Neural Profiles of Fear and Guilt: An Investigation Using Functional Magnetic Resonance Imaging and Spectroscopy

by

Jerry E. Murphy, M. S.

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Presented to:
Jennifer L. Robinson, (Chair) Associate Professor of Psychology
Jeffrey S. Katz, Professor of Psychology
Frank Weathers, Professor of Psychology
Scott Ketring, Associate Professor, Human Development & Family Studies
Darren Beck, Associate Professor, VCOM

Abstract

Fear and guilt are emotional processes that are implicated in the development and maintenance of psychiatric disorders. While research on fear has established a consistent neural network, a corresponding 'guilt' network remains elusive. Few research studies have directly compared these two affective states within a single paradigm. Here, functional magnetic resonance spectroscopy (fMRS) and functional magnetic resonance imaging (fMRI) were used to elucidate neurophysiological changes in response to script-driven imagery tailored to participant's fear- and guilt-evoking experiences. We hypothesized that fear would have greater neural activation in limbic structures and guilt, given its nature as a secondary emotion, would activate structures involved in cognitive processing. Furthermore, we anticipated differences in *gamma*-aminobutyric acid (GABA), glutamate, and glutamine between conditions. When comparing fear to neutral conditions, we corroborate previous evidence demonstrating increases throughout the limbic system using fMRI. A statistically significant network for guilt was not found, when compared to the neutral condition. FMRS analyses, focused in the anterior cingulate cortex, did not reveal any differences between the fear and guilt conditions. Comparing fear and guilt directly, exploratory *post hoc* functional connectivity analyses provided evidence for increased connectivity between limbic structures and regions associated with visualization (i.e., occipital cortex) during fear, and greater connectivity with structures involved in personal moral judgment (i.e., inferior frontal gyrus) and memory (i.e., hippocampus) during guilt. Data from this project provides evidence for differential neural networks for fear and guilt, supporting efforts to reconsider models of psychiatric disorders in which these two emotions are prevalent.

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List of Abbreviations

ACC	Anterior cingulate cortex
ALE	Activation likelihood estimation
ANOVA	Analysis of variance
AUMRIRC	Auburn University MRI Research Center
BA-TE	Behavior Activation and Therapeutic Exposure
BET	Brain extraction tool
BOLD	Blood-oxygen-level dependent
CompCor	Component-based noise correction method
CRLB	Cramer-Rao lower bounds
CSF	Cerebrospinal fluid
dmPFC	Dorsomedial prefrontal cortex
EPI	Echo-planar imaging
ET	Exposure Therapy
FEAT	FSL Expert Analysis Tool
FILM	FMRIB's improved linear model
FLIRT	FMRIB's linear image registration tool
fMRI	Functional magnetic resonance imaging
FMRIB	Oxford center for functional MRI of the brain
fMRS	Functional magnetic resonance spectroscopy
FSL	FMRIB Software Library
FWHM	Full width at half max
GABA	*Gamma*-aminobutyric acid

GM	Grey matter
GRAPPA	Generalized autocalibrating partially parallel acquisitions
IQR	Inter-quartile range
IRB	Institutional review board
MACM	Meta-analytic connectivity modeling
MCFLIRT	Motion correction FLIRT
MNI	Montreal Neurological Institute
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NIFTI	Neuroimaging Informatics Technology Initiative
OFC	Orbital-frontal cortex
PCC	Posterior cingulate cortex
PCL5	Posttraumatic Stress Disorder Checklist 5
PET	Positron emission tomography
PFC	Pre-frontal cortex
PTSD	Posttraumatic stress disorder
rCBF	Regional cerebral blood flow
ROI	Region of interest
SAM	Self-assessment Manikin
SDI	Script-driven imagery
SNR	Signal to noise ratio
SONA	Department of Psychology Research Participation Opportunities

SPM12	Statistical Parametric Mapping version 12
SSRI	Selective serotonin reuptake inhibitors
TRGI	Trauma-Related Guilt Inventory
VA	Veteran's Administration
vmPFC	Ventromedial prefrontal cortex
WM	White matter

Neural Profiles of Fear and Guilt: An Investigation using Functional Magnetic Resonance Imaging and Spectroscopy

Emotions and emotional dysregulation are implicated in many psychological disorders (Mennin, Holaway, Fresco, Moore, & Heimberg, 2007). Understanding the role and type of emotion involved in a disorder is key to developing effective treatment options (Aldao, Nolen-Hoeksema, & Schweizer, 2010). In some cases, the underlying emotion is the focus of treatment. Exposure therapy (ET), a treatment for posttraumatic stress disorder (PTSD), targets aberrant fear processing (Foa, Riggs, Massie, & Yarczower, 1995). While fear is considered to be an integral component in the development and maintenance of PTSD (Marin et al., 2016), other emotions, such as guilt, could be just as salient within the disorder (Frankfurt & Frazier, 2016). Whether one believes fear and guilt are discrete emotions representing different neural processes or only two points on a spectrum of negative affect is dependent on the theoretical approach to emotion that one prefers. Below is a review the literature on theories of emotion regarding fear and guilt.

Theories of Emotion

Understanding fear and guilt depends heavily on how one discerns and defines emotion. Since Plato and Aristotle, philosophers have debated the structure, cause, and meaning of emotions (Sander, 2013). Aquinas, Descartes, Hume, Kant, Wundt, and many other prominent founders of the field of psychology investigated emotion (Fehr & Russell, 1984). The first theory of emotion to demonstrate considerable empirical support was the James-Lange theory which claimed that the physiological response (i.e., autonomic nervous system response) to a stimulus was emotion (James, 1884). Cannon and Bard (1927) criticized this approach and instead claimed that the emotional response to a stimulus produced the autonomic response (Cannon,

1927). A third theory emerged in the early 1960's when Schachter and Singer (1962) published their two-factor theory of emotion. The two-factor theory posits that autonomic arousal in itself is insufficient for the experience of an emotion, but rather the environmental cues provide context for the arousal and thus enable a person to label the emotion experienced (Schachter & Singer, 1962). For example, if a person feels sympathetic nervous system activation (i.e., arousal) in the presence of a venomous snake, one is likely to label the arousal as "fear," but the same activation while watching your favorite sports team get close to scoring is likely to be labeled "excitement". While support for each of these theories is mixed, one critique is that they fail to account for the full range of human emotions (Sander, 2013).

A more recent conceptualization of emotion is the circumplex model, initially proposed by Russell (1980), that describes emotions on a continuum of two dimensions: valence (i.e., how positive or negative the emotion is) and arousal (i.e., how intense the emotion is). Contemporary versions of the circumplex model of emotions employ different labels for the valence axis such as positive to negative, approach to avoidance, or pleasure to pain (Posner, Russell, & Peterson, 2005). Based on this model, two emotions that are both negative, but differ in arousal, might not be considered discrete, but instead, fall on two points of a continuum. Within the circumplex model, fear is considered a negative emotion with high arousal, and guilt is a negative emotion with low arousal, suggesting that one of the primary factors differentiating these two affective states is arousal level (Scherer, 2005). Importantly, while the circumplex model is useful for characterizing emotions, it fails to provide any sense of the biological or neurological underpinnings of emotion. Thus, it is unclear how the differences in arousal may manifest in the central nervous system (CNS).

Not all approaches to emotion are based solely on responses to external stimuli or physical arousal. One approach is to differentiate between emotions that are phylogenetically preserved and can be identified and elicited in an animal, and those generally thought to be exclusive in humans and non-human primates (with few exceptions) (Morris, Doe, & Godsell, 2008). These are typically referred to as primary emotions (e.g., fear and anger), while emotions that are complex and require social or moral elements are considered secondary emotions (e.g., guilt and pride) (Leyens et al., 2000). Primary emotions are easier to study because they are robust and easily manifested in animal models in controlled settings (Liberzon & Ressler, 2016). Secondary emotions are problematic to operationally define, elicit, and to study (Berthoz, Grèzes, Armony, Passingham, & Dolan, 2006; Fourie, Thomas, Amodio, Warton, & Meintjes, 2014). Theoretically, although fear and guilt are both characterized by similar valence (i.e., negative affect), they should represent vastly different neural processes given their characterization as primary and secondary emotions, respectively, and even more so considering the differences in the levels of arousal associated with each emotion. However, empirical evidence examining the neurophysiological differences has yet to emerge, despite both emotions being implicated in several psychological disorders (Lissek & Grillon, 2010; R. A. Morey et al., 2015; Pugh, Taylor, & Berry, 2015; Zahn et al., 2015).

Guilt Versus Fear

Emotions are essential to understand as they play an integral role in many psychopathologies and guide the development of treatment strategies (Aldao et al., 2010; Mennin et al., 2007). For example, given the evidence that fear and/or guilt can be associated with PTSD symptoms (Pugh et al., 2015), it is therefore essential to understand the neurobiological underpinnings of these two disparate emotions to effectively create alternative treatment options.

Here, we briefly outline how these two emotions may form different affective and neurological bases for disorders such as PTSD. At the most basic level, it is important to distinguish that fear is characterized as a basic, reflexive emotion (James, 1884; Matsumoto & Ekman, 2009; Panksepp, 1992) while guilt is classified as a secondary emotion because it requires a cognitive appraisal (Creamer, McFarlane, & Burgess, 2005). However, these classifications do not provide useful characterizations regarding neural network differences that may exist between them.

If one considers fear and guilt as separate emotions representing different underlying processes, then one should expect differences in the neural substrates supporting their manifestation. Neural structures generally involved in fear have been well documented due to the ability to robustly induce fear in animal and human models (Liberzon & Ressler, 2016; Saffari et al., 2015). The ability to conduct animal models of fear has allowed for the fear network to be described at the neuronal level (Tovote, Fadok, & Lüthi, 2015) (for a review of fear networks from animal models please see Maren (2001) or Rokosz & Knapska (2018)). The neural projections of the amygdala involved in the fear network have been identified in humans as well (Paré, Quirk, & Ledoux, 2004). The literature is consistent in the identification of the fear network, which includes much of the phylogenetically preserved limbic system, including the amygdala, hypothalamus, thalamus, hippocampus, periaqueductal gray matter, and the locus coeruleus (Liberzon & Ressler, 2016; Marin et al., 2016; Wilker & Kolassa, 2013). The amygdala is thought to be the central structure in the fear response (Öhman, 2005), and serves to activate the sympathetic neural network responsible for the physiological experience of fear (Friedman, Keane, & Resick, 2014) in addition to enhancing memory formation (Yang & Liang, 2014). As such, this system is particularly vulnerable to trauma experiences as it initiates responses necessary for adaptation, memory formation, and recovery.

Guilt, however, is characterized as a self-reflexive emotion because the object of the emotion is the self, and not just the event (Fontaine, 2009). Guilt is classified as a moral emotion because it is born out of behavior that is incongruent with one's moral beliefs (Tangney, Stuewig, & Mashek, 2007). The neural network of guilt, compared to fear, is far less understood, partially because of difficulties in lab elicitation (Fourie et al., 2014, p. 203), and also because of the variability in the way that individuals process guilt (i.e., internalizing versus externalizing (Novin & Rieffe, 2015)). Using script-driven imagery (SDI) of a guilt-evoking experience, Shin and colleagues (2000) used positron emission tomography (PET) to identify areas of the brain where guilt elicited increases in regional cerebral blood flow (rCBF). Notably, they found that guilt activated the anterior cingulate cortex (ACC), an area of the brain involved in decision making and response inhibition (J. W. Brown & Alexander, 2017; Manza et al., 2016; Neubert, Mars, Sallet, & Rushworth, 2015), the left insula, a region involved in pain processing (Henderson, Gandevia, & Macefield, 2007; Kinoshita et al., 2016; Orenius et al., 2017), and the left inferior frontal gyrus, an area of the brain involved in moral decision making (Greene, Nystrom, Engell, Darley, & Cohen, 2004; White et al., 2017). Other studies that used different paradigms to study guilt report different patterns of activation in the brain. For example, one study that utilized a social prejudice paradigm to elicit guilt noted fMRI activations in the bilateral prefrontal cortex (PFC), anterior and posterior cingulate cortices (ACC and PCC), left anterior insula, precuneus, orbital frontal cortex (OFC), and the right thalamus (Fourie et al., 2014). However, the paradigm used in the preceding study may have produced activations that are linked to the theory-of-mind network rather than guilt, as the study used fabricated stories rather than autobiographical accounts (Dodell-Feder, Koster-Hale, Bedny, & Saxe, 2011). Morey and colleagues (2012), using a stimulus set that included guilt scenarios, found a positive

association between guilt ratings and activation in the left ventromedial PFC (vmPFC) to include portions of the OFC, supramarginal gyrus, dorsal-medial PFC, and the frontopolar cortex. Zahn and colleagues (2009) used descriptions of social behavior to elicit guilt and found only two significant areas of neural activation, the anterior vmPFC and the subgenual cingulate. Together, these results suggest that guilt elicits a highly variable network, and may depend on task/paradigm selection or participant-specific dependencies.

Hoping to provide some clarity on the reported neural activations for guilt, Gifuni, Kendal, and Jollant (2017) performed a meta-analysis. The meta-analysis involved activation likelihood estimation (ALE) and meta-analytic connectivity modeling (MACM) (Robinson, Laird, Glahn, Lovallo, & Fox, 2010) using 16 fMRI studies investigating guilt, including three of the four referenced studies noted previously. Briefly, ALE finds convergence among reported activations from neuroimaging studies, producing maps that are representative of processes irrespective of the tasks used to elicit those processes (Robinson et al., 2010). The meta-analysis found 12 regions that were consistently activated with guilt including the ACC, left anteromedial and superior PFC, right inferior frontal gyrus, the superior temporal cortex, the parahippocampal and middle temporal gyrus, left insula, supramarginal sulcus, and precuneus (Gifuni et al., 2017). These results provide support for a guilt network unaffected by task or paradigm specificity. Notably, the meta-analysis did not find convergent evidence for amygdala activation, suggesting that the amygdala may be differentially activated during fear compared to guilt, potentially accounting for the observed differences in arousal.

Given the evidence noted above, fear and guilt may have substantially different neural underpinnings. The amygdala is central to fear processing but has not been demonstrated to be integral to a guilt response. Furthermore, various PFC areas are implicated in guilt but are not

included in the fear network. This supports the notion that fear is reflexive and guilt is rooted in cognitive appraisals. However, in the context of PTSD, it is presumed that fear conditioning and subsequent failure of extinction are critical components of symptomatology (Amstadter, Nugent, & Koenen, 2009; Privratsky, Cisler, Chung, Bush, & Kilts, 2017; Weaver et al., 2018). The main pathway implicated for fear conditioning and extinction is the bidirectional connection between the PFC and the amygdala (Marek, Strobel, Bredy, & Sah, 2013). Thus, the PFC seems to be critical, regardless of whether fear or guilt are involved in the development of PTSD.

Further emphasizing the amygdala-PFC relationship in fear, several studies have looked at the role of GABA in the relationship between the PFC and the amygdala. The PFC is thought to have inhibitory control of the amygdala in response to fearful stimuli (Schneider et al., 2016), however, activation of the amygdala during fear, specifically the basolateral amygdala, results in inhibition of the PFC (Dilgen, Tejeda, & O'Donnell, 2013; Qi et al., 2018). This bidirectional relationship of the amygdala and PFC may be the result of GABA transmission. Piantadosi and Floresco (2014) used rats and a foot shock paradigm to investigate GABA transmission within the PFC (i.e., inhibition of the PFC) during fear learning and extinction. They discovered that GABA antagonist treatments (i.e., decreases in GABA) within the PFC diminished fear discrimination (Piantadosi & Floresco, 2014). A study conducted by Lin and colleagues (2011) found that rats that experienced fear reinstatement compared to rats that maintained fear extinction had reduced levels of GABA in the amygdala. Taken together, these studies suggest that during fear processing, the amygdala inhibits the PFC through GABA transmission and the strength of the fear experience may be related to the amount of GABA inhibition within the PFC. Thus, there should be a rise in GABA concentrations during the experience of fear. Additionally, these studies highlight the necessity of examining neural activation and neurometabolic changes

in critical structures, such as the amygdala and the PFC, to distinguish differences between fear and guilt networks.

Neuroimaging

Advancements in functional neuroimaging have afforded opportunities to examine neurofunctional activation and dynamics as well as neurometabolites, non-invasively. FMRI measures blood-oxygen-level-dependent (BOLD) changes within the brain (Ashby, 2011). The BOLD changes are considered an indirect (or inferred) measure of neuronal activity that can be used to report areas of activation across the whole brain in response to a stimulus, task, or between conditions (Mark W. Woolrich, Beckmann, Nichols, & Smith, 2009). Magnetic resonance spectroscopy (MRS) measures concentrations of key neurotransmitters and neuro-metabolites within a specified voxel (Harnett et al., 2017). Many MRS studies are concerned with neurometabolites that indicate neuronal health (Karl & Werner, 2010), but MRS and functional MRS (fMRS) are also used to look at specific neurotransmitter concentration changes between behavioral or psychological conditions (Harnett et al., 2017; Levar, van Leeuwen, Puts, Denys, & van Wingen, 2017; Taylor et al., 2015). Combining fMRI and fMRS methods to examine the underlying neurophysiological underpinnings of fear and guilt may represent a more sensitive approach toward identifying differences in neural networks associated with each emotion.

FMRI and fMRS have been used as complementary techniques within the same study targeting specific neurotransmitters. For example, Levar and colleagues (2017) combined fMRI and MRS to study the relationship of GABA transmission between the PFC and the amygdala by collecting spectroscopy data in the ACC. The results of their study suggest that in the dorsal ACC, GABA influences fear extinction and later recovery and correlates with amygdala

activation, indicating that the ACC may be a prime location to investigate emotional network differences (Levar et al., 2017). In another study, Kim and colleagues (2009) investigated the role of GABA and glutamate within the ACC using fMRS. They found that high levels of harm avoidance (an aspect of fear) were positively correlated with ACC GABA concentrations and negatively correlated with ACC glutamate concentrations (Kim et al., 2009). In an implicit facial emotion-processing task, Stan and colleagues (2014) measured GABA and glutamate concentrations in the dorsomedial PFC (dmPFC) and correlated those measurements with fMRI BOLD signals in the ACC. They found dmPFC GABA concentrations negatively correlated with ACC bold signal for sad faces when compared to shapes and a positive correlation between dmPFC glutamate concentration and ACC BOLD signal for the same contrast (Stan et al., 2014).

Glutamine is another neural substance that is of interest in MRS studies as it is used by neurons to produce both glutamate and GABA as part of the glutamate/GABA-glutamine cycle (Bak, Schousboe, & Waagepetersen, 2006). In a combined fMRS and fMRI study, Huang and colleagues (2015) looked at glutamate and glutamine concentrations in the medial PFC during mental imagery. They found glutamate/glutamine concentration increases in the medial PFC together with fMRI BOLD activation in the same area for mental imagery when compared to rest (Huang et al., 2015). These studies illustrate the effectiveness of examining fMRI and MRS together, as they can lend insight into the relationship that neurotransmitters like GABA, glutamate, and glutamine have with BOLD changes. Although fMRI and MRS have been used to examine neural networks and specific neurotransmitters involved in fear, there are fewer studies researching guilt, and to our knowledge, there are no studies making a direct comparison between fear and guilt using the same research paradigm, nor were any studies identified that examined guilt using fMRS.

As an ideal task for fMRS and fMRI, SDI is a robust research paradigm designed to activate salient emotional networks involved in remembering autobiographical events (L. A. Brown et al., 2018; Hopper, Frewen, van der Kolk, & Lanius, 2007; Levin, Cook, & Lang, 1982; Shin et al., 2000). Scripts are prepared from the participant's episodic memories and then played back to the participant while their emotional responses (i.e., physiological or neurological) are recorded (Shin & McNally, 1999). Using SDI to study specific emotions, and PTSD, is well established in the literature (L. A. Brown et al., 2018; Jovanovic, Rauch, Rothbaum, & Rothbaum, 2017; Lanius et al., 2002; Schweizer et al., 2018; Shin et al., 2000). Three papers from the early 2000's (Britton, Phan, Taylor, Fig, & Liberzon, 2005; Lanius et al., 2002; Lanius et al., 2003) established the efficacy of the SDI paradigm for studying emotions, specifically those salient to PTSD, and provided a framework for the current research study.

Hypotheses

To address the aforementioned gaps in the literature regarding methodological limitations in investigations of guilt and fear, this study used a within-subjects approach to characterize the neural underpinnings of fear and guilt. SDI served as a cornerstone in this research design due to its proven efficacy in eliciting emotions (Jovanovic et al., 2017). Individual guilt, fear, and neutral scripts based on the participant's memories were used to elicit each target emotion while undergoing fMRI and fMRS. The aim of this study was to identify neural network differences between fear and guilt to advance our understanding of these emotions which may aid in the development of new pathophysiological models of PTSD.

Hypothesis 1

There is a difference in neuronal activation, as measured by fMRI, in the two affective states. Fear and guilt will differentially activate limbic structures such that fear should activate

more subcortical structures (i.e., amygdalae), and guilt should activate cognition-based structures (i.e., OFC and ACC).

Hypothesis 2

There is a difference in the neurochemical underpinnings of fear and guilt within the anterior cingulate cortex (ACC). Specifically, it was expected that there would be increases in GABA/glutamate/glutamine during fear conditions compared to neutral, based on previous models of fear conditioning and fear responses where the ACC is known to be part of communication pathways between limbic structures and higher cortical regions (Levar et al., 2017). For guilt, only moderate fluctuations in GABA were expected due to the amygdala presumably not playing a role in guilt (Gifuni et al., 2017), but it was expected that guilt would produce higher levels of glutamate/glutamine over neutral, based on fMRI studies that suggest guilt is primarily processed in cortical regions (Rajendra A. Morey et al., 2012).

Methods

The overarching design of this project was the use of SDI to elicit the affective experience of a fearful or guilty episodic memories while collecting whole-brain fMRI and single region of interest (ROI) (i.e., ACC) fMRS data. The study was conducted as a three-phase study. Phase 1 of the study was an online screening survey presented through Qualtrics (Qualtrics, 2005) intended to identify those who met inclusion criteria, described below. Participants meeting inclusion criteria were contacted via e-mail and invited to participate in Phase 2. In Phase 2 of the study, participants were interviewed and recorded concerning a fearful, guilty, and neutral episodic memory. The interviews were used to create written scripts that were then recorded using a gender-matched voice for use in Phase 3. Phase 3 took place at the Auburn University MRI Research Center (AUMRIRC) where participants underwent

functional neuroimaging scans on a Siemens 7T MAGNETOM MRI scanner while listening to the recorded scripts.

Power Analysis

Prior to conducting the study, pilot data (n = 5) were collected and used to conduct an *a priori* power analysis to determine an adequate sample size. The power analysis was conducted using the web-based NeuroPowerTools (http://www.neuropowertools.org/neuropower/neuropowerstart/) (Durnez et al., 2016) applet on the contrast of interest (guilt > neutral). NeuroPowerTools calculated average peakwise power by initially determining the height of activation peaks and the distribution of peak p-values above and below the screening threshold (this data used z = 2.3) (Figure 1), and then estimating the remaining means and standard deviations for various sample sizes using maximum likelihood methods (Durnez et al., 2016). NeuroPowerTools provides a graph depicting the estimated power level for various sample sizes for uncorrected, Bonferroni, and Random Field Theory corrections (Durnez et al., 2016). Results from the power analysis indicated that with a sample size of 15, the estimated power for Random Field Theory (which is used in the current analytic plan) would be 0.82 (Figure 2). However, this number should be interpreted with caution because the pilot data used for this analysis was from five participants and the smallest sample size accepted by NeuroPowerTools is 10. While this may be a liberal estimation for power, unfortunately, existing power estimation programs for fMRI data are not stable at lower sample sizes.

Participants

Participants were recruited through a screening survey (Appendix A). Six-hundred and twelve people took the survey. Of those, 72 met inclusion criteria which were: 19 years of age or older, met the medical and safety requirements for magnetic resonance (MR) scanning, had a

fearful and guilty experience that was salient enough that recalling or talking about the event elicited the affect experienced during the original event, and were willing to describe that experience in detail. Participants were excluded from the study if they were 18 years of age or younger, did not meet medical requirements for MR scanning (i.e., metallic objects in their body, piercings that cannot be removed, or pregnant), did not have a salient fear and/or guilt experience, or were unwilling to discuss their experience in detail, or their experiences were too complex (i.e., the experiences included multiple affective states that would confound the effects of the target emotions). The 72 who met inclusion criteria were contacted via email and invited to participate in Phases 2 and 3. Fifteen participants (six males and nine females) with an average age of 24.67 years (*SD* = 11.76) completed all phases of the study (please see Table 1 for all demographics).

Materials

Phase 1.

Participants were screened using an online screening survey (Appendix A). The screening survey included an Auburn University Institutional Review Board (IRB) approved information letter outlining all aspects of the project, and requiring a response by the participant to either consent to the study or not to consent. If participants consented, they were asked basic demographic information and medical information pertinent to screening for the MRI session. Participants were then asked, "Do you have feelings of guilt associated with an event where your actions or inactions resulted in someone else being hurt (can include physically, emotionally, or spiritually hurt)"? If they endorsed "yes" and indicated that they were willing to talk to the research team about the events, the second portion of the survey was initiated. A negative response led to the end of the survey, where the participant was thanked for their time. Those

that endorsed that they had the required experiences were asked to briefly describe the guilt event and then administered the Trauma-Related Guilt Inventory (TRGI) (Kubany et al., 1996). The TRGI is a 32-item survey instrument with scores ranging from 0-128, designed to measure a person's feelings of guilt about an event. Higher scores indicate higher levels of guilt (Kubany et al., 1996). Following the questions regarding guilt, participants were then asked, "Do you have an experience where you felt a great deal of fear such that thinking about the event or talking about the event causes you to experience sensations of fear?" If they responded "yes" they were asked to briefly describe their fear event, which was then followed by the Posttraumatic Stress Disorder Checklist 5 (PCL-5) (Weathers et al., 2013). The PCL-5 is a 20-item survey instrument with scores ranging from 0-80. Higher scores indicating more PTSD symptom severity (Weathers et al., 2013). Participants were also asked to provide contact information to allow for an invitation to participate in Phases 2 and 3.

Phase 2.

A structured interview was given to participants during Phase 2. Participants were asked to describe in detail a guilty, fearful, and neutral experience. The process for developing the scripts for this study was based on the procedure described by Lanius and colleagues (2001). Participants were given some general instructions at the beginning of the interview as follows:

> "I'm now going to ask you to describe in detail an event where you felt a great deal of fear or guilt (or in the case of the neutral event, no emotion). I'd like you to include in your description the bodily sensations you were aware of at the time. Sometimes it is difficult to think of something "on the spot." It may help to close your eyes and imagine yourself back in the situation. Try to generate the same sensations and feelings that you had at the time. While the image is vivid in your memory, please describe the details of

the scene and the sensations you experienced. Include details such as: where you were; what you were doing; what other people were involved, and what they did or what happened to them; and how you felt."

Participants were also asked to use the names or terms for people or things as they use them in their everyday life. For example, instead of saying "I took my dog for a walk," they should use the dog's name and say, "I took Kodiak for a walk", thus further personalizing the description of events. After reading the instructions to the participant for each condition, the participants were asked to anchor the narrative in a time and place, then allowed to describe the event in detail. Questions were asked during the description of the event to fill in any missing information or to draw out more information. The interviews were recorded using a mobile device. Three events were recorded for each participant: fear, guilt, and a neutral situation which would serve as a baseline for neuroimaging analyses.

Phase 3.

Two instruments were used during Phase 3. Prior to the scan, participants were asked to complete a medical screening form designed to ensure that the participant was medically safe to undergo an MRI scan (Appendix B). After the scan was complete, participants were asked to complete a post-scan survey (Appendix C). The post-scan survey was an 8-item survey designed to measure the efficacy of the scripts at eliciting the target emotions using a 9-point Likert scale and the Self-assessment Manikin (SAM) with 1 indicating no arousal and 9 indicating very high arousal (Bradley & Lang, 1994). The questions provide data on how the emotions elicited from the scripts compared to the original event, and how arousing the emotions were for the first and second time the participants heard the scripts.

Procedure

Phase 1.

The procedures for this study were approved by the Auburn University IRB (16-018 MR 1602). The initial screening survey (Phase 1) was disseminated through the Auburn University Department of Psychology Research Participation Opportunities (also known as SONA) web page. Additionally, with professor permission, several class were briefed on the project and the screening survey link was disseminated by the instructor to the class for extra credit. Participants that completed the survey and met inclusion criteria were contacted via email to set up an appointment for Phase 2.

Phase 2.

Participants that took part in Phase 2, were provided an IRB-approved consent form. Following consent, the structured interviews were conducted and recorded. The recordings of the structured interviews were used to create written scripts approximately 550 words in length, corresponding to approximately 3 minutes and 20 seconds in length when read aloud. Scripts were designed to focus on the most affectively salient portions of the described event. The scripts were then recorded in a gender-matched voice using 2nd person present tense. The audio recordings were then programmed into E-prime 2.0 (Psychology Software Tools, Pittsburg, PA) for time-synced presentation during the functional neuroimaging portion of Phase 3. The program began with a start frame containing “Thank you for your participation. Please relax and remain still while we prepare the scanner” (Figure 3). The start frame remained visible until the scanner started acquiring data, which triggered advancement to the next frame. The next frame contained the words "Relax while we prepare the audio file” (i.e., the ‘Relax’ frame). The Relax frame was followed by an instruction frame which stated “When you hear the audio script, please

close your eyes and imagine yourself in the situation. Allow yourself to feel the emotions you experienced during the original event" (i.e., the 'Instruction' frame). The Relax and Instruction frames repeated between audio files. Each audio file was approximately 200 seconds long (3:20) with the order of presentation always having the neutral script in between the affective script. An effort was made to counter-balanced the order between participants, however, there were participants whose scripts necessitated being presented to the participant in chronological order which negated a fully counter-balanced design. The overall presentation of the E-Prime 2.0 (Psychology Software Tools, Pittsburg, PA) program was 11:30, 15 seconds shorter than the MRI acquisition time (Figure 3). Once the scripts were prepared, participants were contacted to schedule the MRI scan for Phase 3.

Phase 3.

Phase 3 was completed at the AUMRIRC. When the participant arrived for the MRI scan, they were asked to complete the medical pre-screening form (Appendix B) and provided another IRB-approved informed consent form. Participants were asked to change into scrubs, weighed, and checked for metal with a hand-held metal detector before being placed into the scanner. The participants were scanned on the Siemens 7T MAGNETOM scanner outfitted with a 32-channel head coil by Nova Medical (Wilmington, MA). Each participant had their scripts presented to them twice. During the first presentation of the scripts, fMRS data was collected with a separate acquisition for each script. The following instructions were given to the participant for each script, "Allow yourself to feel the emotions you experienced during the original event. Although normally we try to push down our emotions, I want you to focus on the emotion". The second presentation of the script was during fMRI data acquisition. During fMRI acquisition, the three scripts were played for the participant during one continuous scanning sequence using E-prime

2.0 (Psychology Software Tools, Pittsburg, PA). The order of script presentation (guilt, neutral, fear) varied across participants with neutral always presented between the affective scripts. Because the scripts were presented twice, following the MR session, participants were asked to complete the brief in-house survey, described previously, aimed at identifying the effectiveness of the scripts at eliciting the target emotions (Appendix C).

MR Imaging

Following routine set-up scans, a high-resolution structural scan was acquired for functional data registration purposes and to allow for accurate placement of the MRS voxel (T1 MPRAGE: 256 slices acquired ascending, voxel = 0.7mm^3, TR/TE/TI: 2200/2.89/1050ms, flip angle = 7^o, GRAPPA acceleration factor =2, acquisition time= 5:18). The structural scan was resliced on the transverse and coronal planes with slices centered on the ACC, for use in MRS voxel placement. The MRS voxel was 25mm^3 placed in the ACC, aligned with the anterior portion of the corpus callosum and situated with the anterior edge of the voxel dorsal to the genu of the corpus callosum, centered between the two hemispheres. Exact placement of the voxel was subject-specific with slight adjustments made to optimize the volume of grey matter within the voxel space (Figure 4). The MRS acquisition utilized an optimized FASTESTMAP (fast, automatic shim technique using echo-planar signal readout for mapping along projections) shimming protocol that corrects subject-specific field inhomogeneity within the chosen voxel. The MRS spectra were acquired using an ultra-short echo time stimulated echo acquisition mode (STEAM) sequence (TR/TE/TM: 10000/5.0/45ms) with outer volume suppression and VAPOR (variable power RF pulses and optimized relaxation delays) water suppression. Baseline acquisition consisted of 32 averages (acquisition time: 6:00), while functional acquisitions were 16 averages for each condition (e.g., fear, guilt, neutral) while the participant listened to the

script (acquisition time: 3:20 per script). After the fMRS scans, the session switched to fMRI acquisition. FMRI data were collected to provide whole brain activation patterns. The fMRI portion of the study used an optimized echo-planar imaging (EPI) sequence (37 slices acquired parallel to the AC-PC line, resolution = 0.9mm x 0.9mm x 1.5mm, TR/TE: 3000/28ms, flip angle = 70°, base/phase resolution 234/100, A>P phase encode direction, generalized autocalibrating partially parallel acquisitions (GRAPPA) acceleration factor = 3, interleaved acquisition, total acquisition time = 11:45).

Analysis Procedures

Surveys.

The Phase 1 screening survey data was downloaded from Qualtrics (Qualtrics, 2005) into R (R Core Team, 2016) for descriptive analyses of age, sex, TRGI, and PCL5 (Table 1). The Phase 3 medical screening survey was checked for completeness and reviewed by two researchers to verify that the participant met medical requirements for completing an MR scan. The medical screening forms were not used for any statistical purposes and were turned into the AUMRIC staff for record keeping. The Phase 3 post-scan survey data was analyzed in R (R Core Team, 2016) using paired *t*-tests analyzing differences between the first and second script presentations, and to assess differences between affective conditions.

FMRS Processing.

Spectroscopy data were analyzed with LCModel (version 6.3-1J) (Provencher, 2009) software using the default processing parameters and a simulated basis set that included GABA, glutamate, and glutamine along with other neurometabolites not relevant to this project (Tkac, 2008). Spectra were eddy current corrected and quantified using the unsuppressed water signal (2 averages). Spectrum quality was assessed using the signal-to-noise ratio (SNR) and a measure of

fit as indicated by the Cramer-Rao lower bounds (CRLB). Reliability of GABA, glutamate, and glutamine signal was determined by a CRLB < 20%. Additionally, the participant's anatomical data was segmented for grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) within the MRS voxel using locally developed MATLAB code (Reid et al., 2018) that utilized functions of SPM12 (*Statistical Parametric Mapping: The Analysis of Functional Brain Images*, 2006). The segmentation took each participant's anatomical data and created masks for each tissue type (GM, WM, and CSF) within the exact MRS voxel placement for that participant. The percent volume of each tissue type within the voxel was then calculated and used to correct the concentrations of GABA, glutamine, and glutamate according to formulas developed by Gasparovic et al. (2006). The corrected values were then checked for normality. Shapiro-Wilks tests were calculated for each neurotransmitter (GABA: $W = 0.85$, $p < 0.001$; Glutamine: $W = 0.57$, $p < 0.001$; Glutamate: $W = 0.98$, $p = 0.67$). Boxplots of the data confirmed the presence of outliers in the data (see Figures 5-7). Outliers were calculated for the data as greater than 1.5 * inter-quartile range (IQR) above the 3rd quartile or data less than 1.5*IQR below the 1st quartile. There were 60 data points for each neurotransmitter (15 for each baseline, fear, neutral, and guilt). Five data points were identified as outliers, one for GABA, three for glutamine, and one for glutamate, and were Winsorized using first and third quantiles as replacement values (Kwak & Kim, 2017). Subsequent Shapiro-Wilks tests indicated that normality was met (GABA: $W = 0.99$, $p = 0.68$; glutamine: $W = 0.98$, $p = 0.63$; glutamate: $W = 0.98$, $p = 0.47$). Spectroscopy data were standardized within individual and then analyzed for between condition differences of guilt, fear, and neutral using repeated measures ANOVA with R (R Core Team, 2016).

FMRI Processing.

FMRI data were analyzed using the Oxford Center for Functional MRI of the Brain (FMRIB) Software Library's (FSL) Expert Analysis Tool (FEAT) (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). All images were converted to Neuroimaging Informatics Technology Initiative (NIFTI) format using 'dcm2nii' (Li, Morgan, Ashburner, Smith, & Rorden, 2016). Non-brain material was removed using FSL's Brain Extraction Tool (BET) (S.M. Smith, 2002) which automatically extracts the brain based on fractional intensities that can be changed through user input. All data were visually inspected, and parameters were corrected to achieve accurate brain extraction. Motion outliers were determined using FSL's motion outlier script function (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLMotionOutliers). The script defines motion outliers as volumes that fall outside of a predefined threshold (i.e., 3rd quartile + 1.5*IQR). The output of the motion outlier script was a text file identifying volumes that exceeded the default threshold for motion (in a binary "1"/ "0" fashion, where "1" indicates volumes to be regressed out). The text file was then included in the statistical analysis as an explanatory variable which regresses out the aberrant volumes from the analysis. Timeseries data were subjected to local autocorrelation correction. Functional images were registered to each individual's anatomical images that were then normalized to the Montreal Neurological Institute (MNI) T1 2mm brain. Transformation matrices from the registrations were combined to move individual functional data into standard space using FMRIB's Linear Image Registration Tool (FLIRT) using the options of "full search" with 12 degrees of freedom (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001). Data were preprocessed using a smoothing kernel size of 5mm full width at half max (FWHM), slice-time corrected (for interleaved acquisition), and pre-whitened using FMRIB's improved linear model (FILM) (M.

W. Woolrich, Ripley, Brady, & Smith, 2001). Motion correction of the data was performed by Motion Correction FLIRT (MCFLIRT) using standard motion parameters and extended motion parameters (Jenkinson et al., 2002). MCFLIRT standard motion parameters use the middle volume as an initial template image for subsequent comparisons to other volumes within the 4D series and perform an 8mm search for the motion parameters using the specified cost function. An assumed identity transformation between the middle volume and adjacent volumes is calculated and then applied to subsequent volumes (Jenkinson et al., 2002). Following the 8mm search, two additional 4mm searches were conducted following the same process as the 8mm search, each using increasingly tighter tolerances, with all three optimizations using a trilinear transformation. The MCFLIRT extended motion parameters further optimized the data by conducting additional searches using the derivatives from the standard motion parameters and the squares of those derivatives (for more information about how FSL calculates motion correction parameters, please see https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MCFLIRT) (Jenkinson et al., 2002). FEAT provided the analysis platform for both first level (individual) and higher order (fixed effects group) analysis. First level and group level analysis were thresholded at $z > 2.3$ with a cluster threshold of $p < 0.05$. A fixed effects group analysis was chosen due to the modest sample size ($n = 15$) (Avidan & Behrmann, 2009), the participant-specific responses being of interest (McGonigle et al., 2000), and to align with the previously published SDI studies from which this project design was based on (Britton et al., 2005; Lanius et al., 2002; Lanius et al., 2003). The contrasts used in the first-level analyses were: 1) fear > neutral, 2) guilt > neutral, 3) fear > guilt, and 4) guilt > fear. The same contrasts and threshold parameters ($z > 2.3$, $p < 0.05$) were used for the higher order analyses. Two higher order analyses were conducted. The first higher order analysis reported the group level means for each contrast without the use of any

additional regressors. The second higher order analysis included the participant's scores for the TRGI and PCL as regressors, to account for the variance associated with differences in each individual's levels on these measures. To use the scores as regressors in the model, the scores were de-meaned and were added as additional explanatory variables. The higher order analyses resulted in reports of significant local maxima (i.e., clusters of voxels determined to be significant within the group level analysis for each contrast) reported in MNI space. To provide anatomical labels for the local maxima, the MNI coordinates were first converted into Talairach coordinates using BrainMap GingerALE 2.3.6's (http://brainmap.org) "Convert Foci" function. The Talairach coordinates were then processed by the Talairach Client (Lancaster et al., 2000) to produce anatomical labels for the local maxima. All analyses were corrected for multiple comparisons.

***Post-hoc* exploratory analyses.**

Exploratory *post-hoc* ROI time-series and functional connectivity analyses were conducted to further explore the results of this project. Functional connectivity describes the temporal dependency between brain regions by measuring the correlations in neuronal activation or coactivation patterns (van den Heuvel & Hulshoff Pol, 2010). The Conn Toolbox version 18.a (Whitfield-Gabrieli & Nieto-Castanon, 2012) was used to preprocess the functional data (i.e. brain extraction, slice time correction, spatial smoothing using a Gaussian 5mm FWHM kernel, band-pass filtering (0.008 to 0.09), regression of physiological and motion artifacts using component-based noise correction method (CompCor) (please see (Susan Whitfield-Gabrieli & Alfonso Nieto-Castanon, 2012), motion scrubbing, registration to anatomical space, and normalization to MNI space), and conduct functional connectivity analyses. Specifically, key structures involved in guilt and fear processing (i.e., left and right amygdala, left and right OFC,

and bilateral ACC) were chosen from the default ROI atlas list within Conn as seed ROIs for connectivity analyses between conditions of fear and guilt. Pearson's correlation coefficients were calculated for the ROI timeseries to all other voxels in the brain. Correlation coefficients were converted to a normal distribution of scores using Fisher's transform. Seed-to-voxel connectivity maps were then produced with statistical thresholds set for voxel height $p_{uncorrected} < 0.05$ and cluster: $p_{FDR\text{-}corrected} < 0.05$, using two-tailed *t*-tests (Robinson, Salibi, & Deshpande, 2016; Whitfield-Gabrieli & Nieto-Castanon, 2012).

The second set of *post-hoc* analyses involved a timeseries analysis of the key brain structures for this study. Timeseries analysis can yield additional information about the activity in specific ROIs. ROIs for the timeseries analysis were adapted from the Harvard-Oxford Structural Probability Atlas contained within FSL view (Jenkinson et al., 2012). Specifically, masks were created for each anatomical ROI of interest of the same regions used for the connectivity analysis with the exception that the ACC ROI, which was divided into left and right to match the amygdala and OFC ROIs. The Harvard-Oxford masks for the ACC and OFC are bilateral, therefore Mango (http://ric.uthscsa.edu/mango/download.html) was used to derive separate left and right masks (Lancaster, 2016). ROI masks contained values for each voxel as a probability that the voxel lies within the ROI (e.g., 70% probability that the voxel lies within the amygdala). The ROI masks were then thresholded to 75% and binarized using the 'fslmaths' command line (S. M. Smith et al., 2004). The thresholded and binarized ROI masks were then transformed into each participant's fMRI space using FLIRT, and timeseries data were extracted using the 'fslmeants' utility (S. M. Smith et al., 2004). This created a text file for each individual, for each ROI, with approximately 240 values (a value for each volume, or fMRI measurement, representing the average BOLD signal for the selected voxels at each time point)

(Jenkinson et al., 2002). The timeseries text files were combined across participants for each ROI for further analysis. Normality on the resultant timeseries data sets were tested using Shapiro-Wilk's test for normality (Royston, 1982). On average, nine of the 15 participant's time-series data failed to meet normality within each ROI (Appendix D). To improve normality, outliers within the timeseries data were calculated in R (R Core Team, 2016) as those values that were 1.5*IQR above the 3rd quartile or below the 1st quartile within each participant for each ROI. The identified outliers were Winsorized using first and third quantiles for that participant's ROI as replacement values. On average, 93 outliers were identified out of the 3,600 values (2.6%) within each ROI timeseries dataset. Normality was tested again after Winsorization of outliers and normality improved from an average of six out of 15 meeting normality within each ROI to 13 out of 15 meeting normality within each ROI (Appendix D). Timeseries data was then realigned to match time points within conditions, standardized, and collapsed to determine a single mean value for each condition for each participant within each ROI.

Results

Manipulation Check

In this study, the prepared scripts were presented to the participants twice while in the scanner: once during fMRS acquisition, and once during fMRI acquisition. To examine the efficacy of the scripts to elicit the target emotion consistently between presentations, the post-scan survey was administered. Specifically, participants were asked to rate the arousal level of the emotional scripts and to compare the arousal level from the first time they heard the scripts (during fMRS acquisition) to the second time they heard the scripts (during fMRI acquisition). There was no difference in arousal ratings for the fear scripts between the first and second presentation (Table 2). Similarly, there was no observed difference in arousal ratings for the

guilt scripts between the first and second presentation (Table 2). Because the circumplex model suggests that guilt and fear may be differentiated by arousal, we also examined whether there were differences between arousal ratings for fear and guilt during the first and the second presentation. No differences in arousal were observed between conditions for the first presentation (Table 2).

Hypothesis 1 Results

Hypothesis 1 stated that there would be a difference in neuronal activation, as measured by fMRI, between fear and guilt. Specifically, it was hypothesized that fear and guilt would differentially activate limbic and cognitive structures, with fear-eliciting greater activation in subcortically based limbic structures, and guilt activating higher cortical cognitive structures (i.e., OFC and ACC). Results from fMRI group level analyses partially supported this hypothesis. A comparison between the two higher order analyses, with and without additional regressors, showed minimal differences. As such, results from the higher order analysis without the TRGI and PCL as regressors are reported. However, local maxima cluster tables for the higher order analysis with the additional regressors is included in Appendix E for comparison purposes.

Fear > neutral.

When compared to the neutral condition (i.e., fear > neutral), fear network elicited greater activation in limbic and subcortical structures (i.e., bilateral thalamus, bilateral areas of the parahippocampal gyrus, and the right uncus/amygdala), supporting the first hypothesis that fear would elicit activity in these regions (Figure 8). Activations in these areas provide converging evidence with previous literature regarding the fear network (Liberzon & Ressler, 2016; Marin et

al., 2016). Additional areas of activation for fear > neutral include the left cuneus and left middle occipital gyrus (please see Table 3 for a full listing of local maxima).

Fear > guilt.

The fear > guilt contrast also supported Hypothesis 1 with significantly greater activation for fear in limbic structures (Figure 9). Additional activations for fear > guilt included semantic, auditory, and visual networks along with additional, dispersed activations. Results from this contrast also provided evidence for increased activation in the left parahippocampal gyrus, thalamus, and hypothalamus which supported the first hypothesis for fear activating more limbic structures than guilt, but contrary to the hypothesis, there were greater activations for fear in bilateral medial and inferior frontal gyri and the left ACC (please see Table 4 and 5 for a full listing of local maxima).

Guilt > neutral and guilt > fear.

The results from the guilt > neutral and guilt > fear fMRI contrasts did not support Hypothesis 1. It was expected that guilt > fear and guilt > neutral would have greater activations in cognitive structures such as the OFC and ACC, but contrary to expectations, there were no significant differences identified (Figure 10). Overall, the fMRI results confirmed what was previously thought concerning the fear network, but only raised more questions for the networks involved in guilt.

Hypothesis 2 Results

The second hypothesis predicted that there would be a difference in the neurochemical underpinnings of fear and guilt within the anterior cingulate cortex (ACC) as measured by fMRS. It was expected that the results would show increases in GABA, glutamate, and glutamine when comparing the fear to the neutral condition. Additionally, higher levels of

glutamate/glutamine were expected during the guilt condition compared to the neutral condition. A repeated measures ANOVA was calculated for each substance with no statistical significance found between any of the conditions (Table 6). Our second hypothesis was therefore not supported by the data (Figure 11).

Post-hoc Results

The mixed results for Hypothesis 1 and a lack of support for Hypothesis 2 prompted additional *post-hoc* functional connectivity analyses of key structures to interrogate the data further.

OFC connectivity.

Functional connectivity of the left OFC demonstrated increased connectivity with the right cuneal cortex, bilateral lingual gyrus, and bilateral occipital pole during fear processing compared to guilt (Figure 12). There were no significant increases in connectivity in the reverse (i.e., guilt > fear) contrast. The right OFC, however, demonstrated increased connectivity with the left frontal pole, bilateral middle frontal gyrus and bilateral angular gyrus (Figure 13) during fear compared to guilt, and increased connectivity with the right pars opercularis, part of the inferior frontal gyrus when comparing guilt > fear.

ACC connectivity.

The functional connectivity of the ACC also showed increased connectivity for both fear and guilt. Increased connectivity between the ACC and the left lateral occipital cortex superior division, right juxtapositional lobule cortex, right supracalcarine cortex, and the left posterior cingulate cortex (PCC) was observed during the fear compared to guilt condition (Figure 14). The ACC had increased functional connectivity with the left hippocampus and parahippocampal cortex during the guilt condition compared to the fear condition.

Amygdala connectivity.

The functional connectivity of the amygdalae demonstrated differences between the conditions of fear and guilt. The fear > guilt contrast for the left amygdala had increased functional connectivity with the left parietal operculum and the left supramarginal gyrus (Figure15). The right amygdala for fear > guilt contrast showed increased connectivity with the right occipital cortex superior division, bilateral occipital pole, bilateral intercalcarine cortex, right cuneal cortex, and the right lingual gyrus (Figure 16). The guilt > fear contrast resulted in increased connectivity results for the left amygdala and the right precuneus and left cuneal cortex, but there were no increased connectivity results in the guilt > fear contrast for the right amygdala.

Timeseries results.

The other *post-hoc* test, a fMRI ROI timeseries analysis, was conducted to better understand the differences between fear and guilt. The timeseries data for the OFC showed no significant differences between the left OFC and right OFC across conditions ($t(44) = 1.38$, $p = 0.17$) (Figure 17). Additionally, within the OFC there was no significant differences between conditions (guilt, neutral and fear) for the left side ($F(2,42) = 0.152$, $p = 0.86$) or the right side ($F(2,42) = 0.90$, $p = 0.42$) (Table 6). The ACC also had no significant differences between the left and right side across conditions ($t(44) = 1.08$, $p = 0.28$) (Figure 18). The between condition differences were also not significant for the left ACC ($F(2,42) = 0.91$, $p = 0.41$), or for the right ACC ($F(2,42) = 2.38$, $p = 0.11$) (Table 6). The amygdalae had no significant differences between hemispheres across conditions ($t(44) = -0.99$, $p = 0.33$), but there were observed differences between conditions (Figure 17). Specifically, the left amygdala had different activation levels between conditions ($F(2,42) = 3.24$, $p = 0.05$). A *post-hoc* Tukey test revealed a

significant difference between guilt and fear ($p = 0.04$), but not between either emotion and neutral. The right amygdala also had a significant difference between conditions ($F(2,42) = 3.85$, $p = 0.03$). A *post-hoc* Tukey test for the right amygdala also revealed a significant difference between guilt and fear ($p = 0.02$), but not between either emotion and neutral.

Discussion

Here, we used a novel within-subject SDI paradigm within a combined fMRI and fMRS study looking at the neuronal differences between fear and guilt. The results provided convergent evidence regarding the fear network, while highlighting insights into how individual's process guilt. Specifically, connectivity differences were observed between the OFC and ACC between conditions such that the guilt condition was associated with greater connectivity between these regions and the inferior frontal gyrus and parahippocampus, respectively. Furthermore, amygdala activation patterns were identified as a possible biomarker for neural discrimination between fear and guilt memories. Together, these results suggest that fear and guilt are processed by different neuronal networks, and that specific regions may be biosignature candidates, as they preferentially respond to guilt or fear.

Fear

FMRI analyses confirmed previous accounts of a fear network. Namely, there were significant limbic system activations for the fear > neutral contrast and the fear > guilt contrast (Tables 3-5). One interesting finding, however, is the very robust activation of visual and semantic processing centers for both fear > neutral and fear > guilt contrasts (Figures 8-9). The left cuneus and left middle occipital gyrus activations for fear < neutral are involved in visual processing, and the right middle temporal gyrus activation is associated with semantic processing (Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2011). These visual and semantic area

activations in the fear > neutral are congruent with an SDI study conducted by Rauch et al. (1996) and together with the limbic activations conform to the reports of other studies using SDI to investigate the neural activations of fear memories (Lanius et al., 2002; Lindauer et al., 2004). The frontal activations together with the significant activation of the left precuneus for fear > guilt have been implicated in the processing of episodic memories, particularly those involving oneself (Lundstrom et al., 2003).

The fear > guilt contrast also revealed differences in areas associated with memories and semantic processing. Significant fear > guilt activations were found in the inferior parietal lobule along with the supramarginal gyrus and angular gyrus. In a study conducted by Wang and colleagues (2017), they included the supramarginal gyrus and angular gyrus as subregions of the inferior parietal lobule and linked these regions to movement imagination, episodic memories, and semantic processing. The bilateral superior and middle temporal gyri activations resulting from the fear > guilt contrast are associated with auditory and semantic processing (Mesgarani, Cheung, Johnson, & Chang, 2014). There were also significant activations in the right lingual gyrus, associated with visual memory and visual processing (Bogousslavsky, Miklossy, Deruaz, Assal, & Regli, 1987), and the right lentiform nuclei (includes portions of the lateral globus pallidus, and putamen) which, as part of the basal ganglia, is involved in movement, but activation during SDI is likely due to this area being implicated in motor imagery (Oostra, Van Bladel, Vanhoonacker, & Vingerhoets, 2016).

Increased connectivity was observed during the fear condition throughout regions associated with visual and semantic processing. Within the left OFC, fear elicited greater connectivity with the right cuneal cortex, bilateral lingual gyrus, and bilateral occipital pole compared to guilt. These regions are involved with visual processing and visual imagery

(Fulford et al., 2018). Additionally, with the same fear > guilt contrast, the right OFC was associated with increased connectivity with the left frontal pole, bilateral middle frontal gyrus and bilateral angular gyrus, which are brain regions involved in memories (Figure 13). The frontal pole is associated with episodic memories and executive functions (Gilbert et al., 2006). The middle frontal gyri and angular gyri are both elements of the default mode network with many functions, but the angular gyri are thought to be involved with memory retrieval (Seghier, 2013). Together, these results suggest that there was a greater focus on the imagery of the memory within the fear condition than during the guilt condition.

The ACC increases in connectivity observed in the fear > guilt contrast included the left lateral occipital cortex superior division, right juxtapositional lobule cortex, right supracalcarine cortex, and the left PCC (Figure 14). The left lateral occipital cortex, in general, is thought to be involved with object recognition but is also a part of the default mode network (Karten, Pantazatos, Khalil, Zhang, & Hirsch, 2013). The juxtapositional lobule cortex is the area formerly known as the supplementary motor cortex, and is considered to be involved with motor imagery (Auer, Dewiputri, Frahm, & Schweizer, 2018). The supracalcarine cortex is part of the primary visual cortex, and is involved in mental imagery (Klein, Paradis, Poline, Kosslyn, & Le Bihan, 2000). The PCC is involved with many functions; however, Saarimaki and colleagues (2018) investigated basic versus secondary emotions, and they found that the PCC was active for basic emotions like fear, but not for secondary emotions like guilt, consistent with these results. These results suggest that specific stimuli within the fear condition are focused on more than the stimuli within the guilt condition. Additionally, the person's actions or movements within the fear condition is focused on more than during the guilt condition.

The amygdalae connectivity increases for fear > guilt contrast also includes areas involved in visual and semantic processing. Left amygdala fear > guilt contrast had increased connectivity in the left parietal operculum and the left supramarginal gyrus (Figure 15). The parietal operculum is known to be involved with visual and auditory motion (Antal, Baudewig, Paulus, & Dechent, 2008) but also to general somatosensation (Sawamoto et al., 2000). The supramarginal gyrus is involved in movement imagination, episodic memories, and semantic processing (Wang et al., 2017). The right amygdala had greater connectivity with the right occipital cortex superior division, bilateral occipital pole, bilateral intercalcarine cortex, right cuneal cortex, and the right lingual gyrus when comparing fear to guilt. These areas are involved with visual processing (Belliveau et al., 1991; Engel et al., 1994). The amygdala connectivity results for the fear > guilt contrast also suggest that fear was more strongly connected to the imagery within the memory than the guilt condition.

Together, these results suggest that fear memories produce vivid imagery, where the individual re-experiences the events that occurred. Additionally, fear memories may cause people to re-experience the sensations of movement and other sensory inputs as they relive the event in detail. This would support the classification of fear as a primary emotion where the person is responding to the stimuli, and the stimuli (in this case the script) is the focal point as evident with the increases in imagery processing centers. This is likely to be one of the mechanisms behind the perceptual bias to threatening stimuli found within PTSD (Murphy, 2016). Evolutionarily, focusing on the external stimuli within a fear memory may be a means of remembering and thus avoiding threatening situations in the future.

Guilt

A surprising result from the fMRI analysis was the lack of any group level significant activations for the guilt > neutral or guilt > fear contrasts. The variance in the literature for reported neural networks for guilt was discussed in the introduction. The literature suggests that some of the variance might be due to differences in the type of paradigm used in guilt studies. It should be noted that in addition to methodological differences, guilt is also a very complex, secondary emotion. Neural activations for guilt are different if the perceived transgression was intentional, or accidental (Berthoz et al., 2006), or if the transgression harmed the self, or harmed others (Rajendra A. Morey et al., 2012). Additionally, several very closely related emotional terms such as guilt, shame, and embarrassment, are hard to distinguish in autobiographical accounts, and can produce different neural activations (Bastin, Harrison, Davey, Moll, & Whittle, 2016; Stotz, Elbert, Müller, & Schauer, 2015; Teroni & Deonna, 2008). Guilt has also shown differences if the guilt is explicit versus implicit (Bockers, Roepke, Michael, Renneberg, & Knaevelsrud, 2016). It has also been suggested that there are differences in guilt that are related to internalizing versus externalizing (Biaggio, 1969). Internalized guilt/shame have been associated with depression and anxiety, while externalized guilt/shame can lead to anger and risky behavior, like drug use (VanDerhei, Rojahn, Stuewig, & McKnight, 2014). Guilt has also been divided into moral guilt (e.g., behavior incongruent with a person's morals) versus neurotic guilt (e.g., blaming oneself for not preventing rape or abuse) (Malti, 2016). There are also cultural differences in guilt (Onwezen, Bartels, & Antonides, 2014), developmental differences in guilt (Thompson & Hoffman, 1980), and gender differences in guilt (Ferguson & Crowley, 1997). Taken together, guilt may be universally understood, but idiosyncratic in its manifestation. With laboratory contrived paradigms, much of the variance of guilt can be controlled for, and group level activations are more likely to be seen. With our paradigm of

autobiographical SDI, the individual activations for guilt likely contained too much variance between individuals to reach any group level significance. The lack of group level activation patterns for guilt may also indicate that the fear scripts were more vivid or arousing. However, the results from the post-scan survey contradict the notion that the fear scripts were more vivid or arousing than guilt.

The functional connectivity data provides a different possibility for why fear has greater activations of visual and semantic processing centers than guilt. For each ROI tested, fear produced greater connectivity with regions associated with visual, semantic, or motion imagery, all suggesting a focus on external stimuli, but increases in connectivity for guilt seem to suggest a focus on internal stimuli. The right OFC produced greater connectivity with guilt in the right pars opercularis, part of the inferior frontal gyrus, which may indicate personal moral judgements occurring (Greene et al., 2004), and the ACC had greater hippocampal connectivity for guilt which may indicate interoception, or cognitive evaluation of memories and a focus on internal states (Robinson et al., 2016) (Figure 14). This may be indicative of a top-down influence (whereas fear may be accessing memories via a bottom-up approach) (Ochsner et al., 2009). The left amygdala increased connectivity results for guilt included the right precuneus and left cuneal cortex which are visual processing centers (Lundstrom et al., 2003), suggesting that there is visual imagery associated with the guilt scripts, but not to the degree seen with the fear scripts (Figure 13). The precuneus connectivity result for guilt supports the previous reports of the precuneus being associated with guilt (Fourie et al., 2014; Gifuni et al., 2017). These results suggest that the response to guilt memories within the guilt condition was less focused on the specific imagery of the memory, but rather, the person was focused more on an assessment, judgment, or trying to find meaning of the event. This seems to support the classification of guilt

as a secondary emotion in that the individual is responding to what the situation means, or says about the person, and less focused on the specifics of the event.

FMRS

The fMRS data failed to show any significant differences between the conditions of guilt, neutral and fear. This does not mean that fMRS is not a viable method to measure differences between these emotions. There may be several explanations for the lack of observed differences. The voxel may not have been placed in the best area that would give us the largest effect. There was one significant activation cluster in the ACC for the fear > guilt fMRI contrast (Figure 9). However, the location of the cluster within the ACC was slightly caudal to the placement of the fMRS voxel (Figures 4 and 9). Therefore, different placement of the voxel may be more sensitive to differences in neurotransmitter levels. Additionally, the voxel size was large ($25mm^3$), which may have washed out a small effect. Perhaps a different structure altogether, such as the right amygdala, would provide better fMRS results. The spectrum analysis of GABA is also potentially problematic. The GABA signal is possibly unreliable due to its signal being found underlying several peaks from other neurotransmitters that have greater concentrations (Mullins et al., 2014). However, the use of a 7T field strength has been shown to increase the reliability of the GABA signal, but rigorous testing has not been conducted to verify or quantify GABA reliability at 7T (Wijtenburg, Rowland, Edden, & Barker, 2013).

Timeseries

Timeseries data investigated the BOLD signal fluctuations within the target ROIs. For both the OFC and ACC, the timeseries analyses resulted in no significant differences between conditions (Figures 17 – 18). The timeseries analysis for the OFC resulted in no statistically significant differences between conditions. Additionally, looking at the numerical trends, it is

feasible that even with a larger sample size significance would be reached between the affective conditions and neutral (i.e., fear > neutral) before significance between fear and guilt (Figure 17). A similar trend was observed in the ACC timeseries analysis (Figure 18). These results suggest that the OFC and ACC are likely involved in emotional processing but would not be useful to look at for biomarkers to differentiate between fear and guilt. In contrast, the amygdalae timeseries analyses did result in a significant difference in BOLD signal between fear and guilt with increased activity for fear > neutral and decreased activity for guilt > neutral (Figure 19). The amygdala timeseries results support the notion that the amygdala is a key structure in fear and fear memories (Davis & Reijmers, 2018), but not activated for guilt (Gifuni et al., 2017). The significant difference in amygdalae activation between fear and guilt indicated that the amygdalae may be a useful biomarker to distinguish between the emotions of fear and guilt.

Implications

The overarching goal of this project was to identify the neural differences between fear and guilt in autobiographical memories. To this end, we did observe differences between fear and guilt, specifically regarding connectivity between key cognitive and affective processing regions (i.e., ACC and OFC) and regions involved in visual, semantic, and motor processing. Additionally, the amygdalae were shown to activate differentially to fear and guilt with the amygdalae being activated for fear, but not activated for guilt. This is important to consider because the amygdala is a target brain structure for medications common to treat PTSD. Currently, the only approved medications to directly treat PTSD are selective serotonin reuptake inhibitors (SSRI) (Izumi, Kitaichi, An, Inoue, & Yoshioka, 2018). The SSRI class of medications specifically target the serotonin networks of the amygdala (Heim & Nemeroff, 2009; Krystal & Neumeister, 2009; Liberzon & Ressler, 2016). If fear and guilt contribute to PTSD differentially

(i.e., that guilt alone can drive pathology), then the results of the current study would suggest that SSRIs would be effective for fear-driven PTSD but might not be effective for a possible guilt driven PTSD.

Limitations

Importantly, and to our knowledge, this is the first study that assessed the effect of guilt and fear simultaneously, using a within-subjects design. Therefore, several experimental considerations of the present study design should be noted. First, regarding the MRS results; while the placement of the MRS voxel was determined based on the current body of peer-reviewed literature the target for the expected effect requires further investigation. It is plausible that an alternative voxel placement may have led to different results, especially considering that the voxel placement in the current study did not target the area in which fear demonstrated greater activation when compared to guilt upon examination of the fMRI results. In addition, the current study did not interrogate different expressions or factors of guilt and/or emotions often confused with guilt such as shame and embarrassment. This failure to account for the idiosyncratic nature of guilt per se may have contributed to the lack of group level significant neural activations for guilt using fMRI. Additionally, the events the participants described varied greatly, including rape, exposure to death, combat, natural disasters, car accidents, and childhood trauma. The variance in the events used as scripts might also have contributed to the overall variance found in the data. Finally, the scripts were developed from participant interviews to focus and concentrate on the emotional target and we cannot determine with certainty that our measures excluded concurrent effects of other emotional material (i.e., feelings about an involved parent).

Future Directions

The methodologies employed in this study were chosen for the express purpose of applying the results from this study to guide and inform a methodologically similar study examining fear and guilt in traumatic memories of treatment-seeking veterans with PTSD. The purpose of this future PTSD research will be to investigate if there is a guilt-driven or guilt-model of PTSD that differs from the conventional understanding of fear-driven PTSD. Current treatments for PTSD do not reach all patients, particularly in the Veteran's Administration (VA) medical system. In a study conducted by Miles and Thompson (2016), 199 veterans diagnosed with PTSD were followed through treatment at a VA medical facility. Their results show that 26% did not want or did not start psychotherapy and of those who did start therapy, only 54% completed therapy with a net of only 40% of the initial patient population completing therapy (Miles & Thompson, 2016). Similarly, in a study that followed 77,000 veteran outpatients diagnosed with PTSD, 64% received no therapy, and less than 10% completed eight or more sessions of therapy (Cully et al., 2008). The reasons for the high percentages of veterans with PTSD not completing treatment are largely unknown.

One proposed explanation for why receiving treatment does not appeal to some veterans is because exposure treatments used extensively within the VA may not be effective for affective responses other than fear (Pitman et al., 1991). Pitman and colleagues (1991) suggested that negative trauma appraisal during exposure treatment accompanied guilt, and may be implicated in exacerbation of symptoms. They conclude that exposure therapy may not be as effective for negative emotions, such as guilt, as it is for anxiety responses to trauma (Pitman et al., 1991). Regardless, exposure therapy does have empirical support and is effective to many with PTSD (Wolf et al., 2015), but may not be effective for all who suffer from PTSD displaying negative emotions such as guilt (Stapleton, Taylor, & Asmundson, 2006; Yehuda, Vermetten, McFarlane,

& Lehrner, 2014). The results of our study may help explain this conclusion. Exposure therapy focuses on fear and asks the person to relive the events focusing on the responses to the stimuli within the memory (Foa et al., 1995). Our findings for fear activating widespread regions involved in visual and semantic processing seem to which fit with fear being a response to the stimuli within a fear memory and would thus be an effective target of Exposure therapy. In contrast, guilt, according to our results, is focused on the meaning of the events within a guilt memory and not the specific stimuli which would suggest that reliving the specifics of a guilt-related event would not address the issue of evaluation of the events and could possibly make the feelings of guilt worse. This highlights the need to further study the role of fear and guilt within PTSD, as differentiating between the two emotions may lead to the development of treatments that will reach more veterans with PTSD.

Conclusion

The results of this study highlight the complexity of the human emotions of fear and guilt. Nevertheless, the results indicate that a key neuroanatomical structure for differentiating between the affective states of fear and guilt may be the amygdalae. Additionally, fear memories appear to be focused on external events and the person's interaction with them, whereas guilt memories are more focused on internal events. This last finding supports the notion that fear and guilt are not just two points on a continuum but are distinct emotions, with fear classified as a primary emotion (response to stimuli) and guilt as a secondary emotion (appraisal of stimuli). Further research into how fear and guilt influence PTSD is necessary because if there is a sub-type of PTSD where the pathology is driven by guilt, then medications and treatments targeting the amygdala and the receptors located on the amygdala would not be as effective.

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Table

Table 1
Participant characteristics

Demographics and Psychometrics		
Characteristic	*n*	%
Gender		
Women	9	60
Men	6	40
Education level		
Some college	12	80
Master's degree	2	13
Ph.D	1	7
	M	*SD*
Age	24.67	11.76
TRGI	63.73	21.09
PCL-5	27	17.1

Results from the screening survey showing demographic data collected and results from the guilt and fear/PTSD symptom instruments. To protect the confidentiality of the participants, no data concerning the fear and guilt events shared are provided.

Table 2
Results of post-scan questionnaire

		Post-scan questionaire	
Condition	Contrast	*M*	*SD*
Guilt	Script v. Event	6.93	1.49
	1st presentation	7	1.69
	2nd presentation	6.47	1.64
Fear	Script v. Event	6.27	1.39
	1st presentation	6.47	1.39
	2nd presentation	6.13	1.88
		Statistic	
Tests	Guilt 1st > 2nd	$t(14) = 1.95, p = 0.07$	
	Fear 1st > 2nd	$t(14) = 0.96, p = 0.35$	
	Fear 1st > Guilt 1st	$t(14) = -1.20, p = 0.25$	
	Fear 2nd > Guilt 2nd	$t(14) = -1.10, p = 0.29$	

Post-scan questionnaire was used as a manipulation check to see if the scripts were effective at eliciting the target emotions and if there was any decline in effectiveness from first and second presentation. Results indicate no significant decline in effectiveness between presentations or any difference between fear and guilt scripts at eliciting the target emotion.

Table 3

Significant activated cluster results from fear > neutral higher order analysis.

Fear > Neutral Group Feat cluster index with Talairach coordinates and labels						
Z-score	X coor	Y coor	Z coor	Lobe	Region	BA
3.45	0.61	-66.81	-10.13	Anterior Lobe	Left Culmen of Vermis	
3.54	6.39	-34.98	-2.59		Right Culmen	
4.16	-23.98	-52.24	3.33	Limbic Lobe	Left Parahippocampal Gyrus	30
3.38	-22.15	-64.21	11.61		Left Posterior Cingulate	30
4.25	31.13	-7.73	-15.15		Right Amygdala	
3.57	27.41	-1.08	-29.21		Right Uncus	36
3.23	19.78	-9.29	-18.94		Right Parahippocampal Gyrus	34
3.99	-3.27	-86.43	-0.57	Occipital Lobe	Left Lingual Gyrus	18
3.61	-5.21	-90.91	9.98		Left Cuneus	18
3.46	-9.01	-94.78	11.52		Left Middle Occipital Gyrus	18
4.78	-20.26	-86.9	-20.61	Posterior Lobe	Left Declive	
3.96	-1.28	-75.46	-23.37		Left Tuber of Vermis	
4.14	0.61	-70.26	-15.78		Right Declive of Vermis	
4.06	13.84	-83.06	-25.58		Right Uvula	
3.97	2.51	-73.6	-23.23		Right Tuber of Vermis	
4.95	-3.06	-25.88	5.18	Sub-lobar	Left Thalamus	
3.81	10.17	-33.47	2.96		Right Thalamus	
3	36.84	-7.2	-24.12	Temporal Lobe	Right Middle Temporal Gyrus	21

Note. Clusters are organized by lobe and not significance. Multiple activations within the same region were combined and only the most significant *z*-score is reported. Brodmann areas (BA) are only reported for regions that fall within a BA.

Table 4

Significant activated cluster results from fear > guilt higher order analysis, first of two tables.

Fear > Guilt Group Feat cluster index with Talairach coordinates and labels table 1of 2						
Z-score	X coor	Y coor	Z coor	Lobe	Region	BA
3.11	-33.38	-10.76	40.36	Frontal Lobe	Left Middle Frontal Gyrus	6
3.67	-39.02	-1	37.34		Left Precentral Gyrus	6
3.5	-8.51	43.85	16.92		Left Medial Frontal Gyrus	9
4.67	-6.59	46.07	11.65		Left Medial Frontal Gyrus	10
3.76	-14.1	61.54	8.99		Left Superior Frontal Gyrus	10
3.74	-2.74	45.88	-15.48		Left Medial Frontal Gyrus	11
3.47	-0.85	42.31	-19.32		Left Orbital Gyrus	11
3.44	-10.33	40.26	-15.9		Left Inferior Frontal Gyrus	11
4.69	-2.79	28.94	-18.4		Left Medial Frontal Gyrus	25
3.13	-4.67	37.97	-10.58		Left Anterior Cingulate	32
4.28	25.38	8.03	36.51		Right Middle Frontal Gyrus	8
4.55	34.95	27.72	25.19		Right Middle Frontal Gyrus	9
3.17	40.53	9.79	36.72		Right Precentral Gyrus	9
4.49	50.02	6.96	20.31		Right Inferior Frontal Gyrus	44
3.74	44.47	30.69	7.34		Right Inferior Frontal Gyrus	46
4.78	17.97	11.69	-19.39		Right Inferior Frontal Gyrus	47
5.19	-23.77	-12.82	-17.62	Limbic Lobe	Left Parahippocampal Gyrus	28
3.39	-10.39	40.65	7.65		Left Anterior Cingulate	32
4.83	-4.93	-27.18	-3.97	Midbrain	Red Nucleus	
4.52	-29.81	-76.57	27.05	Occipital Lobe	Left Superior Occipital Gyrus	19

Note. Clusters are organized by lobe and not significance. Multiple activations within the same region were combined and only the most significant *z*-score is reported. Brodmann areas (BA) are only reported for regions that fall within a BA.

Table 5

Significant activated cluster results from fear > guilt higher order analysis, second of two tables.

Fear > Guilt Group Feat cluster index with Talairach coordinates and labels table 2of 2						
Z-score	X coor	Y coor	Z coor	Lobe	Region	BA
4.11	-25.97	-61.43	28.06	Parietal Lobe	Left Precuneus	7
4.29	-29.78	-63.64	33.32		Left Angular Gyrus	39
3.78	-50.5	-45.7	23.5		Left Inferior Parietal Lobule	40
3.49	-37.27	-44.39	30.91		Left Supramarginal Gyrus	40
4.66	28.93	-61.8	26.56		Right Precuneus	7
5.02	-1.28	-72.02	-17.72	Posterior Lobe	Left Declive of Vermis	
4.93	-22.14	-88.32	-27.96		Left Tuber	
3.19	-44.8	-38.29	25.83	Sub-lobar	Left Insula	13
4.81	-3.05	-25.77	3.38		Left Thalamus	
4.59	21.65	-4.67	-2.34		Right Lateral Globus Pallidus	
4.35	10.29	-8.13	-6.25		Right Hypothalamus	
4.23	23.64	18.53	-8.05		Right Putamen	
3.82	-59.76	-9.52	-4.97	Temporal Lobe	Left Superior Temporal Gyrus	21
3.79	-57.89	-13.68	0.2		Left Superior Temporal Gyrus	22
4.76	-54.24	-51.51	-4.04		Left Middle Temporal Gyrus	37
5.13	-44.89	-69.93	14.72		Left Middle Temporal Gyrus	39
3.29	-40.96	-37.04	6.03		Left Superior Temporal Gyrus	41
3.12	-40.94	-27.8	10.25		Left Transverse Temporal Gyrus	41
3.52	51.76	-45.32	4.25		Right Middle Temporal Gyrus	21
3	57.43	-52.73	0.19		Right Middle Temporal Gyrus	37
3.63	44.21	-44.79	-3		Right Sub-Gyral	37
3.47	44.09	-66.81	13.66		Right Middle Temporal Gyrus	39
3.95	30.86	-52.22	25.39		Right Superior Temporal Gyrus	39

Note. Clusters are organized by lobe and not significance. Multiple activations within the same region were combined and only the most significant *z*-score is reported. Brodmann areas (BA) are only reported for regions that fall within a BA.

Table 6
Results of all ANOVA testing.

	Guilt		Neutral		Fear			
Item	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*(2,42)	*p*
GABA	-0.146	1.340	0.139	0.867	0.018	0.962	0.264	0.769
Glutamine	-0.183	1.133	0.125	1.115	0.126	1.023	0.399	0.674
Glutamate	-0.103	1.085	0.061	1.011	0.076	0.987	0.139	0.871
Left OFC	-0.032	0.209	0.000	0.133	-0.053	0.172	0.152	0.860
Right OFC	-0.092	0.148	0.005	0.128	-0.055	0.172	0.893	0.417
Left ACC	-0.075	0.164	-0.006	0.182	-0.042	0.165	0.913	0.409
Right ACC	-0.118	0.158	-0.014	0.187	-0.039	0.154	2.378	0.105
Left Amygdala	-0.103	0.171	-0.059	0.190	0.042	0.109	3.243	0.049*
Right Amygdala	-0.095	0.161	-0.014	0.158	0.048	0.098	3.845	0.029*

Note. Significant ANOVA tests are indicated by "*".

Figures

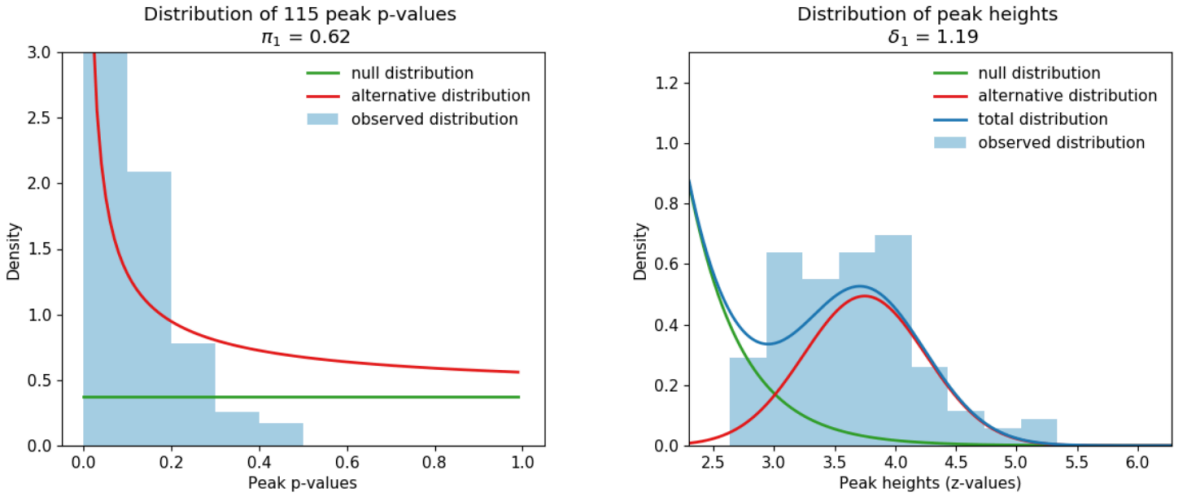


Figure 1. Model fit results from *a priori* power analysis of the guilt > neutral contrast from the pilot study.

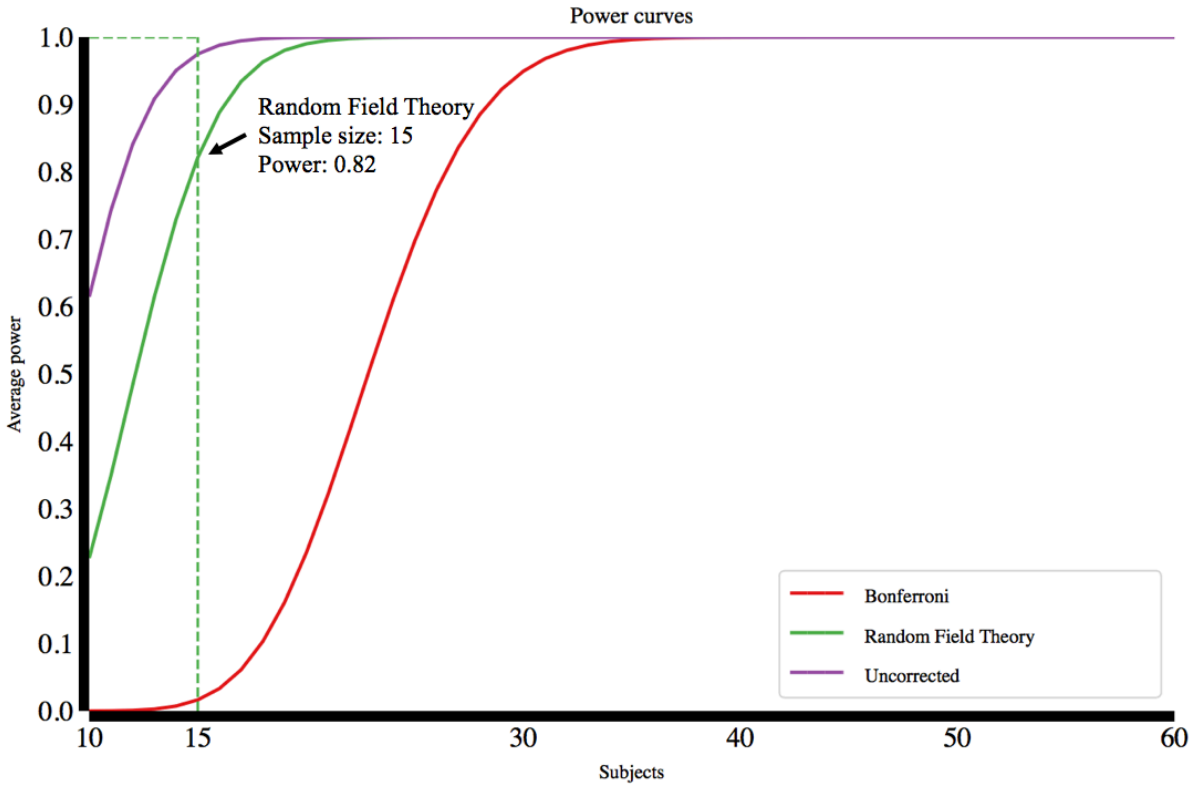


Figure 2. Power curve results from the *a priori* power analysis. The dashed green line indicates that an *N*=15 would result in a power of 0.82. These results should be interpreted with caution as they assumed a pilot sample size of $n = 10$, but were calculated based on an $n = 5$ due to funding limitations.

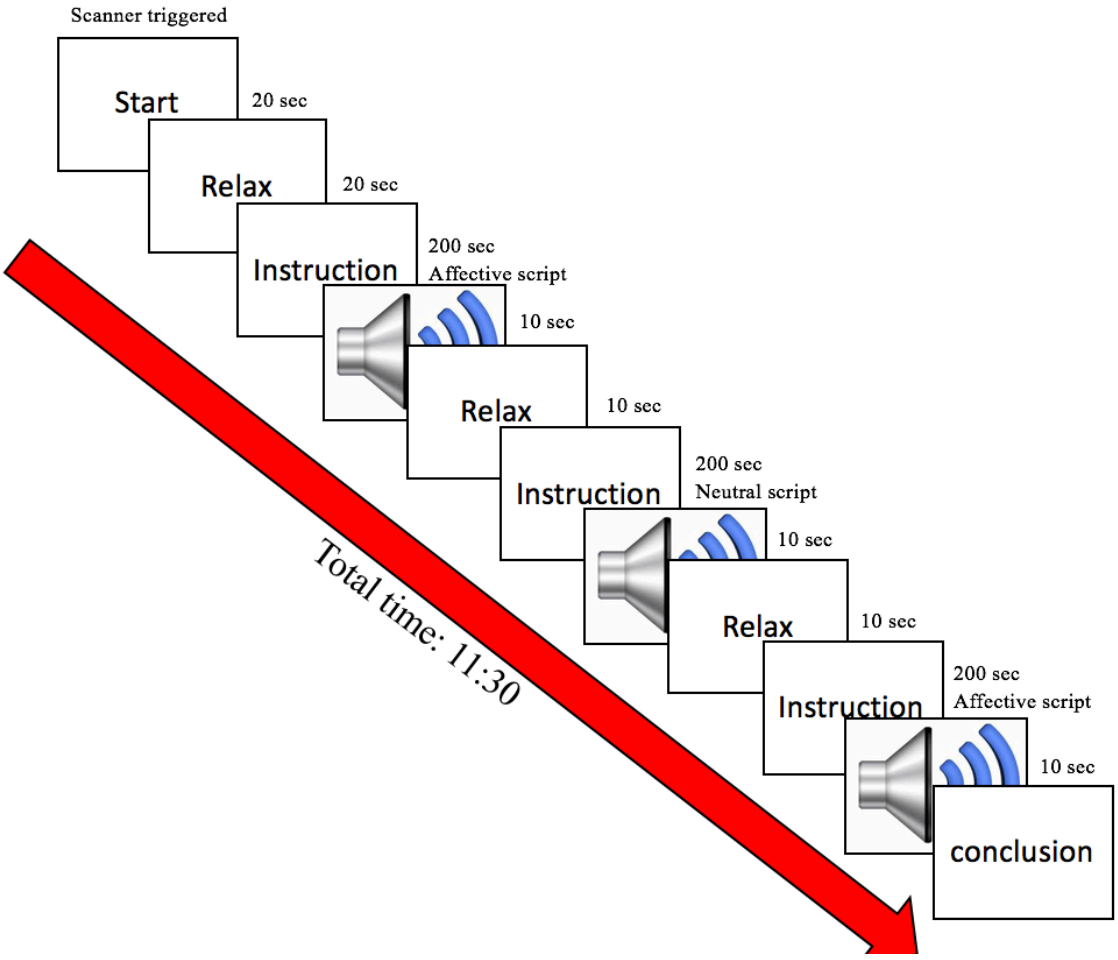


Figure 3. Overview of the fMRI task presentation. Affective scripts were pseudo-counterbalanced. E-Prime 2.0 (Psychology Software Tools, Pittsburg, PA) was used to deliver the stimuli.

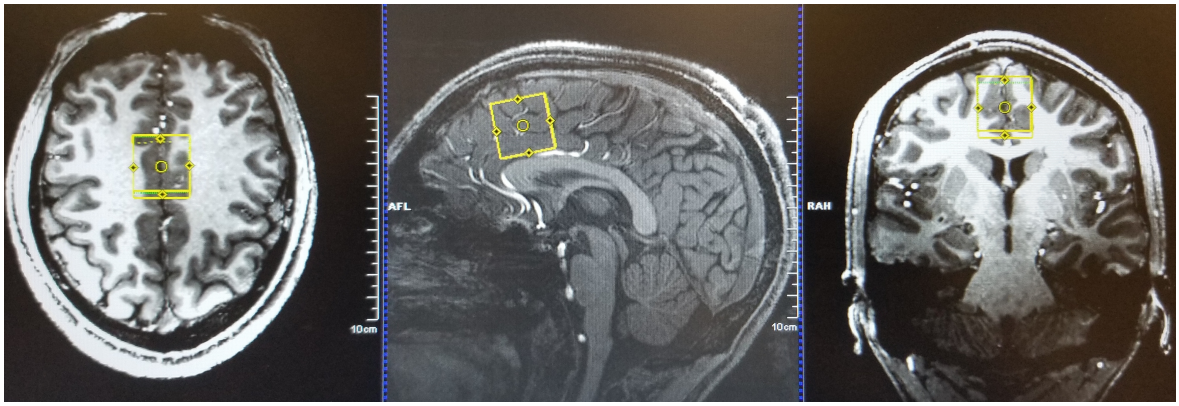


Figure 4. An example of the functional MRS voxel placement on a participant's structural data.

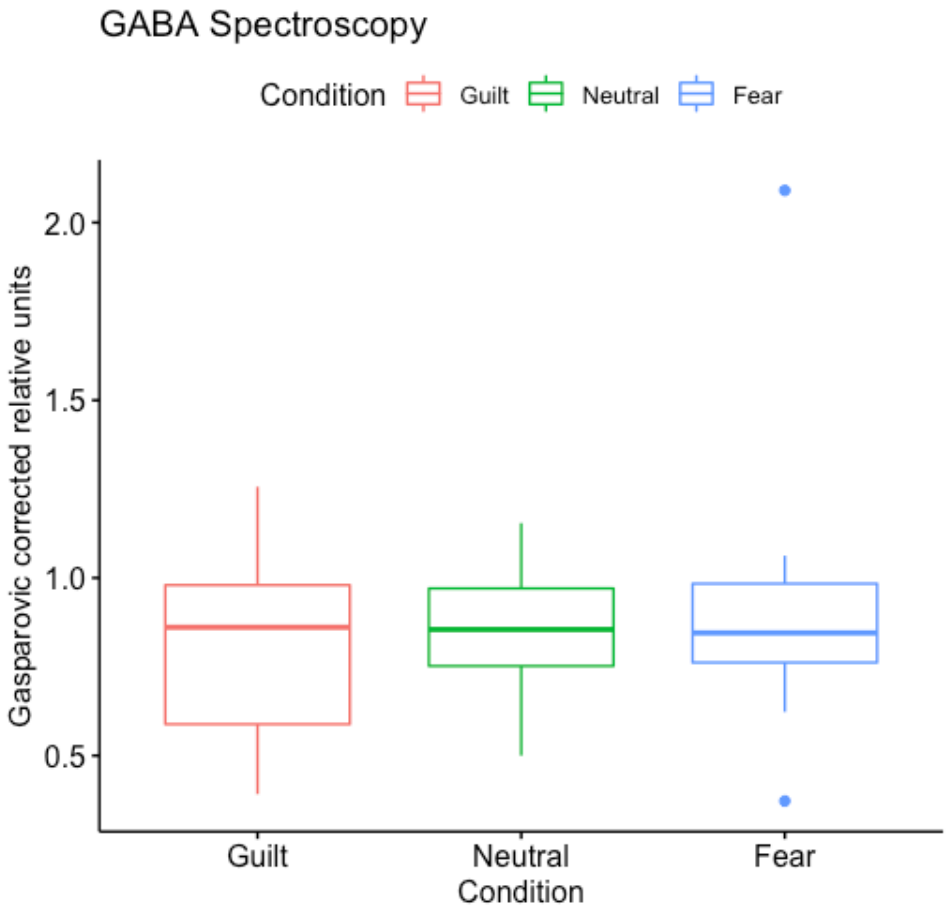


Figure 5. Boxplot of GABA spectroscopy results. The fear condition had one outlier, as identified by the box plot.

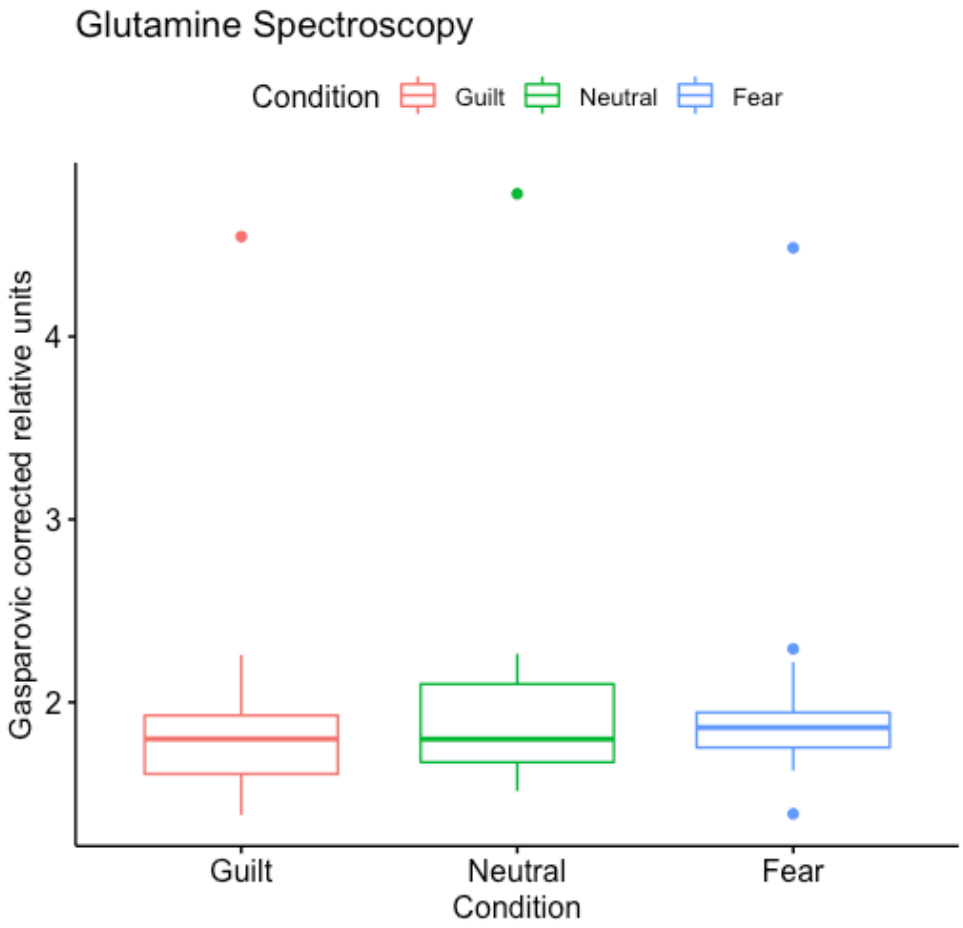


Figure 6. Boxplot of Glutamine spectroscopy. Plot indicates three outliers.

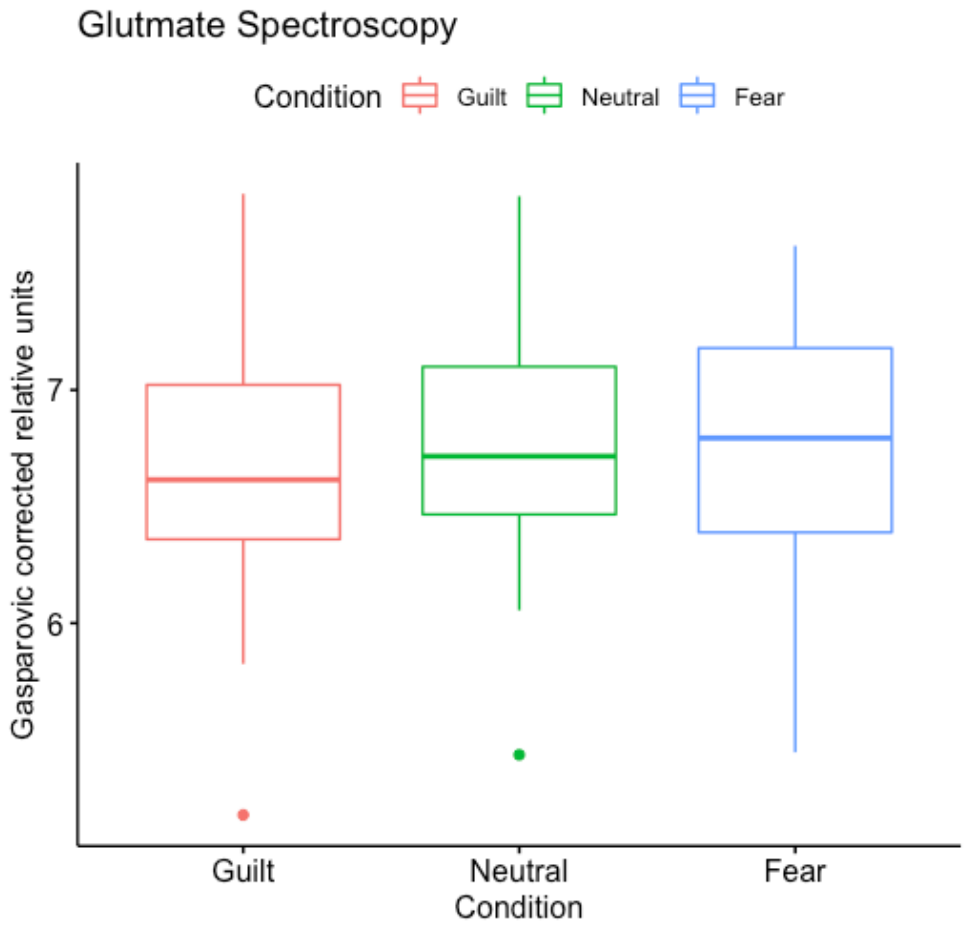


Figure 7. Boxplot of Glutamate spectroscopy. Plot indicates two possible outliers.

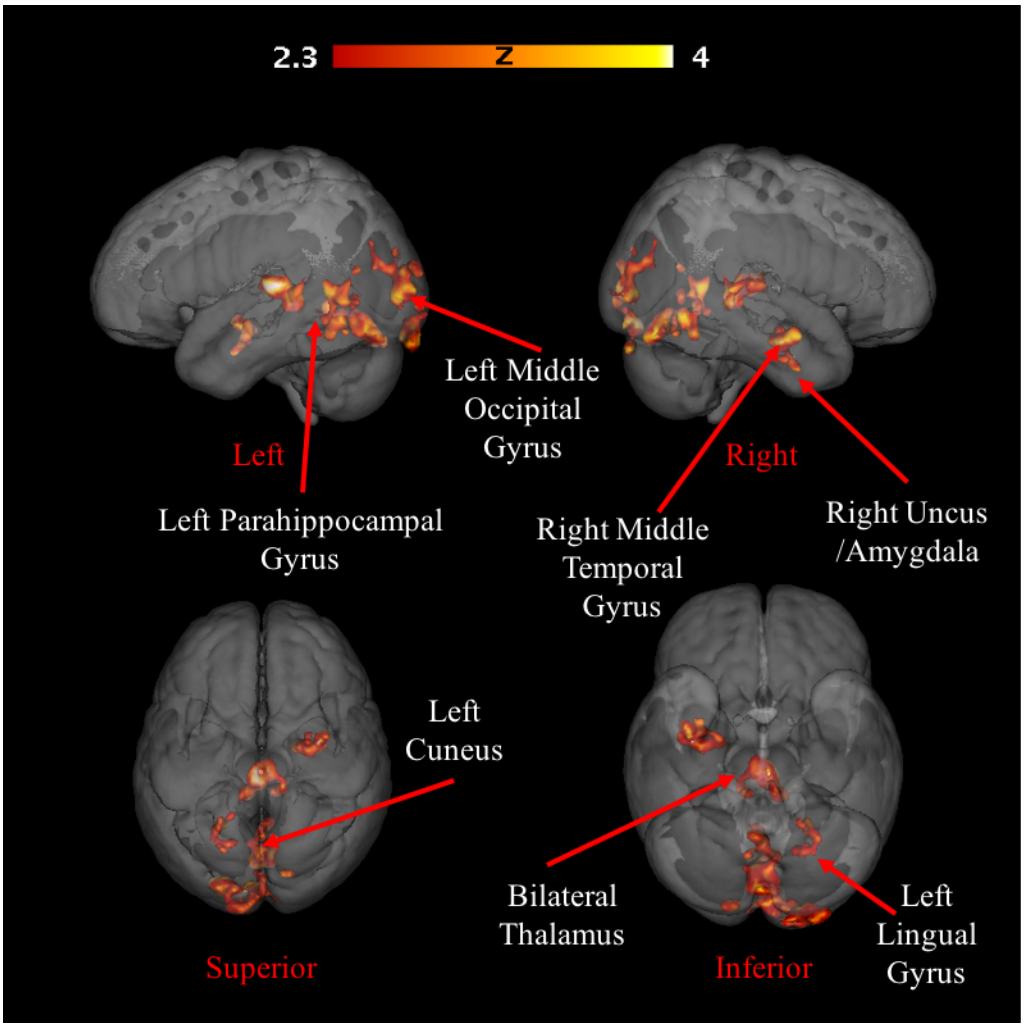


Figure 8. Results from fear > neutral fMRI group level analysis indicating statistically significant areas that the fear condition activated greater than the neutral condition. Statistical maps used cluster thresholding, *z* threshold = 2.3, cluster *p* threshold = 0.05. Color bar indicates cluster *z* score with yellow hues indicating higher *z*-scores.

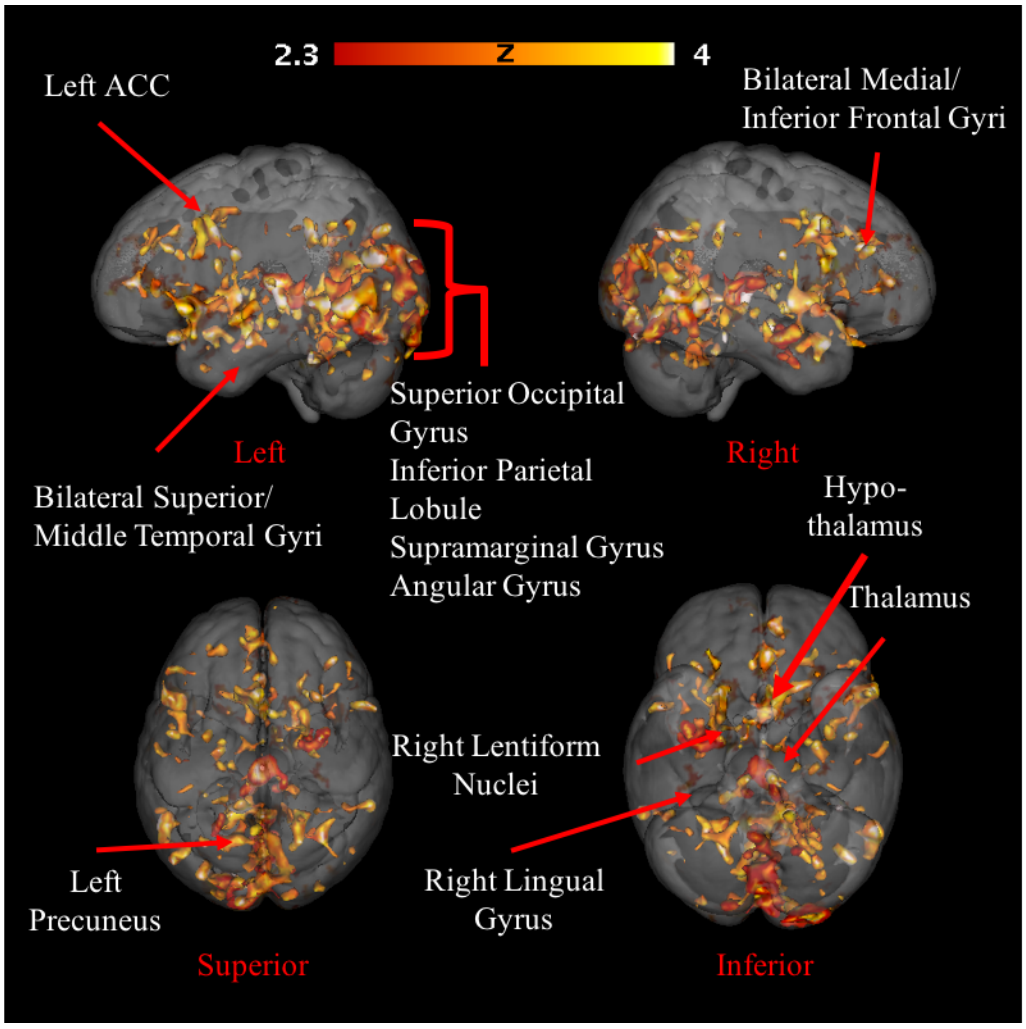


Figure 9. Results from fear > guilt fMRI group level analysis indicating statistically significant areas that the fear condition activated greater than the guilt condition. Statistical maps used cluster thresholding, *z* threshold = 2.3, cluster *p* threshold = 0.05. Color bar indicates cluster *z* score with yellow hues indicating higher *z*-scores.

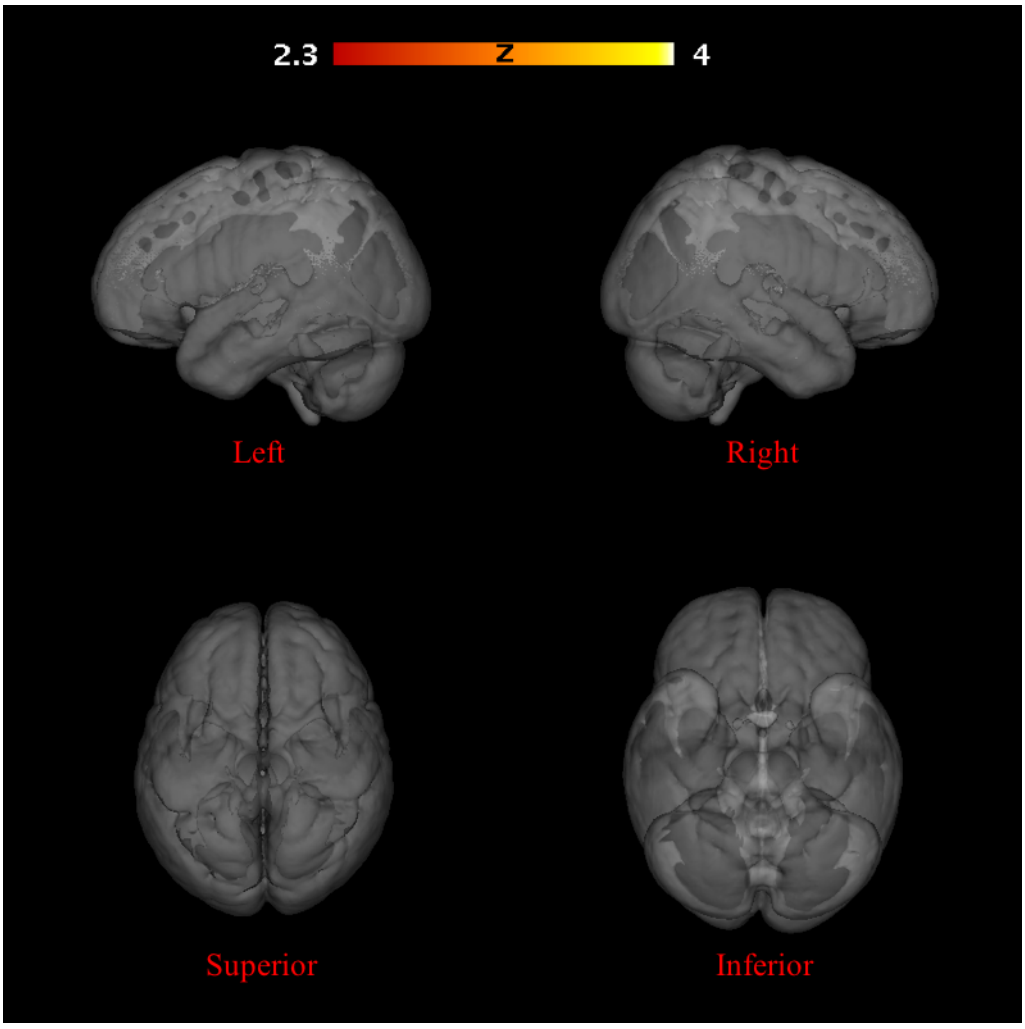


Figure 10. Results from guilt > neutral and guilt > fear fMRI group level analyses. There were no statistically significant areas for either contrast.

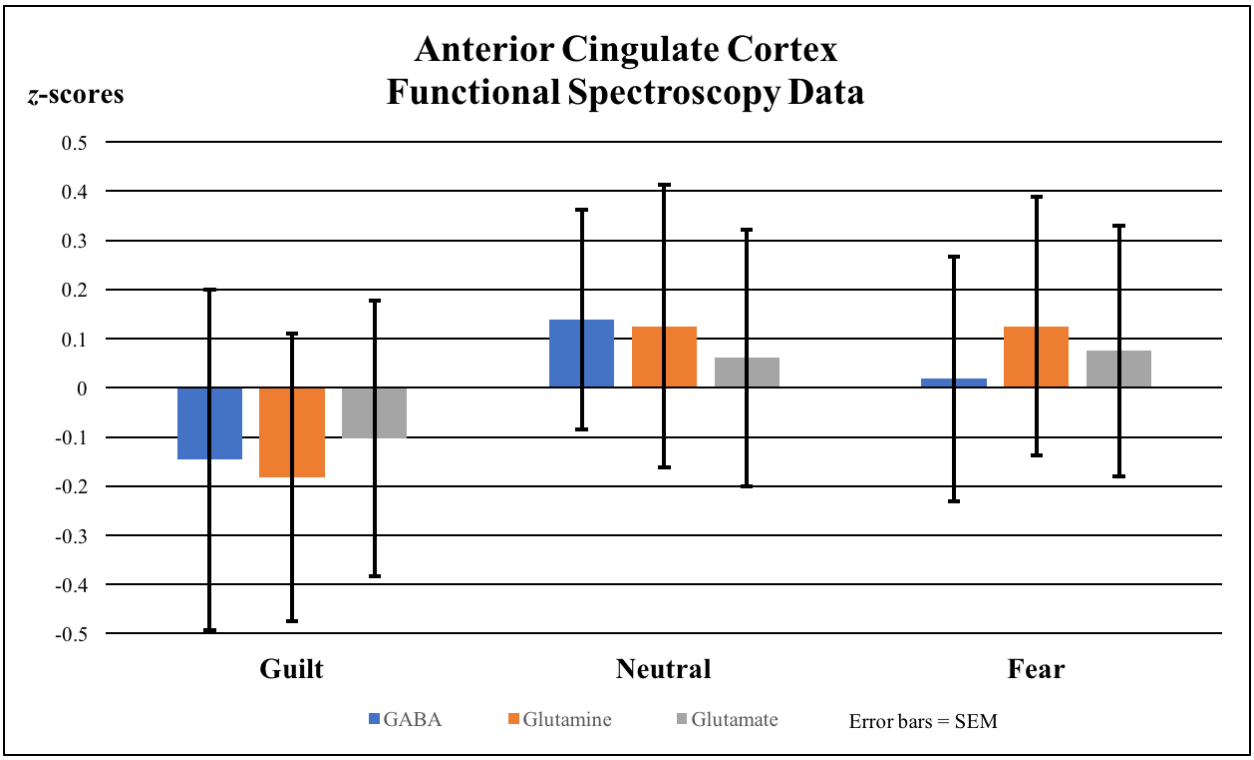


Figure 11. Results of functional magnetic resonance spectroscopy (fMRS) of the anterior cingulate cortex for the neurotransmitters GABA, glutamine, and glutamate for each condition (i.e., guilt, neutral, and fear). Y-axis indicates *z*-scores and error bars indicate standard error of the mean

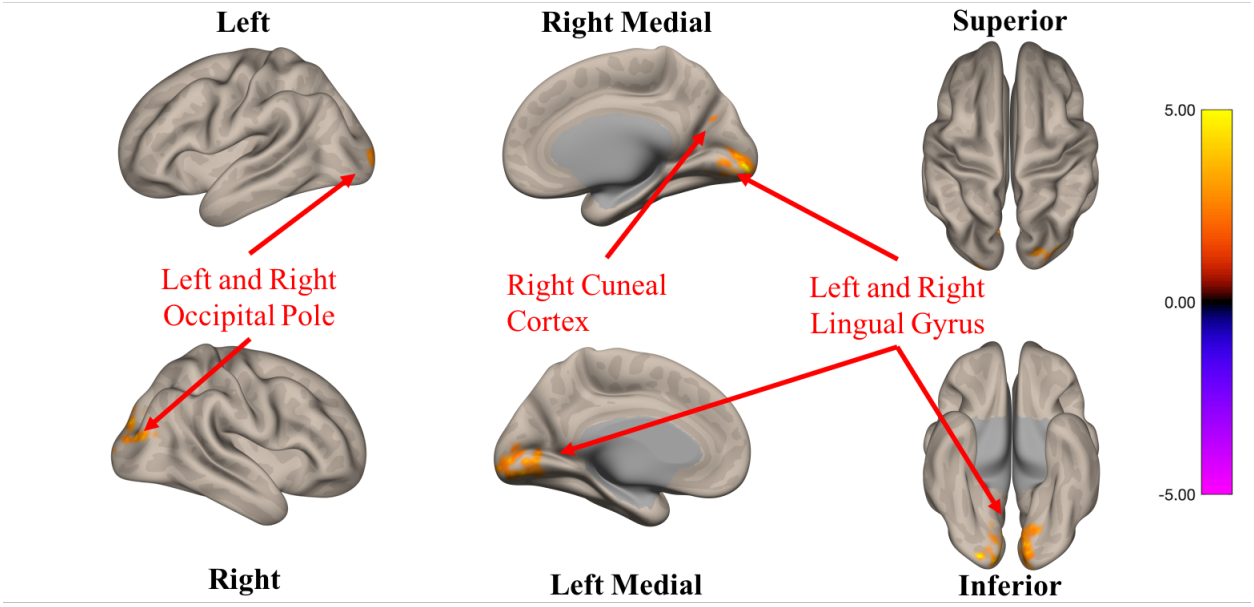


Figure 12. Figure depicts the functional connectivity of the left OFC. Red to yellow colors indicate regions where the fear condition had greater connectivity then the guilt condition. Blue to purple colors indicate regions where the guilt condition had greater connectivity than the fear condition. Statistical thresholds set for voxel height $p_{uncorrected} < 0.05$ and cluster: $p_{FDR\text{-}corrected} <0.05$, using two-tailed t-tests.

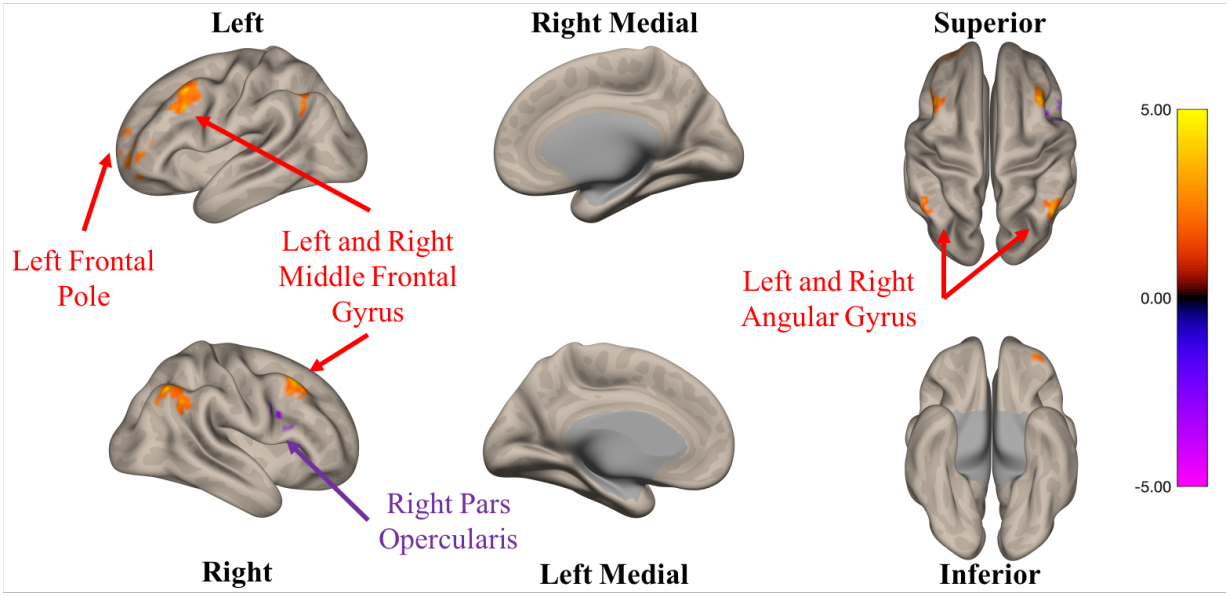


Figure 13. Figure depicts the functional connectivity of the right OFC. Red to yellow colors indicate regions where the fear condition had greater connectivity then the guilt condition. Blue to purple colors indicate regions where the guilt condition had greater connectivity than the fear condition. Statistical thresholds set for voxel height $p_{uncorrected} < 0.05$ and cluster: $p_{FDR\text{-}corrected} <0.05$, using two-tailed t-tests.

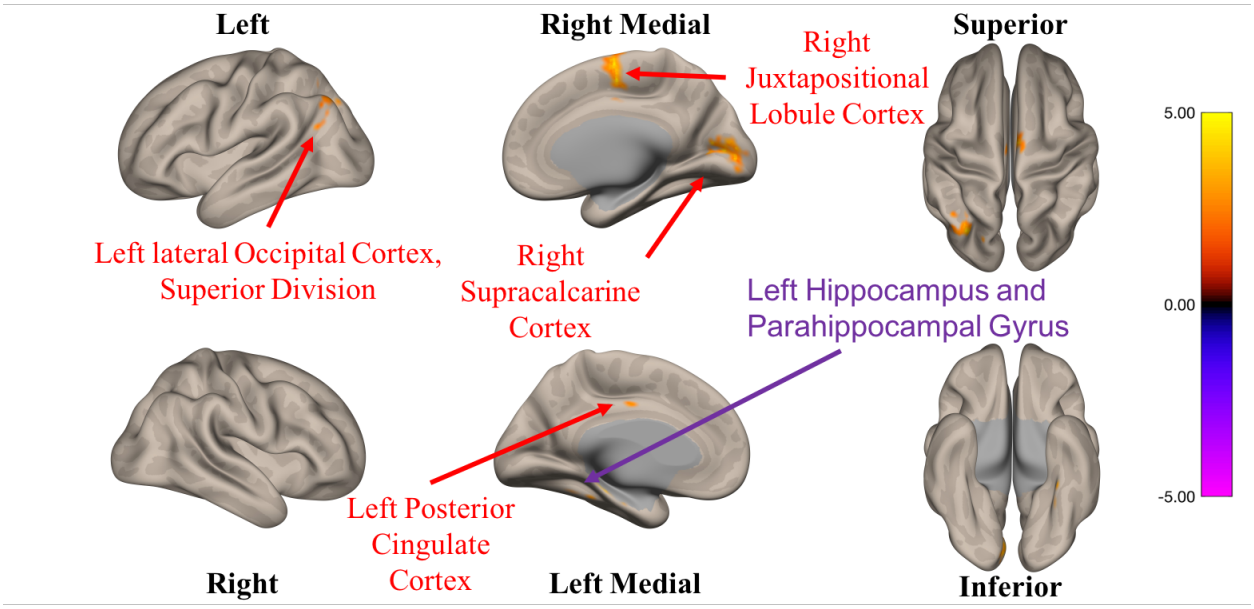


Figure 14. Figure depicts the functional connectivity of the ACC. Red to yellow colors indicate regions where the fear condition had greater connectivity then the guilt condition. Blue to purple colors indicate regions where the guilt condition had greater connectivity than the fear condition. Statistical thresholds set for voxel height $p_{uncorrected} < 0.05$ and cluster: $p_{FDR\text{-}corrected} < 0.05$, using two-tailed t-tests.

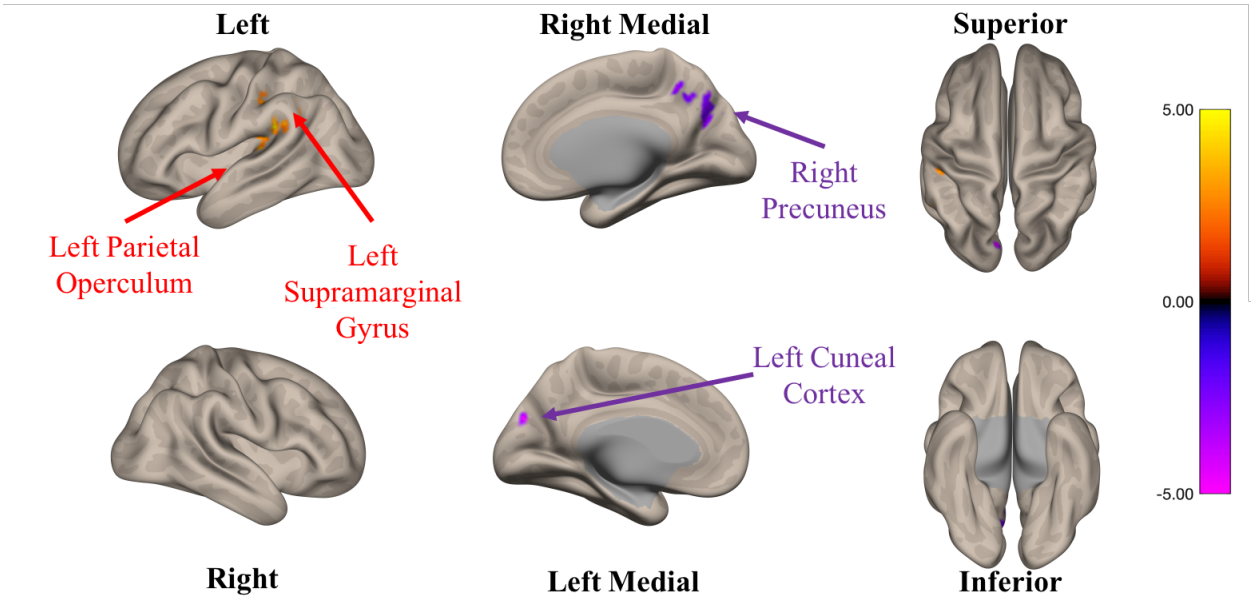


Figure 15. Figure depicts the functional connectivity of the left amygdala. Red to yellow colors indicate regions where the fear condition had greater connectivity then the guilt condition. Blue to purple colors indicate regions where the guilt condition had greater connectivity than the fear condition. Statistical thresholds set for voxel height $p_{uncorrected} < 0.05$ and cluster: $p_{FDR\text{-}corrected} <0.05$, using two-tailed t-tests.

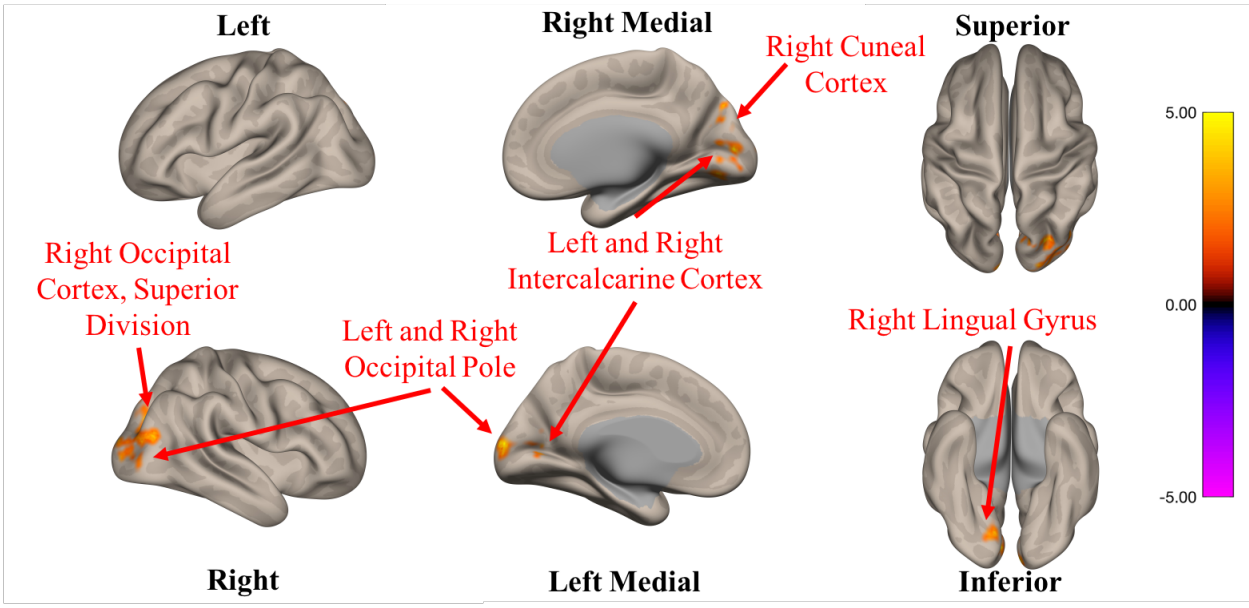


Figure 16. Figure depicts the functional connectivity of the right amygdala. Red to yellow colors indicate regions where the fear condition had greater connectivity then the guilt condition. Blue to purple colors indicate regions where the guilt condition had greater connectivity than the fear condition. Statistical thresholds set for voxel height $p_{uncorrected} < 0.05$ and cluster: $p_{FDR\text{-}corrected} <0.05$, using two-tailed t-tests.

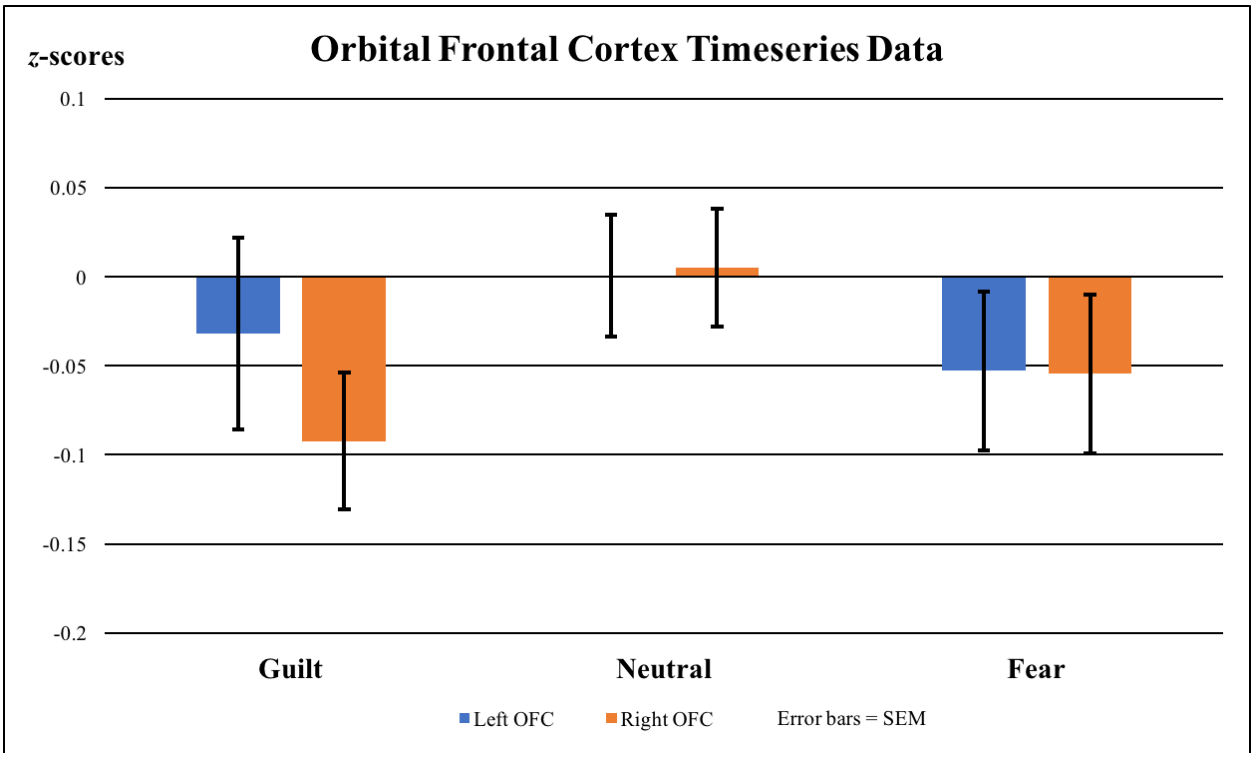


Figure 17. Results of orbital frontal cortex time-series data comparing left and right OFC between conditions (i.e., guilt, neutral, and fear). Y-axis indicates *z*-scores and error bars indicate standard error of the mean.

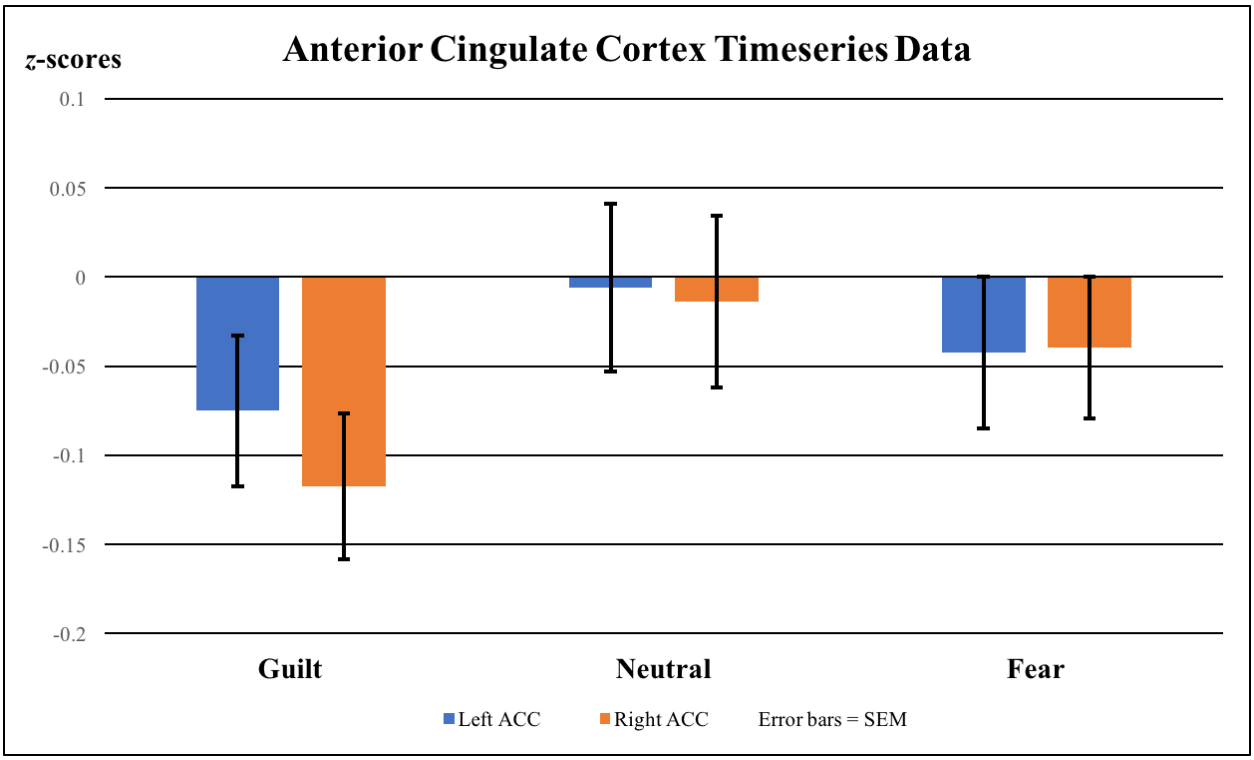


Figure 18. Results of anterior cingulate cortex time-series data comparing left and right ACC between conditions (i.e., guilt, neutral, and fear). Y-axis indicates *z*-scores and error bars indicate standard error of the mean.

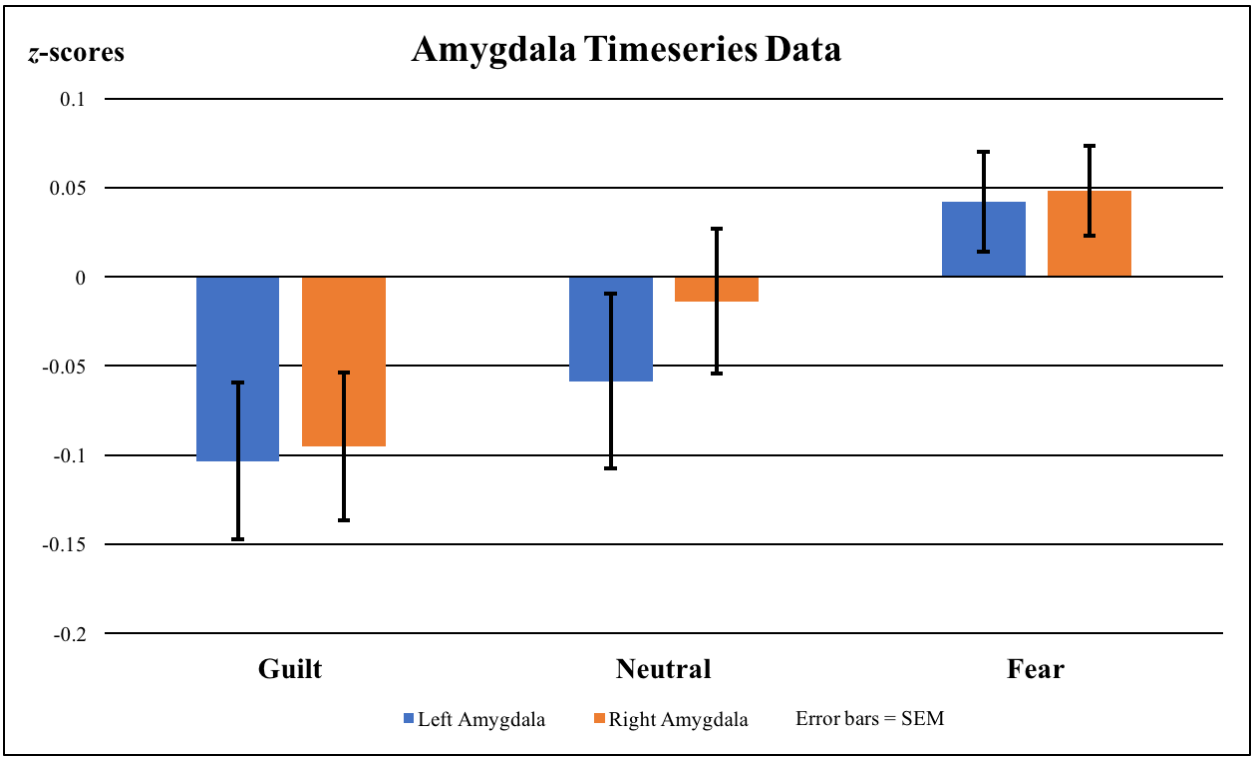
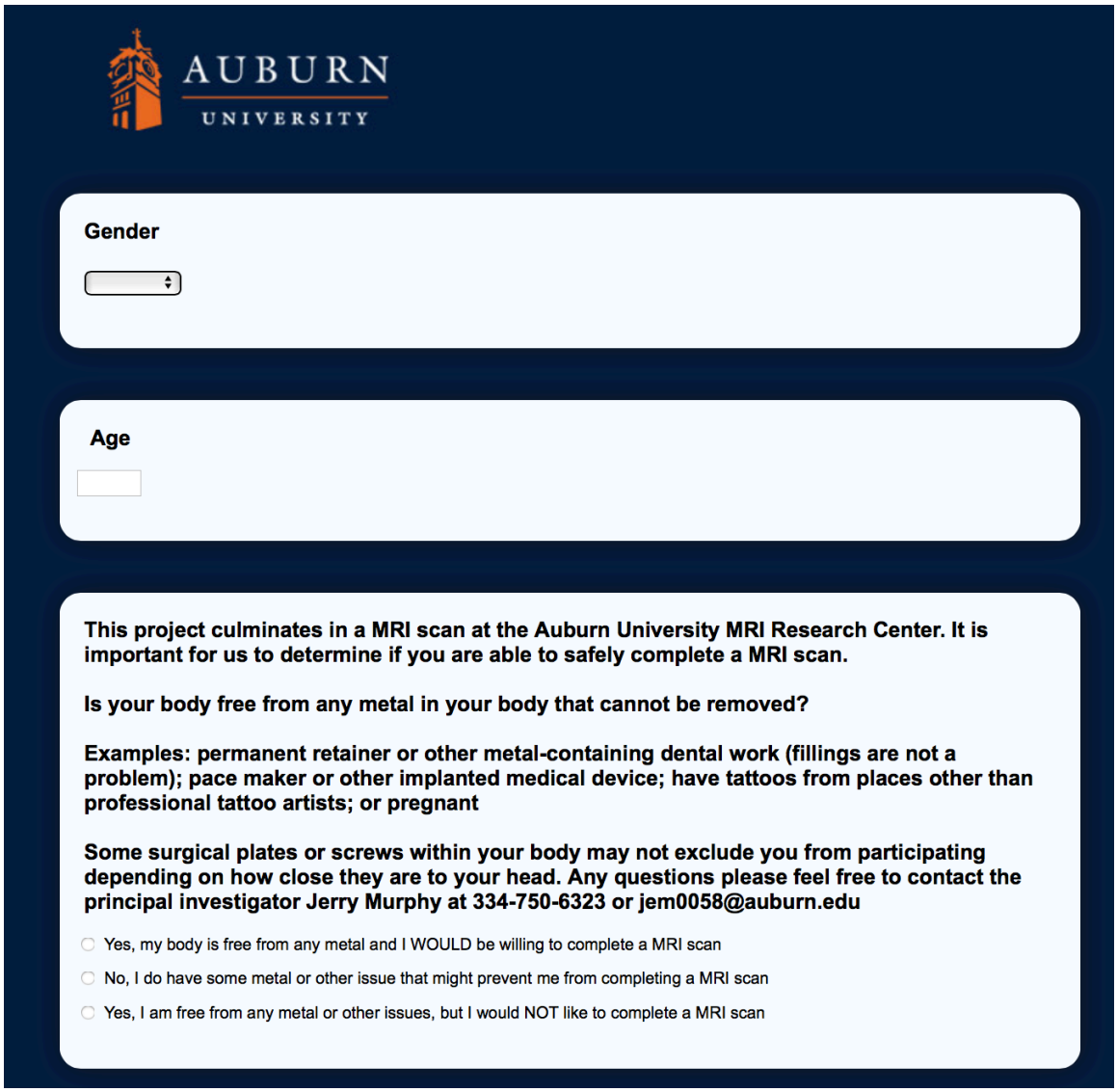
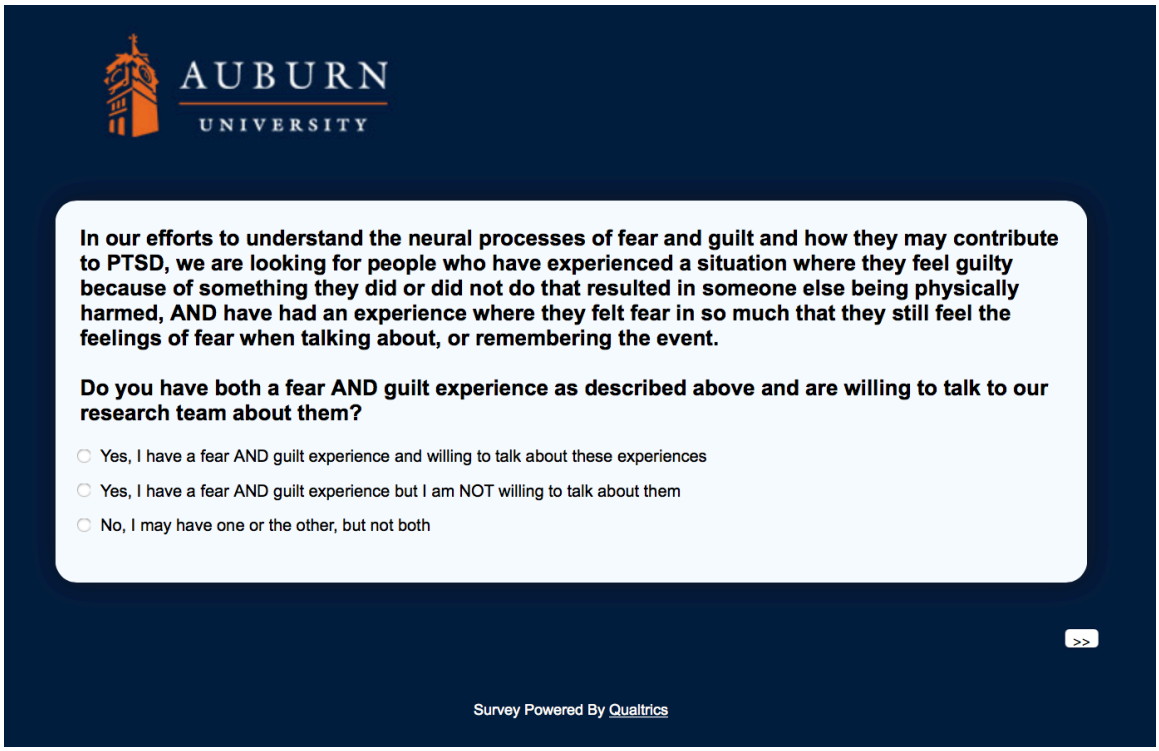
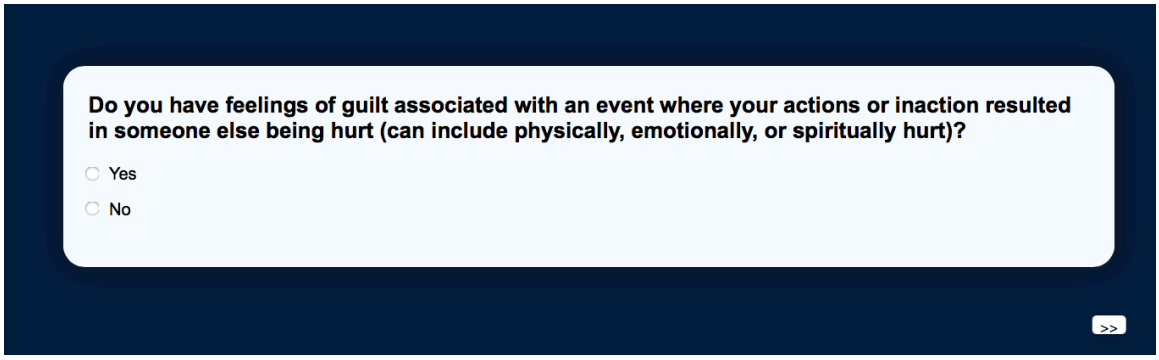


Figure 19. Results of amygdala time-series data comparing left and right amygdalae between conditions (i.e., guilt, neutral, and fear). Y-axis indicates *z*-scores and error bars indicate standard error of the mean.

Appendix A
Screening survey




AUBURN
UNIVERSITY
In our efforts to understand the neural processes of fear and guilt and how they may contribute to PTSD, we are looking for people who have experienced a situation where they feel guilty because of something they did or did not do that resulted in someone else being physically harmed, AND have had an experience where they felt fear in so much that they still feel the feelings of fear when talking about, or remembering the event.
Do you have both a fear AND guilt experience as described above and are willing to talk to our research team about them?
Yes, I have a fear AND guilt experience and willing to talk about these experiences
Yes, I have a fear AND guilt experience but I am NOT willing to talk about them
No, I may have one or the other, but not both
>>
Survey Powered By Qualtrics


Do you have feelings of guilt associated with an event where your actions or inaction resulted in someone else being hurt (can include physically, emotionally, or spiritually hurt)?
Yes
No
>>

AUBURN UNIVERSITY

Individuals who have experienced traumatic events—such as physical or sexual abuse, military combat, sudden loss of loved ones, serious accidents or disasters, etc.—vary considerably in their response to these events. Some people do not have any misgivings about what they did during these events, whereas other people do. They may have misgivings about something they did (or did not do), about beliefs or thoughts they had, or for having had certain feelings (or lack of feelings). The purpose of this questionnaire is to evaluate your response to a traumatic experience.

Please take a few moments to think about what happened. All the items below refer to events related to this experience. Select the answer that best describes how you feel about each statement.

I could have prevented what happened.

Not true at all ☐ Slightly true ☐ Somewhat true ☐ Very true ☐ Extremely true ☐

I am still distressed about what happened.

Never True ☐ Rarely true ☐ Sometimes true ☐ Frequently true ☐ Always true ☐

I had some feelings that I should not have had.

Not true at all ☐ Slightly true ☐ Somewhat true ☐ Very true ☐ Extremely true ☐

What I did was completely justified.

Not true at all ☐ Slightly true ☐ Somewhat true ☐ Very true ☐ Extremely true ☐

I was responsible for causing what happened.

Not true at all ☐ Slightly true ☐ Somewhat true ☐ Very true ☐ Extremely true ☐

What happened causes me emotional pain.

Never true | Rarely true | Sometimes true | Frequently true | Always true

I did something that went against my values.

Not true at all | Slightly true | Somewhat true | Very true | Extremely true

What I did made sense.

Not true at all | Slightly true | Somewhat true | Very true | Extremely true

I knew better than to do what I did.

Not true at all | Slightly true | Somewhat true | Very true | Extremely true

I feel sorrow or grief about the outcome.

Never true | Rarely true | Sometimes true | Frequently true | Always true

What I did was inconsistent with my beliefs.

Not true at all | Slightly true | Somewhat true | Very true | Extremely true

If I knew today—only what I knew when the event(s) occurred—I would do exactly the same thing.

Not true at all | Slightly true | Somewhat true | Very true | Extremely true


I experience intense guilt that relates to what happened.
Never true
Rarely true
Sometimes true
Frequently true
Always true
I should have known better.
Not true at all
Slightly true
Somewhat true
Very true
Extremely true
I experience severe emotional distress when I think about what happened.
Never true
Rarely true
Sometimes true
Frequently true
Always true
I had some thoughts or beliefs that I should not have had.
Not true at all
Slightly true
Somewhat true
Very true
Extremely true
I had good reasons for doing what I did.
Not true at all
Slightly true
Somewhat true
Very true
Extremely true
Indicate how frequently you experience guilt that relates to what happened.
Never
Seldom
Occasionally
Often
Always
I blame myself for what happened.
Not true at all
Slightly true
Somewhat true
Very true
Extremely true

What happened causes a lot of pain and suffering.

Not true at all	Slightly true	Somewhat true	Very true	Extremely true
☐	☐	☐	☐	☐

I should have had certain feelings that I did not have.

Not true at all	Slightly true	Somewhat true	Very true	Extremely true
☐	☐	☐	☐	☐

Indicate the intensity or severity of guilt that you typically experience about the event(s).

None	Slight	Moderate	Considerable	Extreme
☐	☐	☐	☐	☐

I blame myself for something I did, thought, or felt.

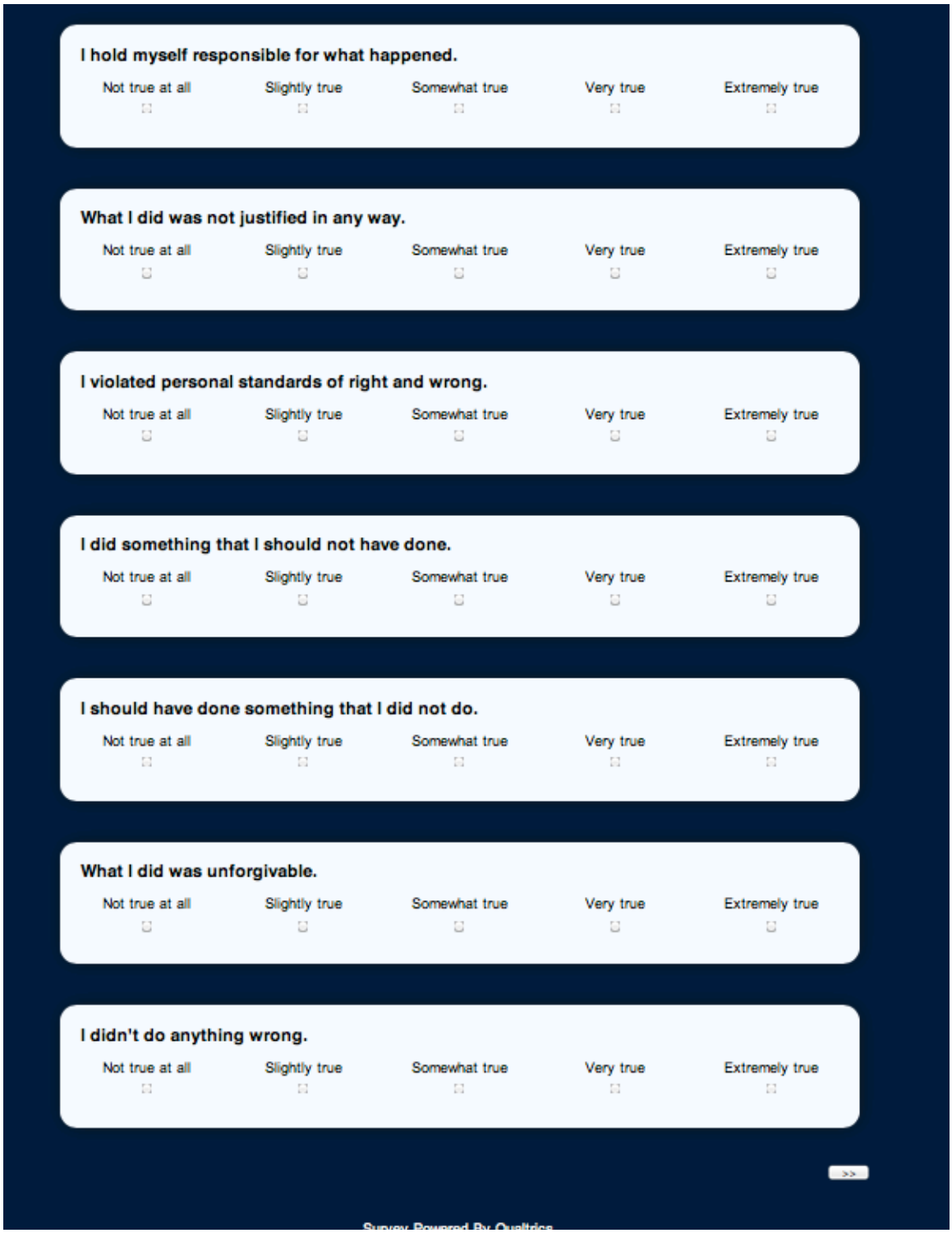
Not true at all	Slightly true	Somewhat true	Very true	Extremely true
☐	☐	☐	☐	☐

When I am reminded of the event(s), I have strong physical reactions such as sweating, tense muscles, dry mouth, etc.

Never true	Rarely true	Sometimes true	Frequently true	Always true
☐	☐	☐	☐	☐

Overall, how guilty do you feel about the event(s)?

Not guilty at all	Slightly guilty	Moderately guilty	Very guilty	Extremely guilty
☐	☐	☐	☐	☐


I hold myself responsible for what happened.
Not true at all
Slightly true
Somewhat true
Very true
Extremely true
What I did was not justified in any way.
Not true at all
Slightly true
Somewhat true
Very true
Extremely true
I violated personal standards of right and wrong.
Not true at all
Slightly true
Somewhat true
Very true
Extremely true
I did something that I should not have done.
Not true at all
Slightly true
Somewhat true
Very true
Extremely true
I should have done something that I did not do.
Not true at all
Slightly true
Somewhat true
Very true
Extremely true
What I did was unforgivable.
Not true at all
Slightly true
Somewhat true
Very true
Extremely true
I didn't do anything wrong.
Not true at all
Slightly true
Somewhat true
Very true
Extremely true
>>
Survey Powered By Qualtrics

Do you have an experience where you felt a great deal of fear such that thinking about the event or talking about the event causes you to experience sensations of fear?

- Yes
- No

In a few short sentences, please describe the event where for felt fearful.

Think back to when you experienced the situation you just described, using the scale below, please indicate how intense your feelings of fear were.

No fear	A Little fear	Moderate amount of fear	Very fearful	Complete fear

When thinking about or talking about the situation you just described, using the scale below, please indicate how close your feels are now to what they were when the event occurred.

No feelings	Feelings are not as intense	About the same	Feelings are more intense	Feelings are much more intense

>>

Instructions: This questionnaire asks about problems you may have had after one of the events you described above. Please consider which of the events you described effects you the most and answer the following questions with that event in mind.

Briefly identify which event you previously described effects you the most.

How long ago did it happen? (please estimate if you are not sure)

Keeping this worst event in mind, read each of the following problems and select the option that indicates how much you have been bothered by that problem in the past month.

Repeated, disturbing, and unwanted memories of the stressful experience?

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

Repeated, disturbing dreams of the stressful experience?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Suddenly feeling or acting as if the stressful experience were actually happening again *(as if you were actually back there reliving it)*?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Feeling very upset when something reminded you of the stressful experience?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Having strong physical reactions when something reminded you of the stressful experience *(for example, heart pounding, trouble breathing, sweating)*?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Avoiding memories, thoughts, or feelings related to the stressful experience?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Avoiding external reminders of the stressful experience *(for example, people, places, conversations, activities, objects, or situations)*?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Trouble remembering important parts of the stressful experience?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Having strong negative beliefs about yourself, other people, or the world *(for example, having thoughts such as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)*?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Blaming yourself or someone else for the stressful experience or what happened after it?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Having strong negative feelings such as fear, horror, anger, guilt, or shame?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Loss of interest in activities that you used to enjoy?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Feeling distant or cut off from other people?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Trouble experiencing positive feelings *(for example, being unable to feel happiness or have loving feelings for people close to you)*?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Irritable behavior, angry outbursts, or acting aggressively?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Taking too many risks or doing things that could cause you harm?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Being “superalert” or watchful or on guard?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Feeling jumpy or easily startled?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Having difficulty concentrating?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Trouble falling or staying asleep?

Not at all | A little bit | Moderately | Quite a bit | Extremely

Appendix B
MRI screening form

MRI Pre-Entry Screening Form	Auburn University MRI Research Center 560 Devall Drive Suite 202 Auburn, AL 36849 Tel: (334) 844-6747 Fax: (334) 844-0214
This form to be used for: Screening of research subjects immediately prior to an MRI study (File completed form with Principal Investigator) *Instructions for completing this form available at http://www.eng.auburn.edu/research/centers/mri/forms*	

Name _____
Last First MI

Address _____ City _____

State _____ Zip Code _____

Phone (___) _____ (___) _____ (___) _____
Home Work Cell

Birthdate _____ Email Address _____

AUMRIRC Use Only

Principal Investigator: _____

IRB Protocol # _____

Subject # _____

Date/Time of MRI study __/__/____ ___:____

Subject Weight (lbs) _____

Primary Physician (Optional):

Name_____ Phone (___) _____

1.	☐Yes ☐No	Have you had prior surgery or an operation (e.g., arthroscopy, endoscopy, etc.) of any kind? If yes, give date and type of surgery, and indicate where on your body using the diagram. Date: __/__/____ Type of surgery: _____ Date: __/__/____ Type of surgery: _____ Date: __/__/____ Type of surgery: _____
2.	☐Yes ☐No	Have you had any medical condition that prevented you completing an MRI exam in the past or had any related to a previous MRI examination or procedure? If yes, please describe: _____
3.	☐Yes ☐No	Have you ever been injured by a metallic object or foreign body (e.g., BB, bullet, shrapnel, etc.)? If yes, please describe: _____

WARNING: Certain implants, devices, or objects may be hazardous to you and/or may interfere with the MR procedure (i.e., MRI, MR angiography, functional MRI, MR spectroscopy). Do not enter the MR system room or MR environment if you have any question or concern regarding an implant, device, or object. Consult the AU MRI Research Center staff BEFORE entering the MR system room. **The MR system magnet is ALWAYS on.**

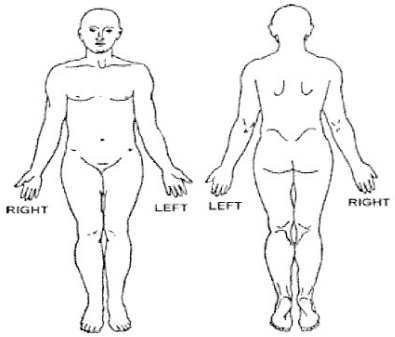
4.	☐Yes ☐No	Do you have a cardiac pacemaker or implanted cardioverter defibrillator (ICD)?
5.	☐Yes ☐No	Is there a possibility of metal in your head (for example aneurysm clips, do not include dental work)? If yes, please describe: _____
6.	☐Yes ☐No	Have you had an injury to the eye involving a metallic object or fragment (for example, metallic slivers, shavings, foreign body), or have you ever needed an eyewash having worked with metals? If yes, please describe: _____
7.	☐Yes ☐No	Do you have an implanted medical device that is electrically, magnetically, or mechanically controlled or activated? If yes, please describe: _____
8.	☐Yes ☐No	**Females Only**: Are you pregnant or is there any possibility that you may be pregnant?
9.	☐Yes ☐No	Do you have a breathing problem or motion disorder?
10.	☐Yes ☐No	Are you claustrophobic?
11.	☐Yes ☐No	Do you have inner ear disorders or experience vertigo or dizziness?
12.	☐Yes ☐No	Do you have tattoos or permanent makeup that contains metal?
13.	☐Yes ☐No	Do you have body piercing jewelry that cannot be removed?
14.	☐Yes ☐No	Do you have a history of cardiovascular disease?
15.	☐Yes ☐No	Do you have a permanent retainer or braces?

WARNING: Certain implants, devices, or objects may be hazardous to you and/or may interfere with the MR procedure (i.e., MRI, MR angiography, functional MRI, MR spectroscopy). Do not enter the MR system room or MR environment if you have any question or concern regarding an implant, device, or object. Consult the AU MRI Research Center staff BEFORE entering the MR system room. **The MR system magnet is ALWAYS on.**

Please indicate if you have any of the following:

16.	☐Yes ☐No	Neurostimulation system
17.	☐Yes ☐No	Spinal cord stimulator
18.	☐Yes ☐No	Internal electrodes or wires
19.	☐Yes ☐No	Bone growth/bone fusion stimulator
20.	☐Yes ☐No	Cochlear, otologic, or other ear implant
21.	☐Yes ☐No	Insulin or other infusion pump
22.	☐Yes ☐No	Implanted drug infusion device
23.	☐Yes ☐No	Any type of prosthesis (eye, penile, etc.)
24.	☐Yes ☐No	Heart valve prosthesis
25.	☐Yes ☐No	Eyelid spring or wire
26.	☐Yes ☐No	Artificial or prosthetic limb
27.	☐Yes ☐No	Metallic stent, filter, or coil
28.	☐Yes ☐No	Shunt (spinal or intraventricular)
29.	☐Yes ☐No	Vascular access port and/or catheter
30.	☐Yes ☐No	Radiation seeds or implants
31.	☐Yes ☐No	Swan-Ganz or thermodilution catheter
32.	☐Yes ☐No	Medication patch (Nicotine, Nitroglycerine)
33.	☐Yes ☐No	Any metallic fragment or foreign body
34.	☐Yes ☐No	Wire mesh implant
35.	☐Yes ☐No	Tissue expander (e.g., breast)
36.	☐Yes ☐No	Surgical staples, clips, or metallic sutures
37.	☐Yes ☐No	Joint replacement (hip, knee, etc.)
38.	☐Yes ☐No	Bone/joint pin, screw, nail, wire, plate, etc.
39.	☐Yes ☐No	IUD, diaphragm, or pessary
40.	☐Yes ☐No	Dentures or partial plates
41.	☐Yes ☐No	Tattoo or permanent makeup
42.	☐Yes ☐No	Body piercing jewelry
43.	☐Yes ☐No	Hearing aid (*Remove before entering MRI scanner room*)
44.	☐Yes ☐No	Other implant _____

Please mark on the figure(s) below the location of any implant or metal inside of or on your body.



IMPORTANT INSTRUCTIONS

Before entering the MR scanner room, you must remove all metallic objects including hearing aids, dentures, partial plates, keys, beeper, cell phone, eyeglasses, hair pins, barrettes, jewelry, body piercing jewelry, watch, safety pins, paperclips, money clip, credit cards, bank cards, magnetic strip cards, coins, pens, pocket knife, nail clippers, tools, clothing with metal fasteners, & clothing with metallic threads.

Please consult the research staff if you have any question or concern BEFORE you enter the MR scanner room.

NOTE: You may be advised or required to wear earplugs or other hearing protection during the MR procedure to prevent possible problems or hazards related to acoustic noise.

I attest that the above information is correct to the best of my knowledge. I read and understand the contents of this form and had the opportunity to ask questions regarding the information on this form and regarding the MR procedure that I am about to undergo.

This form is valid only on the day it is completed.

Signature of Person Completing Form: _____ _____
Signature Date

Form Completed By: ☐ Subject ☐ Relative _____ _____
Print Name Relationship to Subject

Form Information Reviewed By: _____ _____
Print Name Signature

Form Information Reviewed By: _____ _____
Print Name Signature

Appendix C
Script Efficacy survey

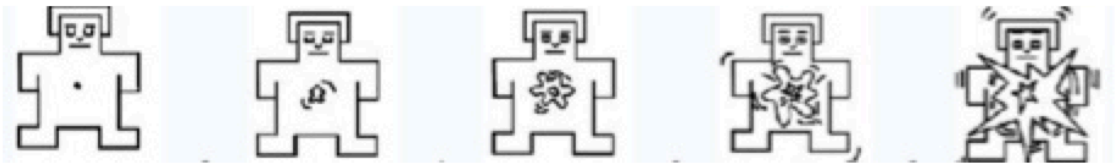
Participant ID _____ Date _____

Please answer each question by circling or filling in the bubble that reflects how you feel.

1. Did you feel the same amount of fear during the fear script as you felt during the original event?

Not at all		Very little		Somewhat		Pretty close		Same or more
O	O	O	O	O	O	O	O	O

2. Please indicate how intense the Fear emotion was that you felt the first time you heard the script?



O	O	O	O	O	O	O	O	O

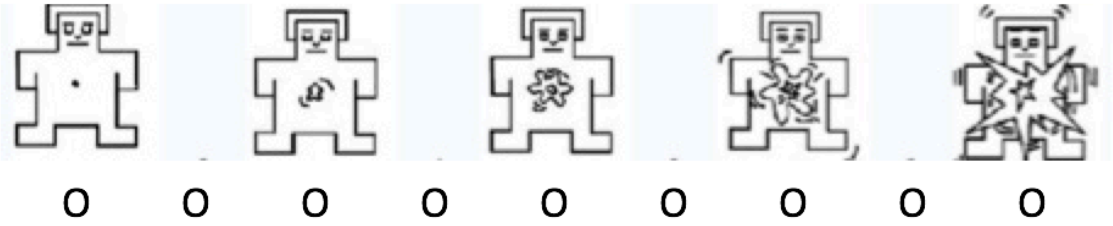
3. Please indicate how intense the Fear emotion was that you felt the second time you heard the script?

O	O	O	O	O	O	O	O	O

1. Did you feel the same amount of guilt during the guilt script as you felt during the original event?

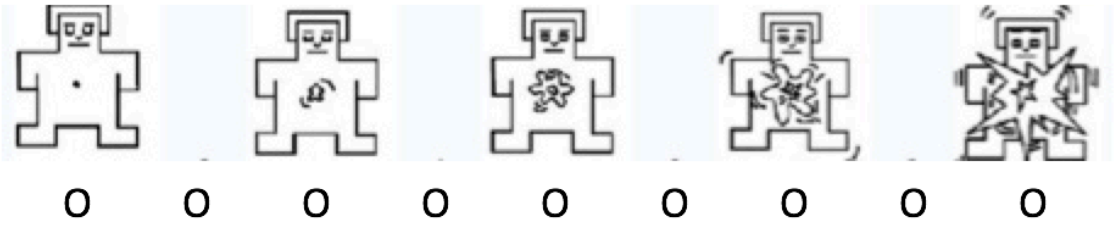
Not at all		Very little		Somewhat		Pretty close		Same or more
O	O	O	O	O	O	O	O	O

2. Please indicate how intense you felt guilt the first time you heard the script?



O O O O O O O O O

3. Please indicate how intense you felt guilt the second time you heard the script?



O O O O O O O O O

4. During the Neutral Scripts, did you feel any emotions associated with the script, or any emotions that were carried over from the other scripts?

YES NO

5. If you answered Yes to the previous question, please describe you felt during the Neutral Scripts? The list of emotions below are there to help you describe how you felt.

_____

_____

_____

Joy	Blissful	Love	Eager	Anxious	Frustrated
Bored	Content	Hopeful	Angry	Irritated	Impatient
Discouraged	Fear	Guilt	Sad	Happy	Insecure
Powerless	Overwhelmed	Grateful	Pride	Serene	Blissful
Relaxed	Delighted	Indifferent	Uneasy	Cheerful	Glad

Appendix D

Results of Shapiro-Wilk Normality tests for timeseries data. The outlier column represents the number of outliers identified out of the 227 data points for that ROI in that participant.

		Shapiro-Wilk Normality Test		
ID	ROI	Before correction	Outliers Winsorized	Outliers
P01	OFC left	W=0.996, p=0.739	W=0.994, p=0.494	3
	OFC right	W=0.993, p=0.452	W=0.995, p=0.732	5
	ACC left	W=0.992, p=0.218	W=0.992, p=0.247	5
	ACC right	W=0.994, p=0.487	W=0.991, p=0.191	2
	Amygdala left	W=0.980, p=0.002*	W=0.995, p=0.700	4
	Amygdala right	W=0.989, p=0.09	W=0.991, p=0.178	2
P02	OFC left	W=0.994, p=0.446	W=0.990, p=0.117	3
	OFC right	W=0.995, p=0.641	W=0.994, p=0.492	1
	ACC left	W=0.998, p=0.978	W=0.993, p=0.319	2
	ACC right	W=0.991, p=0.145	W=0.991, p=0.177	1
	Amygdala left	W=0.983, p=0.008*	W=0.987, p=0.043*	6
	Amygdala right	W=0.995, p=0.618	W=0.992, p=0.251	1
P03	OFC left	W=0.992, p=0.216	W=0.992, p=0.286	3
	OFC right	W=0.985, p=0.014*	W=0.990, p=0.099	7
	ACC left	W=0.905, p<0.001*	W=0.988, p=0.056	6
	ACC right	W=0.899, p<0.001*	W=0.989, p= 0.079	7
	Amygdala left	W=0.981, p=0.003*	W=0.989, p=0.067	3
	Amygdala right	W=0.991, p=0.172	W=0.994, p=0.446	4
P04	OFC left	W=0.981, p=0.003*	W=0.993, p=0.304	10
	OFC right	W=0.982, p=0.005*	W=0.989, p=0.067	3
	ACC left	W=0.990, p=0.116	W=0.993, p=0.363	10
	ACC right	W=0.993, p=0.354	W=0.995, p=0.587	6
	Amygdala left	W=0.990, p=0.102	W=0.989, p=0.067	2
	Amygdala right	W=0.993, p=0.325	W=0.995, p=0.605	7
P05	OFC left	W=0.991, p=0.164	W=0.992, p=0.241	3
	OFC right	W=0.992, p=0.254	W=0.989, p=0.084	2
	ACC left	W=0.993, p=0.378	na	0
	ACC right	W=0.993, p=0.347	na	0
	Amygdala left	W=0.993, p=0.344	na	0
	Amygdala right	W=0.996, p=0.758	W=0.995, p=0.60	1

		Shapiro-Wilk Normality Test		
ID	ROI	Before correction	Outliers Winsorized	Outliers
P06	OFC left	W=0.969, p<0.001*	W=0.991, p=0.168	5
	OFC right	W=0.988, p=0.055	W=0.992, p=0.283	7
	ACC left	W=0.758, p<0.001*	W=0.990, p=0.141	6
	ACC right	W=0.737, p<0.001*	W=0.993, p=0.404	12
	Amygdala left	W=0.985, p=0.013*	W=0.993, p=0.385	4
	Amygdala right	W=0.989, p=0.07	W=0.990, p=0.107	3
P07	OFC left	W=0.947, p<0.001*	W=0.991, p=0.202	13
	OFC right	W=0.979, p=0.002*	W=0.987, p=0.039*	5
	ACC left	W=0.916, p<0.001*	W=0.977, p<0.001*	19
	ACC right	W=0.938, p<0.001*	W=0.983, p=0.007*	14
	Amygdala left	W=0.974, p<0.001*	W=0.997, p=0.895	11
	Amygdala right	W=0.974, p<0.001*	W=0.997, p=0.943	10
P08	OFC left	W=0.993, p=0.463	W=0.992, p=0.273	3
	OFC right	W=0.995, p=0.682	W=0.995, p=0.588	1
	ACC left	W=0.971, p<0.001*	W=0.984, p=0.011*	3
	ACC right	W=0.972, p<0.001*	W=0.988, p=0.061	3
	Amygdala left	W=0.967, p<0.001*	W=0.967, p<0.001*	4
	Amygdala right	W=0.990, p=0.119	W=0.995, p=0.658	5
P09	OFC left	W=0.869, p<0.001*	W=0.992, p=0.231	15
	OFC right	W=0.869, p<0.001*	W=0.991, p=0.138	8
	ACC left	W=0.979, p=0.002*	W=0.991, p=0.148	7
	ACC right	W=0.967, p<0.001*	W=0.990, p=0.127	11
	Amygdala left	W=0.946, p<0.001*	W= 0.996, p=0.792	9
	Amygdala right	W=0.950, p<0.001*	W=0.990, p=0.114	7
P10	OFC left	W=0.898, p<0.001*	W=0.981, p=0.003*	21
	OFC right	W=0.886, p<0.001*	W=0.986, p=0.023*	19
	ACC left	W=0.884, p<0.001*	W=0.971, p<0.001*	27
	ACC right	W=0.869, p<0.001*	W=0.969, p<0.001*	35
	Amygdala left	W=0.913, p<0.001*	W=0.991, p=0.169	10
	Amygdala right	W=0.958, p<0.001*	W=0.964, p<0.001*	5

		Shapiro-Wilk Normality Test		
ID	ROI	Before correction	Outliers Winsorized	Outliers
P11	OFC left	W=0.987, p =0.033*	W=0.992, p =0.288	5
	OFC right	W=0.969, p <0.001*	W=0.992, p =0.229	4
	ACC left	W=0.927, p <0.001*	W=0.995, p =0.591	6
	ACC right	W=0.940, p <0.001*	W=0.940, p <0.001*	4
	Amygdala left	W=0.918, p <0.001*	W=0.993, p =0.393	2
	Amygdala right	W=0.989, p =0.089	W=0.995, p =0.58	3
P12	OFC left	W=0.996, p =0.778	W=0.994, p =0.573	5
	OFC right	W=0.992, p =0.268	W=0.993, p =0.334	1
	ACC left	W=0.966, p <0.001*	W= 0.996, p =0.768	4
	ACC right	W=0.974, p <0.001*	W=0.994, p =0.512	2
	Amygdala left	W=0.995, p =0.648	W=0.995, p =0.70	2
	Amygdala right	W=0.980, p =0.002*	W=0.991, p =0.20	2
P13	OFC left	W=0.980, p =0.002*	W=0.994, p =0.441	9
	OFC right	W=0.989, p =0.077	W=0.989, p =0.077	8
	ACC left	W=0.942, p <0.001*	W=0.992, p =0.272	6
	ACC right	W=0.992, p =0.272	W=0.996, p =0.822	9
	Amygdala left	W=0.985, p =0.019*	W=0.994, p =0.453	3
	Amygdala right	W=0.992, p =0.23	na	0
P14	OFC left	W=0.991, p =0.164	W=0.992, p =0.296	3
	OFC right	W=0.984, p =0.011*	W=0.984, p =0.009*	9
	ACC left	W=0.929, p <0.001*	W=0.994, p =0.508	7
	ACC right	W=0.898, p <0.001*	W=0.989, p =0.090	12
	Amygdala left	W=0.968, p <0.001*	W=0.993, p =0.311	8
	Amygdala right	W=0.982, p =0.005*	W=0.996, p =0.767	4
P15	OFC left	W=0.991; p=0.175	W=0.993; p=0.344	8
	OFC right	W=0.984; p=0.010**	W=0.984; p=0.010**	1
	ACC left	W=0.973; p=<0.001**	W=0.996; p=0.818	7
	ACC right	W=0.979; p=0.002**	W=0.993; p=0.324	7
	Amygdala left	W=0.956; p=<0.001**	W=0.992; p=0.223	6
	Amygdala right	W=0.949; p=<0.001**	W=0.994; p=0.47	3

Appendix E

Local maxima tables from higher order fMRI analysis with TRGI and PCL as additional regressors

Fear > Neutral (PCL and TRGI as regressors) Group Feat cluster index with Talairach						
Z-score	X coor	Y coor	Z coor	Lobe	Region	BA
3.48	0.61	-66.81	-10.13	Anterior Lobe	Left Culmen of Vermis	
3.3	6.39	-34.98	-2.59		Right Culmen	
4.3	31.13	-7.73	-15.15	Limbic Lobe	Right Amygdala	
3.18	19.78	-9.29	-18.94		Right Parahippocampal Gyrus	34
3.51	27.41	-1.08	-29.21		Right Uncus	36
3.01	16.02	-8.8	-26.17		Right Uncus	28
3.12	-22.2	-95.05	-12.11	Occipital Lobe	Left Fusiform Gyrus	18
2.6	-31.67	-93.3	-8.43		Left Inferior Occipital Gyrus	18
4.75	-22.15	-86.89	-20.62	Posterior Lobe	Left Declive	
3.49	-1.27	-73.57	-23.25		Left Tuber of Vermis	
3.39	6.34	-60.6	-18.74		Right Declive	
4.07	13.85	-82.95	-27.38		Right Pyramis	
4.79	-3.06	-25.88	5.18	Sub-lobar	Left Thalamus	
3.96	10.16	-33.58	4.76		Right Thalamus	
3.18	36.83	-7.32	-22.32	Temporal Lobe	Right Fusiform Gyrus	20

Fear > Guilt (PCL and TRGI regressors) Group Feat cluster index table 1 of 2						
Z-score	X coor	Y coor	Z coor	Lobe	Region	BA
3.91	-10.32	40.38	-17.7	Frontal Lobe	Left Inferior Frontal Gyrus	11
4.38	-6.59	46.07	11.65		Left Medial Frontal Gyrus	10
4.14	-4.63	44	-15.62		Left Medial Frontal Gyrus	11
4.74	-2.8	27.04	-18.52		Left Medial Frontal Gyrus	25
3.24	-31.49	-10.78	40.37		Left Middle Frontal Gyrus	6
3.41	-8.51	43.85	16.92		Left Medial Frontal Gyrus	9
3.68	-39.02	-1	37.34		Left Precentral Gyrus	6
4.22	-14.1	61.54	8.99		Left Superior Frontal Gyrus	10
3.19	38.64	6.37	31.06		Right Inferior Frontal Gyrus	9
4.56	21.83	32.63	-19.81		Right Inferior Frontal Gyrus	11
4.53	50.03	7.08	18.51		Right Inferior Frontal Gyrus	44
4.7	17.97	11.69	-19.39		Right Inferior Frontal Gyrus	47
3.72	25.38	8.03	36.51		Right Middle Frontal Gyrus	8
4.21	34.95	27.72	25.19		Right Middle Frontal Gyrus	9
4.56	21.81	26.83	-18.38		Right Middle Frontal Gyrus	11
3.42	40.47	-5.37	35.73		Right Precentral Gyrus	6
3.26	40.52	7.9	36.6		Right Precentral Gyrus	9
3.47	48.16	7.56	11.29		Right Precentral Gyrus	44

Fear > Guilt (PCL and TRGI regressors) Group Feat cluster index table 2 of 2						
Z-score	X coor	Y coor	Z coor	Lobe	Region	BA
3.21	-4.68	37.85	-8.78	Limbic Lobe	Left Anterior Cingulate	32
4.25	-10.76	-42.72	31.18		Left Cingulate Gyrus	31
5.23	-23.77	-12.82	-17.62		Left Parahippocampal Gyrus	28
4.18	-8.83	-33.03	28.2		Left Posterior Cingulate	23
3.6	23.5	8.28	32.9		Right Cingulate Gyrus	32
4.91	-4.93	-27.18	-3.97	Midbrain	Left Red Nucleus	
4.02	-5.14	-58.06	32.02	Parietal Lobe	Left Precuneus	7
4.53	28.93	-61.8	26.56		Right Precuneus	7
4.44	10.29	-8.13	-6.25	Sub-lobar	Hypothalamus	
5	-14.23	16.73	-4.79		Left Caudate Head	
3.35	-35.23	-20.26	10.77		Left Insula	13
3.8	48.17	6.13	3.96		Right Insula	13
4.85	21.65	-4.67	-2.34		Right Lateral Globus Pallidus	
4.35	23.56	2.78	-0.03		Right Putamen	
4.77	-54.24	-51.51	-4.04	Temporal Lobe	Left Middle Temporal Gyrus	37
4.67	-44.89	-69.93	14.72		Left Middle Temporal Gyrus	39
4.59	-59.76	-9.64	-3.16		Left Superior Temporal Gyrus	21
3.72	-46.59	-23.61	5.06		Left Superior Temporal Gyrus	41
3.74	-40.94	-27.8	10.25		Left Transverse Temporal Gyrus	41
3.67	51.76	-45.32	4.25		Right Middle Temporal Gyrus	21
4.09	44.22	-42.9	-2.88		Right Sub-Gyral	7
3.05	53.86	4.53	-1.54		Right Superior Temporal Gyrus	22
4.01	30.86	-52.22	25.39		Right Superior Temporal Gyrus	39