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Effects of citalopram on worry and brain activation in patients with generalized anxiety disorder

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Abstract

The effects of auditory statements describing a personal worry on brain activation as measured by functional magnetic resonance imaging were examined in patients with generalized anxiety disorder (GAD) before and after anxiety reduction with citalopram. Six patients were imaged while listening to verbal descriptions of a personal worry or a neutral statement before treatment with citalopram and after 7 weeks of treatment. Pre–post drug analyses showed treatment with citalopram reduced self-reported anxiety and reduced BOLD responses to a pathology-specific worry and a neutral stimulus. After treatment, worry sentences, compared to neutral statements, elicit reduced BOLD responses in prefrontal regions, the striatum, insula and paralimbic regions. In addition, contrasts before and after treatment revealed reductions in the differential response that existed between worry and neutral statements. Overall reduction of BOLD response was most prominent during neutral statements, particularly in the left hemisphere. These findings support the clinical impression that GAD patients overreact to both pathology-specific and non-specific cues and that the reduction of anxiety attenuates the response to both types of cues.

Keywords: Functional magnetic resonance imaging; Worry; Anxiety; SSRI

1. Introduction

Anxiety is a complex response to potential threat that requires the recognition and evaluation of potential danger signals, induces heightened arousal and activates stress-response systems (Davis and Shi, 1999; LeDoux, 1998; Noyes and Hoehn-Saric, 1998; Reiman, 1997). When such evaluations become difficult, a person starts to worry. Worry is an uncontrollable, verbally mediated activity concerning future events that occurs when one anticipates a potentially hazardous condition and doubts one's ability to cope with a situation (Carter et al., 1986). Thus, worry is characterized by unpleasant and anxiety-provoking ruminations that occur while attempting to find an answer to difficult ambiguous situations. In anxiety disorders, worries become excessive and are often unrealistic (Barlow, 1988); in generalized anxiety disorder

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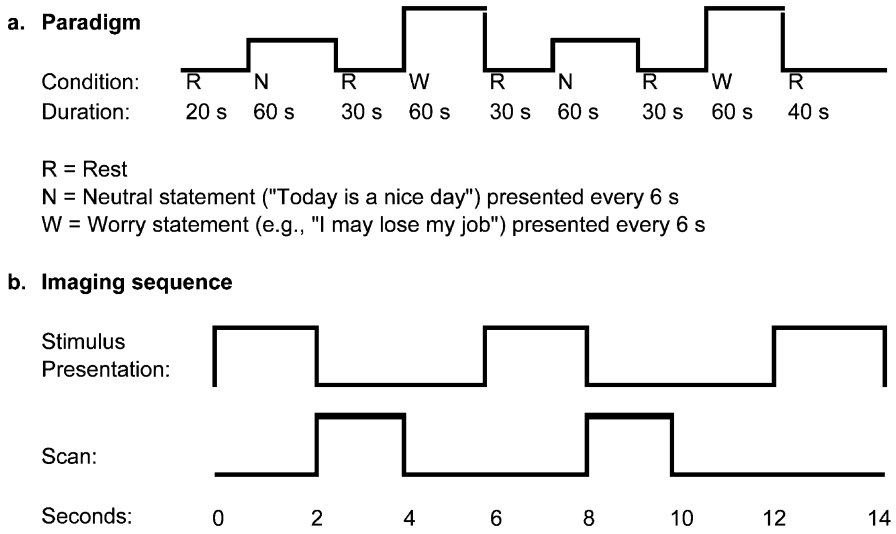

Fig. 1. (a) Sequence and duration of rest (R), neutral (N) and worry (W) conditions. (b) Sequence and timing of imaging acquisition relative to stimulus presentation (neutral or worry statements). Image acquisition lasted 2 s and was repeated every 4 s. Acquisition was timed to coincide with the termination of each stimulus presentation. Stimulus presentation onset was separated by 6 s.

(GAD), they constitute the key symptoms (American Psychiatric Association, 1994).

In contrast to other anxiety disorders, only a few imaging studies have examined patients suffering from GAD (Buchsbaum et al., 1987; Wilson and Mathew, 1993; Wu et al., 1991). Wu et al. (1991) employed PET to examine patients with GAD. Compared to controls, GAD patients showed relative glucose metabolism increases in left inferior area 17 in the occipital lobe, right posterior temporal lobe and right precentral frontal gyrus. Changes in anxiety scores were significantly correlated with changes in the limbic system and basal ganglia in patients receiving placebo. However, the study did not focus on excessive worrying, the most prominent symptom in patients with GAD. Therefore, it is plausible to suggest that exposure to personal worry may be the clinically most appropriate symptom provocation to investigate in patients with GAD. The aim of this study was to measure brain activation with functional magnetic resonance imaging (fMRI) to worry before and after treatment with citalopram. Several controlled studies have demonstrated that psychic symptoms of anxiety, which include worries, respond better to antidepressants with serotonin reuptake inhibitory properties, such as imipramine (Hoehn-Saric et al., 1988; Rickels et al., 1993), venlafaxine (Allgulander et al., 2001) and paroxetine (Pollack et al., 2001), than to benzodiazepines. This investigation examined the effects of citalopram, which is the purest available serotonin reuptake inhibitor. Results of previous investigations suggest citalopram is effective in the treatment of a variety of anxiety disorders, including panic disorder (Perna et al., 2001), obsessive–compulsive disorder (Stein et al., 2001), social phobia (Simon et al., 2001), post-traumatic stress disorder (Seedat et al., 2000) and generalized anxiety disorder (Varia and Rauscher, 2002). We predicted that citalopram would reduce clinical symptoms of anxiety, including the intensity of worries, and brain activation in prefrontal and limbic regions.

2. Methods

2.1. Subjects

Six patients, three male, all Caucasians, with a mean age of 36 (23–44) years and a mean education of 18 (16–20) years carried the DSM-