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INTERSUBJECT VARIABILITY IN THE PROCESSING OF FEARFUL FACES IN HEALTHY ADULTS

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ABSTRACT

Threatening stimuli have a privileged status in the brain, meaning they receive priority in the processing stream. This makes sense from an evolutionary perspective where quickly and accurately identifying threat is necessary for survival. However, how much priority the brain gives threatening stimuli has been shown to vary among individuals, even healthy adults, in the laboratory setting. This has been shown repeatedly with threatening face stimuli, but researchers to date have used limited approaches to study intersubject variability. Some studies have correlated personality measures with brain activation, thereby ignoring behavioral variability. Other studies have looked at behavior but have only looked at behavior in pre-selected groups of subjects (namely high and low anxiety). This thesis investigates intersubject variability in fearful face processing by using variability in behavior to guide analyses and find links to personality traits and neural activation.

In **Study I**, we explored behavioral variability on a novel fearful face categorization task where faces were presented at varying expectation levels. Faster reaction times to fearful faces compared to neutral faces correlated with higher levels of cautiousness, as measured by a harm avoidance personality assessment. Faster reaction times to fearful faces also correlated with increased activation to unexpected fearful faces in a prefrontal-striatal network.

In **Study II**, we explored behavioral variability on a fearful face repetition task where fearful and neutral faces were presented repeatedly and subjects were asked to categorize the face as fearful or neutral. A decrease in reaction time for repeated fearful faces was associated with less state and trait anxiety in our healthy subjects. Additionally the lack of behavioral advantage to categorize repeated fearful faces was also associated with more striatal and early visual activation to the first fearful face. The opposite was found for repeated neutral faces, where subjects who were faster to respond to the repeated neutral face had less activation to the repeated face.

In **Study III**, we explored behavioral variability on a fearful face detection paradigm where subjects were asked to detect a briefly presented (33ms) fearful face that was directly followed by a neutral face mask. Fearful face detection sensitivity correlated with trait anxiety and other personality measures related to trait anxiety, but it did not correlate with state anxiety.

In conclusion, our results demonstrate large amounts of behavioral variability on three different fearful face processing tasks in healthy adults. It is not the case that all healthy individuals showed a processing advantage for fearful faces, in fact, some healthy adults actually showed a processing disadvantage for fearful faces. In **Study I**, neither state nor trait anxiety correlated with the behavioral advantage for fearful faces, but harm avoidance did. While state and trait anxiety directly correlated with a lack of behavioral advantage for repeated fearful faces in **Study II**, trait anxiety directly correlated with a behavioral advantage for detecting briefly presented fearful faces in **Study III**. These results underscore that personality interacts with fearful face

processing differently in different contexts. Behavioral variability was also associated with varying neural activation patterns in **Studies I and II**. These activation patterns were distinctly different from the activation patterns evoked by neutral faces demonstrating that behavioral advantages for fearful faces are uniquely neurally encoded. These results argue that there is no "normal" when it comes to fearful face processing and future studies should avoid lumping healthy individuals together on such tasks.

For everyone who was told they would never succeed.

LIST OF STUDIES

This thesis is composed of three empirical studies that are referred to in the text by their roman numerals (Study I – III).

I. The Interaction between Expectation and Sensitivity to Threatening Stimuli in Healthy Adults: An FMRI Study of Intersubject Variability.

II. Anxiety Prevents Fearful Face Repetition Advantage.

III. Fearful Face Detection Sensitivity in Healthy Adults Correlates with Anxiety-Related Traits.

CONTENTS

LIST OF ABBREVIATIONS

5HTTLPR	Serotonin-Transporter-Linked Polymorphic Region
ANOVA	ANalysis Of Variance
BOLD	Blood-oxygen-level-dependent
Cd	Caudate nucleus
COMT	Catechol-O-MethylTransferase
DNA	DeoxyriboNucleic Acid
FACS	Facial Action Coding System
FFA	Fusiform Face Area
FMRI	Functional Magnetic Resonance Imaging
GSR	Galvanic Skin Response
KDEF	Karolinska Directed Emotional Faces
LSAS-SR	Liebowitz Social Anxiety Scale: Self Report
NAcc	Nucleus Accumbens
NEO-FFI	NEO Five Factor Inventory
OFA	Occipital Face Area
pSTS	posterior Superior Temporal Sulcus
PTSD	Post-Traumatic Stress Disorder
Put	Putamen
ROC	Receiver Operating Characteristic
ROI	Region-Of-Interest
RT	Reaction Time
SD	Standard Deviation
SGC	SubGenual Cingulate
STAI	Spielberger State Trait Anxiety Inventory
TPQ-HA	Harm Avoidance subscale of the Tridimensional Personality Questionnaire
VMPFC	Ventromedial PreFrontal Cortex

1 INTRODUCTION

1.1 THREAT PROCESSING

A threat is defined as something with the intention to inflict pain, injury, or damage. Even though modern man generally no longer has to worry about encountering direct threats on a daily basis, our brains and bodies are still well adapted to evaluate threat in the environment (Bolles and Fanselow, 1980, Tooby and Cosmides, 1990). A real-world example of this adaption would be how suddenly focused and startled you become when you see a long, slender, dark object on the path in front of you. This response occurs because you immediately perceive that the stick directly in front of you could potentially be a snake.

Threat processing creates two related emotional states: fear and anxiety. Generally, fear is seen as the reaction to a real threat that is imminent, while anxiety is the reaction to a potential threat that may or may not occur (Lang et al., 2000, Barlow, 2002). Both emotions are characterized by distress and negative feelings. In the context of the scenario laid out in the previous paragraph, fear would be the emotion felt when first approaching the stick and considering it might be a snake. Anxiety would be the emotion felt prior to seeing the stick if the area was known to have many snakes in it, so therefore, the expectancy of seeing a snake would be high, but no specific snake had been seen.

Fear as a motivational state generally leads to one of three actions: freezing, fleeing, or fighting (Eilam, 2005). Anxiety has been called "unresolved fear," because fear itself is a way of coping with a direct threat by escaping or avoiding the threat; anxiety occurs when there is no way to escape or avoid the threat because it has not been encountered yet (Epstein, 1972, Eilam et al., 2011).

1.1.1 Evolutionary Aspect and Privileged Status

Just as in the real world example presented above where a person quickly identifies a potential threat, our brains give threat a privileged status that leads to enhanced processing (Ohman and Mineka, 2001, Davidson et al., 2004). This privileged status makes sense from an evolutionary perspective, where quickly and accurately identifying and responding to threatening stimuli has been essential for survival (Marks and Nesse, 1994). Indeed, this was first noted by Charles Darwin, who recognized the importance of emotions, including threat related emotions, in both man and non-human animals (Darwin et al., 1872).

In the following sections, threat processing is more fully explored, including how such a basic trait could vary so much from person to person in the healthy population.

1.2 THREAT SYSTEM ANATOMY

Stimuli often used in the laboratory setting to signal threat include threatening words, pictures, sounds, and sensations. Through the study of such stimuli, scientists have begun to better understand the neural anatomy of threat processing in humans.

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Our brain's finely tuned ability to optimize threat detection is supported by a neural network focused on this task.

1.2.1 High Road versus Low Road Processing

In the case of threatening sounds, a relatively crude "low–road" detection system is in place where the sound goes directly from the ear to thalamus to the neural core of threat processing: the amygdala, without ever reaching the auditory sensory cortex (LeDoux, 1996). This work then led to the theory that even threatening face images were also processed automatically by the amygdala – never having to reach visual cortex. Indeed, many studies have reported that briefly presented threatening faces are processed without conscious awareness (Morris et al., 1998, Whalen et al., 1998, Dolan and Vuilleumier, 2003, Whalen et al., 2004, Williams et al., 2006, Yang et al., 2007). However, other studies have argued that attention is essential to the processing of fearful faces (Pessoa et al., 2002, Bishop et al., 2007) and that subjects in previous studies were actually better than chance at detecting threatening faces and were, therefore, consciously aware of the face on some level (Pessoa et al., 2005, Pessoa et al., 2006, Japee et al., 2009). Indeed, neuroanatomical evidence supports the view that there are no direct ("low-road") connections from the visual thalamus to the amygdala that bypass the visual cortex (Pessoa and Adolphs, 2010). While this view may still be debated, the fact that the amygdala plays a large role in threat detection and processing is not.

1.2.2 The Amygdala

The original lesion work of Klüver and Bucy (1937) found that monkeys missing bilateral amygdala were devoid of fear. Instead these monkeys were hyper-exploratory and not scared to interact with their environment, including putting novel objects directly into their mouths. While Klüver and Bucy removed the amygdala from the monkeys in their experiments, doing the same in humans is impossible, due to obvious ethical concerns [although work with a patient with a surgically lesioned amygdala as treatment for self-mutilation gave the first hint (Jacobson, 1986)]. The science community had to wait until the seminal work of Ralph Adolphs to understand the function of the amygdala in humans. His famous patient, H.M., had naturally – occurring bilateral amygdala damage. Once brain imaging technology was available to confirm this fact, it made her the perfect experimental subject. Adolphs found that patient H.M. could recognize the identity of fearful faces but she could not recognize the emotion of fear (Adolphs et al., 1994). This finding created an amygdala revolution and tipped researchers off that this small, almond-shaped grey matter structure deep within the temporal lobe might be important for threat processing in humans. Since those early studies, the amygdala has been extensively studied and confirmed as the hub of threat processing not only in the human brain, but also in the brains of other mammals, including rodents (Sarter and Markowitsch, 1985, Chozick, 1986, Davis and Whalen, 2001).

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1.2.3 The Prefrontal Cortex: Keeping the Amygdala in Check

While early work seated threat processing squarely in the amygdala, the story has since evolved to recognize a wide array of neural structures involved in threat processing. The prefrontal cortex has emerged as an important component of threat processing that, through its many connections to the amygdala, appears to exert a regulatory influence over threat processing in the brain (Ochsner and Gross, 2005, Mechias et al., 2010, Etkin et al., 2011). Two major functions of the prefrontal cortex that have been discovered in the laboratory setting include fear extinction and self regulation of fearful feelings.

Prefrontal cortex

Medial prefrontal cortex

Ventromedial prefrontal cortex

Amygdala

Brain Structures Involved in Dealing with Fear and Stress
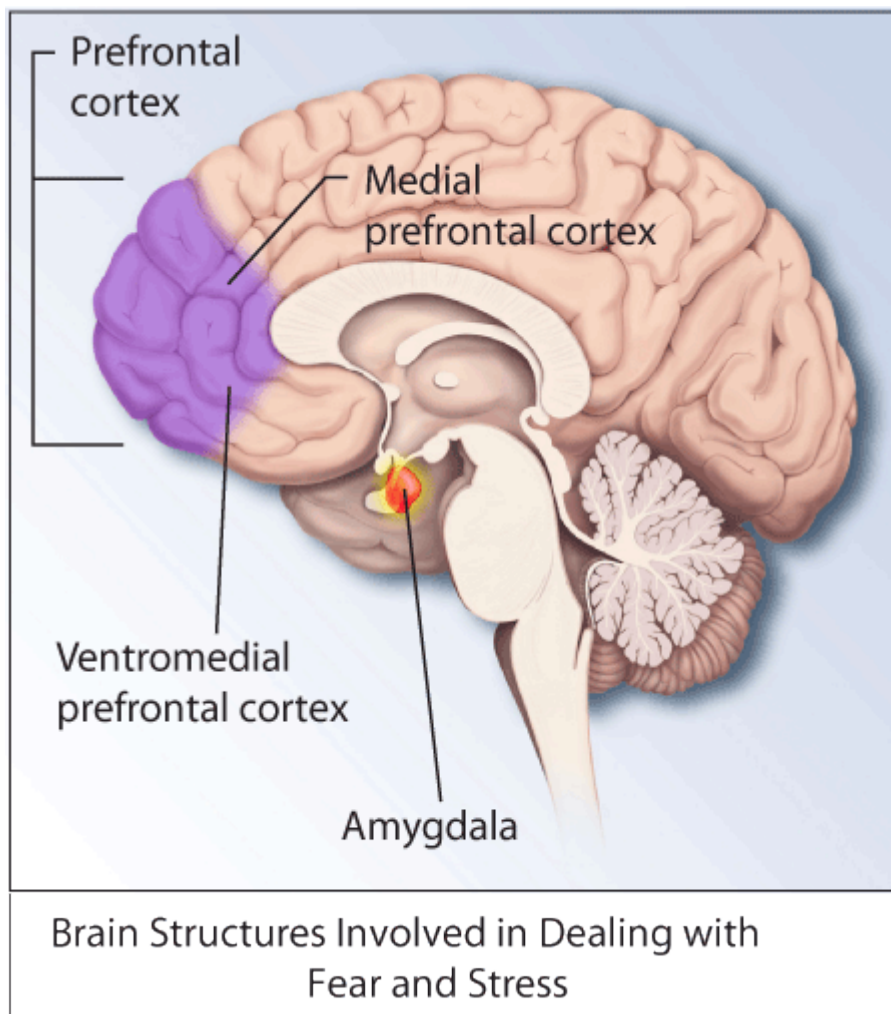
Figure 1. Schematic drawing illustrating the location of the amygdala and the prefrontal cortex in the human brain. [Illustration was taken from the NIMH Post Traumatic Stress Disorder Research Fact Sheet and does not require permission for distribution]

Fear extinction refers to the process of extinguishing a fear response associated with a previously innocuous stimulus. During the process of fear conditioning, this innocuous stimulus (usually a light or a tone in the laboratory setting) is paired with a threatening stimulus (usually a shock). During fear extinction, the innocuous stimulus

is no longer paired with the threatening stimulus, therefore, it no longer signals danger

and it takes humans and rodents some time before the new association is made. This

processing of extinguishing fear is mediated by the ventromedial prefrontal cortex

(Milad and Quirk, 2002, Phelps et al., 2004).

The prefrontal cortex has also been found to control conscious regulation of

fearful thoughts (Ochsner et al., 2002, Hariri et al., 2003). The mechanism behind

emotion regulation is thought to be similar to the mechanism beyond fear extinction,

namely where the prefrontal cortex projects to the amygdala directly to diminish threat-

related responses.

1.3   INTERSUBJECT VARIABILITY

Enhanced processing of threat is a very basic and primitive trait conserved across

many animal species, but the level of enhancement varies greatly across the healthy

human population. Although such intersubject variability may seem surprisingly for a

more basic trait, researchers have long known that quite a bit intersubject variability

exists within the healthy human population.

1.3.1 Genetics and Environment: Epigenetics

Grasping the mechanism behind variability among healthy individuals was

greatly helped along by the discovery of genes and the knowledge that the variability

we recognized between us and others was actually encoded by varying patterns of the

tiny building blocks of life: DNA (deoxyribonucleic acid). While the discovery of DNA

gave neural and behavioral variability a physical basis, one needed only look as far as identical twins to see that genes were only part of the story. And, indeed, the recently created field of epigenetics declares that the environment can directly interact with DNA, turning genes on and off (see review (Tsankova et al., 2007). Variability in genes and variability in environment interact with each other to create neural and behavioral variability among individuals.

While we have a greater understanding of the broad mechanism behind neural and behavioral variability in humans, the specific details mostly remain elusive. However, two genetic variants coding for variability in emotion processing have been discovered and studied extensively.

1.3.1.1 *5HTTLPR polymorphism*

One genetic variant studied comprehensively is a polymorphism in the promoter region of the serotonin transporter genotype (5HTTLPR). In short, healthy individuals with the short allele produce less serotonin than healthy individuals with the long allele, and this effect is heightened with two short alleles, as compared to one short and one long allele (Lesch et al., 1996). Healthy individuals with two short alleles also have been shown to score higher on neuroticism (Schinka et al., 2004, Sen et al., 2004), show an increased risk for depression following stressful life events (Caspi et al., 2003, Eley et al., 2004), can better recognize fearful faces (Defrancesco et al., 2011), and

show heightened amygdala response to fearful faces (Hariri et al., 2002) compared to healthy individuals with two long alleles.

1.3.1.2 *COMT polymorphism*

Another genetic variant related to threat processing that has been studied, albeit less extensively, is Catechol-O-MethylTransferase (COMT): a gene related to how catecholamines are broken down in the brain, which directly affects dopamine availability. The widely studied COMT allelic variation is a substitution between valine (val) and methionine (met). In short, individuals with the met allele have a 1/3 decrease in catecholamine function (Lachman et al., 1996), leading to more tonic dopamine (Bilder et al., 2004). This genotype (met/met) has been associated with increased prefrontal functioning (Egan et al., 2001), but also slower reaction times to categorize angry faces compared to the val/val genotype (Weiss et al., 2007) .

These two genetic variants account for at least some of the variance in threat processing in healthy individuals, but they interact with the environment (e.g. life stressors, as outlined above), with each other (Lonsdorf et al., 2011), and with other genes. While genetics are one piece of the individual variability puzzle, behavioral and neural variability get more at the current state, or the phenotype, of an individual.

1.4 INTRASUBJECT VARIABILITY

While this thesis predominantly focuses on intersubject variability, it is important to note that intrasubject variability does exist. As discussed previously, life stress can

have a large impact on the brain and how it functions. PTSD, or Post-Traumatic Stress Disorder, illustrates this point well.

1.4.1 PTSD as an Extreme Example on Intrasubject Variability

In PTSD, a person having just experienced a traumatic life event will persistently re-experience the event, avoid things that remind them of the event, and experience heightened arousal (American Psychiatric Association. and American Psychiatric Association. Task Force on DSM-IV., 1994). These symptoms persist and become so debilitating for the person that they can no longer function as well in life as they could before the traumatic event. Researchers have extensively studied PTSD and its neuronal substrates. Perhaps unsurprisingly, they have pinpointed altered function and structure in areas related to the threat processing: prefrontal cortex and amygdala (see reviews (Rauch et al., 2006, Liberzon and Sripada, 2007)). These results indicate that even just one event can radically alter intrasubject variability and threat processing in the brain.

1.4.2 Impact of Age on the Brain Throughout a Lifetime

While PTSD is an extreme example of intrasubject variability sparked by one event, all brains undergo structural and functional changes related to ageing. Age related brain changes are a universal source of intrasubject variability. Recent work has shown that the prefrontal cortex is particularly sensitive to age – only reaching full potential in the early 20s (Gogtay et al., 2004). Additionally, as the brain ages, there are

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declines in cognitive performance (Jones and Conrad, 1933, Salthouse, 2009) and many

structures see age-related atrophy (Sowell et al., 2003).

1.5   BEHAVIOR AND FMRI

Many studies in cognitive neuroscience research use functional magnetic resonance

imaging (FMRI) as a way to measure differences in brain activation that occur during

different behavior tasks. The empirical research presented in this thesis correlates

variability in behavior across a task with variability in brain activation across a task for

each subject individually.

1.5.1   Timing in FMRI vs Behavior

FMRI is a technology that has changed how we view the brain, precisely

because it allows us to actually view what is going inside the brain in real time. While

this technology has given us detailed insight into *where* things are happening in the

brain, it unfortunately only gives broad insight as to *when* things happen in the brain.

The temporal limitations of FMRI mean that data cannot capture responses directly

related to neuronal firing, which is known to peak and resolve long before a single

snapshot of the brain in FMRI has been acquired. This is not a huge limitation when

one wants to know what brain areas are generally involved in a task – as FMRI is

measuring how these areas gather more oxygenated blood and therefore we know the

general areas where large numbers of neurons are firing because those neurons are

using oxygen. But if one wants to better understand what is happening directly in

relation to behavior, FMRI is limiting. Fast behavioral responses, like those responses found in the research presented in this thesis, generally happen in less than one second. This means the subject has not only visually recognized the object, but they have also started and completed a motor response based on how the visual object was processed – all within one second. One complete snapshot (or volume) of the whole brain has not even been acquired by FMRI by the time the behavioral response is made. For the empirical work presented in this thesis, a complete snapshot of the brain is collected every two seconds.

The neural firing related to the processing of the visual object and the motor response creates an increase of oxygen in the blood surrounding these neurons. Oxygen is slow to return to homeostatic levels in the blood in that area, which is how researchers can capture areas where large numbers of neurons have fired recently. However, FMRI has lowered sensitivity when it comes to smaller populations of neurons firing and also changes occurring rapidly. FMRI can accurately locate an area where a large population of neurons has recently fired, but it cannot tell you about the changes in firing occurring within quick spurts of time, namely less than 1-2 seconds, or in smaller areas, namely <1 mm^3 (Heeger and Ress, 2002, Logothetis, 2008) .

1.5.2 Difference between correlation and causation

Another additional limitation of studying how FMRI is related to behavior is that we can only make correlational and not causal statements using functional imaging

data. We are unable to state that the brain activation patterns we see during a particular set of behaviors cause that particular set of behaviors, only that those areas are activated during the behavior at that specific time. Critics have questioned how much can be inferred from FMRI research, as the results are limited to correlations found in a specific laboratory setting and do not show that specific areas cause behavior (Hajnal et al., 1995, Uddin et al., 2006). However, other FMRI researchers argue that functional imaging results are an important tool to better understanding how the brain functions but only when such experiments are designed and interpreted correctly (Sarter et al., 1996, Weber and Thompson-Schill, 2010) and/or combined with knowledge from other sources and other techniques (Silvanto and Pascual-Leone, 2012).

We agree that FMRI is only one piece of the puzzle. The work presented in this thesis focuses on behavioral variability on specific tasks and looks for correlations with this variability and FMRI activation as well as personality measures. We believe taking this multimodal approach paints a more comprehensive picture of intersubject variability than FMRI presented alone.

1.6   THREATENING FACES

Threatening faces are one of the most frequently used visual threatening stimuli in the laboratory setting. This is for a good reason, as threatening faces are important social cues for humans; they represent either direct or indirect threats. Fearful faces represent an indirect threat to the viewer, because the person displaying the fearful

expression is afraid of something in the surrounding environment. Angry faces with a

direct gaze indicate a direct threat to the viewer, because the person displaying the

angry expression is upset with the viewer. Both emotions are easily distinguished from

each other (see Figure 2 for an example), and these differences have been eloquently

quantified by Ekman and Friesen (1978) using the Facial Action Coding System

(FACS). Fearful faces are generally associated with a raising of the eyebrows and upper

lids and an opening of the mouth. The configuration of a fearful face not only allows

the person displaying this emotion to communicate their fearfulness to others, but it

also allows that person to gather more sensory information about the potential threat

through opened eyes, opened mouth, and opened nostrils (Susskind et al., 2008). Angry

faces are generally associated with a lowering of the brows, raising of the upper lids,

narrowing of eyes, and pressing together of the lips. While research on the

physiological function of an angry face is lacking (Shariff and Tracy, 2011), the

communicative function of an angry face is to convey dominance to others (Marsh et

al., 2005a, Marsh et al., 2005b, Wilkowski and Meier, 2010).

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FEAR **ANGER**

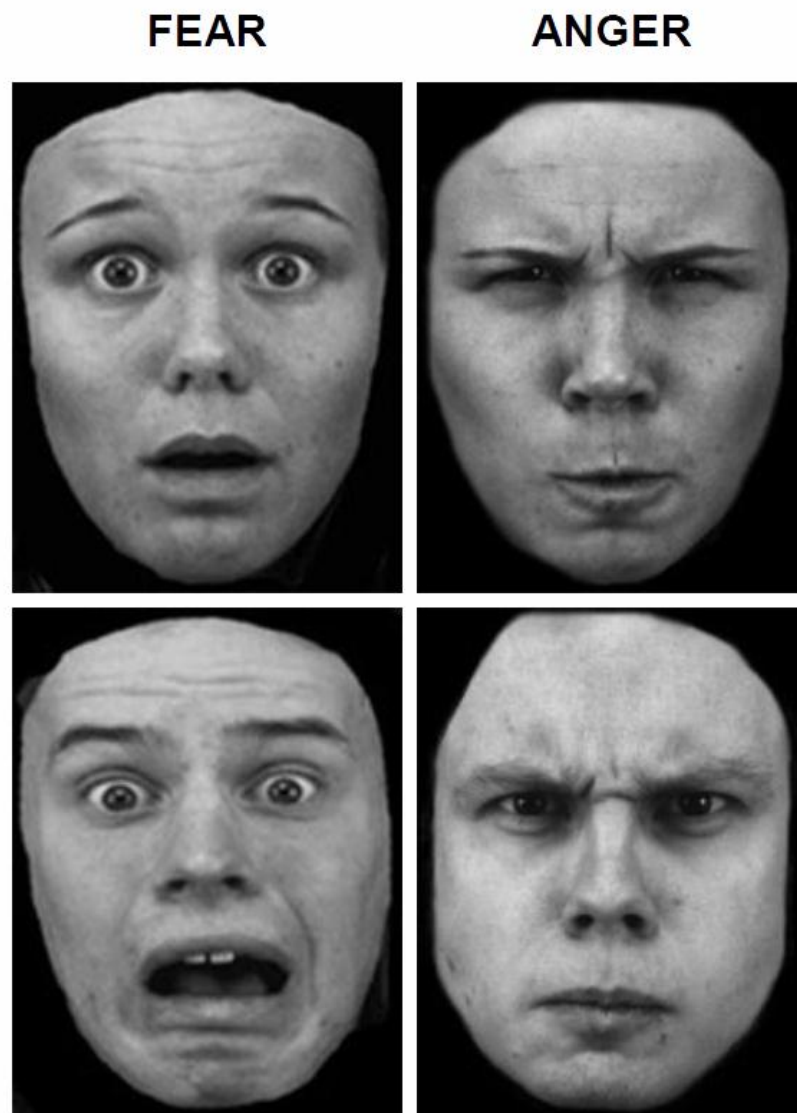Figure 2. Examples of faces displaying fear and anger. The top panel is the same female actor displaying the two facial emotions. The bottom panel is the same male actor displaying both emotions as well. Faces are from the Karolinska Directed Emotional Faces (KDEF) set (Lundqvist, 1998) and have been masked to remove hair and other extraneous visual information.

1.7 FACE PROCESSING IN THE HUMAN BRAIN

The human brain has a localized system focused on processing faces that is centered around the fusiform face area (FFA) (Kanwisher et al., 1997, Haxby et al., 2000). The FFA is a strip of occipital cortex that has been shown to reliability and consistently activate in response to face images. Additionally, the inferior occipital gyrus (referred to as the occipital face area, OFA) and posterior superior temporal sulcus (pSTS) have also been shown to reliability and consistently activate in response to faces (Rossion et al., 2003, Ishai et al., 2005). These areas along with the FFA create the core system of face processing (Haxby et al., 2000, Gobbini and Haxby, 2007). It has been shown that threatening faces enhance processing within this system (Morris et al., 1996, Vuilleumier et al., 2001, Pessoa et al., 2002).

1.8 INTERSUBJECT VARIABILITY IN THE PROCESSING OF THREATENING FACES

The privileged status of threatening face stimuli can either distract from or enhance performance on a task. The level of distraction or enhancement differs among individuals, even healthy subjects.

1.8.1 Intersubject Variability in How Threatening Faces Distract Attention and Decrease Performance

First, threatening faces can distract the brain from task-relevant information. Ladouceur et al., (2009) demonstrated that healthy individuals scoring high on a trait

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anxiety measure were less able to filter out distracting threat information (fearful faces) as evidenced by increased reaction times on a task containing fearful face distracters compared to a task containing neutral face distracters. Peers & Lawrence (2009) found that subjects scoring low on attentional control were more distracted by fearful faces than subjects scoring high on attentional control. However, this distraction effect was independent of anxiety levels. These studies underscore that some healthy individuals have difficulty disengaging their attention from threatening faces, and this effect can be modulated through an interaction of anxious personality traits, perceptual load, and attentional control that is not well understood.

1.8.2 Intersubject Variability in How Threatening Faces Attract Attention and Increase Performance

The second way that threatening face stimuli selectively affect processing is through enhancing performance on tasks. One example is the classic dot probe paradigm where subjects receive a threatening face immediately preceding a target and this target is either placed in the same location as the face or in the opposite visual field. If the threatening face is in the same visual field as the target, high anxiety patients have been found to respond faster to the target (Bradley et al., 1999). Additionally, healthy individuals with higher levels of anxiety showed this same bias towards targets presented following a threatening face (Mogg & Bradley, 1999). However, in another study of healthy individuals, a bias away from angry faces was found as the number of

trials increased, and this bias was associated with increased activation in the occipitotemporal cortex (Monk et al., 2004). These studies further demonstrate the variability healthy adults display during tasks involving threatening faces. However, threat was not task-relevant in these paradigms. Task-relevant threat is more akin to the type of threat we approach in our daily lives, and therefore investigating this type of threat may be a better model to simulate how subjects interact with their everyday environment.

In the realm of task-relevant threat, enhanced detection of threatening faces in healthy individuals has been documented during tasks where subjects searched a visual array for a threatening face (Hansen and Hansen, 1988) (Fox et al., 2000). However, others studies have found no such enhancement for threatening faces in healthy individuals (Purcell et al., 1996, Juth et al., 2005) , adding more evidence to support the claim that there is variation in how healthy adults process threatening faces. Emerging evidence from recent non-spatial threatening face detection tasks further support this claim. Healthy subjects with greater anxiety were also better able to correctly identify a fearful face when less emotional intensity is shown in that face (Richards et al., 2002), and they were more accurate at categorizing fearful faces (Winton et al., 1995, Surcinelli et al., 2006).

1.8.3 How To Quantify Intersubject Variability?

These studies demonstrate that not only do threatening faces have a processing

advantage in the brain (resulting in either distraction or enhanced performance), but that

this advantage is variable among healthy individuals. However, these studies have

either preclassified subjects in advance based on anxiety level or they have directly

correlated personality measures with FMRI activation. These two approaches largely

ignore the continuum of intersubject behavioral variability.

One group of researchers has taken a different approach and has used

behavioral variability to guide analyses. Pessoa and colleagues used signal detection

theory to classify their subjects into one of two groups: subjects who were better than

chance at detecting briefly presented fearful faces and those who were no better than

chance (Pessoa et al., 2005, Pessoa et al., 2006, Japee et al., 2009). They found that

subjects who were better than chance, compared to those who were not, showed

increased activity in the amygdala and in ventral visual cortex. These studies

demonstrate that there is a difference in neural activation between healthy adults who

can detect the presence of fearful faces and healthy adults who cannot, but it is still

unclear what neural mechanisms underlie behavioral variability to process fearful faces

in healthy adults.

These studies point to the possibility that healthy adults can be categorized and

studied based on their differences in behavior to threatening faces. If one could apply

this idea to the study of threatening faces, could we use the continuum of behavioral

responses within a healthy adult population to guide analyses and paint a more

comprehensive picture? If threatening faces were presented in different contexts, could

we learn even more about the threat processing system, how it varies among healthy

individuals, and how it relates to personality?

2 AIMS

AIM 1: TO QUANTIFY BEHAVIORAL VARIABILITY DURING FEARFUL FACE PROCESSING TASKS

SPECIFIC AIMS:

- Quantify the reaction time (RT) bias to fearful faces versus neutral faces across varying expectation conditions for each subject individually (Study I)

- Quantify the repetition speed advantage for repeated presentations of fearful faces and neutral faces separately for each subject individually (Study II)

- Quantify the fearful face detection sensitivity for each subject individually (Study III)

AIM 2: TO INVESTIGATE THE INTERACTION OF BEHAVIORAL VARIABILITY AND PERSONALITY

SPECIFIC AIMS:

- Investigate how personality measures related to threat processing interact with:

  o The RT bias to fearful faces in varying expectation contexts (Study I)

  o The repetition advantage for fearful faces (Study II)

  o Fearful face detection sensitivity (Study III)

AIM 3: TO INVESTIGATE THE NEURAL UNDERPINNINGS OF BEHAVIORAL VARIABILITY FOR FEARFUL FACES

SPECIFIC AIMS:

- Investigate the neural sources of:

  o The RT bias to fearful faces in varying expectation contexts (Study I)

  o The repetition advantage for fearful faces (Study II)

MAIN QUESTIONS

Given the lack of previous research investigating the natural spectrum of variability in behavior during the processing threatening faces in healthy adults, we aimed to quantify this variability and explore its relationship to personality and neural activation (see Figure 3 for schematic). To do this we quantified behavioral variability on three different fearful face processing tasks where threat was task relevant: 1) expectation, 2) repetition, and 3) detection. We then used this behavioral variability to guide our analyses of personality and neural activation.
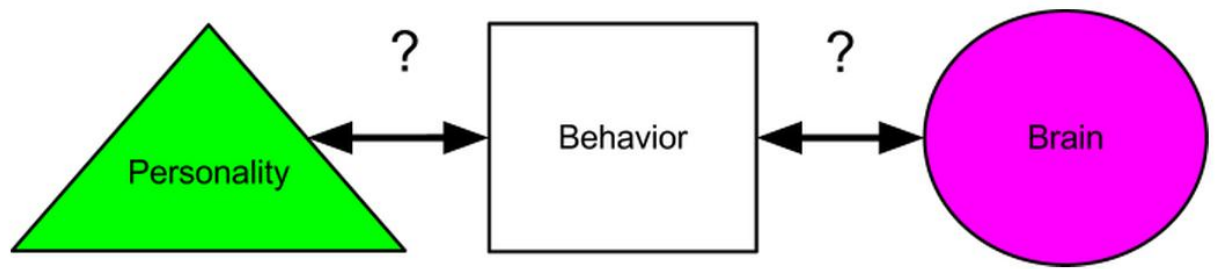
Figure 3. Schematic outlining the aim of this thesis. To better understand individual variability

in the processing of threatening faces, we used variability in behavior to drive our analyses. We

then took this variability and investigated its connection to personality and brain activation

during the behavioral task (as measured by FMRI activation). This unique approach allowed us

to fully study variability among healthy adults.

3 THESIS ANATOMY

This thesis contains 3 empirical studies that are presented in detail.

4 METHODS

4.1 SUBJECTS

For Studies I and II, twenty-four right-handed healthy volunteers (15 females;

mean age 28 years ±6.6 SD, standard deviation) participated. For Study III, twenty-one

right-handed healthy volunteers (16 females; mean age 25 years ±7.6 SD) participated.

All subjects gave written informed consent in accordance with protocols approved by

the National Institute of Mental Health Institutional Review Board. Additionally, all

subjects had no past neurological or psychiatric history as assessed by a physician.

4.2 PERSONALITY ASSESSMENTS

All subjects completed the Spielberger State Trait Anxiety Inventory (STAI) at

the beginning of the experiments (Spielberger and Gorsuch, 1983). For Studies I and II,

a subset of subjects completed two additional questionnaires measuring personality

types related to anxiety: 16/24 completed the NEO Five Factor Inventory (NEO-FFI),

and 13/24 completed the Harm Avoidance subscale of the Tridimensional Personality

Questionnaire (TPQ-HA) (Cloninger et al., 1991, Costa and McCrae, 1992). For Study

III, all subjects (N=21) completed the assessments outlined above as well as the

Liebowitz Social Anxiety Scale: Self Report (LSAS-SR) (Liebowitz, 1987).

4.3 STUDY DESIGN

Studies I and II used different portions of the same overall event-related

FMRI experiment. Subjects were instructed to categorize each face as fearful or neutral

as accurately and quickly as possible by pressing one of two buttons. To manipulate

expectation of fear, we presented fearful and neutral faces in runs containing different

ratios of the two face types. There were three different expectation run types: 1) runs

containing 80% fearful faces and 20% neutral faces (80F:20N); 2) runs containing 20%

fearful faces and 80% neutral faces (20F:80N); and 3) runs containing 50% fearful

faces and 50% neutral faces (50F:50N). Each run contained 50 trials (for schematic of

a single trial see Figure 4). At the beginning of each trial, the white fixation cross

turned red (cue) for 250 ms. Four seconds (s) later a face was presented centrally for

250 ms. The cue itself indicated only the upcoming presentation of a face, and not its

emotional content. Subjects were verbally and visually notified of the expectation run

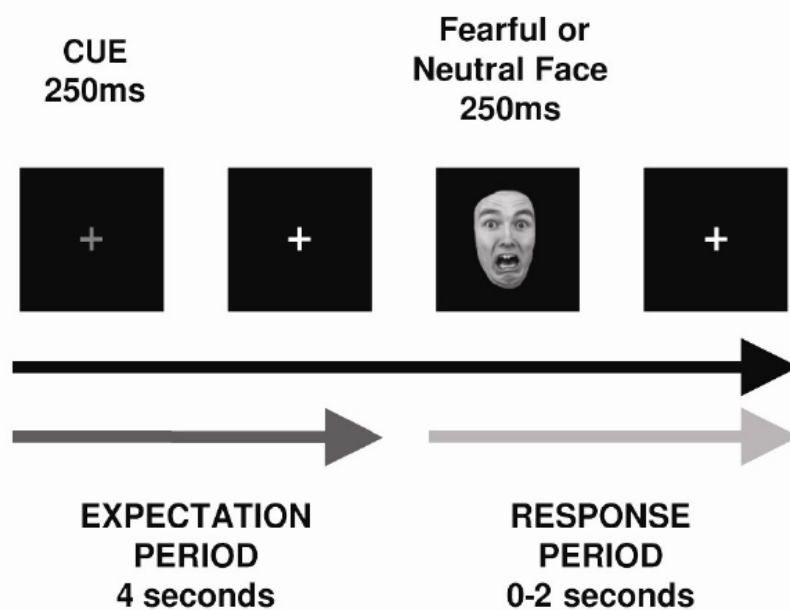type (i.e. 80F:20N, 50F:50N, or 20F:80N) at the beginning of each run.

Figure 4. Experimental Design for Studies I and II.

Study I only used the first presentation of a given face type presented after the opposing

face type. This method allowed us to separate out effects due to expectation from

effects due to repetition. Study I focused solely on the effect of expectation and Study

II focused solely on the effect of repetition. During the 80F:20N and the 20F:80F runs,

the 80% face type was presented repeatedly in a row. For Study I, we only investigated

the 1st presentation of a face type following the opposing face type; therefore repeated

80% and 50% face types were not included in the analysis. For Study II, we only

investigated the 1st, 2nd, and 3rd repetitions of the 80% face type. See Figure 5 for a

schematic.

Figure 5. Experimental Design for Study II.

For Study III, we used the same behavioral paradigm as a previous study

(Pessoa et al., 2006). Each trial began with a white fixation cross shown for 300 ms,

followed by a 50 ms blank screen, followed by a pair of faces presented consecutively

(see Figure 6 below). The first of the two faces was either a fearful, happy, or neutral

target face presented for 33 ms. The second of the two faces was always a neutral face

presented for 117 ms and served as a mask for the first face. Subjects were instructed to

press a button denoted as "fear" when they perceived the first face to be fearful and to

press another button denoted as "no fear" when they did not perceive the first face to be

fearful. Subjects were also instructed that the first face would appear rapidly and the

pair of faces could appear as one single face. They were asked to make the fear/no fear

decision as fast and as accurately as possible, and then wait for a confidence rating

screen to appear. A confidence rating screen appeared after every pair of faces and was

presented for 1.5 s. Subjects were asked to rate their decision of fear/no fear by pressing

1 of 3 buttons: 1 = low confidence, 2 = middle confidence, and 3 = high confidence.

Subjects had 1.5 s to make the "fear/no fear" decision and another 1.5 s to rate their

confidence in that decision. The total trial duration was 3.5 s. Each subject was shown

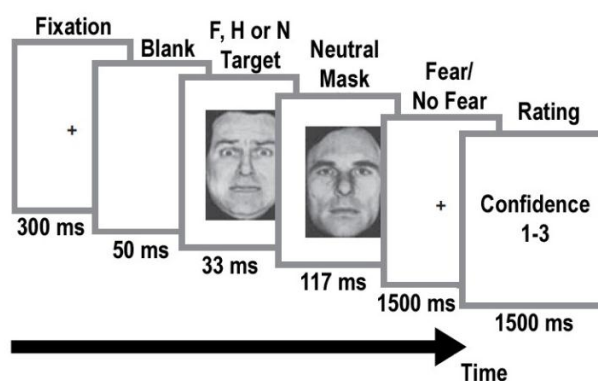54 images of each target face type (fearful, happy, and neutral).

Figure 6. Experimental Design for Study III.

4.4 STIMULI

The stimuli consisted of faces chosen from the Karolinska Directed Emotional Faces (KDEF) set (Lundqvist, 1998), as well as from a set of faces developed and validated at the National Institute of Mental Health (NIMH) (Ishai et al., 2004). A portion of faces from Study III were also obtained from the Ekman set (Ekman, 1976).

4.5 BEHAVIORAL ANALYSIS

4.5.1 Behavioral Analysis Study I

For Studies I and II, accuracy ratings were high (>85% correct for each stimulus type for each subject), so the focus of our behavioral analysis was reaction time (RT). All RT statistical results were computed using a repeated measures 2 x 3 ANOVA (ANalysis Of VAriance) (Valence x Expectation Run Type) and post-hoc analyses were conducted using a Fisher Least Significant Differences Test.

To quantify RT differences across our subject population, we created a Valence Bias measure for each subject which was calculated from the RTs to fearful faces in all three expectation run conditions subtracted from the RTs to neutral faces in all three expectation run conditions. The cumulative Valence Bias measure used was calculated as:

$$\text{Valence Bias} =$$

$$\text{RT [(80F:20N) Neutral} - \text{Fearful]}$$

$$+ \text{RT [(50F:50N) Neutral} - \text{Fearful]}$$

$$+ \text{RT [(20F:80N) Neutral} - \text{Fearful]}$$

In addition to the Valence Bias measure, which showed a continuum of scores across subjects (continuum shown in Figure 7A), we also categorized the subjects into one of two groups. Subjects with a Valence Bias greater than zero were categorized as "Fear Fast Responders", being faster overall to categorize fearful compared to neutral faces. Subjects with a Valence Bias less than zero were categorized as "Fear Slow Responders", being slower overall to categorize fearful compared to neutral faces.

4.5.2 Behavioral Analysis Study II

The group analysis RT statistical results were computed using a 2x3 repeated measures ANOVA (Valence x Repetition) and post-hoc analyses were conducted using a Fisher Least Significant Differences Test.

Just as in Study I we were interested in quantifying behavioral differences across our healthy cohort. To do this we created a Repetition Advantage measure for both fearful and neutral faces separately. The behavioral advantage reported in the literature for repeated presentations of a stimulus have utilized the first presentation of a visual stimulus as a benchmark to compare to the subsequent repeated presentations. Following this logic, our behavioral measure of the repetition advantage for the second and third presentations of the expected face type were compared to the first

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presentation of the face type. This allowed us to index the magnitude of the speed

advantage for repeated presentations within each subject for second and third

repetitions separately. Therefore, for each subject, there were four separate behavioral

indices calculated: 1) Second Fearful Face Repetition Advantage, 2) Second Neutral

Face Repetition Advantage, 3) Third Fearful Repetition Advantage, and 4) Third

Neutral Face Repetition Advantage. Each index was simply calculated by subtracting

the RT to the second or third repetition from the first presentation for fearful and

neutral faces

Behavioral Index	Calculation
Second Fearful Face Repetition Advantage	RT (80F:20N 1st Fearful Face – 80F:20N 2nd Fearful Face)
Second Neutral Face Repetition Advantage	RT (20F:80N 1st Neutral Face – 20F:80N 2nd Neutral Face)
Third Fearful Repetition Advantage	RT (80F:20N 1st Fearful Face – 80F:20N 3rd Fearful Face)
Third Neutral Face Repetition Advantage	RT (20F:80N 1st Neutral Face – 20F:80N 3rd Neutral Face)

Table 1. How the four different behavioral indices were calculated for Study II.

4.5.3 Behavioral Analysis Study III

For Study III data were analyzed using receiver operating characteristic (ROC)

curves (Green and Swets, 1966, Macmillan and Creelman, 1991). We created ROC

curves for each subject individually in a manner previously described (Pessoa et al.,

2005, Pessoa et al., 2006, Japee et al., 2009). These curves were calculated using the

probability of reporting 'fear' given that the target was not a fearful face [P('Fear'|not

Fear), i.e. false alarm]and the probability of reporting 'fear' given that the target was a

fearful face [P('Fear'|Fear), i.e. hit] for every confidence rating (three levels for

reporting 'fear' and three for reporting 'no fear'). We used these six different

proportions of false alarms and hit rates to create the ROC curve. We calculated each

subject's fear detection sensitivity (A') by measuring the area under the ROC curve.

4.6   FMRI ACQUISITION

For Studies I and II, whole brain MR images were collected on a 3T GE Signa

scanner (GE Medical Systems) using an 8-channel GE head coil. Standard parameters

for echoplanar imaging data were used, including: FOV 200 mm, 64 x 64 matrix, 25

axial slices of 5-mm thickness, 3.125 mm in-plane resolution, 2.0 s TR, 30 ms TE, 90º

flip angle. MP-RAGE scans, collected in the same session, were acquired for

anatomical comparison using the following parameters: FOV 22.0 mm, 256 x 256

matrix, minimum full TE, 1.2-mm slice thickness.

4.7   FMRI ANALYSIS

All imaging data were preprocessed, analyzed, and displayed with the AFNI

(Cox, 1996) software package. Individual subject data were preprocessed as follows:

slice timing correction, volume registration, smoothing via a 6-mm full width half max

filter, normalization, and applying a six-parameter rigid motion correction.

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Next, a variable shape deconvolution model was computed for each subject individually. In order to model the fixed length expectation (cue) period that preceded every face stimulus as well as the response period that followed every face, individual subject imaging data were deconvolved using a 16-s tent function. This tent function was time-locked to the TR (i.e. a stick function with 8 sticks), started 4 s before the face in order to model the onset of the cue, and concluded 12 s after the presentation of the face. This analysis method allowed us to estimate the BOLD (Blood-Oxygen-Level-Dependent) signal at each timepoint in the trial individually. The six different stimulus types (i.e. 2 valences x 3 expectation runs) were modeled separately. Additionally, we modeled the 2nd, 3rd, and 4th occurrences of each face type (i.e. repetitions in a train of stimuli). In preparation for the group analysis, each subject's individual beta weights were resampled to a 3 x 3 x 3 mm voxel size and transformed to Talairach space (Talairach and Tournoux, 1988) using AFNI.

For the group analysis, beta weights for each subject were entered into a correlation analysis in order to determine which brain areas (across subjects) had activations that correlated with the measures of behavioral variability calculated for each subject.

For Study I, the Valence Bias (i.e. the measure of RT bias towards either face type, fearful or neutral) was correlated with each of the six stimulus types (two face types and three expectation run conditions) at every timepoint in the trial separately. Data were cluster-corrected for multiple comparisons across all voxels and for the

multiple tests performed (8 timepoints x 3 expectation runs x 2 valences = 48 tests).

This was achieved using a Monte Carlo simulation (via AFNI's AlphaSim program)

with an individual voxel threshold p-value of 0.001 and corrected to a p-value of 0.01,

resulting in a cluster threshold of 33 voxels (cluster volume of 891 mm^3). In order to

better understand the interaction between Valence Bias and time, regions-of-interest

(ROIs) were created using the peaks from clusters in the correlation analysis. These

ROIs were created using a 5-mm radius sphere and timecourses for the two Valence

Bias groups (i.e. Fear Fast and Fear Slow Responders) extracted from the 20F:80N

expectation runs, which were the only expectation runs to yield significant correlations

of Valence Bias and brain activation. We performed post-hoc pair-wise t-tests for each

timepoint in the waveforms extracted from the ROIs. These t-tests were Bonferroni

corrected for the multiple tests performed (i.e. 8 timepoints x 2 face types = 16 tests).

For Study II, the four RT advantage indices were correlated with their

associated contrasts, e.g. the 2nd fear face RT advantage [i.e., RT(1st Fear – 2nd

Fear)]was correlated directly with the contrast between activation evoked by the 1st

Expected Fearful Face and activation evoked by the 2nd Fearful Face [i.e., % Signal

Change (1st Fear – 2nd Fear)]. This analysis was done at each timepoint individually as

it was for Study I. Data were cluster-corrected for multiple comparisons across all

voxels and for the multiple tests performed (8 timepoints x 2 valences x 3 repetitions =

48 tests) as described above for Study I.

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5 RESULTS

5.1 VARIABILITY IN BEHAVIOR

5.1.1 Behavioral Variability for Fearful Faces Presented in Varying Expectation Contexts

The average Valence Bias for our 24 subjects was 22.22 ± 204.11 (SD) and ranged from -369.34 to +366.04; this range indicated that overall some subjects were faster to respond to fearful faces but others were slower (all subject population demographics found in Table 2). To further explore the relationship between Valence Bias and FMRI signal changes within the 20F:80N expectation runs, we created two different groups: Subjects with a Valence Bias greater than zero were categorized as "Fear Fast Responders", being faster overall to categorize fearful compared to neutral faces (N=15), and subjects with a Valence Bias less than zero were categorized as "Fear Slow Responders", being slower overall to categorize fearful compared to neutral faces (N=9) (see Figure 7A for illustration of the Valence Bias variability) (subject population demographics by group found in Table 3) .

Figure 7B shows the RT data for the three different expectation run types for the two groups. While the Expectation Run x Valence x Group interaction was not significant $[F(2,44) = 0.833, p = 0.441]$, the interaction of Valence and Group was $[F(1,22) = 51.10, p = 3.62\text{x}10^{-7}]$. Post-hoc analyses revealed that the RTs for the Fear Fast and Fear Slow Responders were significantly different for fearful faces ($p = 0.04$);

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Fear Fast Responders were faster to respond to fearful faces and Fear Slow Responders

were slower to respond to fearful faces. However, RTs for neutral faces were not

significantly different between the two groups (p = 0.72). Therefore, while the two

groups were established based on the overall difference in RT between fearful and

neutral faces [Fear Slow Responders were faster to respond to neutral than fearful faces

overall (p = 4.5x10^{-5}) and Fear Fast Responders were faster to respond to fearful than

neutral faces overall (p = 3.9x10^{-5})], only the response to fearful faces was significantly

different between the two groups.
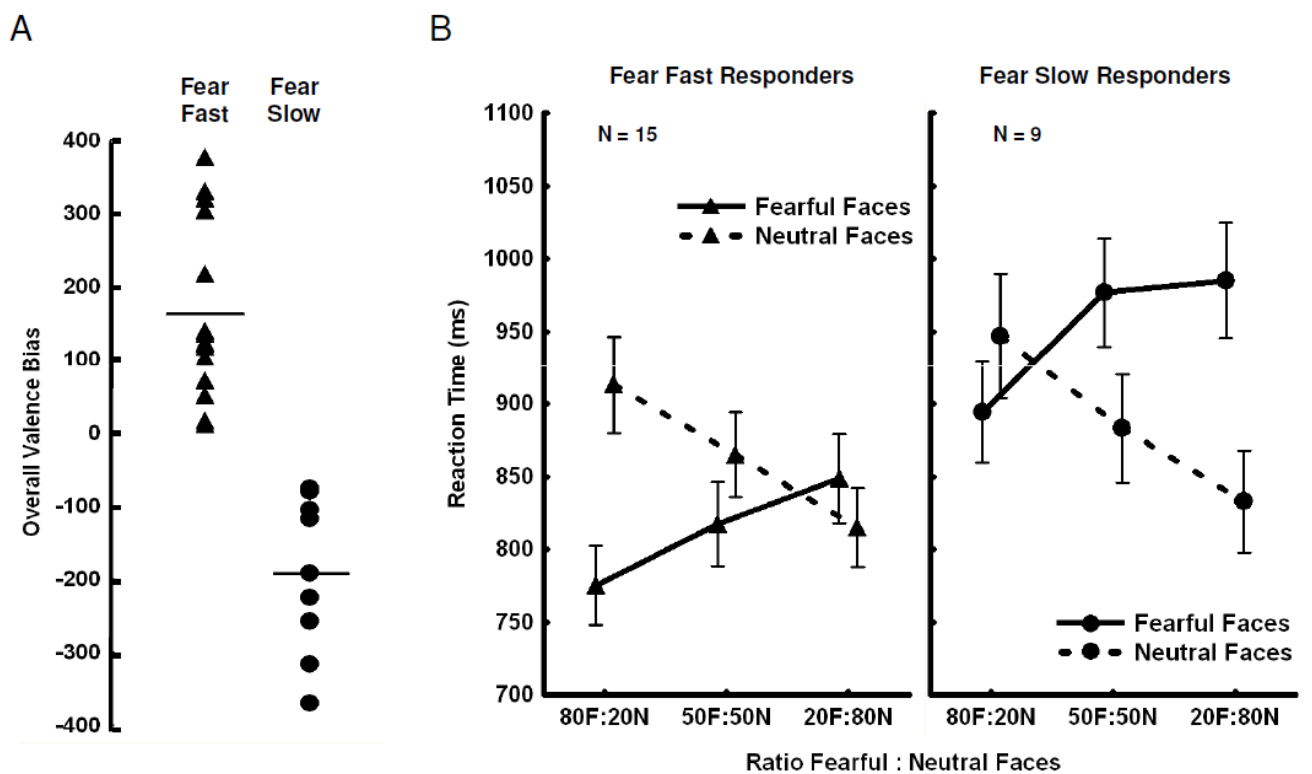

Figure 7. Valence Bias Group Classification and Behavior from Study I.

Table 2. Demographics of Subject Population from Study I

<center>All Subjects N = 24</center>

Mean Reaction Times in milliseconds	
80F:20N Fear	820.10 ± 118.75
80F:20N Neutral	925.87 ± 126.92
50F:50N Fear	877.25 ± 135.01
50F:50N Neutral	871.84 ± 110.09
20F:80N Fear	899.95 ± 134.05
20F:80N Neutral	821.81 ± 103.10
Age	27.8 ± 6.6
Female:Male Ratio	15:9
Valence Bias Scores	22.22 ± 204.11
Mean Personality Measure Scores (N = number of subjects with scores)	
STAI (N = 24)	
Trait Anxiety	32.2 ± 9.3
State Anxiety	28.6 ± 8.5
NEO FFI (N=16)	
Neuroticism	13.6 ± 8.0
Extraversion	32.4 ± 7.0
Openness to Experience	33.7 ± 5.0
Agreeableness	32.4 ± 5.7
Conscientiousness	36.5 ± 5.6
TPQ-HA (N=13)	
Harm Avoidance	9.9 ± 5.9
HA 1: Anticipatory worry & pessimism	2.8 ± 2.2
HA 2: Fear of Uncertainty	3.5 ± 1.5
HA 3: Shyness with strangers	1.8 ± 1.8
HA 4: Fatigability & asthenia	1.8 ± 2.0
Mean Percentage Correct	
80F:20N Fear	$95 \pm 5\%$
80F:20N Neutral	$88 \pm 9\%$
50F:50N Fear	$91 \pm 8\%$
50F:50N Neutral	$95 \pm 5\%$
20F:80N Fear	$87 \pm 10\%$
20F:80N Neutral	$96 \pm 5\%$

Table 3. Demographics of Subject Population by Valence Bias Group from Study I

Demographics by Valence Bias Group

	Fear Fast Responders (N = 15)	Fear Slow Responders (N = 9)
Mean Reaction Times in milliseconds		
80F:20N Fear	775.45 ± 97.46	894.53 ± 118.12**
80F:20N Neutral	913.23 ± 145.33	946.94 ± 92.49
50F:50N Fear	817.54 ± 106.67	976.76 ± 121.11**
50F:50N Neutral	865.07 ± 119.07	883.13 ± 99.01
20F:80N Fear	848.87 ± 108.10	985.09 ± 134.78**
20F:80N Neutral	815.18 ± 97.09	832.86 ± 117.66
Age	27.9 ± 8.1	27.4 ± 3.1
Female:Male Ratio	10:5	5:5
Valence Bias Scores	151.63 ± 118.66	-193.46 ± 106.80
Mean Personality Measure Scores (N = number of subjects with scores)		
STAI (N = 24)		
Trait Anxiety	32.4 ± 9.8 (N = 15)	31.8 ± 8.8 (N = 9)
State Anxiety	29.5 ± 9.3	27.1 ± 7.3
NEO FFI (N = 16)		
Neuroticism	15.3 ± 9.1 (N = 10)	10.8 ± 5.2 (N = 6)
Extraversion	31.3 ± 6.2	34.3 ± 8.4
Openness to Experience	34.7 ± 4.9	32.0 ± 5.2
Agreeableness	31.5 ± 5.9	33.8 ± 5.6
Conscientiousness	36.4 ± 6.2	36.7 ± 5.0
TPQ-HA (N = 13)		
Harm Avoidance	11.9 ± 5.8 (N = 9)	5.5 ± 3.7 (N = 4)
HA 1: Anticipatory worry & pessimism	3.2 ± 2.3	2.0 ± 1.8
HA 2: Fear of Uncertainty	4.1 ± 09	2.0 ± 1.6**
HA 3: Shyness with strangers	1.9 ± 2.1	1.5 ± 1.0
HA 4: Fatigability & asthenia	2.7 ± 1.9	0 ± 0.0*
Mean Percentage Correct		
80F:20N Fear	96 ± 5%	93 ± 5%
80F:20N Neutral	87 ± 11%	89 ± 8%
50F:50N Fear	91 ± 9%	90 ± 7%
50F:50N Neutral	95 ± 5%	96 ± 4%
20F:80N Fear	86 ± 11%	89 ± 9%
20F:80N Neutral	97 ± 5%	94 ± 4%

* p < 0.05 ** p < 0.01, t-test uncorrected

5.1.2 Behavioral Variability for Repeated Fearful Faces

For Study II, we first looked to see if there was an overall repetition advantage for fearful faces versus neutral faces. When all 21 subjects were grouped together, there was an interaction between valence and repetition [$F(2,46) = 6.37$, $p=0.04$; Figure 8]. Post-hoc analyses revealed a selective repetition advantage for fearful faces compared to neutral faces, but only for the 2nd repetition (1st fear compared to 2nd fear : $p=0.02$; 2nd fear compared to 2nd neutral : p 0.0001).
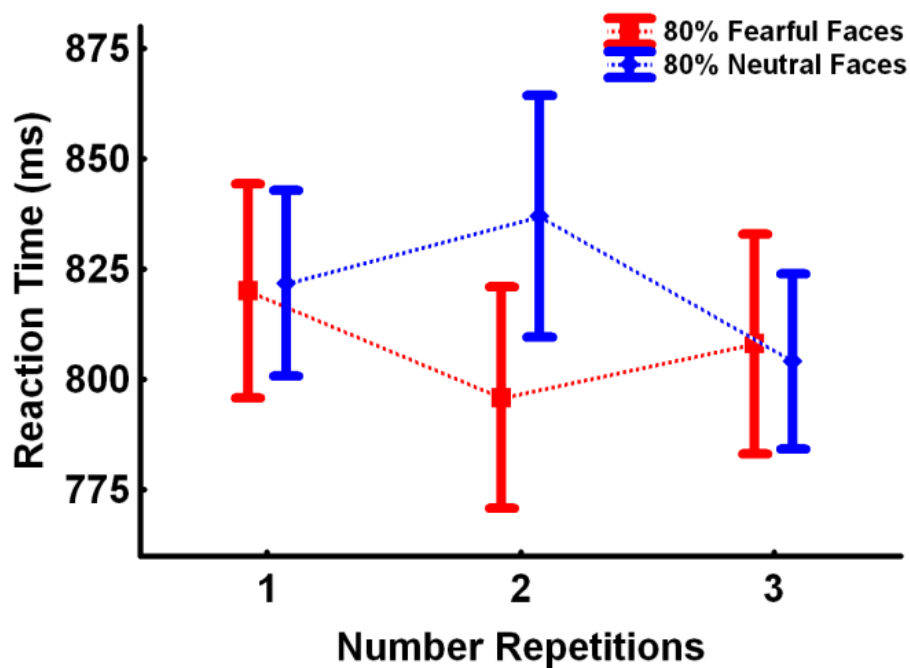

Figure 8. Overall reaction time for repeated fearful and neutral faces for all subjects from Study II.

Next we wanted to make sure that the repetition advantage for fearful faces for individual subjects was not purely a consequence of a repetition advantage for all repeated faces, regardless of valence. To test for this effect, we correlated the 2nd Fearful Face RT Advantage with the 2nd Neutral Face RT Advantage and did the same

thing for 3rd faces as well. In both 2nd and 3rd RT Advantages, we found no significant

correlation between the RT Advantage for fearful faces and the RT Advantage to

neutral faces [(2nd face : r=0.30, p=0.16; Figure 9)(3rd face: r=0.23, p=0.28; Figure 10)].

These results reveal that the overall speeded response to repeated fearful faces was

independent from the overall speeded response to neutral faces. Therefore, the RT

Advantage for repeated fearful faces represents the *selective* advantage for repeated
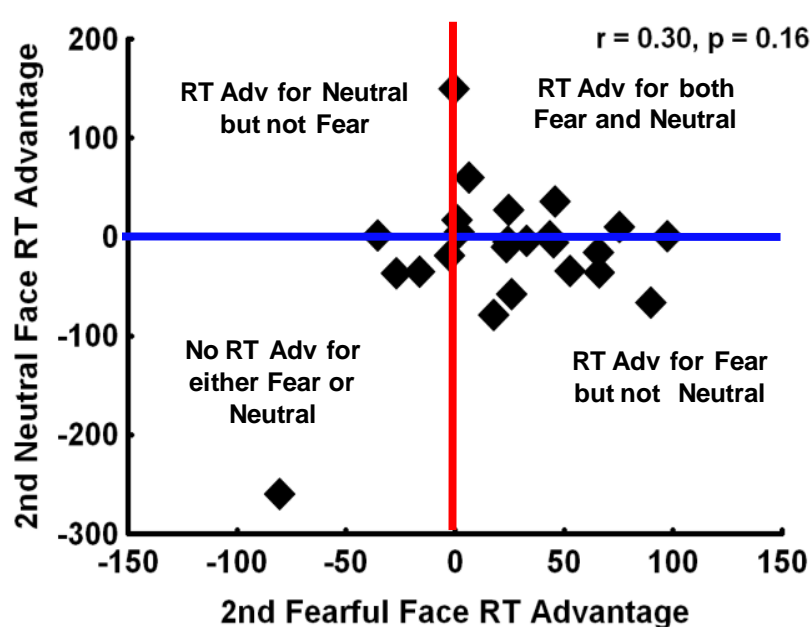
fearful faces.

Figure 9. The 2nd Neutral Face RT Advantage behavioral index plotted against the 2nd Fearful Face RT Advantage behavioral index.
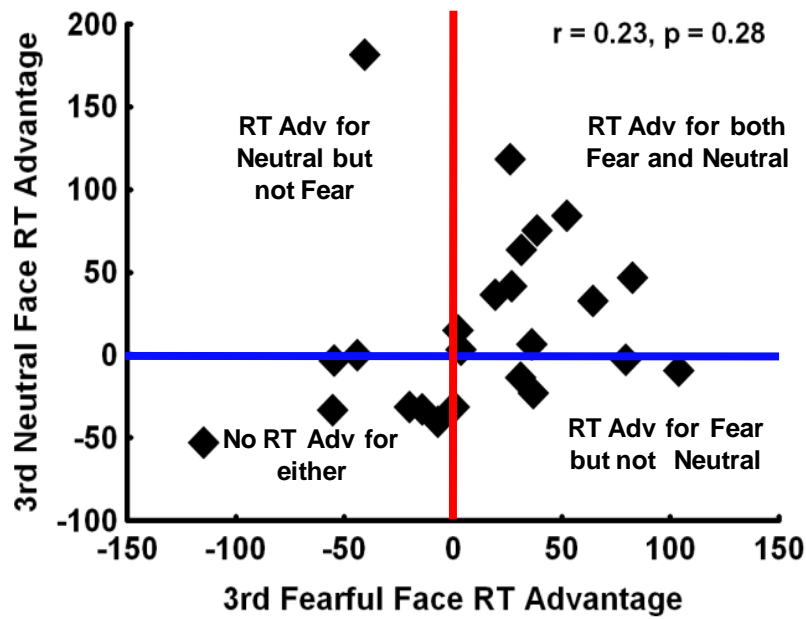
Figure 10. The 3rd Neutral Face RT Advantage behavioral index plotted against the 3rd Fearful Face RT Advantage behavioral index.

5.1.3 Behavioral Variability for Fearful Face Detection

To quantify fear detection sensitivity we computed the area under the ROC curve (A') for each subject (See ROC curves plotted for all 21 subjects in Figure 11; the center diagonal line represents chance performance). The average A' was 0.73±0.11 (0.52-0.93). Only two subjects had A' values that were not significantly different from 0.5 (the value expected by chance). Therefore, the vast majority of our subjects (19/21) could reliably detect a fearful face presented for 33 ms. Because we wanted to assess variability in fear detection sensitivity, we correlated A' values among our subjects with personality traits related to threat processing.
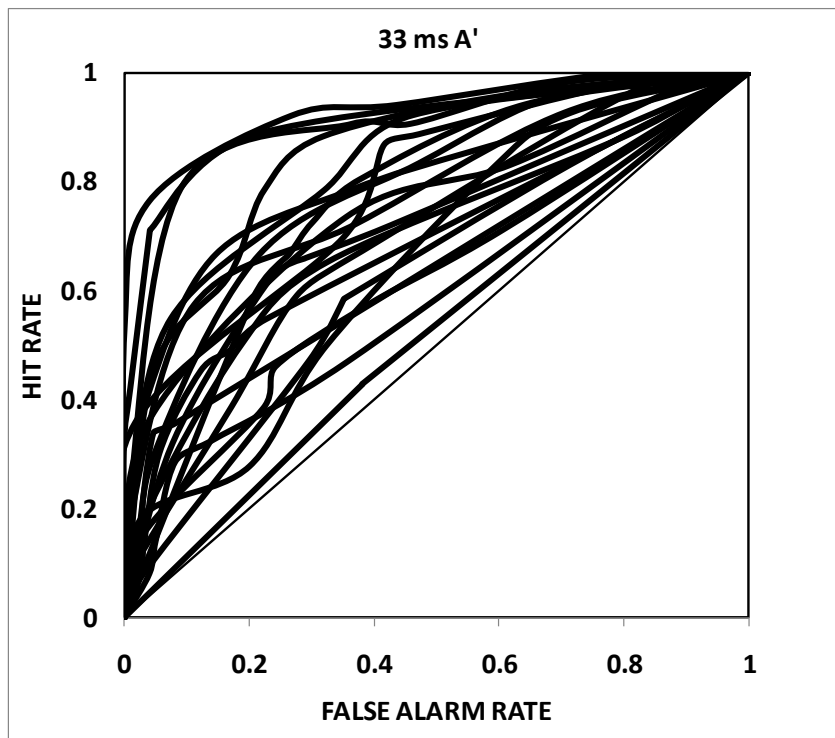
Figure 11. ROC curves for all 21 subjects in Study III plotted together.

5.2 BEHAVIOR AND PERSONALITY

5.2.1 Behavioral Variability for Fearful Face Expectation and Personality Traits

We looked to see if Valence Bias correlated with our personality measures (correlation results found in Table 4). Valence Bias did not correlate with State Anxiety, Trait Anxiety, or with the five personality traits measured by the NEO-FFI. Valence Bias did, however, correlate positively with measures of Harm Avoidance for the 13 subjects who completed this questionnaire ($r = 0.79$, $p < 0.0014$; see Table 4). Those subjects who responded faster to fearful faces were more harm avoidant. Although Valence Bias did not correlate with State Anxiety, Trait Anxiety, or Neuroticism, these three personality measures correlated positively with Harm

Avoidance [State Anxiety (r = 0.84, p < 0.0003), Trait Anxiety (r = 0.85, p < 0.0002), and Neuroticism (r = 0.85, p < 0.002)]. Therefore, subjects scoring higher on the overall Harm Avoidance scale also scored higher on other anxiety-related scales.

	Valence Bias	STAI State Anxiety	STAI Trait Anxiety	NEO-FFI Neuroticism[1]	NEO-FFI Extraversion[1]	NEO-FFI Openness to Experience[1]	NEO-FFI Agreeableness[1]	NEO-FFI Conscientiousness[1]	Harm Avoidance[2]	HA1[2]	HA2[2]	HA3[2]	HA4[2]
Valence Bias	x												
State Anxiety	0.32	x											
Trait Anxiety	0.20	0.75	X										
Neuroticism[1]	0.45	0.70	0.91	X									
Extraversion[1]	-0.38	-0.59	-0.75	-0.78	x								
Openness to Experience[1]	0.33	0.42	0.26	0.42	-0.32	x							
Agreeableness[1]	-0.03	-0.32	-0.18	-0.08	0.48	-0.03	X						
Conscientiousness[1]	-0.12	-0.53	-0.58	-0.55	0.38	-0.19	0.24	x					
Harm Avoidance[2]	0.79	0.84	0.85	0.85	-0.83	0.48	-0.19	-0.46	x				
HA1[2]	0.55	0.60	0.79	0.82	-0.70	0.59	-0.04	-0.35	x	x			
HA2[2]	0.84	0.54	0.47	0.56	-0.60	0.44	-0.01	-0.02	x	0.73	x		
HA3[2]	0.43	0.83	0.85	0.78	-0.77	0.33	-0.27	-0.73	x	0.61	0.38	x	
HA4[2]	0.70	0.68	0.53	0.50	-0.55	0.16	-0.27	-0.33	x	0.28	0.50	0.50	x

Table 4: Behavior and Personality Assessment Correlations for Study 1.

[1]R values found in these cells were calculated with data from sixteen subjects
[2]R values found in these cells were calculated with data from thirteen subjects

5.2.2 Behavioral Variability for Repeated Fearful Faces and Personality Traits

The RT Advantage for repeated fearful faces correlated with State and Trait Anxiety EXCLUSIVELY [(2nd Fear RT Advantage x State Anxiety: r= -0.44, p=0.03;

Figure 12A), (2nd Fear RT Advantage x Trait Anxiety: r= -0.44, p=0.03; Figure 12B)];

this correlation was not seen for neutral faces (Figure 12C and 12D). Additionally, the

RT Advantage measure for both fearful and neutral faces was not found to correlate

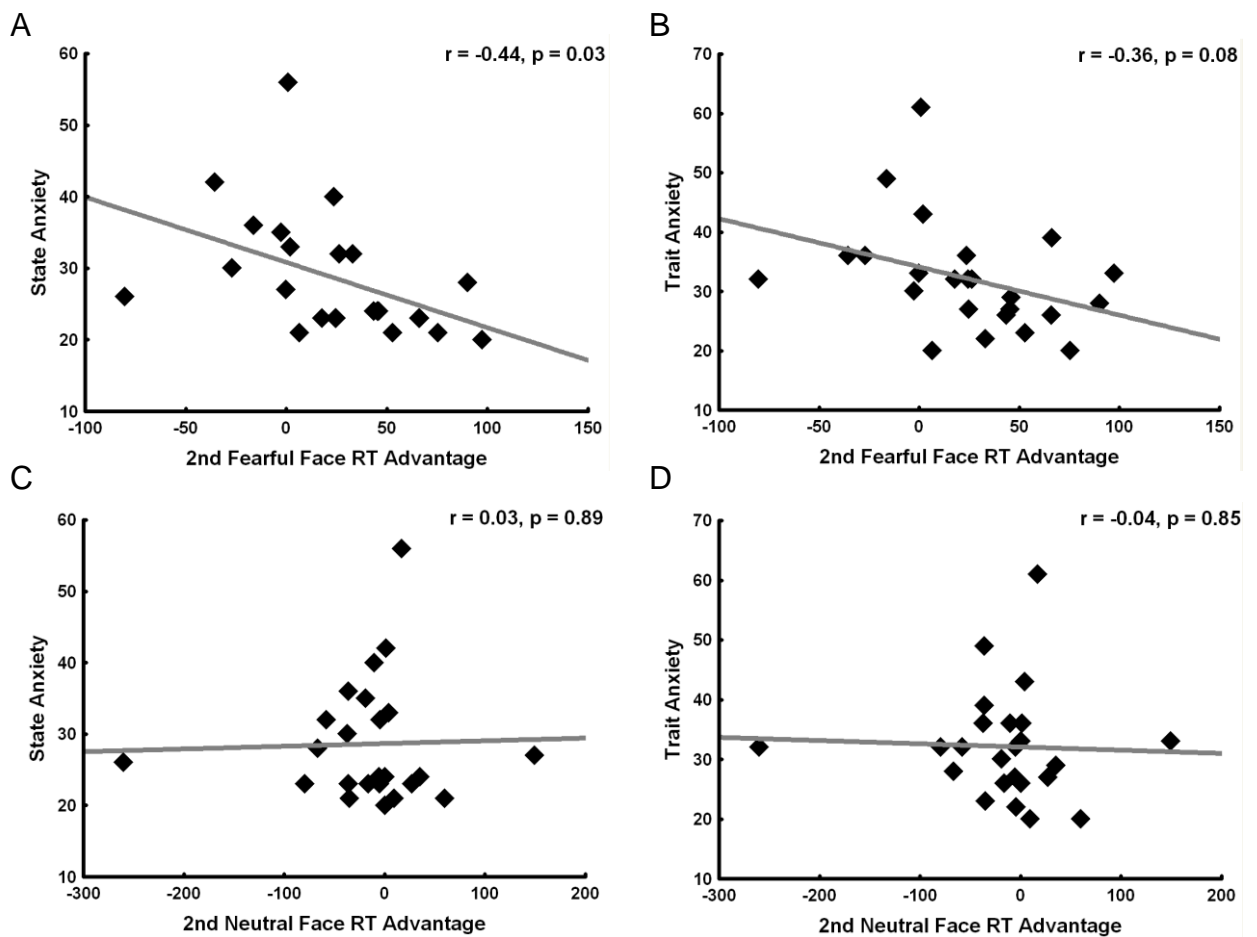with other personality measures.

Figure 12. State and Trait Anxiety plotted against the 2nd and 3rd RT Advantage for Fearful and

Neutral Faces.

5.2.3 Behavioral Variability for Fearful Face Detection and Personality Traits

Personality measurement means and spreads (Table 5) reflected the previously reported values for healthy adults: state anxiety (our sample: 30.10 ± 8.62; previous: 36.17 ± 10.96) and trait anxiety (our sample: 35.95 ± 9.46; previous: 36.15 ± 9.53) (Spielberger and Gorsuch, 1983), neuroticism (our sample: 16.67 ± 8.87; previous: 15.57 ± 7.47) (McCrae and Costa Jr, 2004), harm avoidance (our sample: 10.52 ± 7.31; previous: 10.6 ± 6.0) (Cloninger et al., 1991), and overall social anxiety (our sample: 30.81 ± 15.75; previous: 29.3 ± 20.9) (Blair et al., 2008, Goldin et al., 2009).

Table 5. Personality Measure Scores and Correlations with Fearful Face Detection Sensitivity.

All Subjects N = 21

Personality Measure Scores	Mean ± SD	Correlation with 33ms A': r value (p value)
Spielberger State and Trait Anxiety Inventory (STAI)		
State Anxiety	30.10 ±8.62	0.17 (0.45)
Trait Anxiety	**35.95±9.46**	**0.65 (0.002)**
NEO – Five Factor Inventory (FFI)		
Neuroticism	**16.67 ±8.87**	**0.55 (0.01)**
Extraversion	32.05 ±6.76	-0.20 (0.38)
Openness to Experience	33.05 ±6.29	0.36 (0.11)
Agreeableness	34.24± 6.58	-0.05 (0.84)
Conscientiousness	36.14 ±6.61	-0.40 (0.07)
Tridimensional Personality Questionnaire - Harm Avoidance Subscale (TPQ-HA)		
Harm Avoidance	**10.52±7.31**	**0.50 (0.02)**
HA 1: Anticipatory worry & pessimism	**4.20±3.72**	**0.62 (0.003)**
HA 2: Fear of Uncertainty	2.95±1.77	0.39 (0.08)
HA 3: Shyness with strangers	2.05±1.94	0.23 (0.31)
HA 4: Fatigability & asthenia	1.81±2.40	0.37 (0.10)
Liebowitz Social Anxiety Scale: Self Report (LSAS-SR)		
Overall Social Anxiety	**30.81±15.75**	**0.48 (0.03)**
Fear of Performance	9.81±3.98	0.39 (0.08)
Avoidance of Performance	**6.52±4.18**	**0.46 (0.04)**
Fear of Social Interaction	8.05±4.38	0.40 (0.07)
Avoidance of Social Interaction	**6.43±4.95**	**0.47 (0.03)**
Total Fear	17.86±7.88	0.42 (0.06)
Total Avoidance	**12.95±8.77**	**0.48 (0.03)**

Detection sensitivity (A') for fearful faces significantly correlated with trait anxiety [r(19)=0.65, p=0.002] (Figure 13A). However, A' did not correlate with state anxiety [r(19)=0.17, p=0.45] (Figure 13B), although state and trait anxiety scores were intercorrelated [r(19)=0.48, p=0.03]. Further, there was a significant difference between their correlations with A' (one sided t-test, p=0.04), confirming that the effect of trait anxiety on fear detection sensitivity was separate from the effect of state anxiety.

As predicted, fear detection sensitivity also significantly correlated with other personality measures related to threat detection: neuroticism [r(19)=0.55, p=0.01, Figure 13C], harm avoidance [r(19) =0.50, p=0.02, Figure 13D], harm avoidance subscale 1: anticipatory worry and pessimism [r(19)=0.62, p=0.003], overall social anxiety [r(19)=0.48, p=0.03] , avoidance of performance [r(19)=0.46, p=0.04], avoidance of social interaction [r(19)=0.47, p=0.03], and total avoidance [r(19)=0.48, p=0.03] (See Table 5 for correlations between all personality measures and 33 ms A'). Additionally, while all personality trait measures significantly correlated with each other (i.e. trait anxiety, neuroticism, harm avoidance, and social anxiety), state anxiety only significantly correlated with trait anxiety.
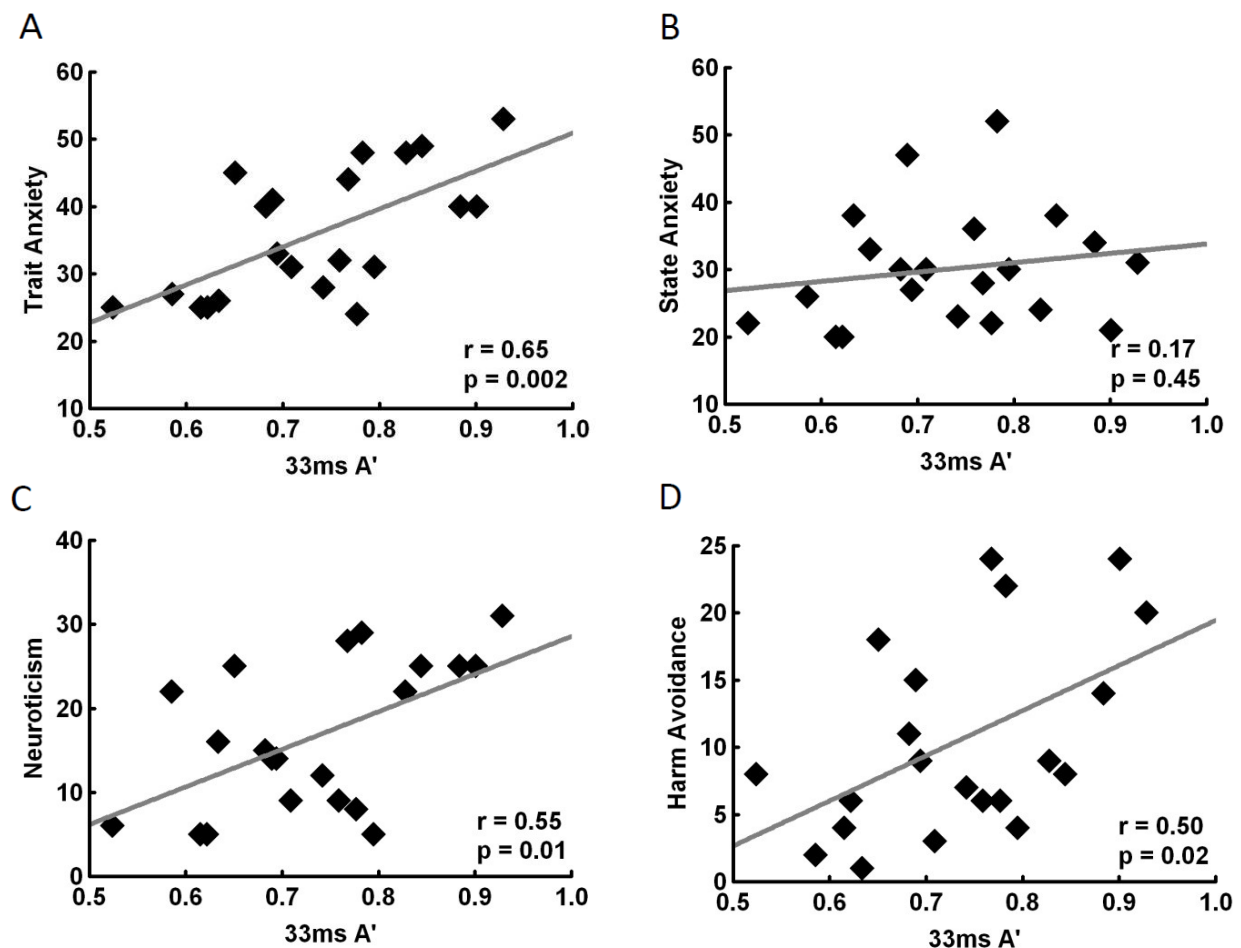
Figure 13. Fearful face detection sensitivity (A') correlated with personality measures.

In addition to A', we also correlated each subject's mean correct RT for fearful

faces and non-fearful faces with our personality measures. We found that state anxiety

negatively correlated with RT to correctly identify fearful faces (r=-0.55, p=0.01). This

result indicates that subjects who were faster to correctly identify a face as fearful were

also the subjects who had higher levels of state anxiety. This result was not driven by a

global RT advantage independent of valence, because state anxiety did not correlate

with RT to correctly identify a face as not fearful (r=-0.30, p=0.18). Also, RTs to

correctly identify faces as fearful or not fearful did not significantly correlate with any other personality measures.

5.3 BEHAVIOR AND NEURAL ACTIVATION

5.3.1 Behavioral Variability for Fearful Face Expectation and Neural Activation

Given the large amount of variability in Valence Bias in our cohort of healthy subjects, we correlated the whole brain FMRI activity at each timepoint with our subjects' Valence Bias scores. We looked at the whole brain FMRI responses for each of the six stimulus types (i.e. fearful faces in 20F:80N runs, neutral faces in 20F:80N runs, fearful faces in 80F:20N runs, neutral faces in 80F:20N runs, etc.) for each subject at all eight timepoints and correlated this activity with Valence Bias scores. This analysis allowed us to see which brain areas, across subjects, showed activations associated with RT differences.

The results showed that Valence Bias scores correlated positively with FMRI signal intensity 8 s after the presentation of unexpected fearful faces (i.e. 12 s post-cue in 20F:80N runs) in a cluster (118 voxels) located in the left medial prefrontal cortex. The strongest correlation in this cluster was located in a peak voxel in left ventromedial prefrontal cortex (VMPFC, Figure 14A-D, r = 0.78; see Table 6 for coordinates and statistics for each peak voxel).

Timepoint	Stimulus	Anatomical Location	Peak Voxel Talairach Coordinates			Peak r value	Peak t-statistic	Number of Voxels in Cluster (Volume mm^3)
			x	y	z			
12 s post-cue (8 s post-face)	20F:80N Fearful Face	L Ventromedial Prefrontal Cortex	-7	44	-1	0.78	5.94	118 (3186)
		L Subgenual Cingulate Cortex	-1	14	0	0.75	5.27	
		R Ventromedial Prefrontal Cortex	17	35	-4	0.72	4.89	44 (1188)
		R Head of the Caudate Nucleus	17	26	-1	0.72	4.97	

Timepoint	Stimulus	Anatomical Location	Peak Voxel Talairach Coordinates			Peak r value	Peak t-statistic	Number of Voxels in Cluster (Volume mm^3)
			x	y	z			
4 s post-cue (0 s post-face)	20F:80N Neutral Face	L Head of Caudate Nucleus	-7	10	-1	-0.70	-4.58	82 (2214)
		R Nucleus Accumbens	8	8	-7	-0.71	-4.73	
		R Putamen	26	5	-4	-0.72	-4.85	

Table 6: Regions Showing Correlated Activity with Valence Bias.
All clusters significant at $p < 0.01$ corrected
1 voxel = 3 mm x 3 mm x 3 mm = 27 mm^3

Additionally, within this cluster, a second peak was found in the left subgenual

cingulate cortex (SGC, Figure 14A, B and F, r = 0.75). A second cluster (44 voxels)

also correlated positively with Valence Bias scores at this timepoint. This cluster

contained two peaks: one was located in the right VMPFC (Figure 14C and E, r = 0.72)

and the other was located in the right head of the caudate nucleus (Cd, Figure 14B and

G, r = 0.72). No other timepoints displayed a significant correlation between Valence

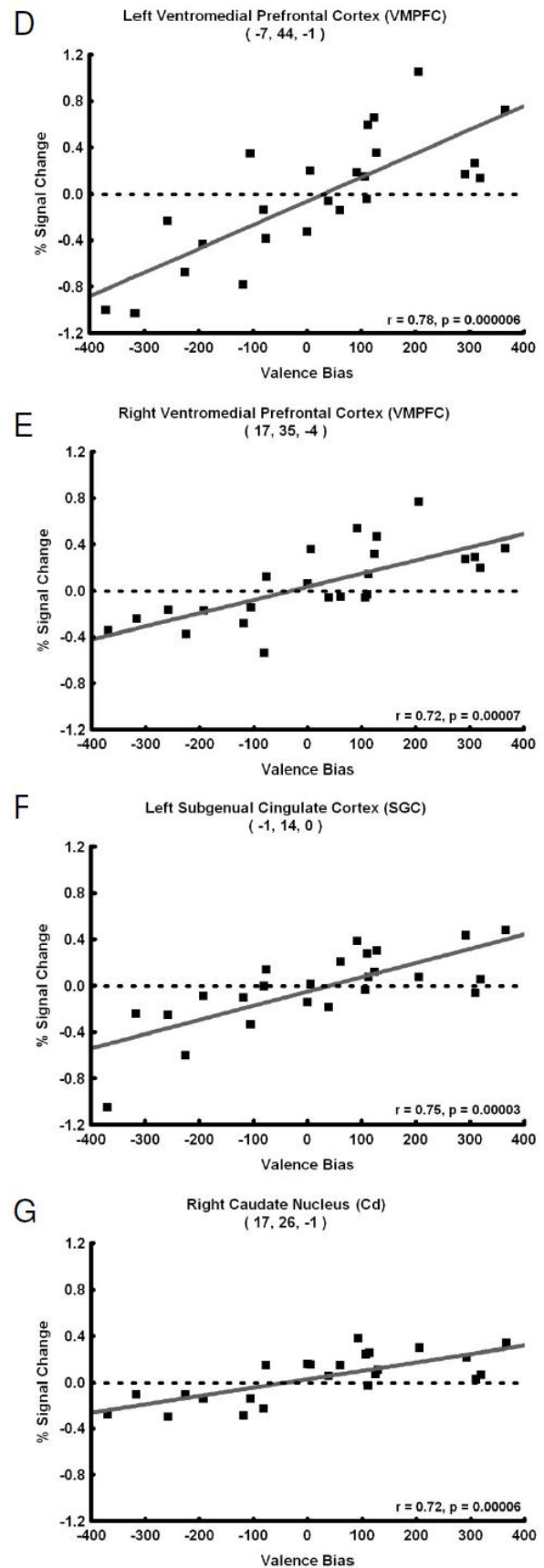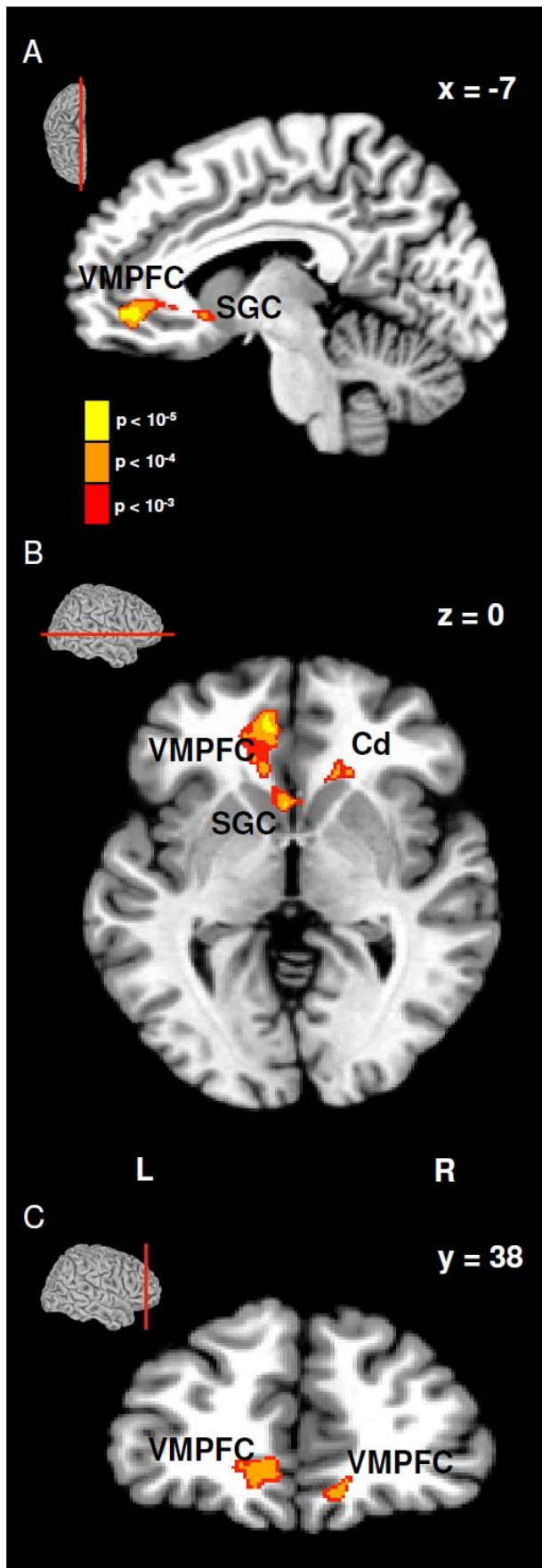Bias scores and percent signal change for unexpected fearful faces.

Figure 14. Positive Correlation of Late Trial (8s after face) 20F:80N Fearful Face Activation with Valence Bias Scores.

In addition to the late positive correlation with unexpected fearful faces,

Valence Bias scores correlated negatively with FMRI signal intensity evoked by

expected neutral faces in the 20F:80N runs 4 s after the cue was presented (i.e.

coincident with the presentation of the neutral face). This negative correlation was

found in a large cluster (82 voxels) encompassing both hemispheres that included peak

voxels in the striatum of the basal ganglia: left head of the Cd (Figure 15A,B, r = -

0.70), right nucleus accumbens (NAcc, Figure 15A,C, r = -0.71), and right putamen

(Put, Figure 15A, D, r = -0.72). No other timepoints displayed a significant correlation

between Valence Bias scores and percent signal change for expected neutral faces.
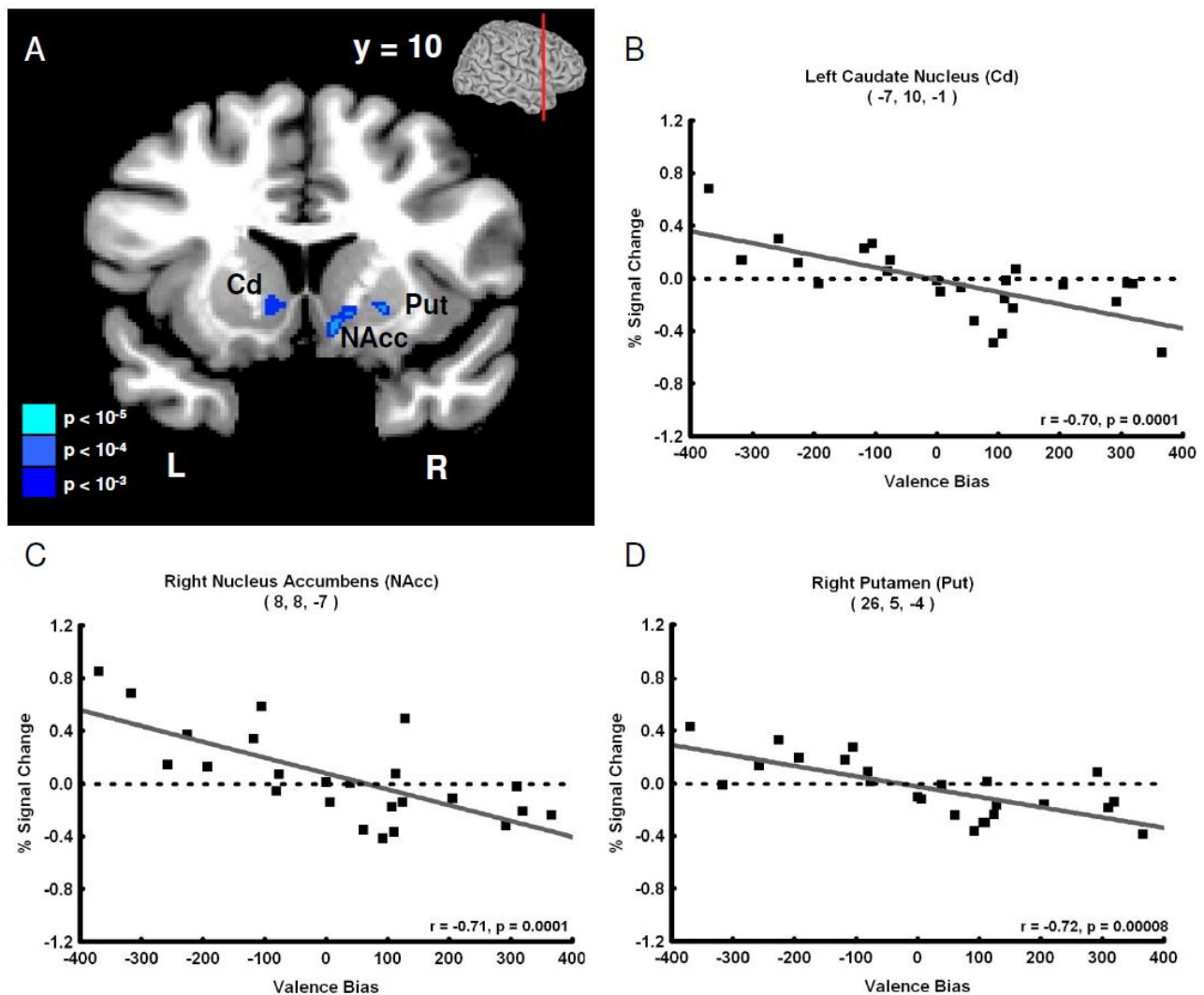
Figure 15. Negative Correlation of Early Trial (4 s after cue) 20F:80N Neutral Face Activation with Valence Bias Scores.

These results indicate that Valence Bias scores correlated positively with late activity evoked by unexpected fearful faces, such that increased activity in areas of the medial prefrontal cortex (including VMPFC and SGC) and caudate nucleus were predictive of faster RTs to fearful faces. This correlation occurred 8 s after the presentation of the face. In contrast, Valence Bias scores correlated negatively with early activity evoked by cues for expected neutral faces, such that increased activity in areas of the dorsal striatum bilaterally (Put and Cd) and right ventral striatum (NAcc)

were predictive of slower RTs to fearful faces. This correlation occurred 4 s after the

presentation of the cue (i.e., coincident with the presentation of the neutral face). Even

though the 80F:20N expectation runs, like the 20F:80N runs, included expected and

unexpected faces, the only significant correlations were found in the 20F:80N

expectation runs.

Our correlation analysis revealed that Valence Bias scores correlated

significantly with FMRI signal change only in 20F:80N runs. There was a positive

correlation late in the trial for unexpected fearful faces and a negative correlation early

in the trial for expected neutral faces. This result led us to further investigate the

relationship between Valence Bias and FMRI signal change during the 20F:80N runs.

We used peak voxels from significant clusters found in the correlation analysis (Table

6) to create ROIs, and then extracted 20F:80N waveforms for Fear Fast and Fear Slow

Responders within these ROIs (Figures 16 and 17).

Prefrontal and subcortical areas included 16A) left and 16B) right ventromedial

prefrontal cortex, 16C) left subgenual cingulate cortex, and 16D) right caudate. These

timecourses illustrate that Fear Fast Responders (dark red lines) had more activation

than Fear Slow Responders (light red lines) in these ventromedial prefrontal and

subcortical areas late (i.e. 10 and 12 s post-cue, 6 and 8 s post-face) in unexpected

fearful face trials. It is interesting to note that although these peak voxels were

significant for the positive correlation between Valence Bias scores and percent signal

change for unexpected fearful faces, these peak voxels also displayed an early (i.e. 2, 4,

and 6 s post-cue) trial enhancement for Fear Slow Responders (light blue lines)

compared to Fear Fast Responders (dark blue lines) for expected neutral faces.

Figure 16. Timecourses Extracted from Peak Voxels Displaying Late Positive Correlation

Between Percent Signal Change for Unexpected Fearful Faces and Valence Bias Scores. (** =

p < 0.01 corrected, * = p < 0.05 corrected, + = p < 0.10 corrected)
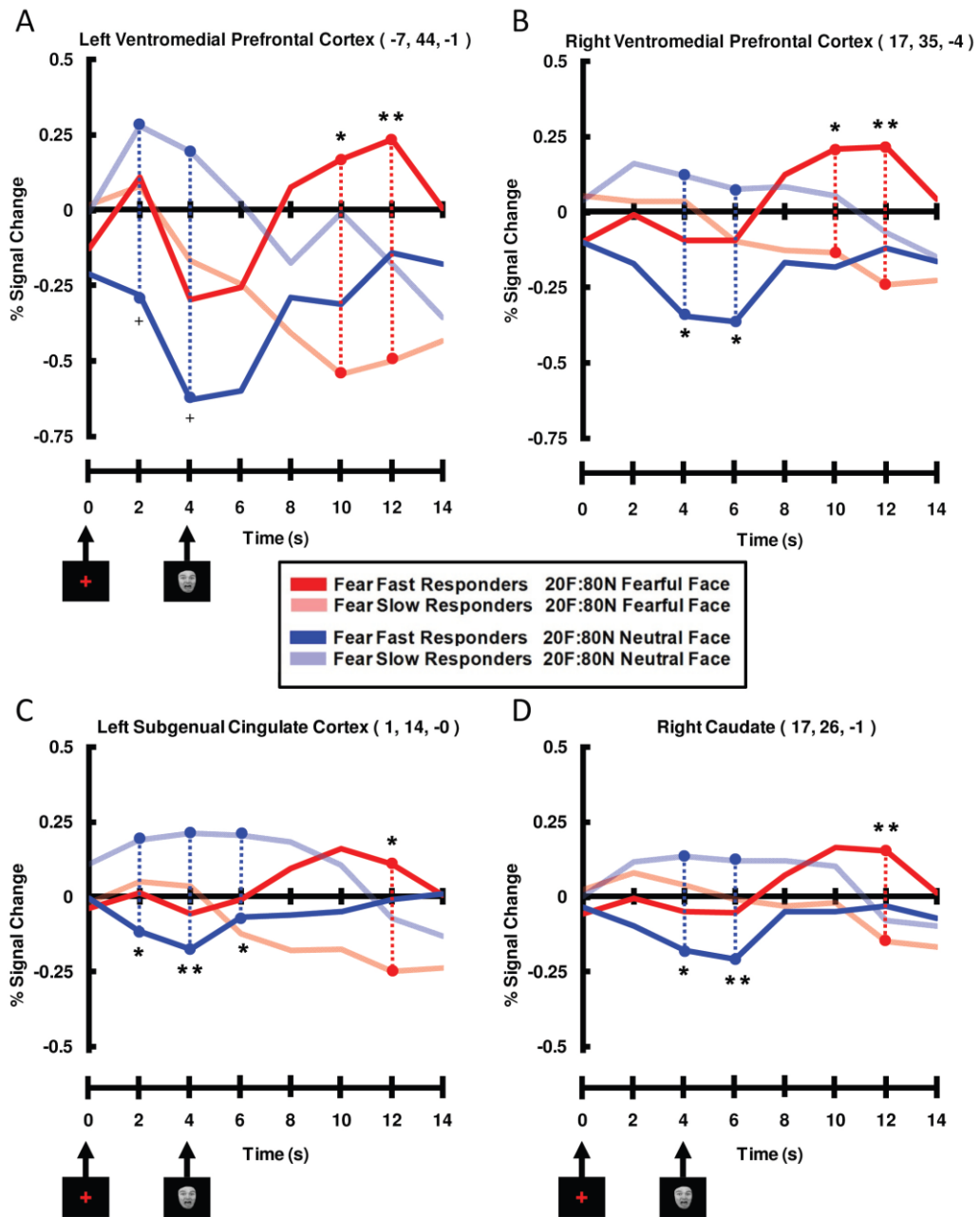
Figure 17. Timecourses Extracted from Peak Voxels Displaying Early Negative Correlation Between Percent Signal Change for Expected Neutral Faces and Valence Bias Scores. (** = $p < 0.01$ corrected, * = $p < 0.05$ corrected, + = $p < 0.10$ corrected)
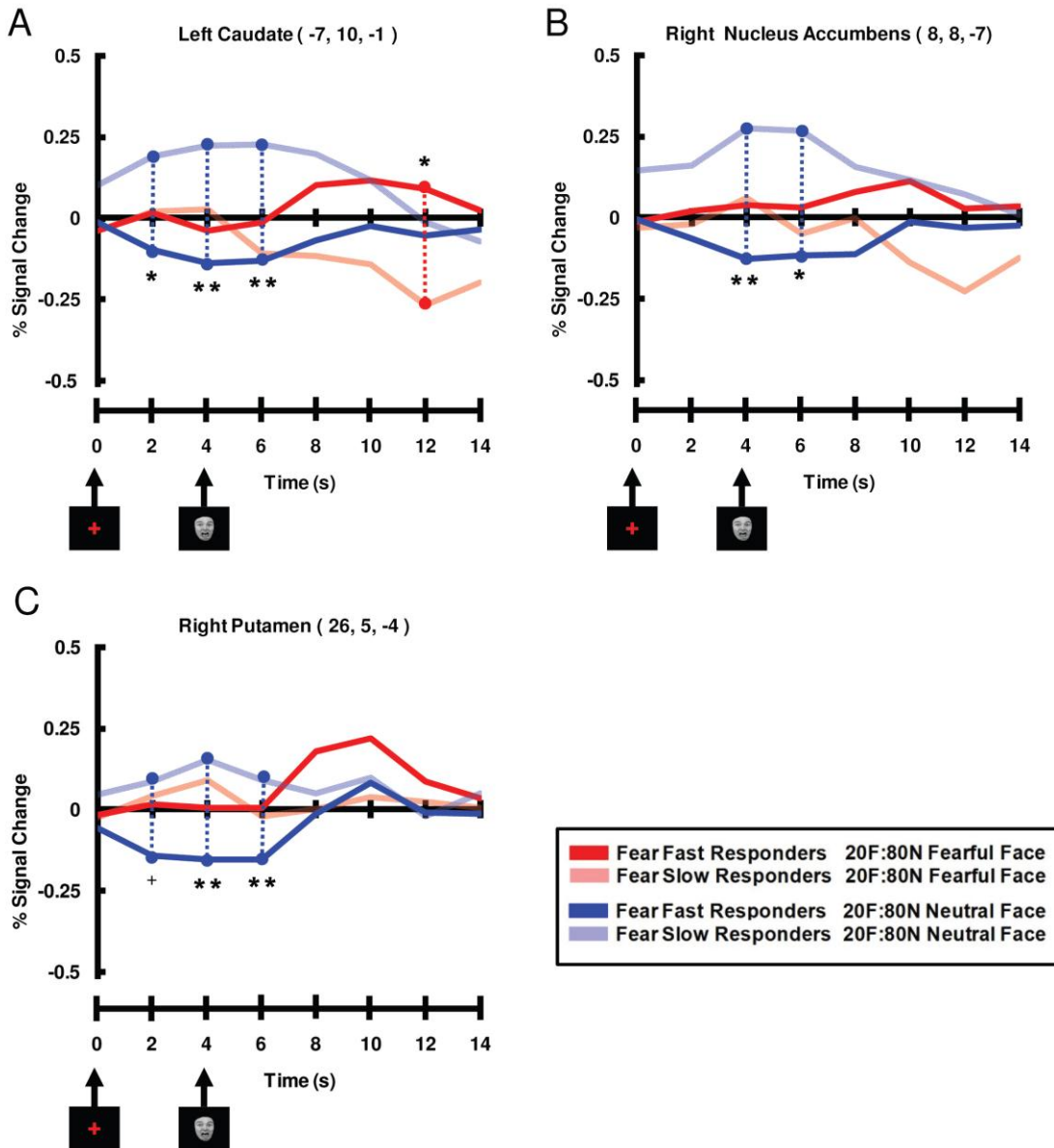
Areas of the striatum of the basal ganglia included 17A) left caudate, 17B) right nucleus accumbens, and 17C) right putamen. These timecourses illustrate that Fear Slow Responders (light blue lines) had more activation than Fear Fast Responders (dark blue lines) early (i.e. 2, 4 and 6 s post-cue, 0 and 2 s post-face) in expected neutral

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face trials. It is interesting to note that although these peak voxels were significant for the negative correlation between Valence Bias scores and percent signal change for expected neutral faces, the left caudate (A) also displayed a late (i.e. 12 s post-cue) trial enhancement for Fear Fast Responders (dark red lines) compared to Fear Slow Responders (light red lines) for unexpected fearful faces.

To summarize, most of the ROIs identified by the correlation analysis demonstrated both early and late trial effects when the data were analyzed by breaking the subjects into two Valence Bias groups; importantly, early trial effects were seen only for expected neutral faces and late trial effects were seen only for unexpected fearful faces .

5.3.2 Behavioral Variability for Repeated Fearful Faces and Neural Activation

For both 2nd and 3rd Fear RT Advantage behavioral indices correlations with FMRI activation were always negative (Tables 7 and 8), meaning that as subjects were getting faster to the expected fearful face, they were activating areas more to the second face. Therefore, subjects who were faster to the repeated fearful faces showed less repetition suppression, i.e. less activation with repeated presentations of a visual stimulus category.

The same was not true for neutral faces. While the 2nd Neutral RT Advantage correlations included negative correlations along with positive (Table 9), all the 3rd

Neutral RT Advantage correlations were positive (Table 10). This means that as

subjects were faster to the repeated neutral face, they were activating these areas less.

Therefore, subjects who were faster to the repeated neutral faces showed more

repetition suppression. See Figure 18 for brain maps illustrating this valence by

repetition difference.

2nd Fear RT Advantage x 1st-2nd Fearful Face Activation						
Timepoint	Anatomical Location	Peak Voxel Talairach Coordinates			Peak t-statistic	Number of Voxels in Cluster
		x	y	z		
2-4 s post-cue	L Calcarine Sulcus	-4	-91	5	-4.80	44
4-6 s post-cue (0-2 s post-face)	L Putamen	-28	8	5	-5.55	152
	L Superior Occipital Gyrus	-13	-82	23	-4.71	62
	R Middle Frontal Gyrus	35	17	35	-4.96	45
	R Superior Frontal Gyrus	20	50	2	-4.21	32
6-8 s post-cue (2-4 s post-face)	L Calcarine Sulcus	-4	-91	2	-4.35	50
8-10 s post-cue (4-6 s post-face)	L Calcarine Sulcus	-4	-91	5	-4.29	57

Starting p value < 0.005, corrected to $p<0.05$ (32 voxels), $p<0.01$ (40 voxels)

Table 7. 2nd Fearful Face RT Advantage x 1st – 2nd Fearful Face Activation

3rd Fear RTAdvantage x 1st-3rd Fearful Face Activation						
Timepoint	Anatomical Location	Peak Voxel Talairach Coordinates			Peak t-statistic	Number of Voxels in Cluster
		x	y	z		
2-4 s post-cue	None					
4-6 s post-cue (0-2 s post-face)	L Putamen	-22	-1	-4	-4.48	134
	R Anterior Insula	38	20	11	-4.50	56
	R Putamen	26	-13	8	-4.78	50
6-8 s post-cue (2-4 s post-face)	L Putamen	-31	-10	8	-5.74	183
	R SMA	11	5	47	-4.52	36
8-10 s post-cue (4-6 s post-face)	L Putamen	-28	-13	8	-4.76	108
	R Posterior Insula	29	-25	7	-4.69	33
10-12 s post-cue (6-8 s post-face)	R Posterior Insula	44	-22	20	-4.34	129
	R SMA	11	-22	47	-6.37	47
	R Supramarginal Gyrus	38	-31	32	-4.39	46
	R Middle Cingulate Cortex	2	2	32	-4.75	39
12-14 s post-cue (8-10 s post-face)	L Superior Frontal Gyrus	-22	41	32	-4.95	44

Starting p value < 0.005, corrected to p<0.05 (32 voxels), p<0.01 (40 voxels)

Table 8. 3rd Fearful Face RT Advantage x 1st -3rd Fearful Face Activation

2nd Neutral RT Advantage x 1st-2nd Neutral Face Activation						
Timepoint	Anatomical Location	Peak Voxel Talairach Coordinates			Peak t-statistic	Number of Voxels in Cluster
		x	y	z		
2-4 s post-cue	L Middle Frontal Gyrus	32	31	41	-5.67	141
	L Angular Gyrus	-28	-49	32	-4.49	62
	L Globus Pallidus	-22	8	-10	6.15	57
	R Angular Gyrus	29	-40	32	-4.54	47
	L Precuneus	-10	-67	41	-5.98	46
	L Lingual Gyrus	-22	-91	-7	-4.96	39
	R Precuneus	14	-67	44	-5.23	33
4-6 s post-cue (0-2 s post-face)	L Posterior Insula	-40	5	-10	8.09	50
	R Posterior Insula	41	-1	-13	6.95	45
6-8 s post-cue (2-4 s post-face)	R Middle Temporal Gyrus	62	-25	-13	-5.16	43
	R Inferior Frontal Gyrus (Triangularus)	50	17	17	-5.98	32
8-10 s post-cue (4-6 s post-face)	None					
10-12 s post-cue (6-8 s post-face)	None					
12-14 s post-cue (8-10 s post-face)	None					

Starting p value < 0.005, corrected to p<0.05 (32 voxels), p<0.01 (40 voxels)

Table 9. 2nd Neutral Face RT Advantage x 1st-2nd Neutral Face Activation

3rd Neutral RT Advantage x 1st-3rd Neutral Face Activation						
Timepoint	Anatomical Location	Peak Voxel Talairach Coordinates			Peak t-statistic	Number of Voxels in Cluster
		x	y	z		
2-4 s post-cue	R Middle Frontal Gyrus	29	35	20	6.05	231
	R Anterior Cingulate Cortex	14	23	26	5.06	40
	R SMA	14	8	47	4.53	36
	R Insula	32	5	8	4.03	32
4-6 s post-cue (0-2 s post-face)	R Middle Frontal Gyrus	29	32	20	5.53	383
	L Anterior Cingulate Cortex	-7	26	14	6.61	36
	R Angular Gyrus	53	-52	26	5.09	36
6-8 s post-cue (2-4 s post-face)	R Anterior Insula	23	26	5	4.58	68
	L Anterior Cingulate Cortex	-7	47	8	4.84	32
8-10 s post-cue (4-6 s post-face)	None					
10-12 s post-cue (6-8 s post-face)	None					
12-14 s post-cue (8-10 s post-face)	None					

Starting p value < 0.005, corrected to p<0.05 (32 voxels), p<0.01 (40 voxels)

Table 10. 3rd Neutral Face RT Advantage x 1st-3rd Neutral Face Activation
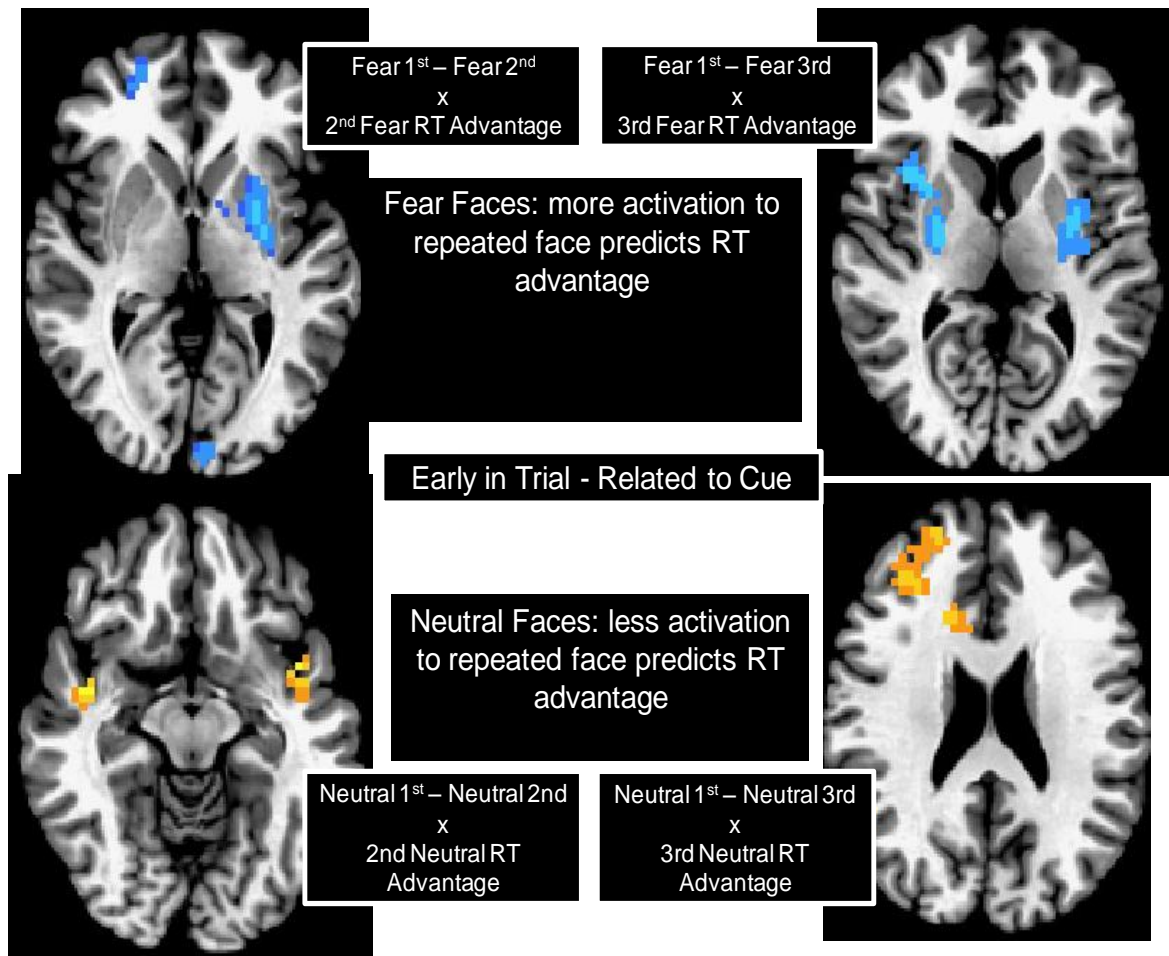
Figure 18. Activation maps illustrating that correlations between 2nd and 3rd Face RT

Advantages and FMRI activation were negative for repeated Fearful Faces and positive for

repeated Neutral Faces early in the trial.

6 DISCUSSION

6.1 BEHAVIORAL VARIABILITY IN FEARFUL FACE PROCESSING

All three studies demonstrated intersubject behavioral variability for the processing of fearful faces. In Study I, about two-thirds (15/24) of the subjects were faster to categorize fearful faces compared to neutral faces, while about one-third (9/24) were actually faster to categorize neutral faces. However, when we compared the RTs between subjects who were faster to categorize neutral faces and those who were faster to categorize fearful faces, we found that the RT differences were driven exclusively by responses to fearful faces. When RT data for Fear Fast and Fear Slow Responders were combined, there was no overall RT advantage for fearful faces.

While studies have reported behavioral enhancement for threatening faces (e.g. better spatial detection, faster detection of a neutral target following a threatening face) in the healthy population (e.g. (Hansen and Hansen, 1988, Fox et al., 2000, Fox, 2002, Wilson and MacLeod, 2003), only one study to date has reported an overall RT advantage for categorizing fearful compared to neutral faces (Ishai et al., 2004). Our results are, therefore, largely consistent with the existing literature: An RT enhancement for fearful faces was seen only in a subset of our population but not in the population overall.

In Study II, we found an overall repetition advantage for fearful but not neutral faces. While two other studies reported neural repetition effects for fearful faces

exclusively, neither of these studies reported a behavioral repetition effect for fearful faces exclusively (Ishai et al., 2004, Ishai et al., 2006). This may be due to differences in task as our task included a cue period and used an expectation block parameter to build repetitions rather than displaying an exemplar image first.

In addition to the group effect, we also found intersubject variability in Study II. As the repetition advantage for fearful faces did not correlate with the repetition advantage for neutral faces, the repetition advantage for fearful faces was selective for fearful faces exclusively and not just a general repetition advantage for repeated stimuli independent of valence.

6.2 HOW PERSONALITY TRAITS RELATE TO BEHAVIORAL VARIABILITY

High anxiety levels have been associated with an attentional bias towards threat in clinical and subclinical populations (see review (Bar-Haim et al., 2007)). In Study I, we found that Valence Bias scores did not significantly correlate with state or trait anxiety, as measured by the Spielberger State Trait Anxiety Inventory. However, Valence Bias scores did significantly correlate with Tridimensional Personality Questionnaire Harm Avoidance (TPQ-HA) scores that were collected from a subset of our cohort (13/24 subjects), such that a more harm avoidant, cautious person was more likely to be hypersensitive to unexpected threatening stimuli. TPQ Harm Avoidance

scores also correlated positively with state and trait anxiety, which is consistent with findings from other groups (Caseras et al., 2003, Stewart et al., 2005) .

In Study II the fear repetition advantage inversely correlated with anxiety and the neutral repetition advantage did not. While it may be surprising that subjects scoring higher on anxiety measures showed no repetition advantage for fearful faces, this may be explained by a lack of extinction on the part of the high anxiety subjects. Anxiety patients display a lessened ability to extinguish fear memories (Lissek et al., 2005). So it may be that our healthy adults with higher anxiety have a diminished ability to habituate to repeated fearful faces.

Study III confirmed a prior report (Japee et al., 2009) that the non-preselected spectrum of trait anxiety scores in healthy adults correlated with a behavioral advantage for fearful faces, as measured by the ability to detect the occurrence of masked fearful faces. Additionally, we found that this behavioral advantage also correlated with other personality traits related to anxiety. This result implies that heightened fearful face detection sensitivity is a behavioral consequence of a wide range of personality traits related to threat processing and that this sensitivity is parametrically related to those personality traits.

Interestingly, state anxiety was not found to correlate with fearful face detection sensitivity; however, state anxiety did correlate with the RT to correctly identify fearful faces. Subjects scoring higher on the state anxiety inventory were faster to correctly identify faces as fearful. This result is an indication that state anxiety plays a role in

speed of detection for briefly presented fearful faces but not in fearful face detection itself. Additionally, this result implies that fear detection sensitivity is related to underlying and more deeply rooted traits and is unaffected by fluctuations in mood.

Neuroticism is a personality trait related to a general increase in negative emotions (Costa and McCrae, 1980) and susceptibility for anxiety and depression (Clark et al., 1994). Therefore it is not surprising that subjects who were better able to detect fearful faces also scored high on this personality trait. The TPQ Harm Avoidance scale also measures amplified responses to negative stimuli via how much a person avoids high harm situations (Cloninger, 1986). In our study, fearful face detection sensitivity correlated most strongly with the first subscale of the harm avoidance TPQ: anticipatory worry & pessimism. These findings give further evidence that fearful face detection sensitivity increases parametrically with increased susceptibility for negative emotions. While neuroticism and harm avoidance scales measure global tendencies towards anxiety and more negative emotions, we also tested whether fearful face detection sensitivity correlated with a more specific subtype of anxiety: social anxiety. Given that our stimuli were social in nature, we expected to see that subjects scoring higher on social anxiety would be those who showed enhanced fearful face detection sensitivity. This is exactly what we found, indicating that fearful face detection sensitivity is also related to this more specific subtype of anxiety.

While Study III focused exclusively on healthy adults, the same effect has been seen in children, where the healthy trait anxiety spectrum was found to correlate with a

behavioral advantage for angry faces (Telzer et al., 2008). Additionally, that study discovered that trait anxiety also correlated with the neural enhancement for angry faces in the dorsolateral prefrontal cortex. These results in children suggest that the healthy spectrum of trait anxiety modulates not only the enhanced behavioral response to threatening faces, but also the enhanced neural response.

In Studies I and III, fearful faces elicited a behavioral advantage, particularly for those subjects with higher levels of trait anxiety or harm avoidance. Other work has shown that fearful faces elicit a behavioral disadvantage when fearful faces are task irrelevant and distracting, particularly for those healthy subjects with higher levels of anxiety (Ewbank et al., 2009, Ladouceur et al., 2009). Those studies combined with the current studies suggest that anxiety and anxiety-related traits prime the processing stream to be biased towards threatening faces and this bias creates either an advantage for performance when the threatening face is task relevant, a disadvantage for performance when the threatening face is task irrelevant, and no increase in performance when the threatening face is repeated.

6.3 HOW NEURAL ACTIVATION RELATES TO BEHAVIORAL VARIABILITY

We found a large amount of variability in how quickly subjects responded to fearful relative to neutral faces in Study I. To understand the neural origins of this variability, we correlated Valence Bias scores with FMRI activations across the brain.

We found that, in runs where fearful faces were unexpected (20F:80N), 8 s after the presentation of the face, activity in the VMPFC, SGC, and Cd correlated positively with Valence Bias scores. Subjects who responded faster overall to fearful than to neutral faces showed higher activity in these regions, while subjects who responded slower overall to fearful than to neutral faces showed less activity in these regions. Activity in these regions was, thus, predictive of whether a subject would be faster or slower in responding to unexpected fearful compared to expected neutral faces.

In contrast to the late positive correlation between activation to unexpected fearful faces and Valence Bias scores, in the same expectation runs (i.e. 20F:80N) we found an early negative correlation in response to expected neutral faces, which occurred 4 s after the cue. The faster subjects were to respond to fearful faces compared to neutral faces, the smaller was the activation in the striatum of the basal ganglia, including the Cd, Put, and NAcc.

We placed the subjects into two groups (Fear Fast and Fear Slow Responders) to probe differences between them to unexpected fearful and expected neutral faces over time. The timecourses within the areas where activation significantly correlated with Valence Bias scores reflected the results from the correlation data. However, the group analysis also revealed that both early and late effects were common to most regions. That is, subjects who were faster to respond to fearful faces had an enhanced response late in the trial in these regions following an unexpected fearful face and also had an attenuated preparatory response early in the trial in the same regions preceding

an expected neutral face; the opposite was true for the subjects who were slower to respond to fearful faces. These results point to a network of regions in medial prefrontal cortex and dorsal and ventral striatum (including VMPFC, SGC, Cd, Put, and NAcc) that show similar effects.

The co-activation of these regions is not surprising since neuroanatomical studies in nonhuman primates have shown that the VMPFC projects to both the dorsal and ventral striatum (Haber et al., 1995) as well as the SGC (Carmichael and Price, 1996). The SGC also projects to the ventral striatum (Kunishio and Haber, 1994). The dense connections between these regions have been confirmed in the human brain using diffusion tensor imaging and functional connectivity mapping (Lehericy et al., 2004, Leh et al., 2007, Di Martino et al., 2008, Johansen-Berg et al., 2008). This evidence provides the anatomical underpinnings for an interconnected network.

What drives the correlation of activity in this network with behavior? We propose that, in Study I, the medial prefrontal – striatal network encodes the affective value of unexpected fearful faces. Affective value is defined here as the biological relevance of an affective stimulus to guide behavior. Thus, subjects for whom fearful faces were more valued (i.e. Fear Fast Responders) engaged these regions more when fearful faces were unexpected, which in turn resulted in faster motor responses to those unexpected valued stimuli. On the other hand, subjects for whom fearful faces were less valued (i.e. Fear Slow Responders) deactivated these regions, which resulted in slower motor responses to the unexpected non-valued stimuli. Thus, activity in this

network appears to be directly proportional to the affective value fearful faces hold for a given subject when they are presented in an unexpected context.

We know from previous work that these regions, the VMPFC in particular, are crucial in evaluating the value of stimuli based on context (Schoenbaum et al., 1998, Schultz and Dickinson, 2000, Schoenbaum and Roesch, 2005, Blair et al., 2006, Tobler et al., 2006). Human imaging studies have shown that the VMPFC is involved in the extinction of conditioned fear (Phelps et al., 2004) and skin conductance changes during a risky decision-making paradigm (Critchley et al., 2000) – where the VMPFC tracks how the affective representation of a stimulus changes based on context. Still others have shown that patients with lesions of the VMPFC have deficiencies in using new information to make advantageous decisions (Bechara et al., 1994, Bechara et al., 2000), have difficulty integrating emotion into their decision-making process during moral decisions (Koenigs et al., 2007), and have trouble judging harmful intentions of others (Young et al., 2010). Neuroimaging and postmortem evidence supports the role of the SGC in the pathology of social phobia and depression and also its role in negative mood (Mayberg et al., 1999, Furmark et al., 2002). Human imaging and monkey physiological studies have both demonstrated that the dorsal and ventral striatum respond to cues that signal an upcoming salient stimulus (Hikosaka et al., 1989, Knutson et al., 2001, Samejima et al., 2005). These wide-ranging studies of the medial prefrontal - striatal network confirm its role in tracking the affective value of stimuli as context changes.

The early trial negative correlation between Valence Bias scores and activation evoked by expected neutral faces trials was not predictive of faster RTs to neutral faces, because the behavioral differences among our subjects were driven by fearful faces exclusively. As this negative correlation occurred early in the trial, we believe that this effect is related to the anticipation of the upcoming stimulus, i.e., the expected neutral face. It is important to note that in order to limit repetition effects we only included in our analysis trials in which a neutral or fearful face was immediately followed by the alternate face type. Thus, on expected neutral trials, subjects were highly certain that the upcoming stimulus would be a neutral face (since they had just received a fearful face on the previous trial). We know from other FMRI studies that expected stimuli can elicit an anticipatory response (Chawla et al., 1999, Kastner et al., 1999). In Study I, subjects who valued fearful faces less (i.e. Fear Slow Responders), showed a normal anticipatory effect, while those subjects who valued unexpected fearful faces more (i.e. Fear Fast Responders) showed greater suppression of this anticipatory response.

It is important to note that activity in the medial prefrontal cortex and striatum does not encode the affective value of fearful faces in general, but rather represents the combination of the value of fearful faces and context, i.e., the likelihood of appearing (expected or unexpected). This is confirmed by the lack of correlation of activity in these regions with Valence Bias during runs where fearful faces were expected and neutral faces were unexpected (80F:20N expectation runs). The interaction between affect and expectation is further confirmed by research showing that low probability

threat produces more anticipatory anxiety (as measured via heart rate and skin conductance responses) than high probability threat (Deane, 1969, Epstein and Roupenian, 1970).

In Study II, while we did not directly correlate FMRI activation with anxiety, we did see a negative correlation between the fearful face RT repetition advantage and activation to 1st vs 2nd/3rd repeated fearful faces in striatum and early occipital areas. This result means that subjects who had no repetition advantage for the repeated fearful faces (the subjects who had higher anxiety) were actually showing more activation to the first fearful face presented as to the repeated presentations. This result argues against the theory that these subjects are not habituating to the repeated fearful faces and that that lack of habituation is the mechanism behind their lack of repetition advantage for fearful faces. Interestingly, lack of habituation IS the neural mechanism behind the repetition advantage for neutral faces (particularly 3rd repetitions). Although that lack of habituation is occurring in more attention and executive function-related areas such as the frontal cortex and angular gyrus. As this is the first study to investigate the neural correlates of intersubject variability in fearful face repetition, we are only just beginning to cover these mechanisms, but the one thing that is clear is that the repetition advantage for fearful faces is subserved by a different network than the repetition advantage for neutral faces.

One brain area that was notably absent in the variability of threat processing in Studies I and II was the amygdala, which is heavily interconnected with those regions

showing a correlation of neural activation with Valence Bias in Study I (Porrino et al., 1981, Russchen et al., 1985, Vogt and Pandya, 1987, Carmichael and Price, 1995). Given that the amygdala has been shown to activate in response to fearful faces over other face types (Breiter et al., 1996, Morris et al., 1996), this was a surprising finding and suggests that the amygdala may respond relatively automatically to threat rather than tracking expectation and repetition (Morris et al., 1998, Whalen et al., 1998).

6.4   WEAKNESSES

Unfortunately we were unable to collect physiological measures during these fearful face processing tasks. Therefore, we can not make any claims about intersubject variability in physiological responses and how that variability might relate to variability in behavior. While we hypothesize that intersubject variability in fearful face behavior would correlate with physiological intersubject variability, this claim needs to be investigated directly using galvanic skin response (GSR), pupillometry, and/or heart rate.

The results presented in this thesis are limited to fearful faces only. While we hypothesize that similar effects would be seen for angry faces, as they are also threatening stimuli, this hypothesis needs to be directly tested. Additionally, it is unclear if our result of large intersubject variability for fearful face tasks would also be found for other threatening stimuli outside of faces. Therefore, we can only speculate

that this behavioral and neural variability would be found for all types of threatening stimuli – not just fearful faces.

6.5 FUTURE RESEARCH DIRECTIONS

In addition to including physiological measures and investigating angry faces, there are many other potential avenues for future research. We believe there are three particularly important avenues for future research that build upon the work presented in this thesis. First, a natural extension of this work is to move into populations of patients with anxiety and other mood disorders. It may be that the continuum of behavior we have categorized here represents only a section of the full continuum. The opportunity to measure behavioral variability on these fearful face processing tasks in patients would greatly advance our understanding of how the brain can go awry in mood disorders. Second, future research should consider how genotypes are related to behavioral variability. As outlined in the introduction, both 5HTTLPR and COMT genetic variants are associated with variability in threat processing, therefore, we hypothesize these genotypes may be related to behavioral variability to process fearful faces. Future work should consider not only genotype, but also the number and magnitude of life stress events for each subject. These measures combined create a more accurate picture of how genes and environment interact. Third, while state anxiety only correlated with the fearful face repetition advantage behavioral measure, we believe it is important to directly test how fluctuations in state anxiety affect behavioral

performance on all tasks and how that performance varies among healthy individuals.

A study including an intrasubject behavioral measure taken before and after a state

anxiety induction could yield great insights into resiliency and how individuals deal

with fluctuations in mood.

7 CONCLUDING REMARKS

In conclusion, this thesis has shown that not only is it possible to use behavioral variability to guide analyses but that by doing so, one can gain a broader view of how intersubject variability in behavior is manifested in personality traits and also in neural activation patterns.

Our results suggest the healthy population is much more variable in threat processing than originally thought. In fact, some of our subjects were actually slower to respond to fearful faces compared to neutral. Our results also suggest that personality and neural systems interact differently with threat in different contexts. Changes in expectation, repetition, and brief presentation all appear to tap into different aspects of personality and neural processing. This work strongly suggests that lumping healthy individuals together on threat processing tasks is not advisable or instructive.

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