



The relation of worry to prefrontal cortex volume in older adults with and without generalized anxiety disorder

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ABSTRACT

Despite the widespread prevalence of generalized anxiety disorder (GAD) in later life, almost nothing is known about the neural aspects of worry in adults over the age of 60. Given the ongoing rapid increase in the older adult population, the relatively poor response rates to current interventions for late life GAD, and the effects of age-related changes to the brain, additional research on worry neurobiology is needed. The study group comprised 15 older GAD patients and 15 matched controls who were compared on clinical measures and brain volumes. It was expected that prefrontal cortex (PFC) volumes [medial orbital cortex (mOFC), dorsolateral cortex (DLPFC)] would show positive relations to worry scores, and weaker relations to more general measures of anxiety and depression. Negative relations were expected between amygdala volumes and worry scores. As expected, mOFC volumes were positively related to worry scores; however, DLPFC and amygdala volumes were not. The mOFC is involved in emotional decision-making under uncertain conditions and has the ability to suppress the amygdala, both of which are hypothesized functions of worry. Results are partly consistent with GAD theory and suggest that worry may involve neural areas that are also involved in the successful control of anxiety.

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1. Introduction

The world's older adult population is increasing at an estimated rate of 800,000 people per month (Kinsella and Velkoff, 2001), which will have a dramatic impact on global health issues. For instance, along with the growing older adult population comes a corresponding expectation of increased rates of psychiatric conditions such as anxiety and depression (Jeste et al., 1999; Blazer, 2003). However, research in anxiety disorders has not kept pace with the aging trend. Mental health specialists now face a burgeoning public health problem, given the relative lack of empirical knowledge to inform the conceptualization and treatment of late life anxiety.

Generalized anxiety disorder (GAD), a condition characterized by excessive, uncontrollable worry, is the most common anxiety disorder among adults over the age of 60, with estimated prevalence rates ranging widely from 0.71 to 7.3% (Flint, 1994; Beekman et al., 1998; Flint, 1999). Current diagnostic criteria according to the *Diagnostic and Statistical Manual IV-TR* (DSM-IV-TR; American Psychiatric Association, 2000) require at least 6 months of frequent worry about several real-life problems, occurring more days than not, accompanied by at least three associated symptoms such as tension, fatigue, irritability, trouble

concentrating, or insomnia. GAD is a prevalent but underrecognized public health problem, associated with significant functional impairment (Mogotsi et al., 2000), serious disability (Kessler et al., 1999), and increased risk for acquisition of additional psychiatric disorders and medical conditions (Brown et al., 1994; Kennedy and Schwab, 1997; Noyes, 2001; Barger and Sydeman, 2005). Response rates in most studies of late life GAD pharmacological and psychosocial treatment are surprisingly low (Mohlman, 2004; Mitte, 2005), highlighting the need for additional data on the causal and maintenance factors of the disorder.

1.1. Neurobiology and theoretical models of GAD

Although the neurobiology of GAD remains largely obscure (Mathew et al., in press; Sinha et al., 2004), neural patterns characterizing two broad types of anxiety have been proposed (Heller et al., 1997; Nitschke et al., 2000). Anxious apprehension, a construct that encompasses cardinal symptoms of GAD such as worry and concern about imminent and future events (Borkovec et al., 1983; Barlow, 1991), is posited to involve increased activity in the left hemisphere, particularly in frontal areas (Heller et al., 1997). By contrast, those emotional states characterized by exaggerated somatic symptoms, sympathetic arousal, and a focus on imminent fear cues (such as panic disorder) are believed to be characterized by right posterior activity (Nitschke et al., 1999).

Models of GAD have posited a more specific relation between the PFC and the amygdala. In addition to a distinct left hemisphere profile,

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GAD may be associated with frontal overcontrol (e.g., excessive worry) and limbic hypoactivity (e.g., blunted sympathetic arousal; Hoehn-Saric et al., 1989; Thayer and Lane, 2000), which is in contrast to the common anxiety disorder profile of limbic overactivity coupled with poor frontal control of negative affect (e.g., Kent and Rauch, 2004; Lorberbaum et al., 2004). According to Borkovec (1994), GAD patients and high worriers use worry instrumentally as a strategy to dampen or avoid strong feelings of emotional arousal, which they may perceive to be more aversive than worry itself. Although it is likely that there are both excitatory and inhibitory processes at work during worry (Gray et al., 2003), these models and the few neurobiological studies that do exist implicate increased activity in the prefrontal cortex (PFC) both at rest and during worry in adults with GAD, perhaps due to the ability of areas of PFC to suppress or inhibit activation of the limbic system (Hoehn-Saric et al., 2005). Neuroimaging findings are mostly consistent with the notion that worry and related states of anxious apprehension recruit areas of the PFC (primarily DLPFC, mOFC), which may then suppress or inhibit activity in limbic regions including the amygdala (c.f. Sinha et al., 2004).

1.2. Additional considerations for older adults

All existing data on neurobiological correlates of worry have been collected from younger adults. However, factors related to aging are associated with changes in PFC structure, and could affect the neurobiological profile of worry. For instance, West's (1996) frontal lobe hypothesis posits accelerated volume loss brought about by cell shrinkage (Hachinski et al., 1987), decreased dopamine (DA) concentration, and a reduction in the number of DA receptors in the frontal cortex (Goldman-Rakic and Brown, 1981) with advancing age. Some evidence exists for inordinate degradation of the PFC relative to other brain areas (Raz et al., 1998; Tisserand et al., 2002) and of the DLPFC relative to other frontal areas (MacPherson et al., 2002). Consistent with the age-related decline of PFC-governed cognitive operations (e.g., executive skills; Hasher and Zacks, 1988), these effects could lead to decreased PFC involvement in worry and states of anxious apprehension in older adults.

Indeed, GAD symptoms are typically less severe in older patients as compared with young patients. Self-report and clinician-rated measures of worry consistently reveal lower mean scores in older (e.g., Beck et al., 1996; Stanley et al., 1996a,b, 2003; Wetherell et al., 2003a,b; Mohlman and Gorman, 2005) than younger GAD samples (e.g., Molina and Borkovec, 1994; Behar et al., 2003; Fresco et al., 2002). Older adults may experience additional age-related physiological changes such as blunted reactivity to stress (Whitbourne, 1985; Kogan et al., 1999), decreased neurochemical reactivity (DeBeurs et al., 1999), long-term habituation effects, increased coping abilities, or less anxiety about future goals (Borkovec, 1988), all of which could produce less severe and frequent emotion states (Lawton et al., 1993; Kogan et al., 1999). Not surprisingly, it can be difficult to distinguish late life GAD from subclinical anxiety states, which are believed to be common among the elderly (Wetherell et al., 2003a,b), and many healthy older adults intermittently experience symptoms of GAD (Stanley and Novy, 2000). This is consistent with recent findings on the taxonomy and structure of worry implicating the appropriateness of a dimensional approach (Ruscio and Borkovec, 2001). Therefore, we expect differences between older GAD and control samples to be of generally lesser magnitude than those found in studies conducted with younger samples, even on measures of worry, the hallmark symptom of GAD.

1.3. The present study

The aim of this study was to test hypotheses derived from the avoidance model of GAD (Borkovec, 1994) regarding the relation of worry to PFC and amygdala volumes in patients and age- and sex-

matched controls, a sample that was meant to represent the full range of scores on a measure of worry. Such data could be useful in identifying regions of interest (ROIs) and neurobiological targets for possible treatment optimization in older worriers, as well as providing support for popular and useful models of GAD and anxious apprehension.

Brain structure and function may be related due to use-dependent neuroplasticity as well as in cases where degraded structure constrains function. Thus, we used structural MRI to test the hypothesis that regional brain volumes would be related to symptom measures. Because worry involves the same neural areas and cognitive processes in nonclinical samples as in GAD patients (e.g., Hoehn-Saric et al., 2004, 2005), we did not expect substantial differences between the GAD and control groups on brain volumetric ROIs. Rather, consistent with a dimensional perspective, it was expected that scores on a continuous measure of worry would show a positive association with DLPFC and mOFC volumes, with stronger associations being found with left hemisphere ROIs due to the verbal component of worry. We also expected to find negative correlations between worry scores and amygdala volumes. Worry scores were expected to be significant predictors of PFC ROIs in linear regression models including variables related to PFC volume (age, hypertension [htn], whole brain volume [WBV]), and to outperform more general measures of anxiety and depression in these models, given the specific function of worry set forth in contemporary models (e.g., Borkovec, 1994).

2. Methods

2.1. Participants

Participants were 30 adults aged 60 and over (mean = 67.87, S.D. = 5.39, range = 60–77), 50% female, mostly Caucasian (90%), recruited from an urban community through media ads and community outreach, and assessed in an outpatient hospital clinic setting. Fifteen met criteria for a primary diagnosis of GAD according to the *Structured Clinical Interview Diagnostic for DSM-IV* (SCID; First et al., 1995), and 15 did not meet criteria for any current psychiatric disorder.

2.2. Measures

The SCID (First et al., 1995) was administered by trained Master's- or Ph.D.-level assessors who completed 6 months of training on administering the interview. Seventy-five percent of patient SCIDs ($n = 10$) were observed by a supervisor to ensure reliability (J.M.). Additionally, a random sample of audiotaped SCID interviews ($n = 12$) was then independently rated by a blind assessor to estimate interrater reliability. The kappa coefficient for the diagnosis of GAD was 0.92; however, all participants passed a preliminary phone screen that included a checklist of GAD symptoms, so this estimate might be somewhat inflated.

Rates of comorbidity were moderate; 57% of those in the GAD group also met criteria for at least one additional disorder, most often dysthymia (20%), specific phobia (20%), social phobia (20%), or panic disorder (14%). Because of the known differences in the neurobiology of GAD versus late life major depression (i.e., reduced PFC volumes in depression; Krishnan et al., 1992; Kumar et al., 2000; Taylor et al., 2004), we excluded any participant who reported major depressive episodes at the time of the interview ($n = 1$). The mean age of GAD onset among patients was 43.50 (S.D. = 24.75; range = 7–76), with 50% ($n = 7$) reporting emergence of GAD at or prior to age 50.

The sample was generally in good health, as determined through self-reported medical history and a review of medical records. Most were retired, had at least a high school diploma, and were married or divorced. Participants were required to be right-handed, have no metal implanted in the body, have intact basic cognitive skills (Mini-

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