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Neurobiological substrates of cognitive rigidity and autonomic inflexibility in generalized anxiety disorder

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ABSTRACT

Generalized anxiety disorder (GAD) is characterized by difficulties in inhibiting both perseverative thoughts (worry and rumination) and autonomic arousal. We investigated the neurobiological substrates of such abnormal inhibitory processes, hypothesizing aberrant functional coupling within 'default mode' (DMN) and autonomic brain networks. Functional imaging and heart rate variability (HRV) data were acquired from GAD patients and controls during performance of three tracking tasks interspersed with a perseverative cognition (PC) induction. After detection of infrequent target stimuli, activity within putative DMN hubs was suppressed, consistent with a redirection of attentional resources from internal to external focus. This magnitude of activity change was attenuated in patients and individuals with higher trait PC, but was predicted by individual differences in HRV. Following the induction of PC in controls, this pattern of neural reactivity became closer to that of GAD patients. Results support, at a neural level, the association between cognitive inflexibility and autonomic rigidity.

1. Introduction

In their "autonomic flexibility-neurovisceral integration model of anxiety", Friedman and Thayer (1998) view anxiety as a systemic inflexibility, grounded in poor inhibition. Indeed, anxious individuals show a reduced capacity to inhibit cognitive (worry), behavioural (avoidance), and accompanying physiological (reduced vagal tone) manifestations. According to this model, vagal tone, indexed by heart rate variability (HRV) may serve as a measure of the integrity of brain networks that regulate inhibition through central-autonomic nervous control in the service of efficient functioning (Friedman, 2007).

An earlier laboratory study applied this model to perseverative cognition (i.e., worry and rumination) in healthy individuals, hypothesizing a link between cognitive inflexibility and autonomic rigidity expressed as reduced HRV (Ottaviani, Shapiro, & Couyoumdjian, 2013). The rationale for collapsing worrisome and ruminative thoughts into a single phenomenal category is corroborated by studies showing no differences between these two processes on their impact on appraisals and strategies (e.g., Segerstrom, Tsao, Alden, & Craske, 2000; Watkins, Moulds, & Mackintosh, 2005) and by the incremental benefits of using perseverative cognition as a transdiagnostic symptom (McEvoy, Watson, Watkins, & Nathan, 2013; Spinhoven, Drost, van Hemert, & Penninx, 2015). In Ottaviani et al. (2013), participants performed a low-demanding tracking task before and after a perseverative cognition induction in which they were asked to recall a past or future personally relevant negative event. The task required participants to keep the cursor inside a white circle in motion on a black screen and press the left mouse button as fast as possible each time the circle turned red. Reaction times were used as an objective index of cognitive rigidity. At different time intervals, probes interrupted the task to inquire about subjects' moods and thoughts. Whenever subjects reported worrying about a future event, or ruminating about a past stressful event, they were asked how much they experienced the thought as intrusive and how much they were trying to suppress it (subjective measures of cognitive rigidity). HRV was monitored throughout the task as an index of autonomic flexibility. Worry and rumination were expressed along attentional (slower reaction times), cognitive (efforts to inhibit intrusive thoughts), affective (mood worsening), and autonomic (lower HRV) dimensions. In line

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with Friedman and Thayer's model (1998), the cognitive inflexibility that characterized perseverative cognition was mirrored, at a physiological level, by autonomic rigidity. Two 24-h ambulatory studies replicate these findings in healthy (Ottaviani, Medea et al., 2015) and depressed participants (Ottaviani, Shahabi et al., 2015).

The present study aimed to extend these results by defining neural substrates of the cognitive rigidity that characterizes perseverative cognition using the same task and induction procedure in an fMRI environment with simultaneous cardiac monitoring. HRV was derived to test, at a neural level, the association with autonomic rigidity. Importantly, we examined these effects in both healthy participants and patients with GAD, a clinical population that has perseverative cognition as a core symptom. The simultaneous assessment of bodily reactions and cognitive processes is particularly needed when studying generalized anxiety, where changes in autonomic nervous function, such as palpitations or sweating, can drive negative cognitions creating a vicious cycle that plays a major role in the maintenance of the disorder.

The integration of cognitive and affective neuroscience with clinical autonomic research has advanced our understanding of the neurobiology of GAD and related anxiety disorders. Anxiety is associated with aberrant (often exaggerated) functional activation of brain regions normally engaged in response to motivational salient stimuli and demanding behavioural challenges. These same brain regions are also implicated in the generation (e.g., anterior cingulate cortex), representation (e.g., insular cortex) or both (e.g., amygdala) of autonomic states of arousal (Critchley, Eccles, & Garfinkel, 2013). These studies are informed by observations in patients with clinical perturbations in autonomic response (e.g., Critchley, Mathias, & Dolan, 2002) and recent studies illustrating how neural responses to feedback from the heart can dynamically shape the perception and processing of threat and safety (reviewed in Garfinkel & Critchley, 2016).

Unfortunately, no published studies examining perseverative cognition in GAD have combined neuroimaging techniques with concurrent measures of peripheral autonomic nervous activity. In fact, to our knowledge, only two published studies directly investigated the brain correlates of worry in GAD patients. One of them had a small sample size (n = 6 patients) and the absence of a comparison group as strong limitations (Hoehn-Saric, Schlund, & Wong, 2004). Although difficult to generalize, patients showed enhanced activation of frontal and anterior cingulate (ACC) cortices in response to worrisome sentences (Hoehn-Saric et al., 2004). The second suggested that worry induction engaged the same neural system in both GAD and healthy individuals (Paulesu et al., 2010). Activity within ACC and dorsal medial prefrontal cortex (DMPFC) was enhanced by worry inducing sentences in both GAD patients and controls but, interestingly, GAD patients also showed a sustained activation of these areas during resting state scans that followed the worrying induction phase. In line with a dimensional view of psychopathology, this persistent activation correlated with dispositional tendencies to worry assessed by the Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990).

Overall there is need for greater neurobiological understanding of difficulties in inhibiting perseverative thoughts and autonomic dysregulation in GAD, perceived as uncontrollable and disruptive to patients' daily life. We therefore undertook a neuroimaging study, acquiring fMRI and concomitant HRV data from GAD patients and healthy controls. Participants performed repetitions of a low-demand tracking task. This task promoted occurrence of self-generated thoughts, and the degree to which these thoughts distracted participants from the task could be measured by examining pre- to post-infrequent targets brain activation patterns.

'Spontaneous' (i.e., task-free) brain activity in functional imaging experiments is no longer simply viewed as noise or a confound to be controlled (e.g., Binder et al., 1999). This motivated our analytical approach: periods of low cognitive, emotional, or sensory demand (as in our pre-target epochs), reliably enhance activity across a specific network of regions proposed to support the brain's default mode (Raichle et al., 2001). The key emergent property of DMN activation is the production of self-generated thoughts or mind wandering (Mason et al., 2007). When a task requires our attention, however, the activation of such network is suppressed (as in our post-target epochs). Deficits in DMN suppression are reported in several mental illnesses, notably anxiety disorders (Anticevic et al., 2012). This observation suggests that difficulties in switching from rest to task are linked to specific symptomatology, e.g., impaired attention and worry (Forster, Nunez Elizalde, Castle, & Bishop, 2015). In line with this approach, instead of looking at what happens while participants perform a task, it can be more informative to compare periods of resting activity before and after infrequent target occurrence. The concept of task-rest interactions acknowledges the modulation of resting brain activation by the preceding stimulus-induced activation or vice-versa (Northoff, Qin, & Nakao, 2010). Thus, 15 s periods immediately preceding experience sampling probes were used to demonstrate activation of DMN regions during mind wandering (Christoff, Gordon, Smallwood, Smith, & Schooler, 2009). Post-stimulus alteration in neural activity is dissociable from stimuli-evoked neural responses (Mullinger, Mayhew, Bagshaw, Bowtell, & Francis, 2013).

Between repetitions of the task, we included an induction of perseverative cognition to increase the likelihood of worry and rumination. From here on, the use of "self-generated thoughts" will indicate thoughts that are unrelated to the immediate external environment (i.e., the ongoing task) and are internally-driven (Andrews-Hanna, Smallwood, & Spreng, 2014). Self-generated thoughts can take the form of perseverative cognition in GAD or – in healthy individuals – after an experimental induction. The term "attentional control" will be conversely used to indicate moments in which participants' attention is on the task (i.e., externally-oriented).

At a behavioural level, we expected to replicate previous findings (Ottaviani et al., 2013) showing that reaction times are delayed and HRV is reduced following induction, due to an increase in rumination and worry. Within the brain, we hypothesized that enhanced self-referential processing (at baseline in GAD and following the perseverative cognition induction in HC) is associated with increased engagement of the default mode network which in turn accounts for difficulties in focusing on the tracking task (i.e., levels of default mode network de-activation at target appearance). To inform our understanding of HRV as a putative marker for neural processes involved in maladaptive cognition (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012), we tested if higher levels of HRV predict better ability to deactivate the default mode network during the transition from internal thoughts to task-focused behaviour.

2. Methods and materials

2.1. Participants

We recruited 40 individuals to take part in the study, which was approved by the National Research Ethics Service (NRES) for the National Health Service (NHS) with university sponsorship granted via the Brighton and Sussex Medical School Research Governance and Ethics Committee. Participants were compensated for their time. One GAD subject had to be excluded from the analyses because of missing data. The final sample was composed of 19 individuals who met diagnostic criteria for generalized anxiety disorder (GAD; 17 women, 2 men; mean age ± S.D. = 29.6 ± 6.9 years) and 20 healthy controls (17 women, 3 men; mean age = 28.7 ± 9.5 years).