# An Electrophysiological Examination of the Insular Cortex and Its Role in Anxiety

Melissa Wingate

A Dissertation Submitted to the Faculty of
The Chicago School of Professional Psychology
In Partial Fulfillment of the Requirements
For the Degree of Doctor of Psychology

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**Abstract**

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The focus of this study is the right anterior insula, which has been associated with interoception, or the awareness of physiological processes. In light of the James-Lange theory of emotion, individuals with greater activity in the right insula may attribute interoceptive information as indicative of something harmful. The study's hypothesis stated that subjects who self-reported anxiety will have an elevated baseline of interoceptive attention as measured by higher levels of right insular cortex activity. Archival EEG data used for this study was obtained from a local psychiatric clinic's database. Patients who had self-reported anxiety or were receiving psychiatric treatment for anxiety were selected. A Chi-Square Test did not support a significant relationship between self-reported anxiety and excess beta activity in the right insula. Future directions should include the establishment of excess activity in the insula using EEG/LORETA and measurement of state and trait anxiety as they relate to insular activity.

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## Chapter One: Nature of the Study

The study of brain structures and their functions serves to facilitate a more comprehensive understanding of psychological processes. This, in turn, can lead to a better sense of the etiology and progression of mental disorders and may subsequently result in more effective treatments. The interest of this paper is the brain structure known as the insular cortex and its role in interoception and the experience of anxiety. First described by Christian Riel in 1809, the insular cortex is a complex structure within the human brain that has undergone extensive research in recent years to better understand its many functions. In the last decade, the insular cortex has been implicated in many neurological and psychological processes. Because of the insula's complex and multi-modal nature, understanding it can appear to be an overwhelming task. A. D. Craig, a well-known researcher of the insula and its properties, has gone as far to call the insula an "enigma" for those studying it (Craig, 2010).

It is important to note that the insula, like the brain, is divided into two hemispheres: the right and the left. Due to the circuitry of the insula, the right hemisphere's insula is implicated in sympathetic processes, withdrawal (aversive) behavior, and processes that are generally arousing to the body. Examples of activation in the right anterior insula are pain, anger, disgust, or anticipatory anxiety (Craig, 2002). The left hemisphere insula is activated by positive and affiliative emotions, as well as parasympathetic (i.e., relaxation) processes, and left hemisphere activation has been

observed while subjects hear pleasant music, seeing or making a smile, and while mothers viewed photos of their children (Craig, 2009).

Interoception is defined as the sense of the physiological condition of the body. This includes: temperature, pain, itch, tickle, sensual touch, muscular and visceral sensations, vasomotor flush, hunger, thirst, air hunger, and others related to the body's state (Craig, 2009). The insular cortex, particularly the anterior insular cortex, is directly involved in interoception (Craig, 2009). An additional focus of insular cortex functioning has been its emotional processes, such as disgust, anger, anticipation, and emotional reactions to music. The focus of this study is the insula's role in one emotional process—anxiety. There is evidence that the right anterior insula plays a major role in subjective emotion (Craig, 2002). Paulus, Rogalsky, Simmons, Feinstein, and Stein (2003) found that anticipation of stimuli that were emotionally aversive in nature activated the right insular cortex. Additionally, the insular cortex has been shown to be active during anxiety-provoking tasks in individuals with anxiety disorders, such as OCD, simple phobia, PTSD, and GAD (Paulus & Stein, 2006).

Recently, researchers have been hypothesizing about a relationship between interoception and subsequent anxiety. This is not necessarily a new concept. In 1884, psychologist William James proposed that physiological processes informed the basis for our emotional states. Today this is known as the James-Lange theory. More recently, researchers have expanded the James-Lange theory by developing emotion-specific theories. For example, it has been hypothesized that people who are more sensitive to anxiety interpret bodily sensations as threatening, and thus the bodily sensations play a causal role in anxiety symptoms. This has been termed "anxiety sensitivity" and was

proposed by Reiss, Peterson, Gursky, and McNally in 1986. Anxiety sensitivity has received support from Critchley et al. (2004), who found that participants with elevated levels of anxiety were more aware of their interoceptive processes, in this case heartbeat. Given what we know about interoception, anxiety, and the insular cortex, it is not surprising that these structures and functions appear to be related. Insular cortex activity, especially anterior insular cortex activity, has been implicated in interoception. Right anterior insular cortex activity has been associated with sympathetic and arousing processes involved in interoception, such as heartbeat and anticipation. There is evidence that anxiety-provoking stimuli arouse right anterior insula activity within participants who have anxiety disorders. It has also been proposed and supported by research that increased attention to interoception is related to anxiety sensitivity, and thus increased activity in the right insular cortex (Clark, 1986; Critchley, 2006; James, 1994).

An important feature of these studies, however, is that these findings have been measured using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) scans. Although fMRI and PET have superior spatial resolution, no study has been conducted utilizing electroencephalography (EEG), which is characterized by superior temporal resolution, low equipment maintenance, and low cost. The present study's hypothesis is that subjects who report anxiety as a presenting problem at a psychiatric clinic will have an elevated baseline of interoceptive attention and thus trait anxiety levels, which corresponds to higher levels of right insular cortex activity in an EEG than those subjects who do not report anxiety.

If the hypothesized relationship between anxiety through increased attention to interoception and insular cortex functioning exists, it should be evident on many

measures. This study is valuable because it adds to the body of knowledge supporting the link between anxiety as mediated by interoception to insular cortex functioning by possibly providing evidence for an elevated baseline of right insular cortex activity, absent of anxiety-provoking stimuli.

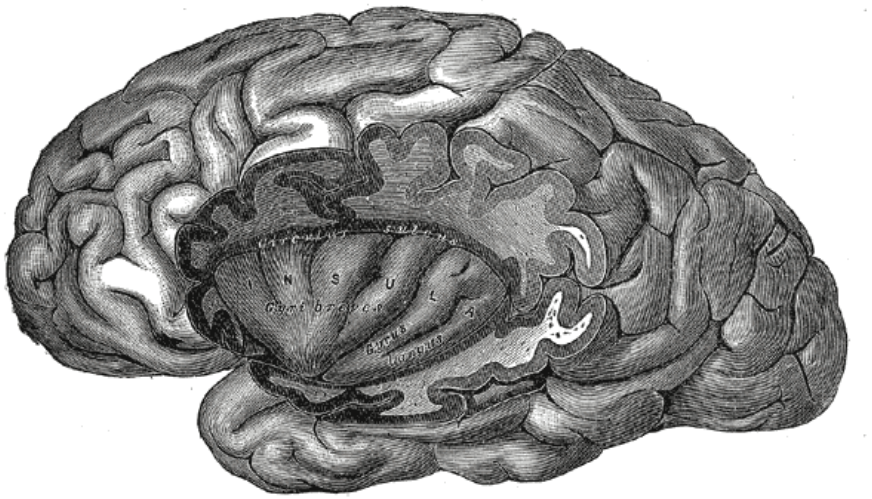
## Chapter Two: Literature Review

*The following information was obtained through a literature search using The Chicago School of Professional Psychology's library database. Searches consisted of the key phrases: insula, anxiety, and interoception. The results were examined and selected based on relevance, and the sources for these studies were then sought out and analyzed.*

### The Insular Cortex

**Location**. The insular cortex is located deep within the lateral fissure of the brain beneath the frontal, temporal, and parietal lobes. It can only be viewed by retraction of the frontal and temporal lobes. The surface of the insula consists of four to six gyri, whose appearance is similar to that of a fan. The insula is outlined by the circular sulcus, and the anterior and posterior regions are separated by the central insular sulcus, in which lies the main branch of the middle cerebral artery (Flynn, Benson, & Ardila, 1999). Beneath the insular cortex lie the basal nuclei, and the insula itself lies below opercula of the inferior frontal gyrus, inferior parietal lobe, and the superior temporal gyrus (Flynn et al., 1999). The illustration in Figure 1, below, reveals the insula's position within the left hemisphere.

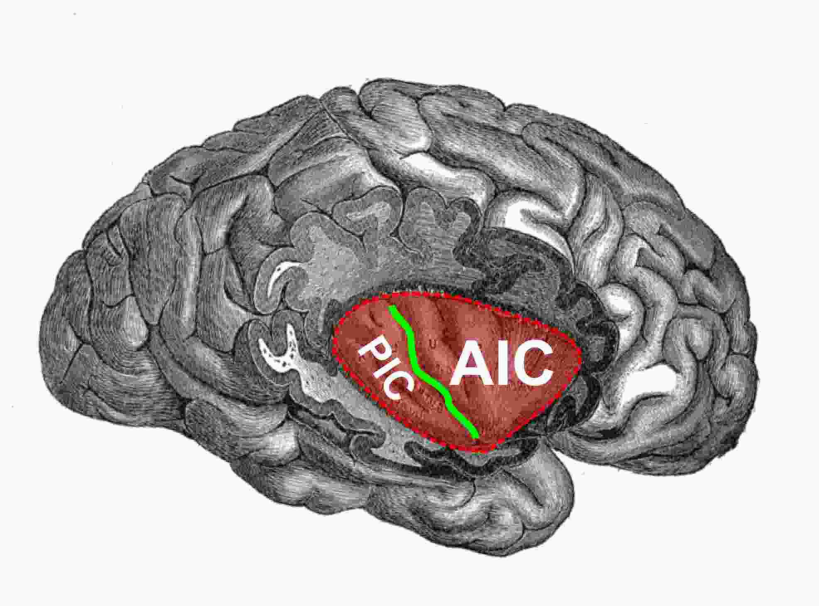
**Figure 1**



Consistent with the majority of structures within the brain, the insular cortices are bilateral, and are located within both the right and left hemispheres of the brain. Each insular cortex is divided into three anatomical areas: the anterior portion, the posterior portion, and the dividing portion. Flynn et al. (1999) identified more specific connections and subsequent functions with the insula based on those subdivisions. The first area is the anterior insula, which is "comprised of an agranular allocortical area" and is a part of the paralimbic belt (Flynn et al., 1999, p. 55). Connections of the anterior insula with limbic, sub-cortical, and brain stem areas highlight its role in "processing and integrating autonomic and visceral information." (p. 55). The second subdivision of the insular cortex is the posterior insula, which consists of an agranular isocortical area that is connected to somatomotor structures such as the thalamus and basal ganglia. These

connections underscore posterior insula's role in somatosensory, vestibular, and motor integration. The third subdivision of the insula is a dysgranular center between the posterior and anterior regions. The function of this area is to allow for communication between the anterior and posterior insula, predominantly from anterior to posterior regions. The divisions within the insula are pictured below in Figure 2, with the AIC representing the anterior insula, the PIC representing the posterior insula, and the green line indicating the center of the insula.

**Figure 2**



**Insular cortex circuitry.** The wide range of functions of the insula is likely based on the many connections it has with other brain structures. Augustine (1996) outlines these connections, grouping them into five major areas: cerebral cortex, basal ganglia, amygdaloid body, other limbic areas, and dorsal thalamus. Within the cerebral cortex, the insula is connected to and receives information from the frontal lobe, parietal lobe, temporal lobe, and cingulate gyrus. The limbic areas involved in the circuitry with the insular cortex include the entorhinal cortex, olfactory bulb, and periamgdaloid cortex. The connections with the amygdaloid body and dorsal thalamus are simpler and correspond to parts of each structure. An example would be the connections of the insular cortex with the medial and anterior parts of the amygdaloid body. Finally, Augustine reported no recent findings for the basal nuclei and the insular cortex. Flynn et al. (1999) also explored the connections of the insular cortex. These authors found that the ventral anterior insula has "prominent connections with the orbitofrontal and frontal opercular cortex," as well as with the olfactory and entorhinal cortices. The posterior dorsal insula was found to have connections with the supplementary motor area within the frontal lobe, the primary and secondary somatosensory cortex, the primary and secondary auditory cortex, and the inferior parietal lobe. The authors also noted that all areas of the insular cortex have connections with the temporal lobe and regions of the cingulate cortex. Additionally, almost all afferent and efferent connections project to the same architectonic tissue. For example, granular areas of the insula project to or arise from areas of granular cortex. Flynn et al. (1999), like Augustine (1996), also categorized connections of the insula into major groups: the basal ganglia, thalamus,

amygdala, limbic areas, and the brainstem. Those connections will be briefly explored below.

The insula has been found to have connections with several parts of the basal ganglia. Efferent projections terminate in the lentiform nucleus, the ventral putamen, and the tail of the caudate (Flynn, 1999). Additional projections are formed with the striatum within two separate pathways; the first pathway stems from the agranular insula to the ventral striatum. The second pathway arises from the granular insula to the dorsolateral striatum. The first pathway, the agranular-ventral striatum pathway, represents a limbic circuit that integrates feeding behaviors with rewards and memory, while the granular-dorsolateral striatum pathway is involved in somatosensorimotor integration. Connections from the dorsal agranular insula to the lateral nucleus accumbens and the ventral striatum appear to overlap parallel projections to these areas from the thalamus and basal nucleus of the amygdala. This circuit may influence the pathway involved in limbic-motor integration. The insular cortices have many connections with the thalamus as well. Afferent fibers to the insular cortices project from the following areas of the thalamus: the centromedial nucleus, the ventral anterior nucleus, the parvocellular region of the ventral posterior medial nucleus, the ventral posterior inferior nucleus, and the ventral posterior lateral nucleus. The posterior nuclei and the suprageniculate nucleus project throughout the insular cortex. The anterior insular receives projections from the ventral posterior medial nucleus and the centromedial nucleus, while the posterior insula receives input from the medial geniculate nucleus. The anterior insula is the only region that receives projections from the mediodorsal nucleus of the thalamus.

The insula has been found to send fibers to the amygdala as well (Augustine, 1996; Etkin & Wagner, 2010; Flynn et al., 1999). Interestingly, both afferent and efferent connections between the insula and the amygdala are greatest in the anterior cortex of the insula. In terms of connectivity within the limbic system, the insula projects to the anterior hippocampus, the nucleus of the stria terminalis, the limbic ventral striatum, and the lateral nucleus accumbens. In turn, the insula receives projections from the periamygdaloid cortex, the olfactory tubercle and the olfactory bulb. Reciprocal connections exist between the posterior hypothalamus and the tuberomammillary nucleus as well.

Finally, evidence suggests that there are projections from the insular cortices to the brainstem and reticular autonomic nuclei. Midbrain structures receiving projections from the insula include the dorsal and superior regions of the central raphe, the periaqueductal gray, and the ventral tegmental area. The locus ceruleus and parabrachial nucleus also receive fibers from the insular cortices. Vestibular information projecting to the posterior insula is believed to be projected from the vestibular nuclei through the thalamus. Flynn et al. (1999) noted that the insula-brainstem interaction is considerably more complicated than is presently recognized.

**Function.** Despite the multitude of proposed roles of the insula, there are functions that have been well supported by research repeatedly. Augustine's 1996 review of the insular cortex supported these findings as well, citing visceral, somatosensory, sensory association area, limbic integration, visceral motor area, motor, vestibular processes, language, and other as functions of the insular cortex.

Flynn et al.'s (1999) article stated that the insula is involved in cardiovascular, gastrointestinal, vestibular, olfactory, gustatory, visual, auditory, somatosensory, and motor modulation. Additionally, Flynn et al. found that the insular cortex plays a role in pain perception, stress-induced immunosuppression, mood stability, sleep, and language. Paulus and Stein (2006) indicated that neuroimaging studies have linked insular activity to modulation of three major processes. The first is affective processing. An example of this may be processing facial expression of disgust. The second process is cognitive and affective processes during learning, i.e., perceptual awareness of threat. Finally, the third process is aversive interoceptive processing, an example of which is coding of pain intensity. These findings indicate the insular cortex "is important for linking emotions to cognitive processes and behavioral responses" (Paulus & Stein, 2006, p. 2).

Craig's (2009) review listed the following roles of the anterior insular cortex: cognitive choices and intentions, music, time perception, attention, awareness of sensations and movements, visual and auditory percepts, the visual image of the self, the reliability of sensory images, subjective expectations, and the trustworthiness of others (p. 65).

Ibanez, Gleichgerrcht, and Manes (2010) reviewed insular damage in humans due to tumor lesions, vascular lesions, traumatic brain injury and subsequent disturbances in functioning to better understand the role of the insula. They found the insula to be involved in autonomic functions, such as cardiac regulation, taste and gustatory perception, auditory processing, somatosensory systems and pain, neglect, emotion, mood and willed action, language, and interoception. (See Appendix A for a short-hand reference to insular cortex functioning based on the reviews described in this section.)

The functions of the insular cortices follow the structure's anatomical divisions. On the most basic and gross level, the insula within the right hemisphere involves sympathetic activity and arousal processes, as well as withdrawal behavior and survival emotions. The insular cortex within the left hemisphere is involved with parasympathetic activity and restful processes, as well as approach behavior and affiliative emotions (Craig, 2009). Within each individual insular cortical region, the posterior and anterior areas differentiate both anatomically and functionally (see The Insular Cortex—Location section for a description of the anatomical differences of the anterior and posterior insula). The anterior portion of the insula is thought to be specifically associated with several processes, including attention, intentions, time perception, subjective expectations, and awareness of sensations and movements of the body (Craig, 2009). The posterior portion of the insular cortex is involved with the integration of extrapersonal sensory stimuli and serves the function of a vestibular and supplementary motor area (Flynn et al., 1999).

Specific to subjective emotions, functional imaging studies have found the right anterior insular cortex to be involved in multiple processes. The right anterior insula has been found to play a role in anger, disgust, sexual arousal, trustworthiness, panic, the anticipation of anxiety and pain, interoception, and emotional reactions to music (Craig, 2002). Craig's findings are also consistent with Damasio's somatic marker hypothesis, which states that the right anterior insula is essential in the interoceptive understanding and is subsequently involved in the motivation to make decisions based on information that affects survival and quality of life (Damasio, 1993). Singer et al. (2009) hypothesized that the insular cortex integrates external information with internal

physiological information. This integration is expressed as a feeling state that directs subsequent social and motivational behavior that follows bodily homeostasis. Because the interest of this study is the insula and interoception, this function will be more closely examined and explored below.

Craig (2002) has identified and described the circuitry involved with interoception and illustrates the insular cortex's role in this circuit. There are two main pathways that bring important homeostatic information to the brain. The first is the lamina I spinothalamocortical pathway. This pathway is provided with afferent sympathetic information. The second pathway connects via the nucleus of the solitary tract, or NTS, and is provided with parasympathetic information. Incoming information is integrated in the parabrachial nucleus, which then projects to the insular cortex through the ventromedial thalamic nucleus.

In humans, the anterior insula is provided with re-representations of these cortical images. The parasympathetic information is re-represented in the left hemisphere of the insula, and the sympathetic information is re-represented in the right hemisphere. "These re-representations provide the foundation for a subjective evaluation of interoceptive state, which is forwarded to the orbitofrontal cortex, where hedonic valence is represented in mammals" (Craig, 2002, p. 659). Put simply, the sympathetic interoceptive information is projected to the right insular cortex and emotional decisions are then made in light of this information.

**Insular Cortex and Interoception**

According to Craig, in 1890, psychologist William James was one of the first to "regard feelings from our bodies as the basis for self-awareness and emotion" (2002, p.

655). The notion that our physiological perceptions serve as the foundation for our emotional states is still supported today and is commonly known as the James-Lange theory of emotion (James, 1994). Evidence that the right anterior insular cortex is responsible for the subjective evaluation of how a person feels physiologically, and subsequently emotionally, has been growing in the past decade (Craig, 2002; Craig, 2009; Critchley et al., 2004; Paulus & Stein, 2006; Paulus & Stein, 2010).

As previously discussed, the insula has been implicated in interoceptive processes, and this function will be the focus of the paper. Interoception is defined by A. D. Craig as "the sense of the physiological condition of the body" and includes "temperature, pain, itch, tickle, sensual touch, muscular and visceral sensations, vasomotor flush, hunger, thirst, air hunger, and others related to the body's state" (2002, p. 655). A. D. Craig is supported in the hypothesis that interoception is a function of the insular cortex by several studies.

For example, Davis et al. (2004) conducted a study to examine the relationship between the insula and the sensation of heat. This experiment exposed ten healthy subjects to cold and hot stimuli on the right hand while the subjects rated their perception of heat or cold, while concurrently measuring their brain responses via fMRI. These authors found that only the right anterior insula was activated in every subject when they experienced paradoxical heat, defined as the sensation of heat when skin was either at or below neutral temperature, and that region of the brain was the right anterior insula. This finding was considered supportive of the right insula's role in interoception, in this case thermal awareness.

Evans et al. (2001) conducted a study exploring the brain regions associated with the experience of air hunger. Six healthy men and women were mechanically ventilated and then subjected to moderate to severe air hunger while the subjects were having their cerebral activity measured via fMRI. Limbic and paralimbic loci activated during air hunger included the anterior insula, the anterior cingulate, amygdala, thalamus, and other areas. The authors stated that the consistency of anterior insular activation across the subjects in this study and across previously published studies examining air hunger suggests the anterior insula is essential to this subset of interoception, and works in concert with a larger neural network. Last, dyspnea, or shortness of breath, was noted to be a frequent symptom of anxiety and panic disorder, further tying together interoception, the insula, and anxiety processes.

A study by Phillips et al. (2003) demonstrated yet another type of interoception that featured right insula activity, esophageal stimulation. Eight healthy subjects underwent non-painful esophageal stimulation while viewing either neutral or fearful facial expressions. Using fMRI, neural responses were measured, and found that right insular activity was significantly greater during esophageal stimulation while viewing fearful faces than while viewing neutral faces. This further indicated that the right anterior insula plays "an important role in processing and modulating visceral sensation" (p. 681).

Paulus and Stein (2006) hypothesized that there are two essential aspects of interoception. The first is that "interoceptive sensations are often associated with intense affective and motivational components," i.e., the sensation of excessive heat is attributed to the held object and is associated with a strong withdrawal action. Second, "the

evaluative component of the signal is highly dependent on the homeostatic state of the individual," i.e., the same amount of heat or cold can be either rewarding or punishing depending on the context of the individual's body temperature (p. 383). Taken together, these indicate the insula is strategically placed to both receive information about appetitive and aversive stimuli and the relative value of the environment and then integrate this information to determine what effect the stimuli could have on the body state. This, in turn, could inform the individual how to respond to these signals and behave.

**Interoception and Its Role in Anxiety**

As previously mentioned, recent findings have illustrated that insular function plays a key role in "the experience of emotion derived from information about bodily states" (Menon & Uddin, 2010). Critchley's 2004 theory of anxiety illustrated this point and hypothesized that anxiety is caused by increased attention to autonomic bodily processes. These autonomic bodily processes could be as simple as a rapidly beating heart. A person with sensitivity towards anxiety may notice this rapid heartbeat and, instead of being attributed to other causes, it is interpreted as a sign of something negative in nature, which is then manifested as anxiety. A study by Critchley, Mathias, and Dolan in 2001 found that subjects suffering from a condition that disrupts autonomic responses had reduced activity in the right insula during stressor tasks, and these subjects additionally reported difficulty feeling emotions or responding emotionally. This finding highlights the insula's role in emotions stemming from bodily information.

Critchley, Wiens, Rotshtein, Ohman, and Dolan (2004) conducted a study to better understand the neural systems involved in interoceptive awareness. They

hypothesized that "individual differences in intensity of emotional experience reflect variation in sensitivity to internal body responses" (p. 189). In order to measure this, Critchley and his colleagues used fMRI to detect regional brain activity in seventeen participants engaged in the interoceptive task of judging the timing of their heartbeats. These patients also took the Hamilton anxiety scale and the Beck depression inventory to assess for the presence of anxious and depressive symptoms. What the authors found was an increase of activity in the insular cortex among other brain areas during the heartbeat detection task. Additionally, right anterior insular/opercular cortex activity correlated positively (Pearson $R = 0.62$) with participants' ability to accurately judge their heartbeats, which demonstrates a positive relationship between interoception and right anterior insular cortex activity.

Moreover, anxiety scores correlated positively with interoceptive accuracy during fMRI (Pearson $R = 0.64$, $P < 0.05$), which illustrates the relationship between interoception and anxiety within these participants. Notably, all participants scored below the diagnostic threshold; thus, although anxiety correlated positively with interoception, the participants' symptoms did not reach the level of an anxiety disorder. This study demonstrates the relationship between interoceptive awareness and emotional feeling states is reinforced by the observation that "subjective anxiety symptoms, correlated with relative interoceptive accuracy, also correlated with activity in the right anterior insula/opercular cortex during heartbeat detection trials" (Critchley et al., 2004, p. 191). This further supports that activity within the right anterior insula reflects interceptive sensitivity and emotional states.

Paulus and Stein (2006) state that persons with "anxiety sensitivity" have a tendency to view interoceptive sensations as threatening or perilous (Reiss et al., 1986). They propose altered interoception is the primary process underlying the initiation of an anxiety state and that the affective, cognitive and behavioral components are a consequence of this altered prediction signal. It should be noted that "anxiety sensitivity" is not a formal diagnosis. However, in the case of the participants in this study, as well as in the case of people with anxiety sensitivity, anxiety symptoms are likely causing quality of life difficulties and merit attention.

Menon and Uddin (2010) have postulated that increased anxiety may be the result of the insular cortex misattributing emotional salience to mundane events. Paulus and Stein (2006) hypothesized that "this [anxiety sensitivity] tendency is mediated through a neural circuit that features a central role for the anterior insula, and that persons with high anxiety sensitivity perceive a heightened interoceptive prediction signal" (p. 384). Indeed, there is evidence of enhanced right insular functioning in patients with anxiety disorders, which will be discussed below. Now that the relationship between the insula and anxiety has been supported as a product of interoception and sensitivity/misattribution to physiological stimuli, research supporting insular activity during anxiety can be explored.

**The Insula and Anxiety**

Functional imaging studies have suggested that several areas of the brain are involved with anxiety, which tend to vary depending on the type of anxiety disorder being studied. Generally speaking, consistent findings implicate the amygdala, the cingulate gyrus, and the prefrontal and insular cortices, among other areas. For example,

Lorberbaum et al. (2004) demonstrated with BOLD-fMRI that when compared to control subjects, social phobia clients had increased blood flow to the insular cortices, striatum, amygdala, and temporal pole, regions that are involved in automatic emotional processing. Areas important in cognitive processing, such as the dorsal anterior cingulate and prefrontal cortex, featured less cortical activity in those participants with social phobia than the controls, which suggests a greater reliance on emotional processing than cognitive processing.

Hoehn-Saric et al. (2004) explored the effects of citalopram on subjects with generalized anxiety disorder, or GAD. In this experiment, auditory statements were read to subjects with GAD before and after taking citalopram, and medication used to treat anxiety, while brain activity was measured using fMRI. Seven weeks of treatment with citalopram reduced the subject's self-reported anxiety levels as well as fMRI responses to worry statements in the prefrontal cortex, the striatum, the insula, and paralimbic regions. Further support for insular involvement in anxiety comes from Malizia, Cunningham, Bell, Liddle, Jones, and Nutt (1998) who found that patients with panic disorder who were not being pharmacologically treated had a reduced number of benzodiazepine binding sites throughout the brain, and in particular within the right insula and right orbitofrontal cortex. Mataix-Cols et al. (2004) studied 16 patients with obsessive-compulsive disorder with fMRI while these subjects viewed obsessive-compulsive related images and imagined scenarios related to these images. Anterior insular activity was found to be associated with washing symptoms of obsessive-compulsive disorder. Mataix-Cols et al. postulated that washing-related anxiety is associated with the insula due to the insula's involvement with processing disgust. Finally, Rauch et al. (1997)

studied 23 patients with obsessive-compulsive disorder, simple phobia, or post-traumatic stress disorder. Cerebral blood flow was measured with a PET scan during symptom provocation paradigms. The results revealed activation within the right inferior frontal cortex, the right posterior medial orbitofrontal cortex, bilateral insular cortices, bilateral lenticulate nuclei, and bilateral brain stem foci, suggesting that these areas mediate symptoms across different anxiety disorders.

Stein et al. (2007) performed a study that demonstrated a relationship between trait anxiety and activity within the amygdala and insula. Thirty-two college students were selected to participate: 16 students who scored in the upper 15$^{th}$ percentile on a measure of trait anxiety, and 16 who scored within the normative range. These subjects participated in fMRI while viewing an emotion face assessment task "that has been shown to reliably engage the amygdala and other associated limbic structures" p. (318). They found that subjects who met criteria for trait anxiety had significantly greater bilateral insula and amygdala activation while viewing emotional faces than did the anxiety-normative control group. Furthermore, the magnitude of activation in the amygdala and insular cortices "correlated moderately with several measures of anxiety proneness, such as anxiety sensitivity and neuroticism" (p. 322), which demonstrates a positive relationship between subclinical anxiety traits with activity in these limbic areas. These authors went on to postulate that interoceptive awareness and subthreshold anxiety, dubbed "anxiety sensitivity," shared many features, and that subjects with anxiety sensitivity would be prone to anxiety disorders. They stated:

> We hope that these observations will lead to more careful scrutiny of insular activity in future studies of psychopathology so that the role of this structure in

emotion processing and its functional relationship to other elements of anxiety related circuitry can be more fully elaborated. (p. 323)

Additional support for both the insular cortex and the amygdala playing a role in anxiety came from Paulus et al. (2005). This study examined 15 healthy (nonanxious), college-aged volunteers who underwent functional fMRI while viewing an emotion face assessment task that had been shown to elicit amygdala activation. Subjects were given either a placebo or a 0.25 mg or 1.0 mg dose of lorazepam one hour before undergoing fMRI. These investigators found that lorazepam significantly attenuated the BOLD-fMRI signal in a dose-dependent manner within the bilateral amygdala and bilateral insular cortices. Paulus et al. (2005) reported that this was the first study to provide evidence through neuroimaging of a "dose-dependent change induced by an established therapeutic agent in brain regions known to be critical for the mediation of anxiety" (p. 282). Paulus and Stein (2006) argued that the anatomical connections between the insular cortex and limbic and executive functioning areas place this brain structure "at the center of altered homeostatic physiological sensations and increased cognitive engagement, consistent with the view that anxiety consists of two key components: sympathetic hyperarousal and worry" (p. 384). Taken together, these findings indicate strong links between increased activity within the insula, perception of one's own bodily state, and the experience of anxious emotion.

**Anxiety Disorders**

Anxiety disorders are a serious and prevalent class of mental illness, affecting about 40 million adults in America in a given year (Kessler et al., 2005). The Center for Disease Control and Prevention (CDC) reports that anxiety disorders are the most

common class of mental disorders present in the general population. The CDC also reports "the lifetime prevalence of any anxiety disorder is over 15%, while the 12-month prevalence is more than 10%" (CDC, 2011). The estimated annual cost of anxiety disorders within the United States was approximately 42.3 billion dollars in the 1990s, the majority of which was due to non-psychiatric medical treatment costs (CDC, 2011). These statistics are significant and merit the attention of psychological research to better understand anxiety disorders, their biological underpinnings, and their possible treatments. The aim of this study is to help provide insight into these questions.

*The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision* (2000), lists 13 different anxiety disorders, and each disorder has different symptoms and features. Despite the many types of anxiety disorders, the National Institute of Mental Health classifies anxiety disorders in general as at least six months of excessive, irrational fear and dread. Authors Denny, Silvers, and Ochsner (2009) define anxiety as agitation or arousal caused by the perception of a real or imagined threat (Amstadter as quoted in Denny et al., 2009). They go on to describe anxiety disorders as chronically activated anxiety states by either specific or general stimuli. Persons who suffer from chronic anxiety may suffer from an "inability to accurately appraise what is threatening, an inability to reappraise threat, or both" (Denny et al., 2009, p. 76).

Etkin and Wager's 2010 summary of the literature of anxiety disorders indicates the insular cortex and the amygdala have been consistently responsive to negative affective states in humans, and are commonly co-activated anxiety circuits. However, they stress that a broad set of systems are relevant for the range of negative affects

involved in human anxiety, and this emotion cannot be boiled down to only one or two areas of involvement.

More specifically, these authors propose that there is a core limbic system involved in negative emotional reactivity, which is likely an important part of anxiety. This is comprised of the amygdala, periaqueductal gray, and insula. However, the authors note that other cortical and subcortical networks likely interact with this main core circuit and alter behavioral and experimental aspects of negative emotions. Two main networks have been found to contribute to fear and anxiety: the executive working memory network and the affective appraisal network. The first network, the executive working memory network, is engaged when the mind is maintaining and manipulating information. The affective appraisal network involves the ventromedial prefrontal cortex, the hippocampus, and the posterior cingulate cortex. This network is involved with monitoring and analyzing the sensory environment. Together, these networks are "thought to work in concert to provide context-based control over the generation and regulation of negative emotion" (p. 194).

**Objective Measures of Brain Activity**

As previously stated, neuroimaging techniques study brain activity by tracking blood flow, oxygenation, or electrical activity. The information these techniques yield gives the field of psychology a more comprehensive understanding of brain processes and, consequently, mental health and illness. The three most common functioning neuroimaging measures this paper will focus on are positron emission tomography (PET) scans, functional magnetic resonance imaging (fMRI), and electroencephalography (EEG).

Positron emission tomography was developed prior to fMRI as a tool to map cerebral blood flow. A radioactive tracer is injected into the blood stream and the PET scan measures the decay of this tracer within the brain. Radioactive decay creates positrons, which are quickly destroyed during a reaction to nearby electrons. This process creates two protons at the site of destruction that travel in exactly opposite directions (Kable, 2011). The location of radioactive decay can thus be established from the aforementioned measurements, with differences in cerebral blood flow.

The advantages of PET scans are exact measure of blood flow as compared to the approximation provided by fMRI, which allows for better comparisons across subjects, sessions, and brain regions. Additionally, PET scans are also able to measure quantities other than blood flow, such as cerebral metabolism (Zald et al., 2004). Drawbacks to PET are the involvement of radioactive substances, the cost, lower spatial and temporal resolution than fMRI and lower temporal resolution to the EEG.

Functional magnetic resonance imaging is the most widely used method in cognitive neuroscience today (Kable, 2011). fMRI involves measurement with an MRI scanner sensitive to oxygenation levels of the blood, also known as T2 contrast (Kable, 2011). Deoxygenated hemoglobin has magnetic properties, and oxygenated hemoglobin does not. "Because local increases in neural activity are associated with increases in blood oxygenation, local increases in neuronal activity are associated with increases in the fMRI signal" (Kable, 2011, p. 67). This signal is referred to as the blood oxygenation level dependent, or BOLD. There are several advantages and disadvantages to the BOLD fMRI method. In terms of advantages, fMRI is able to provide simultaneous measurement of neural activity in almost the entire brain and has high spatial resolution

(Kable, 2011; Pascual-Marqui, 2002). Disadvantages include relatively slower temporal resolution when compared to EEG, the requirement of an expensive MRI scanner and the necessity for no movement while being scanned.

Considering the size and weight of the human brain, it consumes a large and disproportionate amount of energy in order to function. In fact, the brain consistently consumes as much oxygen as muscles do when in active contraction, 24 hours a day, and utilizes about 60% of blood glucose (Thatcher, Biver, & North, 2009). This is used to produce electricity for neurons to communicate with one another (Thatcher et al., 2009). This electrical activity can be recorded through electroencephalography, or EEG. "Whereas other functional neuroimaging techniques such as positron emission tomography and functional magnetic resonance imaging are based on metabolic transactions (e.g., blood flow, oxygenation), EEG allows us to eavesdrop on neural communication directly" (Kaiser, 2005, p. 99). Electroencephalography was first introduced by Hans Berger, a German psychiatrist in the early 1900s. Between 1929 and 1938, Hans Berger published 14 reports on human EEG and its relation to cognition and neurological disturbances (Millett, 2001). Much of what is known today about EEG was first documented by him.

More specifically, EEG records electrical activity from the cerebral cortex. Neurons produce electrical activity for 50–200 ms during post-synaptic potentials, or PSPs, which likely account for the electrical activity being picked up by the EEG (Rowan & Tolunsky, 2003). The combination of inhibitory and excitatory post-synaptic potentials "induces currents that flow within and around the neuron with a potential field sufficient to be recorded on the scalp" (Rowan & Tolunsky, 2003, p. 1). Input from each

electrode placed on the scalp can be represented as absolute power, relative power, coherence or symmetry (Hughes & John, 1999). Absolute power is represented by millivolts squared in each band, while relative power represents the percentage of total power in each channel. Coherence is defined as a measure of synchronization of activity between two channels. Finally, symmetry is defined as the ratio of power in each band between a symmetrical pair of electrodes (Hughes & John, 1999).

EEG activity comprises rhythms that are categorized by their frequency in cycles per second, or hertz (Hz) (Hughes, 1994). Around 98% of brainwave activity in humans falls between 0 and 30 hertz (Thatcher, 1998). There are four subcategories of frequency range, labeled delta, theta, alpha, and beta. The frequency range boundaries of each category are generally agreed upon, but there are some minor variations depending on the researcher. According to Thatcher et al. (2009), the delta category consists of frequencies less than 4 Hz, theta from 4 to 7.5 Hz, alpha between 8 and 12 Hz, beta from 12.5–30 Hz, and finally gamma consists of 30–100 Hz during waking in normal functioning people. Each of these categories corresponds to a different level of arousal. Delta is associated with deep sleep, theta with daydreaming and drowsiness, alpha with a relaxed state of attention, and beta with focused attention, concentration and alertness (Alhambra, Fowler, & Alhambra, 1995), while gamma waves are hypothesized to be associated with learning, working memory, and higher-order cognitive processes (Lutz, Greischar, Rawlings, Ricard, & Davidson, 2004). Isotani et al. (2001) indicated that beta frequencies are associated with increased vigilance, information processing and activation/excitation. Because this study is interested in heightened attention to bodily

processes, a function of the insula, it was most appropriate to select the beta frequency to examine further, as excess beta activity would likely indicate excess attention processes.

Additional support for selecting the beta frequency is that it has been associated with anxiety (Kiloh as cited in Michael, Krishnaswamy, & Mohamed, 2005). Support for the link between anxiety and the beta frequency has been demonstrated by several authors. Gordeev (2006) studied subjects with both high and low trait anxiety as measured by the state-trait anxiety inventory, and found that beta oscillation power was higher in anxiety patients within the bilateral parietal areas and occipital area of the right hemisphere. Jokic-Begic and Begic (2003) studied veterans with and without post-traumatic stress disorder, all of whom were not being treated pharmacologically. What these authors found was increased beta activity in patients with post-traumatic stress disorder than in the controls, particularly within the frontal and central regions of the brain. Sachs, Anderer, Dantendorfer, and Saletu (2003) studied the electrophysiology of individuals with diagnosed social phobia and compared them to normal controls. The participants with social phobia exhibited increased beta activity, indicating hyperarousal "as a pathogenetic factor for social anxiety" (p. 245). Finally, Gabrielli et al. (1982) hypothesized a link between alcoholism and the anxiety and discomfort associated with fast activity in the brain (i.e., beta frequency), postulating that individuals with alcoholism frequently have fast brain activity as a baseline, which likely causes tension and anxiety within these individuals; thus, because alcohol is a depressant drug, alcoholics may use alcohol in order to relieve the uncomfortable feelings associated with fast brain activity. In light of the data linking the beta frequency to both attention and anxiety, this study will specifically focus on excess beta activity.

Since its development in the early 1900s, the analysis of EEG has evolved. Quantitative EEG (qEEG) is a method that involves computerized and statistical extraction of information from the brain's electrical activity that is not apparent when visually examining EEG results, as Berger would have done (Hughes & John, 1999). qEEG involves multichannel recording, where EEG is visually edited and a sample of artifact-free data, typically of one or two minutes duration, is analyzed using fast fourier transform, or FFT. FFT quantifies the power at each frequency of the EEG averaged across the entire sample, and this has been found to be highly reproducible (Hughes & John, 1999).

Because EEG patterns of activity can vary significantly between healthy adults of similar age, there is no narrowly defined "normal" EEG wave pattern (Hughes & John, 1999). Despite this, there are ways to determine if a person's EEG wave pattern is abnormal, primarily through the use of normative databases. These databases comprise a large number EEGs obtained from demographically diverse and neuropsychiatrically "normal" subjects, where normalcy is typically defined as the absence of head injury, birth defect or complication, or cerebral disease of any kind. The results of these normative databases create a Gaussian distribution of EEG results in bell curve form. Accordingly, abnormalities in EEGs are more clearly defined as statistical outliers at ± 2 to ± 3 standard deviations from the mean, and will typically indicate abnormal brain functioning (Hughes & John, 1999). In this study, I hope to demonstrate a link between interoception and anxiety to insular cortex activity by using Robert Thatcher's LORETA normative EEG database to uncover statistical abnormalities (specifically, hyperactivity

at or greater than 2 standard deviations from the norm in order to provide statistical significance).

A major advantage of EEG is its temporal resolution, which is < 1 ms (Kable, 2011). This high degree of temporal resolution allows for more immediate measurement of neural activity, such as synchronized or oscillatory activity. It is also less expensive than fMRI, less physically constraining, and is more compact and portable. As summarized by Hughes and John (1999) "…EEG methods afford the psychiatric practitioner a set of noninvasive tools that are capable of quantitatively assessing resting and evoked activity of the brain with sensitivity and temporal resolution superior to those of any other imaging method" (p. 190).

One significant limitation of the EEG technique is poor spatial localization in comparison to fMRI or PET scan. This is referred to as the "inverse problem." Because EEG measures electrical activity at the scalp, the assessment of deeper brain areas is difficult. Therefore, an inverse solution must be calculated; however, this is only possible by making certain assumptions through mathematical smoothness techniques. Low resolution electromagnetic tomography is a procedure that does just that and has been found to yield accurate results (Pascual-Marqui, 1994). Developed in the early 1990s, the creators of LORETA aimed to solve the inverse problem and allow EEG to calculate the deeper brain structures' contribution to electrical activity measured at the scalp. LORETA will be explored in greater detail within the methods section.

**Hypothesis**

This study's hypothesis is the following: Subjects who self-report anxiety as a presenting problem would likely have an elevated baseline of interoceptive attention and

thus anxiety levels, as measured by excess beta activity, which would correspond to higher levels of right insular cortex activity than those subjects who did not report anxiety. This will be measured by LORETA and EEG to determine baseline resting state insula activity and its relationship to reported clinically relevant anxiety. It is hypothesized that subjects reporting anxiety would have increased activity in the insular cortex, even in a resting state (no direct anxiety-provoking stimulus is presented to the subject) as a measure of trait anxiety. No studies were found by the researcher that assessed resting state insular cortex activity using a method of high temporal resolution, such as EEG, and its relationship to self-reported anxiety. All previous studies were conducted using PET scans of fMRI and provided an anxiety or affect-provoking stimulus.

## Chapter 3: Methods

### Participants

This study utilized archival data from the Advanced Neurodiagnostics clinic in Wheeling, Illinois, in order to test the hypothesis of this study. Archival data consisted of qEEG records and a student-constructed database organizing the results of self-reports completed by subjects regarding demographic and mental health information, including self-report of presenting problem or reason for treatment (i.e., anxiety).

### Patient Group

The total number of cases available within the database consisted of 96 clients of the clinic who were given EEGs in 2009. Data available consisted of age, gender, handedness, current medications, reason for referral, neurological disorders or conditions (e.g., encephalopathy, epilepsy, sleep apnea), and LORETA data. Fifty-one subjects were male and 45 were female, and subject age ranged from 10 to 76 years of age. Among the 96 cases, 68% were on at least one medication for a psychological or neurological condition, and 32% were on greater than two medications to treat psychological or neurological conditions. Neurological conditions included encephalopathy (49%), traumatic brain injury (21%), seizure disorder (19%), concussion (22%), memory loss (7%), attention deficit disorder (3%), headaches (2%), and sleep apnea (1%). This study examined data including reason for referral and LORETA data. Screening criteria applied to all 96 cases within the database and included selecting any cases that reported anxiety to be a presenting problem for further study. Additionally, cases where LORETA data within the right and left insula exceeded two standard deviations from the mean within the beta frequency were selected. Twenty-three cases

(eleven females and nine males) met criteria for excess beta frequency activity, with eight of these subjects also reporting anxiety. Seven cases had findings isolated to the left insula (two anxiety), six patients in the right insula (one anxiety), and ten of these cases in bilateral insular cortices (five anxiety). Of the 23 cases, 74% were taking at least one medication to treat psychological or neurological conditions. Neurological conditions within the excess beta activity group included encephalopathy (11%), traumatic brain injury (3%), seizure disorder (5%), concussion (5%), memory loss (5%), attention deficit (1%), and headaches (1%).

**Measures**

**Quantitative electroencephalography (qEEG).** As discussed in the literature review, qEEG is a record of the electrical activity from the cerebral cortex that has undergone computerized and mathematical analysis to extract functional information that is not easily perceptible by a visual examination of EEG. An EEG is measured through electrodes placed on the scalp that amplify the electrical activity by 1,000,000 times, which converts the PSPs into representations that can be recorded and interpreted. qEEG has been found to be a reliable and valid measure of brain function (Duffy, 1994; Hughes & John, 1999; Thatcher et al., 2004). More detailed information about qEEG can be found in the literature review section of this paper.

**Data Utilized**

**Psychological symptoms.** Subjects who seek psychological services from the Advanced Neurodiagnostics clinic are required to fill out a form prior to treatment to gather pertinent information about the patient, including the reason for referral. Any subject who self-reported anxiety on this form as a reason for referral was included in the

"presence of anxiety" group of this study. Additionally, any subjects that were being seen by the psychiatrist at the clinic primarily to treat anxiety symptoms were included in the presence of anxiety group. No formal measures of anxiety were administered in the intake process at the clinic. This information, as well as demographic information, was obtained via a patient database specific to Advanced Neurodiagnostics.

**Archived EEG protocols.** A laboratory technician recorded the EEGs in 2009 at Advanced Neurodiagnostics. The EEG recording was performed using 19 cephalic electrodes that were placed according to the international 10/20 system. Electrode impedance was <5 kOhm. The acquisition sampling rate was 500 Hz, with the filter setting at 0.1 Hz and 70 Hz. The nose was used as a reference and ear lobe electrodes were actives sites. The awake, eyes closed EEG was then recorded. Quantitative analysis of background activity was performed using NeuroGuide 1.8.1 EEG software. The fast fourier transform was applied to assess the absolute and relative power at each frequency (1 Hz–30 Hz). NeuroGuide's normative database was used to evaluate the level of normality. The results of the statistical comparison were further evaluated by the Key Institute's software LORETA in order to define deviant sources of activity. As previously mentioned, findings with a standard deviation of +/- 2 were considered significant.

**Data Analysis**

For each of the 96 cases in the 2009 database, two processes were administered. First, all qEEG data were processed through the program LORETA, or low resolution electromagnetic tomography. After this was completed, the findings were grouped into

four major categories: self-reported anxiety or no anxiety and excess right insula activity or right insula activity within normal limits.

**LORETA.** LORETA was first introduced in the early 1990s as one of the first true 3D tomographys of the human brain (Pascual-Marqui, Michel, & Lehmann, 1994). In contrast to the EEG, a topography that only reads the surface electrical brain activity, LORETA is a tomography, or a method of producing a three-dimensional image of internal structures in the brain, using EEG data. LORETA utilizes the optimal level of mathematical smoothness, which creates a "unique, optimal and physiological meaningful 3D distribution of electrical activity in the brain" (Pascual-Marqui et al., 1994, p. 50). A drawback of mathematical smoothness is relatively low spatial resolution, which yields a "blurred-localized" image of an electrical source, conserving "the location of maximal activity, but with a certain degree of dispersion" (Pascual-Marqui et al. 1994, p. 50). These authors found, however, that LORETA is capable of accurate localization, up to within one voxel resolution on average (Pascual-Marqui, 2002).

The advantage of LORETA over other well-defined tomography procedures, such as fMRI and PET scans, is temporal resolution. LORETA creates a tomography of electrical activity at every moment in time, whereas the other methods have temporal resolution that is "not high enough to keep up with the speed at which neuronal processes occur" (Pascual-Marqui et al., 2002, p. 92).

LORETA has been met with its fair share of criticism. The other tomography producing systems, such as PET and fMRI have superior spatial localization. Mendez and Andino's (2000) paper stated that for some test sources, LORETA has a localization

error of two or three voxels. Pascual-Marqui, the creator of LORETA, reports that this finding was not omitted in previous papers published on LORETA and the limits of its capabilities (2003). Additionally, De Peralta-Menendez and Gonzales-Andino (1998) stated that LORETA is not capable of source localization on the boundary of solution space, a mathematical construct that represents all possible solutions for a given algorithm. Pascual-Marqui et al. (1999) have proven this statement incorrect due to those authors utilizing an incorrectly programmed algorithm.

In terms of the benefits of using LORETA, 46 studies have provided validation for utilization of this method in different neuroimaging areas of interest (Pasqual-Marqui, 2003). LORETA has been found to localize within 3–6 centimeters, which is less accurate than PET and fMRI, but much better than zero spatial resolution provided by EEG alone (Thatcher et al., 2004). These authors have referred to LORETA as "one of the better localization methods" (p. 4). Herrmann and Fallgatter have found LORETA's localization abilities of widespread cortical areas to be comparable to that of fMRI (2003). Thus, LORETA is an accurate and acceptable localization method.

LORETA data for each patient was evaluated and noted for the presence of abnormally excessive or deficient activity within bilateral insular cortices. The predetermined level of abnormal activity was +/- 2 standard deviations from the mean of a LORETA normative EEG database. LORETA's normative EEG database created by Thatcher et al. was evaluated in 2005 and found to be a valid representation of the Gaussian distribution and demonstrated that the "Z-score normative database was valid with adequate sensitivity" (Thatcher, North, and Biver, 2005, p. 117).

The second process involved grouping the cases into four categories: self-reported anxiety or no anxiety and excess right insula activity or right insula activity within normal limits. The dichotomous nature of these findings allowed for a chi-squared test for independence statistical analysis. According to Gravetter and Wallnau (2011), the chi-squared test for independence assesses the relationship between two dichotomous variables, with the null hypothesis stating that the two variables in question are independent of one another and the alternative hypothesis stating that the two variables are dependent on one another, suggesting a relationship between the two.

**Hypothesis Testing**

In this study, the null hypothesis states that there is no relationship between anxiety and right insular cortex excess activity, primarily in the beta frequency. Stated differently, the null hypothesis states that within persons reporting anxiety, there is no difference between the distribution of excess activity in the right insula and "normal" activity in the right insula. The alternative hypothesis states that there is a relationship between anxiety and right insular cortex excess activity.

## Chapter Four: Results

### LORETA Findings

Sixty-nine cases met the criteria for abnormality. Of these, 22 cases self-reported anxiety, six of which had excess beta activity in the right insula. In terms of significant EEG findings within the insular cortices, six cases, four females and two males, met the criteria (2 standard deviations from the mean) for excess activity within the delta frequency. Three of these cases reported anxiety. Laterality was split evenly, with two cases exhibiting excess delta activity in the left insula, two exhibiting excess delta activity in the right insula, and two subjects with excess delta in both insular cortices.

Twenty cases (twelve females and eight males) had excess theta activity within the insular cortex, with six of these cases also reporting anxiety. Of these cases, six had excess findings in the left insula, six subjects exhibited excess activity in the right insula, and six cases had excess activity in bilateral cortices. Twenty cases exhibited excess alpha activity, with four cases endorsing anxiety. Eight cases had excess alpha activity in the left insula, five cases in the right insula, and seven in bilateral cortices. Twenty-three subjects (eleven females and nine males) met criteria for excess beta frequency activity, with eight of these subjects also reporting anxiety. Seven cases had findings isolated to the left insula (two anxiety), six cases in the right insula (one anxiety), and ten of these cases in bilateral insular cortices (five anxiety).

### Non-Parametric Testing

As previously stated, because the data is dichotomous in nature, the most appropriate method of statistical analysis is the chi-squared test. Two types of chi-

squared testing exist: the chi-squared test for goodness of fit, and the chi-squared test for independence. The chi-squared test for goodness of fit compares the frequency distribution for a sample to the population distribution that is predicted by the null hypothesis. Conversely, the chi-squared test for independence assesses the relationship between two variables. A chi-square test of independence was performed, and yielded the following results:

Table 1

*Anxiety * Beta Crosstabulation*

| | | | Beta | | |
|---|---|---|---|---|---|
| | | | Not Beta 1 | Beta 1 | Total |
| Anxiety | No Anxiety | Count | 64 | 10 | 74 |
| | | Expected Count | 61.7 | 12.3 | 74.0 |
| | | Residual | 2.3 | -2.3 | |
| | | Std. Residual | .3 | -.7 | |
| | Anxiety | Count | 16 | 6 | 22 |
| | | Expected Count | 18.3 | 3.7 | 22.0 |
| | | Residual | -2.3 | 2.3 | |
| | | Std. Residual | -.5 | 1.2 | |
| Total | | Count | 80 | 16 | 96 |
| | | Expected Count | 80.0 | 16.0 | 96.0 |

The results are summarized in the table below:

Table 2

*Chi-Squared Table*

| | Excess Beta in the Right Insula | No Excess Beta in the Right Insula | Totals: |
|---|---|---|---|
| Reported Anxiety | 6 | 16 | 22 |
| No Reported Anxiety | 10 | 64 | 74 |
| Totals: | 16 | 80 | n = 96 |

The total number of cases with excess beta in the right insula was 16, with six of these cases reporting anxiety, and ten not reporting anxiety. Eighty cases did not have excess beta within the right insula, with 64 of these cases also not endorsing anxiety, and 16 of these cases reporting anxiety. Column and row totals are found within the table above.

Based on the values above, expected frequencies were calculated. These results are stated in grid form below:

Table 3

*Expected Frequencies Table*

| | Excess Beta in the Right Insula | No Excess Beta in the Right Insula |
|---|---|---|
| Reported Anxiety | 3.7 | 18.3 |
| No Reported Anxiety | 12.3 | 61.7 |

Due to the lower than desired number in the upper right quadrant, the Fisher's exact test was utilized as the formal measure of significance. According to Gravetter and Wallnau (2011), the chi-squared statistic cannot be utilized when any calculated expected frequencies statistic falls below a value of 5. In instances when a category falls at 5 or less, the Fisher's exact test can be used, as it remains valid even when expected values are small (McDonald, 2009). This measure yielded a non-significant result (Fisher's exact test = .189), indicating the absence of a relationship between self-reported anxiety and excess beta frequency activity in the right insular cortex.

The effect size was also calculated. Gravetter and Wallnau (2011) stated the effect size for a chi-squared test for independence, where data is in a two-by-two matrix, is calculated using the phi-coefficient. The effect size for the Fisher's exact test is phi = 0.16, indicating a small effect size.

## Chapter Five: Discussion

### Summary of Findings

This study set out to better understand the relationship between anxiety, interoception, and activity in the right anterior insular cortex. Subjects obtaining psychiatric treatment at an outpatient clinic for self-reported psychological symptoms filled out a form indicating their chief complaint and underwent a routine electroencephalogram in a resting state. Cases that had self-reported anxiety or were in treatment for anxiety were selected for further examination in this study. In light of the current literature supporting the relationship between anxiety and the right anterior insular cortex, as well as the relationship between interoception, anxiety, and the right insular cortex, a hypothesis was generated that stated a relationship would be observed between the report of anxiety symptoms and excess beta activity in the right insula as measure by EEG. The results did not support the hypothesis.

### Context and Implications

This study joins the existing literature on the relationship between anxiety and beta activity in the right insula. However, there are differences between past studies and this study. First, the measurement techniques and analysis used in this study are different than the majority of studies that have examined the insula, anxiety, and interoception in the past. The method of collection this study used, electroencephalogram and LORETA, emphasized temporal over spatial resolution, while the majority of studies had previously used fMRI and PET scans.

A second difference between this study and the existing literature is that the anxiety in this study was assessed purely by self-report. Previous studies examining the

anxiety-insula relationship have utilized formal measures of anxiety, such as the Hamilton anxiety scale, as well as cases with already existing formal anxiety diagnoses, such as obsessive-compulsive disorder or generalized anxiety disorder. In their self-report, subjects may have been unwittingly reporting symptoms of anxiety, when in actuality their symptoms were related to depression, or were at a subclinical level of anxiety. Conversely, subjects may not have reported anxiety symptoms when they in fact were suffering from anxiety. These possibilities would be expected to lead to measurement error, as well as lowering the effect size.

A third distinguishing feature of this study was that participants in this study were not provoked to stimulate anxiety and its neurological correlates in any way, such as viewing photographs of anxious versus neutral faces. EEG recordings were taken during a resting state, and it is thus likely that the present study measured for a baseline or "trait" type of anxiety.

Although the presence of baseline excess insula activity is certainly possible and has been proposed, this has not been as supported by the literature as often as the relationship between anxiety provocation and excess insula activity. As noted in the literature review, Stein et al. (2007) studied college students who met criteria for trait anxiety, and they found a relationship between students with trait anxiety and activity in the bilateral insula and amygdala as measured by fMRI. Although these measurements were gathered while these students viewed images of emotional faces, the intensity of insula anxiety correlated moderately with aspects of trait anxiety. This study attempted to lend further support to the link between trait anxiety or "anxiety sensitivity" and right insula excess activity, as trait anxiety is likely more disruptive to a person's functioning

than state anxiety. Stein et al. (2007) suggested that people with "anxiety sensitivity" are more likely to go on and develop clinical anxiety disorders due to the fact that they attribute their bodily sensations as indicators of anxiety. Per the James-Lange theory of emotion, these people would be experiencing the emotion of anxiety in response to physical stimuli, such as tachycardia or rapid respiration rate. If interoception was related to trait anxiety and excess activity in the insular cortex, early identification and treatment of anxiety sensitivity could be implemented by measuring insular activity and modifying the way these subjects interpret interoception. The research that exists on the relationship between the insular cortex, anxiety, and interoception has been promising, but requires further support and expansion to better understand these complex phenomena.

**Limitations**

Although it was the aim of this study to provide empirical support demonstrating a relationship between excess activity in the right insular cortex and anxiety through interoception, the results did not support this hypothesis. This finding was inconsistent with previous research conducted in this area, which has generally found a measurable relationship between anxiety and excess activity in the right anterior insular cortex.

However, the fact that the hypothesis was rejected was not surprising for a variety of reasons, most of which can be attributed to the methodology and data set. While archival data is advantageous in that it is readily available, it is inherently unable to be manipulated. And although the majority of the data used in this study was certainly rigorous enough to explore anxiety and its neurological correlates, there were certain

aspects of the data that could have been better suited to understand the relationship between anxiety and excess activity in the right anterior insula, namely the anxiety data.

A formal measure of anxiety data would be more advantageous for two reasons; first, to provide a more accurate indicator of the presence and severity of anxiety symptoms in the patients. Understanding the severity of anxiety symptoms would allow the patients to be grouped into mild, moderate, and severe categories, which could be correlated to the intensity of the excess insula activity. Second, to have a better qualifier of symptom type (i.e., somatic versus mood or cognitive), which could be used to better understand the proposed link between interoception and anxiety using physical symptoms of anxiety as a marker for interoceptive-driven anxiety. An additional limitation of the archival data was the small N size. Ninety-six cases would be a sufficient N size, however, once the cases were separated into categories, the N size for cases that reported anxiety and had excess beta activity was greatly reduced.

Additionally, while LORETA has been found to localize electrical activity to within 3–6 centimeters, it is not as spatially accurate at fMRI; thus, it is possible that the measurements being obtained through this study's EEG methodology were not from the insular cortex, but from another adjacent area that was misrepresented as the insula through LORETA. Additionally, due to the functional differences between the posterior and anterior insula, a difference of 3–6 centimeters could lead to substantially different results.

Another less influential limitation may be the statistics that were utilized. According to Gravetter and Wallnau (2011), parametric statistics are more likely to lead to the rejection of a false null hypothesis because they have more power than

nonparametric statistics. This study's archival and dichotomous data restricted the analysis to a nonparametric chi-squared test, which has limited statistical power. Last, as with any study, the results are vulnerable to human error. This type of error may have occurred during data collection, data entry, and statistical analysis.

**Future Directions**

Although this study had its share of limitations, understanding these limitations can help to guide future studies that would lead to a better understanding of anxiety and its neural correlates. First, it would be important to demonstrate a relationship between anxiety and the right insula using EEG/LORETA and provocation of anxiety through stimuli. The current study used an uncommon method of data collection (electroencephalogram) and a novel methodology in that subjects were not stimulated to provoke anxiety, which may have made it less likely that the hypothesis would be accepted. As noted previously, the benefit of an EEG is its temporal sensitivity and accuracy, which would be most beneficial if this study involved anxiety provocation in its design, as the goal is to immediately and correctly identify the areas affected.

Conversely, in order to better understand the presence of baseline or resting excess right insular activity, fMRI performed while subjects with anxiety disorders are in a resting state may be most beneficial to better understand trait anxiety and its relationship to the insula. fMRI would also be beneficial in that it has better spatial resolution, and thus would be able to differentiate between the anterior and posterior portions of the insula, which have been recognized as being involved in different functions. Additionally, obtaining a formal measure of anxiety symptoms or exclusively

working with subjects who have a currently diagnosed and verifiable anxiety disorder is recommended for future research as noted previously.

More research is needed in the area of state and trait anxiety as related to insula functioning in general. Obtaining functional imaging of insular activity during resting states in persons with high levels of trait anxiety, and comparing these results to imaging anxiety provocation studies would shed light on state-trait insula functioning. To further ensure that anxiety is being achieved, cross-validation through psychophysical markers (i.e., galvanic skin response or pulse rate) would be advantageous and would strengthen validity. Finally, comparisons between left and right insular functioning, as well as between anxious and non-anxious subjects, could provide further understanding of insula functioning and subsequent psychological correlates.

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## Appendix A: Function Table

| | Functions of the Insular Cortex |
|---|---|
| Ibanez Gleichgerrcht & Manes (2010) | Autonomic Functions (i.e., cardiac regulation) |
| | Taste and Gustatory Perception |
| | Auditory Processing |
| | Somatosensory Systems and Pain |
| | Neglect |
| | Emotion |
| | Mood and Willed Action |
| | Language |
| | Interoception |
| Craig (2009) | Cognitive Choices and Intentions |
| | Music |
| | Time Perception |
| | Attention |
| | Awareness of Sensations and Movements |
| | Visual and Auditory Percepts |
| | Visual Image of the Self |
| | Reliability of Sensory Images |
| | Subjective Expectations |
| | Trustworthiness of Others |
| Flynn (1999) | Cardiovascular Modulation |
| | Gastrointestinal Processes |
| | Vestibular Processes |
| | Gustatory Processes |
| | Visual Processes |
| | Auditory Processes |
| | Somatosensory Processes |
| | Motor Modulation |
| | Pain Perception |
| | Stress-Induced Immunosuppression |
| | Mood Stability |
| | Sleep |
| | Language |
| Augustine (1996) | Visceral Sensory Area |
| | Somatosensory/ Pain |
| | Sensory Area (i.e., feeing and neglect) |
| | Limbic Integration |
| | Visceral Motor Area (i.e., autonomic processes) |
| | Motor (i.e., ocular movements) |
| | Vestibular Processes |
| | Language |
| | Involved in Alzheimer's Disease |
| Paulus and Stein (2006) | Modulation of Affective Processing |
| | Cognitive and Affective Processes During Learning |
| | Aversive Interoceptive Processing |