted in Figure 15. Results showed that AMG, FUS, and OFC exhibited significant bidirectional connectivity with the other regions. Within groups analysis found differential connectivity patterns between groups and scenes of interest (ACCL & CARC).
For ACCL scenes, TS exhibited more bidirectional connectivity between FUS and OFC than HC; whereas, HC exhibited more connectivity from OFC to AMG (Figure 16). When ACCL GC values were subtracted from NEUT values, HC exhibited more directional connectivity between OFC to AMG and OFC to FUS than TS. For CARC scenes, NU showed more connectivity from FUS to AMG and FUS to OFC than HC (Figure 17). When subtracted from NEUT GC values, NU continued to exhibit increased directional connectivity from FUS to AMG relative to HC.
### Table 1: Increased activation from interaction analysis between smoking status and passive viewing of smoking vs. neutral scenes

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Hemi</th>
<th>TAL peak coordinates</th>
<th>Cluster size (voxels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFC</td>
<td>Right</td>
<td>14 42 24</td>
<td>232</td>
</tr>
<tr>
<td>Superior Frontal Gyrus</td>
<td>Right</td>
<td>18 61 8</td>
<td>1405</td>
</tr>
<tr>
<td>IFG</td>
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<td>369</td>
</tr>
<tr>
<td>midACC</td>
<td>Right</td>
<td>10 0 45</td>
<td>524</td>
</tr>
<tr>
<td>Claustrum</td>
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<tr>
<td></td>
<td>Right</td>
<td>29 11 -4</td>
<td>482</td>
</tr>
<tr>
<td>Superior Temporal Gyrus</td>
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<tr>
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<tr>
<td>MOG</td>
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<td>439</td>
</tr>
<tr>
<td>IOG</td>
<td>Right</td>
<td>38 -81 -4</td>
<td>1027</td>
</tr>
</tbody>
</table>

Abbreviations: Hemi: Hemisphere; HC: healthy control; NU: nicotine user; CARC: Carcinogenic; NEUT: Neutral; mPFC: medial prefrontal cortex; IFG: inferior frontal gyrus; ACC: anterior cingulate cortex; MOG: middle occipital gyrus; IOG: inferior occipital gyrus
Table 2: Whole brain results showing increased activation when passively viewing smoking & neutral scenes in nicotine users relative to controls (Nicotine Users > Controls)

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Hemi</th>
<th>TAL peak coordinates</th>
<th>Cluster size (voxels)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>CARC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mPFC Right</td>
<td>Right</td>
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<tr>
<td>mPFC Right</td>
<td>Right</td>
<td>21</td>
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</tr>
<tr>
<td>ACC Right</td>
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</tr>
<tr>
<td>PHG Left</td>
<td>Left</td>
<td>-18</td>
<td>-33</td>
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<tr>
<td>PHG Right</td>
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<td>17</td>
<td>-33</td>
</tr>
<tr>
<td>Posterior Cingulate Cortex</td>
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<td>-33</td>
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<tr>
<td>Cuneus Right</td>
<td>Right</td>
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<tr>
<td>MOG Right</td>
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</tr>
<tr>
<td>Fusiform Left</td>
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<td>-66</td>
</tr>
<tr>
<td>NEUT</td>
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<td></td>
<td></td>
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<tr>
<td>Inferior Occipital Gyrus</td>
<td>Left</td>
<td>-27</td>
<td>-81</td>
</tr>
</tbody>
</table>

Abbreviations: Hemi: Hemisphere; CARC: Carcinogenic; NEUT: Neutral; mPFC: medial prefrontal cortex; ACC: anterior cingulate cortex; PHG: parahippocampal gyrus; MOG: middle occipital gyrus
Figure 3. Scene ratings across the sample (N96). A). Pleasantness ratings B). Arousal ratings.

Figure 5. ERP waveforms across the sample (N96). A). EPN; B). LPP; C). ssVEP. Dark blue lines: Erotica; light blue: Acceleration; green: Neutral; orange: Smoking Cues; red: Mutilations. Shaded areas indicate the time epochs extracted for further analysis. Abbreviations: ms: milliseconds.
Figure 6. Steady-state amplitude reversal for emotional relative to neutral scenes. A). Previous ssVEP results from Muller et al. 2008 highlighting increased ssVEP amplitude in response to neutral scenes relative to pleasant and unpleasant scenes. B). ssVEP response in the current paradigm during which dot-probe was preceded by 2000ms static scene. Note the reversal of amplitudes with emotional amplitudes increased relative to neutral.
Figure 7. Extracted raw and z-scored ERP results (N96). Raw extracted data from each ERP measure for each ERP measure is first plotted (A). To better visualize across ERP measures, which differ in range and timing, raw scores were transformed to z-scores (B). In addition, given the nature of the EPN, scores were reversed to allow for easier interpretation. Dark blue bars: Erotica; light blue: Acceleration; green: Neutral; orange: Smoking Cues; red: Mutilations. Black bars indicate standard error.
Figure 8. Z-scored ERP results by group (N96). LPP data for each group is first plotted in (A) followed by the EPN (B), and ssVEP (C). As in Figure 6., the EPN is reversed to allow for easier interpretation. Across groups and ERP type there is striking similarity in responses for each component. There were no significant differences between groups for any ERP component. Dark blue bars: Erotica; light blue: Acceleration; green: Neutral; orange: Smoking Cues; red: Mutilations. Black bars indicate standard error. Abbreviations: HC: Healthy Control; TS: Thrill-Seeker; NU: Nicotine User.
Figure 9. fMRI whole brain results across scene category (N39): Results reveal regions activated by scenes regardless of category relative to rest (FDR-corrected).
Figure 10. Whole brain random-effects ANOVA interaction results (N39). A). Regions that exhibited increased activation as a function of group and category (FDR-corrected, p=.05). B). Bold signal change in amygdala (AMG), fusiform gyrus (FUS), inferior parietal sulcus (IPS), and lateral occipital cortex (OFC) across groups. Dark blue bars: Erotica; green: Neutral; red: Mutilations.
Figure 11. Category by group interaction between Nicotine Users and Controls when viewing smoking and neutral scenes (N26) (p=.01, 25-voxel threshold). Increased activation was found in several regions including, medial prefrontal cortex, mid-anterior cingulate, superior temporal sulcus, superior temporal gyrus, and inferior and middle occipital gyri.
Figure 12. Activation differences in Nicotine Users & Controls to smoking cues (N26). A). Increased reactivity in nicotine users compared to controls when viewing smoking cues (p=.01, 7-voxel threshold). B). Regions exhibiting increased reactivity were extracted. Across regions, nicotine users exhibited significantly higher signal change compared to healthy controls. Green bars: Healthy Controls, Red bars: Nicotine Users. Abbreviations: HC: Healthy control; NU: Nicotine User; MPFC: Medial Prefrontal Cortex; SFG: Superior Frontal Gyrus; ACC: Anterior Cingulate Cortex; PCC: Posterior Cingulate Cortex; PHGL: Left Parahippocampal Gyrus; PHGR: Right Parahippocampal Gyrus; MOG: Middle Occipital Gyrus; FUS: Fusiform Gyrus
Figure 13. Activation differences in Nicotine Users & Controls to neutral scenes (N26). A). Increased reactivity in nicotine users compared to controls when viewing neutral scenes (p=.01, 7-voxel threshold). B). Overlay of regions exhibiting increased activity to smoking cues and to neutral cues show that while adjacent, regions are distinct. Blue: Neutral scenes (Nicotine Users>Controls); Red: Smoking scenes (Nicotine Users>Controls).
Figure 14. Rapidly sampled random-effects ANOVA category interaction results (N38). A). Regions that exhibited increased activation as a function of group and category (FDR-corrected, B).
p=.05). B). Mean percent signal change (4-8s) in amygdala (AMG), fusiform gyrus (FUS), and lateral orbitofrontal cortex (OFC) between groups. Dark blue bars: Erotica; light blue: Acceleration; green: Neutral; orange: Smoking Cues; red: Mutilations. Black bars indicate standard error. Abbreviations: HC: Healthy Control; TS: Thrill-Seeker; NU: Nicotine User.
Figure 15. Directional connectivity across scene category and participants. Granger causality values representing functional influence between each region of interest across participants when viewing all scenes. The dotted line represents the $p < 0.0000005$ threshold of significant influence (all values met significance). Abbreviations: AMG: amygdala; FUS: fusiform gyrus; OFC: orbitofrontal cortex.
Figure 16. Directional connectivity between Thrill-Seekers & Controls when viewing acceleration and neutral scenes. Granger causality values representing functional influence to and from each of the three regions of interest, for control (green bars) and thrill-seeking (blue bars) participants when viewing neutral (A) or fast acceleration scenes (B). (C) Difference in granger causality values between acceleration and neutral scenes. The dotted line represents the p < 0.05 threshold of significant influence. Abbreviations: AMG: amygdala; FUS: fusiform gyrus; OFC: orbitofrontal cortex; NEUT: neutral; ACCL: acceleration; HC: healthy control; TS: thrill-seeker.
Figure 17. Directional connectivity between Nicotine Users & Controls when viewing smoking scenes and neutral scenes. Granger causality values representing functional influence to and from each of the three regions of interest, for control (green bars) and nicotine users (green bars) participants when viewing neutral (A) or smoking scenes (B). (C) Difference in granger causality values between smoking cues and neutral scenes. The dotted line represents the p < 0.05 threshold of significant influence. Abbreviations: AMG: amygdala; FUS: fusiform gyrus; OFC: orbitofrontal cortex; NEUT: neutral; CARC: carcinogenic; HC: healthy control; NU: nicotine user.
CHAPTER 4

DISCUSSION

In this study, we examined the role of emotion and reward processing using the complementary recording modalities of EEG and fMRI. Acquiring standard ERPs and ssVEP along with both rapidly sampled and whole brain fMRI, we sought to identify potential differences in neural measures of emotion and reward processing in two groups of undergraduate participants with distinct reward sensitivities. Specifically, we examined whether individual difference in reward preference modulate neural response to emotional and rewarding scenes of fast acceleration in sensation seekers, and smoking cues in nicotine users. Overall, we found that while ERP amplitudes varied based on emotional content, ERP amplitudes were not affected by individual differences in secondary reward preferences. However, a striking finding was reversal of the ssVEP amplitude modulation with increased ssVEP amplitude to emotional (relative to neutral) scenes, suggesting that the latency at which the flickering stimuli appear (relative to scene onset) affects the pattern of steady-state response to emotional scenes. Whole brain fMRI measures also differed as a function of scene category. Subsequent group analyses showed multiple clusters of enhanced activation for nicotine users relative to controls when viewing carcinogenic scenes. Subsequent GCA analysis found that while AMG, FUS, and lateral OFC were significantly connected regardless of picture category, the pattern of connectivity differed as a function of group and category. The following discussion is broken down by dependent measures starting with EEG.
EEG measures

Amplitudes for the EPN, LPP and ssVEP differed as a function of emotional category. The EPN exhibited a significantly enhanced voltage negativity to erotica relative to all other scenes. The EPN, most often reported as an arousal sensitive ERP, is also reported to be modulated by scene valence, and perhaps specifically erotic scenes. Previous research reports significantly enhanced voltage negativity in response to pleasant and arousing scenes relative to neutral and unpleasant scenes (mutilations) suggesting a pleasant bias (De Cesarei & Codispoti, 2006; Flaisch, Stockburger, & Schupp, 2008; Schupp, Junghofer, Weike, & Hamm, 2004; Schupp et al., 2007). Scenes of erotica appear to be particularly salient and have been shown to elicit enhanced EPN amplitudes compared to a variety of unpleasant scenes (Weinberg & Hajcak, 2011). In the current study, the EPN was not only modulated more by erotic scenes relative to mutilation scenes, but also more so than scenes that were rated as both pleasant and arousing (ACCL). These results suggest that while the EPN may show a pleasure bias in scene perception, that bias may be isolated to erotic content or may be an effect of nude bodies in general, regardless of arousing content (Oliver et al., unpublished data).

As reported in previous work, highly arousing pleasant and unpleasant scenes exhibited increased LPP amplitude relative to neutral scenes (Cuthbert et al., 2000; Liu et al., 2012; Sabatinelli, Bradley, et al., 2007; Schupp et al., 2000; Weinberg & Hajcak, 2011). As with the EPN, erotic scenes elicited the most pronounced enhancement of LPP amplitudes compared to all other scene categories. In addition, acceleration scenes evoked enhanced LPP amplitudes compared to neutral, but to a significantly lesser extent than scenes of erotica or mutilations, suggesting they were moderately evocative stimuli. Previous research suggests that the LPP is modulated by arousing content rather than valence (Cuthbert et al., 2000; Keil, Muller, et al.,
2001; Schupp et al., 2004), which is supported here. However, given the arousal ratings for acceleration scenes, we might have expected to see more modulation of the LPP. Given that the LPP is considered a measure of increased attention to, or facilitated processing of, motivationally relevant or emotional stimuli, this may be due to the engaging nature of each scene (Hajcak et al., 2010; Lang & Bradley, 2010; Schupp et al., 2000). For example, erotica and mutilations capture attention and are evolutionarily important cues, whereas scenes of fast acceleration, while arousing, do not evoke the same degree of attention. Thus, the LPP may be better considered as modulated by scene arousal, given content that engages evolutionary meaningful cues, such as sex and violence (Bradley, Sapigao, & Lang, 2017).

Modulation of the ssVEP ran counter to our predictions. Here, we found enhancement of ssVEP amplitude during emotional relative to neutral scenes. Previous research shows the opposite pattern with enhanced ssVEP response for neutral relative to emotional images (Kemp et al., 2002; Kemp et al., 2004). One major difference underlying this reversal may be due to study design, specifically the relative onset of the flickering dots and scenes. All prior ssVEP research has employed paradigms which presented either (1) the scene flickering from the beginning of the trial or (2) the flickering dots first. To capture standard ERPs (LPP/EPN) unimpeded by the flickering dots, we first presented the scene for 2000ms, then introducing the flickering dots to evoke the ssVEP. Therefore, the timing of the presentation of the flickering dots may have resulted in differential modulation of the ssVEP amplitude. To test this theory, we conducted a second study during which the presentation of the dots was reduced to 100ms after initial presentation of the image; the same pattern was found. A better test of this possibility awaits another study in which the flickering dots precede the scene. However, a possible explanation for the present result is that after brief exposure to a scene, emotional attention can
be drawn toward the processing of that scene, and extend to the perceptual overlay of the
flickering dots. Thus, when attention is captured by arousing scenes, it is reflected in the ssVEP
evoked by the dots. In prior steady state studies, the scene may create a competition for visual
attention resources, leading to reduced ssVEP to the dots. This effect has not been reported in
any prior work and suggests significant implications for how the field understands the dynamic
impact of emotion on attention processes. Of course, to confirm that the delayed dot probe onset
is the cause of this reversal, future research will replicate previous studies with flickering dots
preceding picture onset using the same scene set and paradigm.

While both the LPP and ssVEP were modulated as a function of scene category, ssVEP
amplitudes were weakly correlated with LPP amplitudes. These results are in line with previous
research that report no significant or weak correlation between the two measures in response to
emotional scene processing paradigms (Hajcak et al., 2010; Miskovic et al., 2015). The weak
correlation found between the LPP and ssVEP support the idea that the LPP and ssVEP measure
distinct neuronal processes. One possible explanation is that the two ERP components measure
different mechanisms involved in motivated attention. The LPP is suggested to track activation
in parietal attention networks (Sabatinelli, Lang, et al., 2007), whereas emotionally modulated
ssVEP may reflect lower-tier visual cortical responses from several cortical sources (Keil et al.,
2009). We also did not find any relationship between the ssVEP and BOLD signal obtained from
rapidly sampled fMRI. Previous research using both ssVEP and fMRI during a spatial attention
task and spatial localization techniques correlated the BOLD signal and ssVEP response in
primary and secondary visual cortices (Di Russo et al., 2007). It could be that given the role of
ssVEP in attention processes, that our passive emotional viewing task was inappropriate for
finding a correlation between the two measures.
We found no differences in LPP, ERP, or ssVEP amplitudes between nicotine users and control groups, or group by category interactions. Previous research reports enhanced LPP response to carcinogenic images in both smokers and never smokers and enhanced LPP amplitude in smokers relative to non-smokers when viewing smoking relevant scenes (Deweese et al., 2016; Geier et al., 2000; Robinson et al., 2014). The lack of effect here could be a result of our sample population, which consisted of nicotine users that indicated use of fewer than a pack a day (or liquid equivalent) and reported low nicotine dependence as determined by the Fagerstrom Test of Nicotine Dependence. Previous research has compared populations that were heavy smokers who were seeking help in quitting, never-smokers, and abstinent smokers. Our group falls somewhere in between, as casual smokers. We also did not include images of people using vaporizers. While the images have been used in previous studies, they may not have been appropriate or salient for our young, casual smokers, and subsequently did not evoke a significantly different response than controls. We did not perform a power analysis, and our sample size was comparatively small relative to other studies. Therefore, our sample size may have not been adequate to find differences between groups. We also did not ask participants if they had ever smoked, so our smoking population consisted of only individuals who were current users, and our HC population consisted of individuals who were not current users. Evidently the degree of nicotine addiction moderates ERP reactivity to smoking cues.

LPP, EPN, and ssVEP amplitudes did not differ between thrill-seeking and control groups. There are several possible reasons for a lack of difference in the ERP response. Previous research investigating differences between high and low sensation seekers have reported differential ERP responses towards emotional scenes and during tasks employing images of common objects (Jiang et al., 2009; Lawson et al., 2012; Zheng et al., 2011). One ERP study
examining emotional processing using an emotional odd-ball paradigm reported differences between high and low sensation seeking groups in relation to valence and arousal of scenes and the N2 and P3 ERP components. Specifically, high sensation seekers exhibited an enhanced P3, while low sensation seekers exhibited a higher N2 in response to emotional scenes. High sensation seekers also showed a preference for intensely arousing scenes regardless of valence while low sensation seekers exhibited more attention towards negatively valenced scenes (Zheng et al., 2011). A bias is also reported in behavioral studies, with low sensation seekers preferring pleasant emotional stimuli compared to neutral or unpleasant stimuli, while high sensation seekers prefer both pleasant and unpleasant compared to neutral stimuli (Zaleski, 1984). This idea is supported by research showing that high sensation seekers exhibit stronger skin conductance responses to both erotic and violent scenes (Smith, Davidson, Perlstein, & Gonzalez, 1990), and enhanced affective startle potentiation towards threatening compared to neutral images relative to low sensation seekers (Lissek & Powers, 2003). Given that high sensation seekers may require more intense stimuli, our acceleration scenes may not have been salient enough. Ratings of the acceleration scenes indicated that the scenes were perceived as both pleasant and arousing, however, ratings did not differ between the TS group and HCs. This suggests that the scenes may not be effective in differentiating the TS population from HC. Future research will use individual scene data (both behavioral and neural) to choose stimuli (sounds, video, or virtual reality) that result in the most pronounced neural effects. Another possibility is that the construct of thrill seeking is not a suitable measure of differences in ERP responses. Previous research on novelty and stimuli repetition using images of common objects found no correlation between the thrill-seeking component and ERP measures (Jiang et al., 2009). Experience seeking, another component of sensation seeking, which also involves seeking
potentially dangerous activities, may also play a role. Future research should investigate the role of the experience seeking component alone and in conjunction with the thrill-seeking component.

*fMRI measures*

Findings from the whole brain analysis supported our hypothesis of increased BOLD signal change for arousing relative to neutral scene perception across our sample. When investigating the effects of the secondary reward scenes (acceleration and smoking-related) relative to neutral scenes, we found a significant group by category interaction between the control and nicotine using groups when viewing smoking-related or neutral scenes. Further investigation revealed that nicotine users exhibited significantly increased reactivity to smoking-related scenes in emotional and reward related regions including mPFC, ACC, Posterior Cingulate Cortex, PHG, and superior frontal gyrus. Our findings support previous fMRI smoking research that has reported increased activation in the extended visual system including the lingual gyrus, cuneus, precuneus, and FUS in addition to the ACC, mPFC, insula, and subcortical structures, such as the striatum in smokers (Engelmann et al., 2012; Robinson et al., 2014; Versace et al., 2011). Our findings are also supported by reward research, which report increased mPFC activation to secondary rewards (Sescousse et al., 2013). Together these data suggest that even casual smokers engage specific emotional and reward regions more so than controls when viewing smoking cues. Results from this study also highlight the importance of using more than one neuroimaging modality, as our ERP study found no significant differences between groups.

As with the ERP measures, we found no significant BOLD signal differences between the thrill-seeking and control group in response to scenes of fast acceleration. Our results are
contrary to previous research. Of the two fMRI studies investigating sensation seeking, both report significant differences in BOLD response between high and low sensation seekers. In a study of emotional processing, Joseph et al. (2006) report that high sensation seekers exhibited increased activation to high arousing scenes in right insula and posterior medial OFC, while low sensation seekers exhibited increased activation (and earlier onset) in anterior medial OFC and ACC in response to highly arousing scenes. In addition, low sensation seekers showed more sensitivity to scene valence whereas thrill-seekers were more sensitive to highly arousing scenes regardless of valence. Together these results support previous theories suggesting an overactive approach system in high sensation seekers. Reward research using a gambling task reported that nucleus accumbens activation was strongly correlated in high sensation seekers, specifically high novelty seeking (Abler et al., 2006). Reasons for a lack of difference between groups in our study may be the use of scenes that do not effectively engage the attention of our thrill-seeking sample. Another possibility is that our sample was not large enough to identify potential differences. Previous research has compared groups self-reporting high or low thrill-seeking on the BSSS scale. Unfortunately, we were unable to investigate this comparison as none of our participants scored in the low range. We conducted a secondary analysis to evaluate potential differences between high and low thrill-seekers, and did not find differences between these subset groups. We also investigated medium and high groups on the BSSS scale and found no differences.

Rapidly sampled fMRI and Granger Causality analyses revealed that across the sample and scene type, AMG, FUS, and OFC were significantly bi-directionally connected to one another. Reciprocal connections between AMG and FUS support the re-entrant feedback model of emotion processing (Amaral & Price, 1984). This model posits that after passing through the
ventral visual pathway, the AMG and FUS discriminate the motivational relevance of the scene. The AMG then feeds information back to occipital visual structures along the ventral pathway and exchanges information with prefrontal regions, specifically OFC (Armony & Dolan, 2002; Keil et al., 2009; Sabatinelli et al., 2005; Sabatinelli et al., 2009; Vuilleumier et al., 2004). The bidirectional pattern of connectivity between all three regions suggests that there is significant feedback not only between the AMG and FUS as previously reported (Sabatinelli et al., 2014), but also to and from the OFC during emotional scene processing. This is supported by recent GCA research reporting bidirectional connectivity between OFC and AMG (Frank et al., in prep). Frank and colleagues also reported delayed emotional discrimination of scenes in OFC relative to AMG and FUS, suggesting that information is first discriminated via the reentrant feedback model of FUS and AMG, but then is further processed by prefrontal regions, which in turn send information back to the AMG (Frank et al., in prep). In this model, the AMG appears to act as a hub from which other regions supply and provide information about the scene.

All three groups exhibited differential connectivity patterns in response to secondary rewards of fast acceleration and smoking cues. Compared to neutral scenes, the nicotine using group exhibited significantly more FUS to AMG connectivity as compared to the control group when viewing smoking cues. The exact reason for the difference between the nicotine and control group is unclear; however, one possibility is that smoking cues were more emotionally salient to the nicotine group than the control group. Compared to neutral scenes, the control group exhibited significant directional connectivity from OFC to AMG and from OFC to FUS relative to the thrill-seeking group. When examining GC values for both scene categories, it is notable that the GC values for neutral and acceleration scenes in between these regions are roughly equal in the thrill-seeking group, whereas the control group exhibited increased
connectivity to acceleration as compared to neutral scenes. In contrast, the control group responded with increased directional connectivity to acceleration scenes. One explanation for this difference may be that the thrill-seeking group did not find the acceleration scenes to be arousing, resulting in similar connectivity values as the neutral scenes. This theory would be in line with previous research that suggests that high sensation seekers require more intense stimuli (Zuckerman, 1997). However, in general, the reason for differences in connectivity patterns amongst groups is difficult to resolve without further studies that may target this effect specifically.

Conclusions

The goal of the present study was to examine brain function during the processing of emotional and reward relevant scenes using electrocortical and hemodynamic neuroimaging methods. We also sought to investigate potential individual differences to secondary rewards including fast acceleration and smoking cues in thrill-seekers and nicotine users. Overall, electrocortical LPP and EPN measures replicated prior studies showing significant modulation of each component by emotional scenes. Interestingly, the ssVEP modulatory pattern was reversed; showing increased amplitude in emotional relative to neutral scenes, possibly because of a delayed onset of the flickering stimuli relative to scene onset. Within groups, we found no significant ERP interactions with group, but in the fMRI data, both whole brain and rapidly sampled data revealed differential activation and directional connectivity during reward relevant scene perception. These results suggest that the thrill-seeking component of the sensation seeking scale may be unassociated with reactivity to our chosen scenes depicting fast acceleration. We also found that even casual smokers exhibit increased reactivity to smoking cues relative to non-smokers, however, as apparent in the fMRI data.
This study highlights the value of a multimodal approach to investigating neural functioning. By incorporating these complementary techniques, we observed unique differences compared to previous research, specifically, differences in nicotine users that were only apparent in fMRI data. Preliminary results from a follow-up EEG study examining the ssVEP reversal effect suggests that even a short scene exposure of 100ms is enough to reverse the pattern of ssVEP emotional modulation. An additional study, using the same scenes and paradigm, but reversing the relative onset of flickering stimuli and scene onset has the potential to clarify the origin of this effect. Future studies incorporating heavy nicotine users as well as modifications to acceleration scenes and measures may refine our understanding of the ERP measures of these reward cue evaluations.

In addition, using complementary techniques of standard ERPs, ssVEPs, and fMRI can help further our understanding of the mechanisms involved in the processing of emotional stimuli in both healthy and clinical populations. Given that the LPP and ssVEP appear to measure distinct neural processes, the use of these two ERP components in clinical populations may help us understand and validate the proposed mechanisms behind treatments, both pharmacological and neuromodulatory. Specifically, treatments such as DBS are contraindicated with MRI, and the use of both LPP and ssVEP measures may be beneficial in our understanding of the mechanisms behind such treatments. For example, a study investigating emotional attention using EEG in patients with epidural stimulation of the DLPFC and frontopolar cortex report reduced LPP to negative stimuli when stimulating the DLPFC, but not in patients when stimulating frontopolar cortex suggesting regionally specific regulation to emotional stimuli (Nahas et al., 2010). By incorporating other physiological measures such as the ssVEP, we may
further refine our understanding of such treatment effects and perhaps begin to individually tailor treatments based on neural response patterns.
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