CAN'T GET YOU OUT OF MY HEAD: BRAIN-BODY INTERACTIONS IN PERSEVERATIVE COGNITION

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CAN'T GET YOU OUT OF MY HEAD: BRAIN-BODY INTERACTIONS IN PERSEVERATIVE COGNITION

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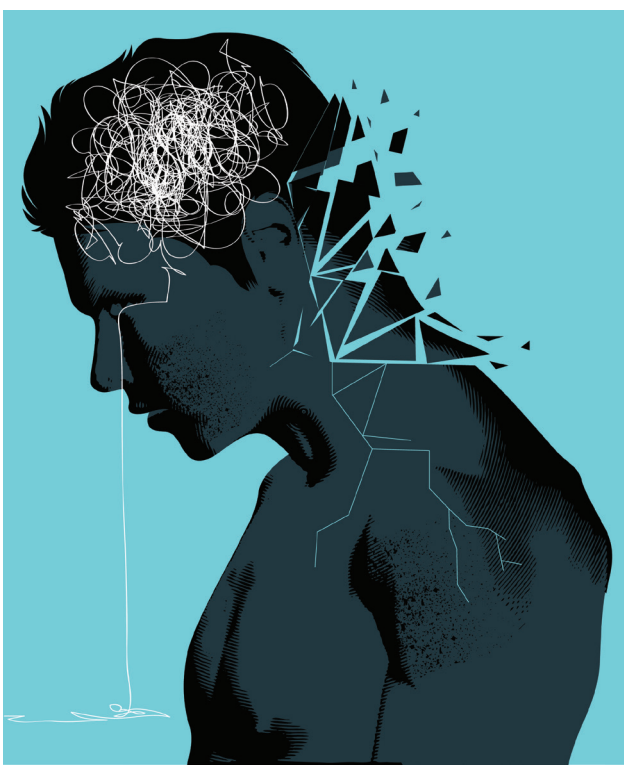

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Perseverative cognition is defined as the repetitive or sustained activation of cognitive representations of past stressful events or feared events in the future and even at non-clinical levels it causes a "fight-or-flight" action tendency, followed by a cascade of biological events, starting in the brain and ending as peripheral stress responses. In the past decade, such persistent physiological activation has proven to impact individuals' health, potentially leading to somatic

disease. As such, perseverative cognition has recently been proposed as the missing piece in the relationships between stress, psychopathology, and risk for health. Perseverative cognition is indeed a hallmark of conditions such as anxiety and mood disorders that are at increased -though still unexplained- cardiovascular risk. Although the pivotal role of ruminative and worrisome thoughts in determining the onset and maintenance of psychopathological disorders has been acknowledged for a long time, its effects on the body via reciprocal influences between mental processes and the body's physiology have been neglected. Moreover, perseverative cognition is definitely not restricted to psychopathology, it is extremely common and likely even omnipresent, pervading daily life.

The objective of the Research Topic is to provide an interdisciplinary examination of cutting-edge neuroscientific research on brain-body signatures of perseverative cognition in both healthy and psychopathological individuals. Despite the evident role of the brain in repetitive thinking and the assumption that our mind is embodied, bran-body pathways from perseverative cognition to health risk have remained largely unexplored.

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EDITORIAL
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Editorial: Can't Get You Out of My Head: Brain-Body Interactions in Perseverative Cognition

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Keywords: perseverative cognition, functional connectivity, heart rate variability, brain-body interaction, generalized anxiety disorder

Editorial on the Research Topic

Can't Get You Out of My Head: Brain-body Interactions in Perseverative Cognition

Perseverative cognition represents a prototypical example of how our internal thoughts can impact our psychological and physical health, as if we were facing an actual environmental stressor (Brosschot et al., 2006). The mechanisms involved—together with other emblematic examples like the placebo effect—provide clear evidence for brain-body interaction. This collection of articles presents recent advances in our understanding of perseverative cognition that have arisen from the integration of multidisciplinary approaches encompassing cognitive and clinical psychology, affective neuroscience, and autonomic physiology. These advances carry with them the promise of more effective treatments to mitigate the negative consequences of maladaptive perseverative cognition on health and well-being.

All contributions to the present Research Topic share a definition of perseverative cognition as a rigid pattern of habitual repetitive thoughts that perpetuates threat/stress responses through a characteristic failure of regulatory inhibition. Physiologically, perseverative cognition is expressed across multiple axes, including cardiovascular, autonomic, and endocrine systems (Ottaviani et al., 2016). Among physiological indices, heart rate variability (HRV) has emerged over the past decade as a biomarker that is particularly well-suited for indexing the inflexibility intrinsic to perseverative cognition. In fact, the adaptive rapid application and withdrawal of vagal parasympathetic inhibition, reflected in HRV, is viewed as a dynamic substrate for flexible behavioral routines (Porges, 2007).

The first group of papers precisely explores this link between perseverative cognition and HRV. Two papers in particular combine the measurement of autonomic inflexibility, indexed by HRV, with measures of attentional/cognitive rigidity that characterizes perseverative cognition: Gazzellini et al. reveal that individuals who are highly prone to worrisome thinking show increased variability in reaction times (following a periodic oscillating pattern), recurrent lapses in attention, and concomitant oscillating heart rate. The authors suggest that, at a central level, these predictable fluctuations are mediated by midline cortical structures belonging to the default mode network. Spangler and Friedman provide relevant evidence for cardiac vagal control as an index of the availability of working memory resources: Anxiety impairs one's ability to focus attention and inhibit distractors. Minimal working memory load can attenuate this detrimental effect of anxiety, but heavier working memory demands may compromise attentional inhibition to the same extent as anxiety itself. Cropley et al. leave the laboratory setting in pursuit of a more ecological

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evaluation of perseverative cognition and HRV. This combined ambulatory assessment, over three consecutive evenings, provides the first evidence that individuals who have a tendency to ruminate about work also have lower HRV after work, when compared to individuals who report low levels of work-related rumination.

The contribution of Williams et al. takes a fairly different perspective in which HRV is considered as a trigger, rather than a consequence, of perseverative cognition. This is based on the assumption that individuals with lower resting HRV are more vulnerable to stress, and therefore are more likely to engage in maladaptive types of perseverative cognition (e.g., brooding rumination). Moreover, an indirect effect of maladaptive perseverative cognition on resting HRV can feedback to make these same individuals more susceptible to anxiety symptoms. Notably, adaptive types of rumination (i.e., reflective rumination) do not significantly mediate this association, suggesting that not all rumination is pathogenic. The paper by Diamond and Fisher applies similar notions to major depressive disorder, generalized anxiety disorder (GAD), and social anxiety disorder by exploring autonomic stress responses to a clinical diagnostic interview in these clinical populations and matched controls. The groups showing the highest autonomic rigidity during the interview were high-worriers, and patients with GAD, who have perseverative cognition as diagnostic requirement. The authors conclude that shared transdiagnostic features, notably worry and suppression, rather than diagnostic comorbidities, account for physiological reactivity across patient groups.

It is important to note that the pathogenic effects of rumination can be partially explained by its capacity to engender behaviors that put health at risk (substance use, alcohol consumption, unhealthy eating, and smoking), as shown by the meta-analysis conducted by Clancy et al. Surprisingly, this route could not be demonstrated for worry. This contribution elegantly illustrates that another plausible route linking rumination to disease is via poorer health behaviors.

Both Toh and Vasey and Meeten et al. provide unique information about the processes underpinning the conceptualization of worry as a strategy of cognitive avoidance in response to threat, via its verbal nature (Borkovec et al., 2004). The contribution by Toh and Vasey clarifies that worry predicts lower autonomic arousal, but only at high levels of effortful control that are characterized by a greater emphasis on verbal thoughts. Meeten et al. further explore the neurobiological correlates of the Borkovec's Cognitive Avoidance Model and theoretical mechanisms of perseveration (i.e., the tendency to deploy goal-directed worry rules; Davey and Meeten, 2016). The authors used a perseverative cognition induction in patients with GAD and controls to quantify decreases in HRV and associated changes in patterns of functional connectivity of the amygdala that provide insight into the biological processes underlying explanatory models of worry.

The Research Topic ends with a contribution that directly addresses treatment interventions: Fresco et al. used resting state functional magnetic resonance imaging before Emotion Regulation Therapy (Fresco et al., 2013) in GAD and tested if functional connectivity patterns predict subsequent treatment-related changes. The authors first confirmed previously reported disruptions in the default mode and salience networks in GAD. Notably, functional connectivity patterns within these networks were associated with treatment-related changes in worry, somatic anxiety, and decentering.

Perseverative cognition remains difficult to treat, despite being a recognized risk factor for health and a transdiagnostic symptom that commonly occurs in everybody's life. Overall, the present Research Topic substantially enhances the understanding of the factors that trigger, maintain, and follow perseverative cognition. Importantly, these fresh insights occur through the perspective of brain-body interactions. The clarification of these factors is essential to inform therapeutic interventions that may take either bottom-up (parasympathetic-to-brain) or top-down (brain-to-parasympathetic) approaches.

AUTHOR CONTRIBUTIONS

All authors (CO, JT, BV, HC, and JB) have contributed to this Editorial. CO has drafted the Editorial, JT, BV, HC, and JB provided intellectual contributions in commenting and revising the manuscript.

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ORIGINAL RESEARCH
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Association between Attention and Heart Rate Fluctuations in Pathological Worriers

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Recent data suggests that several psychopathological conditions are associated with alterations in the variability of behavioral and physiological responses. Pathological worry, defined as the cognitive representation of a potential threat, has been associated with reduced variability of heart beat oscillations (i.e., decreased heart rate variability; HRV) and lapses of attention indexed by reaction times (RTs). Clinical populations with attention deficit show RTs oscillation around 0.05 and 0.01 Hz when performing a sustained attention task. We tested the hypothesis that people who are prone to worry do it in a predictable oscillating pattern revealed through recurrent lapses in attention and concomitant oscillating HRV. Sixty healthy young adults (50% women) were recruited: 30 exceeded the clinical cut-off on the Penn State Worry Questionnaire (PSWQ; High-Worry, HW); the remaining 30 constituted the Low-Worry (LW) group. After a diagnostic assessment, participants performed two 15-min sustained attention tasks, interspersed by a standardized worry-induction procedure. RTs, HRV and moods were assessed. The analyses of the frequency spectrum showed that the HW group presents a significant higher and constant peak of RTs oscillation around 0.01 Hz (period 100 s) after the induction of worry, in comparison with their baseline and with the LW group that was not responsive to the induction procedure. Physiologically, the induction significantly reduced high-frequency HRV and such reduction was associated with levels of self-reported worry. Results are coherent with the oscillatory nature of the default mode network (DMN) and further confirm an association between cognitive rigidity and autonomic nervous system inflexibility.

Keywords: worry, heart rate variability, reaction times, sustained attention, time-frequency analysis

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INTRODUCTION

Excessive worry is a core symptom of generalized anxiety disorder (GAD; DSM-V) and has been conceptualized as a chain of thoughts and images, negatively affect-laden and relatively uncontrollable, containing the possibility of one or more negative outcomes and closely related to the fear process (Borkovec et al., 1983). However, worry is definitely not restricted to psychopathology, in fact it can be extremely pervasive also in people who do not meet a former diagnosis of GAD (Ruscio et al., 2001). In this context, the Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990) is a reliable screening measure for pathological worry in GAD and in non-pathological individuals (Beck et al., 1995).

Pathological worry has been associated with several dysfunctional consequences both at a somatic level (chronic physiological activation; Brosschot et al., 2006) and at a cognitive level (impoverished sustained attention; Rapee, 1993). For instance, when given instructions to actively worry about a personally relevant topic, individuals with high levels of self-reported worry report more negative thought intrusions during an attention focusing task compared with those with low levels of self-reported worry (Borkovec et al., 1983). Consistently, Hayes et al. (2008) have shown that—compared with thinking about other topics—worry depletes the ability to exert attentional control, particularly in pathological worriers. Moreover, Fox et al. (2015) showed that dispositional differences in trait propensity to worry are related to difficulties in ignoring irrelevant material with a significant correlation between the degree of deficit in attentional control and the degree of difficulty in suppressing negative thought intrusions. Ottaviani et al. (2013, 2016b) confirmed that a worry induction is associated with a slowing down in reaction times (RTs) during a sustained attention task, further revealing an association between such attentional/cognitive rigidity and autonomic inflexibility, indexed by reduced heart rate variability (HRV). This association has been demonstrated using both subjective measures of cognitive rigidity (Ottaviani et al., 2013) and neural markers of attentional capacity (Ottaviani et al., 2016b). As to the latter, results indicated an association between difficulties in inhibiting worrisome thoughts (both subjectively reported and indexed by RTs slowing down) and impaired deactivation of areas belonging to the so-called default mode network (DMN; Ottaviani et al., 2016b).

The DMN activates during resting states, i.e., when the individual is awake but not actively engaged and the mind is free to wander (Northoff and Bermpohl, 2004; Doucet et al., 2011, 2012). Previous electroencephalography (EEG)- and functional magnetic resonance imaging (fMRI)-based studies identified the low frequency range (0.01–0.1 Hz) as the range within which the DMN pulses (Buzsáki and Draguhn, 2004; De Luca et al., 2006; Balduzzi et al., 2008; Helps et al., 2008; Knyazev et al., 2011; Doucet et al., 2012). According to the Default Mode Interference Hypothesis (Sonuga-Barke and Castellanos, 2007), DMN deactivation would never be complete in the presence of attention deficits; instead, the DMN would intrude during the execution of active tasks, causing lapses in attention (Weissman et al., 2006).

Rather than being random, the attentional falls follow a periodic pattern and the frequency of such lapses in attention is likely to follow the intrinsic frequency of DMN activation. For example, recent studies using time-frequency analysis (e.g., fast Fourier or wavelet transform) in children with Attention-Deficit/Hyperactivity Disorder (ADHD) reported peculiar RTs oscillations around a peak of 0.05 Hz, indicating lapses in attention occurring about every 20 s (Castellanos et al., 2005). Besides, this oscillation pattern proved to be a good predictor of ADHD diagnosis (Di Martino et al., 2008). Subsequent studies on ADHD mostly employed flanker tasks or sustained attention tasks and consistently found significant oscillation peaks in the very low frequency range (0.027–0.073 Hz; Johnson et al., 2007a,b; Di Martino et al., 2008; Adamo et al., 2014).

The Default Mode Interference Hypothesis has also been used as a plausible explanation for the sustained attention deficit of young patients with frontal lesions after traumatic brain injury (Gazzellini et al., 2016). Gazzellini et al. (2016) applied continuous wavelet transform (CWT) to RTs and theta/beta (qEEG) time series. In order to enhance sensitivity in the low-frequency range, attentional tasks duration was kept longer (up to 15–19 min) compared to that used in previous studies. Results showed significant high-power oscillations around 0.01 Hz in traumatic brain injury patients' performance but not in that of controls for both RTs and theta/beta time series. Results from this and the above-mentioned ADHD studies seem to suggest that very low-frequency oscillation of RTs is a transdiagnostic feature linked to sustained attention deficits irrespective of the underlying specific pathological condition. Indeed, a general increase in RTs variability during attention demanding tasks has been considered as a behavioral biomarker of several psychopathological and neurological conditions (e.g., in bipolar disorder, schizophrenia, ADHD, traumatic brain injury, neurodegenerative pathologies), even in the absence of differences with healthy controls in terms of mean RTs (for a review, see MacDonald et al., 2006).

The main aim of the present study is to determine whether persons who are highly prone to engage in worrisome thoughts do it in a predictable oscillating pattern revealed through increased RTs variability, recurrent lapses in attention, and concomitant oscillating Heart Rate (HR). Such a pattern would be consistent with the hypothesis of a recurrent and intrusive DMN activation during goal-oriented activity (externally directed cognition; Dixon et al., 2014) and the related failure in deactivating such midline structures activity. Given the previously reported association between autonomic and cognitive rigidity, we hypothesize that High-Worry (HW) individuals would show a distinctive pattern of low-frequency spectral power (around 0.01–0.05 Hz) in both HRV and RTs time series, revealing lapses in attention during the execution of a sustained attention task. Lastly, we hypothesized these oscillatory patterns to be associated with state and trait psychological characteristics of the individual.

MATERIALS AND METHODS

Participants

Participants were recruited by the use of flyers and participation in previous studies. The sample was composed of 60 subjects (31 women, 29 men; mean age = 30.4 (6.9) years). The cut-off score for pathological worry on the PSWQ (Meyer et al., 1990) was used to pre-assess eligibility of both pathological worriers ($\geq$54; n = 30) and controls ($<$54; n = 30). This cut-off has been recommended for optimal sensitivity and specificity in selected samples (Salzer et al., 2009). Exclusionary criteria were: being younger than 18, a diagnosis of psychiatric disorder, a diagnosis of heart disease or any other serious illness, use

of drugs/medications that might affect HR and HRV, obesity (body mass index (BMI) > 32 kg/m^2), menopause, pregnancy or childbirth within the last 12 months. Participants were compensated (€15) for their time. The protocol was approved by the Bioethical Committee of S. Lucia Foundation, Rome, Italy.

Procedure

After eligibility assessment, participants came to the lab, read and signed the informed consent form, and filled out a series of questionnaires. Then, electrocardiogram electrodes were attached to the subject and participants performed a sustained attention task for 15 min. After the task, participants underwent a verbal induction procedure designed to engender perseverative cognition (i.e., rumination and worry; 5 min). Then, participants performed again the same sustained attention task for 15 min. Before and after performing each task, participants rated their thoughts and moods over the preceding period using visual analog scales. Psychophysiological data were recorded throughout the session.

Questionnaires

Participants completed a series of socio-demographic and lifestyle (nicotine, alcohol and caffeine consumption, physical exercise) questions and questionnaires to measure levels of: (a) trait rumination (Ruminative Response Scale, RRS; Nolen-Hoeksema and Morrow, 1991); (b) state and trait anxiety (State-Trait Anxiety Inventory, STAI-X2; Spielberger et al., 1970); and (c) depression (Beck Depression Inventory, BDI-II; Beck et al., 1996).

The PSWQ is a 16-item self-report questionnaire commonly used to assess pathological worry in both clinical and non-clinical populations. It has been shown to have good internal consistency with samples consisting of older adults with GAD (Beck et al., 1995), community subjects (Brown et al., 1992) and undergraduates (Meyer et al., 1990). The PSWQ is positively correlated with other self-report measures of worry (e.g., Davey, 1993; Beck et al., 1995; Van Rijsoort et al., 1999). The internal reliability (Cronbach's alpha = 0.92) and psychometric properties of the Italian version of the PSWQ have been demonstrated to be satisfactory (Meloni and Gana, 2001).

The RRS assesses depressive rumination measured by how often people engage in responses to depressed mood that are self-focused (I think "Why do I react this way?"), symptom-focused (I think about how hard it is to concentrate), and focused on the possible consequences and causes of one's mood (I think "I won't be able to do my job if I don't snap out of this").

The STAI consists of two 20-item self-report measures to assess state and trait levels of anxiety. Respondents indicate how they feel right now (state version) or how they generally feel (trait version) using four-point Likert scales.

The BDI-II requires participants to respond how each of 21 statements relates to the way they have felt for the past 2 weeks. This instrument is intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association (1994).

Attentional Task

As a sustained attention to response task, we used a modified version of the Continuous Performance Test (Conners, 2000), adapted for the aims of the present study. Participants were required to respond to all the letters (go condition), with the exception of the consonant "Z" (no-go condition) by pressing the space bar as quickly and accurate as possible. Black letters (size 1 cm $\times$ 1.4 cm) appeared on a white background at the center of the screen. In order to present the stimuli foveally, they were included in a 2° horizontal visual angle; the distance between participants and the monitor was 80 cm. The task comprised 528 randomly presented stimuli, 48 no-go trials and 480 go trials, without any block division. Task duration was 15 min. The inter stimulus interval was 1700 ms.

The stimuli appeared on a video display unit controlled by an IBM Personal Computer. The software E-Prime version 2.0 (Schneider et al., 2002) was used for visual presentation of the stimuli and data collection. The timing accuracy of the software is $\pm$ 0.5 ms.

Induction

"Next I would like you to recall an episode that happened in the past year that made you feel sad, anxious, or stressed, or something that may happen in the future that worries you. Then, I would like you to think about this episode in detail, for example about its possible causes, consequences, and your feelings about it. Please take as much time as you need to recall the episode and tell me about it whenever you are ready".

The experimenter recorded: (1) the topic selected by each participant during the induction; (2) its temporality (past or future); and (3) temporal distance (how long in the past/how far in the future).

Visual Analog Scales

At the beginning and at the end of the sustained attention task, participants were asked to rate their current levels of feeling sad, calm and worried on separate visual analog 100-point scales. For each mood, change scores (task value minus initial baseline value) were computed by subtracting the initial baseline from task values.

Psychophysiological Assessment and Pre-Processing

HR was recorded as beat-to-beat intervals in ms with the Bodyguard 2 (Firstbeat) HR monitor that has been extensively used for HR recording and analysis (e.g., Ottaviani et al., 2015). Frequency-domain measures of HRV were obtained using Kubios Analysis Software (Tarvainen et al., 2014): low-frequency HRV (LF-HRV), high-frequency HRV (HF-HRV), and LF/HF-HRV. According to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996), the HF-HRV

(0.15–0.4 Hz) reflects parasympathetic activity, and the LF-HRV (0.04–0.15 Hz) is proportional to sympathetic activity but influenced by parasympathetic tone. The interpretation of LF-HRV as primarily an index of sympathetic tone has been commonly derived by the calculation of the ratio of LF/HF-HRV. The time series of inter-beat intervals for each participant in the two conditions (before and after induction) were extrapolated from the device. Inter-beat intervals that corresponded to a HR below 30 or above 200 were excluded, as well as any interval resulting in an increase or drop in HR >30% between successive intervals (2.1% of the data). Deleted data were linearly interpolated.

Reaction Times Pre-Processing

RTs under the physiological threshold of 100 ms were considered as anticipations and removed from the distribution. Error variability in the sustained attention task was regressed out by subtracting the corresponding trial type mean from each value. The unstandardized regression residuals represent the portion of each RT score that is independent of response type and correctness (procedure already applied by Helps et al., 2011; Gazzellini et al., 2016). No-go trials, missing data (non-responses to go trials), and anticipations were discarded and linearly interpolated to maintain the temporal structure of the time series.

Continuous Wavelet Transform

CWT is a powerful tool allowing to decompose a continuous-time function into wavelet functions and therefore it is very useful to retrieve the frequency content of the function. The principal difference between the Fourier Transform and the wavelet is that the wavelets are localized both in time and frequency whereas the standard Fourier transform is localized only in frequency. Consequently, the CWT possesses the ability to construct a time-frequency representation of a signal that offers very good time and frequency localization. The CWT with Morlet wavelets with half length of Morlet analyzing wavelet at the coarsest scale equal to 20 was applied to each subject's normalized time series (RTs and inter-beat intervals), obtaining the spectral density of the signal varying over time: scalogram. The scalogram was averaged over the whole task interval to attain the average spectral power per frequency. The maximum powers in each pre-determined range was automatically computed and these values were taken as the dependent variables in the Analysis of Variances (ANOVAs) and Fisher's LSD *post hoc* tests. We adopted the frequency ranges selected by Penttonen and Buzsáki (2003), who argued that a natural logarithmic relationship links brain oscillators from the ultraslow to ultrafast frequencies: Slow-6 (0.0052 Hz–0.010 Hz, centered at 0.006 Hz [period 101–192 s]), Slow-5 (0.010–0.027 Hz, centered at 0.016 Hz [37–101 s]), Slow-4 (0.027–0.073 Hz, centered at 0.044 Hz [14–37 s]), and Slow-3 (0.073–0.17 Hz, centered at 0.12 Hz [6–14 s]). This frequency classification has been previously adopted in dedicated studies (Di Martino et al., 2008; Helps et al., 2008; Gazzellini et al., 2016).

Statistical Analyses

Data are expressed as means standard deviation (SD). *P*-values ≤ 0.05 were considered as significant. Laboratory data processing and analyses were performed using STATISTICA (Statsoft, Inc.). Kolmogorov-Smirnov test was used to test the normality of all variables. The distribution for LF-HRV, HF-HRV and LF/HF-HRV was non-normal; therefore these variables were log transformed (ln).

First, pre-existing group and gender differences were analyzed by *t*-tests.

Second, a series of 2 (Group: High Worriers vs. Low Worriers) × 2 (Induction: Before vs. After) ANOVAs were performed on: (a) HR, ln (LF-HRV), ln (HF-HRV) and ln (LF/HF-HRV); (b) levels of being sad, calm and worried (visual-analog scales); (c) mean, SD and coefficient of variability (CV; SD/Mean) of RTs; and (d) and percentage of errors. CV has the merit to be a measure of RT variability independent of differences in mean RT (Allan Cheyne et al., 2009) and has been used in previous studies on mind wandering and behavioral variability (e.g., Baird et al., 2014).

Third, mixed three-way ANOVAs (Group × Range × Induction: 2 × 4 × 2) with Group as between-subject factor and Range (Slow 6, 5, 4, 3) and Induction as within-subject factors were carried out on RTs and inter-beat intervals series. CWT spectral power peak served as the dependent variable.

Fisher's LSD *post hoc* tests were executed in case of significant main effects.

Finally, correlational analyses were performed between physiological and attentional responses to the induction and state and trait psychological characteristics of the sample.

RESULTS

Table 1 shows pre-existing (baseline) group differences for the main variables of the study. The HW had lower BMI compared to Low-Worry (LW) participants (t = 1.98, p = 0.05). In

TABLE 1 | Group differences in socio-demographic, personality and baseline mood variables.

	High-Worry (n = 30)	Low-Worry (n = 30)	p
Gender	19 F; 11 M	12 F; 18 M	0.07
Age (years)	29.6 (7.3)	31.2 (6.5)	0.37
BMI (Kg/m^2)	21.8 (2.2)	23.3 (3.6)	0.05
Smoking	19 N, 11 Y	16 N, 14 Y	0.43
Alcohol consumption	6 N, 24 Y	3 N, 27 Y	0.28
Caffeine consumption	3 N, 27 Y	1 N, 29 Y	0.30
Exercise	8 N, 22 Y	9 N, 21 Y	0.61
BDI	11.5 (7.9)	5.6 (3.4)	<0.0001
STAI-T	47.3 (7.0)	40.5 (9.4)	0.002
STAI-S	50.9 (8.5)	43.7 (9.1)	0.003
PSWQ	58.5 (5.3)	35.8 (9.7)	<0.0001
RRS	45.6 (13.4)	31.6 (7.4)	<0.0001
Calm	19.9 (21.1)	18.8 (10.5)	0.84
Worried	7.3 (11.3)	3.8 (5.0)	0.13
Sad	4.7 (7.9)	1.7 (3.1)	0.07

Note. BMI, Body Mass Index; M, Males; F, Females; Y, Yes; N, No.

addition to the PSWQ (t = 11.73, $p < 0.0001$), pathological worriers had higher levels of: (a) trait ($t = -3.16$; $p = 0.002$) and state anxiety (t = 3.16; $p = 0.003$); (b) depression (t = 3.74; $p < 0.0001$); and (c) trait rumination (t = 4.99; $p < 0.0001$).

No gender differences emerged for any of the examined physiological variables ($p_s > 0.15$), therefore gender was not included as a covariate in the subsequent analyses. In light of pre-existing differences between the two groups, BMI was included as a covariate in all the subsequent analyses.

With regard to the Induction, n = 1 HW and n = 3 LW participants chose to focus on a past episode. All the remaining participants focused on something that worried them in the future. The average temporal distance of the event was 10.8 (18.3) days. In both groups, most participants chose to worry about work-related issues (n = 18 in the HW and n = 20 in the LW groups), followed by romantic, health and family issues.

Table 2 reports the mean and SDs of the main variables of the study in HW and LW participants before and after the induction, as well as change scores from pre- to post-induction. A significant Group × Induction interaction emerged for HF-HRV ($F_{(1,50)} = 4.61$, $p < 0.05$; $\eta_p^2 = 0.10$). *Post hoc* comparisons showed that HF significantly decreased from pre- to post-induction in the HW group only ($p = 0.002$). The ANOVAs did not yield significant main effects of Group or Induction. BMI did not play a significant role as a covariate in the model. No significant main effects or interactions emerged for HR, LF-HRV or LF/HF-HRV.

A main effect of Group emerged for levels of Worry ($F_{(1,54)}$ = 3.91, $p < 0.05$; η_p^2 = 0.08) and Sad ($F_{(1,54)}$ = 3.99, $p < 0.05$; η_p^2 = 0.08) with the HW group having higher levels of self-rated worry and sadness compared to the LW group, irrespective of the Induction. No other significant effect emerged for scores on the visual-analog scales.

A significant main effect of Induction emerged from the ANOVA on average RTs ($F_{(1,58)}$ = 6, $p < 0.05$; η_p^2 = 0.09). LSD *post hoc* comparisons revealed that mean RTs significantly decreased in the LW group from pre- to post-induction ($p < 0.01$); such an effect was not present in the HW group. Interestingly, a significant pre- to post-induction increase in CV was found in the HW group ($p < 0.05$).

The group averaged CWT was performed on inter-beat intervals time series acquired during task performance and returned the maximum peak in each of the four frequency ranges. The mixed three-way ANOVA reported a significant main factor of Range ($F_{(3,159)} = 43.4$, $p < 0.001$; $\eta_p^2 = 0.45$) and a significant Range × Group interaction ($F_{(3,159)} = 2.7$, $p < 0.05$; $\eta_p^2 = 0.05$; see **Figure 1**). *Post hoc* analyses on the main factor Range revealed the following differences: Slow 6 = 5 > 4 = 3. *Post hoc* comparisons on the Range × Group interaction showed a significant higher spectral power mean value in the HW group compared to the LW group in Slow 6 (0.0052 Hz–0.010 Hz).

The time series of RTs were also subjected to CWT for the time-frequency power spectrum analysis. **Figure 2** depicts the power spectrum of a representative HW participant before and after the induction, showing a clear peak around 0.01 Hz during performance at the second sustained attention task. As far as the time dimension is concerned, the signal at 0.01 Hz increases in power after the first 100 s and remains significantly higher with respect to the other frequencies for the entire task duration (**Figure 2B**). On the contrary, no evident peaks emerged in LW participants. As a consequence of differences in participants' spectrograms (inter-subject variability), the group-averaged spectrogram may be affected by single peaks at slightly different frequencies, and therefore may not be as sharp and evident as those of the single subjects.

Group averaged CWT on RTs series acquired during performances at the sustained attention task returned higher spectral powers at VLF for the HW group: (a) compared to those of the LW group; (b) after the induction compared to pre-induction. As shown in **Figure 3**, a clear power peak around 0.01 Hz is present in the HW group's spectrogram after the induction but not in the LW group or before the induction.

The mixed three-way ANOVA (Group × Range × Induction) on peak power as dependent variable yielded a main effect of Range ($F_{(3,174)}$ = 49.7, $p < 0.001$; η_p^2 = 0.46), whereas

TABLE 2 | Physiological, behavioral and mood variables in High- (HW) and Low-Worriers (LW) during the sustained attention task preceding (Before) and following (After) the induction, and change scores from pre- to post-induction (Δ = After minus Before).

	Before induction		After induction		Δ (after-before)	
	HW	LW	HW	LW	HW	LW
HR (bpm)	76.1 ± 9.6	78.8 ± 13.5	77.4 ± 10.1	76.6 ± 11.9	1.39 ± 4.8	−2.3 ± 6.9
HF-HRV	716.2 ± 533.6	555.8 ± 331.3	582.9 ± 459.2	537.2 ± 324.1	−133.3 ± 238.7	−18.6 ± 186.5
LF-HRV	1602.5 ± 921.4	1379.9 ± 1226.2	1568.4 ± 1013.7	1347.6 ± 944.7	−34.1 ± 603.7	−32.4 ± 631.2
LF/HF-HRV	2.9 ± 1.9	2.8 ± 1.6	3.2 ± 2.0	2.9 ± 2.1	2.6 ± 1.2	0.1 ± 1.2
RTs (ms)	373	387	369	372	−4	−15
RTs SD (ms)	84	89	88	86	4	−3
RTs CV (ms)	0.22 ± 0.1	0.23 ± 0.1	0.23 ± 0.04	0.23 ± 0.1	0.01 ± 0.002	0.06 ± 0.03
Errors (%)	2.3 ± 0.3	1.9 ± 0.3	2.7 ± 0.6	3 ± 0.6	0.4 ± 0.3	1.1 ± 0.3
Calm	17.8 ± 19.6	18.7 ± 19.4	19.9 ± 23.0	22.3 ± 24.4	2.1 ± 10.2	3.6 ± 16.1
Worried	11.8 ± 21.8	2.8 ± 4.6	12.7 ± 24.3	3.2 ± 8.2	0.9 ± 5.8	0.4 ± 4.6
Sad	5.4 ± 9.3	1.8 ± 3.6	7.7 ± 16.8	1.1 ± 2.1	2.3 ± 3.4	−0.7 ± 2.7

Note. HW, High-Worry; LW, Low-Worry; HR, Heart Rate; HRV, Heart Rate Variability; SD, Standard Deviation; CV, Coefficient of Variability.

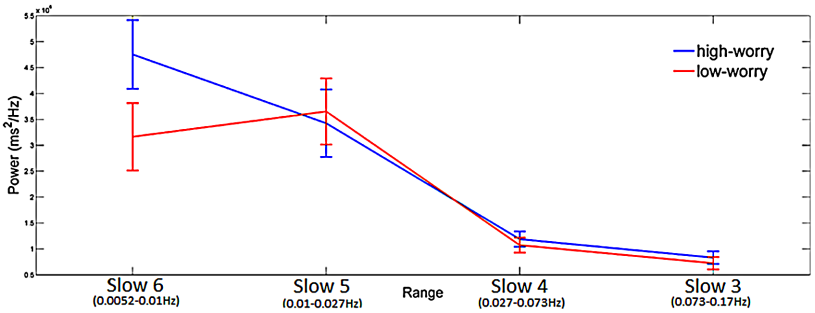

FIGURE 1 | Significant Range × Group interaction emerging from the Analysis of Variance (ANOVA) having spectral power mean value of inter-beat interval as the dependent variable. Blue line is for High-Worry (HW) and red line is for Low-Worry (LW) participants. The four ranges (Slow 6, 5, 4 and 3) are reported on the *X*-axis. Mean maximum peak value (power ms^2/Hz) is reported on the *Y*-axis. *Note*. Vertical bars denote 0.95 confidence intervals.

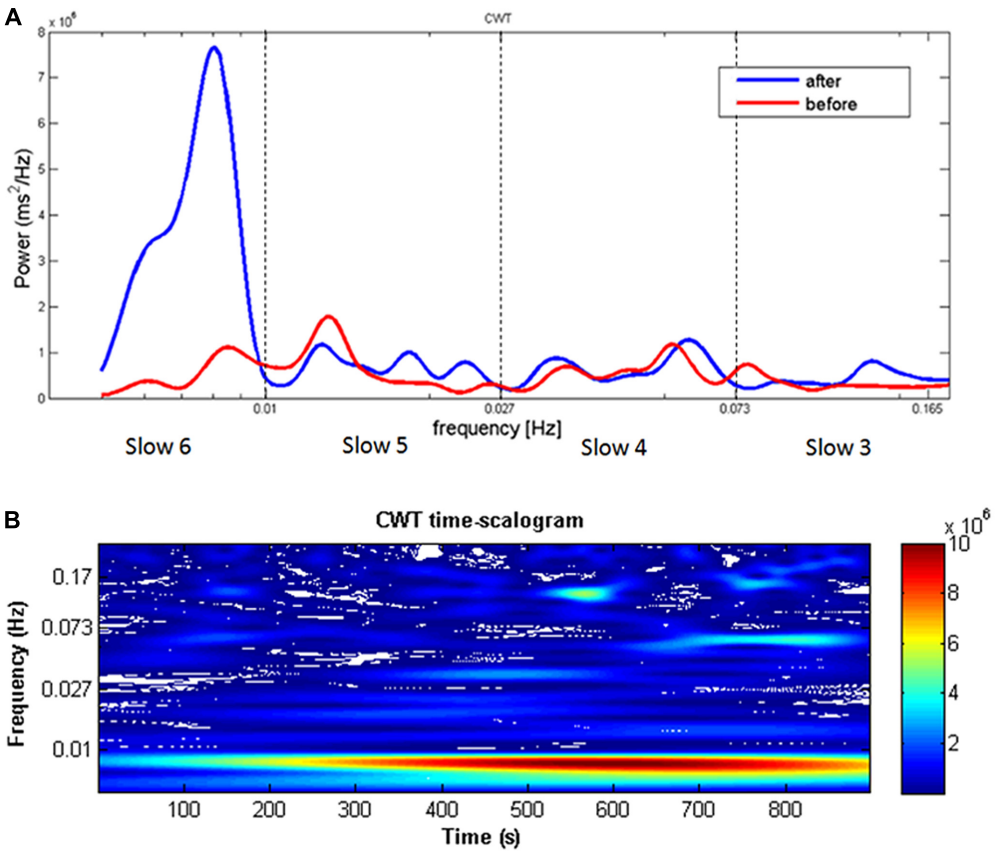

FIGURE 2 | (A) Continuous wavelet transform (CWT) reaction time (RT) spectrogram of a single representative HW participant showing a clear peak around 0.01 Hz when comparing before and after the worry induction procedure. The dotted lines represent the boundaries of the four frequency ranges (Slow 6, 5, 4, and 3). Frequency (Hz) is reported on the *X*-axis and spectral power (ms^2/Hz) on the *Y*-axis. **(B)** Distribution of the power spectrum of RTs collected in the after condition along the time dimension. Warm colors represent higher power values. The signal at 0.01 Hz increases in power after the first 100 s and remains significantly higher with respect to the other frequencies for the entire task duration.

the other main effects did not reach significance. Two significant interactions emerged: Group × Induction ($F_{(3,58)} = 4$, $p < 0.05$; $\eta_p^2 = 0.06$) and Group × Range × Induction ($F_{(3,174)} = 4.3$, $p < 0.01$; $\eta_p^2 = 0.07$). As depicted in **Figure 4**, significant interactions emerged between Group and Induction in Slow 6 and 4 but not in Slow 5 and 3. The interaction in Slow 6 is of particular interest: *post hoc* analysis revealed that whereas HW participant significantly increased their power peaks in

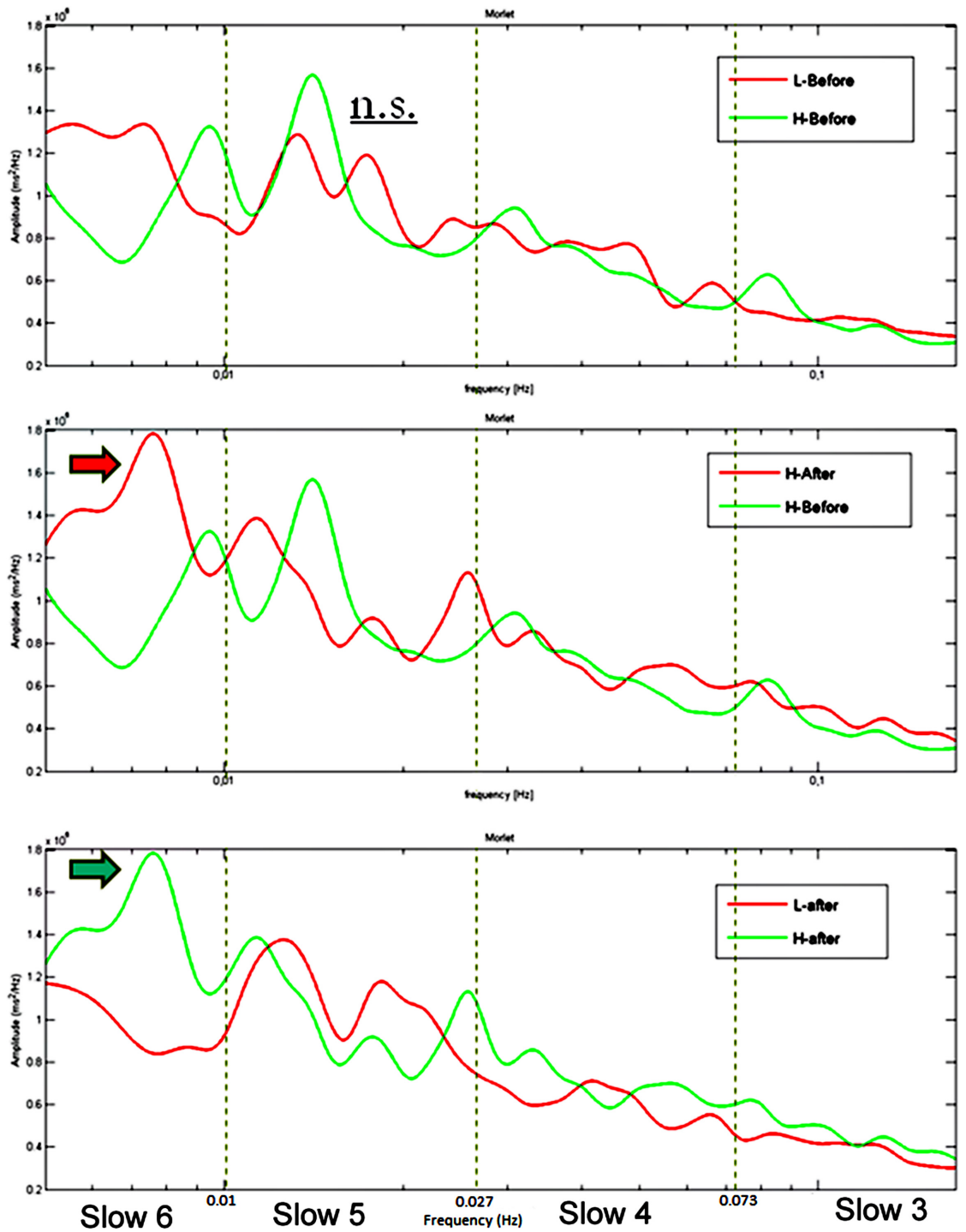

FIGURE 3 | Group average CWT on RTs time series showing no difference between the two groups at baseline (upper panel), a significant greater peak in Slow 6 (0.0052–0.010 Hz) after the induction compared to before the induction in the HW group (middle panel) and a significant greater peak in Slow 6 in the HW compared to the LW group after the induction (lower panel). The dotted lines represent the boundaries of the four frequency ranges. Frequency (Hz) is reported on the *X*-axis and spectral power (ms^2/Hz) on the *Y*-axis.

Slow 6 after the worry induction ($p < 0.05$), the LW group showed an opposite and marginally significant trend, decreasing power peak values in Slow 6 after the induction ($p = 0.07$). The significant Group × Induction interaction in Slow 4 was due to a significant power decrease in the LW group after the induction ($p < 0.05$).

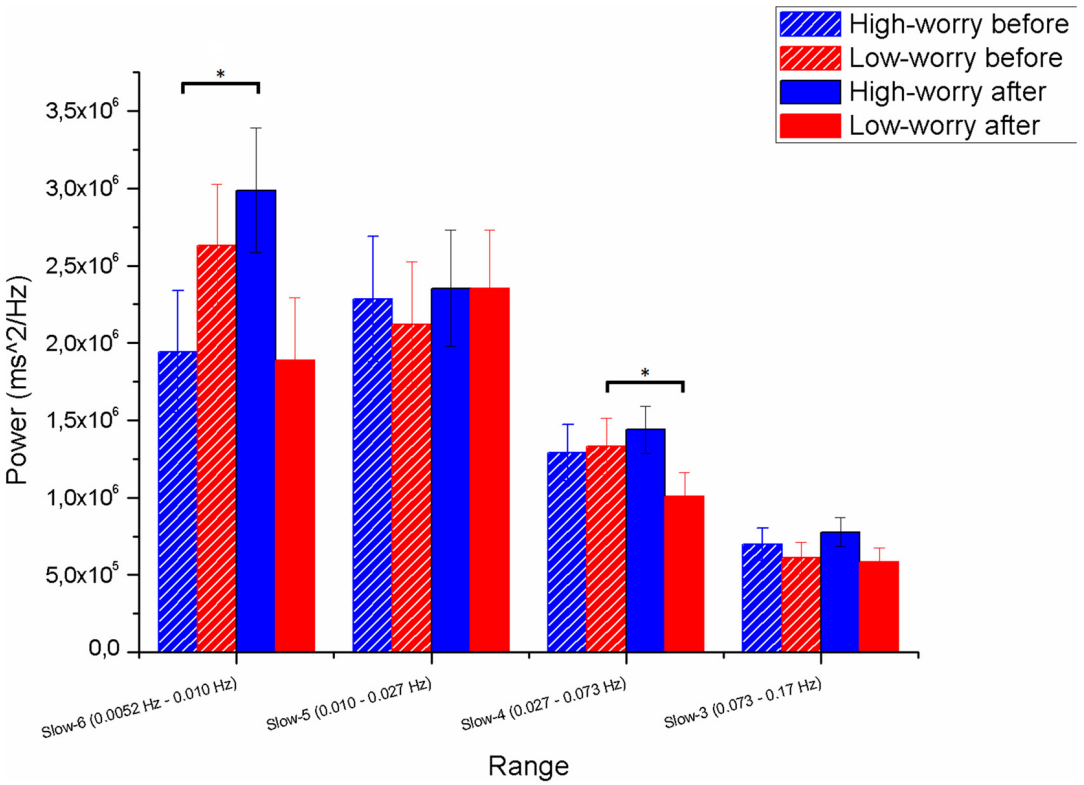

FIGURE 4 | Means and standard deviations (SD) from the Group × Range × Induction interaction on the dependent variable maximum peak value (power ms^2/Hz) in the range, on the *Y*-axis. The four ranges (Slow 6, 5, 4, and 3) and the four conditions (Group × Induction) are reported on the *X*-axis. The horizontal bars point out statistical differences at the LSD *post hoc* test. *Note*. *$p < 0.05$. Session 1 = before the induction; Session 2 = after the induction. Vertical bars denote 0.95 confidence intervals.

Correlation analyses ($ps < 0.05$) showed that HRV reactivity to the induction was negatively associated with changes in state worry ($r = -0.70$) from pre- to post-induction (change scores). RT power in Slow 6 before induction was positively correlated with HR ($r = 0.37$) and inversely correlated with LF-HRV ($r = -0.31$) and HF-HRV ($r = -0.29$). The RT power in Slow 6 after the induction was positively correlated with state anxiety ($r = 0.27$) and increases in levels of sadness from pre- to post-induction ($r = 0.26$). HR power in Slow 6 in the HW group after—but not before—the induction was positively correlated with BDI score ($r = 0.45$).

DISCUSSION

The ability to adjust bodily reactions in response to a changing environment and effectively ignore irrelevant information is crucial for adaptive behavior. The aim of the present study was to investigate the association between such autonomic and cognitive flexibility during worry, by analyzing RTs and HR fluctuations in pathological worriers and controls. To do so, we asked HW and LW participants to perform two sustained attention tasks interspersed by a worry induction and we applied CWT to RTs and inter-beat intervals.

First, previously reported differences between HW and LW in terms of psychopathological characteristics were replicated. Pathological worriers without GAD had higher levels of trait and state anxiety and depression (Ruscio, 2002; Hirsch and Mathews, 2012; Ottaviani et al., 2014). Interestingly, high-worriers were also characterized by higher levels of trait rumination, confirming the usefulness of merging rumination and worry under a unique transdiagnostic construct (e.g., perseverative cognition, repetitive negative thinking; McEvoy et al., 2013).

Irrespective of the induction, pathological worriers reported higher levels of state worry and sadness compared to controls. The fact that levels of worry did not significantly increase after the induction in participants who are prone to engage in this cognitive process may appear surprising. However, this is not an unusual finding and—like in previous studies conducted in patients with GAD—it is simply due to the already higher baseline levels of state worry in these populations (e.g., Makovac et al., 2015).

Participants in the present study chose work-related issues as the most common topic to worry about. This is understandable if we consider that our sample was mostly composed by university students ready to enter the job market at times of economic crisis. Work-related worry and rumination have been previously

associated with dysfunctional consequences at a physiological level, such as flattened cortisol awakening response (Cropley et al., 2015).

In the present study, the induction of work-related and—to a lesser extent—other types of worries had the consequence to decrease vagally-mediated HRV in pathological worriers only, although decreases in HRV were strongly associated with increases in levels of self-reported state worry in the entire sample. Present results are in line with Ottaviani et al. (2014), in which physiological responses to unpredictable bursts of loud white noise were characterized by lower vagally-mediated HRV in HW but not in LW. Indeed, reduced HRV has been proposed as a biomarker of worry, irrespective of the presence of a specific anxiety disorder (Chalmers et al., 2016). The absence of a HRV decrease during worry in controls seems to be in contradiction with data from a recent meta-analysis showing that vagal withdrawal is a signature of worry in *non-pathological* subjects (Ottaviani et al., 2016a). Such an apparent incongruity may be explained by the existence of pathological worry in the absence of a frank psychiatric diagnosis (Ruscio, 2002). For this reason, high-worriers have likely been included in the healthy population examined in the above-mentioned meta-analysis (Ottaviani et al., 2016a). It is imperative that future studies examining worry in healthy population include a measure of dispositional worry and test for potential differences between HW and LW.

The two groups in our study were not only different in terms of autonomic response but also in attentional performance. Whereas RTs decreased in non-worriers during second performance in the sustained attention task, likely indicating a learning effect, this was not the case for pathological worriers. Moreover, only pathological worriers increased their coefficient of RT variability after the induction, whereas their mean RTs did not change. This finding suggests that behavioral variability—instead of average velocity—might be assumed as a biomarker for pathological states, as already documented for other psychopathological and neurological conditions (Castellanos et al., 2005; MacDonald et al., 2006; Gazzellini et al., 2016). The lack of performance improvement in high-worriers and the concomitant increase in the CV possibly signal the presence of intrusive thoughts as suggested by previous studies linking deficits in attentional control to greater difficulty in controlling negative thought intrusions (Fox et al., 2015).

Building on these results, the present study had the aim to provide further evidence that, instead of being random, negative thought intrusion might follows periodic physiological oscillations. The time frequency analysis (CWT) showed that both behavioral and cardiac-autonomic indices oscillate in a very low frequency range (0.005 Hz–0.01 Hz; period 101–192 s) in pathological worriers with a peak value just before 0.01 Hz. In particular, data on RT series in the HW but not in the LW group showed a clear increase of power in the 0.005–0.01 Hz range after the worry induction procedure, suggesting an increase of behavioral variability around 0.01 Hz and therefore possibly the increase of negative thought intrusions at a regular oscillation around 100 s (see **Figures 2**, **3**). Therefore, not only pathological worriers were characterized by increased RTs variability, as documented by the traditional RTs analyses, but such behavioral variability also oscillated within the specific frequency range of 0.005–0.01 Hz. On the contrary, the LW group showed power decrease in the Slow 6 and 4, probably due to a learning effect, which was absent in worriers and is consistent with the already described learning effect indexed by mean RTs.

Time frequency analysis on inter-beat intervals also revealed significant higher powers in the same range (0.005–0.01 Hz) but, in this case, this was already present in worriers at the baseline evaluation and hence did not show any further increase after the worry induction. Taken together, present data may suggest that inter-beat intervals oscillations reflect a "trait" characteristic of high worriers, whereas RT oscillations might be a more sensitive index of "state" pathological worry.

The oscillation frequency of RTs and inter-beat intervals in the 0.005–0.01 Hz range found in this study is consistent with previous observation of DMN frequency activation (Buzsáki and Draguhn, 2004; Vanhatalo et al., 2004; De Luca et al., 2006; Balduzzi et al., 2008; Doucet et al., 2012) and frequency of recurrent lapses in attention in frontal brain damaged patients with attention deficits (Gazzellini et al., 2016). In light of present data, it is reasonable to assume that also in pathological worriers a recurrent activation of DMN may cause propensity to lose attention about every 100 s during goal-oriented activity. Interestingly, data revealed that also HR oscillates at the 0.005–0.01 Hz range in pathological worriers linking its variability to regular lapses in attention during task execution. Such frequency range encompasses the very low- (0.0033–0.04 Hz) and low-frequency (0.04–0.15 Hz) components usually adopted for HRV analysis Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996).

Intriguingly, a negative correlation emerged between RT power in the low frequency range—which seems to be the range within which the DMN pulses—and vagally-mediated HRV. Although indirect, this result adds to the increasing evidence in favor of an association between vagal and DMN activity (Thayer et al., 2012 for a meta-analysis; Jennings et al., 2016). In the context of worry, current data support a recent imaging study in which individuals with high trait perseverative cognition had more difficulties suppressing DMN activity during detection of infrequent targets, and the magnitude of such activity change was predicted by individual differences in HRV (Ottaviani et al., 2016b). Present data are relevant, as they constitute a further proof of the association between the autonomic rigidity and cognitive inflexibility as a signature of perseverative cognition.

A limitation of the present study is that our pathological sub-sample was an "above the cut-off" group, making it difficult to generalize results to psychopathological disorders. Second, we did not collect direct evidence of low-frequency fluctuations in the DMN obtained via fMRI or EEG. Third, the physiological meaning of very low frequencies is disputable, mainly due to the fact that such frequency band is highly

affected by algorithms of trend removal. For this reason, the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) recommend to avoid the interpretation of very low frequencies for short-term recordings of less than 5 min. However, the present study had 15-min recordings and participants were sitting without moving except for pressing the computer space bar, therefore it is unlikely that the reported differences reflect technical artifacts instead of physiological functions. Moreover, the percentage of artifacts was quite low (2.1%), suggesting a reliable electrocardiographic signal. Moreover, previous studies showed higher correspondence between relative power of very low frequency and lower baroreflex sensitivity coupled with lower gain of its efferent component regulating cardiac rhythm, compared to other HRV bands (Davydov et al., 2007). Relative power within the very low frequency band has also been associated with depressive symptoms in children and adolescents (Blood et al., 2015) and predicted changes in depression (with lower very low frequency representing a marker of good prognosis) and treatment outcome in adults with major depression, suggesting its potential role as a biomarker for psychological wellbeing. Other compelling reason to exclude that current results on very low frequency may simply represent an artifact are the following: (a) peaks in this range do not appear randomly but only in the HW group and in the post-induction condition; (b) we have found the same significant differences on RTs, which are free from problematic issues as sweating, movement and electrode drift; and (c) differences in the same frequency range were similarly found in RTs and EEG data by Gazzellini et al. (2016) when comparing frontal patients and healthy controls. Keeping in mind that replications are necessary to clarify this issue, the fact that signals at the 0.0052–0.01 Hz range are typically removed from the analyses and that task duration is usually below 15 min may have hidden frequency peaks in such range in previous studies.

In sum, persons who are highly prone to engage in worrisome thoughts do it in a predictable oscillating pattern revealed through increased RTs variability, recurrent lapses in attention, and concomitant oscillating HR. Pathological worry is associated with detrimental outcomes at a cardiac (decreased HRV), cognitive (increased propensity to lapses in attention) and behavioral levels (increased RTs variability). At a central nervous system level, this association is presumably mediated by the midline cortical structures belonging to the DMN.

AUTHOR CONTRIBUTIONS

SG, CO, FM conceived and designed the experiments. MD, FA, BP performed the experiments. SG, CO, AN analyzed the data. AN, MD, FA, BP contributed materials/analysis tool. SG, CO, AN, FM, MD, FA, BP contributed to the writing of the manuscript.

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A Little Goes a Long Way: Low Working Memory Load Is Associated with Optimal Distractor Inhibition and Increased Vagal Control under Anxiety

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Anxiety impairs both inhibition of distraction and attentional focus. It is unclear whether these impairments are reduced or exacerbated when loading working memory with non-affective information. Cardiac vagal control has been related to top–down regulation of anxiety; therefore, vagal control may reflect load-related inhibition of distraction under anxiety. The present study examined whether: (1) the enhancing and impairing effects of load on inhibition exist together in a non-linear function, (2) there is a similar association between inhibition and concurrent vagal control under anxiety. During anxiogenic threat-of-noise, 116 subjects maintained a digit series of varying lengths (0, 2, 4, and 6 digits) while completing a visual flanker task. The task was broken into four blocks, with a baseline period preceding each. Electrocardiography was acquired throughout to quantify vagal control as high-frequency heart rate variability (HRV). There were significant quadratic relations of working memory load to flanker performance and to HRV, but no associations between HRV and performance. Results indicate that low load was associated with relatively better inhibition and increased HRV. These findings suggest that attentional performance under anxiety depends on the availability of working memory resources, which might be reflected by vagal control. These results have implications for treating anxiety disorders, in which regulation of anxiety can be optimized for attentional focus.

Keywords: anxiety, heart rate variability (HRV), distractor interference, working memory, inhibition

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Anxiety disorders are characterized by distractibility and difficulty with focusing on daily activities (Beck et al., 2005). Such features are thought to partially result from the tendency of anxiety to impair *inhibition of distractor interference*, an executive function that involves overriding the influence of prepotent but irrelevant attentional stimuli (Friedman and Miyake, 2004; Bishop, 2007). Although *inhibition* can refer to suppression of a variety of responses, this term is used in this paper in specific reference to inhibition of distractor interference. Inhibition is a major requirement for attentional focus, and is typically gaged with Stroop-like tasks that involve conflict (Miyake et al., 2000; Lavie et al., 2004; Petersen and Posner, 2012). There are inconsistent findings about whether working memory (WM) load and its autonomic correlate, *cardiac vagal control*, improve or impair inhibition during anxiety (e.g., Pu et al., 2010; van Dillen and Derks, 2012; Berggren et al., 2013). The current study addressed this issue by testing for quadratic relations that encapsulate both the enhancing and impairing effects of WM load and cardiac vagal control on inhibition performance during anxiety.

Anxiety, Inhibition, and the Enhancing Effects of Load

Anxiety Impairs Inhibition

Anxiety and other negative states tend to grab attention and disrupt the ability to inhibit irrelevant stimuli, even when those stimuli have little affective quality (e.g., Pallak et al., 1975; Hart et al., 2010; Dolcos et al., 2011; Choi et al., 2012). This impairment of inhibition might be attributed to cognitive aspects of anxiety (e.g., worry; Mathews, 1990; Borkovec et al., 1998). By consuming limited WM resources, anxiety reduces the capacity for distractor inhibition (Eysenck and Calvo, 1992; Hayes et al., 2008; Verkuil et al., 2009; Lavie, 2010).

A Potential Solution: Working Memory as a Core Feature of Anxiety Regulation

Persistent anxiety and its attentional deficits are often treated with interventions that target the enhancement of emotion regulation (ER) skills that rely on WM (e.g., cognitive restructuring; Beck, 1979; Hofmann and Asmundson, 2008; Hofmann et al., 2009). A shared feature of many cognitive ER strategies is WM load, which involves filling up the capacity-limited "blackboard" for conscious thought (i.e., WM) with non-affective material (e.g., a letter string; Baddeley, 1992; Engle, 2002; Ochsner and Gross, 2008; van Dillen et al., 2009; Buhle et al., 2014). Therefore, in the current study, WM load is conceptualized as a core mechanism underlying voluntary, top–down regulation of emotion and anxiety. WM load increases tend to reduce anxiety and other negative emotional states by shifting cognitive resources away from emotion-laden thoughts (e.g., worry; van Dillen and Koole, 2007; van Dillen et al., 2009; Kanske et al., 2011; King and Schaefer, 2011). Through attenuating anxiety in this way, WM load increases also reduce anxiety-related impairments to inhibition and selective attention (Schutz and Davis, 2000; Bradley et al., 2010; van Dillen and Derks, 2012; Vytal et al., 2012; Clarke and Johnstone, 2013).

Cardiac Vagal Control Relates to Performance-Enhancing WM Load

The notion that WM load enhances concurrent inhibition is consistent with the *Neurovisceral Integration Model* (Thayer and Lane, 2000, 2002, 2009). In this view, prefrontal cortex (PFC) areas related to WM tonically suppress subcortical areas important for anxiety and worry. Such PFC-mediated suppression is manifested as augmented cardiac vagal control, the vagus nerve's inhibitory effect on heart rate (HR; Berntson, 1997; Ter Horst and Postema, 1997). Cardiac vagal control is often quantified by high-frequency variability in the HR time series that often occur in phase with oscillations in respiration (HF-HRV; Malliani et al., 1991). HRV will be hereinafter used to refer to vagally mediated HF-HRV. High HRV at rest and during tasks has been speculated to proxy PFC-mediated cognitive regulation (perhaps load-dependent regulation; see below) of negative emotional states, including anxiety (for reviews, see Thayer and Lane, 2002; Appelhans and Luecken, 2006; Friedman, 2007). High cardiac vagal control (i.e., high HRV), through reflecting the degree of cognitive regulation over performance-harming anxiety or "stress," has been linked to improved inhibition and attentional performance (e.g., Hansen et al., 2003; Johnsen et al., 2003; Thayer et al., 2009; Elliot et al., 2011).

In the present study, we focused on HRV responses that relate to state regulatory efforts, as opposed to resting HRV, which reflects trait processes (Thayer et al., 2012). Within-subject increases in HRV might relate to WM load that regulates anxiety and enhances inhibition (Thayer and Lane, 2009). This possibility is supported by a number of studies. First, within-person increases in HRV tend to co-vary with ER strategies (e.g., reappraisal and expressive suppression) that load WM (Butler et al., 2006; Denson et al., 2011). Second, high HRV has been associated with simultaneously heightened dorsolateral PFC (a WM-related brain area) activity that relates to both reduced emotionality and increased WM load (Lane et al., 2009; Qin et al., 2009).

Anxiety, Inhibition, and the Impairing Effects of WM Load

WM-Dependent ER and HRV as Costs to Inhibition

Contrary to the above-cited research, engagement in WM-dependent ER can impair performance on concurrent or subsequent tasks that require inhibition (Friese et al., 2013; Ortner et al., 2013). These effects may be explained by the *Load Theory of Selective Attention and Cognitive Control*, in which WM capacity is required for inhibition of distractor interference (de Fockert et al., 2001; Lavie et al., 2004). In this sense, ER's inherent WM load is thought to reduce WM capacity for maintaining inhibition-related goals. As an indicator of WM-dependent ER, task levels of HRV might relate to ongoing impairments to inhibition driven by usage of WM resources. Partially supporting this notion, subjects with relatively higher resting (but not task) HRV showed a greater likelihood to use WM-dependent ER during a negative emotion picture paradigm, but showed worse performance on a subsequent Stroop task (Pu et al., 2010). In this prior study, it is possible that high HRV was associated with impaired inhibition because individuals with high HRV exhausted WM resources during ER.

NON-LINEAR MODEL OF WM LOAD AND INHIBITION UNDER ANXIETY

Evidence for the deleterious impacts of WM load and of HRV on concurrent inhibition during anxiety is perplexing, in view of work that highlights the performance-enhancing qualities of WM load. Rather than treating these differing results as incompatible, it may be that both negative and positive relations among WM load and inhibition exist together within a larger non-linear function (Marcovitch et al., 2010). A novel theoretical model is presented here that specifies a quadratic relation between inhibition and WM load under high anxiety, with WM load being conceptualized as a core mechanism of anxiety regulation (Hendricks and Buchanan, 2015; **Figure 1**). In this quadratic function, increased load may help inhibition by reducing anxious cognitions when such increases are in the range of no load to moderate load (i.e., when minimal WM resources are drained from the concurrent inhibition task; **Figure 1A**). In parallel,

WM load increases are also hypothesized to deplete shared resources, which may counteract any performance-enhancing effects, thereby flattening the positive load-inhibition relation from no to moderate load (**Figure 1A**). Moderate load may represent a critical point past which too much WM capacity is used; additional load impairs the ability to reduce distractor interference and hence causes an increasingly negative load-inhibition association (Lavie, 2005; Berggren et al., 2013; Ortner et al., 2013; **Figure 1C**). In that task HRV levels have been speculated to represent a bodily manifestation of load-related regulation of anxiety (i.e., WM load), a nearly identical quadratic function between HRV and concurrent inhibition was predicted (see **Figure 1**; Lane et al., 2009).

Partial support for the theoretical model came from a study that showed a quadratic HRV-performance relation in individuals who frequently use a WM-dependent ER strategy (i.e., *expressive suppression*; Spangler et al., 2015). Because cognitive resources were not manipulated, these effects may be attributable to other factors than WM, such as moderate HRV reflecting optimal levels of arousal for performance (see Marcovitch et al., 2010 for a similar quadratic function in children).

CURRENT STUDY

The primary aim of the current study was to examine quadratic associations between WM load and task HRV to inhibition under high state anxiety, in order to test whether intermediary levels of WM load and vagal control optimize distraction inhibition during anxiety. These aims were approached in an experiment that combined an anticipatory noise blast paradigm (to induce anxious cognition) with a common dual WM-inhibition task adapted from Lavie et al. (2004). While being either safe from or under threat of noise (Patrick and Berthot, 1995; Grillon et al., 2008, 2009), subjects loaded WM capacity and simultaneously completed an Eriksen flanker task, a common measure of inhibition (Lavie et al., 2004).

Under situations of high state anxiety (threat trials), WM load was predicted to show a negative quadratic association with inhibition performance (Hypothesis 1). An exploratory corollary of this hypothesis was that the function's shape would resemble that depicted in **Figure 1**, such that moderate load would be associated with relatively optimal inhibition. Due to its theoretical links with WM-dependent regulation of anxiety (Lane et al., 2009), task HRV was predicted to have a positive linear relation with WM load under high state anxiety (threat trials; Hypothesis 2**).** Insofar that WM load is related to HRV during high anxiety, we predicted that task HRV would also show a negative quadratic association with inhibition performance (Hypothesis 3).

Special focus was given to contrasting relations of WM load and HRV to inhibition between threat and safe trials, in order to investigate unique mechanisms accounting for the "threat" function. Load increases under low anxiety (i.e., safety) should drain WM capacity without performance enhancements via anxiety reduction. Therefore, in testing relations of inhibition to load and HRV under safety, a general absence of curvilinearity was predicted. Hypotheses were tested with a series of multilevel models that were conducted with and without self-reported subjective anxiety as a covariate, in order to assess whether the resultant functions were driven by emotional factors rather than by WM load.

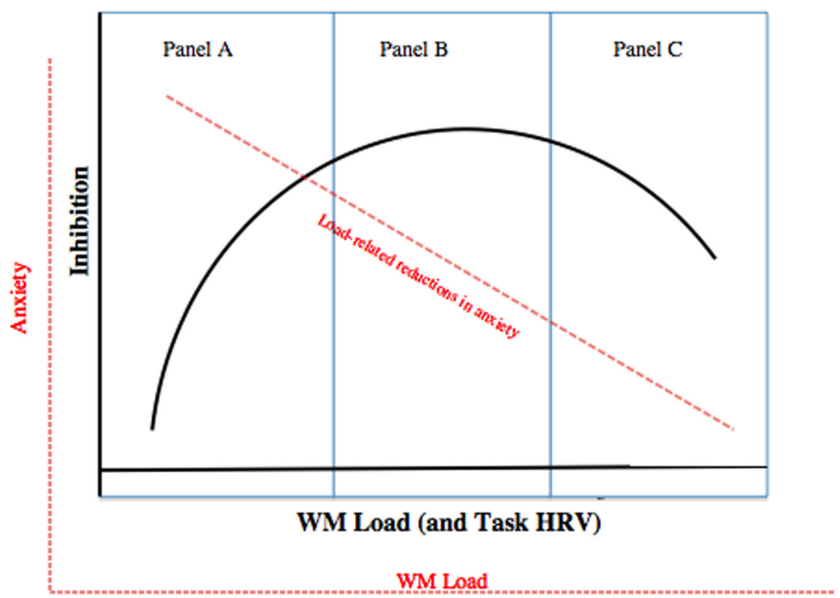

FIGURE 1 | Hypothesized quadratic association between WM load and inhibition under high state anxiety. Sub-axes with dotted lines reflect association between concurrent anxiety levels and inhibition. **(A)** Represents no load (0 digits) followed by low load (2 digits). **(B)** Reflects moderate load (4 digits), and **(C)** represents high load (6 digits).

MATERIALS AND METHODS

Subjects

Subjects were 120 (68 female) undergraduates at Virginia Tech (M_{age} = 19.3 years, SD = 2.8 years), who were recruited both online and with flyers posted on campus. Participation was compensated with extra credit in a psychology course. Exclusionary criteria were made on the basis of self-reported: (1) cigarette smoking or tobacco use, (2) diagnoses of cardiovascular disease, (3) and psychiatric/neurological disorders. Subjects were instructed to abstain from alcohol for 24 h, caffeine for 12 h, food for 2 h, and vigorous exercise for 2 h prior to participation. Four subjects out of 120 enrolled were excluded due to equipment malfunction, yielding 116 subjects retained for analyses (66 female; M_{age} = 19.1 years, SD = 1.85 years). This study was approved by the Virginia Tech Institutional Review Board, and informed consent was obtained from all subjects.

Procedure

Subjects were greeted by the experimenter upon arrival at the lab and informed of the nature of the study and the noise blast paradigm. After providing written consent, subjects were attached to physiological recording equipment, and they completed self-report questionnaires. Next, two practice trials of the experimental task were conducted with noise delivery, and subjects were given the opportunity to ask questions about the task.

After the first physiological baseline recording, subjects performed the experimental task, which was comprised of 28 trials, of which there were seven trials for each level of WM load (0, 2, 4, 6; see below). Each trial included a series of flanker responses (to measure inhibition) as well as WM maintenance; a typical trial is described in detail under the Experimental Task section below. Twelve of the 28 trials involved safety from noise blast (three safety trials per level of load), while another 12 trials included threat of noise blast without actual noise delivery (three threat trials per load level). Of importance, an additional four trials included threat of noise blast with the delivery of actual noise (1 blast trial per level of load). This design yielded 24 retained trials (12 trials for safety and 12 trials for threat); the four threat trials with noise blast were excluded from data analysis due to the confounding effects of startle and pain on performance (Kalisch et al., 2006). In threat trials, delivery of noise, or lack thereof, was randomized with the qualification that 25% of threat trials would involve actual noise (see Procedure above; Kalisch et al., 2006). In these trials, the timing of the blasts was randomly determined so that only one noise occurred during the flanker/WM section of the trial. Randomization of trial and stimulus delivery was implemented within the DMDX software (Forster and Forster, 2003).

Each subject completed all 28 trials and thus experienced 4 threat trials and 3 safety trials for every WM level (0, 2, 4, and 6). For the WM manipulation, digit series lengths of 0, 2, 4, and 6 were chosen to correspond to no, low, moderate, and high WM load, respectively (Lavie et al., 2004; van Dillen et al., 2013). To avoid switching costs, the seven trials with the same level of WM load were blocked together, and safety/threat was randomly counterbalanced within each of the WM blocks (Lavie et al., 2004). This created four WM load blocks that were randomly counterbalanced. Each of the four WM blocks was preceded by a 3-min "vanilla" baseline that was composed of a calming nature film (Jennings et al., 1992). Multiple baselines were incorporated for a more accurate representation of Task HRV for each level of WM. The entire run of the experiment lasted about 1 h.

Experimental Task

A typical trial of the experimental task is depicted in **Figure 2**. Trials were scripted and presented on a PC using DMDX software (Forster and Forster, 2003). At the beginning of the trial, subjects heard one of two tones via headphones. A low tone indicated safety (0% chance) from white noise blast, and a high tone indicated threat (i.e., "some possibility") of noise blast that may be delivered at some point in the upcoming trial. Following

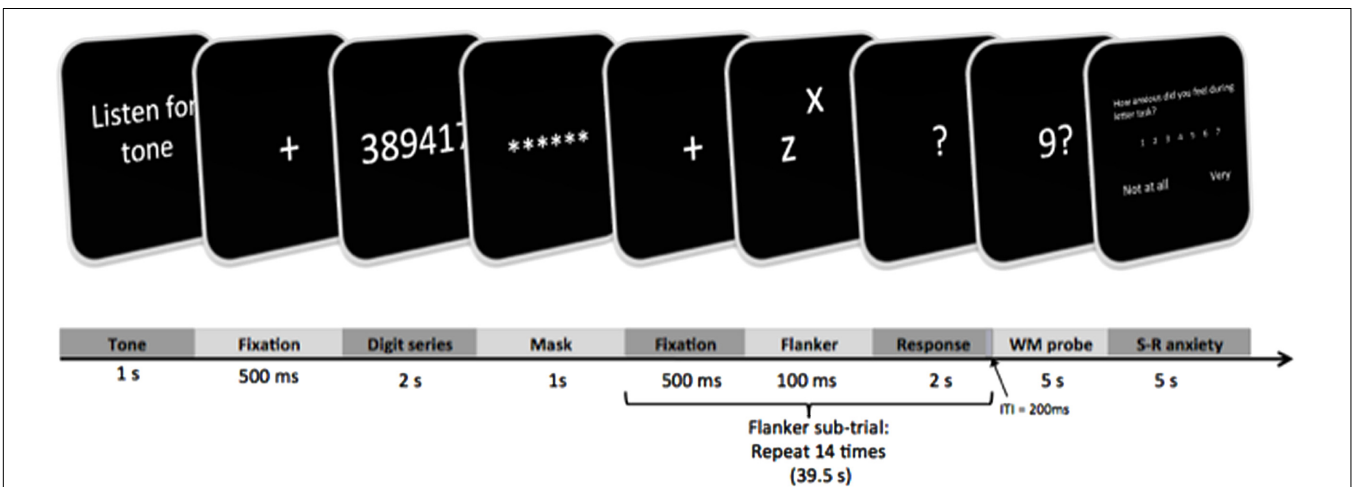

FIGURE 2 | Example of a trial from the experimental task.

tone presentation, a fixation cross appeared on the computer screen for 500 ms. Next, subjects saw a series of digits that were presented for 2 s. When subjects viewed these numbers, they were expected to silently keep in mind the digits for the remainder of the trial, rather than focus on their emotions. They were also expected to correctly answer a recognition probe later in the trial. The length of the presented series (# digits) varied between 0, 2, 4, and 6, depending on the WM block. For each trial, digits in the series were chosen at random from 1 to 9 with the following qualifications: no more than two consecutive digits could appear in the series (e.g., 1, 2, 3, 7), and the same numbers could not be used twice (e.g., 7, 7, 9, 5; Lavie et al., 2004). Once the series disappeared, subjects rehearsed the digit series for the remainder of the trial. Specifications for digit presentation were adapted from Lavie et al. (2004), with the added instructions that subjects should maintain the series rather than focusing on their emotions. A masking array was subsequently presented for 1 s to visually orient subjects for the upcoming flanker task.

While maintaining digits silently, the subject completed a series of 14 flanker sub-trials for each of the 28 trials of the experimental task. Each flanker sub-trial began with a 500 ms fixation cross. In accord with Lavie et al. (2004), a single flanker sub-trial consisted of a target letter in lowercase (the letters *x* or *z*) that was presented in the middle of the screen. At the same time, a peripheral distractor letter was presented at a subtended location relative to the target. For each response, subjects were asked to ignore the peripheral letter and to classify the target letter as an *x* or *z* by typing 1 or 2, respectively, on a computer keyboard. The visual array of letters lasted 100 ms, and then subjects were given 2 s to classify the letter with a typed response. Length of sub-trials did not vary by subjects' response times, such that the next flanker sub-trial was always initiated after 2 s. The intertrial interval for flanker sub-trials was 200 ms. The flanker sub-trials differed such that the target was either congruent with the peripheral letter (e.g., target *z* and peripheral *z*) or incongruent with the peripheral letter (e.g., target *z* and peripheral *x*, or target *x* and peripheral *z*). In each overall trial (safe or threat), 7 of the flanker sub-trials were incongruent and the other 7 sub-trials were congruent, with their order being randomized within each of the 28 trials.

Unlike other studies, 14 sub-trials were combined to create a ∼39.5 s period of dual task performance (flanker responses with concomitant WM maintenance). This was done to satisfy the 30 s length as a potential minimum for reliable HRV recording (G. Berntson, personal communication, September 10, 2014; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

After the series of flanker sub-trials with WM maintenance, a recognition probe appeared on the screen for 5 s. The probe consisted of a single letter; the subject indicated whether or not the letter appeared in the preceding series by pressing 1 or 2, respectively. At the end of the trial, subjects were given another 5 s to retrospectively report anxiety experienced during the preceding flanker/WM task. A single trial of the experimental task lasted approximately 55 s, and the task was scripted so that the length of trials did not vary by response time.

Measures and Apparatus

Experimental Task Measures

WM Load

Digit series length during the flanker task varied such that load level assumed the following values for each subject: 0, 2, 4, and 6. Although these values were the result of an experimental manipulation (see above), they are conceptualized as a variable that is on a continuous ratio-like scale (Braver et al., 1997).

Flanker Performance

Response times (RT) to classify target letters amidst distractors were collected. Accuracy in classifying letters was also attained, but RT was of primary interest for hypothesis testing. As in Lavie et al. (2004), only RTs from correct classifications were included in interference calculations and analyses. Interference scores were computed by subtracting RTs of congruent trials from that of incongruent trials, and this difference score served as a measure of inhibition performance (Stins et al., 2004; Dennis and Chen, 2007; Hart et al., 2010; Qi et al., 2014). This method yielded 28 interference scores for each person (one difference score for each of the seven threat and seven safe trials for each level of WM load). To better compare results to that of other studies, interference scores were reverse scored before being entered into data analyses, such that higher levels on this measure indexed relatively better inhibition. Higher inhibition scores reflected smaller differences between congruent and incongruent trials in RTs to classify targets, suggesting relatively better suppression of incongruent stimuli (Lavie et al., 2004).

Subjective Anxiety

At the end of each trial (threat, safe), anxious experience was reported on a 7-point Likert Scale to the following question: "How anxious did you feel during the letter task?" Higher numbers indicated greater state anxiety, such that 1 indicated that anxiety was "not at all" present and 7 denoted that anxiety was "very" present (van Dillen et al., 2009).

Self-Report Questionnaires

Health History

Information was collected about health issues that could potentially confound the validity of study findings. This questionnaire allowed experimenters to validate whether subjects followed the abstention recommendations outlined above.

Physiological Measures

Electrocardiography (ECG) was continuously recorded throughout the experimental session. ECG was collected with Ag/AgCl spot electrodes on the subject's thorax at a modified Lead II configuration in which one electrode at the right collarbone and the other at the bottom left rib. Analog ECG was amplified with the ECG100C (Biopac Systems Inc., Goleta, CA, USA), and then integrated and sampled with an MP150 device (Biopac Systems Inc., Goleta, CA, USA). Digital signals were next routed and saved to a PC in the next room for offline analysis using AcqKnowledge software (Version 4.3). A modified Pan-Tompkins algorithm was conducted on ECG waveforms to identify R-spikes. R-spikes that were missing or misclassified due to motion artifact (which occurred in less than

<1% of R-spikes) were manually identified and corrected in the ECG record. The rare cases of unidentifiable and ectopic beats (<1% of R-spikes) were removed from the ECG time series (Lippman et al., 1994). Interbeat intervals (IBI) were then computed from the ECG signal as the distance between consecutive R-spikes in millisecond (ms) units. Using Kubios software (Version 2.2), HRV was derived from the IBI signal using a Fast Fourier Transform function and quantified as spectral power (ms^2) in the domain of normal respiration (0.15–0.4 Hz; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Separate HRV estimates were yielded for all four baseline periods. Baseline HRV was derived from the last 2 min of each 3-min IBI time series in order to remove vagal influences related to cardiac stress recovery. To assess task-specific HRV accounting for baseline levels, a series of reactivity difference scores was computed for each trial by subtracting HRV during flanker performance/WM maintenance (duration = 39.5 s) from the preceding baseline HRV value (Llabre et al., 1991). This process yielded 28 different task HRV values per subject. Prior to creating differences scores, HRV values were log transformed to normalize their distribution. Task IBI levels were calculated with reactivity difference scores in the same manner.

Noise Blast Apparatus

The aversive stimulus was a 3-s, 105 dB blast of PC-generated white noise (adapted from Grillon et al., 2008, 2009). Noise level was controlled with an external amplifier, and noise blasts were delivered via headphones.

Data Analyses

Variables were inspected for skew and both HRV and self-reported anxiety were log transformed to normalize their distributions. Before entering data into analyses, severe outliers were excluded (>3.5 SD). With this criterion, 18 inhibition scores (out of 2,784 scores across participants; <1%) and 11 Task HRV values (out of 2,784 values; <1%) were excluded. Hypotheses were tested with a series of random intercept models, a type of multilevel model that accounts for nesting of observations (inhibition performance, HRV) within subjects with a random slope (Raudenbush and Bryk, 2002). This method, unlike ordinary least squares regression, prevents violating assumptions of non-independence and allows for more fine-grained estimation of within- (Level-1) and between-subject (Level-2) variation (Kreft and de Leeuw, 1998). Level-1 intercepts were allowed to randomly vary between subjects and all other predictors were estimated as fixed effects, and can be interpreted as the average of within-person relations among inhibition, HRV, and load across subjects (Kreft and de Leeuw, 1998). The structure of primary models are specified below.

Working memory Load and its quadratic effect were treated as continuous variables. Quadratic terms for WM Load were built by first mean centering and then squaring WM Load's linear term (Cohen et al., 2003). Linear and curvilinear by linear interactions between WM Load and other variables (e.g., Trial and Trait Anxiety) were computed by multiplying terms, and these interactions were probed with simple slope analysis (Aiken and West, 1991; Cohen et al., 2003). In each model, Level-1 continuous variables (e.g., WM Load, Self-reported Anxiety, HRV) were group-mean centered to reduce multicollinearity and to aid interpretation of coefficients (Kreft et al., 1995). For each hypothesis, analyses were conducted to substantiate significant interactions of load or HRV with Trial (Threat, Safe) before testing hypothesized relations in threat and safety contexts separately (Robinson et al., 2013). Trial (Threat, Safe) was coded as a dummy variable, such that 0 and 1 represented threat and safe trials, respectively.

All multilevel models presented in relation to primary hypotheses included self-reported anxiety as a covariate. This was done because, counter to the theoretical model, results indicate that WM load increases were met with increases rather than decreases in anxiety (see below). As such, it became increasingly desirable to examine relatively "pure" effects of WM load and their physiological correlates (Task HRV) apart from the unexpected changes in anxiety.

Multilevel Models for Hypotheses

To test Hypothesis 1, a comprehensive random intercept model was used to assess whether the quadratic association between WM load and performance was moderated by Trial (Safe, Threat).

Level-1: Flanker performance $= \beta_{0j} + \beta_{1j}$ (WM Load)$_{ij} + \beta_{2j}$ (WM Load)$^2_{ij} + \beta_{3j}$ (Trial)$_{ij} + \beta_{4j}$ (Self-reported anxiety)$_{ij} + \beta_{5j}$ (WM Load × Trial)$_{ij} + \beta_{6j}$ (WM Load^2 × Trial)$_{ij} + R_{ij}$

Level-2: $\beta_{0j} = \Upsilon_{00} + U_{oj}$

If the interaction between WM Load^2 and Trial was significant, models containing WM Load, WM Load^2, and self-reported anxiety as predictors and flanker performance as the outcome measure were conducted for threat and safe trials separately (Cohen et al., 2003; Robinson et al., 2013).

Hypothesis 2 was tested with random intercept models of the same form as that which was used to examine Hypothesis 1, except flanker performance was replaced by Task HRV as the outcome measure. Quadratic terms for WM Load were modeled for exploratory purposes. To test Hypothesis 3, models were conducted that were identical to those used for Hypothesis 1, except that linear and quadratic terms for WM Load were switched for Task HRV and Task HRV^2, respectively. Analyses relating to manipulation checks and basic model tenets were conducted with a series multilevel models and t-tests.

RESULTS

Manipulation Checks

Anxiety Manipulation on Self-Report

The effectiveness of the anticipatory noise blast paradigm in increasing state anxiety was examined with a random intercept model, in which Trial (threat, safe) was modeled as a fixed effect on trials from the 0 Load condition (i.e., when there were little to no WM demands). This analysis generated a significant effect of Trial ($B = -0.690$, $p < 0.001$), which suggests that during no WM load there were higher levels of subjective anxiety during threat

than in safe trials. Descriptive statistics for all variables appear in **Table 1**.

Anxiety Manipulation on Cardiac Variables

Paired sample *t*-tests were conducted to examine HRV changes from baseline to threat and from baseline to safety. Compared to baseline, HRV was lower during threat, $t(115) = 4.96$, $p < 0.001$, Cohen's $d = 0.201$, and safe trials, $t(115) = 3.31$, $p = 0.001$, Cohen's $d = 0.127$. Baseline-to-task changes in IBI were handled with the same statistical approach. IBI contrasts for threat, $t(115) = 1.95$, $p = 0.054$, Cohen's $d = 0.058$, and safety, $t(115) = 0.328$, $p = 0.748$, Cohen's $d = 0.008$, were not significant. For a direct examination of threat-of-noise on HRV, a random intercept model containing Trial as a fixed effect was conducted on HRV during no load (i.e., 0 Load) trials, and there was no significant effect for Trial ($B = 0.056$, $p = 0.255$).

WM Load and Self-Reported Anxiety

The model above that tested effects of Trial (Threat, Safe) on self-reported anxiety was used to investigate WM load's effect on diminishing anxiety. In addition to the Trial effect (see above), there was a significant positive association between WM Load and self-reported anxiety ($B = 0.015$, $p = 0.005$) for threat trials. There was also a significant interaction between Trial and WM Load ($B = 0.036$, $p < 0.001$), such that the positive association between WM Load and anxiety was stronger in safe relative to threat trials.

Anxiety Manipulation on Inhibition Performance

To substantiate that threat of noise blast negatively impacted inhibition performance, a multilevel model was conducted only on trials from 0 Load blocks. In this analysis, performance was the outcome measure and Trial was treated as a fixed effect. Inhibition performance was lower during unregulated threat compared to safe trials, as indicated by a significant effect of Trial ($B = 22.39$, $p = 0.002$).

Primary Results

Hypothesis 1: WM Load and Inhibition Performance

The random intercept model examining Load effects on inhibition between threat and safety yielded significant effects for Trial ($B = -13.83$, $p = 0.031$) and WM Load^2 ($B = -1.31$, $p = 0.045$). The main effect of WM Load^2 was qualified by a significant WM Load^2 × Trial interaction ($B = 3.36$, $p < 0.001$). This interaction confirms that the quadratic relation between WM load and inhibition differs between threat and safe trials and justifies follow-up tests of WM Load effects for threat separately. See **Table 2** for a summary of random intercept models that tested load-inhibition relations.

Quadratic relation between WM Load and inhibition under high state anxiety

For the model that examined threat trials, only the effect of WM Load^2 was significant ($B = -1.31$, $p = 0.038$), which indicated a negative quadratic function between WM load and inhibition performance under high state anxiety (i.e., threat). The precise shape of this function can be seen in **Figure 3**.

This quadratic relation can be explained as follows. Load increases from no to low load (0 to 2 digits) were associated with augmentations in performance, such that there was a positive load-inhibition relation. This positive relation reversed completely at low load (2 digits), whereby load increases from low to moderate load (2–4 digits) were met with decreases in inhibition performance (i.e., a negative relation). The negative relation grew stronger as load increased to 6 digits. The quadratic trend indicates that inhibition performance under anxiety is relatively better during low load (2 digits) compared to both no load and higher load (4 and 6 digits).

Negative linear relation between WM Load and inhibition under low state anxiety

The multilevel model examining load effects in safe trials indicated that there was a significant linear relation between WM Load and inhibition ($B = -3.26$, $p = 0.009$), but this

TABLE 1 | Means (standard deviations) of performance, cardiac, and self-report measures.

	Threat trials				Safe trials			
	Load 0	**Load 2**	**Load 4**	**Load 6**	**Load 0**	**Load 2**	**Load 4**	**Load 6**
Performance measures								
Incongruent RT (ms)	647.51 (130.39)	640.04 (135.15)	662.25 (132.19)	676.39 (140.44)	655.84 (134.90)	669.82 (137.20)	682.05 (126.06)	684.85 (155.54)
Congruent RT (ms)	612.59 (119.17)	622.57 (120.75)	623.03 (123.34)	636.90 (136.41)	643.13 (136.28)	634.36 (121.65)	637.68 (124.58)	651.06 (136.87)
WM error rate (%)	–	5.74 (0.23)	6.02 (0.24)	11.41 (0.32)	–	5.81 (0.23)	3.02 (0.17)	6.04 (0.24)
Cardiac measures								
BL HRV [ln(ms2)]	6.70 (1.10)	6.70 (1.07)	6.63 (1.11)	6.66 (1.02)	6.67 (1.09)	6.70 (1.09)	6.64 (1.11)	6.66 (1.02)
HRV ln(ms2)]	6.47 (1.14)	6.59 (1.19)	6.45 (1.16)	6.37 (1.17)	6.50 (1.19)	6.61 (1.15)	6.53 (1.17)	6.51 (1.23)
BL IBI (ms)	837.19 (123.32)	835.98 (131.64)	829.47 (124.52)	836.78 (131.07)	835.38 (123.29)	835.65 (130.80)	830.23 (124.00)	836.96 (131.52)
IBI (ms)	834.45 (120.61)	834.21 (130.53)	822.99 (125.71)	821.63 (129.21)	838.47 (125.30)	836.50 (123.82)	831.65 (125.88)	828.68 (129.86)
Self-report								
Task anxiety (Likert)	3.60 (1.69)	3.70 (1.61)	3.74 (1.73)	3.89 (1.61)	1.82 (1.08)	1.98 (1.12)	2.20 (1.19)	2.44 (1.27)
Trait Anxiety	38.01 (8.03)	Min = 21, Max = 61						

RT, response time; WM, working memory; BL, baseline; HRV, heart rate variability; IBI, interbeat interval.

TABLE 2 | Multilevel Models: Fixed Effects of WM Load and WM Load^2 on Inhibition and Task HRV.

	A) Overall				*B) Threat trials*				*C) Safety trials*			
	B	***SE***	***t***	σ^2	***B***	***SE***	***t***	σ^2	***B***	***SE***	***t***	σ^2
Dependent measure: Inhibition performance (congruent minus incongruent)												
Intercept	−28.05	4.94	−5.67**	617.95**	−27.38	4.82	−5.68**	788.81**	−44.00	5.17	8.52**	473.80**
Load	−1.62	1.17	−1.38		−1.52	1.14	−1.34		−3.26	1.25	−2.61**	
Load^2	−1.31	0.654	−2.01*		−1.31	0.631	−2.07*		2.13	0.667	3.12**	
S-R anxiety	2.35	4.57	0.514		−6.24	7.99	−0.781		−3.88	7.11	−0.546	
Trial	−13.83	6.41	−2.16*		–	–	–		–	–	–	
Load X Trial	−1.94	1.66	−1.17		–	–	–		–	–	–	
Load^2 X Trial	3.36	0.919	3.66**		–	–	–		–	–	–	
Dependent measure: Task HRV (natural log of ms^2)												
Intercept	−0.082	0.048	1.67	0.112**	−0.119	0.048	−2.48**	0.124*	−0.074	0.046	−1.62	0.101**
Load	−0.006	0.010	−0.682		−0.008	0.010	−0.868		−0.005	0.010	−0.447	
Load^2	−0.015	0.005	2.76**		−0.014	0.005	−2.65**		−0.009	0.005	−1.70	
S-R anxiety	−0.096	0.037	2.58*		−0.0006	−0.067	−0.009		0.001	0.066	0.019	
Trial	−0.024	0.053	0.451		–	–	–		–	–	–	
Load X Trial	0.007	0.014	0.519		–	–	–		–	–	–	
Load^2 X Trial	0.006	0.008	0.832		–	–	–		–	–	–	

*Unstandardized regression coefficients are presented. P-value of fixed effects are for t-tests of slopes against zero. P-value of random effect are for Wald-z test of between-subject variance against zero. S-R, self-reported; HRV, heart rate variability. **p < 0.01, *p < 0.05.*

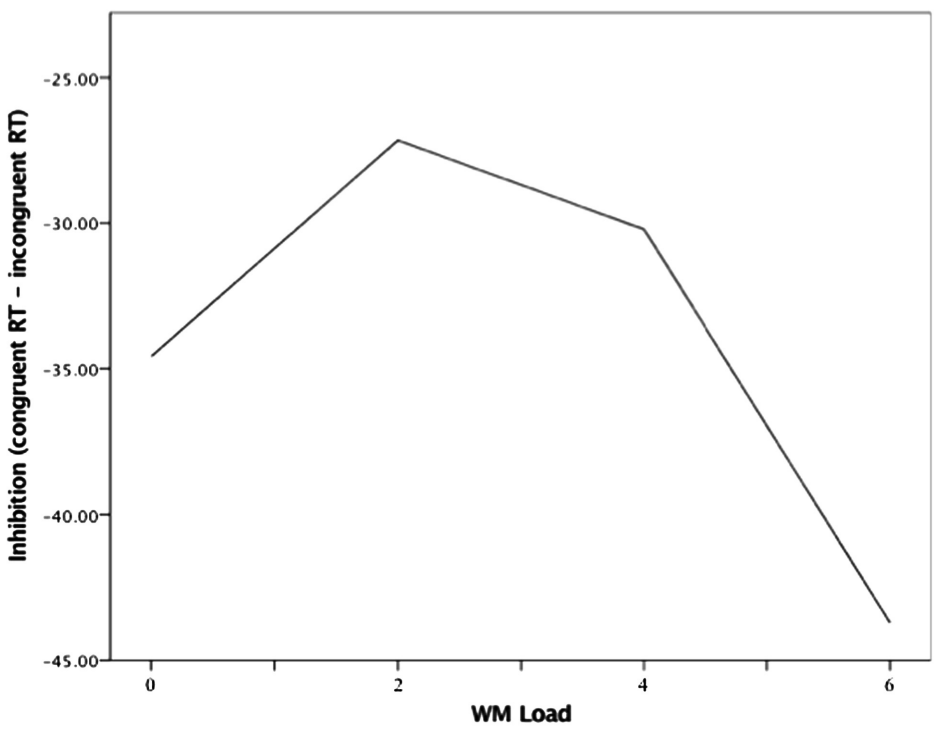

FIGURE 3 | Quadratic association between WM load and inhibition during threat of noise blast. WM load levels: 0 (no load), 2 (low load), 4 (moderate load), and 6 (high load).

linear effect was qualified by a significant quadratic association between WM Load and inhibition ($B = 2.13$, $p = 0.001$). As is seen in **Figure 4**, the negative relation appeared to attenuate and flatten across levels of load, until there was a slight reversal of the load-inhibition association from moderate to high load (4–6 digits).

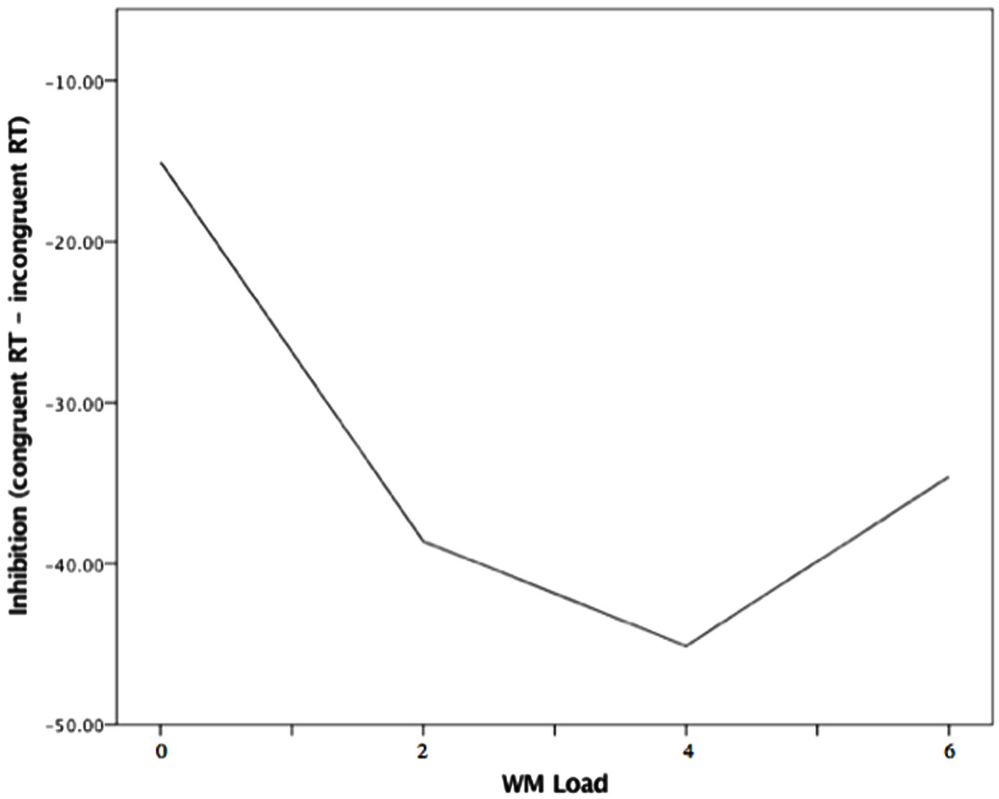

FIGURE 4 | Quadratic association between WM Load and inhibition during safety from noise blast. Note. WM load levels: 0 (no load), 2 (low load),4 (moderate load), and 6 (high load).

Hypothesis 2: Task HRV and Load

The random intercept model that examined load effects on HRV between threat and safety revealed no significant interaction between WM Load and Trial ($B = 0.007$, $p = 0.603$). In examining threat trials singularly, the linear load-HRV relation was not significant (see model statistics in **Table 3**). However, for threat trials, there was an unpredicted significant effect for WM Load^2 ($B = -0.015$, $p = 0.006$), as well as for Self-reported Anxiety ($B = -0.096$, $p = 0.010$). There were no significant effects in the model examining safety trials. Further inspection of WM Load's quadratic effect under threat (see **Figure 5**) indicates that there was a positive load-HRV association from no to low load, which began to reverse from low to moderate low. The association then becomes increasingly negative, such that further increases in load past moderate levels (4 digits) were met with reductions in Task HRV.

TABLE 3 | Multilevel models: fixed effects of task HRV and task HRV^2 on inhibition.

	A) Overall				*B) Threat trials*				*C) Safety trials*			
	B	***SE***	***t***	σ^2	***B***	***SE***	***t***	σ^2	***B***	***SE***	***t***	σ^2
Dependent measure: Inhibition performance (congruent minus incongruent)												
Intercept	−31.88	4.27	−7.47**	614.33**	−32.87	4.15	−7.93**	773.11**	−28.98	3.92	−7.39**	465.06**
HRV	−1.87	3.71	−0.504		−1.21	3.63	−0.336		1.71	3.76	0.456	
HRV^2	−1.26	3.46	−0.364		−0.544	3.58	−0.152		−7.17	3.55	−2.02*	
S-R anxiety	−1.99	4.56	−0.436		−9.14	8.08	−1.13		−10.13	7.93	−1.28	
Trial	1.31	5.29	0.248		–	–	–		–	–	–	
HRV X Trial	3.37	5.19	0.650		–	–	–		–	–	–	
HRV^2 X Trial	−3.91	4.66	−0.840		–	–	–		–	–	–	

*Unstandardized regression coefficients are presented. P-value of fixed effects are for t-tests of slopes against zero. P-value of random effect are for Wald-z test of between-subject variance against zero. S-R, self-reported; HRV, heart rate variability. **p < 0.01; *p < 0.05.*

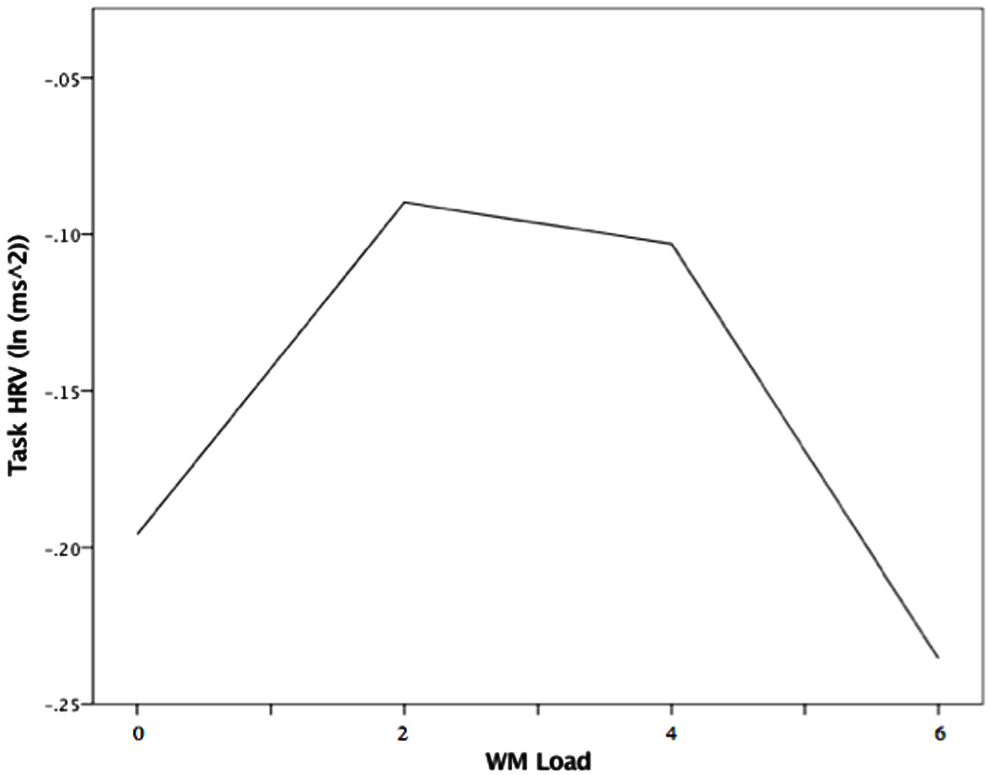

FIGURE 5 | Quadratic association between WM Load and Task lIRV during threat of noise blast, Note. WM load levels: 0 (no load), 2 (low load),4 (moderate load), and 6 (high load).

Hypothesis 3: Task HRV and Inhibition Performance

Quadratic relation between Task HRV and inhibition under high state anxiety

The multilevel model examining effects of HRV and HRV^2 on inhibition between threat and safety indicated that there was no significant interaction between HRV^2 and Trial ($B = 3.91$, $p = 0.401$). In fact, there were no significant main effects or interaction in this model. See **Table 3** for a summary of random intercept models examining HRV's relations to inhibition. In the model examining threat trials only, the quadratic association between Task HRV and inhibition was not significant ($B = 3.91$, $p = 0.401$). In general, these data indicate that there were no associations between Task HRV and inhibition performance.

DISCUSSION

The primary aim of this study was to test for a negative quadratic relation between WM load and inhibition of distractors under high state anxiety, and to examine whether cardiac vagal control reflects WM load that both enhances and impairs inhibition under anxiety. Results partially confirmed hypotheses by showing a negative quadratic function between WM load and inhibition under high state anxiety. A number of unpredicted but potentially fruitful results emerged, which include a quadratic association between WM load and task HRV, in which HRV was highest under low load relative to all other load levels.

Contrary to hypotheses, there were no direct relations of HRV to inhibition. Findings suggest that under high state anxiety, the relation of WM load to distractor inhibition and cardiac vagal control depend on the availability of WM capacity (Lavie et al., 2004; Schmeichel et al., 2008; Thayer and Lane, 2009). As is discussed below, such availability, which might be reflected in task HRV, is the result of opposing effects of load-dependent anxiety reduction and load-dependent consumption of cognitive resources (Pessoa, 2009).

Manipulation Checks and Model Tenets

Differences in anxiety ratings between threat and safety trials indicate that the noise blast paradigm was effective in inducing anxious cognition, as has been shown previously (Grillon and Ameli, 1998; Skolnick and Davidson, 2002; Lissek et al., 2005; Grillon et al., 2008). Further supporting the model and prior research, induced anxiety impaired inhibition, as is shown by worse inhibition in threat relative to safe trials during unregulated anxiety (e.g., Bishop et al., 2004; Hart et al., 2010; Choi et al., 2012). Contrary to the model and previous studies (e.g., van Dillen et al., 2009; Vytal et al., 2012; Patel et al., 2015), WM load increases were related to augmentations, and not reductions, in self-reported anxiety. It is possible that load reduced anxiety's cognitive components (i.e., worry), which are related to WM,

while bodily aspects of anxiety persisted (i.e., "anxious arousal) to be reflected in the self-report (Endler and Kocovski, 2001; Vytal et al., 2012; Sharp et al., 2015). Previous studies suggest that anxiety-related interoceptive cues can be detected consciously and thus self-reported; however, these interoceptive functions implicate neural functions that are not directly tied to WM (Nitschke et al., 1999; Critchley et al., 2004).

Primary Findings

High State Anxiety: WM Load^2 and Inhibition

Hypothesis 1 was partially supported in that there was a negative quadratic relation under high but not low state anxiety. Potential mechanisms that drive the non-linearity in the function can be clarified by focusing on its linear components, as is done below.

Inhibition enhancements

As hypothesized, there was a positive relation between load and inhibition in the range of no to low WM load. This positive relation is consistent with other studies in which relatively high load enhanced concurrent performance through attenuating negative emotional processing (Vytal et al., 2012; Clarke and Johnstone, 2013; Patel et al., 2015). High relative to low levels of WM load can speed reaction times to classify a happy target face amidst an angry distractor face, as well as reduce neural processing of the angry distractor face (van Dillen and Derks, 2012). As suggested in previous research, load increases in the present study may have enhanced inhibition by leaving less WM capacity for maintaining performance-harming anxiety (van Dillen and Koole, 2007). Prior studies have shown better performance under high versus low load, but the current study only showed a performance enhancement for low compared to no load, potentially because high load in the current task was especially demanding (three task demands) compared to prior research. Therefore, it is possible that present load effects across the entire function are restricted to a high range of WM load that is well beyond that of prior studies. That is, all of the present study's load conditions might correspond to "high" load in other studies. Such a possibility is speculative, as a direct comparison of load conditions is difficult due to different tasks being used between studies (e.g., n-back, arithmetic problems, Sternberg WM task). Yet, lack of inhibition enhancements from no to low load under safety supports the notion that enhancements during threat were caused by anxiety reductions, because safety did not likely involve enough anxiety to allow for notable load-dependent anxiety reductions.

Inhibition impairments

In accord with the model, there was a reversal of the positive linear relation between load and inhibition under anxiety such that the relation became negative from low to moderate load. As WM capacity became increasingly scarce, higher load related to relatively worse inhibition under anxiety. The negative load-inhibition relation became even stronger from moderate to high levels of load. These findings may be due to reliance of distractor inhibition on limited WM capacity (Baddeley, 1992; Engle, 2002), and because high load tends to worsen inhibition of irrelevant visual distractors (Lavie, 2005, 2010). The reversal and intensification of the load-inhibition relation suggests that competition between WM load and other cognitive functions (e.g., inhibition) may be stronger when WM capacity limits are reduced and resources are scarce (Cowan, 2001; Pessoa, 2009; Forster, 2013). In effect, as WM was increasingly depleted past low load, performance may have been impaired in proportion to capacity availability, such that load-induced impairments increasingly outweighed concurrent load-dependent performance improvements. As mentioned above, it is possible that load's impairments to inhibitions require heavy taxation of WM capacity. Previous studies may have missed this section of the function because the present study's added task demands made the 6-digit condition sufficiently high to impair inhibition (e.g., van Dillen and Derks, 2012; Vytal et al., 2012).

Revising the Theoretical Model

A discrepancy between the yielded function and the model (**Figure 1**) is that there was neither attenuation nor a plateau in the positive relation at moderate load. In effect, inhibition performance under anxiety was optimal under low rather than moderate load. It is possible that performance would have been even better if three digits were maintained, a condition not included in this study. Another possibility is that low load represents a meaningful level of WM usage past which further load increases drain resources needed for inhibition. If the latter is the case, a logical query arises as to why load increases from no to low load were uniquely associated with inhibition enhancements rather than impairments. A potential explanation might relate to the fact that: (1) emotion-related cognition demands more cognitive resources than low load neutral cognition (Vytal et al., 2012), and (2) the attenuation of anxiety by load is stronger under high relative to low anxiety (van Dillen and Koole, 2007; Stout et al., 2013). By shifting resources away from heavily depleting anxiety, low load likely frees up much more WM capacity than it fills with digit maintenance alone, and this effect may improve concurrent inhibition performance.

Compared to low load neutral information, threatening stimuli strongly consume WM capacity, as measured by neural and behavioral measures (Dolcos and McCarthy, 2006; Stout et al., 2013). In the current study, poor inhibition at no relative to low load may have been caused by unregulated anxiety (0 Load) draining more shared resources than low load maintenance (e.g., Hajcak and Olvet, 2008; Kanske et al., 2011; Dolcos and Denkova, 2014). Second, smaller amounts of WM load might be more effective at clearing anxious cognition from WM capacity when WM resources are increasingly used by these cognitions (van Dillen and Koole, 2007). Thus, from no to low load (when there is increased anxious cognition in WM capacity), minimal task-related increases in load may have dissipated anxious cognition and thus had a net effect of freeing up more WM capacity than was filled by low load manipulation (i.e., 2 digits). As such, this free capacity was available for the concurrent inhibition task. With further increases in task-related load, however, inhibition may have declined because less WM capacity was free for maintaining

inhibition goals (Miller and Cohen, 2001; Lavie et al., 2004; Qi et al., 2014). This "capacity availability" account of results is supported by unexpected HRV findings, as is discussed below.

Quadratic Relation between Load and Task HRV

It was hypothesized that task HRV would reflect WM load used to decrease anxious cognition. Rather than supporting a linear relation between HRV and WM-dependent regulation over anxiety, a more complex non-linear association between WM load and HRV was observed. This quadratic association aligns with elements of the Neurovisceral Integration Model and past studies that view vagal control not as an index of degree of cognitive regulation, but as a reflection of PFC resources available for ongoing cognitive-affective demands (Jorna, 1992; Elliot et al., 2011). In fact, Thayer and Lane (2009, p. 85) have suggested that "HRV functions at both the trait and state levels as a resource."

Heart rate variability changes in response to load followed a similar trend to that of load-induced performance changes. Task HRV was highest at low levels of load (2 digits), when inhibition was optimized; then, the load-HRV association reversed from low to moderate load just as the load-inhibition association did (see **Figures 3** and **5**). Since inhibition is dependent on WM availability, it is possible that task HRV reflected the degree of "free" WM capacity that resulted from both anxiety reduction and load itself (Engle, 2002; Lavie, 2010). At low load, when inhibition performance was optimized, HRV may have reflected a large amount of WM resources that were salvaged through "deleting" anxious cognition and made available for removal of distractor interference (Dolcos and Denkova, 2014). The decline of HRV after low load may reflect WM capacity being increasingly filled with task-related load, consistent with the parallel load-dependent decreases in performance seen in **Figure 3** (Croizet et al., 2004). If HRV is interpreted as an indicator of resource availability, the yielded load-HRV quadratic relation is consistent with studies in which task HRV was negatively related to ongoing task demands and positively related to cognitive performance that requires high levels of available WM capacity (Hansen et al., 2003; Lehrer et al., 2010; Elliot et al., 2011; Allen and Friedman, 2016).

The absence of the predicted quadratic association between HRV and inhibition conflicts with our finding of a quadratic function between HRV and executive function in those who frequently use a WM-dependent ER strategy (Spangler et al., 2015). This quadratic association included resting HRV, which unlike phasic HRV, has been theoretically linked to trait processes whereby ER's costly effects potentially accrue over time (Butler et al., 2006). Although there has been one report of a quadratic association between task HRV and executive function in children (Marcovitch et al., 2010), it might be that task HRV taps into the state-related availability of resources that can be used for inhibition of distraction.

Implications for ER and Intervention

Since many ER strategies entail WM loading, the present findings qualify theoretical perspectives in which ER is held to assist performance via the use of executive control (Thayer and Lane, 2000; Blair and Ursache, 2011; Cohen et al., 2012). Cognitive regulation of high anxiety may only enhance concurrent inhibition insofar as that regulation does not heavily load WM. Clarification is also given to the view of ER as damaging to attentional focus by suggesting that ER strategies may only hurt performance when they are highly loading, as in the case of expressive suppression (Kalisch et al., 2006; Goldin et al., 2008; Friese et al., 2013; Ortner et al., 2013).

Regarding cardiac vagal control, our findings indicate that deploying WM resources in the service of ER does not cause simple increases in HRV, as might be predicted from previously shown HRV augmentations during ER. The present results instead suggest that on-task HRV levels reflect inter-function competition of WM-related regulation, anxiety, and inhibition. This view is somewhat inconsistent with the Neurovisceral Integration Model, which highlights the anatomical-functional integration of ER and "cold" executive functions, which work together in self-regulation (Thayer and Lane, 2009). However, by virtue of integrated neurocognitive resources in the PFC, there is inherent resource competition between emotion, ER, and executive control, of which HRV might be a reflection (Pessoa, 2008, 2009).

The current study also underscores the potential value of using minimally loading ER strategies for treatment in anxiety disorders, of which a major feature is difficulty in concentration (Beck et al., 2005). Interventions like CBT that involve complex cognitive ER strategies (e.g., reappraisal) may do more harm than good by impairing anxious individuals' ability to inhibit irrelevant information, and in doing so, worsen anxious symptoms (Olatunji et al., 2007). ER strategies might be better chosen according to their level of load, so that damaging effects on attention and daily functioning are minimized.

Limitations, Future Directions, and Concluding Remarks

The present study has limitations that might be addressed in future research on the relationships among load, inhibition, and HRV under anxiety. First, state anxiety was only measured via self-report, which has been shown to diverge from other aspects of anxiety (Sharp et al., 2015). Future studies might include measures of eyeblink startle to more comprehensively assess anxious states and to better substantiate the left side of the yielded non-linear functions (Grillon, 2008). There was also no direct WM capacity measure in this study. Future research could include neuroimaging to more directly index resource competition at the central nervous system level. Although HRV data from noise blast trials were removed from analyses, it is conceivable that the noise blasts influenced HRV estimates in surrounding trials. This possibility is somewhat unlikely, as cardiac vagal responses to noise blast return to baseline levels within a time period (i.e., three to four heartbeats; <5 s) shorter than the present study's intervals between HRV measurements (Chen et al., 2014). This study also had a number of strengths that should be noted, including a relatively large sample size and many within-subjects observations. These factors allowed

for a powerful test of hypothesized three-way interactions (e.g., quadratic effects varying between safety and threat).

In sum, this study provides evidence that minimal WM load can attenuate the impairing effects of anxiety on distractor inhibition, while more heavily loading tasks may do just as much harm to inhibition as anxiety itself. The current study also underscores cardiac vagal control as a potential correlate of WM resource availability, a factor that relates to attentional performance under threat. Broadly speaking, this study may inform treatments for anxiety disorders, in which regulation of emotion and anxiety can be modified to prevent lapses in attention.

ETHICS STATEMENT

This study was approved by the Institutional Review Board (IRB) at Virginia Tech. All participants were greeted and the experimenter explained each section of the informed consent form, in order to educate participants on the nature of the study procedures and purpose, risks and benefits, as well as their freedom to withdraw at any point time with no penalty. Participants were then given the opportunity to ask questions, after which they signed the informed consent form. No vulnerable populations were used in this study.

AUTHOR CONTRIBUTIONS

DS wrote this under the mentorship and direction of BF. DS developed the research question and conducted this study as a part of his dissertation, with BF providing invaluable feedback and edits on the project's implementation and on the submitted manuscript

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The Association between Work-Related Rumination and Heart Rate Variability: A Field Study

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The objective of this study was to examine the association between perseverative cognition in the form of work-related rumination, and heart rate variability (HRV). We tested the hypothesis that high ruminators would show lower vagally mediated HRV relative to low ruminators during their leisure time. Individuals were classified as being low (n = 17) or high ruminators (n = 19), using the affective scale on the work-related rumination measure. HRV was assessed using a wrist sensor band (Microsoft Band 2). HRV was sampled between 8 pm and 10 pm over three workday evenings (Monday to Wednesday) while individuals carried out their normal evening routines. Compared to the low ruminators, high affective ruminators demonstrated lower HRV in the form of root mean square successive differences (RMSSDs), relative to the low ruminators, indicating lower parasympathetic activity. There was no significant difference in heart rate, or activity levels between the two groups during the recording periods. The current findings of this study may have implications for the design and delivery of interventions to help individuals unwind post work and to manage stress more effectively. Limitations and implications for future research are discussed.

Keywords: work-related rumination, heart rate variability, unwinding from work, recovery

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INTRODUCTION

Perseverative cognition has been conceptualized as "the repeated or chronic activation of the cognitive representation of stress-related content" (Brosschot et al., 2005). Consistently, studies have shown that it may not be the actual stressors themselves that cause health issues but that it is the continued mental representation of the stressor/s—in the absence of the actual stressor—that is the main contributor. Prolonged perseverative cognition has been associated with a range of negative physical (Brosschot et al., 2006, 2010; Verkuil et al., 2010; Ottaviani et al., 2016), and psychological conditions (Garnefski and Kraaij, 2006; Aldao et al., 2010).

The fundamental principle of the perseverative cognition hypothesis is that disease risk is increased when individuals continue to experience unwanted mental representation of a stressful situation, which in turn elicits prolonged physiological arousal. There are many different possible stressors (e.g., work, home, private); in the present article, we focus solely on the role of mental presentations associated with work, in the form of work-related rumination. Work-related rumination has been defined as a thought or thoughts directed to issues relating to work,

that is/are repetitive in nature (Cropley and Zijlstra, 2011). For example, a worker may ruminate about an important project deadline, an unfinished task, stress over a future meeting, or they may perseverate about something negative that was said to them by their line manager or colleague at work (Cropley and Millward, 2009; Syrek et al., 2016).

Workers need to psychologically detach and unwind from the demands of work during their leisure time to replenish lost resources that were expended at work (Meijman et al., 1998). Delayed psychological recovery in terms of repetitive or ruminative thinking about work has been associated with a range of health complaints (Pravettoni et al., 2007; Gustafsson et al., 2008; Rydstedt et al., 2009; Sonnentag et al., 2010; Querstret and Cropley, 2012; Cropley et al., 2013), but importantly, and of relevance for the present study, failure to unwind from work has been associated with increased cardiovascular disease risk (Suadicani et al., 1993; van Amelsvoort et al., 2003; Kivimäki et al., 2006). For example, a prospective study by Suadicani et al. (1993) found that men who reported an inability to relax after work had an approximately threefold increased risk of Ischemeic heart disease. Another study of 788 industrial workers found that incomplete recovery at weekends was predictive of cardiovascular death (Kivimäki et al., 2006). What was interesting about this study was that the initial cohort was free from cardiovascular disease and that the findings remained significant after controlling for conventional risk factors, including age, sex, cholesterol, systolic pressure, body mass index, smoking, physical inactivity, fatigue and job stress.

The exact mechanism underlying the association between work-related rumination and cardiovascular disease risk is not clear; however, two distinct pathways may be involved: the behavioral and the physiological. The behavioral pathway can be influenced by many factors such as leading a sedentary lifestyle, drinking alcohol to excess, smoking and moderating eating habits, and there is some evidence to suggest that high work-related ruminators consume more foods that contain saturated fats and sugars than low ruminators (Cropley et al., 2012). Regarding the physiological pathway, although not fully understood, two involuntary branches of the autonomic nervous system appear to be closely involved in the progression from stress to disease: the sympathetic and the parasympathetic nervous systems. When the body is under threat or stressed, sympathetic activity (or parasympathetic withdrawal) mobilizes the organism for action by initiating physiological arousal, such as increasing blood pressure, heart-rate, catecholamine and corticosteroid secretion. In the absence of threat or perceived stress, the parasympathetic system counteracts the effects of sympathetic activity and restores homeostasis. These two mechanisms serve to protect the organism in the short-term but can have damaging effects if stress is prolonged such as when people perseverate about work matters.

There are various ways to assess autonomic nervous system activity and many of these are quite intrusive. However, one non-invasive marker that is the subject of this article is heart rate variability (HRV). HRV is considered as an objective, discreet measure of vagally mediated cardiac regulation and a predictor of cardiac disease risk (Tsuji et al., 1996; Hansson and Jönsson, 2006). As a proxy for prefrontally modulated and vagally mediated cortico-cardiac interaction, HRV is thought to be a marker for emotional regulation, responding when individuals are under mental stress (Appelhans and Luecken, 2006; Heponiemi et al., 2006; Thayer and Lane, 2009; Geisler et al., 2010; Forkmann et al., 2016). Vagally mediated HRV can therefore be construed as an indicator of how well people regulate their emotions (Koval et al., 2013).

The purpose of the present study was to examine the effects of perseverative cognition in the form of work-related rumination on HRV. There are a number of studies that have examined rumination and HRV (Ottaviani et al., 2016), but to our knowledge, and following a review of the literature, only one study has examined the effects of work-related rumination on HRV (Vahle-Hinz et al., 2014). Vahle-Hinz et al. (2014) assessed the effects of work stress, work-related rumination, sleep and nocturnal HRV on a work day and over the weekend. No significant associations were observed between work-related rumination and nocturnal HRV on a workday, although work-related rumination measured on Saturday evening was related to nocturnal HRV. However, it was a positive predictor, suggesting greater HRV with high rumination. As the authors state, this finding is quite perplexing, and although they present a rational argument for why this is, they also offer some compelling limitations which could have attributed to these results. In their study, rumination was only measured by one item, "Today I had to think about work-related problems at home" and as the authors point out this only assessed whether workers thought about work in the evening or not, whereas HRV seems to be particularly sensitive to emotional regulation. It was their suggestion that future research should include measures of rumination that explicitly assess affective reactions related to work.

To this end, the present study investigated the association between work-related rumination and HRV over three evenings. Following Vahle-Hinz et al. (2014) suggestion, we chose a measure of affective rumination by Cropley et al. (2012). This measure specifically assesses affective reactions related to thinking about work. It was predicted *that individuals reporting high affective work-related rumination would demonstrate lower HRV during a workday evening relative to low ruminators*. In order to test this hypothesis, we captured continuous data from a wrist band photoplethysmography (PPG) sensor, first passing the sensor data through a paired smartphone and then uploading to a cloud instance, where further analysis could be performed. To our knowledge, this is the first study to use wrist band PPG in order to capture HRV data in a field study.

MATERIALS AND METHODS

Sample and Participants

The sample was recruited from a financial sector organization (BNP Paribas) in collaboration with AXA/PPP, who made it possible for us to interact directly with the employee population.

Participants were drawn from a larger cohort of full-time working adults. One hundred and ninety-five individuals (F = 29.8%, M = 70.2%) with an age range of 20–62 years (M = 38.69, SD = 9.44) completed the affective subscale of the work-related rumination questionnaire and low (n = 55) and high (n = 49) ruminators were identified using quartile splits. As both HRV and tendencies to ruminate have been known to be affected by age (Britton et al., 2007; Sütterlin et al., 2012; Vahle-Hinz et al., 2014), we restricted the upper age eligibility to 45 years. Due to missing data (due to removal of the band from the wrist, signal loss and movement artifacts), the final sample consisted of 19 high ruminators (mean age 34.3 years, SD = 6.7 years, 31.6% females) and 17 low ruminators (mean age 33.3 years, SD = 6.55 years, 17.6% females).

Work Related Rumination

The affective rumination subscale of the work related rumination questionnaire was used to assess people's perseverative cognitions about work (Cropley et al., 2012). Items are responded to on a 5-point Likert scale ranging from 1 = "Very seldom/never, seldom, sometimes, often to 5 = Very often/always", e.g., "Are you troubled by work-related issues when not at work?"; This measure has been used in a number of previous studies (Querstret and Cropley, 2012; Querstret et al., 2016), and has shown good reliability and validity (Querstret and Cropley, 2012; Syrek et al., 2016).

Heart Rate Variability Assessment

The Microsoft Band v2 was selected to capture interbeat intervals because it exposes peak-to-peak (PP) intervals (the duration of every detected heartbeat) through its developer SDK, while most wearables only provide average heart rate, and from which we can derive HRV. Whilst deriving HRV from PPG data is quite novel, there is a precedent for ECG/PPG correlation when looking at HRV data (Selvaraj et al., 2008). Moreover, the device can be programmed to turn on and off the sensors without any explicit interaction with the user, i.e., accelerometer and heart rate sensors can be turned on and off while the user is sleeping, which makes it possible to acquire and analyze data without the potential bias introduced by interaction, which can in itself be a form of intervention. We created an app for iOS, that pairs with the Microsoft Band v2, and periodically collects the data from the sensors, and uploads the collected data to our cloud, for analysis. We implemented an algorithmic policy to balance the amount of captured data and battery consumption to better preserve battery life. The heart rate was captured for three consecutive minutes (in order to acquire a continuous stream of PP data long enough to ensure a minimum level of validity in HRV analysis), then turned off for 3 min (to avoid depleting the battery unnecessarily). Accelerometry data was measured along HRV to assess movement. The accelerometer was periodically turned on for 15 s, then turned off for 45 s. The accelerometer captures data from a triaxial accelerometer and a triaxial gyroscope, at a sampling frequency of 60 Hz. To keep the communication from the smartphone to the cloud to a minimum, we uploaded a small cluster of statistical features of the accelerometer data, instead of all the raw data. The uploaded features provided sufficient information to allow us to discriminate between user activities (still, walking, running, automotive, other). The Microsoft Band's PPG sensor is heavily affected by motion artifacts. To account for this, we filtered the collected heart rate data retaining only the data collected when the accelerometer reported "stationary" activity, discarding the data collected while the accelerometer reported "walking", "running", "automotive" or "other". This filtering step was necessary to ensure that the collected data did not contain noise that would have corrupted the subsequent HRV analysis.

Procedure

The Ethics Committee of the University of Surrey granted a favorable ethical opinion for the research. Information about the study was circulated via the intranet. Interested participants within BNPP were provided with further written information, and once consented, completed the affective work-related rumination measure online. Individuals who chose to participate were each sent a wrist band that was paired to their company-issued smartphone, with an instruction sheet on how to use them together. They were also provided with a help line to a research assistant who could guide them through the set-up procedure if needed. No additional considerations are appropriate as participants were otherwise healthy adults in full time work. Individuals were asked to wear the wristband continually (apart from when bathing). As research shows that people ruminate about work issues more at the beginning of the week compared to the rest of the week (Cropley, 2015) the analysis presented here represents data collected over three weekday evenings (Monday–Wednesday). Theoretically, HRV can be modulated by voluntary actions which could bias the results for example, by practicing breathing exercises individuals can deliberately reduce their heart rate (and improve their HRV); individuals were therefore asked to behave as they normally would during their leisure time, and no self-management intervention or visibility over the data collected was offered during this data collection period.

Heart Rate Variability Analysis

All data were screened for measurement artifacts using ARTiiFACT software (Kaufmann et al., 2011). Artifacts were identified using the algorithm developed by Berntson et al. (1990) by identification of a distribution-based threshold value calculated for each individual. Flagged beat intervals were visually checked and if confirmed as artifacts deleted and substituted by means of cubic spline interpolation of neighboring intervals. The time-domain measure root mean square successive difference (RMSSD), which is considered to indicate vagally mediated HRV, was calculated for each person. Measurements and analyses followed established guidelines (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Previous work has demonstrated that most workers do not instantaneously switch off as soon as they stop working, but gradually cognitively disengage and relax over the course of the evening (Cropley and Millward Purvis, 2003; Cropley et al., 2006). To ensure that individuals were given adequate time

to disengage from work, HRV measurements were sampled between an 8 pm and 10 pm window (10 pm was chosen as the upper time period to minimize the possibility of individuals being asleep when the HRV data was sampled). A continuous 3-min stream of PP data was captured for analysis for each individual as close to 8 pm as possible, alongside concomitant accelerometer data. Prior to analysis, the data was screened for normality and RMSSD was found to be normally distributed. Data analysis was conducted using between groups ANOVAs.

RESULTS

RMSSD was significantly lower in the high ruminators (M = 139.0; SD = 45.819) relative to the low ruminators (M = 178.1; SD = 63.501), $F = 4.556$, $p < 0.02$, $\eta^2 = 0.18$. There was no significant difference between the groups with respect to physical activity (0.993, SD = 0.276, vs. 0.992, SD = 0.022), nor was there a significant difference in the time during the evening when HRV was sampled (20.21, SD = 0.36, vs. 20.24, SD = 0.30). Finally, there was no significant difference in heart rate between the two groups (M = 78.539; SD = 11.647, vs. 82.953; SD = 12.592), $F = 1.194$, ns, $\eta^2 = 0.03$. When the analysis was repeated controlling for age and gender, the overall pattern of the results was unchanged.

DISCUSSION

Research has demonstrated that irregularity of heartbeat intervals is an important marker of health (Kemp and Quintana, 2013). This study adds to this literature as rumination was associated with reduced HRV, which is a known indicator of cardiovascular disease risk (Tsuji et al., 1996). As predicted, individuals reporting high affective rumination were found to demonstrate lower HRV compared to low ruminators. As vagally mediated HRV is recognized as an indicator of how well people regulate their emotions, this suggests that high affective ruminators are less able to regulate their emotional thoughts about work after work, reflecting lower parasympathetic activity during the working week.

To our knowledge, this was the first study to pair wearable sensors with smartphones with a particular focus on examining the association between work-related rumination and HRV. There was noise in the data, which is to be expected when collecting the data in the field, and this led to a loss in sample size and power. Also, data capture was limited to avoid depleting the battery unnecessarily. As it is theoretically possible for people to modulate their HRV, it was deemed important for participants to behave normally during their evenings and not to deliberately practice breathing exercises, as this could have potentially biased the findings. Given that there is inherent and unavoidable loss of data introduced by movement in PPG-acquired HR signal, it may be advisable for future studies to design data collection methods that incorporate periods of passivity, where continuous measures can be taken while participants are completely sedentary, or to use larger samples in order to compensate for the loss of power. In field work, it is impossible to have the same level of control as in the laboratory, and a compromise will always be needed.

Although comparable in size to other HRV studies (Steinmetz et al., 2016; Wojniusz et al., 2016) the current findings were based on a relatively small sample size, and in addition the HRV data was high for both groups, therefore some caution needs to be exercised in the interpretation of the results until the findings are replicated in larger samples. In addition, we did not control for potential confounding factors such as smoking, exercise, use of medication or somatic and psychological illness. Future field studies should include these potential confounders of current health status and health-related behaviors.

As the study had a quasi-experimental design, causality cannot be inferred from the data; nonetheless, the study may have clinical implications. HRV biofeedback has seen a resurgence in recent years, and biofeedback interventions have been shown to be effective in individuals with emotional disturbance (Wheat and Larkin, 2010). Interventions that include mindfulness breathing exercises have also been shown to reduce work-related rumination (Hülsheger et al., 2014; Querstret et al., 2016). It is now possible for mobile health interventions to incorporate biofeedback breathing exercises to help people regulate their emotions during acute periods of stress. mHealth interventions providing this kind of physiological monitoring can offer increased fidelity, portability and functionality over traditional home-based biofeedback monitors (Luxton et al., 2011), and an increasing number of studies show evidence supporting the greater use of technological innovations in psychological care (Hollis et al., 2015). Early precedents for vagal modulation as a self-management mechanism for stress (Benson et al., 1974) have been reinforced by more recent work in neurocardiac training for hypertension to enhance vagal heart control (Nolan et al., 2005). Future research might examine whether such interventions could be incorporated alongside HRV data collection methods to provide instant feedback to users, improving their efficacy, and potentially incorporating findings from computational intelligence research in affect modeling for gameplay (Plans and Morelli, 2012) to have intervention content adapt in real-time to user affect.

Ruminating about work has been associated with negative health and increased risk of disease. To our knowledge, this is the first study to demonstrate an association between a trait marker of work-related rumination and a short-term HRV parameter. This was also the first study to pair smartphone technology with a wearable wristband to record HRV during daily life. The current study is not void of limitations; nonetheless, it does provide further support for the role of HRV as a proxy indicator for how well people regulate their emotions outside of work, and also shows that failure to unwind from work is a possible risk factor for the development of cardiovascular disease.

AUTHOR CONTRIBUTIONS

MC and DP made equal contributions to this work. MC, DP and DM made substantial contributions to the conception and

design of the work. MC, DP, DM and SS drafted the work and revised it critically for important intellectual content; have provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. II, GT and CC made important contributions to the research design contextualization of psychometric data in the workforce for the trial.

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Resting Heart Rate Variability, Facets of Rumination and Trait Anxiety: Implications for the Perseverative Cognition Hypothesis

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The perseverative cognition hypothesis (PCH) posits that perseveration, defined as the repetitive or sustained activation of cognitive representations of a real or imagined stressor, is a primary mechanism linking psychological (or stress) vulnerability with poor health and disease. Resting vagally mediated heart rate variability (vmHRV) is an important indicator of self-regulatory abilities, stress vulnerability and overall health. Those with lower resting vmHRV are more vulnerable to stress, and thus more likely to engage in perseverative cognition and experience subsequent negative mental health outcomes such as anxiety. Recent research suggests that rumination—one of the core mechanisms underlying perseveration—is a construct containing (at least) two maladaptive (depressive and brooding) and one adaptive (reflective) types of rumination. However, to date, research has not examined how the association between resting vmHRV may differ between these three facets of rumination, in addition to these facets' mechanistic role in linking lower resting vmHRV with greater trait anxiety. The current cross-sectional study explores these relationships in a sample of 203 participants (112 females, 76 ethnic minorities, mean age = 19.43, standard deviation = 1.87). Resting vmHRV was assessed during a 5-min-resting period using an Electrocardiogram (ECG). Both trait rumination (including the three facets) and anxiety were assessed via self-report scales. Significant negative associations were found between resting vmHRV and maladaptive, but not adaptive, forms of perseveration. Similarly, mediation analyses showed a significant indirect relationship between resting vmHRV and anxiety through maladaptive, but not adaptive, facets of rumination. Our findings support the PCH such that those with stress vulnerability, as indexed by lower resting vmHRV, are more likely to engage in maladaptive perseverative cognition and thus experience negative outcomes such as anxiety. Our data also lend a novel outlook on the PCH; resting vmHRV is not related to reflective rumination and thus, this facet of perseveration may be a neutral, but not beneficial, factor in the link between stress vulnerability and psychological well-being.

Keywords: perseverative cognition, heart rate variability, rumination, anxiety, reflection

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INTRODUCTION

Perseverative cognition is a common reaction to stressful events and can be defined as the repetitive or sustained activation of the cognitive representations of a real or imagined stressor. The perseverative cognition hypothesis (PCH) proposes that excessive perseveration can have a negative impact on both psychological and physiological well-being, and is often characteristic of those who have difficulties in recognizing signals of safety (Brosschot et al., 2010; Verkuil et al., 2010). Perseverative cognition is thought to be an important mechanism linking psychological or stress vulnerability factors, such as poorer inhibitory control, with psychological outcomes such as burnout, depression and anxiety (Verkuil et al., 2010). Worry and rumination are described as core factors by which perseverative cognition operates. Worry can be defined as the repetitive negative thinking of possible *future* outcomes or events, whereas rumination can be defined as the repetitive thinking of *past* outcomes or events (Nolen-Hoeksema et al., 2008).

Neurophysiological Concomitants of Perseverative Cognition

While these conceptual definitions of worry and rumination indeed differ, the term perseverative cognition is thought to encompass a common neurophysiological process underlying both constructs (for review, see Verkuil et al., 2010). Specifically, the PCH proposes that the neural concomitants of perseveration involve cortical brain areas associated with appraisal and coping, such as prefrontal (PFC) and anterior cingulate cortices (ACC; Ochsner and Gross, 2008) in addition to subcortical brains areas associated with threat, such as the amygdala (Thayer and Lane, 2002; Anderson et al., 2004; Verkuil et al., 2010). In this regard, it is proposed that engaging in perseveration effectively creates a cognitive representation of the stressor that can maintain a vigilant state, which is thought to be a product of both heightened attention to negative stimuli (via hyperactive amygdala) and a failure to recognize safety within the environment (via hypoactive PFC and ACC; for review, see Verkuil et al., 2010). This framework is not without support, as converging imaging evidence showed decreased activity in the PFC and ACC and increased activity in the amygdala is associated with greater perseveration (e.g., Cooney et al., 2010). Interestingly, this neural circuit has direct neuroanatomical connections to preganglionic sympathetic and parasympathetic neurons (for example, see Barbas et al., 2003; for reviews, see Thayer and Lane, 2000, 2009; for example, see Resstel and Corrêa, 2006). Therefore, bi-directional communication between executive brain areas and the amygdala can be reflected in autonomic nervous system (ANS) activity.

Resting Vagally Mediated Heart Rate Variability and Perseverative Cognition

The ANS dually innervates many peripheral organs, including the heart, which is under tonic inhibitory control by the parasympathetic nervous system (PNS: a branch of the ANS; for reviews, see Thayer and Sternberg, 2006; Thayer and Lane, 2009; Thayer et al., 2010). The PNS is a critical mechanism in adaptively regulating physiological functions (e.g., inflammation and cardiovascular function) to produce context-appropriate responses via the vagus nerve—the primary nerve of the PNS (Thayer and Sternberg, 2006; Weber et al., 2010). Resting-state[1] vagally mediated heart rate variability (vmHRV), defined as the rapid beat-to-beat fluctuations in a heart rate (HR) time series, serves as a non-invasive proxy of cardiac vagal control (Task Force of the European Society of Cardiology, 1996; Thayer et al., 2010). As such, resting vmHRV is widely recognized as a psychophysiological index of healthy heart function (Thayer et al., 2010) and overall health (Thayer and Sternberg, 2006; Thayer et al., 2012; Jarczok et al., 2015). Indeed, as resting vmHRV indexes PNS activity (vagal control), resting vmHRV has been linked with activity of executive brain areas, particularly the PFC and ACC. A recent meta-analysis showed that across fMRI investigations, resting vmHRV was positively associated with regional cerebral blood flow in both the PFC and ACC (Thayer et al., 2012), thereby providing neurophysiological evidence of the link between executive brain regions and vagal activity. Behavioral studies also support these notions, having showed resting vmHRV to predict a wide-range of self-regulatory processes, for example emotion regulation (e.g., Williams et al., 2015) and cognitive control (e.g., Anderson et al., 2004; Williams et al., 2016). Therefore, resting vmHRV not only serves as an index of overall health, but also the degree to which the brain's integrative system for adaptive inhibitory control (e.g., emotion regulation) provides flexible modulation of the periphery. Overall, it is suggested that the aforementioned common neural circuit links psychological processes such as perseveration with health-related physiological processes via the vagus, and that the integrity and flexibility of this circuit can be indexed using resting vmHRV (Thayer et al., 2012).

Taken together, as executive brain areas are responsible for both reducing perseveration and adaptively regulate the vagus nerve, those with lower resting vmHRV may not possess necessary inhibitory abilities to down-regulate perseverative cognition and other negative psychological mindsets. Therefore, the PCH posits that lower resting vmHRV reflects poorer emotion regulation and thus, a greater psychological (i.e., stress) vulnerability—or a greater predisposition—for engaging in perseverative cognition (Thayer and Lane, 2002; Brosschot et al., 2010; Verkuil et al., 2010).

Resting Vagally-Mediated Heart Rate Variability, Perseveration and Anxiety

As previously mentioned, individuals with higher resting vmHRV typically show better emotion regulation abilities (for review, see Thayer and Lane, 2000; Williams et al., 2015) in comparison to individuals with lower resting vmHRV, and thus may employ better emotion regulation strategies (Appelhans and Luecken, 2006; Volokhov and Demaree, 2010). However, individuals with lower resting vmHRV typically engage in more maladaptive emotion regulation strategies such as perseveration (Brosschot et al., 2010). In this context, perseverative cognition

[1]"Resting-state vmHRV" is simply referred to as "resting vmHRV" for the remainder of this report.

is often thought of as a negative and nonconstructive process; however, recent reports have highlighted that not all perseveration, specifically rumination, is considered maladaptive (for review, see Nolen-Hoeksema et al., 2008). The authors proposed that rumination is a construct containing at least three facets: (i) brooding rumination, defined as the tendency to wallow and sulk over past stressors (maladaptive); (ii) depressive rumination, defined as the tendency to feel sad and despair over past stressors (maladaptive); and (iii) reflective rumination, defined as the tendency to engage in analytical thinking in response to past stressors (adaptive). However to date, research has not yet explored how the relationship may differ between resting vmHRV and these varying facets of perseveration (in this instance, rumination). Likewise, it is well known that rumination plays an important role in anxiety (and depressive) disorders, however little research has reported on the relationship between rumination as a multi-faceted factor and trait anxiety (Nolen-Hoeksema, 2000; for review, see Nolen-Hoeksema et al., 2008).

Moreover, we previously reported that perseverative cognition is an important mechanism linking stress vulnerability (e.g., lower resting vmHRV) with psychological outcomes such as anxiety (for review, see Brosschot et al., 2010; Verkuil et al., 2010) and depression (Stange et al., 2017). A longitudinal report provides evidence in support of this idea, showing that perseveration, specifically rumination, was a significant mediator linking stressful events with both anxiety and depression over the lifespan (Michl et al., 2013). Additionally, a recent fMRI investigation showed that induced perseveration decreased functional connectivity between PFC and amygdala activity in healthy controls—a pattern seen in patients with generalized anxiety disorder in the absence of perseveration (i.e., at rest; Makovac et al., 2016). Importantly, such reductions in connectivity predicted reductions in vmHRV for both groups. Similarly a recent study also showed resting vmHRV to predict the capacity for neural activity to shift from an internally-directed pattern (supporting perseverative cognition) to activity associated with control of externally-directed attention (decreasing perseverative cognition via goal-focused behavior; Ottaviani et al., 2016). Overall, converging neural, physiological and psychological evidence supports the idea that, in comparison to those with higher resting vmHRV, people with lower resting vmHRV have a greater psychological predisposition for perseveration, which can be a maladaptive mechanism linking lower resting vmHRV with negative psychological outcomes, especially anxiety. However to date, no study has investigated the direct relationship among these three variables, especially in light of rumination being described as multi-faceted—including a possible adaptive—factor (Nolen-Hoeksema et al., 2008).

Present Study

Understanding the strength and direction of the association between resting vmHRV and everyday adaptive and maladaptive perseverative tendencies is warranted due to the paucity of research on reflective rumination and its psychophysiological concomitants. As this form of perseveration—reflective rumination—has the potential to be either non-harmful or beneficial, it is also important to understand the possible mediating impact each facet of rumination may have on the relationship between resting vmHRV and negative psychological outcomes. Thus, the current study sought to explore the direction and strength of the association between resting vmHRV and self-reported ruminative tendencies, including the three aforementioned forms of rumination. We also used mediation models to determine if and how each type of rumination severed as a mechanism linking lower resting vmHRV (an indication of psychological vulnerability for perseverative cognition) with trait anxiety (one possible consequence of lower resting vmHRV coupled with perseverative cognition; Verkuil et al., 2010). If executive brain function is critical in the regulation of both the vagus and perseverative cognition processes, and if the vulnerability of this circuit can be indexed using resting vmHRV, then we hypothesized that lower resting vmHRV would be associated with greater reports of day-to-day perseverative cognition, particularly in both a brooding and depressive (i.e., maladaptive) manner. We also hypothesized that both maladaptive forms of rumination would significantly mediate the association between lower resting vmHRV and greater trait anxiety. We sought to explore the association between resting vmHRV and reflective rumination, in addition to mediating role reflective rumination may (or may not) have on the link between resting vmHRV and anxiety.

MATERIALS AND METHODS

Subjects were recruited from the Research Experience Program (REP) pool at The Ohio State University, allowing students to participate in research for partial class credit in an introductory level psychology course. Data were pooled across six studies conducted within our lab. Funding from The Ohio State University College of Social and Behavioral Sciences and College of Arts and Sciences also allowed us to recruit and compensate participants outside of the REP pool resulting in a diverse sample across the university (i.e., students from various majors and cohorts). No individual participated in more than one of the six studies. A total of 203 participants' (112 females, 76 ethnic minorities, mean age = 19.43, standard deviation = 1.87) data were available for analysis. We asked all participants not to smoke, undergo vigorous physical activity, or drink caffeine 6 h prior to the experiment. Each study was approved by the Ohio State University Institutional review board, and all participants signed written informed consent. A portion of these data has been published elsewhere; however, the focus of those data and results were unrelated to the current investigation (Williams et al., 2015).

In all studies, participants were placed in a soundproof experimental room, equipped with a camera and microphone for safety and instructional reasons, and a high definition TV for stimuli presentation. Participants were given a detailed explanation of the procedures that would take place without indicating the specific hypothesis under the study or manipulations applied. Electrocardiogram (ECG) leads were attached to the subjects and while in a separate control room, the experimenter led the subjects to the initial phases of the

experiment. Participants first completed a 5-min baseline period, in which they sat in a resting position with the television displaying a blank, gray screen, and were instructed not to move or fall asleep (spontaneous breathing). Participants either completed an experimental task[2] followed by a set of self-report questionnaires, or completed a set of self-report questionnaires followed by an experimental task. The total duration for each study was approximately 60 min.

Vagally Mediated Heart Rate Variability

Cardiac data was recorded continuously throughout each experiment via a 3-lead ECG at a 1000 Hz sampling rate using a Mindware^{TM} 2000D (MW2000D) Impedance Cardiograph package. Electrodes were placed: (1) below the right clavicle; (2) on the left side of the abdomen (below the heart); and (3) on the right side of the abdomen. The variability between successive R-spikes was obtained from ECG recordings to calculate HRV during the baseline. Participants' successive IBIs, in milliseconds, were extracted using HRV 2.51 Analysis software. IBIs were written in a text file and analyzed using Kubios HRV analysis package 2.0 (Tarvainen et al., 2014), allowing for the calculation of time- and frequency-domain indices of resting vmHRV. Artifacts within the R-to-R series were visually detected, and we applied an artifact correction level that would differentiate and remove artifacts (differing abnormal IBIs from the mean IBI) using a piecewise cubic spline interpolation method. The root mean square of successive differences (RMSSD), measured in milliseconds, was calculated and is considered to be a stable (Li et al., 2009) and valid (Thayer et al., 2010), time-domain measure of vmHRV. Autoregressive estimates were also calculated, yielding high frequency power HRV (HF-HRV, 0.15–0.4 Hz; Thayer et al., 2010). In the present study RMSSD correlated highly with HF power (r = 0.90, $p < 0.001$), and thus we only report RMSSD results. Results were identical using HF-HRV (results not shown). Additionally, high-frequency peak values (HF peak) were obtained from the autoregressive analysis as a measure of respiration frequency to control for potential bias (Thayer et al., 2002). RMSSD values were natural log transformed (ln) to fit assumptions of linear analyses.

Self-Report Questionnaires

Rumination was assessed using the 22-item Ruminative Responses Scale (RRS; Treynor et al., 2003). Participants answered on a scale from 1 (*almost never*) to 4 (*almost always*), (sample item: *How often do you think* about how alone you feel), with higher values representing higher trait rumination (Cronbach's α = 0.922). The RRS contains three subscales used to assess the aforementioned forms of rumination, including: (i) brooding (wallowing and sulking; 5-items; α = 0.759); (ii) depressive (sadness and despair; 12-items; α = 0.886), and reflective (analytical thinking; 5-items; α = 0.773) rumination.

[2]Experimental tasks in each study were specific to the primary aims of each investigation.

Trait anxiety was assessed using the 20-item Spielberger Trait Anxiety Inventory (STAI-T; Spielberger, 1983). Participants answered on a scale from 1 (*almost never*) to 4 (*almost always*), (sample item: "*I feel pleasant*"). The STAI-T showed excellent internal consistency (Cronbach's α = 0.922).

Statistical Analyses

All statistical tests were conducted using SPSS (ver. 20, IBM Chicago, IL, USA). Median splits are frequently performed in literature on vmHRV and thus, we performed a median split on lnRMSSD (median value = 3.817) to stratify subjects into high and low resting vmHRV groups to allow for easier comparisons to previous studies. Independent samples *t*-tests were conducted to explore potential differences between groups on all included variables. Zero-order correlation (Pearson's *r*) tests were used to assess the relationship between lnRMSSD values, RRS scores (including subscales), and STAI-T scores. Partial *r* correlation coefficients were also conducted to assess these relationships while accounting for several important covariates (see "Covariates" section below for details).

A SPSS custom dialog called *PROCESS* (Hayes, 2012) was used to examine how each form of rumination, including total (all forms combined) rumination, may independently mediate the link between resting vmHRV and trait anxiety. In PROCESS, "Model 4" allowed us to specify an independent variable (IV: resting vmHRV), up to four mediating variables (M; total, depressive, reflective and brooding rumination), and a dependent variable (DV; trait anxiety). Relevant covariates were also included in this model (see "Covariates" section below for details). Bootstrapping confidence intervals (CI; 95% interval) with a sampling rate of 5000 (Preacher et al., 2007; see MacKinnon et al., 2004, for details regarding the bootstrapping procedure) were used to determine the significance of each mediating or *indirect* effect. Statistics reported include unstandardized betas (B), standard error (in brackets), and the bootstrapping CI's (lower limit, upper limit) for each path of the model. CI's that do not include zero indicate statistical significance. All tests were two-tailed and were analyzed using a set level of significance of α = 0.05.

Covariates

Ethnicity and sex differences exist in resting vmHRV (Hill et al., 2015; Koenig and Thayer, 2016) and thus, both variables were used as covariates (sex coded as 1 = male, 2 = female; ethnicity coded as 1 = European American, 2 = Other). Other covariates thought to influence vmHRV included respiration (as indexed by HF peak values; Thayer et al., 2002), age (in years; Choi et al., 2006) and BMI (kg/m^2; Koenig et al., 2014; Williams et al., 2016). To examine potential bias by pooling data across studies, three univariate analysis of variance (ANOVA) tests were conducted to examine differences in RMSSD, rumination, and anxiety across studies. Results showed that there was a significant differences in mean RRS scores across studies only ($F_{(5,197)}$ = 2.97, eta = 0.265 p = 0.013). Thus, the six studies were given dummy codes (1–6) and was also used as a covariate. In sum, ethnicity, sex, respiration, gender, BMI and experiment

number was controlled for in all partial *r* and mediation analyses. In partial *r* correlation tests between rumination subscales and both resting vmHRV and trait anxiety, those coefficients are controlling for the other two respective subscales (i.e., brooding and depressive rumination, in addition to aforementioned covariates).

It is important to note that mediation analyses, in addition to aforementioned covariates, tested the unique variance that each type of rumination contributed to the link between resting vmHRV and trait anxiety (in other words, each test included one form of rumination as a mediator between resting vmHRV and anxiety, while controlling for above mentioned covariates *and* the other two types of rumination).

RESULTS

Group analyses showed that those in the low resting vmHRV group reported higher trait rumination (including each of the three subtypes) and higher trait anxiety in comparison to the high resting vmHRV group (each $p < 0.05$; see **Table 1** for means and standard deviations for both high and low resting vmHRV groups).

Zero order correlations showed that lower resting vmHRV was related to higher reports of total rumination ($r = -0.236$, $p = 0.001$; **Figure 1A**), depressive rumination ($r = -0.273$, $p < 0.001$; **Figure 1B**), brooding rumination ($r = -0.175$, $p = 0.013$; **Figure 1C**) and anxiety ($r = -0.276$, $p < 0.001$). Resting vmHRV was not significantly related to reports of reflective rumination ($r = -0.097$, $p = 0.168$; **Figure 1D**).

Partial *r* correlations controlling for the aforementioned covariates showed a significant inverse relationship resting vmHRV with anxiety ($r_{partial} = -0.278$, $p < 0.001$), total rumination ($r_{partial} = -0.241$, $p < 0.001$), but not brooding ($r_{partial} = 0.028$, $p = 0.703$) or reflective ($r_{partial} = 0.080$, $p = 0.268$) rumination. Results also showed no significant relationship between reflective rumination and trait anxiety ($r_{partial} = -0.127$, $p = 0.078$). **Table 2A** for zero-order correlation coefficients between all variables, and **Table 2B** shows partial *r* correlation coefficients between all variables.

Mediation (PROCESS) analyses showed significant mediation (indirect effects) of resting vmHRV on trait anxiety through total rumination (C': $B = -3.76$ (1.12), [−5.97, −1.65], $p < 0.05$) depressive rumination (C': $B = -3.70$ (1.09), [−6.09, −1.80], $p < 0.05$), and brooding rumination (C': $B = -1.01$ (0.49), [−2.29, −0.25], $p < 0.05$). Reflective rumination did not emerge as a significant mediator (C': $B = 0.22$ (0.21), [−0.03, 0.87]), $p > 0.05$). Specifically, with the exception of reflective rumination, lower resting vmHRV was associated with higher rumination (path A), and higher rumination was associated with higher anxiety (path B). As a result, rumination (total, depressive, brooding) significantly mediated the relationship between resting vmHRV and trait anxiety (significant indirect effect or path C'; see **Figure 2** for all path statistics). It is important to note that total, depressive, and brooding rumination only partially mediated the relationship between resting vmHRV and anxiety as the direct effect remained significant despite significant mediation.

DISCUSSION

The purpose of the current investigation was to explore the possible differential association between resting vmHRV and three facets of rumination, and how each facet may mediate the link between resting vmHRV and trait anxiety. The current results showed that those with lower resting vmHRV reported greater maladaptive perseveration (depressive and brooding rumination). There was no significant relationship found between resting vmHRV and reflective rumination. When examining the association between resting vmHRV and each facet of rumination controlling for other two respective forms of rumination, only depressive rumination was significantly related to resting vmHRV, suggesting that brooding and depressive rumination share similar characteristics as it relates to resting vmHRV. Moreover, both brooding and depressive rumination, but not reflective rumination, mediated (or carried) the relationship between resting vmHRV and trait anxiety, such that lower vmHRV was associated with greater maladaptive perseveration, which was associated with greater trait anxiety.

TABLE 1 | Vagally mediated heart rate variability (vmHRV) group comparisons for variables of interest.

	Range of data (min, max)	High vmHRV	Low vmHRV	*t*	*p*
n		101	102		
Age	18, 30	19.50 (1.93)	19.36 (1.82)	−0.540	0.590
BMI	16.54, 47.51	24.06 (4.91)	23.69 (4.91)	−0.542	0.589
Resting vmHRV	2.71, 4.78	4.21 (0.24)	3.45 (0.26)	−21.61	**0.000**
Respiration	0.15, 0.40	0.265 (0.049)	0.268 (0.052)	0.658	0.606
Total rumination	23, 77	42.02 (11.83)	47.75 (12.16)	3.41	**0.001**
Depressive	12, 44	22.11 (6.73)	24.86 (6.42)	2.74	**0.007**
Brooding	5, 20	10.12 (3.17)	11.46 (3.37)	2.92	**0.001**
Reflective	5, 20	9.37 (3.45)	10.33 (3.36)	2.03	**0.044**
Trait Anxiety	22, 74	39.40 (10.29)	44.11 (10.10)	3.29	**0.004**

Note. This table gives the range of data, mean and standard deviation (in brackets) values on baseline measures. Independent samples t-test statistics include both t and p values on the difference between high and low vmHRV groups (significant p values in bold). Age was measured in years; body mass index (BMI) was measured in kg/m^2; resting vmHRV is represented as the natural log transform of the root mean square of successive differences (lnRMSSD); total rumination represents total score on the Ruminative Reponses Scale (RRS); "Depressive": depressive rumination subscale of RRS; "Brooding": brooding rumination subscale of RRS; "Reflective": reflective rumination of the RRS; Trait Anxiety was indexed using the 20-item Spielberger Trait Anxiety Inventory. Bold values denote statistical significant ($p < 0.05$).

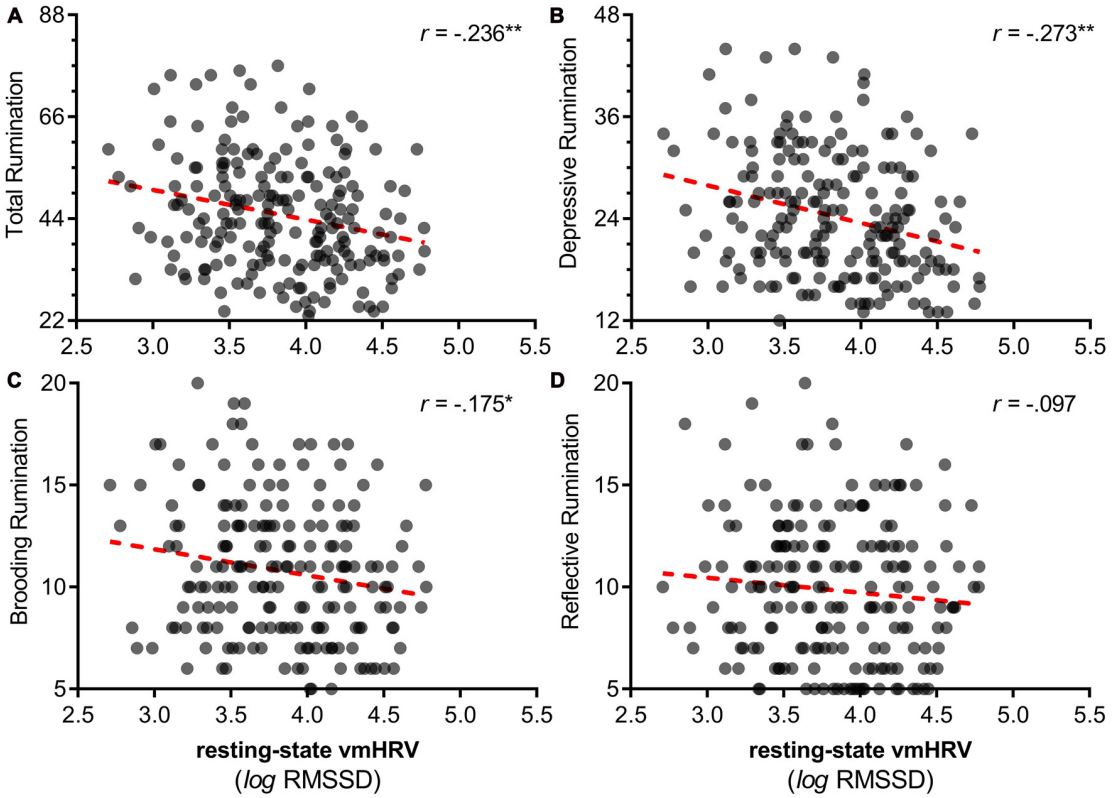

FIGURE 1 | Scatterplots of resting vagally mediated heart rate variability (vmHRV) and different facets of perseveration. *Note*: This figure illustrates scatterplots between resting vmHRV and different facets of perseveration (rumination). **(A)** Resting vmHRV and total (depressive, brooding, reflective) rumination. **(B)** Resting vmHRV and depressive rumination. **(C)** Resting vmHRV and brooding rumination. **(D)** Resting vmHRV and reflective rumination. Resting vmHRV is represented as the natural log transform of the root mean square of successive differences (lnRMSSD). Total rumination represents total score on the Ruminative Reponses Scale (RRS). "Depressive": depressive rumination subscale of RRS. "Brooding": brooding rumination subscale of RRS. "Reflective": reflective rumination of the RRS. $^{*}p < 0.05$ $^{**}p < 0.01$.

These data lend support for PCH (Brosschot et al., 2010; Verkuil et al., 2010); our data is the first to provide direct evidence that, individuals with lower resting vmHRV report higher maladaptive perseverative cognition and thereby possibly experience negative psychological outcomes such as anxiety.

Importantly, our data also provide a novel outlook on the PCH; although lower resting vmHRV remains a vulnerability trait for maladaptive perseveration, it was not a significant predictor for a more adaptive (Nolen-Hoeksema et al., 2008) form of perseveration, reflective rumination (Path A; see **Figure 2**). This is further supported by our data, as controlling for aforementioned covariates, including both brooding and depressive rumination, reflective rumination was not a significant predictor of trait anxiety (partial *r* correlation, see **Table 2B**; path B for reflection rumination, see **Figure 2**). As a result, reflective rumination did not significantly mediate the relationship between resting vmHRV and anxiety. Although there was no evidence of any benefits of reflective rumination, these null relationships suggest a potentially non-harmful or neutral form of perseveration that is not related to similar stress vulnerabilities (i.e., lower resting vmHRV) that give rise to maladaptive PC.

Implications

From a neurophysiological perspective, converging evidence links emotion regulation capabilities with executive brain function, such that those with lesser executive brain activity show poorer regulation of negative emotions (Ochsner et al., 2012). During and immediately following a threating or stressful event, amygdala activity is increased, which may be a common and adaptive response given the context specifics. Executive brain regions including the lateral (e.g., Tillfors et al., 2002) and medial (e.g., Sinha et al., 2004) PFC, in addition to the ACC (Drevets and Raichle, 1998), have been implicated in the proper regulation of amygdala activity and any subsequent negative emotions. Therefore when a stressor is no longer present (i.e., under safe conditions), these executive brain regions should exert top-down inhibitory control over the amygdala and other subcortical regions associated with threat and stress (see Wang and Saudino, 2011; for review, Thayer and Lane, 2000, 2002; Verkuil et al., 2010). However, when an individual has reoccurring negative thoughts under safe (stress and threat free) conditions, there can be amygdala activation preceding (worry) or following (rumination) a negative event, coupled with disinhibition (or deactivation) from executive brain regions (Thayer and Lane,

TABLE 2 | Zero-order and partial *r* correlation matrices.

(A) Zero-order correlation coefficients

	1	2	3	4	5	6
1. vmHRV	-					
2. Anxiety	**−0.276****	-				
3. Rumination	**−0.236****	**0.708****	-			
4. Depressive	**−0.273****	**0.723****	**0.953****	-		
5. Brooding	**−0.175***	**0.643****	**0.821****	**0.707****	-	
6. Reflection	−0.097	**0.380****	**0.768****	**0.610****	**0.475****	-

(B) Partial correlation coefficients

	1	2	3	4	5	6
1. vmHRV	-					
2. Anxiety	**−0.278****	-				
3. Rumination	**−0.241***	**0.720****	-			
4. Depressive	**−0.238***	**0.525****	**0.950****	-		
5. Brooding	0.028	**0.273****	**0.825****	**0.702****	-	
6. Reflection	0.080	−0.127	**0.760****	**0.594****	**0.476****	-

*Note. Table 2A represents zero-order correlations between variables of interest and Table 2B represents partial correlations controlling for ethnicity, experiment, gender, body mass index, respiration and age. Table 2B represents correlations with additional covariates; in these boxes are correlation coefficients between rumination subscales and both resting vmHRV and trait anxiety controlling for the other two respective subscales (i.e., brooding and depressive rumination). "vmHRV" represents resting vmHRV (the natural log transform of the root mean square of successive differences; lnRMSSD); "Anxiety" represents trait anxiety and was indexed using the 20-item Spielberger Trait Anxiety Inventory; "rumination": represents total scores on the Ruminative Reponses Scale (RRS); "Depressive": depressive rumination subscale of RRS; "Brooding": brooding rumination subscale of RRS; "Reflective": reflective rumination of the RRS. *$p < 0.05$ **$p < 0.01$. Bold values denote statistical significant ($p < 0.05$).*

2002; Verkuil et al., 2010). Therefore, perseverative cognition is often characterized as amygdala hyperactivity surrounding a stressful event which is maintained via decreased executive brain inhibition (Thayer and Lane, 2002; Hofmann et al., 2005; Verkuil et al., 2010). It is suggested that a lack of inhibition by executive brain regions does not allow the organism to respond to environmental demands and organize their emotional and behavioral responses adaptively. As such, individuals with lower resting vmHRV under conditions of no apparent threat or stress (i.e., in a safe, resting-state position) are thought to struggle with recognizing signals of safety and thus, are potentially more susceptible to engaging in perseverative cognition (Brosschot et al., 2010; Verkuil et al., 2010). These tendencies can have a negative impact on both psychological (e.g., anxiety) and physiological (e.g., resting vmHRV) well-being and thus, serving as a positive feedback loop that can be detrimental to overall health (Brosschot et al., 2010; see Ottaviani et al., 2016, for meta-analysis; Thayer and Lane, 2002; Verkuil et al., 2010). However, our data do suggest that those who have lower resting vmHRV are not more likely to engage in reflective perseveration as they are to engage in maladaptive perseveration. Therefore, it is possible that the neural concomitants that underlie maladaptive rumination are not completely in line with reflective rumination (Johnson et al., 2009). Further research is needed to fully understand possible neuropsychophysiological mechanisms underpinning reflective rumination, as this may be crucial in understanding how to neutralize the negative impact of maladaptive perseveration (brooding and depressive rumination) on psychological outcomes (i.e., anxiety).

As it relates to stress and disease, this idea of reflective rumination as being a neutral form of perseveration is supported by both the current and prior research. For example, one study found brooding, but not reflective, rumination to mediate the relationship between childhood emotional abuse and depressive symptoms (Raes and Hermans, 2008). Another study found brooding but not reflective rumination to predict the development of depressive symptoms overtime in adolescences (Burwell and Shirk, 2007). In both of these specific examples, reflective rumination showed null results. Likewise, our data showed a null relationship between reflective rumination and both resting vmHRV and trait anxiety, particularly when controlling for other respective rumination facets. In contrast, depressive rumination remained significant under such conditions, and brooding remained significantly related to anxiety but not resting vmHRV. This is important, as taken together, it suggests that the unique variance associated with reflective rumination was unrelated to both resting vmHRV and trait anxiety, possibly generalizing to stress factors and negative outcomes, respectively (Burwell and Shirk, 2007; Raes and Hermans, 2008). In sum, we propose that research examining resting vmHRV and perseverative cognition should consider analytic and reflective forms of perseveration as this may lend further insight on controlling the impact of stress and stress vulnerability on health.

Interestingly, a recent review (Verkuil et al., 2010) on perseverative cognition proposed that perseveration that includes *critical-thinking* and *problem-solving* only further promotes perseveration, and therefore are also associated with negative psychological (and physiological) outcomes (e.g., anxiety). These claims are not without evidence, as those who engage in problem-solving perseveration often find problems unsolvable and over whelming (e.g., Lyubomirsky et al., 1999) and fail to find constructive solutions. In contrast, items of the reflective rumination subscale (e.g., "*Analyze recent events to understand why you are depressed*") of the RRS are not directed at problem solving and instead, this subscale is thought to reflect the tendency for an individual to *analyze* possible reasons why they are thinking/feeling in a negative manner (i.e., critical thinking) despite being in the presence of safety (for reviews, see Treynor et al., 2003; Nolen-Hoeksema et al., 2008). We propose that this conceptual distinction between adaptive forms of perseveration (i.e., problem solving vs. analytical thinking) serves as an important distinction within the PCH.

Limitations and Future Directions

One limitation of the current investigation is that the sample consisted of college-aged adults and thus, the current results may not extend to other age ranges. While we are confident that resting vmHRV would be related to perseveration in all age groups, we are not sure of how this relationship may change as a function of reflective rumination. Thus, future research should attempt to examine the link between resting vmHRV and various forms of perseveration in individuals of various age ranges. Other

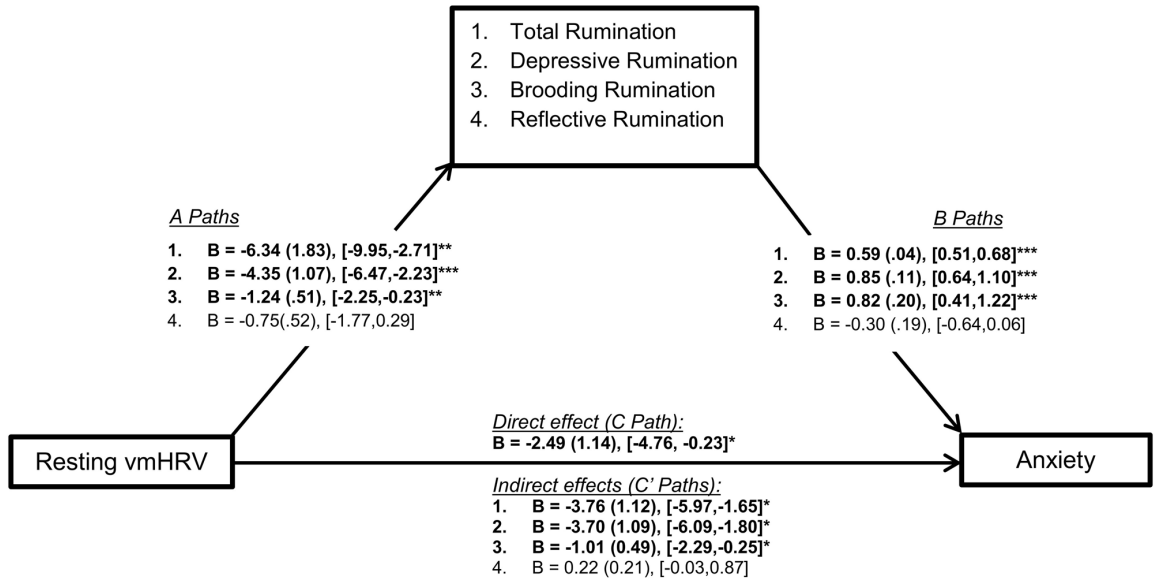

FIGURE 2 | Illustration of mediation model paths and statistics. *Note*: This figure represents the mediation models conducted in the current study. Statistics reported include unstandardized betas (B), standard error (in brackets) and the bootstrapping CI's (lower limit, upper limit) for each path of the model. CI's that do not include zero indicate statistical significance. Numbered statistic lines correspond to the respective mediator (facets of rumination). Path A represents the association between the independent variable (resting vmHRV): (1) total (depressive, brooding, reflective) rumination; (2) depressive rumination; (3) brooding rumination; and (4) total rumination. Path B represents the association between these rumination variables and trait anxiety. Path C represents the direct effect between resting vmHRV and anxiety (controlling for all covariates, including total rumination), and Path C' represents the indirect effect of resting vmHRV on trait anxiety through the varying facets of rumination. Resting vmHRV is represented as the natural log transform of the root mean square of successive differences (lnRMSSD). Total rumination represents total score on the Ruminative Reponses Scale (RRS). "Depressive": depressive rumination subscale of RRS. "Brooding": brooding rumination subscale of RRS. "Reflective": reflective rumination of the RRS. Trait Anxiety was indexed using the 20-item Spielberger Trait Anxiety Inventory. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

demographic factors, for example socioeconomic status, should be included in future investigations as well.

A second limitation is that the current investigation is cross-sectional and thus, causation cannot be determined. It is plausible to view correlational results as perseveration influencing lower resting vmHRV (i.e., resting vmHRV as DV and perseveration as the IV), as the PCH proposes that resting vmHRV can determine the likelihood of perseveration, which can further impact vmHRV. This positive feedback loop is thought to be a key negative psychophysiological mechanism maintaining the link between stress and disease (see Thayer and Lane, 2002; for reviews, see Brosschot et al., 2010 for empirical study example). However, resting vmHRV has been recently described as an endophenotype (including for anxiety disorders), thus supporting our current conceptualization as an independent variable (for review, see Thayer and Lane, 2009). A recent study lends further evidence in this regard, as it displayed a relationship between parasympathetic inflexibility (i.e., resting-to-reactive vmHRV) and *prospective* symptoms of depression was exacerbated by perseverative cognition (Stange et al., 2017).

Additionally, while bootstrapping techniques in mediation are thought to lend strong support for theorized causal relationships (Hayes, 2012), alternate models for the current study could be proposed. Specifically, models that include resting vmHRV, total rumination only, and anxiety showed significant mediation no matter the variable's place within the model (i.e., resting vmHRV could have served as an IV, M and DV using these three variables). However, it is important to note that subscales of rumination did not show a similar pattern, as mediation models were only significant with rumination subscales as mediating variables. Moreover, mediation was not significant with trait anxiety as an independent variable, rumination (and three facets) as a mediator, and resting vmHRV as a dependent variable (a switch of the IV and DV in the current study). Thus, differences amongst relationships between resting vmHRV, trait anxiety and *different facets* of rumination are specific to the model as outlined in the current investigation. That is, lower resting vmHRV (independent variable), serves as a psychological predisposition for maladaptive but not adaptive perseveration (mediating variables), which can lead to greater trait anxiety (the dependent variable).

We also acknowledge that the current study is only applicable on a trait, but not state, level; our mediation models cannot determine how individuals may perseverate and experience subsequent consequences from situation to situation. In other words, there may be situations in which individuals may be motivated to ruminate, and thus not experience negative outcomes such as anxiety. Therefore, future work should consider the link between vmHRV, rumination and anxiety as state (situation-to-situation) variables.

A final limitation of the current investigation is that, as resting vmHRV is significantly associated with total rumination scores, some may argue a possibility that non-significant finding between vmHRV and reflective rumination result is

a type II error. To explore this issue, we tested if the zero-order correlation coefficients between resting vmHRV and the three subscales significantly differed from one another. The only marginally significant difference found between correlation coefficients was those involving depressive and reflective rumination (p = 0.06) such that the correlation between resting vmHRV and depressive rumination was greater than the correlation between resting vmHRV and reflective rumination. No other differences were found. Therefore, despite the significant association between resting vmHRV and total RRS scores, we propose that it is likely due to the unique variance associated with brooding and especially depressive, but not reflective, facets of rumination. Additionally, our median split results showed the high vmHRV group reported significantly lesser reflective rumination compared to the low vmHRV group. Zero-order correlation coefficients also showed a significant positive association between reflective rumination and anxiety. Such patterns of results are inconsistent with our current discussion. However here, we must point out that in paths A and B of the mediation model—when several important covariates are included—only depressive and brooding rumination were significantly related to both resting vmHRV and anxiety. Likewise, partial r correlations between resting vmHRV and facets of rumination were controlling for the other respective forms of rumination; resting vmHRV remained related to depressive rumination, and anxiety to both depressive and brooding rumination. However, the associations regarding reflective rumination remained insignificant and small. Taken together, these data suggest that there may indeed be unique characteristics that differentiate reflective and maladaptive, especially depressive, rumination. However as mentioned, future research in needed to better understand each facet of rumination and their unique contributions to stress and disease.

CONCLUSION

In sum, our data are the first to provide direct evidence that trait perseveration, specifically self-reported maladaptive rumination (brooding and depressive) are both related to resting vmHRV and can mediate the link between resting vmHRV and self-reported trait anxiety. However, we also find that irrespective of resting vmHRV, individuals are equally likely to report engaging in reflective rumination, and this factor did not mediate the association of resting vmHRV and trait anxiety. Thus, for individuals with stress vulnerability and deficiencies in controlling perseverative cognition processes (e.g., those with lower resting vmHRV), we note that not all forms of perseverative cognition are involved in linking stress vulnerability with the development of anxiety and other negative psychological states.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication. NRF and DPW are co-first authors; they contributed equally to this manuscript.

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Heterogeneity in Autonomic Arousal Level in Perseverative Worry: The Role of Cognitive Control and Verbal Thought

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One puzzle in high worry and generalized anxiety disorder (GAD) is the heterogeneity in the level of autonomic arousal symptoms seen among affected individuals. While current models agree that worry persists, in part, because it fosters avoidance of unpleasant internal experiences, they disagree as to whether worry does so by suppressing activation of autonomic arousal or by fostering persistent autonomic hyperarousal. Our Cognitive Control Model predicts that which pattern of autonomic arousal occurs depends on whether or not a worrier has sufficient cognitive control capacity to worry primarily in a verbal versus imagery-based manner. Because this model has been supported by only one study to date, the present study sought to replicate and extend that study's findings. Results from an online survey in an unselected sample of over 900 college students provide further support for our model's central tenet and initial support for its prediction that higher effortful control is associated with a higher percentage of verbal thought during worry. Finally, we report tentative evidence that autonomic arousal symptoms in worry and GAD vary as a function of individual differences in cognitive control capacity because higher capacity is linked to a greater predominance of verbal thought during worry.

Keywords: worry, generalized anxiety disorder, autonomic arousal, verbal worry, cognitive avoidance, effortful control, cognitive control capacity

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INTRODUCTION

Excessive and uncontrollable worry is a common form of perseverative cognition that, at its most severe levels is the hallmark of generalized anxiety disorder (GAD; American Psychiatric Association, 2013). Until recently, such worry was seen as being characterized by low levels of autonomic arousal, a pattern predicted by the Cognitive Avoidance (CognAv) Model of worry (Borkovec et al., 2004). That model posits, in part, that worry is characterized by suppression of fear-provoking images and the autonomic arousal they would typically engender, by shifting to a verbal mode of threat processing. This model is supported by numerous studies finding that worry and GAD are indeed characterized by a lack of elevated autonomic arousal. However, despite such support, a similarly large body of studies shows instead that worry and GAD are characterized by high levels of autonomic arousal. In light of such findings, another model of GAD, the Contrast Avoidance (ContrAv) Model (Newman and Llera, 2011), posits that worry does not serve to limit activation of autonomic arousal but rather to increase and maintain heightened autonomic arousal and negative emotionality more broadly, which permits worriers to avoid unpredictable spikes in such emotional states, which they find aversive. However, whereas the CognAv model cannot account for findings that worry and GAD are characterized by high levels of autonomic arousal,

neither can the ContrAv model easily accommodate the opposite pattern. To resolve this conflict, Vasey et al. (2016) recently proposed and tested an integrative model, which posits that only when worriers have sufficient cognitive control capacity to suppress intrusive threatening imagery and shift instead to verbal processing of threat can they avoid the autonomic arousal that such images would otherwise elicit. Absent such capacity, worry will instead be characterized by heightened autonomic arousal. In the initial study, the pattern of results was consistent with this prediction, in both a large, unselected sample and in an analog GAD subsample. Using another sample of over 900 individuals, the current study sought to replicate and extend these findings to show why cognitive control capacity matters.

Prior to the fourth edition of the Diagnostic and Statistical Manual (DSM-IV; American Psychiatric Association, 1994) autonomic arousal symptoms were among the defining features of GAD. Specifically, in the DSM-III-R (American Psychiatric Association, 1987), GAD was defined by unrealistic and excessive worry accompanied by at least 6 of 18 symptoms from three clusters, including *autonomic hyperactivity* (e.g., shortness of breath, accelerated heart rate). However, with the introduction of DSM-IV (American Psychiatric Association, 1994), autonomic arousal symptoms were dropped and remain absent in the DSM-5 (American Psychiatric Association, 2013). This decision was based on the CognAv model and on findings that GAD patients infrequently endorsed these symptoms (e.g., Marten et al., 1993).

There is, in fact, striking heterogeneity in the level of autonomic arousal in worriers and GAD samples (see Vasey et al., 2016 for a review). This is true whether autonomic arousal is measured subjectively (e.g., Marten et al., 1993; Brown and McNiff, 2009) or objectively using heart rate (HR; e.g., Lyonfields et al., 1995; Thayer et al., 1996), non-specific skin conductance responses (NS-SCRs; Andor et al., 2008; Pruneti et al., 2010), and salivary alpha amylase (sAA; Fisher et al., 2010; Fisher and Newman, 2013). There is also evidence of heterogeneity in autonomic arousal in response to emotional provocation whether using threat stimuli (e.g., Grillon, 2008; Pruneti et al., 2010) or worry inductions (e.g., Andor et al., 2008; Llera and Newman, 2014). Neuroimaging studies also reveal such heterogeneity. GAD samples either show significantly less than or do not differ from controls in amygdala activation in response to threat stimuli, while others show significantly higher activation (e.g., Monk et al., 2006, 2008). As a whole, it appears that pathological worry is at times characterized by low levels of autonomic arousal that are not significantly different from levels displayed by healthy controls, and at other times characterized by high levels of autonomic arousal which are not significantly different from that of individuals with panic disorder.

Importantly, several studies have found that worry may blunt autonomic arousal in response to fear-provoking imagery (e.g., Borkovec and Hu, 1990; Borkovec et al., 1993). To the contrary, others have found that a worry period did not suppress autonomic arousal in response to fearful imagery in absolute terms (e.g., Peasley-Miklus and Vrana, 2000; Llera and Newman, 2014). Rather, worry significantly increased HR from baseline, which prevented further increases in HR during presentation of fearful stimuli.

To account for the well-documented heterogeneity in level of autonomic arousal among worriers and individuals with GAD, Vasey et al. (2016) proposed an integrative model. They predicted and found that individual differences in effortful control, a broad self-regulatory construct which encompasses attentional, inhibitory, and activation control (Rothbart, 2007), accounts for this heterogeneity. Specifically, they found that effortful control was negatively associated with autonomic arousal symptoms. Importantly, that negative association was strongest at the highest levels of worry and GAD symptom severity.

Even though worry is generally seen as being associated with deficits in cognitive control resources such as attentional control (e.g., Armstrong et al., 2011; Hirsch and Mathews, 2012), worriers and those with GAD nevertheless vary considerably in their capacity to control their attention. As reviewed in Vasey et al. (2016), worriers and individuals with GAD vary in effortful control and related constructs when measured using self-report (e.g., Armstrong et al., 2011; Rosellini and Brown, 2011), behavioral measures (e.g., Derryberry and Reed, 2002; Olatunji et al., 2011), neuroimaging (e.g., Etkin et al., 2009; Price et al., 2011), and a physiological index of capacity for top–down control (i.e., resting heart rate variability [HRV; see Thayer et al., 2009 for a review; Brosschot et al., 2007; Aldao et al., 2012]).

Such individual differences in effortful control among worriers and GAD samples are especially important given that there appears to be a negative relationship between executive function and autonomic arousal symptoms (Beaudreau and O'Hara, 2009; Etkin et al., 2009; Richey et al., 2012). For example, in addition to finding an atypical pattern of functional connectivity between the amygdala and the dorsolateral prefrontal cortex (dlPFC) in GAD patients, Etkin et al. (2009) found that the strength of that connectivity was significantly *negatively* associated with scores on the Beck Anxiety Inventory (BAI; Beck and Steer, 1990), which is predominantly a measure of autonomic arousal symptoms (Leyfer et al., 2006). Consequently, they concluded that at least some GAD patients exhibit habitual engagement of an executive control system to regulate autonomic arousal symptoms.

However, the demonstration that effortful control moderates the association between worry/GAD symptom severity and autonomic arousal does not elucidate the mechanism by which it does so. Vasey et al. (2016) proposed that a closer examination of the CognAv model reveals a mechanism by which individual differences in cognitive control capacity can impact the level of autonomic arousal triggered by worry. As stated by Borkovec et al. (2004, p. 83), "...when aversive images occur in the process of worry...the shifting of attention to [verbal] worrisome thinking upon each occurrence...results in escape from or avoidance of the somatic element of the fear response...," suggesting that heterogeneity in autonomic arousal symptoms may depend on the extent to which verbal or imaginal processing predominates during worry.

The proposed mechanism of the CognAv model is supported by several points. First, visual images rather than verbal thoughts of feared stimuli are more likely to activate autonomic arousal responses (e.g., Tucker and Newman, 1981; Vrana et al., 1986).

Additionally, studies have found that people spontaneously shift from imagery to verbalization to reduce autonomic arousal when processing aversive material (Tucker and Newman, 1981; Borkovec et al., 1998). Moreover, verbal thoughts predominate over imagery during worry (Borkovec and Lyonfields, 1993), especially in GAD patients (Hirsch and Mathews, 2012). Indeed, worry is characterized by a predominance of left-frontal cortical activity (e.g., Wu et al., 1991; Hofmann et al., 2005), which has been linked to verbal thought (Tucker, 1981; Pinker, 1994). Additionally, sustaining a verbal linguistic mode of worry is more taxing on working memory resources than worrying in an imaginal form (Leigh and Hirsch, 2011), suggesting that high effortful control capacity may be instrumental in maintaining a predominantly verbal form of worry. Nevertheless, despite the evidence that verbal processing predominates over imagery during worry, others have found otherwise (e.g., Borkovec et al., 1993; Stapinski et al., 2010). Furthermore, it appears that differences in the extent to which verbal worry predominates can account for differences in autonomic arousal (Borkovec et al., 1993). For example, Borkovec et al. (1993) found that percentage of verbal worry reported by participants was significantly negatively correlated with HR response whereas in the relaxation condition, percentage of imagery was significantly positively correlated with HR response. Thus, it appears that the presence of autonomic arousal symptoms depends on the extent to which verbal or imaginal processing predominates during worry, which in turn depends on the worrier's cognitive capacity to emphasize the former mode of processing over the latter.

The current study was an attempt to replicate Vasey et al.'s (2016) findings about the role of cognitive control capacity (specifically effortful control) in the heterogeneity of autonomic arousal symptoms in worry and GAD, especially when worry is pathological. Second, the current study extended prior work by testing the second major aspect of the model. No previous study has tested our model's prediction that individual differences in effortful control capacity moderate the association between worry/GAD symptoms and the extent to which worry involves verbal thought. Specifically, the current study employed self-report questionnaires in an unselected sample to test the following predictions:

(1) Effortful control will moderate the positive association between worry/GAD symptoms and autonomic arousal symptoms, such that it is strongest when effortful control is low and weakest when effortful control is high.

    (a) In an analog GAD subsample, effortful control will be significantly negatively correlated with autonomic arousal.

(2) Effortful control will moderate the association between worry/GAD symptoms and candidate mediators, including (a) verbal thoughts during worry, (b) imagery during worry, and (c) efforts to transform images into thoughts, such that higher effortful control will predict more verbal thoughts and efforts to transform images into thoughts and less imagery during worry.

(3) If effortful control emerges as a significant moderator of the association between worry/GAD symptom severity and any of the candidate mediators, we expect that moderated mediation (Hayes, 2013) will be observed, such that the indirect path from worry/GAD symptoms to autonomic arousal symptoms through the mediator will vary significantly as a function of effortful control.

MATERIALS AND METHODS

Participants and Procedure

The sample comprised 990 undergraduates at a large Midwestern university (mean age = 18.8 [*SD* = 1.4]; 54.4% female, 80% White, 4% African American, 9% Asian, 3% Latino/Latina, 1% Native American, and 4% mixed ethnic heritage) who received partial course credit for participation. Participants received a broad description about a 30-min online set of questionnaires related to worry and psychological adjustment. Participants were informed that they were free to decline to participate, stop at any point during the questionnaire, or decline to answer any question without penalty. De-identified responses were collected using Surveymonkey, a secure, web-based data collection service.

Measures

The Generalized Anxiety Disorder Questionnaire IV (GADQ-IV)

The Generalized Anxiety Disorder Questionnaire IV (GADQ-IV) (Newman et al., 2002) is a self-report questionnaire designed as a screening measure that captures the full diagnostic criteria for GAD according to the DSM-IV. The GADQ-IV has good test–retest reliability, convergent and discriminant validity, and good agreement with diagnostic interviews (Newman et al., 2002; Moore et al., 2014). We used the GADQ-IV as a measure of GAD symptom severity and scored it without the skip structure as reported in Vasey et al. (2016) and as recommended by Rodebaugh et al. (2008). As shown in **Table 1**, the internal consistency of the GADQ-IV was high in the present study.

Worry and Anxiety Questionnaire (WAQ)

The Worry and Anxiety Questionnaire (WAQ) (Dugas et al., 2001) consists of 11 items covering DSM-IV diagnostic criteria for GAD. The WAQ has satisfactory test–retest reliability and good known-groups validity (Dugas et al., 2001). As shown in **Table 1**, the internal consistency of the WAQ was high in the present study.

Penn State Worry Questionnaire (PSWQ)

The Penn State Worry Questionnaire (PSWQ) (Meyer et al., 1990) is a self-report measure of pathological worry, which comprises 16 items rated on a Likert scale ranging from 1 (Not at all typical) to 5 (Very typical). This scale has excellent psychometric properties (Meyer et al., 1990). As shown in **Table 1**, the internal consistency of the PSWQ was high in the present study.

TABLE 1 | Descriptive statistics.

		Full sample $N = 926$		GAD sample (12.9%) $N = 120$	
	Cronbach's alpha	*M*	*SD*	*M*	*SD*
GADQ-IV	0.85	5.5	3.2	10.7	0.75
WAQ	0.92	36.8	17.2	58.7	11.9
PSWQ	0.93	49.9	13.6	67.1	10.0
DASS-Anxiety	0.87	6.6	6.2	26.9	6.9
DASS-Depression	0.93	7.9	8.1	30.3	9.9
DASS-Stress	0.92	11.6	8.2	35.7	8.1
EC	0.82	45.3	6.8	42.2	7.2
CAQ-Transform	0.84	12.2	4.5	14.6	4.4
Percentage of thoughts	–	64.3	26.5	70.8	19.2
Percentage of images	–	25.7	19.7	25.4	16.7

GADQ-IV, Generalized Anxiety Disorder Questionnaire-IV; WAQ, Worry and Anxiety Questionnaire; PSWQ, Penn State Worry Questionnaire; DASS, Depression, Anxiety, and Stress Scale; EC, Effortful Control Scale; CAQ-Transform, Cognitive Avoidance Questionnaire – Transformation of Images into Thoughts subscale.

The Depression, Anxiety, and Stress Scales (DASS)

The Depression, Anxiety, and Stress Scales (DASS) (Lovibond and Lovibond, 1995) is a 42 items questionnaire comprising three 14 item subscales measuring symptoms of anxiety (DASS-A), stress and depression. Participants rate each item on a four-point Likert scale ranging from 0 (Did not apply to me at all) to 3 (Applied to me very much, or most of the time) regarding how much the item applied to them over the past week. The current study focused on the DASS-A, which predominantly measures autonomic arousal symptoms (Brown et al., 1998). The DASS-A has good psychometric properties (Lovibond and Lovibond, 1995) and, as shown in **Table 1**, its internal consistency was high in the current sample.

Effortful Control Scale (ECS)

The Effortful Control Scale (ECS) (Lonigan and Phillips, 1998, Unpublished) comprises 24 items rated on a five-point scale from 1 (Not at all) to 5 (Very much) with regard to how much each describes the individual most of the time. The ECS yields two subscale scores reflecting Persistence/Low Distractibility (ECS-PLD; 12 items) and Impulsivity (ECS-I; 12 items). In this study we focused on the ECS-PLD subscale, which focuses on attention control and the capacity to persist in activities despite reactive motivation to avoid. Example items from this subscale include, "It's very hard for me to concentrate on a difficult task when there are noises around (R)" and "I can quickly switch from one task to another." The measure has good psychometric properties in college samples (Vasey, 2014, Unpublished) and, as shown in **Table 1**, it had high internal consistency in the current study. In an independent unselected college sample of over 700 subjects, the ECS-PLD subscale correlated strongly with the Adult Temperament Questionnaire EC Scale ($r = 0.61$, $p < 0.0001$). ECS-PLD scores also behave in the expected fashion in other contexts. For example, Vasey et al. (2014) used the ECS-PLD subscale to demonstrate that individual differences in self-regulatory capacity moderate the associations of negative and positive emotionality with depressive symptoms. The ECS-PLD subscale is hereinafter labeled EC.

Percentage of Thoughts and Images

These constructs were assessed with two open-ended questions. This self-report method was used successfully to assess the percentage of thoughts and images during worry in a large unselected sample (Freeston et al., 1996), and the findings were consistent with percentages found in thought sampling studies (e.g., Borkovec and Inz, 1990). To ensure that participants understood the question, they were first given an explanation of imagery versus verbal thought: "Images are when you are generating a picture in your mind and really concentrating on what you can see, feel, smell, hear, and taste in the image. Images are often very vivid because you're tuning into all of your senses. Verbal thoughts are when you're thinking using words and silently talking to yourself, like an internal running commentary or dialog. When you're thinking in verbal thoughts you are thinking in words and sentences" (Leigh and Hirsch, 2011). Participants were then asked to report the percentage of time spent in thoughts and images during worry. The questions about images and thoughts were as follows: "What percentage of your worry is made up of thoughts?" and "What percentage of your worry is made up of images?"

Cognitive Avoidance Questionnaire (CAQ)

The Cognitive Avoidance Questionnaire (CAQ) (Gosselin et al., 2002) contains 25 items assessing efforts to use cognitive avoidance strategies such as thought replacement, thought suppression, and distraction. This scale has been validated and translated into English (Sexton and Dugas, 2008). The CAQ has very good test–retest reliability over 4 weeks, $r = 0.81$, and shows evidence of convergent validity and criterion-related validity (Gosselin et al., 2002). In the current study, we used the Transformation of Images into Verbal Thought subscale (CAQ-Transform), which measures efforts to transform images into thoughts. This subscale has a good psychometric properties and, as shown in **Table 1**, it had good internal consistency in the current sample.

Data Analytic Strategy

Study hypotheses were tested through multiple linear regression (MLR) analyses. All non-dichotomous predictors were mean-centered by z-transformation in these analyses (Aiken and West, 1991). All product terms used in these analyses to test interactions were computed from the standardized predictor variables. Additionally, all dependent variables (i.e., DASS-A and CAQ-transform) except those with readily interpretable scales (i.e., percentage of thoughts and images) were also standardized. Regression diagnostics were examined for each model to determine if extreme data points were present that might be exerting excessive influence on overall model fit or on individual regression coefficients. Specifically, for each model we examined the standardized DFFITS and DFBETA values using ± 1.0 as a cutoff (Cohen et al., 2002). No high influence cases were identified in any analysis.

Significant interactions were probed using PROCESS, a computational tool for SPSS (Hayes, 2013)[1]. Specifically, PROCESS utilizes the Johnson–Neyman technique for deriving regions of significance, which identify the range of values of the moderator where the simple slope of the predictor is significant (Preacher et al., 2007). In this manner we reported the regions of significance and illustrated interactions by depicting the predictors' effect on the dependent variable at high (90th percentile) and low (10th percentile) levels of the moderator. Because we were primarily interested in those with high worry/GAD symptom severity, we also tested EC's effect on the dependent variable at high (90th percentile) levels of worry/GAD symptom severity.

Statistical power to detect an interaction is a function of the variability in the product term representing that interaction (McClelland and Judd, 1993). Because the WAQ measures GAD symptoms using a Likert scale rather than the mostly dichotomous items on the GADQ-IV, we expected that the product term representing its interaction with EC would have more variability than the product terms involving the GADQ-IV. For that reason, we chose it as our primary predictor. Ancillary tests based on the GADQ-IV and PSWQ are reported in the Supplementary Material. Consistent with this rationale, the standard deviation for the WAQ × EC interaction ($SD = 1.09$) was descriptively larger than that of the GADQ-IV or PSWQ × EC interaction ($SD = 1.06$ and 1.02, respectively).

Finally, we examined EC as a moderator for the indirect path between worry/GAD symptom severity and autonomic arousal symptoms for any candidate mediator that was significantly predicted by the worry/GAD symptom × EC interaction. Specifically, PROCESS (Model 8) was used to conduct tests of moderated mediation as depicted in **Figure 1**. A bootstrapping approach was used in these tests as recommended by Preacher et al. (2007) because it avoids the assumption of normally distributed products of the coefficients. Specifically, using PROCESS, we conducted bootstrapped (5000 resamples) tests of each mediator at the 10th, 25th, 50th, 75th, and 90th percentiles of the moderator. Furthermore, because we were most interested in individuals with high levels of worry/GAD symptoms, we also examined EC's indirect effect on autonomic arousal symptoms via the mediator at high (90th percentile) levels of worry/GAD symptom severity. These tests should be interpreted with caution due to the cross-sectional nature of the current study. Recent simulation studies show that cross-sectional tests of mediation can produce biased estimates of the indirect effect (e.g., Maxwell et al., 2011). However, like Hayes and Rockwood (2016), we believe that such tests can still be useful in theory testing. In the present case, we believe such a test is a reasonable, albeit tentative, initial test of the plausibility of our model. At any given point in time, high trait worriers will engage in more verbal thought during worry when they have high versus low levels of trait effortful control. To the extent that they do so, such high effortful control worriers should show less activation of autonomic arousal than those lower in effortful control.

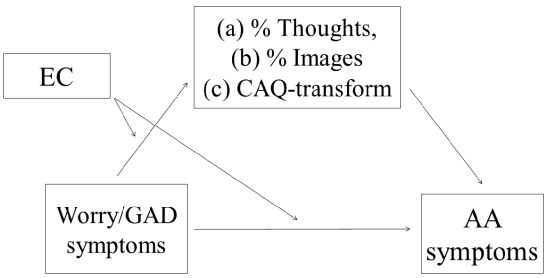

FIGURE 1 | Conceptual model for tests of moderated mediation.

Additionally, to determine if our model holds even at very high levels of worry/GAD symptom severity, we also tested our first hypothesis in an analog GAD sample. That is, among individuals with high levels of GAD symptom severity, EC should be significantly negatively correlated with autonomic arousal. In this context it is important to note that the viability of our model does *not* require that the GAD Symptom Severity × EC interaction be significant in such a subsample. Although we found that interaction to be significant in the analog GAD subsample in our original study (Vasey et al., 2016), we have since realized that result was surprising. That reflects the fact that as one constrains the range of GAD symptom severity, one reduces variance in the product term representing the GAD Symptom Severity × EC interaction. That, in turn, reduces statistical power to find an effect of the interaction (see McClelland and Judd, 1993). To be clear, that reduction in power is above and beyond any reduction in power associated with the smaller sample size of the analog GAD subsample. In essence, as one constrains the range of GAD symptom severity to very high levels, the interaction term becomes redundant with the EC main effect because it ceases to vary much beyond the variance in EC because the range of GAD symptom severity has been severely restricted. Instead, at high levels of GAD symptom severity, our model is most powerfully evaluated in terms of the magnitude and significance of the EC main effect (controlling for remaining variance in GAD symptom severity). Provided that main effect is significantly negative, our model would be

[1]http://www.afhayes.com

supported. With that in mind we tested EC's effect predicting DASS-A scores while controlling for WAQ scores in our analog GAD group.

There are several approaches for identifying those likely to meet criteria for GAD on the GADQ-IV (Moore et al., 2014). In the current study, the analog GAD subsample included all participants who met DSM-IV criteria based on the GADQ-IV.[2] Our only additional requirement was that their score on the GADQ-IV $\geq$ 9, a cutoff found by Newman et al. (2002) to yield 97% specificity and a false positive rate of only 4% in a similar college sample. That approach yielded a group of 120 cases (72.5% female). As shown in **Table 1**, this approach resulted in an analog GAD group characterized by very high levels of worry and GAD symptoms. Specifically, this group had a mean score of 67.09 ($SD = 9.96$) on the PSWQ, higher than the mean for analog GAD samples (i.e., 63.58) and comparable to clinical GAD samples (i.e., 67.16) as reported by Startup and Erickson (2006).

Second, we also tested our first hypothesis using an analog GAD group drawn from a large sample created by combining the current sample with the sample from the Vasey et al. (2016) study. From the resulting group of 2249 cases we chose a subsample of cases based on the GADQ-IV score[3] (scored following the original scoring approach of Newman et al., 2002). Specifically, we identified the GADQ-IV score defining approximately the top 5% of cases.[4] A cutoff GADQ-IV score of 11.0 identified 5.3% of cases ($N = 119$; $n = 73$ [5.5%] from Vasey et al. (2016) and $n = 46$ [5.0%] from the current sample). All but two members of this group (i.e., 98.3%) met DSM-IV criteria based on the GADQ-IV. They had a mean score of 69.08 ($SD = 9.05$) on the PSWQ – a value which is significantly above the average PSWQ score across studies of analog GAD samples ($p < 0.001$) and comparable to clinical GAD samples (see Startup and Erickson, 2006). Additionally, their mean score on the GADQ-IV was 11.52 ($SD = 0.48$). That value is significantly higher than in our previous analog GAD sample ($p < 0.001$) and roughly comparable to most other analog GAD samples (e.g., Fisher et al., 2010; Fisher and Newman, 2013). Finally, PSWQ, WAQ, GADQ-IV, EC, and DASS-A scores did not differ significantly by sample ($ps > 0.12$), suggesting that both subsamples were comparable in severity.

[2]Applying the criteria used in Vasey et al. (2016) identified only 55 subjects. However, those criteria (i.e., meeting DSM-IV criteria for GAD based on the GADQ-IV and scoring 70 or higher on the PSWQ) were unusually very stringent and the resulting group was considerably more extreme on the PSWQ ($M = 75.5$ [$SD = 3.1$]) than typical analog GAD samples ($M = 63.58$ [$SD = 10.8$]) or even clinically diagnosed samples ($M = 67.16$ [$SD = 9.2$]; see Startup and Erickson, 2006).

[3]Generalized Anxiety Disorder Questionnaire-IV scores were used as a measure of GAD symptom severity because the initial sample did not complete the WAQ.

[4]This subsample overlaps with the analog sample in the current study. Specifically, the 46 subjects in the combined sample which were drawn from the current sample were all members of the analog sample drawn from the current sample (i.e., they comprised the most severe 38.3% of that analog sample).

RESULTS

Preliminary Analyses

Data from 926 of 990 participants are reported (93.5% of the original sample, 55% female). Data from the other 64 participants were excluded because they exhibited suspicious patterns of responding (i.e., excessive missing data [>50% of all questionnaires], nonsensical values, repeat entries, or a repetitive pattern of responding). For the remaining 926 participants, incomplete items and missing data were handled using a two-step process. First, for participants with incomplete data who had less than 50% missing items within a questionnaire, their individual means were used to compute their total score. Individual mean substitution when internal consistency of a questionnaire is strong does not produce substantial bias and is more desirable than discarding individuals from the dataset (Osbourne, 2013). Next, the expectation-maximization (EM) method was used to impute missing values for single-item questions as well as total scores for questionnaires (participants missing more than 50% of items within the questionnaires; 9 cases [1.0%] had 1 missing scale score, 7 cases [0.8%] had 2 missing scale scores, and 2 [0.2%] had 3 missing scale

TABLE 2 | Zero-order correlations.

	Sex	GADQ- IV	WAQ	PSWQ	DASS-A	DASS-D	DASS-S	EC	% Thoughts	% Images
GADQ-IV	0.27***									
WAQ	0.24***	0.77***								
PSWQ	0.32***	0.75***	0.68***							
DASS-Anxiety	0.03	0.54***	0.57***	0.42***						
DASS-Depression	0.02	0.53***	0.56***	0.42***	0.70***					
DASS-Stress	0.15***	0.66***	0.70***	0.60***	0.74***	0.70***				
EC	0.02	−0.32***	−0.38***	−0.24***	−0.44***	−0.44***	−0.39***			
% Thoughts	0.10**	0.15***	0.16***	0.17***	0.02	0.09**	0.12***	−0.02		
% Images	−0.04	0.03	0.03	−0.03	0.08*	0.03	0.03	−0.04	−0.41***	
CAQ-Transform	0.06†	0.27***	−0.33***	0.22***	0.36***	0.29***	0.30***	−0.26***	−0.05	0.16***

*N = 926. ***p < 0.001; **p < 0.01; *p < 0.05; †p < 0.10. GADQ-IV, Generalized Anxiety Disorder Questionnaire-IV; WAQ, Worry and Anxiety Questionnaire; PSWQ, Penn State Worry Questionnaire; DASS, Depression, Anxiety, and Stress Scale; EC, Effortful Control Scale; CAQ-Transform, Cognitive Avoidance Questionnaire – Transformation of Images into Thoughts subscale.*

scores). Data were missing completely at random (Little's MCAR test: $p = 0.353$) and the group with missing values did not differ significantly from the group with complete data on any variable[5].

Descriptive Statistics

Means, standard deviations (*SD*), and internal consistency reliabilities for all measures (i.e., Cronbach's coefficient alpha) are presented in **Table 1**. Zero-order correlations are presented in **Table 2**. Several correlations were particularly noteworthy. As expected, GADQ-IV, WAQ, and PSWQ scores were significantly negatively associated with EC scores but only moderately so ($r = -0.32$, -0.38, and -0.24, respectively). Next, EC scores were significantly negatively associated with DASS-A scores ($r = -0.44$). Finally, as expected, GADQ-IV, WAQ, and PSWQ scores were significantly positively associated with percentage of thoughts ($r = 0.15$, 0.16, and 0.17 respectively).

Did Effortful Control Interact with GAD Symptom Severity to Predict Autonomic Arousal?[6]

Table 3 shows that on average DASS-A scores were significantly positively predicted by the WAQ and significantly negatively predicted by EC. The WAQ × EC interaction was also significant. WAQ scores significantly positively predicted DASS-A scores across all levels of EC. However, that association was stronger when EC was low ($B = 0.57$, $p < 0.001$) versus high ($B = 0.38$, $p < 0.001$; see **Figure 2**). From the reverse perspective, EC scores significantly negatively predicted DASS-A scores when the WAQ score was high ($B = -0.35$, $p < 0.001$).

Was Effortful Control Negatively Correlated with Autonomic Arousal in the Analog GAD Groups?

Current Sample

Consistent with expectation, results showed that after controlling for WAQ scores, the EC main effect was significantly negative (semi-partial $r = -0.23$, $p = 0.008$) in the analog GAD group.

Combined Sample

In the analog GAD group from the combined sample, results showed after controlling for GADQ-IV score, the EC main effect was significantly negative (semi-partial $r = -0.31$, $p < 0.001$). Furthermore, this association was not significantly moderated by sample ($p = 0.69$). Thus, EC behaved in similar fashion at high levels of GAD symptoms in both samples.

Did Effortful Control Interact with GAD Symptom Severity to Predict Percentage of Thoughts?[7]

Table 4 shows on average that percentage of thoughts was significantly positively predicted by the WAQ but not significantly negatively predicted by EC. However, the WAQ × EC interaction was also significant. WAQ scores significantly positively predicted percentage of thoughts when EC > −0.126 *SD*. Thus, that association was significant when EC was high ($B = 6.73$, $p < 0.001$) versus low ($B = 2.51$, $p = 0.081$; see **Figure 3**). From the reverse perspective, EC significantly positively predicted percentage of thoughts when the WAQ was high ($B = 3.18$, $p < 0.019$).

Did Effortful Control Interact with GAD Symptom Severity to Predict Percentage of Imagery?[8]

As shown in **Table 3**, there were no significant effects of WAQ, EC, or their interaction predicting percentage of imagery during worry.

Did Effortful Control Interact with GAD Symptom Severity to Predict Efforts to Transform Images into Thoughts?[9]

As **Table 3** shows, on average CAQ-transform scores were significantly positively predicted by WAQ ($B = 0.27$, $p < 0.001$) and significantly negatively predicted by EC ($B = -0.16$, $p < 0.001$). However, the WAQ × EC interaction did not achieve significance ($B = 0.04$, $p = 0.143$).

Did Percentage of Verbal Thoughts Mediate the Association between GAD Symptom Severity and Autonomic Arousal Conditional upon Level of Effortful Control?[10,11]

Given that EC moderated the link between the WAQ and percentage of thoughts, we also examined whether this effect was related to autonomic arousal symptoms. Specifically, we used a moderated mediation model to test whether the relationship between WAQ and DASS-A was mediated by percentage of thoughts but conditional upon level of EC. Based on the MLR

[5] All analyses were ran without the 18 cases with one or more missing scale scores. All significant results remained significant.

[6] See the online supplement for a test of the PSWQ × EC and GADQ-IV × EC interaction predicting DASS-A scores. The interaction was significant in both cases.

[7] See the online supplement for a test of the PSWQ × EC and GADQ-IV × EC interaction predicting percentage of thoughts during worry. The interactions were not significant and marginally significant respectively.

[8] See the online supplement for a test of the PSWQ × EC and GADQ-IV × EC interaction predicting percentage of imagery during worry. The interactions were significant and not significant respectively.

[9] See the online supplement for a test of the PSWQ × EC and GADQ-IV × EC interaction predicting efforts to transform imagery into thoughts. The interactions were not significant.

[10] See the online supplement for a test of the indirect effect of GADQ-IV × EC interaction predicting DASS-A scores through percentage of thoughts during worry. The interaction was not significant but was in the direction expected.

[11] Only a test of the indirect effect of percentage of thoughts was done because the other two candidate mediators were unrelated to the interaction.

TABLE 3 | Regression model testing WAQ × EC predicting DASS-Anxiety, percentage of imagery, and CAQ-transform.

	DV:DASS-A			*DV:% Imagery*			*DV:CAQ-transform*		
Step/variable	**R^2/B**	**ΔR^2/SE**	***sr***	**R^2/B**	**ΔR^2/SE**	***sr***	**R^2/B**	**ΔR^2/SE**	***sr***
Step 1	0.383***	–		0.002	–		0.130***	–	
Step 2	0.389**	0.006***		0.003	0.001		0.132	0.002	
Intercept	−0.01	0.03		25.69***	0.65		0.01	0.03	
WAQ	0.47***	0.03	0.44***	0.37	0.70	0.02	0.27***	0.03	0.25***
EC	−0.26***	0.03	−0.23***	−0.73	0.70	−0.03	−0.16***	0.03	0.14***
WAQ × EC	−0.07**	0.02	−0.08**	0.58	0.60	0.03	0.04	0.03	0.05

*N = 926. ***p < 0.001; **p < 0.01. WAQ, Worry and Anxiety Questionnaire; DASS-A, Depression, Anxiety, and Stress Scale – Anxiety subscale; EC, Effortful Control Scale; CAQ-Transform, Cognitive Avoidance Questionnaire –Transformation of Images into Thoughts subscale.*

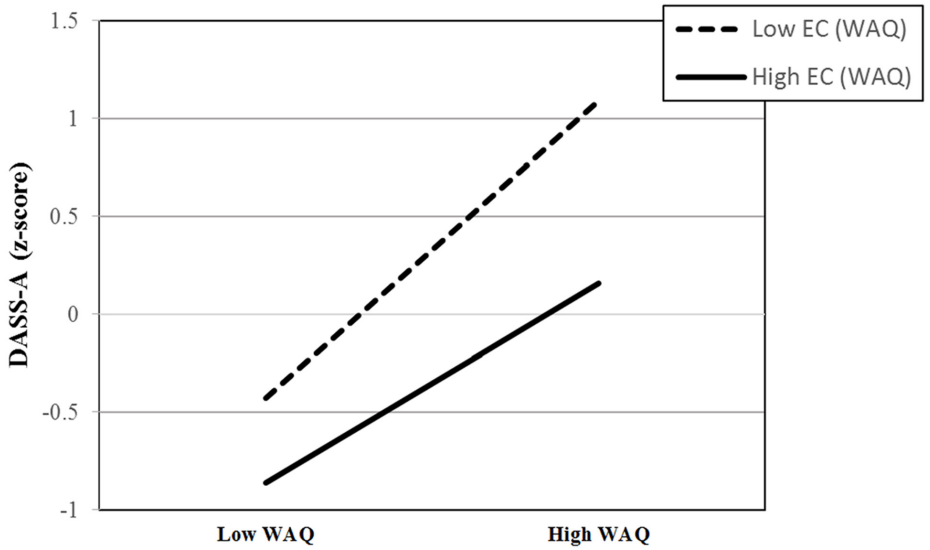

FIGURE 2 | Graph of the WAQ × EC interaction predicting DASS-A at the 10th and 90th percentile of WAQ and EC.

model shown in **Table 5**, results supported significant moderated mediation predicting DASS-A (index of moderated mediation [Hayes, 2015][12] = −0.0038; *SE* = 0.0028; lower limit of CI [LLCI] = −0.0117; upper limit of CI [ULCI] = −0.0001), with the effect being significantly stronger at high versus low levels of EC. As shown in **Table 5**, the pattern was as expected, such that at high EC, WAQ predicted a higher percentage of thoughts, which in turn predicted lower DASS-A scores. As predicted, that indirect path weakened at lower levels of EC. Importantly, as reported in **Table 5** and as expected, viewed from the reverse perspective, when WAQ was high (i.e., 90th percentile), there was a negative indirect effect of EC on DASS-A by virtue of its association with higher percentage of thought[13].

[12]The index of moderated mediation is an estimate of the slope of the line relating the indirect effect to the moderator (Hayes, 2015). If this index is statistically different from zero, there is significant moderated mediation.

[13]We also tested an alternate model in which autonomic arousal interacted with effortful control to predict level of worry and percentage of verbal thoughts. The DASS-A × EC interaction was significant and produced a pattern consistent with expectation.

DISCUSSION

This study extended work on the Cognitive Control Model of pathological worry in two significant ways. First, it offers additional evidence by providing a replication of Vasey et al.'s (2016) findings that cognitive control capacity acts as a moderator to explain the heterogeneity in level of autonomic arousal associated with worry and GAD, especially in the pathological worry range. As expected, the current results provide support for this integrated model in self-reported data from an unselected sample as well as in two overlapping analog GAD subsamples. Specifically, in the current unselected sample we found that individual differences in effortful control moderated the link between worry/GAD symptom severity and autonomic arousal symptoms such that this link is strongest when effortful control was low and weakest when effortful control was high. That analysis also showed that the effortful control was most strongly negatively correlated with autonomic arousal symptoms among those highest in GAD symptoms (i.e., those at or above the 90th percentile). Furthermore, results from both analog subsamples lend confidence to the conclusion that this negative association

TABLE 4 | Moderated mediation results involving WAQ × EC predicting DASS-A through percentage of thoughts.

	Predictor: WAQ		
Step/variable	**R^2/B**	***SE***	***sr***
DV: Percentage of thoughts	0.0317***		
Intercept	64.30	0.86	
WAQ	4.71***	0.93	0.16***
EC	1.21	0.93	0.04
WAQ × EC	1.58*	0.79	0.07*
DV: DASS-A	0.393***		
Intercept	0.13†	0.07	
Percentage of thoughts	−0.002*	0.001	−0.06*
WAQ	0.48***	0.03	0.44***
EC	−0.25***	0.03	−0.24***
WAQ × EC	−0.07**	0.02	−0.07**

*N = 926. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; †$p < 0.10$. WAQ, Worry and Anxiety Questionnaire; DASS-A, Depression, Anxiety, and Stress Scale – Anxiety subscale; EC, Effortful Control Scale.*

between effortful control and autonomic arousal occurs even at very high levels of GAD symptoms.

The strongest evidence for this comes from a subsample of the most severe worriers (i.e., the top 5.3% of scorers on the GADQ-IV) from over 2200 members of a sample combining the current sample with that from our original study (Vasey et al., 2016). Even in that analog GAD subsample EC was significantly negatively correlated with autonomic arousal symptoms (semi-partial $r = -0.31$), which bolsters confidence that such estimates of the effect (i.e., simple slope) of EC at high levels of GAD symptoms from large unselected samples are likely to generalize to those with pathological levels of worry and GAD symptoms.

The second goal of this study was to extend our previous findings by testing the second major aspect of the Cognitive Control Model. Specifically, no previous study has tested the model's prediction that individual differences in effortful control capacity moderate the association between worry/GAD symptoms and the extent to which worry involves verbal thought. Consistent with that prediction, individual differences in effortful control interacted significantly with GAD symptom severity to predict percentage of verbal thoughts during worry. Most importantly, effortful control was significantly negatively associated with percentage of verbal thoughts when GAD symptoms were high. Although the variance accounted for by this regression model was small, it is important to remember that the dependent variable was a single, retrospective questionnaire item. As such, its reliability is undoubtedly limited.

Finally, the moderated mediation analysis further offers tentative support for the plausibility of our model. Specifically, GAD symptom severity predicted higher percentage of thoughts during worry which in turn predicted lower autonomic arousal symptoms when effortful control was high versus low. This effect is perhaps clearer when viewed from the perspective of the indirect effect of effortful control on autonomic arousal symptoms at high (i.e., 90th percentile) GAD symptoms. Specifically, the indirect effect was significantly negative, by way of effortful control's positive association with verbal thought percentage, which in turn was negatively associated with autonomic arousal. This is consistent with our model's view that worry predicts lower autonomic arousal at high levels of effortful control because effortful control permits greater success in emphasizing verbal thought during worry. Nevertheless, we must emphasize the tentative nature of this support since all variables in the moderated mediation model were collected concurrently (Maxwell et al., 2011). Although our results are consistent with predictions of our model, prospective study designs, preferably with experimental manipulation of effortful control resources, are needed to support strong confidence in this aspect of our model.

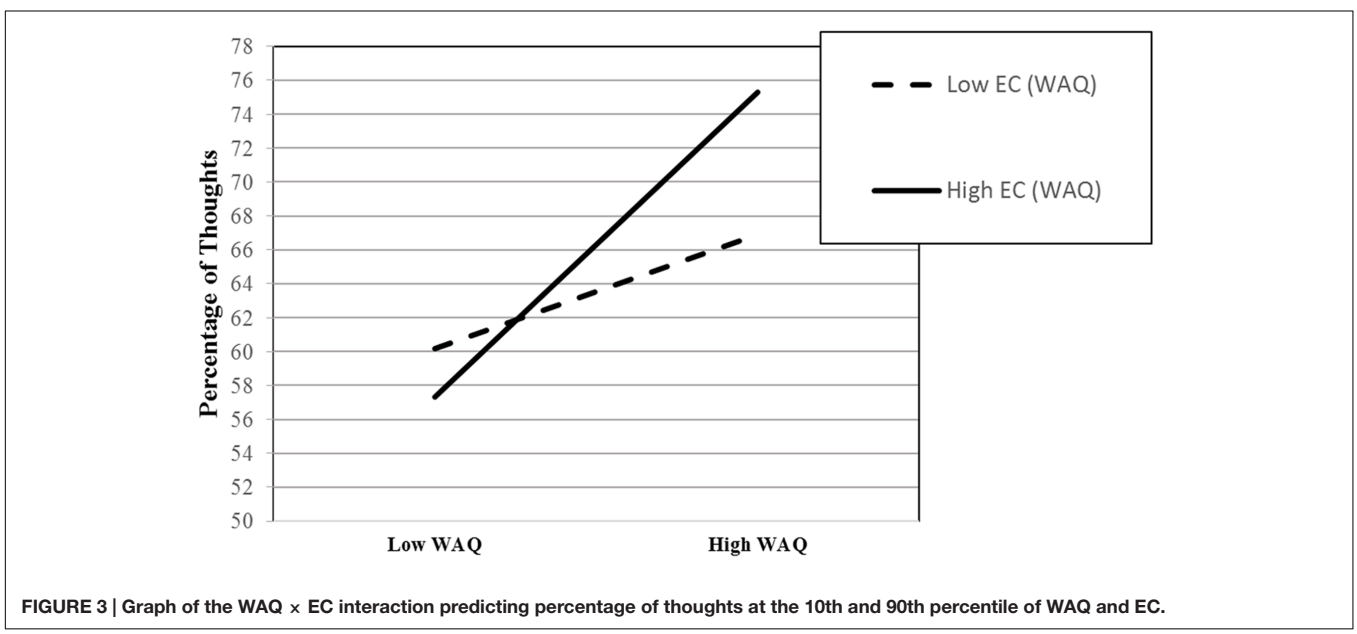

FIGURE 3 | Graph of the WAQ × EC interaction predicting percentage of thoughts at the 10th and 90th percentile of WAQ and EC.

TABLE 5 | Bootstrapped estimates of the conditional indirect paths for the effect of WAQ and EC on DASS-A through percentage of thoughts.

	Indirect effect	Bootstrapped *SE*	Bootstrapped LLCI	Bootstrapped ULCI
Indirect effects of WAQ at varying levels of EC				
10th	**−0.0061**	**0.0046**	**−0.0185**	**−0.0002**
25th	**−0.0089**	**0.0047**	**−0.0209**	**−0.0017**
50th	**−0.0117**	**0.0056**	**−0.0248**	**−0.0025**
75th	**−0.0140**	**0.0067**	**−0.0297**	**−0.0030**
90th	**−0.0162**	**0.0080**	**−0.0360**	**−0.0035**
Indirect effect of EC at 90th percentile of WAQ	**−0.0077**	**0.004**	**−0.0195**	**−0.0011**

N = 926. Bootstrapped estimates are based on 5,000 samples. Significant effects appear in bold. LLCI, lower limit of confident interval; ULCI, upper limit of confident interval. WAQ, Worry and Anxiety Questionnaire; EC, Effortful Control Scale.

Taken together with results from Vasey et al. (2016), the current findings suggest that there are pathological worriers and GAD patients who have the cognitive control capacity required to maintain a verbal mode of processing necessary, which is required to access negative reinforcement contingencies stemming from limiting activation of autonomic arousal. On the other hand, those who lack such capacity tend to experience fewer verbal thoughts during worry and consequently higher autonomic arousal as a consequence of worry. Such a pattern fits with the prerequisites for the negative reinforcement stemming from contrast avoidance.

We expected to find that the association between GAD symptom severity and percentage of images during worry was strongest when effortful control is low. However, the fact that we did not is perhaps not surprising given that another study using the same single item retrospective questionnaire failed to find it to be significantly associated with GAD symptoms. Specifically, another self-report study found no significant differences between GAD analogs and normal controls in the percentage of images reported during worry (Freeston et al., 1996). Furthermore, a laboratory study also found that controls and GAD patients did not differ in percentage of imagery during a worry period (Borkovec and Inz, 1990). Consistent with past findings, our study found that worry is predominantly verbal (65% verbal versus 25% imagery). Because of this low average percentage of imagery, it may be that statistical power to find effects is limited by range restriction. Future studies using mentation sampling during worry and relaxation periods may yield a more sensitive measure of variation in percentage of imagery during worry.

Also contrary to expectation, the interaction between worry/GAD symptom severity and effortful control was unrelated to self-reports of efforts to transform images into thoughts. One reason could be that accurate self-report of this construct rests on an untested assumption that this construct is consciously accessible to individuals (Sexton and Dugas, 2008). Furthermore, in validating the CAQ, Gosselin et al. (2002) reported that three of the five items from the CAQ-Transform scale loaded more highly on a different factor, suggesting that this construct is complex. As such, use of tasks such as mentation sampling may increase validity in future studies.

To this point we have focused on effortful control as a stable trait-like construct and its association to inter-individual differences in the level of autonomic arousal symptoms experienced during worry. However, effortful control capacity can vary within an individual (e.g., due to varying levels of cognitive load or stress). Given that, our integrative model thus also suggests the potential for intra-individual differences in autonomic arousal symptoms as a function of variations in a worrier's ability to emphasize verbal worry. There are at least two possible paths to such differences. First, evidence suggests that constraining worry to such verbal modes of processing depletes cognitive resources (Leigh and Hirsch, 2011), which can lead to increased negative intrusions (Stokes and Hirsch, 2010) and promote further attention to threat (Williams et al., 2014). This suggests that worrying in a verbal manner may deplete the very resources needed to maintain such a verbal mode of processing. If so, even worriers and those with GAD who have high trait-level capacity for effortful control may experience increasing autonomic arousal symptoms during prolonged periods of worry, as their ability to suppress images and shift to a verbal mode of processing wanes. Second, during periods of other cognitive load or stress, such individuals may experience heightened autonomic arousal symptoms during bouts of worry because their capacity for effortful control and ability to constrain worry to a verbal mode has been depleted (Steinhauser et al., 2007). Furthermore, such heightened arousal may lead to an upward spiral in worry and autonomic arousal symptoms because perceptions of arousal appear to maintain worry among those high in GAD symptoms. An experimental study found that when asked to relax following a worry induction, GAD patients who were given false arousal feedback maintained their levels of worrying while those who were given false relaxation feedback decreased their levels of worrying (Andor et al., 2008). This suggests that during periods of prolonged stress worriers for whom worry usually functions to limit autonomic arousal symptoms may instead experience increased vulnerability to intrusive images and autonomic arousal symptoms as a result of stress-related effortful control resource depletion. Unfortunately, a test of this hypothesis awaits future research.

Limitations

This study's results should be considered in the context of several limitations. Although significant, it should be

noted that the magnitude of variance accounted for by the interaction between GAD symptom severity and effortful control predicting autonomic arousal and, especially, percentage of thought during worry was small. However, in this regard it is important to recall that power to detect interactions is highest and such interactions will be strongest in samples that include many individuals who fall at the confluence of the extremes of the interacting dimensions in question (McClelland and Judd, 1993). In this case, it is most important for a sample to include as many individuals with high GAD symptom severity combined with either high or low effortful control. Because the current study utilized an unselected sample, in which most individuals inevitably fell toward the middle of the bivariate distribution defined by the interacting variables, the interaction term cannot account for much variance in the sample as a whole. Future studies should seek to oversample for such individuals to maximize statistical power to detect the interaction effect (McClelland and Judd, 1993).

With regard to the small amount of variance accounted for in predicting percentage of thoughts during worry, it is important to recall that the dependent variable was derived from a single-item measure. Single-item measures have been shown to have much poorer reliability than multi-item measures (Nunnally and Bernstein, 1994). Nevertheless, we thought such measures offered a reasonable starting point since they have been used successfully in other self-report studies using unselected samples especially for reports of thoughts during worry (e.g., Borkovec and Lyonfields, 1993; Freeston et al., 1996). Furthermore, that the single-item measure (i.e., percentage of thoughts) revealed the expected effect may be cause for optimism about the robustness of the effect. However, to increase the likelihood of replication of these findings, future studies should utilize more reliable and valid measures (e.g., thought sampling [Borkovec and Inz, 1990; Hirsch et al., 2012]).

This study was also limited because we did not obtain diagnostic information and cannot be sure how many members of our analog GAD group actually met DSM criteria for GAD. That said, we believe research on such samples is still useful, especially given that studies have shown that worry is continuously distributed in the population and that there are no clear boundaries between subclinical and clinical levels of worry and GAD symptoms (Ruscio et al., 2001; Olatunji et al., 2010). Moreover, our analog GAD group's average PSWQ score ($M = 67.09$, $SD = 9.96$) is comparable to those reported for either analog GAD samples ($M = 63.6$, $SD = 10.8$) or clinical GAD samples ($M = 67.2$, $SD = 9.2$; Startup and Erickson, 2006). Nevertheless, replication in clinical GAD samples is needed to increase confidence that this model applies to a clinical population.

A further limitation was our exclusive reliance on self-reports. Future studies are needed to replicate these findings with objective measures of autonomic arousal and effortful control. However, with regard to such measures of autonomic arousal it is important to note that our model does not require that subjective and objective measures be concordant. In other words, the reinforcement mechanisms in the CognAv and ContrAv models should both operate even if they only involve subjective autonomic arousal. For example, in the case of the CognAv model, the negative reinforcement mechanism associated with a verbal mode of worrying would operate even if it were only linked to reductions in subjective experience of autonomic arousal. Similarly, it should be sufficient for the ContrAv Model if worry is linked to high levels of subjective arousal. Nevertheless, many of the studies of verbal versus imaginal processing of threat on which the CognAv Model is based used objective measures. Therefore, we certainly expect that our model can also account for heterogeneity in objective measures. Indeed, we recently completed an initial test of that hypothesis and found the self-reported GAD symptom severity (using the GADQ-IV) and effortful control (using the Adult Temperament Questionnaire – Effortful Control scale; Evans and Rothbart, 2007) interacted significantly in predicting mean HR during a baseline period (Free, 2017, Unpublished). Second, that study replaced self-reported effortful control with a measure of resting HRV, which provides a physiological measure of top–down control capacity (see e.g., Thayer et al., 2012). Results showed that like self-reports of effortful control, HRV significantly moderated the association between GAD symptom severity and autonomic arousal symptoms.

Future Directions

In sum, this study's findings provided a replication of the results reported by Vasey et al. (2016), showing that the Cognitive Control Model can account for the well-documented heterogeneity in level of autonomic arousal symptoms in worry and GAD. Furthermore, they serve to increase confidence that the model's hypothesized effect of individual differences in cognitive control capacity on autonomic arousal does indeed occur even at very high levels of worry and GAD symptoms. Furthermore, the current findings extend prior work by offering initial support for the proposed mechanism of this model. Specifically, the percentage of verbal thoughts during worry varies as a function of level of effortful control capacity such that it is highest among worriers with high capacity for effortful control. Furthermore, it appears that the positive correlation between effortful control and verbal worry involves the same variance as the negative correlation between effortful control and autonomic arousal symptoms. Our test of moderated mediation thus supports, albeit preliminarily, the plausibility of our model's prediction regarding the interplay between cognitive control capacity, predominance of verbal thought during worry, and autonomic arousal. Thus, the Cognitive Control Model can potentially reconcile the CognAv and the ContrAv models by showing how worry can serve either of the two models' avoidant functions for worriers depending on their cognitive control capacity. In short, a worrier with high cognitive control capacity should have greater success in making and maintaining the shift to a verbal mode of threat processing posited by the CognAv Model, thereby limiting activation of autonomic arousal. In contrast, a worrier low in such capacity should have difficulty doing so, resulting in heightened autonomic arousal, thereby fostering avoidance of aversive contrasts due to unpredictable

spikes in emotional arousal as postulated by the ContrAv Model. Thus, our findings have implications for better understanding the avoidant functions of worry in the etiology and maintenance of GAD. Although promising, however, a replication of these findings using multiple measures of worry, effortful control, and autonomic arousal at more comprehensive levels of analysis is needed to further foster confidence in our model. Specifically, future studies using a worry induction and monitoring the process of worry in real time (as opposed to retrospective self-report) would be an important advance. Similarly, use of EEG during relaxation and worry periods may yield objective measures of differing patterns of activation during verbal versus imagery-based worry. While subjective and objective autonomic arousal need not show concordance for our model to function as expected, because heterogeneity in the level of autonomic arousal is seen among worriers it is important for future work to evaluate the model in the context of psychophysiological measures of autonomic arousal. Finally, these findings should be replicated using behavioral measures of effortful control. These include behavioral measures (e.g., the Attention Network Test [ANT]) and physiological measures (e.g., resting HRV).

ETHICS STATEMENT

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Ohio State University Behavioral and Social Sciences Institutional Review Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

AUTHOR CONTRIBUTIONS

GT: Designed the study, collected the data, performed analyses, and co-wrote the manuscript. MV: Designed the study, performed analyses, and co-wrote the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnhum.2017.00108/full#supplementary-material

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Goal Directed Worry Rules Are Associated with Distinct Patterns of Amygdala Functional Connectivity and Vagal Modulation during Perseverative Cognition

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Excessive and uncontrollable worry is a defining feature of Generalized Anxiety Disorder (GAD). An important endeavor in the treatment of pathological worry is to understand why some people are unable to stop worrying once they have started. Worry perseveration is associated with a tendency to deploy goal-directed worry rules (known as "as many as can" worry rules; AMA). These require attention to the goal of the worry task and continuation of worry until the aims of the "worry bout" are achieved. This study examined the association between the tendency to use AMA worry rules and neural and autonomic responses to a perseverative cognition induction. To differentiate processes underlying the AMA worry rule use from trait worry, we also examined the relationship between scores on the Penn State Worry Questionnaire (PSWQ) and neural and autonomic responses following the same induction. We used resting-state functional magnetic resonance brain imaging (fMRI) while measuring emotional bodily arousal from heart rate variability (where decreased HRV indicates stress-related parasympathetic withdrawal) in 19 patients with GAD and 21 control participants. Seed-based analyses were conducted to quantify brain changes in functional connectivity (FC) with the amygdala. The tendency to adopt an AMA worry rule was associated with validated measures of worry, anxiety, depression and rumination. AMA worry rule endorsement predicted a stronger decrease in HRV and was positively associated with increased connectivity between right amygdala and locus coeruleus (LC), a brainstem noradrenergic projection nucleus. Higher AMA scores were also associated with increased connectivity between amygdala and rostral superior frontal gyrus. Higher PSWQ scores amplified decreases in FC between right amygdala and subcallosal cortex, bilateral inferior frontal gyrus, middle frontal gyrus, and areas of parietal cortex. Our results identify neural mechanisms underlying the deployment of AMA worry rules. We propose that the relationship between AMA worry rules and increased connectivity between the amygdala and prefrontal cortex (PFC) represents attempts by high worriers to maintain arousal and

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distress levels in order to feel prepared for future threats. Furthermore, we suggest that neural mechanisms associated with the PSWQ represent effortful inhibitory control during worry. These findings provide unique information about the neurobiological processes that underpin worry perseveration.

Keywords: generalized anxiety disorder, perseverative cognition, amygdala, functional connectivity, worry stop rules

INTRODUCTION

Worry is a cognitive activity experienced by most individuals, but for some this activity can become pathological, uncontrollable and distressing, and lead to regular bouts of perseverative cognition that negatively affects many forms of daily functioning. Pathological worry of this kind is the cardinal diagnostic feature of Generalized Anxiety Disorder (GAD; DSM-5, American Psychiatric Association, 2013), and is also an important transdiagnostic process, which contributes to the symptoms observed in a range of other psychopathologies (Barlow et al., 2004; Ehring and Watkins, 2008).

A commonly cited approach to understanding worry has conceptualized it as a strategy of cognitive avoidance in response to threat (Borkovec, 1994; Borkovec et al., 2004). Individuals with GAD perceive the world as being a threatening place and one way of managing physiological and psychological feelings of fear is to anticipate what may happen in the future and try to prepare oneself for them. From this perspective, worry is considered as a mental attempt to solve problems (Sibrava and Borkovec, 2008). However, on a more mechanistic level, proximal models of individual pathological worry have only recently been developed (Hirsch and Mathews, 2012; Davey and Meeten, in press), and will be required to understand the individual neurological and psychological mechanisms that generate a worry experience that is perseverative, seemingly uncontrollable, and increasingly distressing as the bout continues.

There is a need to examine the psychological processes that underlie pathological worry, and differentiate it from non-clinical worry, in terms of autonomic and neurobiological correlates of worry. One approach is to explore the goal-directed rules that people use when worrying, to understand why some people persevere with worry after others have stopped. For most people, worrying has a purpose, whether it be to solve perceived problems of daily living (Davey, 1994), as an attempt to repair negative mood (Schwarz and Clore, 1983), or as a means to try and ensure that "bad" things don't happen or to avoid future catastrophes (Davey et al., 1996; Breitholtz et al., 1998; Borkovec et al., 1999; Wells, 2010). Worrying of this kind usually comes with a set of implicit goal-directed rules that are deployed to maximize goal attainment (Chaiken et al., 1989; Martin et al., 1993). These rules don't necessarily tell the worrier how to achieve the goal, but they have a motivational influence by stressing the importance of the goal and activating processes for monitoring whether the goal has been achieved (Davey, 2006; Davey and Meeten, in press).

The endorsement of goal-directed worry rules is highly correlated with a variety of worry-relevant variables (Davey et al., 2005), including measures of trait worry (as measured by the Penn State Worry Questionnaire, PSWQ; Molina and Borkovec, 1994) and beliefs about the positive consequences of worry (as measured by the Consequences of Worry Scale; Davey et al., 1996). Furthermore, the reported use of goal-directed rules significantly predicts perseveration on behavioral measures of catastrophic worrying (Davey et al., 2005).

A recent cognitive model of the perseverative worry bout (Davey and Meeten, in press) describes how potential worries or threats activate the pathological worrier's positive beliefs about a need to worry (Wells, 2007, 2010), and how these beliefs are operationalized in the deployment of goal-directed rules for worrying. Consequently, the pathological worrier "continues to worry until he/she assesses that he/she will be able to effectively cope with anticipated threat" (Wells, 2007, p.19). Identified threats act to prime habitual goal-directed worry rules in an automatic fashion (Bargh, 1989; Aarts and Dijksterhuis, 2000), and these same strict rules for completion of the worry bout also directly contribute to perseveration (ensuring all eventualities are considered).

In addition to psychological models of pathological worry, there have been recent attempts to examine the neurological and autonomic correlates of worry. Research has highlighted specific autonomic, and neurobiological responses to worry, and perseverative cognition including a number of somatic reactions (Brosschot et al., 2006; Ottaviani et al., 2016a), one of which is reduced heart rate variability (HRV). Reduction in HRV is a recognized feature of worry and has been shown to mirror cognitive and emotional inflexibility in worry and rumination (Ottaviani et al., 2013, 2015). Borkovec and Hu (1990) demonstrated that worry can reduce emotional responding to a negative stressor (where worry is assumed to function as a way of avoiding negative emotional states). Reduced HRV can be seen as the physiological component of cognitive perseveration (Thayer et al., 1996).

Brain imaging studies have shown reduced connectivity between the amygdala and prefrontal cortex (PFC) in GAD patients as compared to healthy controls (HC; Monk et al., 2008; Roy et al., 2013). This pattern of aberrant connectivity between amygdala and pre-frontal areas is associated with poor emotional regulation (Borkovec et al., 2004; Banks et al., 2007; Hamm et al., 2014).

The relationship between autonomic and neurobiological signatures of pathological worry has recently been examined by Makovac et al. (2016) where resting state functional magnetic resonance imaging (fMRI) techniques and physiological recordings were combined to characterize the interplay between psychological and physiological symptoms of worry. This study

reinforced earlier findings of lower connectivity between the right amygdala and pre-frontal areas (namely right superior frontal gyrus, right paracingulate/anterior cingulate cortex (ACC) and right supramarginal gyrus) in individuals with GAD. The study also highlighted shared neural correlates (centered on amygdala connectivity) of worry and autonomic dysregulation in GAD participants, which suggests a common mechanism underlying affective and physiological symptomatology. Aberrant connectivity between the amygdala and PFC is an established resting state finding in high anxious populations, however the functional differences between anxious and non-anxious populations while engaging in a worry bout are less well understood.

The purpose of the present study is to supplement this knowledge of the role of the deployment of goal-directed rules (i.e., "as many as can" (AMA) stop rules) in pathological worrying. Functional changes in brain activity and autonomic bodily responses (HRV) were measured following a perseverative cognition induction and related to the use of goal-directed worry stop rules. Further, we also report the relationship between neural and autonomic responses following the perseverative cognition induction and individual differences in the level of trait worry (measured using the PSWQ; Meyer et al., 1990). Together these approaches aimed to enhance our understanding of pathological worrying by characterizing associations between stop-rule deployment and functional brain activity and autonomic arousal state.

It was hypothesized that:

1. AMA stop rules correlate with validated measures of worry, anxiety and rumination.
2. Based on the finding that a perseverative cognition induction resulted in increased connectivity between the amygdala and PFC in GAD participants (Makovac et al., 2016), we predicted that trait AMA stop-rule adoption is associated with a shift towards increased connectivity between the amygdala and PFC following the perseverative cognition induction.

MATERIALS AND METHODS

Participants

One participant who did not complete the full experiment was excluded and the final sample encompassed 19 patients (17 women, 2 men; mean age = 29.58 (6.93) years) who met diagnostic criteria for GAD and 21 HC (18 women, 3 men; mean age = 28.67 (9.45) years). Only one 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 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 dependance, heart disease, obesity (body mass index >30 kg/m^2), pregnancy, claustrophobia or other MRI exclusions. Two GAD patients 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 from the Brighton and Sussex Medical School Research Governance and Ethics Committee. Participants were compensated for their time.

Procedure

The Structured Clinical Interview for DSM-IV (SCID) was administered by a trained postdoctoral fellow (FM) to patients and controls to confirm/exclude the diagnosis of GAD. Participants then completed 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.

Questionnaires

Worry Stop Rule Checklist

The Worry Stop Rule Checklist (Davey et al., 2005) is a measure designed to assess trait stop rules, or specific beliefs used to decide when to discontinue a worry bout or episode (Davey et al., 2005). The measure consists of two subscales. The first scale consists of 10 items measuring the degree to which individuals endorse goal-directed or AMA stop rules while worrying (e.g., "I must keep worrying about this, otherwise things won't get done properly"). The second scale consists of 9-items that assess the degree to which individuals use a "feel like continuing" (FL) stop rule (e.g., "Stop worrying- in the long run this just won't matter very much"). This measure has shown to have adequate internal consistency (α = 0.82–0.88), and validity, as moderate to strong correlations have been found between this measure and the PSWQ (Davey et al., 2005, 2007; Turner and Wislon, 2010).

Penn State Worry Questionnaire

The PSWQ, (Meyer et al., 1990) is the most widely used valid measure of the frequency and intensity of worry. The PSWQ consists of 16-items (e.g., "Many situations make me worry"), which are rated on a 5-point Likert scale ranging from (1) "not at all typical of me" to (5) "very typical of me". The PSWQ has good test-retest reliability (r = 74–0.93; Molina and Borkovec, 1994), internal consistency (α = 90; Brown et al., 1992), and discriminant validity (Meyer et al., 1990).

State-Trait Anxiety Inventory Form Y

The State-Trait Anxiety Inventory Form Y (STAI; Spielberger et al., 1983) consists of two parts, each comprising 20 questions. STAI-Y1 measures state anxiety, that is the respondent's current level of anxiety, by asking how they feel "right now", with a four-point scale of responses from "not at all" to "very much so" for statements such as "I am tense" and "I feel nervous". STAI-Y2 measured trait anxiety, or differences in proneness to anxiety, by asking how participants generally feel, with a four-point scale from "almost never" to "almost always" for statements such as "I feel like a failure" and "I have disturbing

thoughts". Internal consistency coefficients for the scale have ranged from 0.86 to 0.95; test-retest reliability coefficients have ranged from 0.65 to 0.75 over a 2-month interval (Spielberger et al., 1983).

Ruminative Responses Scale

The Ruminative Response Scale (RRS) is a subscale of the Response Styles Questionnaire (Nolen-Hoeksema and Morrow, 1991) consisting of 24 items, revealed as highly reliable and valid in measuring reactions to experiencing negative emotions ($\alpha = 0.92$). Individuals must respond to a series of captions such as "Think about how passive and unmotivated you feel" where possible responses are "almost never/sometimes/often/almost always".

Experimental Design

During scanning, participants underwent a series of four 5-min resting state periods, each followed by a 6-min easy visuomotor tracking task (described elsewhere; Ottaviani et al., 2016b). During resting state periods participants were instructed to rest with their eyes open without thinking of anything and not falling asleep. After the second or third resting block, participants underwent a recorded verbal induction procedure designed to engender perseverative cognition:

> "*Next I would like you to recall an episode that happened in the past year that made you feel sad, anxious, or stressed or something that may happen in the future that worries you. Then, I would like you to think about this episode in detail, for example about its possible causes, consequences, and your feelings about it. Please keep thinking about this until the end of the next tracking task. Thank you. Please take as much time as you need to recall the episode and press the button whenever you are ready*".

To assess state levels of perseverative cognition, at the end of each resting-state period, participants rated their thoughts over the preceding period.

The perseverative cognition induction has established efficacy in eliciting worrisome thoughts that were reproduced in this group (described Makovac et al., 2016).

Physiological Data Processing

Cardiac signal was collected using MRI-compatible finger pulse oximetry (8600FO; Nonin Medical) recorded digitally (via a CED power 1401, using Spike2 v7 software; Cambridge Electronic., Design CED). Pulse data were manually checked and corrected for artifacts. After extracting inter-beat intervals, HRV was estimated by calculating the root mean square successive difference (RMSSD) a reliable parameter for assessing vagally-mediated HRV (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). RMSSD was derived using RHRV 4.0 analysis software[1]. Individual HRV estimates were obtained for the duration of each resting state scanning period. Attention was given to HRV measures before (Pre) and after (Post) the perseverative cognition induction.

[1]http://rhrv.r-forge.r-project.org/

MRI Acquisition and Preprocessing

MRI images were acquired on a 1.5-Tesla Siemens Magnetom Avanto scanner. Structural volumes were obtained using the high-resolution three-dimension magnetization-prepared rapid gradient-echo sequence (HiRes3DMPRAGE). Functional datasets used T2*weighted echoplanar imaging (EPI) sensitive to blood oxygenation level dependent (BOLD) signal (TR = 2.52 s, TE = 43 ms, flip-angle (FA) = 90° 34 slices, slice thickness = 3 mm; FOV = 192 mm, voxel size 3 mm × 3 mm × 3 mm).

Data were pre-processed using Statistical Parametric Mapping (Wellcome Department of Imaging Neuroscience; SPM8[2]), and in-house software implemented in Matlab (The Mathworks Inc, Natick, MA, USA). For each participant, the first four volumes of the fMRI series were discarded to allow for T1 equilibration effects. The pre-processing steps included correction for head motion, compensation for slice-dependent time shifts, normalization to the EPI template in standard space (MNI) coordinates provided with SPM8, and smoothing with a3D Gaussian Kernel with 8 mm^3 full-width at half maximum. The global temporal drift was removed using a 3rd order polynomial fit. To remove other potential sources of bias, data was further filtered regressing against the realignment parameters, and the signal averaged over whole brain voxels. Then, all images were filtered by a phase-insensitive band-pass filter (pass band 0.01–0.08 Hz) to reduce the effect of low frequency drift and high frequency physiological noise.

Statistical Analyses

Questionnaire, Behavioral, and HRV Analyses

All data are expressed as means (±SD). Differences at $p \leq 0.05$ are regarded as significant unless corrections for multiple comparisons are stated. Data analysis was performed with SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Pearson's r correlations were conducted to test for associations between worry stop-rules (AMA and FL) and validated questionnaire measures of worry, anxiety, depression and rumination.

Seed-Based fMRI Analysis

Given the organization of the brain into functional networks, functional connectivity (FC) is a valuable tool as it measures inter-regional synchrony of low frequency fluctuations in BOLD fMRI (Biswal et al., 1995; Fox et al., 2005). In the present study, we used seed-based analyses as our approach was hypothesis-driven.

Anatomical ROIs were constructed using an anatomical toolbox in SPM (Tzourio-Mazoyer et al., 2002) for bilateral amygdala. The average resting state fMRI time-series over the ROIs were extracted for GAD and HC groups. These time series were then used as a regressor in a 1st level SPM analysis.

A correlational analysis was then carried out between the difference in FC after the perseverative cognition induction

[2]http://www.fil.ion.ucl.ac.uk/spm/

(Δ = post − pre-induction) and AMA, FL and PSWQ scores, using a *t*-test with Group (GAD, HC) as main factor and AMA, FL and PSWQ scores as variables of interest.

RESULTS

There were no significant group differences for any of the assessed socio-demographic and lifestyle variables (see Makovac et al., 2016).

Questionnaires

The GAD group had significantly higher scores on the Worry Stop Rule Checklist "AMA" scale [GAD; $M = 36.28$, $SD = 5.62$, HC; $M = 22.57$, $SD = 5.42$, $t_{(38)} = 7.35$, $p = < 0.001$, $r = 0.77$] and significantly lower scores on the "FL" scale, as compared to the HC group [GAD; $M = 18.56$, $SD = 6.24$, HC; $M = 29.10$, $SD = 9.21$, $t_{(38)} = 4.19$, $p = < 0.001$, $r = 0.56$]. The GAD group also had significantly higher scores on the PSWQ, the STAI, and the RRS and significantly lower HRV than the HC group (see Makovac et al., 2016).

Correlation analysis was performed to examine the relationship between the Worry Stop Rule Checklist and validated trait measures of worry, rumination and anxiety (see **Table 1**). An accepted significance level $p = 0.01$ was used in correction for multiple comparisons. The AMA stop rule scale was significantly positively correlated with the PSWQ, the STAI-Y2 and RRS and the FL scale was significantly negatively correlated with the PSWQ and the STAI-Y2 measures, and shows a trend to negative correlation with RRS.

Heart Rate Variability (HRV)

HRV showed a significant reduction following the perseverative cognition induction. Change scores (post − pre) were negatively correlated with AMA stop rules, $r = -0.45$, $p = 0.004$ and positively correlated with FL stop rules, $r = 0.40$, $p = 0.01$. There was no significant relationship between PSWQ and pre to post induction change in HRV, $r = -0.27$, $p = 0.09$.

Correlation Between Pre- to Post-Induction Changes in Amygdala Functional Connectivity and Scores on the Worry Stop Rule Checklist

A positive correlation was obtained between AMA score and pre- to post-induction changes in FC [Δ = post − pre-induction] between right amygdala and locus coeruleus (LC), a brainstem (pons) center for noradrenergic projections up and down the neuraxis (**Table 2**). Similarly, a positive correlation was observed between AMA score and Δ FC between left amygdala and superior frontal gyrus. Thus, higher AMA scores predicted a stronger increase in FC (i.e., higher Δ FC values) between amygdala and LC and superior frontal gyrus, respectively (see **Figure 1**).

TABLE 1 | Pearson's *r* correlations between worry rules as measured by the Stop Rule Checklist and trait measures of worry (Penn State Worry Questionnaire, PSWQ), anxiety (State-Trait Anxiety Inventory Form, STAI), and rumination (Ruminative Response Scale, RRS).

Questionnaires	AMA stop rule	FL stop rule	PSWQ	STAI-Y2	RRS
AMA stop rule	–	−0.626**	0.686**	0.703**	0.491**
FL stop rule	−0.626**	–	−0.633**	−0.595**	−0.328*

*Note: *p < 0.05, **p ≤ 0.001.*

TABLE 2 | Correlations between pre- to post-induction changes in amygdala functional connectivity (FC) and scores on the "as many as can" (AMA) subscale of the Stop Rule Checklist and PSWQ and significant interaction effects when both measures are simultaneously entered into the model.

Brain region		Cluster		Voxel			
	Side	*k*	*p FWE*	*Z*	*MNI xyz*		
Positive correlation with AMA							
Right amygdala seed							
Locus coeruleus	R	374	0.004	4.31	−8	−28	−18
Left amygdala seed							
Superior frontal gyrus	L	983	0.000	4.32	−8	36	56
	R			4.02	8	38	56
Middle frontal gyrus	R			3.69	36	34	48
Negative correlation with PSWQ							
Right amygdala seed							
Lateral occipital cortex	R	1311	0.000	5.16	40	−78	26
Precuneus	R			4.53	20	−64	32
Precentral gyrus	R	608	0.000	4.56	56	−2	22
	L	559	0.000	4.35	−56	6	38
Middle frontal gyrus	R	353	0.000	3.79	34	−2	46
Left amygdala seed							
Inferior frontal gyrus	L	820	0.000	5.23	−56	12	26
Lateral occipital cortex	R	859	0.000	4.19	40	−78	24
Angular gyrus	R			4.00	44	−50	32
AMA × PSWQ interaction							
Right amygdala seed							
Superior frontal gyrus	R	525	0.000	4.42	10	40	56
Middle frontal gyrus	L			3.53	−32	30	50
	R			3.18	38	32	48
Anterior cingulate cortex	R	237	0.051	3.98	16	−4	40
Left amygdala seed							
Superior frontal gyrus	R	751	0.000	4.33	10	42	56
	L			4.03	−22	40	50
Middle frontal gyrus	R			3.76	36	36	48

Correlation Between Pre- to Post-Induction Changes in Amygdala Functional Connectivity and Scores on the Penn State Worry Questionnaire

A negative correlation was obtained between scores on the PSWQ and the change in FC between right amygdala and lateral occipital cortex, precentral gyrus and middle frontal gyrus and between PSWQ score and the change in FC between left amygdala and lateral occipital cortex and inferior frontal gyrus (for a complete list of brain areas, see **Table 2**). Higher PSWQ scores predicted a stronger decrease in amygdala FC with these areas from pre- to post-induction (see **Figure 1**).

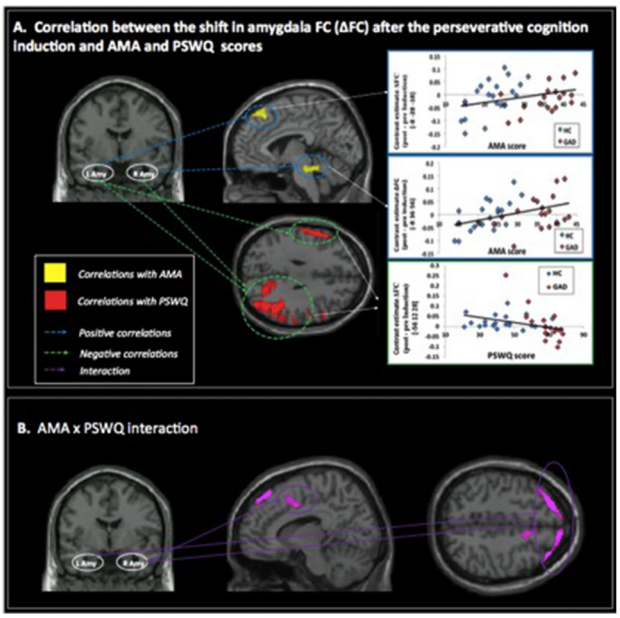

FIGURE 1 | (A) Correlations between pre- to post-induction changes [Δ = post − pre-induction] in amygdala functional connectivity (FC) and "as many as can" (AMA) and trait worry (Penn State Worry Questionnaire [PSWQ]) scores. Positive correlations are represented with blue dashed lines and indicate that higher AMA scores were associated with stronger FC increases following the perseverative cognition induction; negative correlations are represented with a green dashed line and indicate that higher scores on the PSWQ were associated with stronger decreases in amygdala FC following the perseverative cognition induction. **(B)** Significant AMA × PSWQ interactions when scores on both questionnaires were simultaneously entered in the model.

AMA × PSWQ Interaction

When both AMA and PSWQ were simultaneously entered in the regression model, the above mentioned amygdala connectivity patterns did not change. Moreover, a significant AMA × PSWQ interaction emerged for the FC between the bilateral amygdala and areas of the middle frontal gyrus, bilaterally. A significant AMA × PSWQ interaction also emerged for the FC between the right amygdala and the ACC. In detail, higher scores on the PSWQ were associated with decreased amygdala FC with these areas, whereas higher scores on AMA were associated with increased amygdala connectivity following the perseverative cognition induction (see **Table 2** and **Figure 1**).

DISCUSSION

A recent model conceptualizes AMA goal-directed worry stop rules within an integrated network of behavioral and cognitive responses that occur during perseverative worry (Davey and Meeten, in press). A key aim of the present article was to extend our knowledge of perseverative worry more generally, and goal directed worry rules specifically, by examining the neurobiological processes that are related to AMA stop rule use and compare this with processes associated with a measure of trait worry (PSWQ) after a perseverative cognition induction. We examined responses to the Worry Stop Rule Checklist (Davey et al., 2005) by individuals with GAD as compared to the HC group. The GAD group scored significantly higher on the AMA subscale and significantly lower on the FL subscale than the HC group. The AMA subscale was also significantly positively correlated with validated measures of trait worry, anxiety and rumination. To our knowledge, this is the first time that the Worry Stop Rule Checklist has been completed by individuals with GAD. The present findings are consistent with previous research, which has shown that in a non-clinical sample, the tendency to adopt an AMA approach to worrying was positively associated with higher PSWQ scores and beliefs about positive and negative consequences of worry (Davey et al., 2005). Furthermore, previous research has shown that, over the course of a catastrophic worry task, individuals have a tendency to shift from endorsing AMA stop rules at the outset of the task, to FL rules at the end of the task (Davey et al., 2007). This suggests that FL stop rules are associated with cessation of worry.

Using seed-based fMRI analysis, we found that GAD participants with high AMA worry rule endorsement displayed larger decreases in HRV after a perseverative cognition induction and also displayed increased connectivity between right amygdala and brainstem. Higher AMA scores were also coupled to increased connectivity between amygdala and rostral superior frontal gyrus. In contrast, higher PSWQ scores were associated with stronger post induction decreases in FC between right amygdala and more ventral and lateral frontal regions (subcallosal cortex, bilateral inferior frontal gyrus).

The AMA worry rules and PSWQ shared a representation within the middle frontal gyrus, a region implicated as part of the cognitive regulation network (e.g., effortful regulation of affect), where activity is typically inversely correlated with spontaneous activity in the amygdala (Roy et al., 2009). Interestingly, we observed that lower scores on the PSWQ were associated with increased amygdala FC with this area during the perseverative cognition induction (i.e., a negative correlation), whereas higher scores for AMA were associated with increased amygdala connectivity (i.e., a positive correlation). Previous research has shown that increased connectivity between the right amygdala and left middle frontal gyrus is observed during threatening scenarios (Gold et al., 2015). Similarly, in the induction of worry in elderly patients with GAD, participants displayed enhanced connectivity between the paraventricular nucleus seed and middle frontal gyrus (Andreescu et al., 2015). Moreover, decreased amygdala FC with the middle frontal gyrus is observed after emotion regulation training (Li et al., 2016). Thus our findings enhance a growing literature concerning the contribution of middle frontal gyrus to affective regulation.

In the present study, we report that as an individual's worry score (PSWQ) decreased, the perseverative cognition induction produced a greater increase in FC between the amygdala and the middle frontal gyrus. Makovac et al. (2016)

reported that a HC group consistently displayed greater connectivity between the right amygdala and frontal pole regions (right superior frontal gyrus) compared to GAD patients. One possibility is that the present findings reflect attempts at effective top-down control of the amygdala where low anxious individuals may curb a worry bout through emotion regulation strategies such as reappraisal (e.g., Ochsner and Gross, 2005). Furthermore, connectivity between the amygdala and PFC has predicted lower levels of anxiety and effective emotional regulation (Kim et al., 2011).

In the present study, findings concerning trait worry (as examined by the PSWQ) support previous research findings in a GAD population (Hilbert et al., 2014). However, we propose that the AMA stop rule endorsement captures a different aspect of worry, which relates to the perseverative nature of pathological worry. For example, high anxious individuals have been shown to consider worry as a useful strategy to cope with threat and catastrophic worriers endorse positive beliefs about worry (Wells, 2004). We propose that the association between AMA stop rule endorsement and increased connectivity between the amygdala and middle frontal gyrus may capture successful attempts by the worrier to maintain chronic arousal and feelings of distress. For example, the contrast avoidance model of worry proposes that worry is reinforced because pathological worriers prefer to feel chronically distressed in order to prepare for the worst outcome (Newman and Llera, 2011). In high anxious individuals, a chronic state of cognitive and physiological readiness to deal with threat (e.g., worry perseveration) means that they avoid a potential future shift from a positive or benign mental state to a negative one (Newman and Llera, 2011).

Higher PSWQ scores were also uniquely associated with diminished pre- to post-induction connectivity of amygdala with the inferior frontal gyrus and the occipital cortex. Aberrant FC between these areas is implicated in functional impairments in socioemotional learning, anxiety, and self-referential insight (e.g., Singh et al., 2015). For example, exaggerated negative connectivity with lateral occipital cortex occurs in patients with social anxiety disorder (Pannekoek et al., 2013). The inferior frontal gyrus is also reported to show increased connectivity with the right amygdala during anxiety regulation engaged during threat exposure (Gold et al., 2015), consistent with a role in inhibitory control to cope with elevated task demands. Similarly, activation of lateral PFC with simultaneous attenuation of amygdala activity is reported during cognitive control of anxiety states from threat-related distractors and reappraisal of threat stimuli (for a meta-analysis see Buhle et al., 2014).

The pattern of results reported is consistent with a model of pathological worrying in which chronic worriers attempt to inhibit representations of the potential bad outcomes associated with the worry, while simultaneously maintaining arousal in order to seek out potential solutions to the issues raised by the worry. Thus, as a measure of the pathological frequency of worry, the PSWQ is not only associated with the deployment of AMA worry rules (to facilitate the finding of solutions to the worry through an internal narrative process), but also with attempts to inhibit threatening images of the potential worry entering conscious awareness. This latter process is consistent with the avoidance model of worry proposed by Borkovec et al. (2004) in which worry reflects a process of effortful inhibitory control of the fearful images associated with the worry, and this effect is implied by the relationship between PSWQ scores and diminished pre- to post-induction connectivity of amygdala with the inferior frontal gyrus and the occipital cortex. In contrast, the deployment of AMA worry rules is associated with increased connectivity between the right amygdala and the LC, which is the major noradrenergic nucleus of the brain and plays a central role in the regulation of arousal and autonomic activity. This finding supports the view that the deployment of AMA worry rules operationalizes a strategy to remain in a state of arousal reflecting preparedness for future negative outcomes and the need to persevere with worry in order to seek solutions for the worry. This is consistent with the contrast-avoidance model of worry that proposes that worry is reinforced because pathological worriers prefer to feel chronically distressed in order to prepare for the worst outcome. This also means that they avoid a potential future shift from a positive or benign mental state to a negative one (Newman and Llera, 2011). In addition, this interpretation is supported by the relevant physiological data showing that HRV exhibited significant reduction following the perseverative cognition induction, and HRV change scores were negatively correlated with AMA worry rule scores.

When both AMA and PSWQ are simultaneously entered in the model, the above-examined inverse amygdala connectivity patterns do not change, with the exception of a further relation between the right amygdala and the ACC that was positive for AMA and negative for PSWQ. The ACC is involved in the regulation of negative affect via its connections to the amygdala and the outflow to the autonomic system (reviewed in Bush et al., 2000; Lavin et al., 2013). A negative covariation between the amygdala and ACC in fear perception reflects reduced amygdala responses with greater ACC activity that is efficient top-down modulation of the amygdala (e.g., Das et al., 2005). Again, results are in agreement with scores on the PWSQ mirroring inhibitory control of fear and scores on AMA stop rules reflecting the proactive maintenance of fear, as indicated by greater ACC activity accompanied by enhanced amygdala activation.

In conclusion, we report that endorsement of AMA goal directed worry rules is associated with neural and autonomic responses to a perseverative cognition induction which can be characterized as an attempt to maintain a state of cognitive and physiological readiness for potential future feared outcomes. In contrast the PSWQ captures attempts to inhibit or avoid intrusive negative thoughts (Borkovec and Roemer, 1995). This is, to our knowledge, the first time that goal directed worry rules have been explored at a neurological level. Gaining a greater understanding about the psychological and physiological processes that drive worry perseveration will enable the development of more specific

treatment approaches, which focus on factors that are likely to drive the excessive perseveration of worry that is reported in common psychopathologies such as GAD.

AUTHOR CONTRIBUTIONS

CO, HDC, FM, GCLD, DRW and SNG contributed to study design. CO, EM, SNG, DRW, HDC and FM contributed to data analysis. FM, GCLD, EM, CO, HDC, DRW contributed to writing the article.

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REVIEW
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Perseverative Cognition and Health Behaviors: A Systematic Review and Meta-Analysis

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Recent developments in stress theory have emphasized the significance of perseverative cognition (worry and rumination) in furthering our understanding of stress-disease relationships. Substantial evidence has shown that perseverative cognition (PC) is associated with somatic outcomes and numerous physiological concomitants have been identified (i.e., cardiovascular, autonomic, and endocrine nervous system activity parameters). However, there has been no synthesis of the evidence regarding the association between PC and health behaviors. This is important given such behaviors may also directly and/or indirectly influence health and disease outcomes (triggered by PC). Therefore, the aim of the current review was to synthesize available studies that have explored the relationship between worry and rumination and health behaviors (health risk: behaviors which, if performed, would be detrimental to health; health promoting: behaviors which, if performed, would be beneficial for health). A systematic review and meta-analyses of the literature were conducted. Studies were included in the review if they reported the association between PC and health behavior. Studies identified in MEDLINE or PsycINFO ($k = 7504$) were screened, of which 19 studies met the eligibility criteria. Random-effects meta-analyses suggested increased PC was generally associated with increased health risk behaviors but not health promoting behaviors. Further analyses indicated that increases in rumination ($r = 0.122$), but not reflection ($r = -0.080$), or worry ($r = 0.048$) were associated with health risk behaviors. In conclusion, these results showed that increases in PC are associated with increases in health risk behaviors (substance use, alcohol consumption, unhealthy eating, and smoking) that are driven primarily through rumination. These findings provide partial support for our hypothesis that in Brosschot et al.'s (2006) original perseverative cognition hypothesis, there may be scope for additional routes to pathogenic disease via poorer health behaviors.

Keywords: stress, worry, rumination, alcohol, smoking, exercise, diet, health

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INTRODUCTION

In 2006, Brosschot, Gerin, and Thayer introduced the perseverative cognition hypothesis (PCH), which suggested that worry and/or repetitive thinking may lead to disease by prolonging stress-related physiological activation by amplifying short-term responses, delaying recovery, or reactivating responses after a stressor has been experienced. In the last decade, a number of

important reviews and papers have been published clearly demonstrating that **perseverative cognition** is associated with somatic outcomes (e.g., Brosschot et al., 2005; Verkuil et al., 2010; O'Connor et al., 2013; Ottaviani et al., 2015).

More specifically, the PCH proposes that worry, rumination and related thought processes are not only psychological phenomena but can also impact on physical health. It is argued that perseverative cognition (PC)—the cognitive representation of past stressful events or feared future events—mediates the relationship between stress and physical disease as, when stressors are perseverated upon in thought, the damaging physiological activation associated with stress is also protracted, thus increasing susceptibility to stress-related ill-health. The hypothesis states that, in such instances where the physical stressor is absent, the cognitive representation alone can induce a physiological stress response, which, when prolonged, increases the likelihood of stress-related diseases. In this sense, the direct relationship between stress and disease is intensified when a stressor is subject to thought.

Since the PCH was proposed, a substantial amount of evidence has been identified which supports the main tenets of the theory. In one of the first reviews published, Verkuil et al. (2010) presented convincing research evidence of a link between the prolonged physiological activation associated with PC and somatic health outcomes. More recently, Ottaviani et al. (2015) conducted a comprehensive meta-analysis to synthesize the physiological concomitants of PC in healthy participants. These authors concluded that there was clear evidence that PC affects cardiovascular, autonomic, and endocrine nervous system pathways consistent with a pathogenic route to long-term disease outcomes. Specifically, they found higher levels of heart rate, blood pressure, and cortisol activity and lower heart rate variability during PC or related to trait PC.

However, despite the accumulating evidence for a direct pathway from PC to disease outcomes, we were interested in exploring the existence of an additional indirect pathway via health behaviors. In the broader stress literature, it is well-established that stress can affect health indirectly, through the modification of health behaviors (Rod et al., 2009; O'Connor and Conner, 2011). Stress induced modifications of habitual health behaviors such as food choice and eating behavior have been shown to be particularly important in understanding physical disease risk (Steptoe et al., 1998; O'Connor et al., 2008). Recent findings have confirmed that stress is frequently associated with increased unhealthy food intake in laboratory-based and naturalistic studies (e.g., Adam and Epel, 2007; O'Connor et al., 2008; Dallman, 2010; Van Strien et al., 2012).

For example, in a 28-day diary study, O'Connor et al. (2008) showed that daily stressors were associated with increased consumption of high fat and high sugar between-meal snack foods and with a reduction in main meals and vegetable consumption. Moreover, evidence is beginning to emerge showing associations between rumination and the consumption of unhealthy foods such as cakes, crisps, and confectionary (e.g., Cropley et al., 2012). Therefore, it remains possible that PC might also amplify, prolong, and reactivate the same physiological and psychological processes that account for the negative effects of stress on eating behavior.

Other studies have provided evidence of a relationship between stress and increased alcohol consumption, which has been identified as a significant risk factor for chronic disease (Rehm et al., 2009). For example, in a daily diary study, Grzywacz and Almeida (2008) reported that participants were more likely to binge drink on days when they experienced more severe stressors. Similarly, in an experimental study, a blunted cortisol response to a laboratory stressor was associated with greater post-stressor alcohol consumption (Pratt and Davidson, 2009). Corbin et al. (2013) suggest that alcohol may be used to deal with negative emotion when alternative coping strategies are not available. In the sample of college students they surveyed, stress levels were positively associated with drinking to cope, and drinking problems. Moreover, those who reported drinking to cope drank more heavily. Again, similar to eating behavior, data are emerging showing that measures of (negative work) rumination are associated with more alcohol consumption on workdays (Frone, 2015).

Nevertheless, taking the above findings together, it is surprising how little research has explicitly explored the relationship between measures of PC and health behaviors. In addition, it is important to distinguish between health promoting and health risk behaviors. Health-promoting behaviors are health-enhancing behaviors which individuals are encouraged to perform more to protect their health; whereas health risk behaviors are health-damaging behaviors which individuals are encouraged to perform less. Given that PC exacerbates the relationship between the experience of stress and the physiological response, it is also possible that, as the experience of the stressor is prolonged by worry, or ruminative processes, so too may be its detrimental impact on different types of health behaviors. For example, PC might be more strongly associated with health risk behaviors such as alcohol consumption, smoking, and high fat food intake compared to health promoting behaviors such a physical exercise, given the former may be strategies to help alleviate rumination, and worry. Furthermore, over time, PC-induced increases in health risk behaviors and decreases in health promoting behaviors are likely to influence pathogenic pathways to long-term disease outcomes. **Figure 1** represents the original model proposed by Brosschot et al. (2006) with an additional route to the pathogenic disease state via poorer health behaviors (e.g., higher levels of alcohol, tobacco and unhealthy food consumption, and lower physical activity levels and lower consumption of healthy foods). In this conceptualization, we theorize that rumination about past stressful events or worry about feared future events will mediate the effects of stressors on health behaviors (particularly those previously shown to be influenced by stress), which will have negative consequences for health outcomes and disease processes. Therefore, the primary aim of the current review and meta-analysis was to quantify the existing evidence relating any measure of PC to health behaviors.

A secondary aim of the current review and meta-analysis was to establish whether different types of PC had a differential impact on health behaviors. As outlined above, PC is an umbrella term which encompasses repetitive, negative thought processes related to the experience of a stressor. This term was developed as it was thought that disparate concepts such as rumination and worry were either too narrowly or too broadly defined to

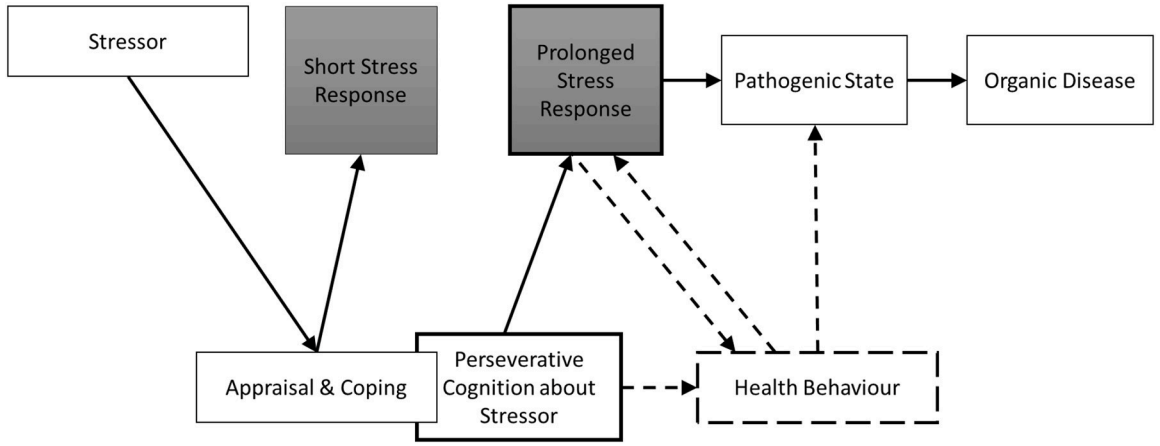

FIGURE 1 | Brosschot et al.'s (2006) model of PC and health extended to include additional pathways to illness via health behaviors (represented by dashed lines). PC may mediate the negative effects of stressors on health behaviors that will influence the pathogenic state (pathway #1). PC may also influence health behaviors through its effects on the prolonged stress response (pathway #2) and health behaviors may also have a bi-directional influence on the prolonged stress response (pathway #3).

allow for a model which linked negative, repetitive thought, and somatic health (Verkuil et al., 2010). Indeed, there has been recent debate about whether rumination and worry ought to be considered separately or collapsed into a single phenomenal category (cf., Ottaviani et al., 2015). Nevertheless, the most widely researched of these thought processes are depressive rumination and worry (Verkuil et al., 2010). Nolen-Hoeksema et al. (2008) described rumination as "thinking perseveratively about one's feelings and problems" (p. 400) regardless of thought content (positive or negative). However, although ruminative thoughts can be positive, within the PCH, PC only encompasses negative thoughts (Verkuil et al., 2010).

Moreover, there is good agreement that rumination is best conceptualized as having two components: brooding and reflection (Treynor et al., 2003). Brooding is described as a passive and judgemental form of rumination, whereas reflection is more contemplative with a focus on problem-solving. Treynor et al. (2003) provided evidence that brooding is the more maladaptive component of rumination as brooding predicted symptoms of depression one year later, whereas, although reflection predicted current depression, it predicted lower levels of depression over time. Reflection is thus considered to be a somewhat adaptive component of rumination.

Whereas rumination has been shown to be associated with depression, worry is a central aspect of anxiety disorders, and particularly generalized anxiety disorder (Borkovec and Inz, 1990). Borkovec et al. (1983) were the first research group to aim to define and categorize the process of worrying and to distinguish it from related processes such as anxiety, fear, and mental problem-solving. Borkovec et al. (1983) defined worry as "a chain of thoughts and images, negatively affect-laden, and relatively uncontrollable. The worry process represents an attempt to engage in mental problem-solving on an issue whose outcome is uncertain but contains the possibility of one or more negative outcomes. Consequently, worry relates closely to fear processes" (p. 10). Therefore, within the PCH, worry is viewed as worry about feared events (or stressors) in the future.

To summarize, the primary aim of the current review was to systematically review empirical studies which have investigated the relationship between any type of PC and any health behavior outcome. As the PCH aimed to model how stress-related thinking may impact on health outcomes in otherwise healthy populations, the aim here was also to review studies involving physically and mentally healthy participants. It was hypothesized that higher levels of PC would be associated with more health risk behaviors (defined as those behaviors which, if performed, would hinder health) and less health promoting behaviors (defined as those behaviors which, if performed, would benefit health). The secondary aim was to explore whether different types of PC (rumination and worry) had differential effects on health behaviors.

METHODS

Eligibility Criteria

To be eligible, studies had to (1) include a measure of PC, (2) a measure of health behavior and, (3) report the relationship between the measures of PC and the health behavior within a statistical analysis that could be used to estimate an effect size (even if the relationship between PC and health behaviors was not the primary outcome of the study). Studies were excluded if they were (1) not peer-reviewed, (2) not an empirical investigation, (3) were reviews, editorials or "think pieces," dissertations, book chapters, protocols, or unpublished, (4) if all study participants had been diagnosed with physical or mental health problems (but included if a sample of healthy participants was analyzed separately). Finally, studies that related to sleep ($n = 75$) were excluded from the current review paper (see **Figure 2**) because we considered sleep to be different from the other health behaviors under consideration. It is a complex behavior that is measured in many different ways and has multiple features (e.g., hours slept, sleep latency, sleep quality, insomnia, etc.) that sets it apart from behaviors such as smoking, physical activity, or eating. In addition, we felt that combining the relatively large number of

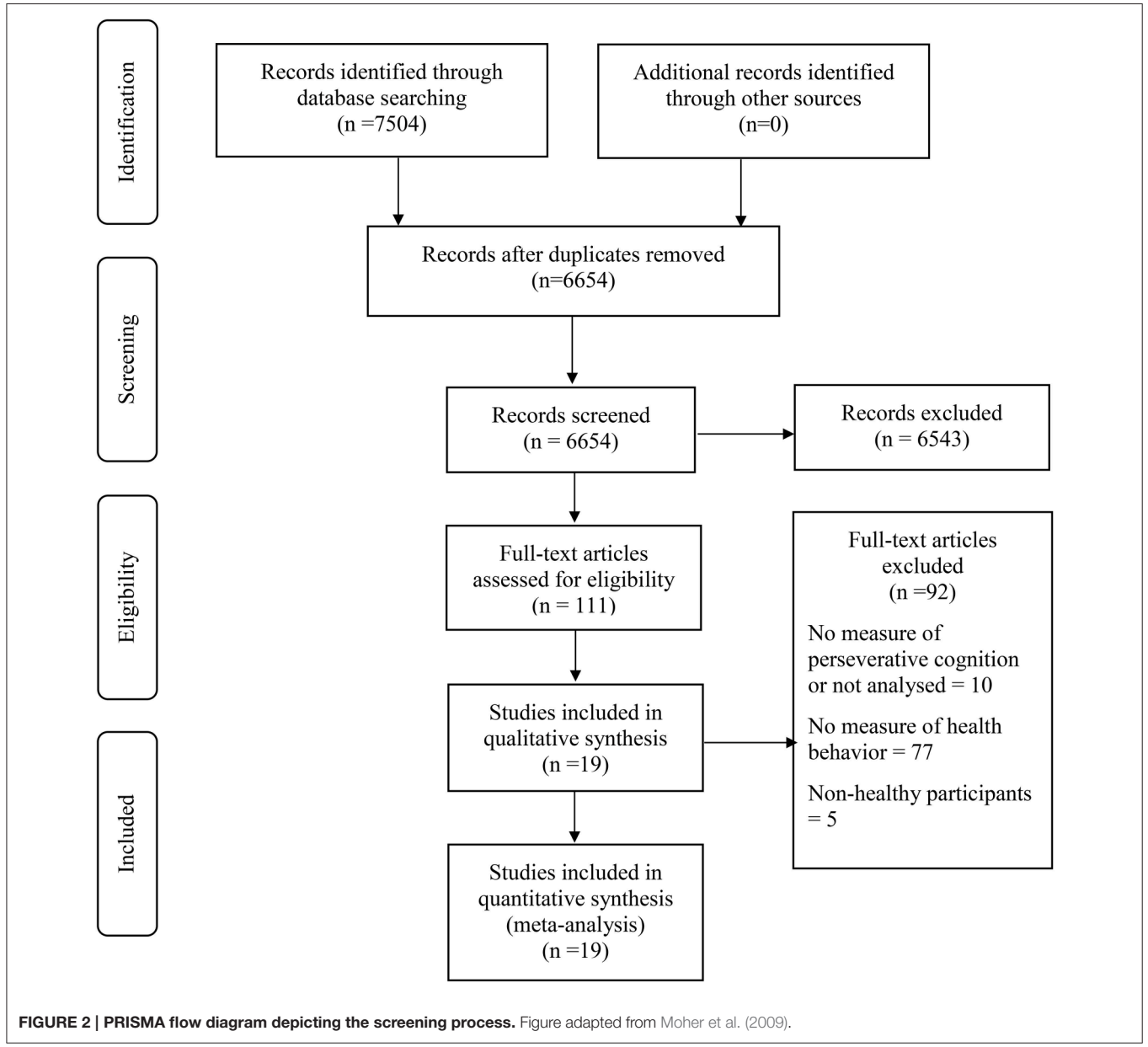

FIGURE 2 | PRISMA flow diagram depicting the screening process. Figure adapted from Moher et al. (2009).

sleep studies with the other health behaviors could potentially bias the results of the review. Therefore, given these points, the sleep studies will be synthesized in a separate review paper.

In terms of eligibility criterion (1), some researchers have argued that concepts such as angry rumination and co-rumination are separate forms of rumination. Angry rumination is a type of rumination in which the focus of the rumination is on an anger-inducing event and has been found to predict aggressive behavior (Denson, 2013) and was included in our conceptualization here. However, co-rumination is described as a group form of rumination in which interpersonal discussion focuses upon emotions and problems (Rose, 2002) but was not included here as it is not a purely cognitive form of PC (a similar approach was adopted by Ottaviani et al., 2015). Also, despite research which suggests that reflection may serve as an adaptive component of rumination, studies measuring reflection were retained in order to assess whether this type of rumination is still adaptive in terms of health behaviors (but analyzed separately from PC).

Search Strategy

PsycINFO (1806 to Present) and Medline (1946 to Present) were searched using OVID. The search was last run on the 11th of February 2016 using search terms relating to PC and health behavior. The search was limited by (1) English language, (2) human studies, and (3) studies published from 1990 [i.e., the year the Penn State Worry Questionnaire (Meyer et al., 1990) was published and shortly before the publication of key papers

using the Ruminative Responses Scale (e.g., Nolen-Hoeksema, 1991)]. As with other systematic reviews, we wanted to strive for an appropriate trade-off between specificity (proportion of non-relevant articles that are not retrieved) and sensitivity (proportion of relevant articles that are retrieved). By restricting the search strategy to articles published from 1990 onwards (i.e., at the time several of our key measures were published), we anticipated a much greater increase in specificity with a relatively small reduction in sensitivity. Indeed, of the articles included in our review, none were published prior to 2003, suggesting few, if any, studies published prior to 1990 would have met our inclusion/exclusion criteria. The titles were screened by the first author. All abstracts and full-texts that were not excluded at the title screening stage ($n = 206$) were independently double-screened. There was 100% agreement between the two reviewers regarding the studies to be included.

Search Terms

Perseverative cognition terms (adapted from Querstret and Cropley, 2013; Ottaviani et al., 2015) combined with OR:

(1) perseverati* AND cogniti* (2) reflection (3) brooding (4) ruminat* (5) reflect* AND thought* OR thinking (6) brood* AND thought* OR thinking (7) perseverative AND thought* OR thinking (8) repetitive AND thought* OR thinking (9) intrusive AND thought* OR thinking (10) negative AND thought* OR thinking (11) self-referential AND thought* OR thinking (12) stress AND thought* OR thinking (13) obsessive AND thought* OR thinking (14) worry (15) unconscious stress* (16) implicit stress* (17) anticipat* stress* (17) cognitive intrusion*

To increase the specificity of the search strategy, we removed terms used by Querstret and Cropley (2013) which related to anxiety, depression, and stress as, although these concepts overlap with perseverative cognition, they are not specific to perseverative cognition. Aspects of perseverative cognition which do relate to stress and anxiety should be captured by terms such as "stress" combined with "thought* or thinking" and depressive thoughts should be captured by "brooding" and/or "ruminat*." The bulk of the search terms were derived from Querstret and Cropley (2013) and therefore the only term relating to perseverative cognition taken from Ottaviani et al. (2015) was "self-referential" as all of the other relevant terms in this review had already been covered.

Health behavior terms (alcohol terms adapted from Kaner et al., 2007; exercise from Foster et al., 2005; eating from Nield et al., 2007; smoking from Secker-Walker et al., 2002; and sleep from Hu et al., 2015) combined with OR:

(1) exp alcohols/ (2) Alcohol$.tw. (3) exercise.sh. (3) physical activity.sh (4) sports.sh (5) dance.sh (6) [physical$ adj5 (fit$ or train$ or activ$ or endur$)].tw. (7) [exercis$ adj5 (train$ or physical$ or activ$)].tw. (8) sport$.tw. (9) walk$.tw. (10) bicycle$.tw. (11) (exercise$ adj aerobic$).tw. (12) [(lifestyle or life-style) adj5 (activ$)].tw. (13) [(lifestyle or life-style) adj5 physical$].tw. (14) Diets.sh (15) Eating behavio?r.sh (16) weight control.sh (17) (diet$ adj5 carbohydrat$).tw (18) (diet$ adj5 fat$).tw (19) (diet$ adj5 weigh$).tw (20) (diet$ adj5 sugar$).tw (21) (diet$ adj5 fiber$).tw (24) (diet$ adj5 fiber$).tw (22) (diet$ adj5 salt$).tw (23) (diet$ adj5 calorie$).tw (24) healthy eating.tw (25) smok$.mp. (26) nicotine.mp. (27) tobacco.mp. (28) cigarette$.mp. (29) exp sleep/ (30) sleep adj3 (promot* or help* or support* or initiat*).mp. (31) sleep.ti,ab

Alcohol terms were not changed from the source but were the only terms relating to alcohol consumption from a larger number of search terms. The same strategy of selecting relevant terms was used in regards to physical activity, diet, smoking and sleep terms. Eating terms were removed which referred to diabetes as this was not relevant to the current review.

The items below were developed by the research team as they were not captured by the terms adapted from the previous reviews cited:

(32) hypophagi* (33) hyperphagi* (34) caffein* (35) snack* (36) meal* (37) junk food* (38) fast food* (39) vegetable* (40) fruit* (41) unhealthy food* (42) unhealthy diet (43) healthy food* (44) alcohol* intake (45) alcohol* unit (46) alcohol* consum* (47) caffein*.

Adding these terms increased the number of papers retrieved and ensured that potentially relevant papers were not missed. Perseverative cognition and health behavior terms were then combined with AND.

Data Extraction

The following data were extracted (see **Table 1**) by the lead author for each study: lead author name, publication year, study design, geographical location, study setting, behavioral outcome (and whether this measure had been previously validated), the type of PC (and whether this measure had been previously validated), the measure of PC, the number of participants included in the analyses, the percentage of female participants and the age of participants (preferably the mean and SD if reported). To maximize reliability of the data extraction process, each section of the data extraction sheet was checked by the co-authors of this paper. Each co-author took responsibility for checking different sections of the data extraction form.

Data Synthesis

Comprehensive Meta-Analysis (Borenstein et al., 2005) was used to calculate effect sizes reflecting the relationship between measures of PC and measures of health behaviors. Effect sizes were calculated based on correlation co-efficients and, when not available, were based on other statistical information (e.g., beta or *p*-values). Effect sizes were meta-analyzed within studies when necessary (e.g., when the same variables were assessed at multiple time-points; when different measures of the same behavior were taken in the same study etc.). Effect sizes were combined across studies, where appropriate, using random effect models (where each study estimates different underlying effect sizes) rather than fixed effects models (where all studies are assumed to be estimates of the same one true effect size) because (1) we assumed that the true effect should vary across studies because they differ in critical ways (e.g., type of behavior; type of PC) and (2) our sample of studies, selected systematically, should reflect a random sample of the relevant distribution of effects.

After considering the overall association between PC (worry and rumination) and health behaviors, additional analyses were conducted to identify the association between different types of

TABLE 1 | Overview of included studies.

Lead authors, year	Design	Location	Setting	Behavioral domain	Type of PC	Measure of PC	Pps included in Analysis (n)	% Female	Age of Pps (years)
Adrian et al., 2014	Prospective	US	School	Substance use	Rumination (brooding and reflection)	RRS[a]	428	48%	12–16
Aldridge-Gerry et al., 2011	Daily diary	US	University	Alcohol consumption	Emotional rumination	Factor analysis Roesch et al., 2010 of Brief COPE, children's coping strategies checklist & how i coped under pressure scale to produce emotional rumination factor	365	69%	Mean = 20 (*SD* = 2)
Bernat et al., 2015	Cross-sectional	US	University	Physical activity	Dispositional cancer worry	Brief worry scale & revised impact of events, intrusive thoughts subscale	451	100%	Mean = 20 (*SD* = 3)
Ciesla et al., 2011	Cross-sectional	US	University	Alcohol consumption	Rumination, angry rumination and worry	RRS, angry rumination scale and PSWQ[b]	447	65%	80% 18–20, 10% 21–25, 2% 25+
Cropley et al., 2012	Cross-sectional	UK	Workplace	Eating	Rumination	Measure of "switching off from work"	268	59%	Mean = 37 (*SD* = 13)
Dijkstra and Brosschot, 2003	Prospective	Netherlands	Home	Smoking cessation	Health worry*	4 items developed (worry about the physical consequences of smoking)	704 (380 smokers, 324 ex-Smokers)	Smokers (71%); Ex-Smokers (67%)	Smokers (16–80, mean = 44); Ex-Smokers (15–78, mean = 45)
Dvorak et al., 2011	Cross-sectional	US	Online	Smoking cessation*	Rumination	Depressive rumination subscale of RRS	53	79%	Mean = 20 (*SD* = 3)
Ferrer et al., 2013a	Cross-sectional	US	Home	Eating	Health-related worry*	1 item developed (worry about overall health in past year)	3397	52%	31% 18–34, 36% 35–54, 33% 55+
Ferrer et al., 2013b	Cross-sectional	US	Home	Eating and physical activity*	Cancer-related worry*	1 item developed (worry about cancer)	10,230	52%	Mean = 45 (*SD* = 0.06)
Frone, 2015	Cross-sectional	US	Home	Alcohol consumption	Rumination*	Negative and positive work rumination scale developed**	2831	47%	Mean = 41
Harwell et al., 2011	Cross-sectional	US	University	Alcohol consumption	Anxious rumination	Anxiety rumination questionnaire adapted from rumination on sadness scale	113	82%	Mean = 26
Li et al., 2009	Prospective	US	Home	Physical activity	Health worry*	1 item developed (worry about health in past year)	7527	62%	Mean = 77 (*SD* = 6)
Malmi et al., 2010	Case-control	Finland	Home	Prostate cancer screening (objective measure)	Worry*	3 items developed (worry about urinary continence and bowel and sexual function)	423	0%	Attended Screening (mean = 60, *SD* = 4); Non-Attenders (mean = 61, *SD* = 5)

(Continued)

TABLE 1 | Continued

Lead authors, year	Design	Location	Setting	Behavioral domain	Type of PC	Measure of PC	Pps included in Analysis (n)	% Female	Age of Pps (years)
Rutten et al., 2011	Cross-sectional	US	Home	Smoking*	Cancer worry*	2 items developed (worry about lung cancer and fear of screening)	1765 (918 never smoked, 524 former smokers, 323 current smokers)	By smoking status: Never smoked (61%); Former smokers (47%); Current Smokers (46%)	Never Smoked (35% 18–34, 30% 35–49, 21% 50–64, 14% 65+); Former smokers (13% 18–34, 27% 35–49, 34% 50–64, 26% 65+); Current Smokers (39% 18–34, 34% 35–49, 19% 50–64, 8% 65+)
Shoal et al., 2005	Prospective	US	University	Substance use	Worry	6 items from STAI[c] assessing intrusive thought and worries items from CBCL[d] (combined to form worry measure)	257	0%	T1 (mean = 11, *SD* = 1); T2 (mean = 16, *SD* = 1)
Swayampakala et al., 2013	Longitudinal	Mexico	Home	Smoking*	Health worry*	1 item developed (worry about whether smoking will damage health)	1206	32%	18 or over
Willem et al., 2011	Cross-sectional	Belgium	School	Substance use	Rumination (brooding and reflection)	RRS	189	50%	Mean = 17 (*SD* = 1)
Willem et al., 2014	Longitudinal	Belgium	School	Substance use	Rumination (brooding and reflection)	RRS	216	38%	Mean = 17 (*SD* = 1)
Yong et al., 2014	Longitudinal cohort	Australia, Canada, UK, US	Home	Smoking cessation	Health Worry*	Items not described (worry about damage from smoking)	5065	By age group: 18–24 (89%), 25–39 (68%), 40–54 (66%), 55+ (77%)	18 or over

** measure not validated (or at least one measure not validated if more than one measure of PC or health behavior), ** only the negative scale was analyzed here. [a]Ruminative Responses Scale (Nolen-Hoeksema, 1991), [b]Penn State Worry Questionnaire (Meyer et al., 1990), [c]State Trait Anxiety Inventory (Spielberger et al., 1983), [d]Child Behavior Checklist (Achenbach and Edelbrock, 1983).*

health behavior (health promoting and health risk) and different types of PC (rumination; worry-health; general worry; plus, the related adaptive construct of reflection). In most instances, formal moderation analyses were not conducted because there were studies in which the same participants completed multiple measures (e.g., participants in the study by Cropley et al., 2012, completed measures of health promoting and health risk behaviors; the participants in the study by Ciesla et al., 2011, completed measures of rumination and worry). In terms of the worry measures, it is worth noting that a number of studies included a measure of health-specific worry (e.g., worry about overall health in the past year, or worry about developing cancer) which is distinct from general worry (e.g., I worry too much about making mistakes, about my parents, about things that may happen, and about what others think of me).

Sensitivity analyses were conducted to examine if the results changed when measures that related to quit attempts were removed (given its qualitative difference from standard measures of performing health behaviors; sensitivity analysis 1) or when other types of unique measure were removed (sensitivity analysis 2 excluded the study by Harwell et al., 2011, given they only considered drinking in negative situations rather than drinking across all situations, and removed the measure of affect-related substance use from the effect size calculation for Shoal et al., 2005, for similar reasons). In the case of quit attempts, we felt it was unclear whether a high number of quits is positive (indicative of greater desire to stop smoking) or negative (indicative of more failed attempts). It is also not a clear measure of health behavior (in the same sense as the other measures included); it could be argued to be a measure of "trying" or "motivation." Therefore, we felt it was appropriate to examine in our sensitivity analyses.

In all analyses, a positive correlation reflects an association between increased levels of PC and increased unhealthy behavior (i.e., either more health-risk behavior or less health promoting behavior). A negative correlation reflects an association between increased levels of PC and increased healthy behavior (i.e., either less health-risk behavior or more health promoting behavior).

RESULTS

Overview of Included Studies

The search returned 7504 papers which were screened for inclusion. Screening identified 19 relevant studies (see **Figure 2** and **Table 1**). Of the 19 included studies, 9 measured rumination (emotional rumination: Aldridge-Gerry et al., 2011; rumination: Ciesla et al., 2011; Dvorak et al., 2011; Willem et al., 2011; Cropley et al., 2012; Adrian et al., 2014; Frone, 2015; Willem et al., 2014; angry rumination: Ciesla et al., 2011; anxious rumination: Harwell et al., 2011), 9 studies measured health-related worry (Dijkstra and Brosschot, 2003; Li et al., 2009; Malmi et al., 2010; Rutten et al., 2011; Ferrer et al., 2013a,b; Swayampakala et al., 2013; Yong et al., 2014; Bernat et al., 2015), and 2 studies measured general worry (Shoal et al., 2005; Ciesla et al., 2011). In addition, four studies measured reflection (Willem et al., 2011, 2014; Cropley et al., 2012; Adrian et al., 2014). Note that Ciesla et al. (2011) also measured co-rumination but this was removed as our conceptualization of rumination did not include this and the Cropley et al. (2012) measure of problem-solving pondering was classified as reflection in our analyses.

Health behaviors investigated were alcohol consumption (Shoal et al., 2005; Aldridge-Gerry et al., 2011; Ciesla et al., 2011; Harwell et al., 2011; Willem et al., 2011, 2014; Adrian et al., 2014; Frone, 2015), marijuana use (Shoal et al., 2005; Willem et al., 2011; Adrian et al., 2014; Willem et al., 2014), smoking behavior and cessation (Dijkstra and Brosschot, 2003; Dvorak et al., 2011; Rutten et al., 2011; Swayampakala et al., 2013; Yong et al., 2014), eating behavior (Cropley et al., 2012; Ferrer et al., 2013a,b), cancer screening uptake (Malmi et al., 2010) and levels of physical activity (Li et al., 2009; Ferrer et al., 2013b; Bernat et al., 2015). See **Table 1** for a more detailed overview of the included studies. **Table 2** presents the results of the meta-analyses.

Main Results

Averaging across all types of PC (rumination and worry), behaviors and time-points, PC was initially unrelated with health behaviors, $r = 0.066$, 95% $CI = -0.015$ to 0.147, $Z = 1.599$, $p = 0.110$, with very heterogeneous effect sizes, $Q_{(18)} = 324.562$, $p < 0.001$, $I^2 = 94.454$ (see **Table 2**). However, in the sensitivity analyses, the relationship between PC and health behaviors became significant, albeit still small. Specifically, more PC was associated with unhealthier behaviors (a combination measure of more health risk behaviors/fewer health promoting behaviors), $r = 0.079$, 95% $CI = 0.017$–0.140, $Z = 2.493$, $p = 0.013$ (sensitivity analysis 1), $r = 0.057$, 95% $CI = 0.001$–0.113, $Z = 1.987$, $p = 0.047$ (sensitivity analysis 2).

PC Type

Increases in rumination were associated with unhealthier behaviors (combination measure of more health risk behaviors/fewer health promoting behaviors), $r = 0.103$, 95% $CI = 0.046$–0.160, $k = 9$, $Z = 3.527$, $p < 0.001$. Reflection, $r = -0.008$, 95% $CI = -0.074$ to 0.058, $k = 4$, $Z = -0.231$, $p = 0.817$, and worry, $r = 0.013$, 95% $CI = -0.096$–0.122, $k = 11$, $Z = 0.238$, $p = .812$, were unrelated with health behaviors. The heterogeneity in effect sizes were particularly large for the studies that included a measure of worry, $Q_{(10)} = 217.972$, $p < 0.001$, $I^2 = 95.412$. Comparing the studies that incorporated a measure of worry related to health ($k = 9$) against those that included an alternative measure of worry ($k = 2$), based on random effects models, the effects were similar (health-related worry and health behaviors: $r = 0.019$, 95% $CI = -0.111$ to 0.148, $Z = 0.286$, $p = 0.775$; other worry and health behaviors: $r = -0.002$, 95% $CI = -.142$ to 0.139, $Z = -0.021$, $p = 0.983$; $Q_{(1)} = 0.044$, $p = 0.834$. The results of the sub-group analyses, split by PC type, were influenced little by the sensitivity analyses.

Type of Behavior

PC was unrelated to health promoting behaviors but was significantly related with health risk behaviors. Regarding the latter, increases in PC were associated with increased performance of health risk behaviors. These relationships were consistent across both sets of sensitivity analyses (see **Table 2**).

TABLE 2 | Summary of meta-analyses.

Type of PC	Health Behavior	*k*	*R*	95% CI		*Z*	Sensitivity Analyses: *Z*	
				Lower	Upper		Analysis 1	Analysis 2
All	All	19	0.066	−0.015	0.147	1.599	2.493*	1.987*
Rumination	All	9	0.103	0.046	0.160	3.527***	3.371**	4.886***
Reflection	All	4	−0.008	−0.074	0.058	−0.231	-	-
Worry (all)	All	11	0.013	−0.096	0.122	0.238	0.864	0.850
Worry (health)	All	9	0.019	−0.111	0.148	0.286	0.895	0.895
Worry (other)	All	2	−0.002	−0.142	0.139	−0.021	-	−0.002
All	Health promotion	6	−0.038	−0.101	0.025	−1.181	-	-
All	Health risk	15	0.106	0.005	0.205	2.055*	3.564***	3.160**
Rumination	Health promotion	1	0.000	−0.085	0.085	0.000	-	-
Rumination	Health risk	9	0.122	0.058	0.184	3.758***	3.606***	3.932***
Reflection	Health promotion	1	−0.080	−0.198	0.040	−1.305	-	-
Reflection	Health risk	4	0.012	−0.061	0.085	0.320	-	-
Worry (all)	Health promotion	5	−0.045	−0.120	0.030	−1.188	-	-
Worry (all)	Health risk	7	0.048	−0.113	0.207	0.585	1.495	1.432

*k, number of studies; r, effect size r; 95% CI, 95% confidence interval of effect size r; *p < 0.05, **p < 0.01, *** p < 0.001; Sensitivity Analysis 1: Quit attempts for smoking are excluded from the analyses; Sensitivity Analysis 2: Excludes quit attempts for smoking, Harwell et al. (2011) (negative reinforcement drinking), Shoal et al. (2005) (affect-related substance use measure removed but measure of drug use still incorporated). In the sensitivity analyses, "-" indicates the results match the original analyses.*

PC Type and Behavior

Increases in rumination were associated with increased performance of health risk behavior but not health promoting behavior (though only one study, Cropley et al., 2012, has considered the latter association). Worry and reflection were both unrelated to health promoting and health risk behaviors (though only one study, Cropley et al., 2012, considered the association between reflection and health promoting behaviors). These results did not change substantively in either set of sensitivity analyses.

Publication Bias

Egger's regression coefficient was significant for the relationship between PC and health behaviors (combination of health risk and health promotion behaviors; $p = 0.005$) suggesting some degree of publication bias. To consider the potential impact of these missing studies, Duval and Tweedie's Trim and Fill analyses were conducted. These results suggested that no studies were missing from the left-side of the mean effect but six studies were missing from the right-side of the mean effect. After imputing these, the imputed point estimate, $r = 0.142$, 95% $CI = 0.033$–0.248, suggested, if anything, that the relationship between PC and unhealthy behaviors is slightly stronger than estimated in the main analyses.

DISCUSSION

The main findings of this systematic review and meta-analysis are that increases in PC are associated with increases in health risk behaviors (substance use, alcohol consumption, unhealthy eating, and smoking) that are driven primarily through rumination. In contrast, measures of worry and reflection were not associated with health behaviors. These results are important for a number of reasons. First, they provide partial support for our hypothesis that in Brosschot et al.'s (2006) original PCH, there may be scope for an additional route to pathogenic disease via poorer health behaviors. In this conceptualization, we theorize that rumination about past stressful events will mediate the effects of stressors on health behaviors (particularly those previously shown to be influenced by stress), which will have negative consequences for health outcomes and disease processes.

Second, from a brain-body point of view, the current findings are important in the context of the development of **allostatic load**. McEwen (1998) introduced the concept of allostatic load to capture the wear and tear the body experiences as a result of repeated and prolonged adaption to environmental and psychosocial stressors. He proposed that the long-term impact of stress affects the body at cardiovascular, metabolic, neural, behavioral, and cellular levels. Similar to basic homeostatic systems such as body temperature, the **HPA axis**, the autonomic nervous system and the cardiovascular, metabolic and immune systems protect the body by adapting to internal and external stress. This is known as **allostasis**. However, if the activation of these systems (allostasis) is repeated and prolonged, allostatic load will be experienced in the form of increased stress hormone, immune cell, brain activity, and cardiovascular responses, ultimately, overtime leading to heightened risk of developing disease (McEwen, 1998, 2007). Numerous factors may contribute to the development of allostatic load including genes, early life experiences and disturbances of the sleep-wake cycle (McEwen, 2007). However, McEwen also argues that lifestyle choices such as alcohol consumption, diet, smoking, and exercise, that may be learned overtime (and triggered by PC), contribute to allostatic load by influencing the reactivity of the biological systems that release the physiological stress mediators (e.g., cortisol,

adrenaline, blood pressure, heart rate, immune cells). In other words, environmental and psychosocial stressors give rise to PC, which in turn triggers maladaptive behavioral responses that may influence and exacerbate the prolonged stress response as conceptualized in the PCH, leading to increased risk of disease. Moreover, we also contend that the relationship between the prolonged stress response and health behaviors may be bi-directional (see **Figure 1**). Interestingly, in the short term, engaging in health risk behaviors such as comfort eating or alcohol consumption (triggered by stressors and then PC) may be perceived by individuals as beneficial, however, overtime these behaviors are likely to be damaging for health.

In addition to the PC-induced health behavior-prolonged stress response pathway, it is highly likely that PC-induced health risk behaviors will directly impact on pathogenic states such as changes in somatic health outcomes (see second dashed pathway in **Figure 1**). For example, for eating behavior, it is well established that stress (and possibly PC) contributes directly to diseases like cardiovascular disease and obesity risk to the extent that it produces deleterious changes in diet and helps maintain unhealthy eating behaviors (O'Connor et al., 2015). In terms of physical activity, a recent systematic review and meta-analysis, showed that greater time spent sedentary was linked to increased risk of diabetes, cardiovascular events, cardiovascular mortality, and all-cause mortality (Wilmot et al., 2012). Therefore, again the extent to which PC can disrupt habitual health behaviors such as exercise, eating behavior, alcohol consumption, and smoking, is likely to increase its direct effects on behavioral mediated changes in pathogenic states.

Nevertheless, we recognize that the current results ought to be considered preliminary at this stage precluding any firm conclusions. We are mindful that our analyses did not find evidence that worry about feared future events was associated with health behaviors. This is surprising given that worry has been identified as important in recent narrative reviews and meta-analyses in the context of the PCH (Verkuil et al., 2010; Ottaviani et al., 2015). A likely explanation for the absence of a significant effect here might be related to the heterogeneity of effect sizes across the studies and/or to do with the variability in types of worry measures utilized (e.g., health-related worry, cancer worry, trait worry, etc. as well as single-item vs. multi-item measures). Alternatively, this null finding may reflect that there are relatively few studies that have directly investigated the relationship between worry (and rumination) and health risk and health promoting behaviors. In many of the studies reviewed, exploring the relationship between worry (and rumination) has been of secondary interest. It might also be that worry, triggered by fear-appeals, has the capacity to promote some health behaviors, thereby, contributing to the observed mixed findings (Tannenbaum et al., 2015). We also acknowledge that limiting our search strategy to studies published from 1990 onwards may have resulted in our missing some important studies. However, we feel the potential impact of this approach is likely to be fairly minimal given that of the articles included in our review, none were published prior to 2003, suggesting few, if any, studies published prior to 1990 would have met our inclusion/exclusion criteria.

We hope the current findings will spur on PC researchers to include measures of health behaviors in their future studies and to adopt a myriad of different approaches to investigate the precise processes and mechanisms through which PC is linked to health behaviors in the context of the PCH. It is likely that these processes will differ dependent on the nature of the health behavior (i.e., health risk vs. health promoting, frequency of the behavior etc.) and in relation to the type of PC (rumination vs. worry; health-related worry vs. general worry etc.). Future research ought to attempt to replicate the current findings utilizing innovative techniques such as ecological momentary assessment, diary methods and time-lagged designs in combination with measures of the physiological concomitants of PC (Verkuil et al., 2012; Gartland et al., 2014). There is also scope to manipulate PC in carefully controlled laboratory studies in order to investigate whether changes in PC are associated with changes in health behaviors (such as food intake; cf., Newman et al., 2007).

In conclusion, this systematic review and meta-analysis showed that increases in PC are associated with increases in health risk behaviors (substance use, alcohol consumption, unhealthy eating, and smoking) that are driven primarily through rumination. These findings provide partial support for our hypothesis that in Brosschot et al.'s (2006) original PCH, there may be scope for an additional route to pathogenic disease via poorer health behaviors.

Key Term	Definition
Worry	Negative, repetitive cognitions regarding feared future events
Rumination	Negative, repetitive thoughts regarding feelings and problems (past-focused)
Perseverative Cognition	Negative, repetitive, cognitive representations of past stressful events or feared future events
Allostatic Load	The wear and tear the body experiences as a result of repeated and prolonged adaption to environmental and psychosocial stressors
Allostasis	When the autonomic nervous system and the cardiovascular, metabolic and immune systems protect the body by adapting to internal and external stress
Hypothalamic-Pituitary-Adrenal-Axis (HPA Axis)	Biological feedback loop between the hypothalamus, pituitary gland and adrenal glands which controls the body's stress response

AUTHOR CONTRIBUTIONS

DO, FC, and AP conceived of the systematic review and meta-analysis. FC and LC conducted the data extraction and

coding with input from AP and DO. AP and FC performed the meta-analysis. DO, AP, and FC drafted the manuscript. All authors approved the final version and agree to be accountable for this work.

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Comparative Autonomic Responses to Diagnostic Interviewing between Individuals with GAD, MDD, SAD and Healthy Controls

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Dysregulation of the autonomic nervous system (ANS) has been well documented in individuals diagnosed with a range of psychological disorders, including generalized anxiety disorder (GAD) and major depressive disorder (MDD). Moreover, these disorders both confer an increased risk of cardiovascular disease—which may relate to increased sympathetic and decreased parasympathetic tone. Extant research has indicated a reduction in autonomic flexibility in GAD, and while reduced flexibility has also been seen in MDD, the specific physiological alterations have been more difficult to categorize due to methodological limitations, including high co-morbidity rates with anxiety disorders. Prior studies have largely assessed autonomic functioning in stress paradigms or at the trait level, yet to date, no research has investigated the ANS during a diagnostic interview, a ubiquitous task employed in both research and clinical settings. In this study we sought to identify physiological differences in both branches of the ANS across diagnostic categories in the context of a diagnostic interview. Participants (n = 82) were administered a structured clinical interview, during which heart rate (HR), respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP) were recorded in participants carrying a diagnosis of GAD (n = 34), MDD (n = 22), Social Anxiety Disorder (SAD; n = 15) and healthy controls (n = 27). Person-specific linear regression models were employed to assess the level and slope for HR, RSA and PEP throughout the course of the interview. A multivariate analysis of variance (MANOVA) model was conducted to baseline differences in HR, RSA and PEP between diagnostic groups. Multiple regression models were then conducted to differences in slope of HR, RSA and PEP throughout the course of the interview amongst diagnostic groups, including both suppression and worry as moderators. Results indicated significant increases in RSA throughout the interview in MDD (p = 0.01) compared to healthy controls. Worry itself was found to be a more significant predictor of both decreased PEP (p = 0.02) and increased HR (p = 0.05). Suppression exhibited a dampening effect on individuals with worry and GAD, whereby those who suppressed had dampened HR responsiveness compared to those who did not suppress. These findings are consistent with existing literature supporting a decreased autonomic flexibility in certain psychological disorders, as well as indicate distinct physiological differences across certain transdiagnostic features of mood and anxiety disorders.

Keywords: clinical interview, perseverative cognition, autonomic nervous system, generalized anxiety disorder, major depressive disorder

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INTRODUCTION

The autonomic nervous system (ANS) is a principal driver of physiologic regulation (Berntson and Cacioppo, 2007), helping to facilitate adaptive responses to environmental demands. Under even moderate stress conditions such as mental arithmetic (Sloan et al., 1991) or social stress tasks (Nater et al., 2006; Hellhammer and Schubert, 2012), inhibitory signals from the parasympathetic nervous system (PNS) are typically downregulated and sympathetic nervous system (SNS) arousal upregulated as a part of an adaptive stress response. Research has consistently shown, however, that individuals with generalized anxiety disorder (GAD) exhibit reduced autonomic flexibility (Hoehn-Saric and McLeod, 2000)—muted PNS and SNS responses to experimental and ecological stress (Thayer et al., 1996; Hoehn-Saric et al., 2004; Fisher et al., 2010; Fisher and Newman, 2016). Rigid or inflexible ANS responsiveness may inhibit adaptive responses to environmental demands, and autonomic rigidity has been considered an indicator of poor health and has been associated with increased susceptibility to cardiovascular disease (Thayer and Lane, 2007). Autonomic inflexibility has also been seen in major depressive disorder (MDD; Udupa et al., 2007; Koschke et al., 2009), although evidence has suggested that reduced PNS activity in MDD is a result of high comorbidity rates with anxiety disorders, rather than an effect of depression itself (Friedman, 2007; Rottenberg, 2007). Nevertheless, there is evidence that individuals with mood and anxiety diagnoses exhibit regulatory impairments in autonomic functioning.

Although the traditional doctrine of autonomic reciprocity has heuristic value in understanding the counteracting up-regulation of SNS activity and down-regulation of PNS activity during stress, Berntson et al. (1991) have demonstrated that the PNS and SNS exist on independent axes. Thus, researchers investigating stress responsiveness should capture concurrent measurements of parasympathetic and sympathetic indices in order to investigate potential patterns of activation. As a target organ that is dually-innervated by PNS and SNS efferents and easily captured via cardiographic methods, the heart is an ideal and widely measured basis for assessing the concurrent influences of the SNS and PNS. The primary source of increased cardiovascular reactivity during stress is drawn from increased SNS activity (Hjemdahl et al., 1989), as the SNS predominantly regulates changes in heart rate (HR) during periods of increased metabolic demand. A measure of cardiac sympathetic control, cardiac pre-ejection period (PEP), can be continuously acquired through thoracic impedance cardiography (ICG). PEP is defined as the period between electrical invasion of the ventricular myocardium (Q wave of the ECG) and the opening of the aortic valve, and is obtained by measuring the period of time between depolarization of the left ventricle of the heart and the onset of ejection of the blood into the aorta. Shorter PEP reflects increased sympathetic activation. Conversely, parasympathetic regulatory influences predominate cardiac control at rest. These signals are inferred via the calculation of respiratory sinus arrhythmia (RSA) from the interbeat intervals of the ECG signal. RSA is the fluctuation of heart period related to respiratory oscillations, and is used as a proxy measurement for parasympathetic control, given that vagal signaling cannot be directly measured or observed in humans.

Investigations of autonomic regulation in mood and anxiety populations have employed a number of methods for stress induction, including the Trier social stress task (Hellhammer and Schubert, 2012), mental arithmetic and other performative challenges (Fisher and Newman, 2013), emotionally-evocative images and video (Fisher et al., 2010), as well inductions of worry and perseverative cognition (Borkovec and Hu, 1990). Defined by Brosschot et al. (2006) as the repeated or chronic activation of the cognitive representation of one or more physiological stressors, perseverative cognition encompasses elements of both worrisome thinking and rumination, putative cardinal features of both GAD and MDD, respectively. Utilizing this broader terminology, researchers have shown that perseverative cognition is associated with lower levels of cognitive flexibility and increased autonomic rigidity (Ottaviani et al., 2013, 2016), elucidating a possible connection between cognitive processes and ANS dysfunctions.

Worry itself, regardless of diagnosis, has also been related to diminished stress reactivity (see Borkovec and Hu, 1990). Worrisome thinking prior to exposure to phobic imagery has been shown to inhibit cardiovascular response in anxious individuals (Borkovec and Hu, 1990; Borkovec et al., 1993; Llera and Newman, 2010) and, in a laboratory setting, worry inductions have been shown to lead to dampened RSA in both anxious and non-anxious individuals (Lyonfields et al., 1995; Thayer et al., 1996). Furthermore, in healthy adults, experimentally-induced worry has been shown to predict higher HR and lower RSA when compared to a non-worry resting baseline (Verkuil et al., 2009), and lastly, in an ambulatory study of healthy adults, worry consistently predicted higher HR and lower RSA during waking, and the duration of worry significantly predicted lower RSA in both waking and sleeping conditions (Brosschot et al., 2007). Thus, there is strong evidence to suggest a potential causal relationship between worrisome thinking and diminished ANS responsiveness.

Brosschot et al.'s 2006 perseverative cognition hypothesis presents a coherent framework for understanding the association between cognitive representations of stressful events and ANS changes. Consistent with Lazarus' paradigm-shifting proposal that stress reactions can result from purely psychological representations of threat (see Lazarus and Folkman, 1984), the perseverative cognition hypothesis posits that stress reactions can occur regardless of a stressor's presence. Thus, individuals can form mental representations of stressful events both before and after the events are meant to happen, even if the events do not actually occur. In turn, normative physiologic stress responses can result from these cognitive representations. A number of theoretical and empirical observations have supported this hypothesis (Borkovec and Hu, 1990; Lyonfields et al., 1995; Thayer et al., 1996; Aldao et al., 2014).

Perseverative cognition as an emotion regulation strategy has been posited as a vehicle of experiential avoidance (Borkovec et al., 2004; Roemer et al., 2005; Tull et al., 2011). In particular, experiential avoidance theories of worry in GAD propose that because individuals with GAD find emotionally-evocative experiences threatening, worry is employed to suppress negative emotionality (Mennin et al., 2005), provide distraction from emotional topics (Borkovec and Roemer, 1995) and preclude the emotional processing of fearful stimuli (Borkovec et al., 2004). Perhaps foremost of these theories is Borkovec's Avoidance Model of Worry (Borkovec, 1994; Borkovec et al., 2004), which proposes that worry is a verbal-linguistic cognitive process that prevents engagement with more emotionally-evocative mental imagery and thus distracts worriers from more emotional topics (Borkovec and Roemer, 1995).

Physiologic data support the theory that worry suppresses engagement with—or at least the somatic experience of—negative emotions, as stated previously. Moreover, this effect has also been extended outside of GAD. Speech-anxious individuals who engaged in worrisome thinking prior to a public speaking exposure showed lesser cardiovascular reactivity compared to those who did not worry prior to exposure (Borkovec and Hu, 1990), and levels of self-reported worry across healthy control and GAD participants negatively predicted the degree of HR reactivity to a laboratory stress paradigm (Fisher and Newman, 2013). Thus, there is consistent support for the notion that perseverative cognition suppresses physiologic reactions to stress. Yet, there is also evidence that individuals with GAD, MDD and social anxiety disorder (SAD; Amstadter, 2008; Spokas et al., 2009; Beblo et al., 2012) engage in emotion regulation strategies beyond perseverative cognition, including emotional suppression, an overt and specific form of emotional avoidance that involves the conscious inhibition of emotional experiences during emotionally-evocative events or experiences (Gross and Levenson, 1993). Suppression is often characterized as ineffective and maladaptive, with associated deleterious effects such as memory impairment (Richards and Gross, 1999, 2000), reduced cognitive abilities (Richards and Gross, 1999) and decreased emotionally-expressive behavior. Consistent with experiential avoidance, emotional suppression has been shown to result in attenuated HR reactivity for fear and disgust (Gross and Levenson, 1993; Gross, 1998; Sloan, 2004; Reynaud et al., 2012).

Several research paradigms have attempted to leverage the Lazarus model of stress to investigate the physiologic stress response by inducing or invoking stress-related cognitive representations through worry (Fisher and Newman, 2013) or other imaginal procedures (Ottaviani et al., 2015). Yet, a compelling and relevant area that has received little empirical attention is the clinical diagnostic interview. During clinical interviews such as the Structured Clinical Interview for the DSM (SCID; First, 1995) and Anxiety and Related Disorders Interview Schedule (ADIS; Brown and Barlow, 2014), interviewers ask interviewees to bring to mind thoughts, feelings and experiences that reflect potential underlying psychopathology. For those who meet clinical criteria, such pathology is inherently distressing—a condition required by the Diagnostic and Statistical Manual of Mental Disorders, fifth Edition (DSM-5) to meet diagnostic criteria (American Psychiatric Association, 2013). Anecdotally, both researchers and clinicians have presupposed that clinical diagnostic interviews are stressful to interviewees (Lichstein, 1990), however; to our knowledge no one has examined this empirically to date.

The goals of the present study were to examine the potentially stressful nature of clinical diagnostic interviews in order to assess the degree to which these interviews induce physiologic stress reactions. Due to the high comorbidity rates among mood and anxiety disorders, we assessed for the presence vs. absence of three relevant diagnoses—GAD, MDD and SAD—allowing for overlapping co-occurrence, rather than investigate primary diagnoses. Thus, we were interested in distinguishing the shared and unique contributions of these diagnoses on ANS functioning. Given the robust research literature on diminished physiological flexibility in GAD, we were primarily interested in examining the relative reactions in individuals with a diagnosis of GAD compared to healthy controls, however we included individuals with MDD and SAD in order to further isolate the potentially unique contributions of GAD pathology to diminished physiological flexibility, when compared to diagnostically and phenomenologically similar diagnoses. Additionally, because worry has been specifically implicated as a suppressant of autonomic reactivity, we were interested in the degree to which *worry itself*, regardless of diagnosis, would possibly affect observable ANS responsiveness. Finally, due to previous findings of attenuated HR reactivity with emotional suppression, we were interested in examining the additional contribution of emotion suppression to the phenomenology and physiologic reactivity of individuals with GAD, MDD, SAD and healthy controls.

Individuals with principal diagnoses of GAD, MDD, SAD and healthy controls completed the ADIS-5 semi-structured clinical interview. During this interview electrocardiography (ECG) and ICG were measured in order to obtain HR, RSA and PEP. We examined the effect of: (1) the presence of any psychological diagnosis vs. healthy controls; (2) the presence of specific GAD, MDD and SAD diagnosis; (3) the effect of worry; and (4) the effect of suppression on trajectories of HR, RSA and PEP across the interview. The present study represents an exploratory examination of the degree to which clinical diagnostic interviews engage with and map onto psychological representations of stressful experiences and the potential effects of transdiagnostic features (i.e., worry, suppression) on such experiences.

MATERIALS AND METHODS

Participants

The sample was composed of 82 participants: 24 individuals with a primary diagnosis of GAD, 18 individuals with a primary diagnosis of MDD, 13 individuals with a primary diagnosis of SAD and 27 healthy controls who did not meet criteria for any DSM-5 diagnoses. **Table 1** provides participant

TABLE 1 | Participant characteristics by principal diagnosis.

	Control (*n* = 27)	GAD (*n* = 24)	MDD (*n* = 18)	SAD (*n* = 13)
Age	Mean: 34.46 *SD*: 14.59	Mean: 32.50 *SD*: 12.11	Mean: 35.28 *SD*: 14.98	Mean: 26.38 *SD*: 10.06
Sex	Male: *n* = 10 (37%) Female: *n* = 17 (63%)	Male: *n* = 8 (33%) Female: *n* = 16 (67%)	Male: *n* = 7 (39%) Female: *n* = 11 (61%)	Male: *n* = 3 (23%) Female: *n* = 10 (77%)
Education	Median = 4	Median = 4	Median = 4	Median = 4
BMI	Mean = 24.81 SD = 4.91	Mean = 24.81 SD = 5.82	Mean = 27.24 SD = 13.48	Mean = 22.85 SD = 6.90

Note: GAD, Generalized Anxiety Disorder; MDD, Major Depressive Disorder; SAD, Social Anxiety Disorder; BMI, body mass index. Education coded as: 3 = "some college", 4 = "4 year college degree".

characteristics by group. Of the 82 participants, 44% were Caucasian (*n* = 36), 21% were Asian American (*n* = 17), 17% were Latino (*n* = 14), 9% were African American (*n* = 7), 4% were Native American (*n* = 3) and 6% designated their cultural background as "other" (*n* = 5). Twenty-two of the participants who met criteria for a clinical disorder also met diagnostic criteria for at least one comorbid Axis I disorder (GAD, *n* = 10; MDD, *n* = 4; SAD, *n* = 3; bipolar disorder, *n* = 2; agoraphobia, *n* = 1; panic disorder, *n* = 1; posttraumatic stress disorder, *n* = 1), resulting in a sample of 34 individuals carrying a diagnosis of GAD, 22 individuals carrying a diagnosis of MDD and 15 individuals carrying a diagnosis of SAD. Participants were recruited by the use of flyers and craigslist advertisements, and underwent a phone screening before being included in the study. Exclusion criteria were: not being between the ages of 18 and 65, not having English proficiency (both written and spoken), not being able to commute to the UC Berkeley Campus, not having regular access to a mobile phone that receives text messages, has internet access, and has a touchscreen, and having current CBT or having had CBT in the past year. All participants consented to the study, and were compensated for their time ($35). IRB approval was obtained by the University of California, Berkeley Institutional Review Board. Verbal consent was obtained during the first phone screening to rule out exclusionary criterion. Written consent was obtained upon the first lab visit, prior to any experimental procedures.

Procedure

After a pre-screening phone interview, participants came into the lab, read and signed the informed consent form, and completed a series of questionnaires covering psychopathological constructs and socio-demographics (biological sex, age, income, race, ethnicity, religion, marital status, occupational history and education). Following this, participants were outfitted with electrodes for measurement of peripheral physiology, (see below), and completed the Anxiety Disorders Interview Schedule (ADIS-IV; Brown et al., 1994), administered by a graduate student or post-graduate research assistant. The ADIS-IV is a semi-structured interview developed to establish differential diagnoses of anxiety and mood disorders, and has excellent retest reliability and high interrater reliability (Brown et al., 2001). Assessors also completed the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959), Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) and CSRs for GAD and comorbid disorders. Following the interview, participants received monetary compensation.

Measures

Self-report measures collected prior to diagnostic interview included the following: the emotion regulation questionnaire and Penn State worry questionnaire.

Emotion Regulation Questionnaire (ERQ10; Gross and John, 2003)

The ERQ10 measures participants' tendency to regulate their emotions in two ways: (1) cognitive reappraisal; and (2) expressive suppression. Participants respond to each item on a 7-point likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). Previous analyses on the ERQ10 have indicated alpha reliabilities of 0.79 for reappraisal and 0.73 for suppression, and test-retest reliability across 3 months was 0.69 for both scales (Gross and John, 2003).

Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990)

The PSWQ is a 16 item self-report measure of pathological worry. Factor analysis indicated that the PSWQ assesses a unidimensional construct with internal consistency of 0.91 (Meyer et al., 1990). High retest reliability (ranging from 0.74 to 0.93) has also been demonstrated across periods ranging from 2 to 10 weeks (Molina and Borkovec, 1994).

Physiological Recordings

HR and RSA data acquisition followed standard guidelines (Berntson et al., 1997) using a Bioamp data acquisition system (MindWare Technologies, Inc., Gahanna, OH, USA). Disposable silver/silver-chloride (Ag-AgCl) electrodes were placed on participants. For the electrocardiogram (ECG), electrodes were placed on participant's right collarbone and 10th-left and right ribs. For ICG, two voltage electrodes were placed below the suprasternal notch and xiphoid process, and two current electrodes were placed on the back 3–4 cm above and below the voltage electrodes. All electrodes were placed by a same-sex RA. ECG and ICG were recorded throughout the duration of the clinical interview at a sampling rate of 500 Hz.

RSA was scored and quantified by extracting the high frequency spectral component of the R-R peak time series

(0.15–0.40 Hz). Artifacts were detected and corrected manually using standard procedures (Berntson et al., 1997). RSA was then derived using spectral analysis (Berntson et al., 1997), using 30-s epochs.

Cardiac PEP was derived from the ECG and ICG in 30 s epochs, using MindWare ICG V. 2.3. PEP was indexed as the time interval in milliseconds from the onset of the Q-wave to the B point of the dZ/dt wave, using validated methods (Berntson et al., 2004). Using the software, artifacts were examined and removed via visual inspection.

Approach to Statistical Analyses

Linear trajectories for changes in HR, RSA and PEP during diagnostic interviewing were assessed on a person by person basis via ordinary least squares regression. A regression model was conducted for each individual such that time-varying HR, RSA and PEP values were regressed on time (epoch number). The standardized regression coefficients were then extracted and aggregated into a standard nomothetic data set in order to assess individual differences in slopes per study hypotheses.

To evaluate the effects of diagnosis on baseline HR, RSA and PEP, a multivariate analysis of variance (MANOVA) was conducted for differences in HR, RSA and PEP during the introductory module of the ADIS-5, while controlling for sex and age.

To investigate the effect of clinical diagnoses on physiologic stress responses to the diagnostic interview, three multiple regression models were conducted for HR, RSA and PEP, respectively, with GAD, MDD and SAD as predictors. We covaried age, sex and baseline levels of the dependent variable as control variables. To examine the moderating role of suppression in GAD, MDD and SAD, for each model we tested the moderating role of suppression via an interaction term between diagnosis and the ERQ suppression subscale.

To examine the role of worry on physiological functioning in GAD, MDD and SAD, three multiple regression models were conducted for HR, RSA and PEP respectively, with worry as a predictor. Worry was defined as PSWQ score. We covaried age, sex and baseline levels of the dependent variable as control variables. Again, to examine the role of emotional suppression on worry, for each model we tested the moderating role of suppression via an interaction term between diagnosis and the ERQ suppression subscale. All statistical analyses were performed in R 2.1 (R Core Team, 2015).

RESULTS

Preliminary Analysis of Baseline Differences

In order to examine baseline differences in autonomic arousal across individuals with GAD, SAD, MDD and healthy controls, a MANOVA was conducted for differences in HR, RSA and PEP during the introductory module of the ADIS-5, while controlling for sex and age. Results of the MANOVA revealed that age ($F_{(3,67)} = 17.77$, $p < 0.001$) was a significant predictor of baseline differences with no significant effects for sex ($F_{(3,67)} = 0.50$, $p = 0.69$), GAD ($F_{(3,67)} = 1.04$, $p = 0.38$), MDD ($F_{(3,67)} = 1.18$, $p = 0.32$) or SAD ($F_{(3,67)} = 1.73$, $p = 0.17$). *Post hoc* univariate analyses revealed that age was a significant, positive predictor of RSA at baseline ($F_{(5,76)} = 8.35$, $p < 0.001$).

Assessing Differences Amongst Clinical Groups vs. Healthy Controls on the Moderating Role of Suppression in HR, RSA and PEP across Diagnostic Interview

In order to investigate the presence of physiologic stress responses to the diagnostic interview, three multiple regression models were conducted for RSA, PEP and HR trajectories, respectively. For each model, in addition to testing the main effects for group differences between healthy controls and those with the presence of GAD, MDD and SAD diagnoses, we covaried age, sex and baseline levels of the dependent variable as control variables. Given our hypothesis related to the role of emotional suppression, for each model we tested the moderating role of suppression via an interaction term between GAD, MDD and SAD and the ERQ suppression subscale. Results for both the main effect and interaction models are presented in **Table 2**.

Healthy controls exhibited a significant decrease in RSA throughout the course of the interview. Relative to healthy controls, individuals with MDD exhibited a significant increase in RSA throughout the course of the interview. Coefficients for RSA slope for individuals with GAD and SAD did not significantly differ from health controls. Suppression exhibited a significant main effect, such that higher levels of suppression predicted reductions in RSA across the interview in all participants. Finally, baseline levels of RSA were a significant predictor of RSA slope such that higher levels of RSA at baseline predicted decreased RSA across the interview.

The addition of interactions between suppression and diagnoses explained an additional 7% of the variance, compared to the main effect model ($R^2 = 0.31$, $R^2 = 0.38$, respectively). For healthy controls, those who suppressed exhibited significantly decreased RSA compared to those who did not suppress. Additionally, the interaction between GAD and suppression indicated that individuals with GAD who suppressed had significantly dampened RSA responses compared to healthy controls. No significant moderating effect of suppression was found for MDD or SAD participants. Results of RSA trajectory by group, as a function of emotional suppression, are depicted in **Figure 1**.

Results for PEP indicated that baseline PEP was a significant predictor of PEP slope in both the main effect and interaction models. No other significant predictors were found in the main effect model. However, given small cell sizes among the subgroups under analysis, it is prudent to point to medium effect sizes for healthy controls and individuals with GAD and SAD. These effects reveal that healthy controls appeared to show an increase in PEP across the interview (reflecting a decrease in SNS arousal) and GAD and SAD participants appeared to exhibit relative decreases in PEP (reflecting relative increases in SNS arousal). No moderating effects were found in the interaction model.

TABLE 2 | Regression model for interactions between suppression and clinical diagnosis on physiological responses.

	RSA					PEP					HR				
	beta	SE	*t*	*p*	*d*	beta	SE	*t*	*p*	*d*	beta	SE	*t*	*p*	*d*
Main effect model (R^2 = 0.31; R^2 = 0.26; R^2 = 0.19)															
Intercept	−0.41	0.19	−2.12	0.04	−0.58	0.39	0.20	1.98	0.05	0.54	−0.23	0.19	−1.12	0.23	−0.30
GAD	0.26	0.22	1.18	0.24	0.29	−0.47	0.23	−2.03	0.05	−0.49	0.27	0.22	1.23	0.22	0.30
SAD	0.32	0.31	1.05	0.30	0.38	−0.41	0.34	−1.23	0.22	−0.45	0.32	0.31	1.05	0.23	0.38
MDD	0.68	0.25	2.65	0.01	0.80	−0.22	0.27	−0.82	0.42	−0.25	−0.04	0.25	−0.14	0.89	−0.04
Suppression	−0.23	0.11	−2.04	0.04	−0.32	−0.13	0.12	−1.06	0.23	−0.17	0.15	0.12	1.27	0.21	0.20
Sex (male)	−0.01	0.24	−0.03	0.98	−0.01	−0.11	0.25	−0.46	0.65	−0.10	0.21	0.24	0.90	0.37	0.20
Age	0.02	0.13	0.14	0.89	0.02	0.05	0.12	0.46	0.65	0.07	−0.08	0.11	−0.68	0.50	−0.11
Baseline	−0.36	0.13	−2.82	0.01	−0.44	−0.38	0.12	−3.15	<0.001	−0.49	−0.27	0.11	−2.36	0.02	−0.30
Interaction model (R^2 = 0.38; R^2 = 0.25; R^2 = 0.30)															
Intercept	−0.27	0.20	−1.36	0.18	−0.37	0.42	0.20	2.07	0.04	0.56	−0.38	0.20	−1.96	0.05	−0.53
GAD	0.17	0.22	0.74	0.46	0.18	−0.52	0.24	−2.12	0.04	−0.51	0.37	0.22	1.37	0.10	0.33
SAD	0.34	0.32	1.06	0.30	0.39	−0.34	0.37	−0.93	0.35	−0.34	0.31	0.31	1.00	0.32	0.37
MDD	0.41	0.27	1.52	0.14	0.46	−0.25	0.28	−0.89	0.38	−0.27	0.24	0.26	0.91	0.37	0.27
Suppression	−0.67	0.21	−3.19	<0.001	−0.50	−0.27	0.20	−1.30	0.20	−0.20	0.63	0.20	3.12	<0.001	0.49
Sex (male)	0.12	0.24	0.52	0.61	0.11	−0.07	0.25	−0.26	0.79	−0.06	0.06	0.23	0.28	0.78	0.06
Age	0.06	0.13	0.45	0.65	0.07	0.06	0.12	0.47	0.64	0.07	−0.08	0.11	−0.74	0.46	−0.12
Baseline	−0.29	0.13	−2.32	0.02	−0.36	−0.36	0.12	−3.07	<0.001	−0.48	−0.26	0.11	−2.32	0.02	−0.36
GAD × Supp.	0.51	0.24	2.15	0.04	0.52	0.04	0.25	0.16	0.87	0.04	−0.57	0.22	−2.55	0.01	−0.62
SAD × Supp.	0.54	0.36	1.50	0.14	0.55	0.36	0.40	0.91	0.37	0.33	−0.57	0.35	−1.61	0.11	−0.59
MDD × Supp.	0.28	0.27	1.04	0.30	0.31	0.29	0.29	0.10	0.32	0.03	−0.30	0.26	−1.15	0.26	−0.35

*Note: Reference group = healthy controls; GAD, Generalized Anxiety Disorder; MDD, Major Depressive Disorder; SAD, Social Anxiety Disorder; d = Cohen's d (calculated as d = t * sqrt[2/n]).*

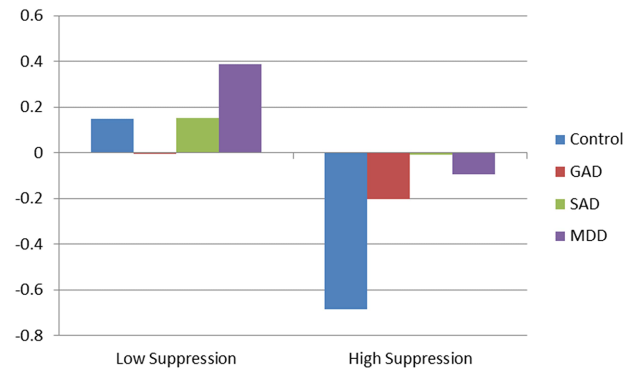

FIGURE 1 | Effect of clinical diagnosis on respiratory sinus arrhythmia (RSA) during diagnostic interview.

Results for the main effect model for changes in HR during the diagnostic interview indicated only a significant effect for baseline HR. Consistent with both RSA and PEP, higher HR at baseline predicted decreases in HR across the interview. However, the addition of interactions between diagnosis and suppression revealed a significant effect of suppression on HR trajectory in healthy controls, such that higher suppression predicted significant increases in HR during the interview. Conversely to this, individuals with GAD with higher levels of suppression exhibited significantly flattened (i.e., muted) HR responses, compared to controls and GAD participants with low levels of suppression. Results of HR trajectory by group, as a function of emotional suppression, are depicted in **Figure 2**.

Assessing Differences in Levels of Worry on the Moderating Role of Suppression in HR, RSA and PEP across Diagnostic Interview

In order to assess the role of worry as a predictor of autonomic responses across the diagnostic interview, each of the analyses reported above were repeated with the dimensional construct of worry severity inserted in the place of clinical diagnosis. We once again covaried age, sex and baseline levels of the dependent variable as control variables. For each model we tested the moderating role of suppression via an interaction term between the PSWQ score and the ERQ suppression subscale. Results for both the main effect and interaction models are depicted in **Table 3**.

Main effects for RSA again revealed a significant effect of baseline RSA, with no additional significant predictors of RSA trajectory. The addition of the interaction between suppression and worry accounted for an additional 10% of the variance, revealing a significant interaction. For individuals with low worry severity, higher levels of suppression predicted reductions in RSA across the interview and lower levels of suppression predicted increases in RSA, however, higher levels of worry severity mitigated these results, promoting muted RSA responses across all levels of suppression. Results of RSA trajectory by worry level, as a function of emotional suppression, are depicted in **Figure 3**.

Worry significantly predicted decreases in PEP throughout the course of the interview, reflecting increases in SNS arousal as a function of worry severity. Baseline levels of PEP were also significant predictors of PEP trajectories, with higher

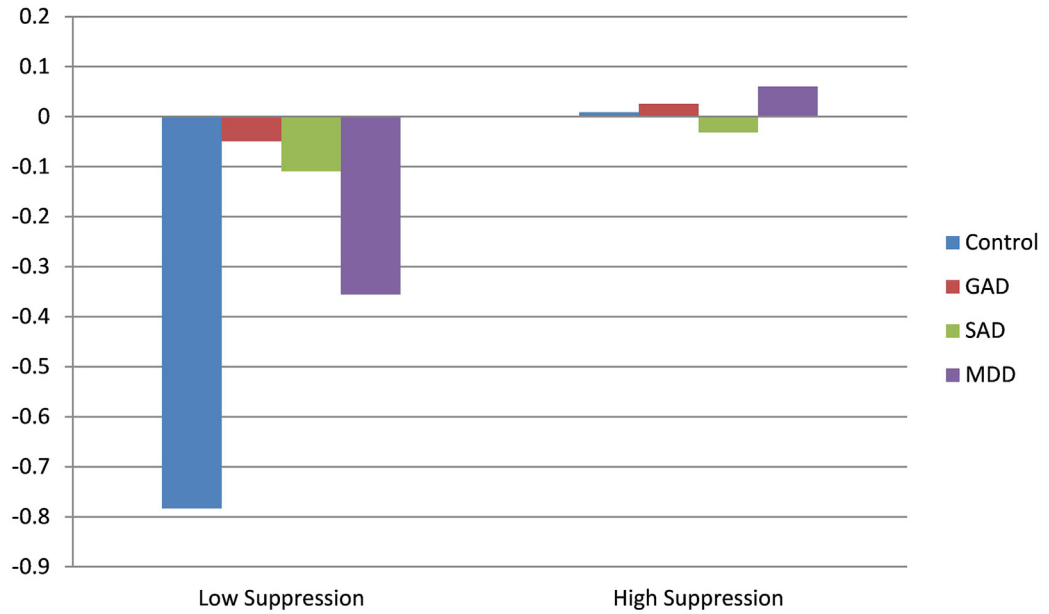

FIGURE 2 | Effect of clinical diagnosis on heart rate (HR) throughout the course of the diagnostic interview.

TABLE 3 | Regression model for interactions between suppression and worry on physiological responses.

	RSA					PEP					HR				
	beta	**SE**	***t***	***p***	***d***	**beta**	**SE**	***t***	***p***	***d***	**beta**	**SE**	***t***	***p***	***d***
Main effect model (R^2 = 0.22; R^2 = 0.31; R^2 = 0.23)															
Intercept	−0.10	0.14	−0.74	0.47	−0.12	0.11	0.13	0.86	0.40	0.13	−0.11	0.13	−0.88	0.38	−0.14
Worry	0.19	0.13	1.50	0.14	0.23	−0.42	0.12	−3.64	<0.001	−0.57	0.27	0.12	2.27	0.03	0.35
Suppression	−0.24	0.12	−1.97	0.05	−0.31	−0.16	0.12	−1.35	0.18	−0.21	0.17	0.11	1.51	0.14	0.24
Sex (male)	0.16	0.26	0.63	0.53	0.14	−0.29	0.24	−1.21	0.23	−0.27	0.27	0.24	1.14	0.26	0.25
Age	0.09	0.14	0.66	0.51	0.10	0.01	0.12	0.08	0.94	0.01	−0.07	0.11	−0.62	0.54	−0.10
Baseline	−0.29	0.14	−2.06	0.04	−0.32	−0.40	0.11	−3.52	<0.001	−0.55	−0.24	0.11	−2.23	0.03	−0.35
Interaction model (R^2 = 0.32, R^2 = 0.32, R^2 = 0.32)															
Intercept	0.00	0.13	0.01	0.99	0.00	0.13	0.13	0.98	0.33	0.15	−0.20	0.12	−1.65	0.10	−0.26
Worry	0.11	0.12	0.86	0.39	0.13	−0.43	0.12	−3.70	<0.001	−0.58	0.35	0.12	3.03	<0.001	0.47
Suppression	−0.33	0.12	−2.78	0.01	−0.43	−0.17	0.12	−1.45	0.15	−0.23	0.26	0.11	2.32	0.02	0.36
Sex (male)	0.06	0.25	0.23	0.82	0.05	−0.31	0.24	−1.29	0.20	−0.28	0.36	0.23	1.59	0.12	0.35
Age	0.11	0.13	0.83	0.41	0.13	−0.00	0.12	−0.02	0.99	−0.00	−0.06	0.11	−0.59	0.55	−0.09
Baseline	−0.24	0.14	−1.78	0.08	−0.28	−0.41	0.12	−3.54	<0.001	−0.55	−0.23	0.10	−2.22	0.03	−0.35
Worry × Supp.	0.35	0.12	2.78	0.01	0.43	0.12	0.11	0.98	0.33	0.15	−0.32	0.11	−2.79	0.01	−0.44

*Note: Reference group, healthy controls; GAD, Generalized Anxiety Disorder; MDD, Major Depressive Disorder; SAD, Social Anxiety Disorder; d = Cohen's d (calculated as d = t * sqrt[2/n]).*

levels at baseline predicting decreases across the interview. The interaction between worry and suppression was not significant.

Results for the main effect model of HR revealed significant effects for worry and baseline HR. Higher levels of worry predicted increases in HR throughout the course of the interview and higher baseline levels of HR predicted decreases in HR. The interaction model indicated a significant effect of suppression, whereby individuals with low levels of worry and low levels of suppression exhibited decreases in HR throughout the course of the interview. Higher levels of worry appeared to mitigate the effect of suppression on HR response, with high worry predicting non-significant change in HR, regardless of suppression level. Results of HR trajectory by worry level, as a function of emotional suppression, are depicted in **Figure 4**.

DISCUSSION

The present study investigated autonomic stress responsiveness in the SNS, PNS and HR during a semi-structured clinical interview in individuals with diagnoses of GAD, MDD, SAD and healthy controls. To our knowledge, this is the first study

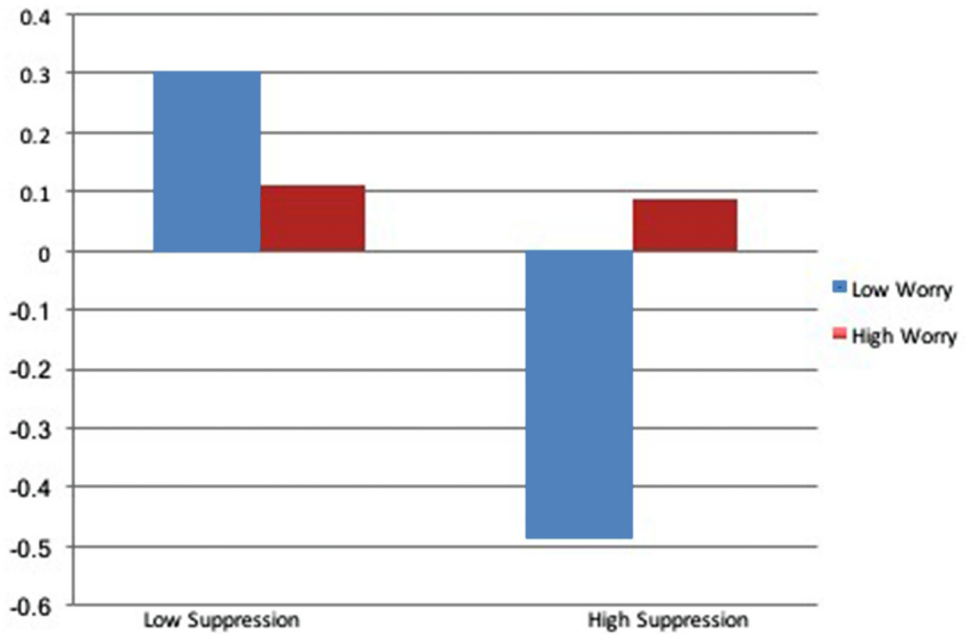

FIGURE 3 | Effect of worry on RSA throughout the course of the diagnostic interview.

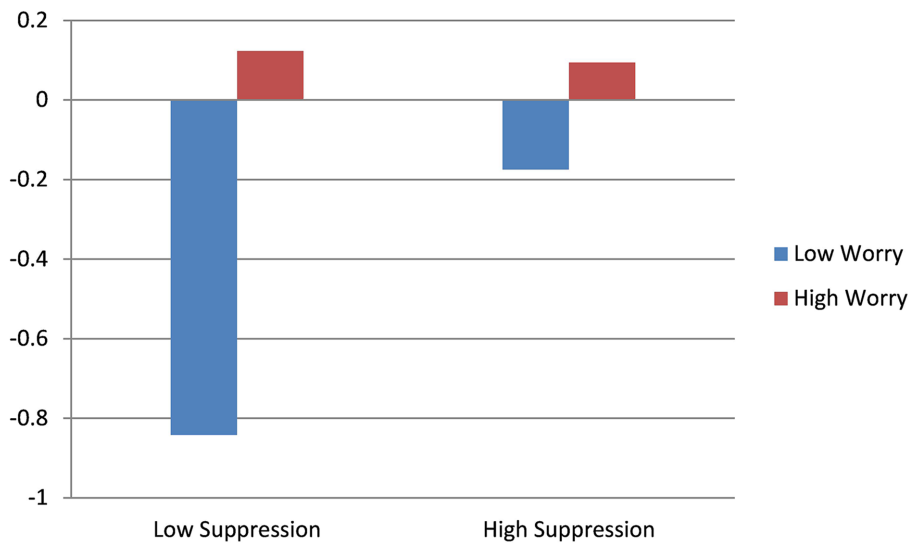

FIGURE 4 | Effect of worry on HR throughout the course of the diagnostic interview.

to directly explore autonomic stress response to a clinical diagnostic interview. Results indicated that baseline levels were significant predictors of RSA, PEP and HR trajectories, such that higher baseline levels predicted regression-to-the-mean reductions in level across the interview. Within the DSM-diagnosis models, there were no additional main or moderating predictors of PEP, although effect sizes indicated that PEP increased in healthy controls and decreased in GAD and SAD participants—indicating possible decreases in SNS arousal in controls and increases in SNS arousal in anxious participants. Suppression was a main and moderating predictor of RSA, such that greater suppression predicted reductions in RSA across all participants in the main effect model. However, the interaction model revealed that suppression predicted strong reductions in RSA for healthy controls, but that this effect was mitigated in individuals with GAD. Similarly, for HR, suppression predicted increased HR trajectories for healthy controls, with this effect mitigated for individuals with GAD. These data provide further

evidence for the presence of physiological rigidity in GAD, which has been well documented in this diagnostic group (Thayer et al., 1996; Hoehn-Saric et al., 2004; Fisher et al., 2010; Fisher and Newman, 2016).

In order to examine the relative contribution of perseverative cognition to physiologic stress responsiveness, we reran analyses for RSA, PEP and HR with the transdiagnostic construct of worry in the place of clinical diagnosis. Consistent with the diagnostic models for HR and RSA, whereas trajectories for HR and RSA in those with low degrees of worry reflected increased stress responsiveness in the presence of higher suppression and decreased stress responsiveness in the absence of suppression, those with high worry exhibited flattened trajectories, regardless of the level of suppression. Also consistent with the DMS-diagnosis models, the interaction between worry and suppression on PEP was non-significant. However, contrary to the diagnostic model, worry was a significant predictor of PEP response, wherein greater worry severity predicted increased SNS arousal during the clinical interview. That worry was predictive of autonomic rigidity across clinical diagnoses suggests that the transdiagnostic feature of worry may be more predictive of a rigid, less flexible autonomic response system than the diagnosis of GAD itself, which is consistent with extant work investigate the effect of worrisome thinking on autonomic responsiveness (Borkovec and Hu, 1990; Borkovec et al., 1993; Llera and Newman, 2010).

As noted above, worry has been shown to preclude robust autonomic response to stress (Lyonfields et al., 1995), with these results extending to populations other than individuals with GAD (Borkovec and Hu, 1990). Our results suggest that engagement with worry employed those attentional and emotional systems that underpin the attenuating effect of GAD diagnosis on autonomic stress responsiveness—that is, the transdiagnostic feature alone had a stronger effect than the GAD diagnosis on measures of cardiac regulation. Though the GAD diagnosis model explained more of the variance, this finding suggests that there may be transdiagnostic features of mood and anxiety disorders, rather than specific, discrete diagnostic categories, that may be the driving physiological responsiveness to threatening or stressful demands. Future research should endeavor to investigate additional transdiagnostic features and their effects on cardiac functioning.

Results further indicated that GAD participants and individuals with high levels of self-reported worry exhibited significantly decreased PEP values over the course of the interview, indicative of greater SNS activation. Increases in RSA were also observed for low suppression GAD participants and participants with high levels of worry. Thus, the present data seem to reflect a coactivation of PNS and SNS responses—at least insofar as the 30-s epoch granularity reflected changes over time—in these individuals. The observed increases in both the PNS and SNS possibly indicate that a SNS stress response elicited a counteracting parasympathetic response. However, a larger sample of individuals with GAD and study methodology specifically aimed at disentangling these effects is likely warranted to support this hypothesis. For instance, future work, assessing the temporal structure of these data, could test the time-lagged cross-predictions between RSA and PEP time series to better understand the directionality of this effect. Additionally, there were both main and interacting effects of emotional suppression on RSA and HR trajectory during the interview for healthy controls and individuals with low levels of self-reported worry, whereby greater emotional suppression *dampened* HR and RSA response. The latter finding is consistent with existing affective literature documenting attenuating effects of emotional suppression on HR (Gross and Levenson, 1993). Again, GAD participants and those with high levels of worry were immune to these attenuating effects, indicative of physiological rigidity.

Taken together, we believe that these findings reflect both how physiologically complex a clinical interview is and how that complexity changes based on diagnostic categories and transdiagnostic features of mood and anxiety disorders. We believe that this is important for many reasons. First, a clinical interview is a ubiquitous task used by researchers and clinicians alike, oftentimes at the start of an empirical study. To understand how that may be affecting the phenomenology and physiology of an individual is crucial—for example, our findings are the first so demonstrate that suppression moderates responses in HR and RSA for healthy controls and individuals with low worry in a diagnostic interview, yet not for GAD participants and individuals with high worry—and this study is, to our knowledge, the first to examine this question. Second, our findings of reduced HR attenuation in high worriers and GAD participants throughout the interview and of the dampened moderating effect of suppression in these groups are consistent with existing literature supporting decreased autonomic flexibility in GAD (Thayer et al., 1996; Hoehn-Saric et al., 2004; Fisher et al., 2010; Fisher and Newman, 2016), while also pointing to worry being a broader preditor of this decreased flexibility, capturing variance across diagnoses. Third, these findings support current conceptualizations of emotional suppression and its effects on physiology for healthy controls and low worriers; these participants who indicated high levels of emotional suppression exhibited smaller physiological changes; that is, their physiological HR responses were diminished as a result of not fully engaging with the interview material. These findings may extend outside of the context of the interview to other situations, suggesting that healthy individuals who suppress may be predisposed to the same deleterious physical effects of autonomic rigidity as high worriers and GAD. Finally, our findings indicate distinct physiological differences across transdiagnostic features of mood and anxiety disorders. While it has been suggested that physiological responses in MDD are due to underlying comorbidities with anxiety disorders, our findings support the notion that differences may be due to shared transdiagnostic features, such as worry or suppression, rather than diagnostic comorbidities.

The present study had some key limitations, including our sample size for MDD and SAD participants being relatively small. As indicated above, trends for changes in HR with suppression were seen in GAD, MDD and SAD groups, yet only GAD was found to be significant. Future work should aim to recruit a larger

sample of SAD and MDD participants. Additionally, we did not assess respiration frequency, which may have a direct influence on autonomic responses. Without controlling for respiration, it may be less clear if changes in RSA are due to changes in the parasympathetic outflow, or due to changes in respiration. Future research should endeavor to include assessments of respiration rate in order to include it is a control variable. Despite these limitations, the current study is among the first to investigate physiologic responses during a clinical diagnostic interview, and provides strong evidence for the complex nature of autonomic functioning in GAD, MDD and SAD participants in response to a diagnostic interview.

AUTHOR CONTRIBUTIONS

All authors contributed extensively to the work presented in this article. AJF designed the experiment. AED assembled and organized the data. AED and AJF ran the statistical analyses, analyzed output data, created the tables and figures and contributed to the writing of the manuscript.

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Distinct Functional Connectivities Predict Clinical Response with Emotion Regulation Therapy

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Despite the success of available medical and psychosocial treatments, a sizable subgroup of individuals with commonly co-occurring disorders, generalized anxiety disorder (GAD) and major depressive disorder (MDD), fail to make sufficient treatment gains thereby prolonging their deficits in life functioning and satisfaction. Clinically, these patients often display temperamental features reflecting heightened sensitivity to underlying motivational systems related to threat/safety and reward/loss (e.g., somatic anxiety) as well as inordinate negative self-referential processing (e.g., worry, rumination). This profile may reflect disruption in two important neural networks associated with emotional/motivational salience (e.g., salience network) and self-referentiality (e.g., default network, DN). Emotion Regulation Therapy (ERT) was developed to target this hypothesized profile and its neurobehavioral markers. In the present study, 22 GAD patients (with and without MDD) completed resting state MRI scans before receiving 16 sessions of ERT. To test study these hypotheses, we examined the associations between baseline patterns of intrinsic functional connectivity (iFC) of the insula and of hubs within the DN (anterior and dorsal medial prefrontal cortex [MPFC] and posterior cingulate cortex [PCC]) and treatment-related changes in worry, somatic anxiety symptoms and decentering. Results suggest that greater treatment linked reductions in worry were associated with iFC clusters in both the insular and parietal cortices. Greater treatment linked gains in decentering, a metacognitive process that involves the capacity to observe items that arise in the mind with healthy psychological distance that is targeted by ERT, was associated with iFC clusters in the anterior and posterior DN. The current study adds to the growing body of research implicating disruptions in the default and salience networks as promising targets of treatment for GAD with and without co-occurring MDD.

Keywords: generalized anxiety disorder, major depressive disorder, worry, somatic anxiety, decentering, resting state functional connectivity

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DISTINCT FUNCTIONAL CONNECTIVITIES PREDICT CLINICAL RESPONSE WITH EMOTION REGULATION THERAPY

Generalized anxiety disorder (GAD) and major depressive disorder (MDD) are prevalent and impairing conditions when they occur alone. However, when they co-occur, GAD and MDD are associated with increased public health burden and are more treatment refractory (e.g., Whisman et al., 2000; Stein and Heimberg, 2004; Farabaugh et al., 2010; Newman et al., 2010; Tully et al., 2013). Psychological models characterize GAD and MDD as conditions illustrative of a profound disruption between mind and body motivated by a fraught attempt to avoid unpredictability and acute intense emotionality brought about by actual or perceived threat (GAD) or actual or perceived loss/reinforcement deprivation (MDD). Specifically, individuals with GAD and/or MDD characteristically respond to aversive and often conflicting emotional and somatic experiences with the use of repetitive or perseverative reactive cognitive processes such as worry and rumination (Mennin and Fresco, 2013). These processes are enacted to create control and predictability, but instead more often result in vacillation between a worried or ruminative mind and chronically distressed body. When individuals are momentarily successful in staving off the aversive experience of strong emotional responses by invoking such self-evaluative processes, reliance on these self-evaluative processes is reinforced (Borkovec et al., 2004; Nolen-Hoeksema et al., 2008; Watkins, 2008; Newman and Llera, 2011; Mennin and Fresco, 2013, 2014; Olatunji et al., 2013). Similarly, behavioral activation models of depression posit that depressive rumination serves an avoidance function by promoting unhelpful self-reflection on one's negative events instead of engaging behavioral actions to respond or resolve the particular circumstances (e.g., Ferster, 1973; Jacobson et al., 2001; Papageorgiou and Wells, 2004). As a result, worry and rumination are associated with considerable deficits in cognitive and behavioral responding (e.g., Lissek, 2012; Whitmer and Gotlib, 2012) as well as an inferior treatment response and greater relapse (e.g., Jones et al., 2008).

Although worry may temporarily reduce acute and intense somatic arousal, over the long run, it may actually promote persistent negative emotions and physical stress (e.g., Brosschot et al., 2006; Newman and Llera, 2011). For instance, ambulatory monitoring studies indicate that individuals with GAD as compared to healthy individuals have relatively higher heart rate (e.g., Hoehn-Saric et al., 2004). Similarly, laboratory studies utilizing worry induction methodology reveal that worry is associated with greater heart rate and skin conductance (e.g., Vrana and Lang, 1990; Lyonfields et al., 1995; Thayer et al., 1996). Relatedly, individuals with GAD evidence chronically low vagal tone especially in relation to worry (Thayer et al., 1996; Brosschot and Thayer, 2003; Hoehn-Saric et al., 2004; Brosschot, 2010), which may reflect a diminished physiological flexibility brought about by the physiologic changes induced by chronic anxiety. As a result of this diminished capacity for physiological self-regulation, individuals may become increasingly reliant on maladaptive strategies such as repetitive thought to manage distress (e.g., Hoehn-Saric et al., 2004). Similarly, the relationship between worry and physiological arousal may reflect the very way that individuals with GAD learn to cope with negative emotionality. Individuals with GAD commonly exhibit paradoxical acute anxiety when instructed to relax (e.g., Heide and Borkovec, 1984) and express greater success in coping with fear and sadness inducing probes with worry as compared to relaxation or neutral instructions (e.g., Llera and Newman, 2010).

In an effort to synthesize these transdiagnostic features of GAD and MDD, Mennin and Fresco (2013, 2014) have posited an emotion dysregulation model, in which these conditions are marked by heightened emotional experience (i.e., motivational intensity) coupled with repetitive and perseverative forms of self-referential thinking (i.e., worry, rumination, self-criticism) that serve as compensatory strategies to reactively escape or avoid strongly felt emotional and somatic experiences. The combination of these clinical features may reflect an underlying profile or endophenotype common to GAD and MDD, and may also account for the relative underperformance of otherwise efficacious treatments in resolving these conditions, particularly when comorbid (e.g., Olatunji et al., 2010). A greater focus on the underlying features of emotionality and self-referentiality may provide a more refined target of investigation than simply examining diagnostic symptoms of GAD. This model is congruent with transdiagnostic approaches to these conditions (e.g., Nolen-Hoeksema and Watkins, 2011) and is consistent with the Research Domain Criteria project (e.g., Insel et al., 2010), which represents an effort to leverage our knowledge of both normative and disordered human functioning at many levels of analysis (e.g., genetic, molecularly, neural, behavioral, socio-cultural, etc.,). Using an experimental therapeutics framework, the Research Domain Criteria promotes investigations of novel intervention principles for their action on biobehavioral targets in hopes of producing superior and enduring clinical improvement (Kozak and Cuthbert, 2016).

Negative self-referentiality and intense emotionality, the primary characteristics of the endophenotype posited in Mennin and Fresco (2013, 2014) emotion dysregulation model, correspond to two well researched neural networks: the *default network* (DN; e.g., Raichle et al., 2001) and the *salience network* (SN; e.g., Craig, 2009; Menon, 2015), respectively. In particular, self-referentiality is commonly associated with neural activation in the DN, regarded as a network associated with autobiographical, self-monitoring and social cognitive functions. The DN is anchored by activity in the medial prefrontal cortex (MPFC; narrative and autobiographical self) and the posterior cingulate cortex (PCC; experiential self-reflection; e.g., Buckner et al., 2008; Qin and Northoff, 2011; Brewer et al., 2013).

The MPFC is also implicated in the detection of emotionally salient stimuli (Morris et al., 1998; Phillips et al., 2003), agentic or aspirational self-reflection (Johnson et al., 2006, 2009), and determining whether beliefs are "acceptable" or "unacceptable" (Paulus and Stein, 2010). Similarly, the PCC has been implicated

in self-reflection especially in relation to duties and obligations (Johnson et al., 2006, 2009). Psychiatric disorders are often marked by excessive activation of the DN thereby preventing or delaying purposeful activation of neural regions associated with executive control (e.g., Whitfield-Gabrieli and Ford, 2012) as well as undermining cognitive load and emotion regulation capacities (e.g., Brewer et al., 2011; Whitfield-Gabrieli and Ford, 2012). With respect to GAD and MDD, resting state fMRI studies clearly implicate disruption in DN regions (e.g., Hamilton et al., 2011, 2013; Chen and Etkin, 2013; Andreescu et al., 2014; Wang et al., 2016). Similarly, task-based studies examining trait levels of worry or depressive rumination (e.g., Paulus and Stein, 2010; Hamilton et al., 2011) or instructions to worry or ruminate (e.g., Cooney et al., 2010; Paulus and Stein, 2010; Ottaviani et al., 2016) demonstrate neural activations in nodes of the DN.

The SN governs our attention to the external and internal world (Menon and Uddin, 2010), and as such, integrates sensory, emotional and cognitive information to facilitate optimal communication, social behavior and self-awareness (Menon, 2015). A critical node of the SN is the insular cortex, which has been implicated in interoceptive awareness (e.g., Mussgay et al., 1999; Critchley et al., 2004; Craig, 2011; Farb et al., 2015), and afferent information that arises from anywhere and everywhere within the body (Cameron, 2001). Greater interoceptive awareness is associated with increased anxiety and panic, especially when those bodily sensations are catastrophized (Schandry, 1981; Ehlers and Breuer, 1992; Barlow, 2002; Pollatos et al., 2009; Paulus and Stein, 2010) during self-referential processing, such as in worry (e.g., Pollatos et al., 2009; Paulus and Stein, 2010). This self-referencing may thus exaggerate arousal (i.e., positive or negative). According to Paulus and Stein (2010), individuals with anxiety and depression exhibit a reduced signal to noise ratio of interoceptive afferents: interoceptive signals have a propensity to be interpreted negatively, resulting in increased sympathetic arousal, and in turn, increased escape or avoidance behaviors. Consequently, low fidelity interoceptive afferents result in overactive top-down brain modulatory areas (e.g., MPFC) that engage constantly to differentially amplify or attenuate body signals.

The insula is thought to also serve a role in evaluating the impact of stimuli on the body (Paulus and Stein, 2006), including generation and regulation of affective responses and detection of emotionally salient stimuli (Paulus and Stein, 2010). Focus has been on the right anterior insula (e.g., Critchley et al., 2004) but increasingly, evidence also indicates a role for the posterior insula (e.g., Simmons et al., 2013; Kuehn et al., 2016) as well as bilateral insulae (e.g., Stein et al., 2007; Avery et al., 2014). Neuroimaging studies support the contention that disorders such as GAD and MDD are associated with SN abnormalities. For instance, compared to healthy individuals, depressed patients show reduced connectivity between anterior insula and other nodes of the SN (Yuen et al., 2014). Consistent with the predictions of Paulus and Stein (2010), task-based studies with MDD and GAD patients consistently show hyperactivity of the anterior insula often accompanied by increased connectivity with nodes of DN including the PCC (e.g., Paulus and Stein, 2010; Hamilton et al., 2013; Yuen et al., 2014). Similarly, a recent study by Kaiser et al. (2015) found that in comparison to healthy control participants, patients with MDD evidenced increased connectivity of the MPFC to the insula and the strength of this connectivity was predictive of depression severity.

In contrast to the maladaptive relationship between negative self-referentiality and intense emotionality (e.g., somatic arousal) proposed in the emotion dysregulation model of Mennin and Fresco (2013, 2014) in their emotion dysregulation model, decentering represents a metacognitive process that involves the capacity to observe items that arise in the mind (e.g., thoughts, feelings, memories, bodily sensations) with healthy psychological distance, greater self-awareness and perspective-taking (Safran and Segal, 1990; Fresco et al., 2007a,b; Bernstein et al., 2015). Depressed individuals tend to score lower on self-report (Fresco et al., 2007a) or objective behavioral measures (Shepherd et al., 2016) of decentering. Improvements in decentering consistently predict acute and enduring treatment effects for patients suffering from MDD (Fresco et al., 2007b), GAD (Hoge et al., 2015) and GAD (with and without MDD; Mennin et al., 2015, under review; Renna et al., under review) as well as the prevention of MDD relapse following prophylactic treatment with mindfulness based cognitive therapy (Bieling et al., 2012). However, few studies have examined the neurobehavioral underpinnings of decentering. Some studies, primarily with normative samples reveal patterns of neural activation in DN and SN networks consistent with decentering's theorized role in reducing negative self-referentiality. For example, in a recent study examining the meta-awareness of mind wandering, low levels of meta-awareness were associated with greater activity in the medial and lateral anterior PFC, PCC and precuneus (Christoff et al., 2009). Similarly, in a sample of meditation practitioners, Hasenkamp et al. (2012) found that greater meta-awareness of mind wandering was linked to activity in the bilateral anterior insula and dorsal anterior cingulate cortex whereas mind wandering with low meta-awareness was associated with greater activation of the PCC, medial PFC, posterior parietal/temporal cortex, and parahippocampal gyrus (Hasenkamp et al., 2012).

In summary, GAD and ruminative MDD patients exhibit intense emotional experiences (e.g., somatic arousal) coupled with excessive negative self-referentiality and low ability to effectively decenter from their emotions and somatic responses (e.g., Mennin and Fresco, 2013), likely reflecting disruption in the DN and SN (e.g., insula). This potential endophenotype of patients who frequently evidence suboptimal treatment response to otherwise efficacious treatments motivated the development of Emotion Regulation Therapy (ERT), which represents a theoretically-derived, mechanism focused treatment designed to target and normalize these hypothesized neurobehavioral deficits (Fresco et al., 2013; Mennin et al., 2015, under review). Teaching skills that increase one's capacity for decentering lies at the core of ERT and has been shown to mediate treatment gains (e.g., Mennin et al., under review).

Given the promising preliminary treatment efficacy evidence for ERT, the current study sought to demonstrate treatment-

related neurobehavioral correlates commonly associated with mind-body phenomena that may also reflect this hypothesized endophenotype. The current study is a secondary analysis of the latest open label clinical trial of ERT (parent study) with findings reported elsewhere wherein 31 patients were treated with ERT (Renna et al., under review). Findings revealed impressive reductions in GAD (Hedges' g = 4.05) and MDD (g = 2.82) severity following treatment. Similarly, patients evidenced reductions in disability (g = 1.40) as well as gains in perceived quality of life at post-acute treatment (g = 1.72). Finally, patients also evidenced clinical improvement on the ERT model variables relevant to the current study at post-acute treatment: worry (g = 2.79), anxious arousal (g = 1.82) and decentering (g = 2.60).

Thus, using ERT as a probe, we sought to examine the intrinsic functional connectivity (iFC) of the DN and the insula (as an index of the salience network) associated with treatment-related changes in theoretically motivated model variables (e.g., worry, anxious arousal, decentering). In particular, we used seed-based region of interest (ROI) analyses related to the DN (e.g., MPFC, PCC) and the insula (e.g., bilateral anterior and posterior insular cortices), using data acquired during resting state fMRI scans at pre-treatment. Based on previous findings and conceptualizations, we hypothesized that: (1) ERT will decrease negative self-referential processing and aversive body awareness (i.e., worry and hyper focus on bodily signals) and increase healthier self-consciousness and detached body awareness (i.e., decentering). We also hypothesized that; (2) changes in self-referencing (i.e., worry) and body awareness (i.e., anxious arousal) will be predicted by pre-treatment connectivity of specific networks (worry by DN areas and anxious arousal by insula); and (3) in contrast, more distributed network connectivity among nodes of the DN and the SN (i.e., insula) at pre-treatment will be associated with improvements in decentering.

METHOD

Participants

Participants consisted of 22 treatment seeking young adults drawn from a larger sample (N = 31; Renna et al., under review) of undergraduate and graduate students from a large, urban university, who completed baseline fMRI assessments and a 16-week trial of ERT (Mennin and Fresco, 2014). Participants were recruited through a variety of different strategies including direct referrals from an on-campus counseling center, fliers posted throughout campus, e-mail announcements sent to the entire student body, and through research staff handing out business cards to students on campus. Participants had a mean age of 21.9 years old (SD = 2.62, Range 18–29). Seventeen participants were female (77.3%). The sample was racially diverse: Caucasian (36.4%), African American (9.1%), Asian/Pacific Islander (22.7%), Other/mixed race (31.8%).

Inclusion/Exclusion Criteria

The main eligibility criterion was the presence of a primary or secondary GAD diagnosis (primacy was determined by clinical severity). In the current study, 16 patients had a primary diagnosis of GAD. Sixteen patients (72.7%) also met criteria for MDD; 14 (63.6%) patients met criteria for at least one additional anxiety disorder diagnosis. Other diagnoses included social anxiety disorder (n = 10), panic disorder (n = 6), specific phobia (n = 4), obsessive compulsive disorder (n = 3), post-traumatic stress disorder (n = 1). Participants were required to be stabilized on any psychotropic medications for a period of at least 3 months prior to the start of treatment (n = 1 receiving antidepressant medication) and could not be enrolled in any other form of psychological treatment during the acute phase of ERT (16 weeks). Finally, participants had to be free of active suicidal ideation/intent, psychosis, bipolar I disorder, primary anorexia or bulimia nervosa, somatoform disorders, or substance and alcohol dependance. Given the use of fMRI assessment, other exclusionary criteria included standard MRI contraindications (e.g., ferromagnetic implants; head trauma with loss of consciousness; tattoos above the elbow; pregnancy).

Diagnostic Assessment

Current and lifetime psychiatric disorders were assessed with the *Structured Clinical Interview for DSM-IV* (SCID; First et al., 2002). Graduate students and senior research assistants, extensively trained on the diagnostic assessment protocol administered this assessment. A principal investigator and an independent assessor, both of whom were blind to the participant's diagnoses assigned at the intake interview, then confirmed participants' diagnoses. Reliability was high, with kappa ratings ranging from 0.708 to 1.000, demonstrating good to excellent reliability. Reliability for diagnoses of GAD was 100%, whereas MDD was 87.10%. Independent assessors, who remained blind to treatment status of patients, assessed clinical improvement at mid-treatment, post-acute treatment, as well as three-, and 9-months following the end of treatment.

Treatment

ERT consists of 16-session individual weekly psychotherapy sessions completed within a 20-week span. The first half of the treatment (Phase I) focuses on psychoeducation and cultivating mindful emotion regulation skills. During these first eight sessions, participants are taught attention regulation (i.e., orienting, allowing) and meta-cognitive regulation (i.e., distancing/decentering, and reframing) skills. In particular, these skills include cue detection wherein individuals are instructed on how to better attend to emotional and motivational cues that arise in daily life so that these cues are noticed with greater acuity and closer to when they first arise. Cue detection is supported by training participants in a variety of meditation practices that improve attention and metacognitive capacities. These meditation practices are introduced to patients who then practice them each day. Briefer versions of these meditation practices are also introduced so that they can be utilized in both predicted and impromptu stressful situations to reduce a patient's reliance on negative self-referentiality and behavioral

responses associated with escape or avoidance. The second half of treatment (Phase II) focuses on context engagement, which involves developing a proactive approach towards life with the goal of living more consistently with one's values through the use of imaginal exposures and internal dialog tasks. Here, therapists direct patients in conducting in-session exposure exercises where patients envision a situation, goal, or outcome that they desire but it presently missing from their lives. This imaginal exposure serves to elucidate the motivational inclinations for reward and approaching the goal as well as the motivations associated with protecting one's self from the threat associated with taking the action and/or costs associated with not succeeding. By giving voice to these motivational inclinations, patients learn to decenter from the intensity of these pulls and derive a behavioral response that reflects a more optimal balance of risk and reward. More information regarding the structure and specific components of ERT are described elsewhere (see Fresco et al., 2013; Mennin and Fresco, 2014; Renna et al., under review).

Clinicians consisted of seven doctoral students in clinical psychology who were trained to administer ERT and received 2 h of weekly supervision. These modal number of cases treated by each clinician was 3 (M = 2.75; Range = 1–4). To establish adherence to the treatment protocol, all treatment sessions were audio recorded, and a team of research assistants, not involved in the administration of ERT or assessment of treatment effects, coded 40% of all cases, with 25% of these cases reviewed by a second coder to establish reliability. Reliability rates between the coders were 100%. Coders rated the accuracy of the frequency and skillfulness of actions taken by the study therapists. Overall, skillfulness ratings of the therapists coded were 98.4% (Range = 95%–100%), while frequency of actions consistent with the treatment protocol was 91.2% (Range = 71%–100%). The adherence ratings for this trial indicate that therapists uniformly delivered ERT with a high degree of adherence and fidelity. Examination of treatment effects associated with particular clinicians revealed equivalence for self-report and clinician-assessed clinical outcomes (p's > 0.70) across the seven trial therapists.

Clinical Outcomes

The *Penn State Worry Questionnaire* (PSWQ; Meyer et al., 1990) is a 16-item self-report measure of pathological worry with scores ranging from 16 to 80. This extensively used measure has excellent psychometric properties across numerous studies. Fresco et al. (2003) reported that scores greater or equal to 65 reliably identified patients with a diagnosis of GAD in a heterogenous sample of patients seeking outpatient treatment. Cronbach's alpha in the current sample was good ($\alpha = 0.80$).

The *Mood and Anxiety Symptom Questionnaire-Short Form (MASQ,* Watson and Clark, 1991*)* was designed to capture symptoms of anxiety and depression along dimensions of Watson and Clark (1991) tripartite model. Overall, four factors are derived—two of which demonstrate symptoms associated with anxiety and two with depression—and yield scores for four subscales: General Distress Anxiety, Anxious Arousal and, General Distress Depression, Anhedonic Depression. For each of these subscales, higher scores indicate greater anxious and depressive symptoms, respectively. Given the focus of the current study on somatic anxiety outcomes, only Anxious Arousal (MASQ-AA) was examined in the present study, which demonstrated excellent internal consistency ($\alpha = 0.91$).

The *Experiences Questionnaire-Decentering Subscale* (Decentering; Fresco et al., 2007a) is an 11-item measure assessing the meta-cognitive strategy of decentering, or viewing oneself as separate from their emotional experience. Sample items include, "I can separate myself from my thoughts and feelings", "I can observe unpleasant feelings without being drawn into them", "I am consciously aware of a sense of my body as a whole", and "I view things from a wider perspective". The Decentering subscale has demonstrated strong psychometric properties and treatment sensitivity. Cronbach's alpha in the current sample was good ($\alpha = 0.80$).

Procedure

The Institutional Review Board of the college approved all aspects of the study. Participants provided written informed consent for all procedures at the outset of study. At the initial intake visit participants were assessed for current and lifetime psychiatric history via the SCID interview and also completed a battery of self-report questionnaires delivered in paper-and-pencil format. Prior to the start of treatment, participants completed an independent assessment with a different interviewer who re-assessed the diagnoses that were of clinical threshold at the initial intake. Finally, participants completed the fMRI scan. Following the first eight sessions (i.e., mid-treatment) and after sixteen sessions (i.e., post-treatment), participants returned to the lab to complete another independent assessment and self-report questionnaire packet. They were also invited to complete another fMRI session post-treatment, but only the pre-treatment data are being analyzed for this study. Participants were compensated for all research related study visits.

Analytic Plan

MRI Data Acquisition

Imaging data were collected on a 3.0T Siemens Allegra head-dedicated MRI scanner with a standard quadrature head coil at the NYU Center for Brain Imaging in New York, NY, USA. Scan sessions lasted 90 min during which participants completed a resting state fMRI scan (R-fMRI), and an anatomical scan, and three task-based scans (not examined in the current study). The resting state scan was always acquired prior to the task-based scans. During the 6-min resting-state sequence, participants were asked to keep their eyes open while a white crosshair was displayed on a black screen. The resting-state scan comprised 180 contiguous whole-brain functional volumes, acquired using a multi-echo echo planar imaging (EPI) sequence (repetition time = 2000 ms; echo time = 30 ms; flip angle = 90°; 33 slices; matrix = 64 × 64; voxel size = 3 × 3 × 4 mm). High-resolution T1-weighted MPRAGE structural images (TR = 2500 ms; TE = 3.93 ms, flip = 8°, 1 × 1 × 1 mm voxels) were

acquired to facilitate localization and coregistration of functional data.

MRI Data Preprocessing

MRI preprocessing and data analysis were completed using an alpha version of an innovative software package: the Configurable Pipeline for the Analysis of Connectomes Version 3.9.1 (C-PAC[1]). CPAC is a configurable, open-source, Nipype-based[2], automated processing pipeline for R-fMRI data. Preprocessing consisted of the following: slice time correction (first slice as reference, interleaved acquisitions, Fourier interpolation), 3D motion correction, despiking of extreme time series outliers using a continuous transformation function, spatial smoothing (FWHM = 6 mm), mean- based intensity normalization of all volumes by the same factor, and temporal band-pass filtering (0.01–0.1) in order to isolate the low-frequency BOLD fluctuations of interest. Structural images were registered to a common stereotaxic space (Montreal Neurological Institute, MNI) using Advanced Normalization Tools (Avants et al., 2011[3]). Functional image registration was completed using Boundary Based Registration as implemented in FSL (Greve and Fischl, 2009). Single participant nuisance regression included linear and quadratic trends, 24 Friston motion parameters (Friston et al., 1996), and five CompCor signals (Behzadi et al., 2007). All analyses were Gaussian random field (GRF) corrected at $p < 0.05, Z > 2.3$.

As micromovements have been shown to potentially introduce artifactual correlations, mean framewise displacement (FD) was computed, per recently described methods (Power et al., 2012; Van Dijk et al., 2012). No subjects were excluded on the basis of motion (all had mean FD < 0.25 mm). To further control for the impact of motion on group results, each subject's mean FD was included as a covariate in group-level analyses.

Region of Interest Selection

To test study hypotheses, we utilized ROIs from the (DN) and the insula (see **Figure 1**). Three spherical ROI seeds (2 mm radius) were created to assess DN iFC based on Andrews-Hanna et al. (2010): the anterior MPFC (aMPFC) and PCC were selected because they represent hubs of the DN, and the dorsal (dMPFC) was selected to probe the dMPFC subsystem which has been implicated in social cognition, mentalizing and introspection about mental states (e.g., Wagner et al., 2016). Due to insufficient coverage of medial temporal and ventral prefrontal regions (see **Figure 2**), we were unable to examine the medial temporal lobe (MTL) subsystem. Anatomical bilateral posterior and anterior insula ROIs were taken from the two-cluster parcellation results from a recent multimodal examination of the functional organization of the insula (Kelly et al., 2012).

The mean time series of each ROI seed was calculated by averaging the time series of all voxels within each ROI. For each participant, ROI connectivity strength was assessed across the whole brain using Pearson correlations between the ROI time series and all other voxels in the brain. This resulted in individual Fisher's Z-transformed participant-level maps of all voxels exhibiting significant iFC with the aMPFC, vMPFC and PCC, anterior insula (bilateral) and posterior insula (bilateral; GRF corrected: $p < 0.05, Z > 2.3$).

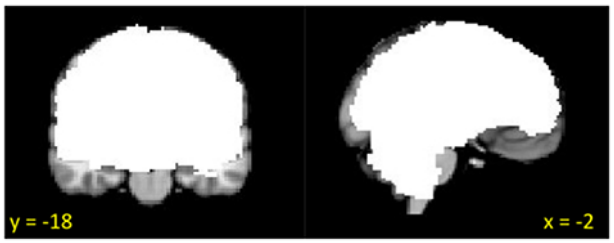

FIGURE 1 | Group mask (n = 22) indicating coverage of fMRI signal.

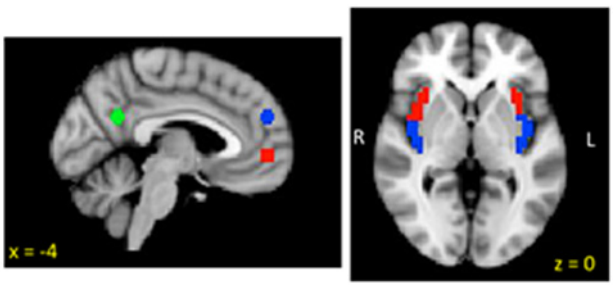

FIGURE 2 | Insula and default network (DN) regions of interest (ROIs).

Group Level MRI Analyses

Three separate group-level analyses were conducted using a random-effects, ordinary least-squares model in FSL FEAT[4] to assess the associations between iFC and worry, anxious arousal and decentering. Each model included three nuisance regressors (age, sex and mean FD), the pre-treatment measure of interest as a covariate, and post-treatment measure of interest as the primary predictor. Group-level analyses were conducted using cluster-level GRF theory for multiple comparison correction ($p < 0.05$, $Z > 2.3$) resulting in thresholded Z-score maps indicating clusters where iFC of each ROI was significantly related to the post-treatment variable of interest. To conduct additional *post hoc* analyses, we extracted the average partial regression coefficients for each significant cluster for each participant.

Corrections for Multiple Comparisons

Although all theoretically motivated and defensible, the analyses reported herein did use three ROI seeds associated with the DN and four ROI seeds associated with the salience network. Thus, to prevent the likelihood of Type I statistical errors, we report findings with p values less than 0.05 and make note of findings that do not survive a Bonferroni correction of 0.05/3 in the DN and 0.05/4 in the salience network.

[1]http://fcp-indi.github.io/
[2]http://nipy.org/nipype/
[3]http://www.picsl.upenn.edu/ANTS
[4]https://fsl.fmrib.ox.ac.uk

RESULTS

Pre-Treatment iFC Associated with Treatment-Related Changes in Worry

Regression analyses estimated from changes in worry revealed associations with iFC of both the DN and insula. With respect to the DN, reduced iFC of the aMPFC with posterior regions including the precuneus and the occipital cortex, was associated with greater reductions (improvement) in worry following treatment (see **Table 1** and **Figure 3A**). No significant results were observed for the PCC or dMPFC ROI analyses. With respect to the insula, greater reductions in worry following treatment were associated with weaker iFC of right anterior and posterior insula with the superior parietal lobe (see **Figure 3B**). A similar cluster was observed for the right anterior insula but this did not survive Bonferroni correction ($p > 0.0125$). No significant clusters emerged for the left insula.

Pre-Treatment iFC Associated with Treatment-Related Changes in Somatic Anxiety

Regression analyses estimated from changes in somatic anxiety revealed no significant findings for any of the DN ROIs. However, similar to the worry analyses, reduced iFC between bilateral posterior insula ROIs and a cluster in the superior parietal lobe was associated with greater reductions in somatic anxiety. See **Table 1** and **Figure 3B**. Additionally, greater iFC between the left posterior insula and inferior parietal lobe was associated with lower post-treatment anxious arousal, as shown in **Figure 3A**. No results were found for the right or left anterior insula.

Pre-Treatment iFC Associated with Treatment-Related Changes in Decentering

Finally, regression analyses estimated from changes in decentering revealed associations with iFC of both the DN and insula. Reduced iFC between the aMPFC and a cluster in occipital lobe was associated with higher post-treatment decentering scores (greater improvement). Of note, this cluster overlapped with that obtained in the aMPFC iFC analysis for worry. Multiple regions emerged from the dMPFC iFC analysis. Here, greater iFC between dMPFC and the left anterior insula/inferior frontal gyrus was associated with higher post-treatment decentering. Clusters were also detected in the rostral ACC extending to striatum and superior frontal gyrus but these did not survive correction for multiple comparisons (p's > 0.017). Finally, greater connectivity between the PCC ROI and a cluster extending from dorsal to rostral ACC and a cluster encompassing striatum and anterior insula was associated

TABLE 1 | Clusters with significant associations in relation to clinical change in worry, somatic anxiety and decentering.

	Cluster size	*x*	*y*	*z*	Max *Z*	*p*
Worry with DN ROIs						
aMPFC						
Precuneus	368	18	−78	42	4.59	0.00269*
Occipital cortex	539	−8	−80	18	4.31	0.000119*
Worry with insula ROIs						
Right posterior insula						
Superior parietal cortex	241	−30	−38	40	3.77	0.00897*
Right anterior insula						
Inferior parietal cortex	189	−50	−28	42	4.3	0.0484
Somatic anxiety with insula ROIs						
Right posterior insula						
Superior parietal lobe	251	−34	−36	40	3.85	0.00517*
Left posterior insula						
Superior parietal lobe	433	−32	−38	48	3.9	0.000125*
Inferior parietal lobe	269	46	−38	28	2.24	0.00573*
Decentering with DN ROIs						
aMPFC						
Occipital pole	336	16	−90	16	3.68	0.00407*
dMPFC						
Rostral ACC	225	0	42	0	4.62	0.0486
Superior frontal gyrus	226	−2	−2	68	4.18	0.0475
Left anterior insula/inferior frontal gyrus	363	−26	12	−16	3.81	0.00258*
PCC						
Striatum (caudate and putamen)	537	−20	8	−8	3.48	0.000329*
Rostral ACC	606	2	36	4	3.95	0.000113*
Decentering with insula ROIs						
Right posterior insula						
Lateral occipital cortex	245	−42	−80	−14	3.77	0.021
Right anterior insula						
Central opercular cortex	220	−42	−22	18	4.31	0.0361

*Note: *Denotes findings that survive a Bonferroni correction for multiple comparisons.*

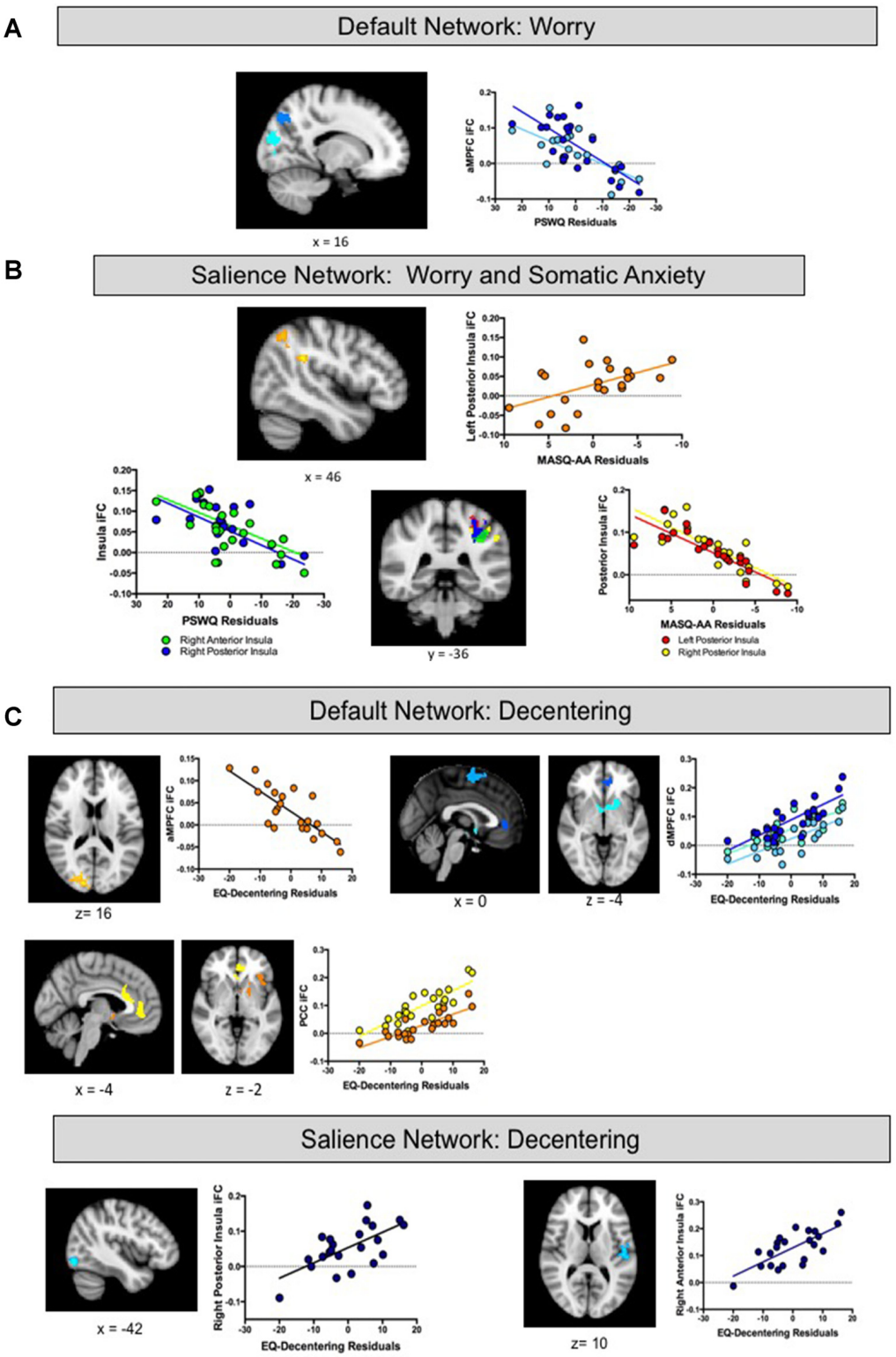

FIGURE 3 | (A,B) Intrinsic functional connectivity (iFC) of default and salience regions associated with treatment-related changes in Worry and Somatic Anxiety Findings. **(C)** IFC of default and salience regions associated with treatment-related changes in Decentering. aMPFC, anterior medial prefrontal cortex region of interest; dMPFC, dorsal medial prefrontal cortex region of interest; PCC, posterior cingulate cortex region of interest.

with greater improvements in decentering. With respect to the insula, greater iFC between the right posterior insula and lateral occipital cortex as well as iFC between the right anterior insula and central opercular cortex were associated with higher decentering at post-treatment. However, these findings were no longer significant after controlling for multiple comparisons (p's > 0.0125). No significant results were found for the left insula. See **Table 1** and **Figure 3C**.

DISCUSSION

The present study took a novel approach to examining the neural predictors of specific outcomes of ERT for GAD patients with and without comorbid MDD. In particular, much of the psychological theorizing about the nature of GAD and MDD in terms of disruption of mind and body has been predicated on a functional relationship between the kinds and intensity of visceral and psychological sensations that one experiences (i.e., motivational intensity) and the ways by which one attempts to respond to their arising (i.e., negative self-referentiality; Borkovec et al., 2004; Nolen-Hoeksema et al., 2008; Watkins, 2008; Newman and Llera, 2011; Mennin and Fresco, 2013, 2014; Olatunji et al., 2013). Extending this model to an examination of neurobehavioral systems that subserve emotion and motivation (i.e., salience network) as well as self-referential mentation (i.e., DN) motivated the current study, in which we focused on two constructs characteristic of the pathology of GAD and MDD, worry and somatic anxiety, and one treatment-related construct associated with reduced negative self-referentiality, decentering. From a neural perspective, we hypothesized that change in these variables would be differentially associated with the iFC of insula-based and DN regions. Specifically, because worry is regarded as a destructive form of self-referentiality, we hypothesized that changes in worry would be related primarily to DN connectivity. Conversely, we hypothesized that changes in somatic anxiety would be associated primarily with pre-treatment insula iFC. Finally, given that decentering is a metacognitive capacity associated with reductions in negative self-referentiality and a consistent mechanism of clinical improvement, we predicted that gains in decentering would be associated with both DN and insula iFC at pre-treatment.

Overall, we found some distinctions between iFC patterns associated with improvements in worry and somatic anxiety, although there was greater overlap than predicted. As hypothesized, DN iFC was associated with treatment-related reductions in worry but not in somatic anxiety. Specifically, individuals with weaker iFC between the anterior MPFC and posterior regions demonstrated greater improvements in worry. Conversely, insula iFC was not unique to changes in somatic anxiety. Although individuals with weaker pre-treatment iFC between bilateral posterior insula and superior parietal lobe showed greater improvements in somatic anxiety, iFC of right anterior and posterior insula with same regions was also associated with changes in worry. This pattern of results bears some resemblance to the findings of Kaiser et al. (2015), who in their recent meta-analysis of MDD, reported abnormal connectivity patterns in both the dorsal and ventral attention networks, potentially reflecting altered or biased salience monitoring. Similarly, Andreescu et al. (2014) found that broad scale hyperconnectivity of the insulae was associated with greater GAD severity. Further, Paulus and Stein (2010) postulate a role of negative self-referentiality in aberrant insula activity. The findings from the current study are largely consistent with this interpretation and suggest that weaker pre-treatment iFC of the insula (both posterior and anterior ROIs) with regions of the dorsal attention network (i.e., post-central gyrus, superior parietal lobe) is a non-specific indicator of ERT treatment gains.

Psychological models have identified decentering as a metacognitive process that occurs naturally in individuals but can be cultivated by psychosocial interventions, especially interventions that include training in mindfulness meditation (e.g., Bernstein et al., 2015). Decentering is central to the ERT treatment model as it represents an important mechanism of change (Mennin and Fresco, 2013, 2014; Mennin et al., under review). Bernstein et al. (2015) posit that decentering helps individuals reduce time spent engaging in negative self-referentiality and allowing them to better attend to cues associated with goal directed behavior; thus, we postulated that ROIs from both the default and salience networks would be associated with ERT linked gains in decentering. Consistent with our initial predictions, clinical gains in decentering were associated with pretreatment iFC of several ROIs from the DN and the insula. With respect to the DN, findings revealed that reduced connectivity between the anterior MPFC and the occipital pole at baseline was associated with greater increases in decentering over the course of ERT. This finding is comparable to that of reduced anterior MPFC—occipital cortex iFC predicting improvement in worry suggesting overlap in these constructs (or in treatment gains related to these constructs). As reflected in the operational definition of decentering and the content of items in the decentering subscale, decentering is believed to be a metacognitive capacity that leads to less self-referentially biased awareness of exteroceptive and interoceptive cues. Similarly, previous task-based work has shown that reduced co-activation of these regions predicts greater prevention of relapse in patients with remitted depression (Farb et al., 2011). It may be that reduced connectivity between the aMPFC and visual processing regions is associated with less negative self-referentiality and greater engagement of imagery (i.e., potentially indicating emotional processing; Foa and Kozak, 1986). Individuals with GAD are suggested to engage in verbally-based processing (i.e., worry) as a strategy for avoiding intense and aversive internal experiences (Borkovec et al., 2004). Similarly, individuals with MDD show reduced concreteness during rumination (Watkins and Moulds, 2007), and individuals with MDD and anxiety disorders, including GAD, show a reduced ability to generate prospective positive imagery (Morina et al., 2011). Greater imagery engagement may indicate emotional processing (e.g., Foa and Kozak, 1986) and therefore be important in treating disorders involving a high level of perseverative cognitive processing—for example, an interpretation modification bias

paradigm found that imagining positive future events, vs. thinking about their meaning in words, had a protective effect against a subsequent negative mood induction (Holmes et al., 2009).

Greater pretreatment connectivity of the dMFPC and PCC ROIs with various regions were associated with greater gains in decentering. One area that evidenced greater connectivity to the PCC was the rostral ACC. Although the ACC is broadly associated with many neural functions including conflict monitoring and adaptation (i.e., confronting and resolving situations marked with conflicting information, Botvinick et al., 2001; Etkin et al., 2006), particular connectivity between the dMPFC and the rostral ACC has been implicated in the conscious appraisal of emotion (Etkin et al., 2011), which seems consistent with one's ability to decenter from negative emotions. Likewise, connectivity between the rostral ACC and the MPFC may simply reflect its role within the default network (e.g., Buckner et al., 2008). Interestingly, recent findings implicate hypoactivation of the rostral ACC especially in conjunction with the MPFC in emotion regulation deficits in GAD (Klumpp et al., 2011; Mochcovitch et al., 2014). Recent theories suggest that the rostral ACC may be a node for more implicit emotion regulation, especially when not co-activated with aspects of the dorsal attention network (i.e., DLPFC, dorsal ACC; Christoff et al., 2011). Thus, this greater connectivity observed between the rostral ACC to the PCC may reflect increased ability to notice and resolve emotionally laden self-relevant information, which in turn could facilitate treatment-linked gains in decentering.

With respect to the observed connectivity between the dMPFC with the left anterior insula/IFG cluster, these areas have been implicated in effective emotion regulation especially in the context of affect labeling (e.g., putting feeling into words; Lieberman et al., 2007) among individuals with high trait mindfulness (Creswell et al., 2007). Such connectivity may suggest that adaptive emotion regulation requires coordination between the default and salience networks. Although no studies have formally examined decentering in the context of affect labeling, these two constructs are conceptually similar. Thus, these patterns of findings may indicate that pretreatment iFC in these regions facilitates gains in decentering for patients receiving ERT.

Findings from the current study add to a growing body of research demonstrating the clinical efficacy and hypothesized mechanism model of ERT (Mennin and Fresco, 2013, 2014). For instance, in the context of a randomized clinical trial using a modified attentional control as the comparator, Mennin et al. (under review) reported acute and enduring treatment effects for patients receiving ERT for a broad range of clinical outcomes associated with GAD and MDD (Hedge's *g*'s of 0.48–1.50). Treatment effects in that trial were mediated by gains in self-reported decentering (e.g., Fresco et al., 2007b). Similarly, one mechanism finding from an earlier ERT trial consistent with the present findings relates to heart rate variability, an index of parasympathetic flexibility (Porges, 2001; Thayer et al., 2012). Heart rate variability was assessed while watching a fearful film in a subset of ERT patients from prior trials. At pre-treatment, patients displayed a flattened response throughout the experimental period, suggesting reduced cardiac flexibility. At mid-treatment, patients displayed a quadratic pattern of vagal withdrawal (i.e., reactivity) and vagal rebound (d = 0.81). This relative normalization of parasympathetic flexibility from pre- to mid-treatment predicted treatment gains in diagnostic severity, anxiety and mood symptoms (Mennin et al., in preparation).

Although these findings are encouraging, they must be regarded as preliminary given some notable limitations. First, our sample was relatively small (N = 22), which prevented us from examining specific effects in patients with GAD with and without MDD to assess the impact of this comorbidity. It also prevented more sophisticated hierarchical analyses that would include all three constructs in one model. Our small sample, comprised mostly of women, also did not allow us to adequately test gender differences in treatment response and neural patterns. However, this imbalance in gender distribution favoring women is consistent with treatment seeking patterns for all anxiety disorders including GAD (e.g., McLean et al., 2011). Second, the findings are based upon patients receiving ERT in an open-label format. Thus, this trial lacked a comparator treatment to contrast the potential association of pre-treatment neural activations to treatment changes uniquely attributable to ERT. These limitations speak to the need of a larger ERT trial with a proper comparator arm and an assessment schedule with multiple fMRI visits—thereby allowing for a careful examination of ERT specific neural changes associated with clinical improvement for patients suffering from GAD and MDD. Finally, our MRI acquisition did not allow us to adequately image and examine the MTL subsystem including the bilateral amygdala, which has been implicated in GAD and MDD (Roy et al., 2013; Oathes et al., 2015). Although the specific hypotheses of the current study were not unduly affected by this limitation, future studies will benefit from MRI acquisition that can simultaneously examine all the neural systems associated with GAD and MDD.

Despite these limitations, the present findings add to the growing body of research implicating disruptions in the DN and salience networks in GAD and MDD and demonstrate the association of functional connectivity in these networks to patterns of treatment-related changes in central components of these disorders (i.e., worry, somatic anxiety) and their amelioration (i.e., decentering).

AUTHOR CONTRIBUTIONS

DMF, AKR, SS, EG-L and DSM: substantial contributions to the conception or design of the work; DMF, AKR, SA, SS, EG-L, CL and DSM: the acquisition, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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