

Anxiety in Alzheimer's Disease
An Investigation of the Relationship Between Two Pathologies

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Abstract

Researchers familiar with Alzheimer's disease have often noted the presence of comorbid anxiety symptomatology. Likewise, the occurrence of anxiety before the development of Alzheimer's disease has been prevalent enough to warrant attention. This review seeks to elaborate on the pathophysiology behind these two conditions, and to accentuate overlapping aspects that promote a causal relationship between these two pathologies on the macroscopic and cellular levels. Subsequent evidence will show that these pathologies are not independent of each other, and that cellular mechanisms of pathology hint at their interrelatedness. Areas requiring further research that would clarify the relationship between Clinical Anxiety and Alzheimer's disease will be identified.

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In the year 1906, a psychiatrist by the name of Alois Alzheimer presented an interesting medical case at the 37th Meeting of South-West German Psychiatrists (Hippius & Neundörfer, 2003). For the leading clinical practitioners of mental health and neuroanatomy of the area, he presented the case of a 50-year-old woman who exhibited delusions, sleep and memory disturbance, and overall cognitive decline until her subsequent death in an immobilized state (Alzheimer, 1907; Stelzmann, Norman Schnitzlein, & Reed Murtagh, 1995). Upon her death, the autopsy revealed aggregations of proteins, termed senile plaques, and neurofibrillary tangles of tau protein. Additional cases were also documented by Alzheimer for patients who suffered the same fate (Hippius & Neundörfer, 2003).

Over 100 years later, a clear definition for the mechanisms behind this disease's cause exceeds the grasp of clinicians and researchers. Cases of Alzheimer's Disease (AD) that are seen to be familial have made finding genetic causes simpler. Genes such as the Amyloid- β Precursor Protein (A β PP) gene and the Presenillin 1 and 2 (PSEN1 and PSEN2 respectively) have been extensively characterized with respect to their roles in causing AD (Goate, 2006; Kelleher & Shen, 2017). Yet the genetic form of AD only contributes to less than one percent of all AD cases by some estimations (Swerdlow, 2007).

This considerable gap in the knowledge behind causes of AD makes a review of certain risk factors necessary. Anxiety and anxiety symptomatology have been specifically witnessed as prevalent in the stages prior to and during clinical AD by many researchers and clinicians. For this reason, a review of the relationship between these two pathologies is necessary to ascertain the mechanisms by which one neural dysfunction might have a hand in causing the other. The

goals of this review are to investigate the viability of clinically relevant anxiety as a causal risk factor for AD, to identify the role of AD pathophysiology in the dysfunction of anxiety neurocircuitry, and to characterize the nature of a possible positive feedback mechanism between anxiety and AD. These goals will be accomplished by an extensive review of the pathophysiology behind both disorders, specifically referencing areas of overlap. The conclusions that can currently be defined will be identified, and areas where further research might lead to a more informed consensus will be accentuated as well.

Methods

To ensure the quality of literature reviewed, a number of simple procedures were followed during the collection of information to be incorporated in this review. An extensive search of peer-review journals was undertaken using a broad range of keywords applicable to the pathophysiology of clinical anxiety (CA) and AD, including clinical anxiety, HPA-axis response, corticotropin releasing factor or hormone, adrenocorticotropic hormone, cortisol, urocortin, γ -aminobutyric acid signaling, amyloid- β cascade, cholinergic hypothesis, and tau hypothesis among others. Two main databases were searched: The Jerry Falwell Library Database and Google Scholar. These search procedures uncovered 118 peer-reviewed articles that were able to be included based on their applicability in providing necessary information to answer the above-mentioned research questions, specifically regarding the pathophysiology of CA and AD, and the potential relationship between the two. Articles that did not provide necessary information for defining the physiology of these two disorders, undertake an investigation of the relationship between them, or provide useful epidemiological information were excluded.

Anxiety as a Causal Risk Factor for Alzheimer's Disease

Introduction. Anxiety is a familiar term to many, yet it can connote a multitude of ideals depending on perspective. In many instances the term has become so commonplace as to lose its clinical definition, and perhaps this is a foretold effect of the adoption of a commonplace term for clinical purposes. For the purposes of this research, it is then necessary to develop a proper clinical definition of anxiety. Clinical Anxiety (CA) describes affective disorders that can be characterized by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) whose main symptoms involve overall anxiety and feelings of panic due to irrational causes or for prolonged periods; some examples of disorders falling under this blanket category might include Generalized Anxiety Disorder (GAD), Social Anxiety Disorder (SAD), Posttraumatic Stress Disorder (PTSD), Panic Disorder, and various phobia disorders among others (American Psychiatric & American Psychiatric Association, 2013). For the purposes of this review, anxiety symptomatology that warrants clinical treatment or attention might also be considered CA. Anxiety disorders are widespread, and the combination of the prevalence of multiple disorders increases the overall occurrence of CA. In a survey population of Americans over the age of 18, the prevalence of lifetime sufferers of SAD was estimated to be 5.0% (Grant et al., 2005). Other surveys of American populations have determined the lifetime prevalence for GAD to be approximately 4.0-7.0% (Kessler, Keller, & Wittchen, 2001). The lifetime prevalence of PTSD has recently been defined at around 7-8% in a sample of Americans (PTSD, 2018). As will be discussed later in the study, the potential for anxiety as a risk factor for Alzheimer's Disease development puts a considerable proportion of the population at risk. It is therefore necessary to characterize anxiety conditions and their biological effects to determine the viability of early-to-mid-life anxiety as a causal risk factor for AD. Resultantly, it is necessary to determine potential psychological causes of anxiety and the progression to disorders that fall under the clinical

category. Furthermore, the mechanism of anxiety's action must be analyzed on a pathophysiological level to determine the biological changes in the central nervous system associated with prolonged stress that might be involved in AD development. Conclusions will be drawn after research and data are presented that determine the relationship between anxiety and AD, specifically referencing the debate of whether anxiety is a prodromal symptom of AD or an independent risk factor.

Evidences for connection in clinical studies. In later sections, the pathophysiology of Clinical Anxiety will be reviewed and defined on a macroscopic and cellular level. A characterization of the mechanisms behind these psychiatric dysfunctions will be necessary to grasp the large and impactful effect anxiety pathology has on the CNS. This vast array of developmental ramifications has the potential to produce drastic consequences. For this reason, evidence of these consequences will be identified by analyzing clinical studies wherein anxiety has led to AD development. This section will introduce convincing evidences that the various Clinical Anxiety conditions might be risk factors in the development of AD.

Clinicians often make note of the presence of anxiety conditions in older populations. Seemingly concomitant with these symptoms was the presence of cognitive decline, or mild cognitive impairments (MCI). It was therefore deemed necessary to investigate both the existence and nature of a potential relationship between these two conditions; resultantly, several clinical investigations have been undertaken to identify a relationship. A consideration that must be made note of regarding a potential relationship between anxiety and MCI is that if a relationship is identified, the sequential order is still an issue; anxiety could represent a prodromal symptom of MCI and cognitive decline, or it could induce cognitive damage that might increase the risk for age-related decline and MCI (Beaudreau & O'Hara, 2008). One study

found that older patients complaining of anxiety disturbances performed worse on tests of working memory than subjects with no reported anxiety, yet the anxiety group still performed better on this assessment of memory than a group with MCI; this might indicate anxiety as an intermediate in the progression of cognitive decline, but the results are not conclusive (Christian, Jean-Robert, & Lucette, 2004). Another study compared 19 patients with GAD to two other groups: one of normal subjects and one of those diagnosed with Major Depressive Disorder (MDD). This study revealed that GAD subjects were impaired in areas of short-term and delayed memory when compared with physiologically normal individuals, and MDD patients showed more general cognitive impairments (Mantella et al., 2007). In a sample of older community-dwelling individuals, anxiety was shown to be associated with delayed memory recall; although the presence of anxiety caused only a slight deficiency, it was also noted in this study that most of the subjects would not have met psychiatric requirements for a clinical diagnosis of anxiety disorders (Booth, Schinka, Brown, Mortimer, & Borenstein, 2006). In many instances, clinical studies attempted to predict cognitive decline using analysis of individuals with common traits of anxiety; these studies failed to determine a relationship after multi-year longitudinal analysis, yet in all instances of this technique (as in the previous study), the subjects did not meet the requirements for clinically diagnosed anxiety, perhaps indicating an essential difference in populations with CA and elderly populations with anxiety-like traits (Beaudreau & O'Hara, 2008). Another complication often encountered is the presence of MDD in the analyzed populations, and in some cases, comorbid with CA. This might obscure the causes of cognitive decline and memory loss in some studies. Some researchers have undertaken screenings to analyze CA specifically without the presence of MDD as it pertains to decline and memory loss. One such study made use of regression analysis to show that CA was a significant predictor of

cognitive decline, and also that memory loss was mediated by anxiety in cognitive decline in a longitudinal study of 100 participants (Sinoff & Werner, 2003). Another four-year longitudinal study analyzed patients diagnosed with MDD separated into groups of those diagnosed with comorbid anxiety (GAD and PD) and those without; the results showed that the CA group had greater memory deterioration than the group with only MDD (DeLuca et al., 2005). From the above results, one can conclude that anxiety has a differing effect on the deterioration of cognition and memory than depression. Furthermore, it is necessary that the form of anxiety analyzed matches a clinical diagnosis for the deterioration of memory and cognitive impairment to be pronounced. In many cases, a sub-clinical level of anxiety was seen to facilitate cognitive performance on appropriate scales of measurement (Beaudreau & O'Hara, 2008). These results seemingly contradict hypotheses that have anxiety as a risk factor in cognitive decline and impairment, yet deeper analysis would hold that these results are to be expected according to the Yerkes-Dodson Law (Teigen, 1994; Yerkes & Dodson, 1908).

Another important consideration in the relationship of CA and progressing deficiency of memory and cognition, perhaps leading to AD, is the presence of anxiety symptomatology in the prodromal stage of AD. Perhaps anxiety is simply a prodromal symptom that occurs before progression to clinically diagnosed AD, and therefore its independence as a risk factor for AD is invalid. What has recently complicated this question is the absence of prolonged research on the topic. Many studies are limited in their supposed characterization of the relationship between CA and AD because they are short-term in length, which would lead one to conclude anxiety is merely prodromal (Gimson, Schlosser, Huntley, & Marchant, 2018). For example, researchers accumulated a large amount of data (12,083 subjects were used) from AD treatment centers across the United States to identify psychological risk factors for the development of AD; among

other mood disorders, anxiety was found to be a significant predictor of conversion to AD (Burke, Cadet, Alcide, O'Driscoll, & Maramaldi, 2018). However, this study's method for measuring anxiety was self-report by the subjects, and only for a duration of two years prior (within the range for prodromal symptom presentation). The presence of anxiety symptomatology as a prodromal process in AD development is not mutually exclusive with CA also being an independent risk factor for the disease. A 16-year longitudinal analysis of 2,071 individuals observing the development of AD characterized the prodromal stage of cognitive decline leading to clinically diagnosed AD as commencing 5 to 6 years prior (Wilson, Leurgans, Boyle, & Bennett, 2011). Therefore, evidence of a correlation between clinically diagnosed mid-life anxiety and AD onset in advance of this prodromal stage would be convincing evidence of CA as an independent risk factor. A review study found four examples of primary research that investigated this relationship with an average of 10 years between CA diagnosis and ensuing AD diagnosis; each of the four studies reviewed found a positive relationship between clinically diagnosed anxiety disorders and AD development at least 10 years from the initial anxiety assessment (Gimson et al., 2018). This evidence suggests anxiety is capable of standing independently as a risk factor for AD development (when also correcting for comorbid depression or controlling for its absence in the abovementioned studies).

Besides mere association of these two pathological conditions, further evidences have been uncovered with clinical research of the brain structures and processes that also support the hypothesis of CA as an independent risk factor rather than prodromal symptom. Researchers utilized imaging data from the Alzheimer's Disease Neuroimaging Database (ADNI) to compare effects of anxiety on the conversion of amnesic mild cognitive impairment (aMCI) to AD; after controlling for depression, cognitive decline, and baseline atrophy rates of AD regions of interest

(ROI, such as the hippocampus, amygdala, etc.), this study confirmed that anxiety symptomatology significantly predicted conversion to AD (Mah, Binns, & Steffens, 2015). Furthermore, anxiety also was significantly associated with more pronounced atrophy of the entorhinal cortex (EC), and it is hypothesized that anxiety mediates its deteriorative effects via this process (Mah et al., 2015). Other researchers undertook the similar research goal of identifying factors that might prognosticate the development of AD from MCI. One such study analyzed multiple factors, including mood-related depression, motivation-related depression, and anxiety symptomatology; the data found that persons with anxiety and MCI developed AD at twice the rate of those with MCI but no anxiety (Palmer et al., 2007).

Psychological Considerations. The various psychological diagnoses described by the blanket phrase Clinical Anxiety are numerous and distinct from each other; likewise, the causes of anxiety conditions are similarly distinct on a patient-by-patient basis (or client-by-client basis, following the counseling customs of terminology). Certain psychological considerations are necessary to understand the development of CA pathologies and the often environmental causes associated with its development. The Biopsychosocial Model is perhaps the most popular approach in defining the various methods by which psychiatric pathologies occur; this holistic approach takes into account the biological aspects (such as genetics, developmental abnormalities, neurotransmitter abnormalities), the psychological aspects (client perceptions, personality, ego strength, self-esteem), and social aspects (life experiences, social networks and support, cultural norms) (Engel, 1980). The biological aspect of anxiety pathology is essential to defining the relationship of CA as a potential independent risk factor for AD development, and therefore it will be elaborated on in the "Pathophysiology" section below.

In order to describe the psychological factors that often correlate with the development of anxiety, several studies have undertaken research that attempted to characterize clients that deal with these pathologies. One study's goal was to identify certain personality traits that put one at risk for CA development. It was determined that anxiety is predicted to develop more frequently in individuals with increased novelty-seeking, harm-avoidance, and persistence, as well as decreased self-directedness (Matsudaira & Kitamura, 2006). The self-directedness attribute is inclusive of several attributes some consider essential in the coping method paradigm, such as self-esteem, locus of control, and problem-solving. Low self-esteem has long been associated with numerous pathological conditions, including anxiety (Leary, Schreindorfer, & Haupt, 1995). Locus of control is an essential concept commonly referred to in psychological studies of personality traits, and it is especially noted in many cases as having pertinent impact on an individual's ability to cope with certain stressors. Locus of control is a researcher's concept developed to define individuals' cognitions and ideals that cause them to attribute the source of reinforcement to one of two categories. Two paradigms exist for this aspect of personality: an individual perceives occurrences as under the control of the individual (an internal locus of control), or an individual perceives occurrences as due to chance, fate, or others (an external locus of control) (Archer, 1979). The connection between externality (having an external locus of control) and anxiety has long been under investigation. A meta-analysis of these investigations has identified a significant correlation between externality and trait anxiety (anxiety that is an aspect of one's nature and personality, contrasted with state anxiety which is dependent on one's reaction to specific adverse situations). This study also found that for internality, there is a significant negative correlation with trait anxiety (Archer, 1979).

Also applicable to the development of CA disorders are social aspects, or stressors, that cause a decompensation by the client, allowing the deterioration into a psychiatric disorder. One category of events that might cause social distress are developmental crises. Developmental crises are various crises of personality that one encounters throughout a lifetime; developmental crises present themselves at various stages, and represent a struggle to overcome certain fears that are prominent at the specified age. Most psychologists still recognize the work of Erik Erikson, and his eight stages of psychosocial development as the most applicable theory in the field of developmental crises (Erikson, 1968). Developmental crises are a more specific category of adverse life encounters, also referred to as crises. The occurrence of a psychological crisis in response to an adverse life experience is considered to have four parts according to professionals: (1) a precipitating event occurs which (2) the individual perceives as threatening or damaging; (3) this perception leads to emotional distress that in turn (4) causes impairment in functioning resulting from the failure of the individual's habitual coping mechanisms (Kanel, 2014). The concept of ego strength is important in an individual's handling of a crisis situation. According to this theory of cognition, ego strength refers to an individual's psychological capacity to deal with distressing events and continue to meet one's needs physically and mentally; ego strength is diminished by the accumulation of distressing crises, and the addition of more stressors leads to decompensation by the individual in the form of psychosis, depression, or anxiety (Kanel, 2014). This state of decompensation and diminished ego strength is referred to as a transcisis state. These psychological concerns often have root in the development of certain CA conditions over prolonged periods of time.

Pathophysiology. The physiology of anxiety is largely related to the stress response, being that anxiety is the experience of a stressed state for an unnaturally prolonged duration or

for irrational reasons. The stress response has been extensively characterized by numerous studies that validate a central role of the endocrine system.

Hypothalamus and amygdala. Corticotropin-releasing factor (CRF) is the hormone that initiates the cascade leading to the stress response. Over 30 years ago, the 41-amino acid sequence of CRF was determined after its isolation from ovine hypothalamic extracts; the action of this newly purified hypothalamic protein was to stimulate the release of corticotropin-like hormones and β -endorphins (hence the nomenclature) (Vale, Spiess, Rivier, & Rivier, 1981). Most of the CRF of the CNS was discovered to reside within the soma of neurons in the paraventricular nucleus (PVN) of the hypothalamus, which most now recognize as a common characteristic of the hypothalamic tropic hormones that act mostly on the anterior pituitary gland (Arborelius, Owens, Plotsky, & Nemeroff, 1999). Besides its action on the anterior pituitary, CRF-producing interneurons are also distributed throughout the CNS in certain regions of the cerebral cortex (Arborelius et al., 1999). CRF and its respective receptor are also found in high concentrations in the amygdala, one of the most foundational nuclei of the CNS integral in emotional response (Gray & Bingaman, 1996) More specifically, the amygdala is essential in response to negative emotions, most notably fear and anger; many studies have been performed making use of positron emission tomography (PET) to demonstrate both the central role of the amygdala in fear response and the absence of fear recognition in facial expression (visual) or in vocal emotion (auditory) in patients with lesions of the amygdala (Broks et al., 1998; Scott et al., 1997). From the evidence provided in these studies of the amygdala's function, and also from the discovery of CRF in interneurons of the advanced cerebral cortex and the amygdala, the connection between CRF and the induction of anxiety response becomes more complex. The presence of CRF innervation in interneurons might suggest the role of CRF not only as a tropic

hormone for the anterior pituitary, but also as a paramount signaling peptide involved in the cognitive and behavioral aspects of emotion (Arborelius et al., 1999). Furthermore, animal studies have revealed that direct introduction of CRF into the amygdala induces a typical anxiety response, and the administration of receptor antagonists of CRF has anxiolytic results (Gray & Bingaman, 1996). Thus, the high concentration of CRF and receptors in the amygdala allows the development of a hypothesis for stress response starting with a stimulus: the distressing stimulus' detection by the various modes of sensory reception (visual, auditory, perhaps tactile) leads to signal transduction and activation of the amygdala, inducing CRF interneuron circuits that lead to the cognitive processing of fear or anxiety. CRF release from the hypothalamic PVN initiates the pathway of physiological stress response.

Biology and Emotion. There are various theories attempting to describe the conscious process that allows the experience of emotions. Although the biological occurrences of emotion can be described, the determination of the correct theory is not as certain, and is perhaps a matter of timing. The James-Lange theory would have one believe that the initiation of physiological arousal occurs prior to the induction of cognitive processing of the fearful stimulus, and that the cognitive processing leading to fear is induced by the consciousness of physiological arousal. According to the Cannon-Bard theory, the initiation of physiological arousal and the cognitive processing induced by the amygdala and CRF interneuron communication occur simultaneously, attributed in large part to signal distribution by the thalamus (the reason this theory is also referred to as the Thalamic theory) (Cannon, 1931). The Schacter-Singer two factor theory of emotion might postulate that physiological arousal alone is insufficient to produce an anxiety response, and that the cognitive label given to a stimulus (supposedly by CRF interneuron

communication) is necessary to produce the emotional experience of anxiety and fear specifically (Schachter & Singer, 1962).

The HPA-axis and stress response. Regardless, it is clear that CRF is involved in both the cognition of anxiety as well as the physiological changes associated with it. As noted, CRF is released from the PVN of the hypothalamus to act on the anterior pituitary; much like other hypothalamic tropic hormones, it is transported to have effect on the pituitary via the hypothalamic-hypophyseal portal system, which induces the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary (Plotsky, 1991). ACTH reaches the adrenal glands via the circulatory system and initiates the release of cortisol, a glucocorticoid that has a wide variety of effects that result in the physiological responses of prolonged anxiety and stress (Arborelius et al., 1999; Henckens, Deussing, & Chen, 2016).

CRF and urocortin effects. Before elaboration of the exact physiological effects of this hypothalamic-pituitary-adrenal (HPA) axis, another crucial signaling molecule operating in unison with (or perhaps as a counter to) CRF must be described to explain its role in the physiology of anxiety cognition. After the sequencing of CRF, a related neuropeptide with 45% sequence identity to CRF was isolated and named urocortin (UCN) (Vaughan et al., 1995). Three subtypes of this neuropeptide were eventually defined: urocortin 1 (UCN1), UCN2, and UCN3, the latter two also known as stresscopin-related peptide and stresscopin, respectively (Dautzenberg & Hauger, 2002). Also essential in defining stress physiology was the parallel discovery of the receptors on which these neuropeptides (CRF and the various UCNs) act. Two types of receptors, CRF receptor 1 (CRFR1) and CRFR2 were identified and sequenced as proteins with seven transmembrane helix domains; these typical G protein coupled receptors (GPCRs) mediate their action by coupling with G_s to stimulate alterations in cyclic adenosine

monophosphate (cAMP) concentrations in the targeted cells (Chang, Pearse, O'Connell, & Rosenfeld, 1993; Perrin et al., 1995). The difference between these two types of the CRF receptor occur in their respective ligand-binding specificities. The CRFR1 receptor has high affinity for CRF; UCN1 binds both receptors with equal specificity, and UCN2/3 both prefer CRFR2 (Henckens et al., 2016). The activation of CRFR1 by its respective ligands is associated with increased anxiety (anxiogenesis), and the introduction of CRFR1 receptor antagonists has been shown to decrease anxiogenic motor activity in animal studies (Henckens et al., 2016; Zorrilla, Valdez, Nozulak, Koob, & Markou, 2002). For this reason, many have hypothesized that overstimulation of CRFR1 is central to the development of various psychological anxiety pathologies, and the production of receptor antagonists of CRFR1 will have beneficial anxiolytic effects (Henckens et al., 2016). The role of CRFR2 is less certain among researchers, although most concede that it is still as essential as CRFR1 in the physiology of anxiety. Some postulate that the action of CRFR2 G protein signaling is to contradict the effects of CRFR1 signaling by returning the individual from a stress-induced state to a normal physiological homeostasis. Certain murine studies lead to this conclusion, as mice lacking functional CRFR2 exhibited an anxiogenic phenotype as well as increased serotonin (5-HT) turnover and decreased 5-HT levels, especially in the dorsal raphe nucleus (RN) (Issler et al., 2014). This indicated an inability of these knockout mice to cope after stressful stimuli for prolonged periods of time when compared with wildtype individuals. Other researchers hypothesized that the CRFR2 pathway represents a separate mechanism of dealing with stressful stimuli. Whereas the CRFR1 signaling triggers active stress compensation, CRFR2 might initiate a passive, decompensation response; studies cite the involvement of CRFR2 signaling with increased serotonin concentrations in the dorsal RN as evidence (Maier & Watkins, 2005). This physiological mechanism is presumed to be the

biological foundation for learned helplessness in response to a stressor that cannot be coped with (Maier & Watkins, 2005). Another consideration in the function of CRF and the related peptides is the presence of corticotropin releasing factor binding protein (CRF-BP). Subsequently, this protein binds and limits the concentration of available ligand for the CRFR receptors; the positive modulation of its activity by glucocorticoids might suggest its role in facilitating the negative feedback mechanism of the HPA axis (Behan et al., 1995). As mentioned, both types of CRFR GPCRs associate with G_s , and therefore initiate the classic cAMP/ protein kinase A (PKA) pathway. The downstream targets subsequently are cAMP-response element (CRE) genes that induce dendrite stabilization, ion channel permeability, and transcription of additional CRE binding protein (CREB, an essential component in the pathway of long-term potentiation) (Barco, Alarcon, & Kandel, 2002; Henckens et al., 2016). The synaptic modulation that occurs as a result of dendrite stabilization and long-term potentiation is an indicator of the drastic effects CRF signaling might have on cognitive processing over a long duration. After ligand binding to the CRFRs and signal transduction, GPCR kinases (GRKs) phosphorylate the receptors and dissociate them from the G proteins to halt signal transduction. β -arrestins then internalize the CRFRs from the cell surface which are either returned to the cell surface after dephosphorylation in the presence of lower signal molecule concentration, or degraded in lysosomes in response to prolonged increased signal molecule concentration (Benovic, Strasser, Caron, & Lefkowitz, 1986; Kelly, Bailey, & Henderson, 2008). Researchers have noticed an anomaly occurring in some cases when the phosphorylated CRFRs are not internalized despite the proper action of the GRKs. It is hypothesized that the failure of this desensitization to stressful signals is what might be the cause of debilitating anxiety (Henckens et al., 2016).

Cortisol and gonadotropin receptor signaling. As previously mentioned, the end result of HPA axis activation is the production of cortisol by the adrenal cortex. Researchers first noted the importance of cortisol signaling in the production of the stress response after administration of cortisol was found to cause hypertension and elevated fasting blood glucose levels (Whitworth, Saines, & Scoggins, 1984). The mechanism of cortisol's action was soon to be defined. Further investigation unveiled the receptor that mediates cortisol's genomic effects. As a steroid hormone, it was no surprise that an intracellular receptor of the nuclear receptor superfamily recognized cortisol as its ligand. The glucocorticoid receptor (GR) was identified as this steroid hormone receptor (Kadmiel & Cidlowski, 2013). It is important to note that while most of the genes affected by GR binding are positively regulated, some genes are downregulated, including the gene producing β -arrestin (the molecule essential for internalization of CRFRs) (Kadmiel & Cidlowski, 2013; Oakley, Revollo, & Cidlowski, 2012). This relationship could indicate the potential negative effects of cortisol signaling on essential processes important for the downregulation of CRFR receptors to prevent prolonged anxiety. Cortisol signaling has several classic effects that are recognized as part of the stress response. In hepatocytes, cortisol and GR gene activation result in the initiation of glycogenolysis and gluconeogenesis, a cause of the previously mentioned increased blood glucose during fasting (Kadmiel & Cidlowski, 2013). Glucocorticoid signaling in blood vessels inhibits vasodilator production, leading to the commonly noted hypertension effects. Cortisol signaling is also essential in inducing immunosuppression, commonly seen during prolonged periods of distress; consequently, glucocorticoids and derivatives are often used to suppress the immune system during organ transplants (Kadmiel & Cidlowski, 2013).

The effects of cortisol and glucocorticoid signaling on the nervous system are noteworthy in that they are active components of some psychiatric dysfunctions. Increased levels of cortisol and GR response signaling have been witnessed in certain mood/affective disorders such as PTSD (Kadmiel & Cidlowski, 2013). Certain murine studies have shown that individuals with non-functional GR protein in the nervous system display impaired response to distressing signals as well as decreased anxiety (Tronche et al., 1999). Other researchers found that overexpression of GR in the early life of murine populations altered the patterns of gene expression for the lifetime of the animal, and led to increased anxiety (Wei et al., 2012).

Clinical studies of cortisol signaling. Following the hypothesis of altered cortisol stress response cell signaling as a potential source of psychiatric dysfunctions, investigators undertook several clinical studies to identify human correlates for the murine studies that were performed. One such study researched prospectively by determining the amount of glucocorticoid receptors in military servicemen and women prior to, 1 month after, and 6 months after deployment; those diagnosed with drastic PTSD symptoms 6 months post-deployment had exhibited significantly higher numbers of GR before deployment occurred when compared with a control sample of psychologically normal servicemen (Van Zuiden et al., 2011). Other researchers have hypothesized a “blunted” cortisol response in those with anxiety disorders as a potential cause of the psychiatric disorder. A study of women reporting childhood physical abuse reported a blunted cortisol response to the Trier Social Stress Test (TSST), a common evidenced-based method for inducing stress response in human subjects (Carpenter, Shattuck, Tyrka, Geraciotti, & Price, 2011). It is notable that this study included only women that had been physically abused as children, but had minimal or no current psychopathologies. In continuation of this postulate, other studies have attempted to replicate this blunted cortisol effect finding with samples of

diagnosed anxiety patients. A meta-analysis of 732 diagnosed CA patients (including patients with PTSD, SAD, and PD) had limited success in replicating the blunted response. This study found that women with anxiety disorders in general exhibited a blunted cortisol stress response to the TSST, while men with SAD had an increased cortisol response (Zorn et al., 2017).

Cortisol effects on memory and cognition. As has been shown, uncovering the cortisol and glucocorticoid receptor signaling processes has been of paramount importance in defining the physiological response to stressful stimuli; for this reason, many researchers continue to form hypotheses that attribute a central role to these signaling pathways in pathological stress conditions. Some studies have identified cortisol and its signaling pathways as having a role in certain brain structure and HPA-axis modifications that might lead to pathological anxiety conditions. One revelation contributing to this theory was the discovery of high GR concentrations in the hippocampus and limbic system compared with the rest of the structures in the brain (de Kloet, Joëls, & Holsboer, 2005). This is indicative of the vulnerability of the hippocampus (an essential structure in memory storage and retrieval) to altered concentrations of cortisol. The effects were evident in the hippocampal atrophy that ensues upon exposure to excessive cortisol (Goosens & Sapolsky, 2007). Researchers thus identified a glucocorticoid cascade hypothesis because the damaging of hippocampus from excessive cortisol exposure results in the inability of the brain to regulate cortisol secretion via the normal negative feedback mechanism, leading to increased atrophy; it is further hypothesized that the negative consequences of this debilitating pathway are mediated by cortisol induced neurotoxic effects and even neuroinflammation (Frodl & O'Keane, 2013). Other researchers directly performed experiments that manipulated the concentration of cortisol in human populations and analyzed the effect of these altered concentrations on cognition and memory. One such study made use of

a younger human population to test this hypothesis; using a method of decreasing cortisol concentration and then restoring it, this study found that after a decrease in cortisol, memory recall was impaired compared to the placebo-treated control group, and also that recall was restored after cortisol levels were restored (Lupien et al., 2002). Furthermore, when researchers increased the concentration of cortisol in the morning (a time when the circadian rhythm has cortisol levels at their peak), the alteration in concentration had drastic negative effects on cognition, while injection of the same concentration in the afternoon (when cortisol levels are at a daily low) had positive effects on cognition (Lupien et al., 2002). A meta-analysis of cortisol administration studies and the effects thereof on memory performance tested similar conditions of cortisol administration. This review found that patients administered cortisol before retrieval was tested saw a decrease in memory performance, while administration before learning occurred had no effect on average; this study was able to replicate the discoveries of the previously mentioned researchers, finding that cortisol administration in the morning impaired memory while cortisol administration in the afternoon enhanced it (Het, Ramlow, & Wolf, 2005). It appears that an increase in cortisol concentration above the naturally occurring maximum concentration functions to impair memory and cognition, while maintenance of cortisol concentrations at a certain maximum is sufficient to enhance cognitive performance and recall according to the results of these studies. These evidences combined with other data collected on memory performance given certain cortisol concentrations have led to the development of an optimal concentration theory of cortisol's effect. A bell curve depicting this hypothesis visually displays that memory can be impaired when cortisol levels fall below a certain concentration, or rise far above the optimal concentration (Goosens & Sapolsky, 2007). Because of the high concentration of GRs in the hippocampus, it was presumed that the effect of

cortisol on learning and memory was mediated by its action in this brain region; likewise, chronic stress (prolonged elevated cortisol concentration) rather than sudden changes in cortisol levels (as had been tested in the previous studies) was discovered to have a more consistent effect of impairing memory performance. Chronic stress was shown to impair hippocampal-dependent spatial learning in classic tests of murine spatial learning performance (Goosens & Sapolsky, 2007). Similar deficits have been recognized in studies of humans with chronic stress, specifically pertaining to episodic memory (Bergdahl, Larsson, Nilsson, Åhlström, & Nyberg, 2005). Glucocorticoids (GCs) were identified as the likely cause of these adverse effects. Removal of adrenal glands prior to chronic stress was able to prevent these stress-caused memory impairments, and prolonged GC injection (simulating chronic stress) was sufficient to produce the same hippocampal-centered memory task impairments (Goosens & Sapolsky, 2007). Therefore, prolonged activation of the HPA axis and exposure to cortisol (as seen in Clinical Anxiety conditions) is sufficient to produce certain memory impairments and has adverse effects on brain structures essential in cognitive performance.

GABAergic communication and anxiety. Other essential signaling molecules that are crucial to understanding the pathology behind anxiety disorders are neurotransmitters. More specifically, many researchers have identified the central role of γ -aminobutyric acid (GABA) signaling and GABAergic neural pathways in the regulation of anxiety cognition. Several GABA-related compounds have been tested for their various effects regarding the subjective experience of anxiety; it was shown that GABA agonist administration (for example, many types of benzodiazepines) was sufficient to produce anxiolytic effects, while the administration of GABA antagonists and chloride ion channel blockers exhibited an anxiogenic response (Kalueff & Nutt, 1996). GABA is the main inhibitory neurotransmitter of the nervous system, often seen

modulating the effects of glutamine, the main excitatory neurotransmitter of the CNS. In the various nuclei of the amygdala, GABAergic modulation is essential to the inhibition of over-anxious presentations; glutamatergic communication between the previously mentioned BLA and the central nucleus (CeA) of the centromedial amygdala complex is modulated by additional inhibitory GABAergic communication from certain interneurons (referred to as intercalated neurons) to inhibit the CeA (Nuss, 2015). Likewise, it has been suggested that PFC inhibitory regulation of the BLA and subsequently the CeA is necessary in attenuating the spread of neural output from the amygdala (Nuss, 2015). Investigating the role of various medial PFC nuclei, researchers discovered that the lesion of these areas in murine studies disabled the extinction of fear, and thus produced a persistent anxious emotional response. Likewise, the higher dorsal nuclei exhibited more activation in the cognitive processing of anxiety and fear, while lower ventral nuclei exhibited more influence on the emotional presentation of anxiety (Etkin, 2009). The main clinical target of various pharmacological treatments for anxiety has largely been the GABA_A receptors. These receptors are ionotropic chloride ion channels that induce the hyperpolarization of the postsynaptic membranes being acted upon. The receptor itself is a five-subunit transporter with two α subunits, two β subunits, and one γ subunit; two GABA molecules are capable of binding between the α and β subunits that exhibit positive cooperativity, allowing the opening of a centrally located ion channel (Sieghart, 2006). It was also discovered that benzodiazepines bind allosterically between the α and γ subunits, and increase the cooperativity of GABA binding to the two active sites; the ease of channel opening provided by benzodiazepines leads to increasing likelihood of inhibition and attenuation of anxiety (Sigel & Ernst, 2018). Various negative side effects have been exhibited with the use of benzodiazepines however, mainly including sedative effects such as ataxia and varied resting/sleeping posture in

studies of primates (Duke et al., 2018). Therefore, further investigation of different agonists for the GABA_A receptor that act on different allosteric areas would prove necessary both for developing new clinical applications and understanding the role of this receptor in the pathology of anxiety. Neurosteroids were widely investigated for their role as endogenous modulators of GABA_A receptors; they were seen to act as positive allosteric molecules supporting the association of GABA, and were identified as capable of opening the GABA_A channels themselves (Nuss, 2015). To identify the potential role of neurosteroids in pathological anxiety, researchers compared CA patients (exhibiting GAD) and healthy controls; it was determined that CA patients had significantly lower plasma levels of the neurosteroid pregnenolone than did the controls (Semeniuk, Jhangri, & Le Mellédo, 2001). The neurosteroid hypothesis of pathological anxiety is further supported by evidence that treatment of CA with selective serotonin re-uptake inhibitors (SSRIs) might exhibit its effectiveness by the molecule causing increased neurosteroid synthesis in the CNS (Nuss, 2015). Subsequently, molecules that exhibit similar effects as neurosteroids or promote the synthesis of neurosteroids should produce more natural anxiety-attenuating effects. One promising pharmacological solution that follows this logic is etifoxine; it was shown to produce positive allosteric effects when binding to its unique location on the GABA_A receptor (Schlichter, Rybalchenko, Poisbeau, Verleye, & Gillardin, 2000). Fortunately, etifoxine was also seen to promote the synthesis of certain neurosteroids, as seen by their increasing concentrations upon administration of etifoxine even in adrenalectomized and castrated murine subjects; it is suggested that the neurosteroid-synthesizing effect is due to the interaction of etifoxine with peripheral benzodiazepine receptors (PBRs) (Verleye et al., 2005). Other compounds produce anxiolytic effects for different reasons. Tiagabine is a selective inhibitor of GABA transporter 1 (GAT-1, responsible for re-uptake of GABA from the synapse);

a mutation in this specific transporter that might be responsible for a decrease in GABA concentration at the synapse is a promising genetic candidate for the cause of anxiety disorders (Thoeringer et al., 2009).

CNS structural changes in anxiety. Magnetic resonance imaging (MRI) has proven a useful tool in determining the exact effects on brain structure that Clinical Anxiety conditions can produce due to prolonged distress. Data has shown that higher PTSD scores are associated with increasingly pronounced hippocampal atrophy, as well as reduced total white matter volume when compared with data from pathologically normal individuals (Villarreal et al., 2002; Weniger, Lange, Sachsse, & Irle, 2008). It is notable that many researchers have also found hippocampal atrophy to be a common presymptomatic occurrence in the development of AD, and this brain structure is severely atrophied throughout the progression of the disease as well (Carlesimo et al., 2015; Fox et al., 1996). Similar to hippocampal atrophy, data collected on other brain regions has shown that prefrontal lobe areas and other cortices of the cerebrum show significant atrophy as well with age; these regions contain high levels of GR, indicating the potential importance of the role of the HPA axis in this age-related deterioration (Goosens & Sapolsky, 2007). These regions are important targets of the cholinergically supplied reticular activating system (RAS), and the deterioration of neural communication in these regions is a primary component of AD pathology (see “Cholinergic Hypothesis” in *Pathophysiology of Alzheimer's Disease* section) (Hampel et al., 2019).

In murine studies, researchers have attempted to define the events leading to neuronal atrophy and cell death due to HPA axis activity. Prolonged GC administration has been shown to decrease the process of long-term potentiation (LTP), the process long associated with cognitive development and learning (Pavlidis, Watanabe, & McEwen, 1993). The causes of neuronal cell

death are more difficult to define, but evidence shows that neuronal death related to HPA axis activation may be due to the interaction of two variables: high GC concentration and age.

Comparing two murine groups, one with increased HPA axis activity and one with normal activity, the differences in hippocampal volume were only pronounced after the two populations reached advanced age. The increased HPA activity group showed significant atrophy compared with the control group (Meaney, Aitken, Bhatnagar, & Sapolsky, 1991). It was also determined that age-related neuronal death is more pronounced in hippocampal regions that have a higher density of GC receptors compared with other regions of the hippocampus (Goosens & Sapolsky, 2007).

These brain region changes (specifically hippocampal atrophy) have been identified by researchers as a result of the development of pathological psychiatric conditions (namely PTSD) due to childhood abuse and maltreatment; it is hypothesized that maltreatment during a young age increases the CNS susceptibility to age-related changes or negative reactions to adulthood stressors that in turn have detrimental effects on the function of the HPA-axis (Frodl & O'Keane, 2013). As previously mentioned, the glucocorticoid cascade hypothesis, whereby hippocampal atrophy and decreased negative feedback leads to increased cortisol secretion and further atrophy, is essential in describing the transition from CA to cognitive deficits seen in AD. The consequences of this pathway are exacerbated by the neurotoxic effects of cortisol and neuroinflammation (Frodl & O'Keane, 2013). This mechanism of pathology hints at anxiety's role in the Tau Hypothesis of AD pathology (discussed later), which relies on the dysfunction of the CNS immune system in attempting to combat the effects of neuroinflammation, leading to the deregulation of certain kinases that cause tau phosphorylation and neurofibrillary tangle (NFT) formation (Maccioni, Farías, Morales, & Navarrete, 2010).

The Development of Anxiety in Alzheimer's Disease

Introduction. Among the total population of Americans today, 5.3 million are currently afflicted with Alzheimer's Disease (AD). By 2050, the projected rate of new cases of AD diagnosis will amount to 1 million individuals per year (Alzheimer's, 2015). Alzheimer's Disease is widespread in its affliction of individuals in western societies, and seems to be a trade-off of the long life that many in such Western countries are privileged to reach due in large part to advanced developments in medical care. For this reason, AD has become the focus of many researchers and studies in the developed west. This pathology came to the forefront of clinical attention after its first diagnosis in the year 1906; Alois Alzheimer first noted an elderly female patient at his psychiatry institute in a bizarre demented condition of delusion and memory loss, and upon her death, discovered the neurofibrillary tangles and amyloid- β plaques that were to become all too familiar in the ensuing years (Stelzmann et al., 1995). Highlighted by the many clinicians familiar with this original case is the fact that this original patient is better characterized by the genetic form of the disease, Autosomal Dominant Alzheimer's Disease (ADAD). The reasoning behind this (also the reasoning for another name of ADAD being Early Onset AD) is that the patient developed these characteristics earlier than 65 years of age (Stelzmann et al., 1995). ADAD has been extensively characterized as the result of two different genes: A β PP and PSEN1, both of which cause the AD pathology from dysfunction of the amyloid- β precursor protein processing via the action of enzyme γ -secretase (Goate, 2006; Kelleher & Shen, 2017). The non-genetic form of the disease is remarkably harder to characterize with respect to causes, and the exact action of such structures as amyloid- β (A β) plaques and their effects on the progressions and impairments associated with AD are debated by many researchers. Some voice the opinion of the aggregation of these plaques directly causing

the pathology, and others opt for a theory that holds reactive oxygen species (ROS) produced from these aggregations more responsible for neuronal degradation in the central nervous system (Aminzadeh, Roghani, Sarfallah, & Riazi, 2018; Seino et al., 2018). Some researchers highlight the dysfunction of cholinergic communication as essential in disease development, while other focus on the processes of tau phosphorylation. For these reasons, a review of these topics is necessary to determine where exactly the scientific community stands in characterizing this pathology, and also in developing treatments effective against this debilitating disease.

Subsequently, the physiological changes caused by AD that lend themselves to involvement with the pathways of CA dysfunction will be analyzed.

Pathophysiology. The difficulty in finding effective treatments for Alzheimer's Disease is in large part due to the lack of a clear pathophysiological mechanism that defines the cellular complications involved in causing the symptoms of AD. Many researchers have found promising hypotheses, yet in certain areas these hypotheses are unable to account for some of the cellular complications seen in AD. Despite this indeterminacy, the most widely accepted theory for AD progression is the amyloid- β cascade hypothesis

Amyloid- β Cascade Hypothesis. The amyloid- β precursor protein (A β PP) is encoded by the gene of the same name, mapping to the 21st chromosome; this protein had long been the suspect of AD pathology because of the correlation between Down syndrome (Trisomy 21) and the development of Early Onset AD (it is this gene's various mutations that are responsible for the genetic form, ADAD) (George-Hyslop et al., 1987; Information, 2018). An in depth look at this locus of pathology allowed a more sophisticated understanding of the complex enzymatic pathway behind AD. The A β PP gene product is habitually cleaved in one of two pathways: by either α -secretase or β -secretase, the latter of which is more often expressed in the CNS; after

ensuing cleavage by β -secretase, one of the two protein fragments (the C99 fragment) is aberrantly cleaved by γ -secretase, causing an abnormal amount of A β 42 with respect to A β 40 levels (Goate, 2006; Kumar, Singh, & Ekavali, 2015; Salomone, Caraci, Leggio, Fedotova, & Drago, 2012). The supposed main contributor to pathological symptoms is the aggregation of these A β 42 peptides into oligomers, leading to their coalescence into β -sheets and ensuing deposition into senile plaques characteristic of AD (Hardy, 2009; Kumar et al., 2015; Seino et al., 2018). These A β oligomers cause oxidative damage of cellular structures mediated by ROS, and also increase tau phosphorylation, specifically impairing the synaptic structures of neurons (Kumar et al., 2015). A β oligomers are also involved with the destruction of membranes high in cholesterol content, specifically those of the oligodendrocytes, glial cells that myelinate axons in the CNS (Roth, Ramírez, Alarcón, & Von Bernhardi, 2005). The loss of myelination likely results in some of the characteristics of an AD-afflicted CNS, yet more profound debilitating effects are produced by the mechanism of A β oligomers' interference specifically in the cells surrounding the extracellular matrix at the synaptic gap. Astrocytes are the glial cells that are perhaps the most prototypical cells of the various neuron supporting cells; they exert their effects on the neurons in part by regulating the blood-brain barrier, and also by controlling the molecular and ionic concentrations of the synapse whilst also holding the pre- and post-synaptic neurons in appropriate articulation with each other (Kimmelberg & Nedergaard, 2010). At a certain point in A β oligomer production and concentration in an afflicted neuron, its release to the extracellular matrix (ECM) will become inevitable, putting them in high concentration to act on the neighboring astrocytes in support of the neuron; a certain subtype of acetylcholinergic receptor (α 7 nicotinic) directly binds the A β oligomers on the surface of the astrocytes (Kumar et al., 2015; Talantova et al., 2013). The binding of oligomers signals an intracellular increase of

calcium ions (Ca^{2+}) and their influx into the astrocytes, which mediates calcium-dependent glutamate release to the ECM (Talantova et al., 2013). This effect of $\text{A}\beta$ oligomers and the increased glutamate concentration is sufficient to activate the extracellular N-methyl d-aspartate receptors (eNMDARs) on the neurons intimately involved with the astrocyte under analysis; the intracellular effects on the surrounding neurons is an increase in calcium, which is known to have various adverse effects intracellularly depending on the concentration, especially with respect to the mitochondrial system (Talantova et al., 2013). The end result is the expulsion of ROS from mitochondria, causing oxidative damage, caspase 3 (a known apoptotic protein) activation, and tau hyperphosphorylation, all of which result in the loss of synaptic spines and therefore communication between pre- and post-synaptic neurons in close proximity to the dysfunctional astrocyte (Kumar et al., 2015; Talantova et al., 2013).

Cholinergic Hypothesis. Some researchers may find the amyloid- β cascade hypothesis to be less inclusive of some data among AD patients that can be more simply explained with the use of other theories. Because the majority of current clinically approved treatments for AD involve aspects of cholinergic synapse communication, researchers have formulated the cholinergic hypothesis, and their claims have largely been substantiated by certain evidences in the pathophysiology of AD patients. The role of brain acetylcholine content and its involvement in cognition and memory has been under investigation for over 40 years. Studies made use of the drug scopolamine (which functions as a nervous system cholinergic blockage) to compare young subjects treated with the drug with older subjects left untreated. The ensuing performances of both groups on examinations of cognitions and memory were highly comparable, indicating a possible link between loss of cholinergic synaptic communication and age-related dementia (Drachman & Leavitt, 1974). Other researchers found a lack of acetylcholine (ACh) synthetic

enzymes in the brain samples of deceased AD patients; additional relationships were uncovered such as cholinergic dysfunction correlating with memory loss, and supplementary cholinergic stimulation correlating with memory improvements among aged subjects. These findings led to the formulation of the cholinergic hypothesis in its fledgling state, before the exact pathophysiology was understood (Bartus, Dean, Beer, & Lippa, 1982; Hampel et al., 2019). The cholinergic hypothesis became more specific in scope with the discovery of the nucleus basalis of Meynert (NbM) as the central source for cholinergic innervation to the cerebral cortex, and also the atrophy of neurons in this very brain region among AD patients (Mesulam & Van Hoesen, 1976; Whitehouse et al., 1982). The current understanding of the cholinergic hypothesis and the actions of the cholinergic synapses in the processes of memory as well as their dysfunction in cognitively impaired patients (such as those with AD) mainly relate to the NbM brain region. It is notable that the NbM is paramount in providing innervation to the cerebral cortex as part of the RAS, which many cite as essential for consciousness and higher level cognitions including memory (Yeo, Chang, & Jang, 2013). The Ch₄ neurons of the NbM form the nucleus basalis, which witnesses significant loss and shrinkage of cholinergic neurons (Kordower, Gash, Bothwell, Hersh, & Mufson, 1989). These same neurons often appear to be the targets of NFTs in AD; the high density of NFTs in the NbM Ch₄ neurons appears to be the cause of synaptic destruction, further supporting the notion that loss of cholinergic innervations (especially those innervations that link the “primitive brain” regions to the complex cerebral cortex via the RAS) is the cause of observable AD pathology (Hampel et al., 2019).

According to the provided evidence from many researchers, and also according to the conventional treatment of AD with cholinesterase inhibitors, it should be evident that intact cholinergic innervation is essential for normal cognitive processes, and also that dysfunction in

the cholinergic innervation to the cerebral cortex is one of the trademarks of AD-affected brains that causes the common pathologies of cognitive impairment and memory loss. Although most researchers favor one of the above hypotheses over the other, it does not appear that the two previously mentioned hypotheses need be mutually exclusive of each other. In fact, there is substantial evidence that might indicate the exact opposite. Studies have shown that high concentrations of A β were associated with increased loss of cholinergic innervation, and also that A β levels showed positive correlation with brain atrophy in specific NbM regions (Hampel et al., 2019; Kerbler et al., 2015). More research is required to further affirm the relationship between these two hypotheses, yet it would appear that the expression of A β cascade processes that lead to ROS release and apoptotic pathways among neurons at dysfunctional synapses could be localized specifically for expression in cholinergic neurons, especially the synapses thereof which innervate the cerebral cortex in the RAS.

Tau Hypothesis. Another sect of research on AD pathophysiology is unsure of the negative effects of the A β protein altogether. Some researchers have characterized this protein as an anti-microbial immune system factor that acts in protection of the CNS (Soscia et al., 2010). Others also argue that its exhibition in senile plaques late in the progression of AD pathology is further evidence not of their malevolency, but rather their neuroprotective role (Maccioni et al., 2010). As mentioned above, NFTs are the other characteristic component of an AD-inflicted CNS. Resultantly, other researchers opt for the protein component of these NFTs (tau) and its phosphorylation as the source of AD pathology. The tau protein was originally identified in the NFTs as a microtubule-associated protein; its modification in AD brains was hypothesized to result in the instability of the cytoskeletal structure to which it was associated, leading to neuronal death (Kosik, Joachim, & Selkoe, 1986). The current tau hypothesis postulates that

NFT formation from tau phosphorylation is not the first step in the neurobiological pathway of AD pathology, yet it is the common pathway at the end of multiple pathways resulting from cellular stressors, such as ROS, aberrantly folded proteins, A β oligomers, iron overload, and cholesterol/ low density lipoprotein (LDL) interference (Maccioni et al., 2010). Various studies have produced evidence of a cascade that ends in NFT formation: the cellular damage caused by the aforementioned mechanisms results in the activation of microglial cells as part of the immune response. The production of cytokines then ensues in excess, which cascade into the deregulation of certain kinases and phosphatases, causing the hyperphosphorylation of the tau protein and consequent neuronal cell death as mentioned (Fernández, Rojo, Kuljis, & Maccioni, 2008; Maccioni et al., 2010). Logically, cell death of the neuron with accumulated phosphorylated tau leads to its expulsion to the ECM, resulting in a cascade of this process in surrounding areas. The microglial cells are again activated as a result of hyperphosphorylated tau's presence in the ECM, triggering the pathway to stimulate cytokine release again, resulting in a positive feedback loop causing neurodegeneration of the CNS (Maccioni et al., 2010). The specific protein responsible for the hyperphosphorylation of tau is cyclin-dependent kinase 5 (CDK5). The proinflammatory cytokines released by the microglial cells in the CNS are responsible for the pathway that is deregulated in the AD nervous system that activates CDK5, usually a cell cycle regulatory kinase, which in turn hyperphosphorylates the tau proteins (Alvarez, Muñoz, & Maccioni, 2001; Maccioni et al., 2010). One study which made use of murine hippocampal cells noted that the deregulation of CDK5 can be induced by β -amyloid introduction and lead to subsequent tau phosphorylation (Alvarez et al., 2001). Other researchers note that A β protein interaction induces inflammatory-like response in astrocytes, and also causes the production of nerve growth factor (NGF) in these cells; NGF causes an aberrant pathway of signaling via the

p75 neurotrophin receptor, and results eventually in the hyperphosphorylation of tau proteins (Sáez, Pehar, Vargas, Barbeito, & Maccioni, 2006). Investigations into the clinical effects of tau phosphorylation and NFT formation have led to the following conclusions among researchers: the severity of AD-caused dementia correlates with NFT accumulation in the CNS, there is a positive relationship between CSF phosphorylated tau concentration and cognitive impairment, and tau-targeting drugs help decrease cognitive impairment in AD (Maccioni et al., 2010).

The data provided might be analyzed so that the three hypotheses provided can be considered supplementary to each other. As was mentioned, most A β oligomers and aggregates have been localized to the cholinergic neurons of the CNS, specifically, the RAS. The action of A β oligomers on astrocytes, as defined in the *A β Cascade Hypothesis* section, might be thought of as occurring mostly in the cholinergic system of CNS neurons. The aberrant actions that this cascade causes in the destruction at cholinergic synapses also leaks over into tau-phosphorylating pathways as mentioned above. Part of the effects according to researchers are the overproduction of NGF at synaptic astrocytes (one can also say the overproduction of glutamate according to the cascade hypothesis). Both of these chemicals released then cause the hyperphosphorylation of tau proteins, and likely activation of the inflammatory pathway in neighboring microglial cells, which induces the release of cytokines which trigger the exact same result. The obvious connection is a positive feedback mechanism producing further destruction, and leading to the clinical symptoms of AD as mentioned because of the accumulation of NFTs. This process's localization to the cholinergic neurons of the CNS is what causes the specific cognitive and memory process impairments that are seen in the clinical form of the disease.

Anxiety in Alzheimer's Disease. Earlier in this review, evidence was presented to analyze the viability of Clinical Anxiety (CA) as an independent risk factor for the development

of AD. Several convincing studies indicate this may be a possibility. After the presentation of AD pathophysiology, it is now necessary to provide evidence supporting the hypothesis that the aberrant CNS development caused by AD is sufficient to produce comorbid anxiety conditions. In order for this evidence to be convincing, it should distinctly identify disruption of neural circuitry sufficient to cause CA, and exclude the possibility of CA development due to psychological distress associated with the consciousness of an individual's deteriorative state.

It is well established that anxiety symptomatology is present in many cases of those affected by AD. One study identified an unusually high proportion of patients with anxiety and anxiety symptomatology among a population of nursing home residents with dementia (Goyal, Bergh, Engedal, Kirkevold, & Kirkevold, 2018). The limitation of this study was that it did not specifically address AD patients but dementia subjects in general. Other researchers sought to distinguish between AD and other types of dementia. An analysis was performed comparing AD patients with subjects that had other forms of dementia: Vascular Dementia (VaD) and Frontotemporal Dementia (FTD) were used. This study's results were unexpected in that the patients with other types of dementia than AD exhibited higher proportions of anxiety (Porter et al., 2003). This research also identified a trend of increasing anxiety as cognitive deterioration increased (assessed by the Mini Mental Status Examination, or MMSE), and also an increase in anxiety with earlier age of AD onset (Porter et al., 2003). A hypothesis was made regarding the reason for the other forms of dementia exhibiting higher anxiety rates: VaD and FTD increasingly involve frontal lobe deterioration, a region essential in the subjective perception of anxiety (Porter et al., 2003). An analysis of a cohort of 1,015 AD patients discovered that anxiety syndromes were some of the most prevalent neuropsychiatric syndromes experienced by this grouping; furthermore, this study found that these syndromes often occurred at a clinically

significant level, indicating the severity of AD pathological effects on the CNS (Spalletta et al., 2010). This study, however, was not able to replicate the findings of Porter et al. that a positive correlation exists between the severity of AD and the occurrence of anxiety; affective disorders were the only disorders examined that did not exhibit this correlation (Spalletta et al., 2010). Researchers have found that certain anxiety symptoms are highly prevalent in AD patients, including anxious appearance, tension and fidgeting, and sleep disturbance; of the subjects in this study, however, only 6% met DSM criteria for clinical diagnosis (GAD was the only disorder measured) (Ferretti, McCurry, Logsdon, Gibbons, & Teri, 2001). This study also found that anxiety symptoms were associated with increased cognitive impairment, and hypothesized that treatment of anxiety symptomatology might prove useful for the management of AD (Ferretti et al., 2001). Further research attempted to characterize the relationship of GAD and AD specifically. When using the DSM-IV to determine diagnostic criteria, a group of 552 AD patients exhibited GAD among 15% of its sample; the most common symptoms for this population were restlessness, irritability, muscle tension, fear, and respiratory disturbances (Starkstein, Jorge, Petracca, & Robinson, 2007). The genetic form of the disease, Early Onset Alzheimer's Disease (EOAD) provides a useful model for the determination of this relationship. Patients with this form develop AD shortly after the fifth decade of life. Analysis of these patients provides a model that is certain to exhibit AD (penetrance of the various EOAD gene mutations is virtually 100%), and therefore eases the characterization of AD comorbid symptomatology (Tanzi et al., 1996). One study made use of this technique and analyzed the prevalence of anxiety in patients with EOAD compared with patients who have the more common Late-Onset Alzheimer's Disease (LOAD, referred to in this review as the default form). Findings indicated that anxiety symptomatology was present in both populations of AD patients,

yet was more prevalent in patients with EOAD as opposed to LOAD (70% versus 27%, respectively) (Kaiser et al., 2014). Initially, this might be informative of the nature of anxiety in AD. One might hypothesize that psychological factors are the main cause for the formation of anxiety in AD, because it could be stated that patients of EOAD have greater consciousness and understanding of their condition, having expected its development due to its genetic nature in their cases. LOAD patients, accordingly, might be less conscious of their deteriorative condition because of the inability to be informed of its development; subsequently this might lead to less psychological cause for the development of anxiety in AD and explains the results of this study. This interpretation would need more evidence to support such a hypothesis, and certain evidences also collected in the aforementioned study might negate its validity. A distinction was made in the correlates of anxiety for the EOAD and LOAD groups; the anxiety in the EOAD subset of this study was notably associated with caregiver separation among the patients, while in the LOAD group anxiety was associated with comorbid psychiatric and behavioral symptoms (Kaiser et al., 2014). The differences in manifestation of anxiety symptoms might instead be indicative of the separate causes of AD development in the cases of EOAD as opposed to LOAD. Again, this hypothesis would also need additional information to clarify its validity.

As evidenced, a substantial relationship exists between AD and subsequent development of clinically significant anxiety. Simple correlations between the two disorders do not necessarily indicate causation; rather, investigation into the effects of AD pathology on neural circuits related to anxiety psychology might provide more convincing evidence. Various studies performed exhibit certain examples where AD pathology (in the form of A β plaques and NFTs) was discovered to be especially prevalent in nuclei associated with anxiety pathology. One study of the posthumous anatomy of AD-afflicted individuals allowed for the development of six

stages that describe the progression of AD; it was determined that the amygdala (mentioned in the “Anxiety Pathophysiology” section as a crucial nucleus for anxiety generation and conditioning) is among the first subcortical nuclei to exhibit the characteristic plaques and NFTs with respect to AD progression in the six stages (Braak & Braak, 1991). Furthermore, the extent of A β and NFT accumulation was seen to increase with the progression of the disease; if it could be shown that AD pathological interference in the amygdala was sufficient to produce anxiety symptomatology, this might support the findings of previously mentioned studies that anxiety was associated with increased cognitive impairment (Braak & Braak, 1991). In order to determine whether anxiogenic effects occurred in response to A β accumulation in the amygdala, researchers España et al. performed an in depth analysis of fear and anxiety conditioning in AD-transgenic mice, as well as postmortem brain examination of the amygdala in both murine subjects and humans. It was determined that various AD-transgenic models all exhibited increased conditioned and instinctive fear responses when compared with wild-type controls (España et al., 2010; Sterniczuk, Antle, Laferla, & Dyck, 2010). The fear or startle responses analyzed in murine studies are supposedly analogous to the human subjective experience of anxiety and fear, but to be sure, these researchers clarified this correlation by noting that anxiolytic drugs were sufficient to decrease the fear or startle response in transgenic subjects while having no effect on wild-type individuals (España et al., 2010). Transgenic mice that had this anxious presentation were seen to also have impaired hippocampal-dependent spatial memory and notably increased concentrations of A β oligomers (España et al., 2010). Furthermore, immunostaining of autopsied murine subjects revealed the accumulation of A β in either GABAergic interneurons or glutamatergic interneurons of the basolateral amygdala (BLA) depending on the transgenic model analyzed (APP versus 3xTg-AD, respectively);

phosphorylated tau was also identified in the 3xTg-AD models (España et al., 2010). Likewise, analysis of human specimens revealed the presence of A β accumulation in GABAergic and glutamatergic neurons in the BLA of AD brains in significantly increased concentrations compared with normal individuals; lastly, this study determined that phosphorylation of ERK1 and 2 was increased in the BLA of AD-transgenic mice (España et al., 2010). The ERK/MAPK signaling pathway in this nucleus is essential for fear acquisition, indicating the role of AD pathological changes in the positive regulation of its function. Therefore, the findings of this study provide convincing evidence for the possibility of AD pathology disrupting neural circuitry intimately involved in the biological processes that induce the psychological experience of anxiety. Previously described, the amygdala nucleus and neurotransmitter signaling involved with it is essential in the psychological mechanism of anxiety development. Furthermore, the accumulation of A β in GABAergic neurons of this nucleus might indicate the specificity of AD pathology in disrupting anxiety signaling when considering the importance of GABAergic communication in anxiety pathology (see *Anxiety Pathophysiology* section).

Characterizing the Relationship between Anxiety and Alzheimer's Disease

Over the course of this review, a plethora of evidence was presented in an effort to provide a comprehensive understanding of two pathologies: anxiety and Alzheimer's Disease. In developing this exhaustive collection of knowledge and evidence on these disorders, various examples of overlap have been identified between the two diseases that might indicate a causal relationship between CA and AD development, and also the inverse of that relationship. Scientific research questions, however, should never start with the goal of *proving* anything, but should commence with the ultimate goal of *uncovering* the truth that already is. If substantial evidence could be presented that CA is a causal risk factor for AD due to the pathological

changes it produces in the CNS, and if further substantial evidence also characterized the disease morphology seen in AD as significant in disrupting the mechanisms of anxiety, then a unique relationship would exist between these two pathologies. A positive feedback of sorts would exist between these two pathologies, with CA leading to AD, and AD in turn producing the side effect of CA along with mental deterioration. Even with the evidence presented, however, these two speculations are still rather large *ifs*. The availability of evidence specifically on the relationship between these pathologies is relatively low compared to other topics, and the overlaps presented between the two diseases are not without their complications. In some instances, evidence is varied with regard to the overlap between these pathologies. In other cases, correlation between CA and AD might not prove causation of one by the other, but a third factor could be the cause of both. In this section, evidence presented will be reviewed with these issues in mind, and an attempt will be made to clarify what conclusions can be stated about the causal relationship of these two pathologies with the current knowledge base.

Anxiety as a risk factor. Clinical studies were previously identified that tested the relationship between CA and AD by pure correlation, specifically looking for an increased chance of AD development when anxiety symptomatology or CA diagnosis was present. A few of these clinical studies might be considered *soft evidence* of a relationship, due to the lack of CA diagnosis among the subjects, and also the identification of cognitive deterioration or MCI rather than AD as the result. Even so, research identified anxiety symptomatology subjects as having increased cognitive decline, and decreased performance on appropriate memory assessments (Booth et al., 2006; Christian et al., 2004). In many instances however, groups of patients with sub-clinical levels of anxiety failed to exhibit increased rates of cognitive deterioration; similarly, patients with a clinical diagnosis often displayed this relationship (Beaudreau &

O'Hara, 2008; Mantella et al., 2007). Studies that controlled for additional factors such as MDD produced further convincing evidence of a relationship between CA and cognitive decline or memory deterioration (DeLuca et al., 2005; Sinoff & Werner, 2003). The evidence presented in these studies leads to the conclusion that anxiety has differing deteriorative effects on cognition than does MDD, and also that a clinical level of anxiety diagnosis is necessary for the cognitive decline to be pronounced.

Perhaps the most convincing evidence identified by simple correlation is the increased rate of AD development in patients who had been assessed as having CA a minimum of 10 years prior to AD diagnosis (Gimson et al., 2018). This review by researchers Gimson et al. was able to identify four examples of primary literature where this was the case; evidently, clinically-diagnosed anxiety in these studies was well in advance of 5 to 6 years, disqualifying the hypothesis that CA in these subjects was a prodromal symptom of AD. The limitations of this study are obvious: only four examples of this significant relationship were found. Further research should be undertaken to identify the correlation between CA diagnosis 10 years in advance of AD development in order to strengthen the evidence of this relationship. Furthermore, while the correlation between the development of these two pathologies may be confidently said to exist, this still does not prove the causation of AD by CA. Rather, this correlation should invite further research into the cellular pathophysiology of CA that might lend itself to AD development, a topic which will be concluded about next using the current knowledge base.

The next level of analysis regarding this issue is the effect of CA on brain structures that might initiate conversion to AD. Convincing evidence comes from researchers Mah et al., who identified anxiety as a significant predictor of conversion to AD from aMCI by analyzing

Alzheimer's ROI in imaging studies (Mah et al., 2015). This study highlighted the increased rate of deterioration in the EC, and further hypothesized that this is the process by which anxiety mediates the deterioration from MCI to AD. Additional and wider-reaching evidences should be collected regarding the importance of the EC in anxiety-mediated deterioration in order to increase the robustness of this hypothesis, yet this sizable study (n = 376) remains convincing. Further brain imaging evidence highlights the increased frequency of hippocampal atrophy among CA patients, namely those with PTSD (Villarreal et al., 2002; Weniger et al., 2008). Hippocampal atrophy is a common pre-clinical occurrence witnessed in AD development, and the atrophy of that brain region is progressive throughout the timeline of the disease (Carlesimo et al., 2015; Fox et al., 1996). This combination of evidence might suggest a convincing causal relationship between CA and AD, yet other research negates this premise for good reason. A study of twins in which one twin experienced combat while the other did not determined smaller hippocampal volume is more likely a cause of increased PTSD susceptibility, rather than PTSD development being the cause of atrophy of the hippocampus (Lasko et al., 2002; Sapolsky, 2002). Further investigation of the relationship between hippocampal development and PTSD diagnosis should be undertaken to characterize this relationship. The nature of twin studies might suggest that the genotype of certain individuals could predispose them toward smaller hippocampal volume and hence increased chance of developing PTSD, but more data is required to make an informed conclusion.

The final level of analysis important in this issue is the cellular level. Research has been identified that attributes a central role of GR signaling and hypersecretion of cortisol in mediating the pathological effects of anxiety conditions, especially with relation to the hippocampus. Firstly, certain PFC and other cerebral brain regions exhibit high instances of

atrophy, supposedly mediated by increased concentration of GRs, making these regions susceptible to cortisol hypersecretion (Goosens & Sapolsky, 2007). These regions are often crucial endpoints of the RAS, a circuit of cholinergic communication that witnesses increased deterioration in AD, and is the basis of clinical treatment with cholinesterase inhibitors (Hampel et al., 2019; Hollander, Mohs, & Davis, 1986). This is a convincing correlation, but more research should be undertaken targeting more specific regions of the cerebrum to determine if a fundamental relationship exists. It would be essential to note the rate of deterioration of these brain regions in MCI patients that convert to AD, and whether anxiety is a significant predictor of increased deterioration. Furthermore, increased GC levels and HPA axis activity has been associated with decreased LTP and hippocampal volume, becoming more pronounced with age (Meaney et al., 1991; Pavlides et al., 1993). Higher GR levels are seen in hippocampal regions with an increased rate of neuronal death (Goosens & Sapolsky, 2007). Some researchers synthesize this evidence into the glucocorticoid cascade hypothesis. This proposes that excessive levels of cortisol due to prolonged states of distress (seen in CA) lead to hippocampal cell death and atrophy because of the neurotoxicity of these high cortisol levels; consequently, this atrophy causes a decreased ability of the hippocampus to cope with cortisol levels by activating the normal negative feedback mechanism wherein it down-regulates the secretion of cortisol via the HPA axis. Therefore, the absence of this regulation leads to a detrimental positive feedback mechanism of hyper cortisol secretion and hippocampal damage (Frodl & O'Keane, 2013). Transition to AD pathology might be confirmed by the evidence that increased plasma cortisol levels are seen in AD patients compared to normal controls (Armanini et al., 2003). The previously mentioned researchers Frodl & O'Keane claimed neuroinflammation is also a result of the glucocorticoid cascade hypothesis. This might contradict the normal effects of cortisol,

which usually promotes decreased inflammation. Yet the neuroinflammatory consequences of this cascade could be mediated by increased hippocampal cell death leading to cellular debris accumulation; this hypothesis would need further testing of its validity. Regardless, if neuroinflammation is seen as a result of excessive cortisol secretion, this could represent a pathological mechanism leading to AD development that follows the Tau hypothesis: the dysfunction of the CNS immune mechanisms in countering neuroinflammation causes the aggregation of phosphorylated tau proteins (Maccioni et al., 2010).

Anxiety in Alzheimer's Disease. The second half of this potential positive feedback mechanism of pathologies must now be briefly analyzed and concluded about. In order to conclude that AD increases the development of CA more so than the regular processes of senescence, evidence should show that aberrant CNS development caused by AD is sufficient to produce comorbid anxiety conditions, and that this anxiety is likely due to these developmental malfunctions rather than the subjective distressing experience of the patients in question. This is a difficult task at hand, and although certain convincing evidences exists, further experimental investigation would aid in making such a conclusion.

Much evidence currently exists, however, for the increased proportion of anxiety conditions and symptomatology in patients with AD than normal controls (Goyal et al., 2018; Porter et al., 2003; Spalletta et al., 2010). Other researchers were more selective in including only DSM-diagnosed conditions, yet they still found high instances of anxiety diagnosis (Ferretti et al., 2001; Starkstein et al., 2007). A few researchers found a correlation, identifying increasing anxiety as cognitive decline increased in rate, although not all studies corroborated this evidence (Porter et al., 2003). More studies are necessary to obtain more conclusive data on this specific aspect, but if this were proven true, this could support the hypothesis that increasing anxiety with

cognitive decline is caused by the increase in plaque or NFT formation in the amygdala throughout the six-stage progression of AD (Braak & Braak, 1991). This is significant evidence of a possible causal relationship that requires further investigation.

As mentioned earlier, researchers España et al. further investigated the role of A β accumulation in the amygdala in causing anxiety pathology. They noted that increased A β concentration was associated with increased anxiety presentation, and highlighted the dysfunction of GABAergic neurons in the BLA of both transgenic mice and humans with AD (España et al., 2010). Given the paramount importance of GABAergic signaling (especially its dysfunction in pathological conditions previously mentioned), this researcher provides substantial direct evidence for a causal role of AD pathophysiology in producing anxiety conditions. More investigation should be undertaken, specifically with regard to the mechanisms by which A β accumulation or the oxidative stress caused thereof mediates the negative effect on fear acquisition via the ERK/MAPK signaling pathway in the BLA.

Conclusion

Conclusively, substantial evidence has been presented to identify the interrelatedness of these two pathologies, CA and AD. Defining the exact mechanism by which these two CNS dysfunctions have a hand in causing the other has been more difficult. Sizeable reviews of the pathophysiology behind each disorder have shown significant overlap between these diseases in critical areas. A few investigators sought to answer research questions specific to these areas of overlap, and have thus identified potential methods of defining the mechanisms by which these diseases are related on a cellular level. However, the proposed positive feedback mechanism between CA and AD would benefit from additional evidences, of which a few can be identified. Firstly, additional clinical studies should seek to identify evidence of AD development at least 10

years from baseline anxiety diagnosis to further support the correlation between CA and AD and exclude the interference of prodromal stage symptoms. More research is also required in determining the importance of the entorhinal cortex in anxiety-mediated deterioration during AD. Likewise, future work should determine if the rate of deterioration of the PFC in patients that convert from MCI to AD is significantly increased by the presence of anxiety. Determining the cause of neuroinflammation that might initiate the cascade of tau-phosphorylation is of the utmost importance; the hypothesis that hippocampal cell death caused by the glucocorticoid cascade mediates neuroinflammation requires further investigation. Furthermore, it would be essential to note if anxiety increase in AD is paralleled by increasing aggregation of NFTs in the amygdala. Lastly, the effect of A β accumulation in the BLA on the ERK/MAPK pathway of fear acquisition should be investigated. Scientific investigation and discovery in these areas could enable researchers to clarify the relationship between these two pathologies. If a further understanding of the identified correlations is brought about, clinicians could introduce new treatments to patients suffering from anxiety or AD with respect to the relationship between these conditions.

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