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The verbal nature of worry in generalized anxiety: Insights from the brain

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ABSTRACT

Background: The Cognitive Avoidance Theory of Worry argues that worry is a cognitive strategy adopted to control the physiological arousal associated with anxiety. According to this theory, pathological worry, as in Generalized Anxiety Disorder (GAD), is verbal in nature, negative and abstract, rather than concrete. Neuroimaging studies link the expression of worry to characteristic modes of brain functional connectivity, especially in relation to the amygdala. However, the distinctive features of worry (verbal, abstract, negative), and their relationship to physiological arousal, have not so far been mapped to brain function.

Methods: We addressed this omission by undertaking a resting-state functional magnetic resonance neuroimaging study of 19 patients with GAD and 21 controls, before and after induction of perseverative cognitions, while measuring emotional bodily arousal from heart rate (HR). Seed-based analyses quantified brain changes in whole brain functional connectivity from the amygdala.

Results: In GAD, the induction increased negative thoughts and their verbal content. In line with predictions, the verbal expression of worry in GAD was associated with higher HR at baseline and attenuated HR increases after induction of perseverative cognitions. Within brain, the increased use of words during worry, and the associated dampening of HR after induction were mediated by the strength of functional connectivity between the amygdala and default mode network 'hubs' and the opercular cortex. The negative content of worry was further related to functional communication between amygdala and cingulo-opercular and temporal cortices.

Conclusions: Findings provide a neurobiological basis for the impact of verbal worry on HR in GAD.

1. Introduction

Worry describes repetitive thoughts about potentially negative events in the future. Although worry is common to almost everybody's experience, it becomes chronic and uncontrollable in Generalized Anxiety Disorder (GAD; DSM-5, American Psychiatric Association, 2013). One puzzle underlying pathological worry is why individuals engage in this form of cognition in the absence of evidence that it serves an adaptive purpose.

The Cognitive Avoidance Theory of Worry is an influential account for understanding why patients with GAD spend so much time worrying. This theory proposes that worry is implemented by patients as an avoidance strategy, aimed at controlling physiological arousal engendered by anxiety (Borkovec, 1994; Borkovec et al., 2004). Pathological worry is typically verbal: both healthy and psychopathological individuals shift the nature of their cognitions towards negative verbal thoughts when instructed to think about a current concern (Behar et al., 2005; Borkovec and Inz, 1990; Stöber et al., 2000). Moreover, successful therapeutic outcomes for patients with GAD are accompanied by reduction in the ratio between reported words and mental imagery (Borkovec and Inz, 1990). Consistent with the model, verbal articulation of fearful thoughts attenuates cardiovascular

Abbreviations: GAD, Generalized Anxiety Disorder; rsfMRI, resting-state functional magnetic resonance neuroimaging; HR, heart rate; NYC-Q, New York Cognition Questionnaire; DMN, default mode network; HC, Healthy Controls; SCID, Structured Clinical Interview for DSM; BDI, Beck Depression Inventory; RRS, Ruminative Response Scale; PSWQ, Penn State Worry Questionnaire; STAI, Spielberger State Trait Anxiety Inventory; EPI, echoplanar imaging; BOLD, blood oxygenation level dependent; PCC, posterior cingulate cortex

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reactivity, whereas mental imagery of the same material elicits exaggerated cardiovascular responses (e.g., Borkovec and Hu, 1990; Borkovec et al., 1993; Hazlett-Stevens and Borkovec, 2001; Peasley-Miklus and Vrana, 2000; Vrana et al., 1989). Lastly, in support of the notion that individuals with GAD use their worry to try to control emotional arousal, when asked why they worry, patients answer that 'worry helps distract me from more emotional topics' or 'prepare for the worst' (Borkovec and Roemer, 1995; Davey et al., 1996; Freeston et al., 1994). Nevertheless, this mechanism can also explain the chronic nature of anxiety in GAD patients: the reduction in emotional processing following 'successful' verbal worrying limits exposure to anxiety-provoking material, and thereby prevents normal adaptive habituation (Borkovec et al., 2004). Despite this evidence supporting the Cognitive Avoidance Theory, not all studies show attenuated physiological arousal during worry (see Ottaviani et al., 2016a for a meta-analysis) and alternative theoretical explanations have emerged (e.g., the Contrast Avoidance Model by Newman and Llera, 2011).

Our study combined functional brain imaging with peripheral physiological monitoring to test for a hypothesized association between worry and up-regulation of regions linked to language and cognitive control processes (including lateral prefrontal cortex and inferior frontal gyrus) with concurrent down-regulation of brain regions implicated in affective processing and emotion-related cardiovascular reactivity. This work extends previous observations regarding the neurobiological signatures of pathological worry that are consistent with the Cognitive Avoidance Theory of Worry. A negative association between worry scores and amygdala-prefrontal functional connectivity was observed after a worry induction, suggesting efficient top down suppression of fearful imagery associated with the worry (Meeten et al., 2016). Moreover, stronger engagement of the prefrontal cortex (reflected by increased connectivity with bilateral amygdala) is associated with attenuation of dysregulated autonomic arousal during worry in individuals with GAD, confirming that worry may act as to suppress physiologic arousal in this clinical population (Makovac et al., 2016b).

Building on these results, our study aimed to characterize patterns of resting state functional connectivity in relation to the modality of participants' thoughts during worry in patients with GAD and healthy controls. We employed a validated measure of ongoing cognition, the New York Cognition Questionnaire (NYC-Q; Gorgolewski et al., 2014, see also Sanders et al., 2017). The questionnaire has established utility in neuroimaging studies, where self-generated verbal cognitions, across a large normative sample, were inversely associated with engagement of regions of retrosplenial cortex closely linked to the hippocampus (Gorgolewski et al., 2014). In our study, we specifically tested how the content and form of worry, measured by the NYC-Q, related to the functional connectivity of the amygdala at rest and bodily arousal indexed by heart rate (HR). We focused on the dimensions of the NYC-Q that measure well-recognized characteristics of worrisome thoughts (i.e., verbal, abstract/vague, and negative). To obtain measures of bodily arousal and the form of thoughts during worry, a behavioural induction of perseverative cognition was used. We predicted that the induced worry would be predominantly verbal, negative, and vague particularly in individuals with GAD. Considering that functional connectivity under multiple mental states is essential to disentangle connectivity differences that are transient versus those that represent more stable, trait-like characteristics of an individual (Geerligs et al., 2015), we measured functional connectivity at rest, and also quantified changes in functional connectivity from pre to post-induction of perseverative cognitions. As hypothesized by the Cognitive Avoidance Theory of Worry, we predicted that there are differences in amygdala functional connectivity during verbal, compared to imagery-related, worry and that these differences are linked to attenuation of physiological arousal after worry induction. Borkovec's Theory not only describes worrisome thoughts as verbal, but also as negative and abstract in nature; therefore, we also tested how distinct patterns of amygdala functional connectivity were associated with these specific features of worry. Previous findings linking resting state functional connectivity in healthy individuals to dimensions of the NYC-Q, led us to broadly predict that functional connectivity to the limbic region and to default mode network (DMN) respectively would be associated with more negative and more abstract thoughts.

2. Methods and materials

2.1. Participants

The present study is based on a secondary analysis of data from a larger longitudinal functional magnetic imaging (fMRI) study (Makovac et al., 2016a, 2016b, 2016c; Meeten et al., 2016; Ottaviani et al., 2016b). Nineteen patients (17 women, 2 men; mean age = 29.58 ± 6.93 years) who met diagnostic criteria for GAD and 21 healthy controls (HC; 18 women, 3 men; mean age = 28.67 ± 9.45 years) participated in the study. Only 1 participant was non-Caucasian. Patients and HC were recruited from public advertisement. All participants were right-handed, native English speakers, and had normal or corrected-to-normal vision. Exclusion criteria were: age below 18 years, past head injury or neurological disorders, history of major medical or psychiatric disorder (other than GAD and co-morbid depression in the patients), cognitive impairment, history of substance or alcohol abuse or dependence, heart disease, obesity (body mass index $> 30\ kg/m^2$), pregnancy, claustrophobia or other MRI exclusions. None of the participants had a formal diagnosis of comorbid major depressive disorder. Two patients with GAD were included who took long-term medication (1 Citalopram, 1 Pregabalin) at the time of the study. All other participants were medication free. All participants provided written informed consent. The study was approved by the National Research Ethics Service (NRES) with local approval the Brighton and Sussex Medical School Research Governance and Ethics Committee. Participants were compensated for their time.

2.2. Procedure

The Structured Clinical Interview for DSMIV (SCID) was administered to patients and controls to confirm/exclude the diagnosis of GAD. Participants then completed a series of online sociodemographic and dispositional traits questionnaires. Participants were subsequently familiarized with the neuroimaging environment, connected to the physiological recording equipment, and then underwent the MRI protocol.

2.3. Questionnaires

Each participant completed a set of questionnaires accessing sociodemographic and lifestyle information (nicotine, alcohol, and caffeine consumption, physical activity), and dispositional measures of: 1) depressive mood (Beck Depression Inventory, BDI; Beck et al., 1961); 2) anxious worry (Penn State Worry Questionnaire, PSWQ; Meyer et al., 1990); 3) depressive rumination (Ruminative Response Scale, RRS; Nolen-Hoeksema and Morrow, 1991); and 4) state and trait anxiety (Spielberger State Trait Anxiety Inventory, STAI; Spielberger, 1989).

The New York Cognition Questionnaire (NYC-Q; Gorgolewski et al., 2014) was used to assess content and form of worry during the resting state period following the perseverative cognition induction. All participants completed the questionnaire at the end of MRI scanning session, immediately after the last resting state scan. For each question (e.g., "During the task my thoughts were in the form of words"), participants are asked to indicate how well each statement described their thoughts on a scale from 1 - Completely did not describe my thoughts to 9 - Completely did describe my thoughts.

Scoring followed a previously described procedure (Gorgolewski et al., 2014): questions were decomposed using exploratory factor analysis to find interpretable latent components and the number of factors was estimated using parallel analysis (Horn, 1965). Factors were