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Response time as a proxy of ongoing mental state: A combined fMRI and pupillometry study in Generalized Anxiety Disorder

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Abstract

In Generalized Anxiety Disorder (GAD), fluctuations in ongoing thoughts (i.e., mind-wandering) often take the form of rigid and intrusive perseverative cognition, such as worry. Here, we sought to characterize the neural correlates of mind-wandering and perseverative cognition, alongside autonomic nervous system indices of central arousal, notably pupil dilation. We implemented a protocol incorporating the dynamic delivery of thought-probes within a functional neuroimaging task. Sixteen individuals with GAD and sixteen matched healthy controls (HC) underwent functional magnetic resonance imaging with concomitant pupillometry. Participants performed a series of low-demand tracking tasks, responding to occasional changes in a target stimulus. Such a task is typically accompanied by self-generated, off-task thinking. Thought-probes were triggered based on an individual's response time (RT) when responding to the change in the target. Subjective reports showed that long RT predicted off-task thinking/mind-wandering. Moreover, long RT and mind-wandering were also associated with larger pupil diameter. This effect was exaggerated in GAD patients during perseverative cognition. Within brain, during both pre-target periods and target events, there were distinct neural correlates for mind-wandering (e.g., anterior cingulate and paracingulate activation at target onset) and perseverative cognition (e.g., opposite patterns of activation in posterior cingulate and cerebellum at target onset in HC and GAD). Results suggest that not only attention systems but also sensory-motor cortices are important during off-task states. Interestingly, changes across the 'default mode network' also tracked fluctuations in pupillary size. Autonomic expression in pupillary changes mirror brain activation patterns that occur during different forms of repetitive thinking.

Key Words: Generalized Anxiety Disorder; pupil; mind-wandering; perseverative cognition; response time

1. Introduction

Generalized anxiety disorder (GAD) includes repetitive negative thinking as a core symptom (American Psychological Association, 2013). In this disorder, patterns of ongoing thought are constrained to rigid and intrusive perseverative cognitions, i.e. worry and rumination. Studies suggest that unlike the more common patterns of mind-wandering seen in the general population, perseverative cognition is characterized by reduced parasympathetic drive to the heart (Ottaviani et al., 2016a for a meta-analysis), which contributes to another pervasive symptom of GAD, the feelings of physiological arousal (e.g., Andor et al., 2008). Recent work combining peripheral physiological monitoring with functional magnetic resonance imaging (fMRI) has highlighted the neural processes that shape aberrant cognitions in anxiety through their bidirectional interaction with autonomic bodily states of arousal (e.g., Makovac et al., 2018; Meeten et al., 2016). Increased self-reported levels of worry following an induction of perseverative cognition leads to decreases in heart rate variability (an index of parasympathetic nervous control of the heart) and in prefrontal-amygdala functional connectivity in GAD patients and controls (Makovac et al., 2016b). Moreover, individual differences in heart rate variability predict the degree to which healthy individuals can suppress unwanted thoughts (Gillie et al., 2015) and also predict the neural correlates of worry in GAD patients and controls (Ottaviani et al., 2016b). The present study aimed to contrast more 'normal' patterns of mind-wandering with less adaptive patterns of perseverative cognition in GAD, applying the technique of triangulation (Smallwood and Schooler, 2006) that combined neural activity, as assessed by fMRI with autonomic function, indexed by pupillometry and with self-reported measures of ongoing thought. The overall goal was to investigate whether functional and dysfunctional forms of repetitive thinking have distinctive autonomic and brain correlates, based on the assumption that mind-wandering and perseverative cognition can be viewed as distinct aspects of ongoing thought (e.g., Christoff et al., 2016; Ottaviani, 2018).

Over the past ten years, fMRI studies have focused both on mind-wandering in healthy individuals (Fox et al., 2015 for a meta-analysis) and on perseverative cognition in patients (e.g., Hamilton et al., 2015 for a meta-analysis on depressive rumination; Ottaviani et al., 2016a and Paulesu et al., 2010 for worry). To the best of our knowledge, however, none of them have tested directly if these two types of ongoing thought have distinct neural substrates. Initial studies aimed at examining off task thought, focused on the default mode network (DMN; Raichle et al., 2001), given its tendency to deactivate during external tasks (e.g. McKiernen et al., 2003). However, this task-negative view of the DMN, has been challenged by studies that show that it can play an active role in task states, even when they lack strong autobiographical content, if cognition is guided by information from memory rather than constrained by perception (Konishi et al., 2015; Murphy et al., 2018; Vatansever et al., 2017). More importantly, converging evidence from experience sampling studies have shown that ongoing thought is more complex than previously recognised (Christoff et al., 2016; Smallwood et al., 2016). Indeed, recent evidence has shown that the DMN can represent the level of detail of task-related experiences (Sormaz et al., 2018), a process that may emerge from the connectivity of this system with the visual cortex (Turnbull et al., 2018). These latter studies highlight that off-task states may entail changes in attention systems (dorsal and ventral) as well as also sensory-motor cortices, likely reflecting changes in the ability to appropriately represent task-relevant information in working memory when attention is off task (McVay and Kane, 2009).

Many studies examining mind-wandering use a simple attention task, during which participants are randomly probed with experience sampling probes which require the participant to describe aspects of their experience, such as whether it is related to the task or not (Weinstein, 2018 for a review). In this study, we use a novel method of experience sampling in which we utilise information from ongoing measures of behaviour and autonomic function with experience sampling. We hoped that this would enhance the ability of the self-reported information to discriminate between different types of ongoing thought. Previous evidence from sustained attention tasks indicates that mind-wandering and perseverative cognition are reported after slower RT responses, as compared to on-task reports on faster RT trials (e.g., Henríquez et al., 2016;

Ottaviani et al., 2013; Smallwood et al., 2008). We combined information from behaviour with a measure of autonomic function derived from the pupillary response. Pupillometry can index rapid changes in autonomic activity associated with cognitive processes through continuous integrated measure of arousal level and usage of attentional resources (e.g., Rigato et al., 2016). It has been proposed that fluctuations in pupil size reflect the state of the brain norepinephrine system, originating in the locus-coeruleus and projecting to areas associated with attentional processing and gated by interoceptive cardiac signals (e.g. Critchley and Garfinkel, 2016; Murphy et al., 2014). Given that the locus coeruleus is also implicated in the successful retrieval of emotional memories (Sterpenich et al., 2006), it is possible that this region would emerge as a crucial structure mediating pupil response during perseverative cognition. Proximally, the pupil response reflects both tonic and phasic changes in sympathetic and parasympathetic activity (McDougal et al., 2015 for a review). Heuristically, larger pupil size correlates with heightened emotional arousal state, and with increasing task demand/difficulty (Henderson et al., 2014; Konishi et al., 2017; Mandrick et al., 2016; Peysakhovich et al., 2015). Importantly, Smallwood and colleagues (2011) demonstrated that periods of longer response time (RT) prior to an error could be related to retrospective characterisations of ongoing thought as off task, suggesting that the combination of RT and pupil data could provide a converging method to understand the neural basis of ongoing thought.

In this study, we used RT and pupil data as an additional constraint when examining the relationship between patterns of ongoing thought and neural activity. Participants (individuals with GAD and controls) performed a low-demand sustained attention task in which they responded to occasional targets. We also acquired measures of pupil dilation while participants performed the task and used the combined metrics provided by behaviour and pupillometry, to provide a window into the neural substrates of both normal and abnormal patterns of ongoing thought. In particular, we employed response contingent thought-probing (Franklin et al., 2011), in which we exploited the hypothesised relationship between behaviour and self-reported descriptions of ongoing thoughts in periods when performance was either very fast or very slow. Behaviourally, we expected that the greater intensity of perseverative cognition would lead to a stronger increase in RT than would be observed during mind-wandering (as in Ottaviani et al., 2013). Based on previous findings, highlighting increasing pupil size variations in response to emotional valence and arousal state (e.g., Bradley et al., 2008) and decreasing associations with off task thought (Konishi et al., 2017), we hypothesized that pupils would be smaller during mind-wandering than in more pathological perseverative cognition. Lastly, we hypothesized that neural activity uniquely associated with the perseverative nature of worry and rumination would be characterized by engagement of regions controlling psychophysiological arousal and autonomic rhythmicity, including the anterior cingulate cortex (Ottaviani et al., 2016b; Paulesu et al., 2010). In addition, studies that have examined neural processing associated with states of off-task or mind-wandering, have implicated a range of different large scale systems in the experience, including dorsal and ventral attention (Tunbull et al., 2018; Wang et al., 2018) aspects of the default mode and fronto-parietal networks (Fox et al., 2015), as well as sensory-motor areas (Sormaz et al., 2018; Turnbull et al., 2018).

2. Methods and Materials

2.1. Participants

The current study presents data from the follow-up component of a larger multilevel longitudinal investigation of the neurobiological correlates of perseverative cognition in GAD (see Makovac et al. 2016a,b,c; Makovac et al., 2018a,b; Meeten et al. 2016; Ottaviani et al. 2016b for time 0 and longitudinal resting state functional connectivity analyses).

The participant sample at time of follow-up was composed of 16 individuals (14 women; mean age = 29.6 ± 7.5 years) who met DSM-IV diagnostic criteria for GAD, and 16 healthy controls (HC; 13 women; mean age = 28.1 ± 10.1 years). Across the GAD group, the average illness duration at the beginning of the study (time 0) was 16.8 ± 8.0 years.

The study was approved by the National Research Ethics Service (NRES) for the National

Health Service (NHS) with university sponsorship granted via the Brighton and Sussex Medical School Research Governance and Ethics Committee. Participants were compensated for their time. GAD patients were recruited by public advertisement and from Access and Recovery Services clinics of Sussex Partnership NHS (Mental Health) Foundation Trust. Healthy control participants were recruited by advertisement from staff and students of the University of Sussex and Brighton and Sussex Medical School. All participants were right-handed, native English speakers, and had normal or corrected-to-normal vision. Exclusionary criteria were: Age younger than 18 years, prior history of head injury, major medical, neurological or psychiatric disorder (other than GAD and co-morbid depression for the patient group), cognitive impairment, history of substance / alcohol abuse or dependence, diagnosis of heart disease, obesity (body mass index > 30kg/m^2), pregnancy, claustrophobia and other MRI exclusions. Two GAD participants were included who used long-term medications (1 citalopram, 1 pregabalin) at the time of the study. All other patients and controls were medication-free. All participants provided written informed consent.

2.2. Procedure

The Structured Clinical Interview for DSM-IV (SCID) was administered by a trained postdoctoral fellow (FM) to both patient and controls to confirm/exclude the diagnosis of GAD and comorbidities. Participants then completed a series of online socio-demographic and dispositional traits questionnaires. Participants were subsequently familiarized with the neuroimaging environment, connected to the physiological recording equipment, and then underwent the fMRI protocol. Unfortunately, due to time constrains linked to availability of the MRI machine, the timing of the scans was variable within participants, although most of it took place in the early afternoon. Caffeine consumption was not restricted, but participants were carefully screened to exclude excessive consumers of coffee or caffeine containing products drinkers (detailed in Makovac et al., 2016b). Moreover, the pre-scanning testing lasted on average longer than 1 hour, thus, our participants were caffeine-free for at least 1 hour before scanning.

2.3. Experimental Task and Design

In the scanner, the participants performed a series of three low-demand 6-min long visuo-motor tracking tasks (for a total of 18 min), preceded by one 5-min block of resting-state acquisition. The total scanning duration was 23 min. Data obtained during the resting-state acquisition go beyond the scope of this study and will not be presented here (see Makovac et al., 2016b).

The tracking tasks (adapted from Ottaviani et al., 2013) required each participant to follow a white target circle, transiting slowly from left-to-right and back on a black background, across the field of view. Intermittently, the circle would briefly turn red. When this target event occurred, the participant was required to press a button on a button box in the right hand as quickly as possible. The colour change lasted 100 ms after which the circle returned to white and the task continued. Each transit across the screen lasted approximately 1 minute. There were never more than two target events in any transition and all events were separated by at least 30 sec. The order of transits with 1 or 2 targets was randomized. The level of difficulty remained very low to encourage the likelihood of mind-wandering and perseverative cognition. The task structure was implemented in Matlab 7.0 (MathWork, Natick, MA).

The first tracking task session differed from the other two sessions. Its purpose was to assess the typical range of RT for each participant, in order to establish the appropriate RT range for the subsequent probe runs. In this session, 9 targets were presented over 6 transitions, and the participant simply tracked the moving circle and responded with a button press whenever it changed colour.

During the second and third tracking sessions, visual analogue scale (VAS) thought probes were deployed immediately after participants' responses to a subset of the targets. Probe appearance was restricted following three criteria: First, thought probes were only presented following an unusually short or an unusually long RT, determined from the data obtained in the first tracking session. For each individual, RT above the third quartile of the distribution were considered unusually long (suggestive of off-task cognitions). Those below the first quartile were considered unusually short (suggestive of a sharp focus on task). One additional criterion was set such that probes could not be deployed on two consecutive targets. These conditions were intended to limit the number of thought probes and therefore prevent the individual from being accustomed to probe appearance, interfering with episodes of being on- or off-task. Session two and three consisted of 18 targets presented over 12 transits.

Thought probes consisted of 3 short (5 sec) cues, to which the participant responded by quickly moving a pointer along a horizontal scale, appeared on the screen beneath. The cues assessed participant's thoughts immediately prior to target appearance. Participants were required to estimate how much they were engaged in perseverative cognition, mind-wandering, or how much they were on task. The scales were labelled at the left-hand end "0" and the right-hand end "100". The intention of each of these cues was carefully described and explained prior to commencement of the task session, especially for what regards the difference between mind-wandering ('*how much is your mind-wandering, i.e. thinking about different things or events, without being stuck in one particular thought'*) and perseverative cognition ('*how much are you thinking of a past stressful event or worrying about a future possible event. This thought has to be perceived as being intrusive - i.e. difficult to disengage from*'). Each participant was permitted to practice until they were fully comfortable with the response procedure.

2.4. Visual analogue scales (VAS)

At the end of each tracking task, to assess state levels of perseverative cognition and mood over the preceding period, each participant was asked to report his/her thoughts. The participants were asked to rate on separate 100-point VASs, how much: "Were you ruminating (thinking over and over) about yourself, the past, or worrying about the future?"; "Was your mind just wandering, without getting stuck on any particular thought?"; "Were you focused on the task?"; "Did you experience your thought as being intrusive?"; "Were you feeling sad?"; "Were you feeling tired?";

“Were you feeling anxious?”; “Were you feeling angry?”; and “Were you feeling happy?”

2.5. Socio-demographic and dispositional traits questionnaires

Participants completed questionnaires assessing sociodemographic information, symptoms of GAD (Generalised Anxiety Disorder Questionnaire, GAD-7; Spitzer et al., 2006); trait anxiety (Taylor Manifest Anxiety Scale, TMAS; Taylor, 1953 and Spielberger State Trait Anxiety Inventory, STAI; Spielberger, 1989); depression (Beck Depression Inventory, BDI; Beck et al., 1988), trait worry (Penn State Worry Questionnaire, PSWQ; Meyer et al., 1990), and trait depressive rumination (Ruminative Response Scale, RRS; Nolen-Hoeksema and Morrow, 1991). Higher scores on these questionnaires indicate increased severity of GAD symptoms, more dispositional anxiety, more severe symptoms of depression, a stronger tendency to engage in worrisome thoughts and in depressive rumination, respectively.

2.6. Pupil size acquisition and pre-processing

Pupil measurements were acquired at 120 Hz, via an ASL EyeTrac6000 system with long-range optics (ASL Applied Sciences). Eye blinks and anomalous pupil values were automatically detected by the EyeTrac6000 software, and artifacts were corrected by interpolating values. The resulting time-series were exported to Matlab and further visually inspected and, where necessary, manually corrected by removing artificial time-points. Pupil data were then smoothed and down-sampled using in-house built Matlab scripts to provide an interpolated measure of pupil diameter at 1-sec intervals. Next, pupil size was averaged across each 3-sec interval preceding target appearances and used in subsequent analyses. However, technical issues constrained analysis of this parameter to a subset of 18 participants, comprised of 6 HC (mean age = 29.50 ± 6.64 years) and 12 GAD (mean age = 23.33 ± 5.39 years), all women.

2.7. MRI acquisition and image pre-processing

Neuroimaging datasets were acquired on a 1.5 Tesla MAGNETOM Avanto Scanner (Siemens AG, Munich, Germany). Functional Magnetic Resonance images (fMRI) comprised of T2*-weighted echo planar imaging (EPI), sensitive to blood oxygenation-level dependent signal (RT = 2.52 secs, ET = 43 msec, flip angle 900, 34 slices, 3 mm slice thickness, FOV=192 mm, voxel size = 3 x 3 x 3 mm). Data were processed using MATLAB 7.0 (MathWork, Natick, MA) and SPM12 (Statistical Parametrical Mapping, http://www.fil.ion.ucl.ac.uk). In the two fMRI runs including thought probes, the first four volumes were removed to allow for T1 equilibration effects. EPI images were realigned to the first image and normalized to a standard EPI template. Normalized functional scans were smoothed with a Gaussian kernel of 8-mm (full-width half maximum).

3. Statistical Analyses

3.1. Analysis of behavioural (RT) and pupil data

All data are expressed as means ± *SD*. Differences at $p < 0.05$ are regarded as significant. In order to validate RT and pupil size as proxies of the ongoing mental state (i.e., episodes of being on task, mind-wandering, perseverative cognition), we first tested the associations between RT and VAS scores and then between pupil size, RT, and VAS scores. Then, we examined the intercorrelations among VAS scores obtained during the task, to disentangle the effects of mind-wandering and perseverative cognition on mood and perceived intrusiveness of thoughts, further testing the validity of our in-task operationalization of these variables.

We used mixed random effects regression models to test our hypotheses taking into account the likely heterogeneity in the periodicity of RT, VAS, and pupil changes, and using all sampling moments instead of aggregated scores within these analyses. This procedure also accommodated interindividual variation and dealt with missing values by modelling each participant as a random effect. General linear mixed modelling with Restricted Maximum Likelihood estimation was implemented using the PROC MIXED program (SAS Institute). Covariance analyses modelled observations within subject using a random intercept plus autoregressive model. Random slopes were not estimated. The "ADJUST" option was implemented to perform multiple comparison adjustments on the differences of LS-Means.

Two complementary statistical approaches were used to test whether RT could be effectively used as an indicator of the ongoing mental state of the participant. First, we used a random effects regression model where scores on the VAS for each specific cognitive state (on-task, mind-wandering, perseverative cognition) were related to the dependent variable RT, with Group membership (GAD vs HC) was included as a predictor in the model. Second, we performed a median-split, based on each participant's RT, to obtain the dichotomous variable of (Long- and Short-) RT. A series of *t*-tests were then performed to test for differences in levels of self-reported episodes of being on task, mind-wandering, and perseverating for Short and Long RT.

Similarly to RT, we adopted a random effects regression model to explore the relationship between pupil diameter (prior to targets) and participants' reported ongoing mental state. First, pupil diameter was related to RT (Long vs Short), Group, and RT x Group interaction. Second, to test whether the central effects were moderated by VAS scores, the same model was repeated by entering the moderator and the moderator x RT, and moderator x Group x RT as predictors. Three models were run, testing for moderation by a) VAS on perseverative cognition; b) VAS on mind-wandering; and c) VAS on being on task, respectively.

3.2. fMRI data analysis

All analyses were undertaken using the SPM platform (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). First-level analyses, estimating contrasts of interest for each participant, were followed by second-level analyses for statistical inference at the group level (Friston et al., 2002).

3.2.1 Neural correlates of Long RT versus Short RT during target detection and pre-target periods

The dichotomous variable Long- and Short-RT, for each participant and each run, was entered into the first-level analysis. In this way, we were able to allocate *a posteriori* target detection periods as being characterized by Long RT (a proxy for being off-task) or Short RT (a proxy for being on-task). We carried out two different first-level models to test for neural activity associated with periods during which participants disengage from on-task mental state; 1) to press the button, in order to detect changes in fMRI signal in response to the transition from internally- to externally-oriented attention; or 2) when cognitive or sensory demand is low and the likelihood of mind-wandering and perseverative cognition is elevated (i.e., pre-target periods).

First, we modelled two conditions, corresponding to the target detection, separately for Long RT- and Short RT-target detection. The model included one regressor, corresponding to the onset of each target type; next, we modelled the pre-target periods (i.e. the time-window before the appearance of the target). The window in which neural data was investigated was limited to a 15-sec pre-target window. Based on the Long vs Short RT, we can infer that such pre-target period was characterized by more or less effective external attention, respectively. We opted for a 15-sec window based on evidence showing that 15 sec approaches the typical length of mind-wandering episodes (Klinger, 1978) and based on previous studies which consistently showed that this time window coincides with mind-wandering and introspective states (e.g., He et al., 2011; Ottaviani et al., 2016b; Smallwood et al., 2011).

For both first-level models, we constructed linear compounds (contrasts) to determine the effect of the two relevant trial types (Long RT and Short RT), averaged across the two fMRI runs.

3.2.2 Neural correlates of pupil responses for Long RT versus Short RT

In order to determine the neural correlates of pupil responses within each target detection condition (Long vs Short RT), the average pupil dimension (averaged across the 3 sec preceding each target appearance) was entered into a third GLM as separate parametric modulator to the corresponding RT conditions (Long and Short RT). This analysis was conducted for the sub-group of 18 participants (detailed in section 2.6). All of our variables were modelled as a boxcar within the time-series, all predictors of neural activity were convolved with the SPM12 hemodynamic response function, and realignment parameters (six head movement parameters, estimated during realignment) were included as covariates of no interest.

3.2.3 Neural correlates of mind-wandering and perseverative cognition during target detection and pre-target periods

In second level analyses, for both the target detection and the pre-target models, four conditions resulting from the Group (GAD, HC) x RT (Long, Short) combination were modelled with a 2 x 2 flexible factorial ANOVA. We tested for the main effect of RT across the two groups, the main effect of groups across the two RT conditions, and for the Group x RT interaction. Statistical threshold was set to $p < 0.05$, FWE-corrected at cluster level (cluster size defined using uncorrected voxel-level threshold $p < 0.005$) at a whole-brain level.

A whole-brain correlational analysis was carried out for each of our two models of interest (i.e., during target detection and pre-target periods). This analysis allows the neural correlates of mind-wandering and perseverative cognition during periods of effective and ineffective external attention to be interrogated. VAS scores for mind-wandering and perseverative cognition were introduced into the model as covariates of interest. This allows the identification of those regions where activity was positively or negatively associated with scores on the perseverative cognition VAS (whilst controlling for mind-wandering) and, *vice versa*, regions associated with scores on the mind-wandering VAS (while controlling for levels of perseverative cognition).

3.2.4 Effects of mind-wandering and perseverative cognition on pupil-related brain activations during target detection

A parametric analysis was used: First, to test for the main effect of pupil size variation on brain activity during target detection, across the two conditions of Long and Short RT; then, to test for the difference between Long and Short RT. Group membership was treated as a covariate of no interest, since the small sample size did not allow for meaningful group comparisons. Nevertheless, this analysis remained consistent with our dimensional view of psychopathology and perseverative cognition, which should be only quantitatively but not qualitatively different in HC and GAD (e.g., Ruscio and Borkovec, 2004). VAS scores that quantified subjective perseverative cognition and mind-wandering were introduced as covariates of interest at second level, to explore the possible effects of the ongoing mental state on pupil-related brain activation.

4. Results

4.1. Descriptive results

As shown in Table 1, both groups were broadly comparable in the socio-demographic variables assessed (i.e., age, sex, education). These were, therefore, not included as covariates in the subsequent analyses. As to scores on dispositional questionnaires, participants with GAD reported higher levels of depressive rumination, anxious worry, symptoms of generalized anxiety, trait anxiety, and depression.

At the end of the two runs, GAD participants reported higher levels of self-reported (VAS) perseverative cognition (GAD = 54.59 ± 25.59 vs HC = 27.53 ± 23.29; $t(15) = 3.41$; $p = 0.004$); anxiety (GAD = 53.38 ± 25.93 vs HC = 25.53 ± 29.12; $t(15) = 3.07$; $p = 0.007$); sadness (GAD = 26.25 ± 22.72 vs HC = 7.78 ± 10.42; $t(15) = 3.09$; $p = 0.006$); and lower levels of happiness (GAD = 42.28 ± 22.93 vs HC = 64.75 ± 16.19; $t(15) = 3.46$; $p = 0.003$) compared to HC (Figure 1). There were no differences in the number of probes occurring within the trials between the two groups (GAD = 3.45 ± 1.88 vs HC = 3.38 ± 1.70; $t < 1$).

As expected, higher self-reported levels of perseverative cognition were associated with significantly higher levels of intrusiveness, sadness, and anxiety. In contrast, self-reported levels of mind-wandering did not show any significant association with scores on these rating scales (Table 2). Interestingly, the more the thought was reported to be intrusive, the more the participant felt tired, anxious and angry (Table 2).

4.2. RT as a proxy for ongoing mental state

Results of the first random effects regression model that had scores on the VAS for each specific cognitive state (on-task, mind-wandering, perseverative cognition) and Group membership (GAD vs HC) as predictors of RT are depicted in Figure 2. The Figure shows that the perseverative cognition slope starts as low as at about 20/100 and at a lower point than the mind-wandering slope: This is not unexpected if we consider that, contrary to other studies using the same methodology in healthy individuals and patients with GAD (e.g., Ottaviani et al., 2013; 2016b), the present investigation did not include a perseverative cognition induction. The model yielded a significant effect of being on task, $F(1, 429) = 46.09$, $p < 0.0001$, with higher VAS scores for being on task characterized by faster RT. Levels of perseverative cognition, $F(1, 429) = 14.30$, $p < 0.001$ and mind-wandering $F(1, 429) = 5.76$, $p = 0.02$ were also significantly associated with RT: Higher VAS scores for these descriptors of off-task thinking were characterized by slower RT. Group membership was also a significant predictor in the model, $F(1, 429) = 5.20$, $p = 0.02$: HC showed faster RT than participants with GAD (Figure 2).

A second complementary statistical approach was based on a median-split of each participant's RT, to obtain the dichotomous variable of (Long- and Short-) RT. Consistent with results of the first random effects regression model, self-reported cognitive states differed significantly between periods associated with Short and Long RT. Participants reported being more on task during periods associated with Short RT, compared to Long RT (47.7 ± 25.04 vs 60.7 ± 26.51, respectively; $t = 5.27$, $p < 0.0001$). Correspondingly, levels of mind-wandering ($t = 2.74$, $p = 0.01$) and perseverative cognition ($t = 3.52$, $p < 0.0001$) were higher during Long RT (68.2 ± 24.02 and 32.7 ± 27.42, respectively) compared to Short RT (61.20 ± 29.14 and 23.63 ± 26.54, respectively).

4.3. Pupil size as a proxy for ongoing mental state

Larger pupil diameter was observed during periods of Long- compared to Short-RT ($F(1, 242) = 4.17$; $p = 0.04$). There was also a significant Group x RT interaction: individuals with GAD had larger pupil diameters in association with long RT compared to HC ($F(1, 241) = 6.05$; $p = 0.01$). The association between pupil size and RT was mediated by self-reported perseverative cognition ($F(1, 237) = 12.29$; $p < 0.0001$), and by the interaction of perseverative cognition with RT ($F(1, 237) = 11.09$; $p < 0.0001$). Thus, longer RT was associated with larger pupil diameter only in combination with higher scores on this VAS (see Figure 3). Interestingly, pupil size was not larger during self reported mind-wandering ($p > 0.77$).

4.4. FMRI results

4.4.1. Neural correlates of Long RT versus Short RT during target detection

During target detection, greater activity was observed in the cerebellum (right IX lobule) and right inferior and middle temporal gyrus for events associated with Long- compared to Short- RT (Figure 4, A; Table 3). A Group x RT interaction was observed in right superior temporal gyrus, driven by a deactivation of this area in GAD patients during target detection events associated with Long RT. Deactivation in this region occurred in HC during target detection characterized by Short RT (Figure 4, B; Table 3).

4.4.2. Neural correlates of mind-wandering and perseverative cognition during target detection

When controlling for VAS scores of perseverative cognition, the reported level of mind-wandering correlated with activity within paracingulate, anterior cingulate cortex, and postcentral/superior parietal lobule during Long RT vs Short RT events (Figure 5A; Table 3). This result indicates that, regardless of the level of perseverative cognition, periods of mind-wandering, exhibited increased activity in these areas during Long- compared to Short-RT trials. No interaction with GAD was observed.

When controlling for VAS scores of mind-wandering, a GAD x HC interaction was observed for the correlation between reported level of perseverative cognition activity within areas of posterior cingulate cortex and cerebellum during Long RT vs Short RT events (Figure 5, B; Table 3). The effect was driven by a positive effect in HC, and a negative effect in GAD patients. This result suggests that, in GAD individuals, greater perseverative cognition is associated with less neural activity in these areas during Long-RT trials, whereas in HC, an opposite effect was observed.

4.4.3. Neural correlates of Long RT versus Short RT during the pre-target period

During the pre-target period, an increased activity was observed during Long vs Short RT trials in right postcentral gyrus and superior temporal gyrus (Figure 6, A). No Group X RT interactions were observed.

4.4.4. Neural correlates of mind-wandering and perseverative cognition during pre-target periods

Across both groups of GAD individuals and HC, when controlling for VAS scores of perseverative cognition, self-rated mind-wandering was positively correlated with activity in bilateral precentral gyrus and left superior temporal gyrus during pre-target periods preceding Long RT vs Short RT (Figure 6, C). Similarly, when controlling for VAS scores of mind-wandering, a negative correlation was observed for self-rated perseverative cognition and cerebellar activation during pre-target periods preceding Long RT vs Short RT (Figure 6, B).

4.4.5. Neural correlates of pupil responses for Long RT versus Short RT

At target detection, brain correlates of trial-by-trial pupil response revealed significant differences between Long and Short RT trials (Figure 7, A; Table 4): activity within the superior frontal gyrus showed a negative association with pupil size during Short-RT trials, and a positive association with pupil size during Long-RT trials. We did not observe suprathreshold associations between brain activity and pupil size variations that were sustained across all Long and Short RT conditions.

4.4.6. Effects of mind-wandering and perseverative cognition on pupil-related brain activations

When controlling for VAS scores of perseverative cognition, self-rated levels of mind-wandering interacted with neural activity tracking pupil size at target detection in the right superior frontal gyrus and right precentral gyrus depending on the associated RT (Figure 7, B; Table 4). During Short RT periods there was a negative association, indicating that higher levels of mind-wandering were linked to less pupil-related activity. In contrast, during Long RT periods there was a positive association, indicating that higher levels of mind-wandering were linked to greater pupil-related activity in these frontal regions. A Short x Long RT interaction was evident for the association between scores on the VAS about perseverative cognition and activity in pupil-related brain areas (whilst controlling for scores on the VAS about mind-wandering), in right precentral/postcentral area (Figure 7, C; Table 4). The interaction was driven by a positive association during Short RT and a negative association during Long RT.

5. Discussion

Motivated to understand the difference between normal mind-wandering and maladaptive perseverative cognition, we combined fMRI techniques with measures of behaviour (RT) and peripheral physiology (pupil size) to disentangle the neural correlates of functional and dysfunctional forms of ongoing thought, in individuals with a diagnosis of GAD and in healthy controls. We used a novel approach in which experience sampling probes were administered when RT was slow or fast, allowing us to capture clearly distinct behavioural episodes. Self-reports following periods of slow RT were linked to greater off task thinking, strengthening evidence showing that mind-wandering experiences can be predicted from trial-to-trial RT changes (e.g. Franklin et al., 2011). While earlier work has linked the occurrence of task-unrelated thoughts to preceding RT patterns (Smallwood et al., 2008), this observation has not always been replicated (e.g. McVay et al., 2012) and others conclude that RT alone is not a reliable index of the occurrence of mind-wandering episodes (e.g. Henríquez et al. 2016; Konishi et al., 2017). Many of these behavioural studies, however, use different versions of the sustained attention to response task (SART; Robertson et al., 1997), many of which are of longer duration and require the additional demand of response inhibition. In such tasks, it has been argued that failure to predict the ongoing cognitive state by the use of RT is mostly due to anticipations (i.e., where a substantial proportion of slow RT precede on-task reports) (Henríquez et al., 2016). RT increases across blocks, hence these problems are mitigated by the use of a shorter and less demanding task. Moreover, *"the dichotomy between on- and off-task conditions might not be subtle enough to capture the richness of phenomenological experience"* (Henríquez et al., 2016, page 8). More generally, therefore, we provide evidence in support of the idea that at least some of the behavioural consequences that emerge from patterns of ongoing thought can depend on features of the experiences themselves (Smallwood and Andrews-Hanna, 2013).

When we looked at the association between behaviour and ongoing physiology, long RT was reflected in larger pupil diameter, replicating prior observations (e.g. Konishi et al., 2017; Smallwood et al., 2011). For example, Konishi et al. (2017) found that pupil diameter during periods when behavioural performance was less efficient (as assessed by RT and accuracy), was associated with larger pupil diameter, while periods of off task thinking were not. We found that this was particularly true in individuals with GAD, compared to controls, and when participants reported higher levels of perseverative cognition. Pupil dilation reflects the balance between central sympathetic activation driving the dilator muscle, and to parasympathetic inhibition reducing constriction (Beatty and Lucero-Wagoner, 2000). Our findings suggest that off-task attentional drift, repetitive perseverative form of thoughts, and pathological anxiety states are all reflected in indices of pupil dilation, and by extension, arousal related shifts in autonomic balance. The complexity of these results may partially explain previous inconsistency in relating mind-wandering to pupil diameter. Larger pupil diameter is reported by some studies (e.g., Franklin et al., 2013; Smallwood et al., 2011), but not others (e.g., Grandchamp et al., 2014; Konishi et al., 2017; Unsworth and Robison, 2016; 2018), suggesting that understanding the links between pupil size and ongoing thought are likely to depend on taking account of the content of the episodes themselves (Konishi et al., 2017). Indeed, studies that examined pupil size in association with perseverative cognition show a consistent positive association between dilation and self-report measures of rumination (Duque et al., 2014; Siegle et al., 2003). Data on worry and GAD, however, are more mixed (e.g., Greenberg et al., 2013; Oathes et al., 2011). On the other hand, autonomic and behavioural measures, perseverative cognition appears to act as if one was facing an actual environmental stressor (Brosschot et al., 2006; Ottaviani et al., 2016a). Thus, our finding of increased pupil dilation, when distracted or absorbed by rumination or worry is not unexpected, particularly for individuals with GAD.

While many studies have explored the brain correlates of patterns of ongoing thought in healthy individuals, ours is one of the first to explore this question in a psychopathological population (individuals with GAD), who experience excessive perseverative cognition as a diagnostic criterion (American Psychiatric Association, 2013). It is also one of the first to explore the neural correlates of multiple aspects of experience (although see Sormaz et al., 2018). We found that periods preceding target detection 'tagged' by long RT were associated with decreased activation of cerebellum when participants were engaged more in perseverative cognition, independent of effects of mind-wandering. The cerebellum is implicated in the pathophysiology of many disorders including attention deficit hyperactivity disorder (ADHD; Ivanov et al., 2014; Kucyi et al., 2015; Valera et al., 2007), a condition associated with higher frequencies of mind-wandering (Seli et al., 2015). The middle temporal gyrus also showed enhanced activity during long RT pre-target periods. This region is important for aspects of semantic representations which may play a role in certain aspects of off task experiences (Davey et al., 2015; Smallwood et al., 2016).

More directly, when participants reported being strongly engaged in mind-wandering, activity was enhanced within anterior cingulate/paracingulate cortex, postcentral and superior parietal lobule during target detection and bilateral precentral gyrus and left superior temporal gyrus during the period before target occurrence. Such activation, proportional to the level of pre-target mind-wandering, may reflect motor readiness due to target occurrence. Many of these brain regions are present in a meta-analysis of prior studies of mind-wandering using functional imaging (Fox et al., 2015). More recently Sormaz and colleagues (2018) used representational similarity analysis to show that patterns of activity in regions of sensory-motor cortex are linked to the degree of off task thinking during a simple working memory paradigm, while signals within the default mode network were related to how detailed patterns of thought were. Similarly, Turnbull et al. (2018) demonstrated connectivity between the ventral attention network and regions of sensori-motor cortex underlies the regulation of off task thinking in the same task paradigm. Together with the current data, these studies provide an important source of converging evidence that simple-minded associations between activity within the DMN and states of off task thinking are unwarranted.

Pre-target, episodes of increased self-reported perseverative cognition in long-RT trials involved decreased activation in the cerebellum in all participants. At target detection, the same episodes were accompanied by decreased activation in posterior cingulate cortex and cerebellum in GAD, a pattern that was reversed in healthy individuals. Increased activation in the posterior cingulate cortex is associated with rumination in depressed individuals (e.g., Berman et al., 2011; Cooney et al., 2010) but not with worry, with some studies reporting activation in the anterior cingulate cortex (e.g., Hoehn-Saric et al., 2004; Ottaviani et al., 2016b; Paulesu et al., 2010). Moreover, dispositional tendency to ruminate and worry (as measured by the RRS and PSWQ) is inversely related to amygdala connectivity with the posterior cingulate cortex in both individuals with GAD and controls (Makovac et al., 2016b). The posterior cingulate cortex is activated by target detection tasks and has specifically been implicated in the anticipatory allocation of spatial attention (e.g., Small et al., 2003). It has been argued that this region is a representational hub in which signals from other regions of cortex are integrated to produce different mental states (Leech and Sharp, 2014 for a review; Smallwood et al., 2016). Accordingly, it is possible that the lower task-related activation associated with higher levels of perseverative cognition in GAD participants may reflect an inability to redirect attention to external information in this clinical population.

More generally, our data highlights neural differences between adaptive mind-wandering and maladaptive perseverative cognition (worry and rumination). When target events were modelled, pupil size was negatively associated with activation of the superior frontal gyrus for short RT (on-task) periods, and with enhanced activation of the same area in the case of long RT (off-task) periods. Furthermore, higher self-ratings of mind-wandering (ruling out the effects of perseverative cognition) attenuated pupil-related activity within the right superior frontal gyrus and right precentral gyrus when on-task (short RT) and enhanced activity within these brain regions when off task (long RT). This region of cortex is thought to be important in the control of memory, allowing individuals to suppress unwanted trains of thought (Levy and Anderson, 2012). Since this region was more active in mind-wandering than perseverative cognition, it is possible, therefore, that this region is important in allowing patterns of ongoing thoughts to be less detrimental to the individual. In contrast, perseverative cognition was linked to enhanced pupil-related activation in right precentral/postcentral area while on-task (short RT) yet attenuated this activity when off- task (long RT). The precentral and postcentral gyri are part of the somatomotor network, possibly underlining the important role that signals arising from the body play in perseverative patterns of ongoing thought. More generally, our study reinforces the value of mapping brain-body interactions in attempts to understand the genesis and maintenance of different aspects of ongoing thought (Ottaviani et al., 2017; Ottaviani, 2018).

Although the present study focused on GAD, perseverative cognition is a transdiagnostic factor (e.g., Drost et al., 2014) and current findings are in line with the current integrated cognitive neurobiological model of depression, in which the neurobiological underpinning of core symptoms (in particular the subgenual section of the ACC), plays an important role as risk or maintenance factor for the disorder (Disner et al., 2011).

While our study provides a fine-grained investigation into the mechanisms of normal and pathological self-generated thoughts, there are a number of open questions that future studies should address. First, the statistical power of our study was constrained by our sample size. In particular, the analyses on pupil diameter were conducted on a subsample of participants, where the number of participants with GAD was the double (*n* = 12) compared to the number of controls (*n* = 6). This uneven ratio suggests a need for replication and in our fMRI analysis of pupil data, group was not included as a variable of interest. Thus, it remains unclear whether the impact of pupil dilation is consistent across healthy and anxious populations. Second, there was an unequal gender distribution in the GAD group, reflecting population levels distributions of GAD diagnosis (McLean et al., 2011). Future studies with a larger sample size could explore whether patterns of neural activity, and their associations with ongoing thoughts, are similar across gender. Third, due to difficulties in keeping patients with GAD in the scanner for a longer period of time, the duration of testing, and hence statistical power, was limited to more exhaustive investigations (i.e. in Sormaz et al., 2018 in which participants were studied for a two-hour session). Studies on brain arousal assessed by electroencephalography showed that vigilance already decreases after 10 min (Huang et al., 2017; Olbrich et al., 2011), and our participants had already been in the scanner for a 5-min resting state period before starting the task. All considered, it is important to note that Sormaz et al.'s and our results provide converging evidence for the involvement of the sensorimotor cortex in off task states.

Such limitations notwithstanding, our study is the first aimed at disentangling the pupillary and neural correlates of mind-wandering and perseverative cognition in healthy controls and GAD. We used a novel method that allowed insight into the neural processes underling different patterns of experience during episodes when behaviourally they were disengaged from the external world. Moving forward, replication of this study in a larger sample size using a greater number of probes would provide important insights into the neural mechanisms that underlie the differences between patterns of more and less pathological modes of perseverative cognition that characterizes GAD. In the future our approach may have the potential to inform the development of preventive strategies and therapeutic programs for anxiety disorders and other disorders by helping determine the neural patterns that characterise patterns of cognition in different psychiatric disorders.

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Figures captions

Figure 1. Differences between the two groups in the visual analogue scales (VAS) ratings over the tracking task periods.

Note. GAD = Generalized Anxiety Disorder; HC = Healthy Controls; MW = Mind-wandering; PC = Perseverative cognition; INTR = Intrusiveness. * $p \leq 0.05$.

Figure 2. Association between scores on the visual analogue scales (VAS) and response time (RT) in participants with Generalized Anxiety Disorder (GAD) and Healthy Controls (HC). Trial level data, rather than aggregated scores were used for all analyses and for illustrative purposes. Overall, across the two groups, a positive correlation was evident between RT and scores on the VAS about perseverative cognition (VAS PC) and VAS about mind-wandering (VAS MW), whereas a negative correlation was observed between RT and scores on the VAS about being on task (VAS On task).

Note. Black lines indicate regression lines.

Figure 3. Relationship between pupil size and ongoing levels of perseverative cognition. Longer response times (RTs) were associated with larger pupil diameter only in combination with higher scores on the visual analogue scales (VAS) about perseverative cognition (VAS-PC).

Note. Low-PC = Low scores on the VAS on perseverative cognition and High-PC = High scores on the VAS on perseverative cognition set as +/- 1 standard deviation from the mean. Error bars: 95% confidence interval.

Figure 4. Brain regions showing: A) Long > Short RT difference for the target detection event (upper panel) and B) A Group X RT interaction (lower panel). The signal plot shows the significant Group X RT interaction effect, driven by a deactivation within right superior temporal gyrus during target detection events characterized by Long RT in GAD, and by Short RT in HC.

Note. GAD = Generalized Anxiety Disorder; HC = Healthy Controls; RT = Response Time.
The parameter estimates are mean-adjusted across the 4 conditions and are expressed in arbitrary units (a.u., ± 90% confidence interval). SPM display threshold: p-unc = 0.005, minimum cluster size = 96 voxels

Figure 5. A. Brain areas showing a correlation between scores on the visual analogue scales (VAS) for mind-wandering (VAS-MW) and VAS scores for perseverative cognition (VAS-PC). B. Contrast Long > Short Response Time (RT) in healthy controls (HC) and individuals with Generalized Anxiety Disorder (GAD).
Note: The parameter estimates are mean-adjusted and are expressed in arbitrary units (a.u., ± 90% confidence interval). SPM display threshold: p-unc = 0.005.

Figure 6. A) Brain regions showing increased activity during the pre-target period preceding Long vs Short response time (RT). B) Brain areas showing a positive correlation (across groups) between scores on the visual analogue scales (VAS) on mind-wandering (VAS-MW) and the Long > Short contrast, controlling for scores on the VAS on perseverative cognition (VAS-PC). C) Brain areas showing a negative correlation (across groups) between scores on the VAS-PC and Long > Short contrast, controlling for scores on the VAS-MW.
Note. GAD = Generalized Anxiety Disorder; HC = Healthy Controls. The parameter estimates are mean-adjusted and are expressed in arbitrary units (a.u., ± 90% confidence interval). SPM display threshold: p-unc = 0.005.

Figure 7. A) Brain correlates of trial-by-trial pupil response for Short and Long response time (RT) trials. B) Brain areas tracking pupil response that exhibited a correlation with scores on the visual

analogue scale (VAS) about mind-wandering (VAS-MW), when controlling for scores on the VAS about perseverative cognition; VAS-PC. C) Brain areas associated with pupil response that exhibited a correlation with VAS-PC scores, when controlling for scores on the VAS-MW.

Table 1

Table 1. Sociodemographic and dispositional trait differences between individuals with generalized anxiety disorder (GAD) and healthy controls (HC)

	GAD (n = 16)	HC (n = 16)	Statistics
Age (years)	29.62 ± 7.51	28.12 ± 10.11	$t < 1$
Sex (M/F)	2/14	3/13	$\chi 2 = 0.23$, $p = 0.63$
Education (years)	13 ± 1.78	12 ± 2.73	$t(15) = 1.22$, $p = 0.23$
Disease duration (years)	16.12 ± 8.26		
RRS	51.44 ± 11.87	40.06 ± 10.82	$t(15) = 3.04$, $p = 0.008$
PSWQ	67.06 ± 6.79	39.43 ± 14.05	$t(15) = 9.72$, $p < 0.0001$
GAD	10.18 ± 4.87	4.18 ± 4.49	$t(15) = 4.04$, $p = 0.001$
STAI	53.43 ± 9.07	35.43 ± 7.04	$t(15) = 7.72$, $p < 0.0001$
TMAS	25.12 ± 4.80	11.50 ± 6.50	$t(15) = 6.60$, $p < 0.0001$
BDI	21.56 ± 12.09	4.81 ± 4.47	$t(15) = 9.06$, $p < 0.0001$

Note. M = Males; F = Females; RRS = Ruminative Response Scale; PSWQ = Penn State Worry Questionnaire; GAD = Generalized Anxiety Disorder Questionnaire; STAI = Spielberger State Trait Anxiety Inventory; TMAS = Taylor Manifest Anxiety Scale; BDI = Beck Depression Inventory.

Table 2

Table 2. Correlations between scores on the administered visual analogue scales (VAS).

		MW	PC	Intrusive	Sad	Tired	Anxious	Angry	Happy
MW	r	**1**	-0.056	0.034	-0.083	0.198	-0.098	0.121	0.180
	p		0.760	0.853	0.652	0.278	0.595	0.510	0.325
PC	r		**1**	**0.555****	**0.586****	0.334	**.563****	0.328	-0.152
	p			**0.001**	**<0.001**	0.062	**0.001**	0.067	0.405
Intrusive	r			**1**	0.295	**0.372***	**0.508****	**0.449***	-0.006
	p				0.101	**0.036**	**0.003**	**0.010**	0.974
Sad	r				**1**	**0.419***	**0.653****	**0.377***	**-0.604****
	p					**0.017**	**<0.001**	**0.034**	**<0.001**
Tired	r					**1**	**0.349**	0.086	0.034
	p						**0.050**	0.641	0.854
Anxious	r						**1**	**.395***	**-.440***
	p							**0.025**	**0.012**
Angry	r							**1**	-0.240
	p								0.186

Note. ** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed). PC = Perseverative cognition; MW = Mind-wandering.

Table 3

Table 3. Brain areas showing a main effect of Response Time type (RT; Long RT > Short RT), Group by RT interaction, and correlations with the visual analog scales (VAS) for mind-wandering (MW) and perseverative cognition (PC) both at target detection (1) and during the pre-target periods (2).

		Cluster		**Voxel**	
Brain region	Side	*k*	*p FWE*	*z*	*MNI xyz*
(1) Target detection event					
Long RT > Short RT					
Cerebellum	R	266	0.005	4.06	*27 -52 -38*
				3.45	*12 -49 -44*
Inferior temporal gyrus	R	183	0.033	3.92	*54 -43 -14*
Middle temporal gyrus	R			3.77	*51 -43 -5*
Group x RT interaction					
Superior temporal gyrus	R	96	0.013	3.53	*51 -4 -8*
Positive correlation between the Long RT > Short RT contrast and VAS-MW					
Paracingulate	R	183	0.015	3.82	*3 2 52*
Anterior cingulate cortex	R			3.14	*0 17 31*
Postcentral gyrus/superior parietal lobule	L	303	0.001	3.76	*-36 -37 64*
HC x GAD interaction for in the association between VAS-PC and the contrast Long RT > Short RT					
Cerebellum. Right I-IV	R	364	<0.001	3.82	*6 -49 -11*
Posterior cingulate cortex				4.05	*9 -58 28*
(2) Pre-target task-free period					
Long RT > Short RT					
Post-central gyrus	R	369	<0.001	3.62	*48 -22 61*
Superior temporal gyrus	R	414	<0.001	3.45	*66 -16 7*
Positive correlation between the Long RT > Short RT contrast and VAS-MW					
Precentral gyrus	R	265	0.015	3.77	*39 -13 61*
	L	199	0.029	3.28	*-30 -16 43*
Superior temporal gyrus	L			3.58	*-21 -10 58*
Negative correlation between the Long RT > Short					

RT contrast and VAS-PC				
Cerebellum	404	0.002	4.14	*45 -52 -35*

Note. *GAD =* Generalized Anxiety Disorder; HC = Healthy controls; *RT =* Response time; VAS-PC = scores on the VAS for perseverative cognition; VAS-MW = scores on the VAS for mind-wandering. FWE = family wise error correction; k = cluster size; MNI = Montreal Neurological Institute brain template; z = z-values.

Table 4

Table 4. Activity in pupil-related brain areas.

Brain region	Side	Cluster *k*	Cluster *p FWE*	Voxel *z*	Voxel *MNI xyz*
Long RT > Short RT					
Superior frontal gyrus		133	<0.001	3,26	*-6 32 58*
Short x Long RT interaction for VAS-MW					
Superior frontal gyrus	R	131	<0.001	3,89	*9 32 58*
Precentral gyrus	R	105	0,001	3,68	*57 14 31*
Short x Long RT interaction for VAS-PC					
Pre-central/post-central gyrus		292	<0.001	3,81	*36 -22 52*

FWE = family wise error correction; k = cluster size; MNI = Montreal Neurological Institute brain template; z = z-values.

Figure 1

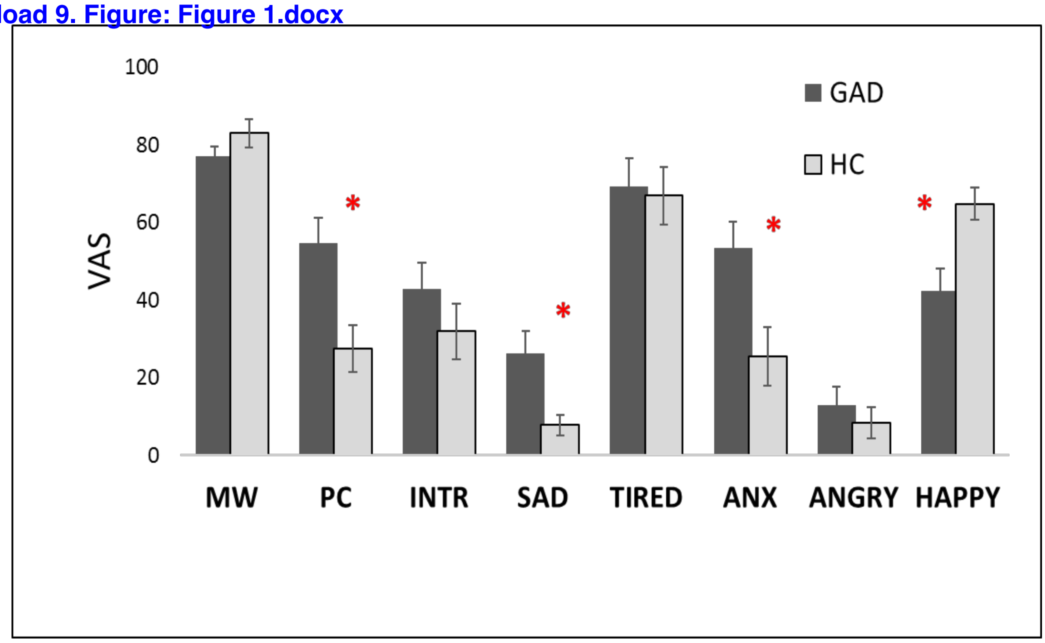

Figure 2

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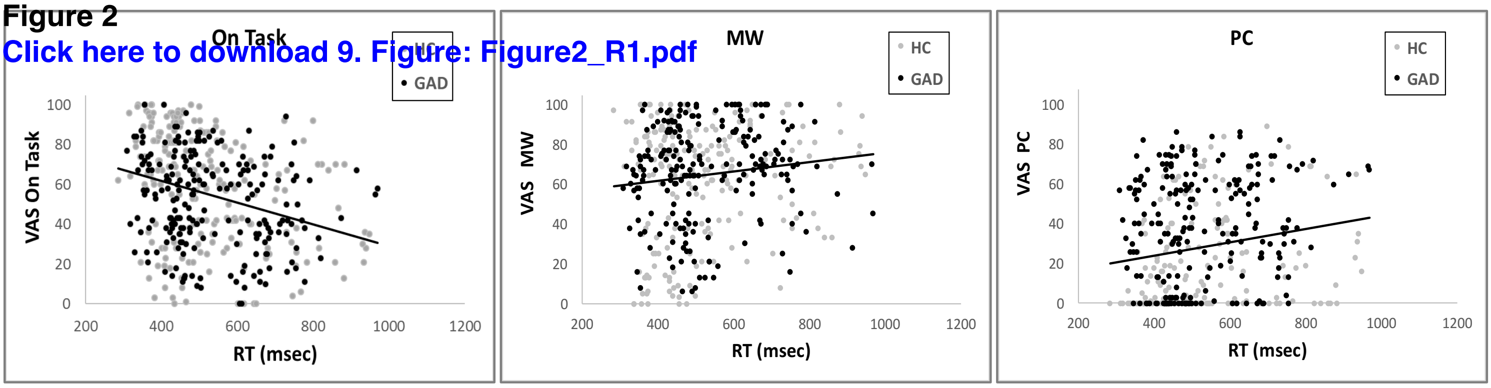

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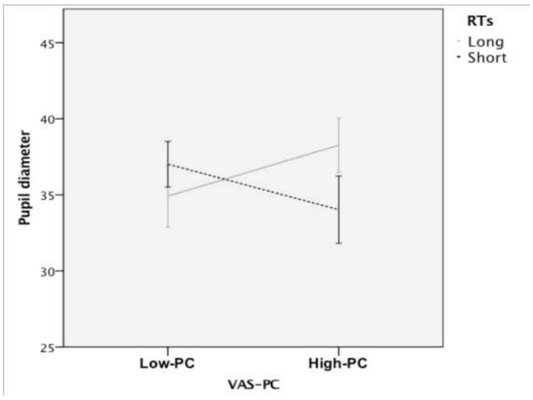

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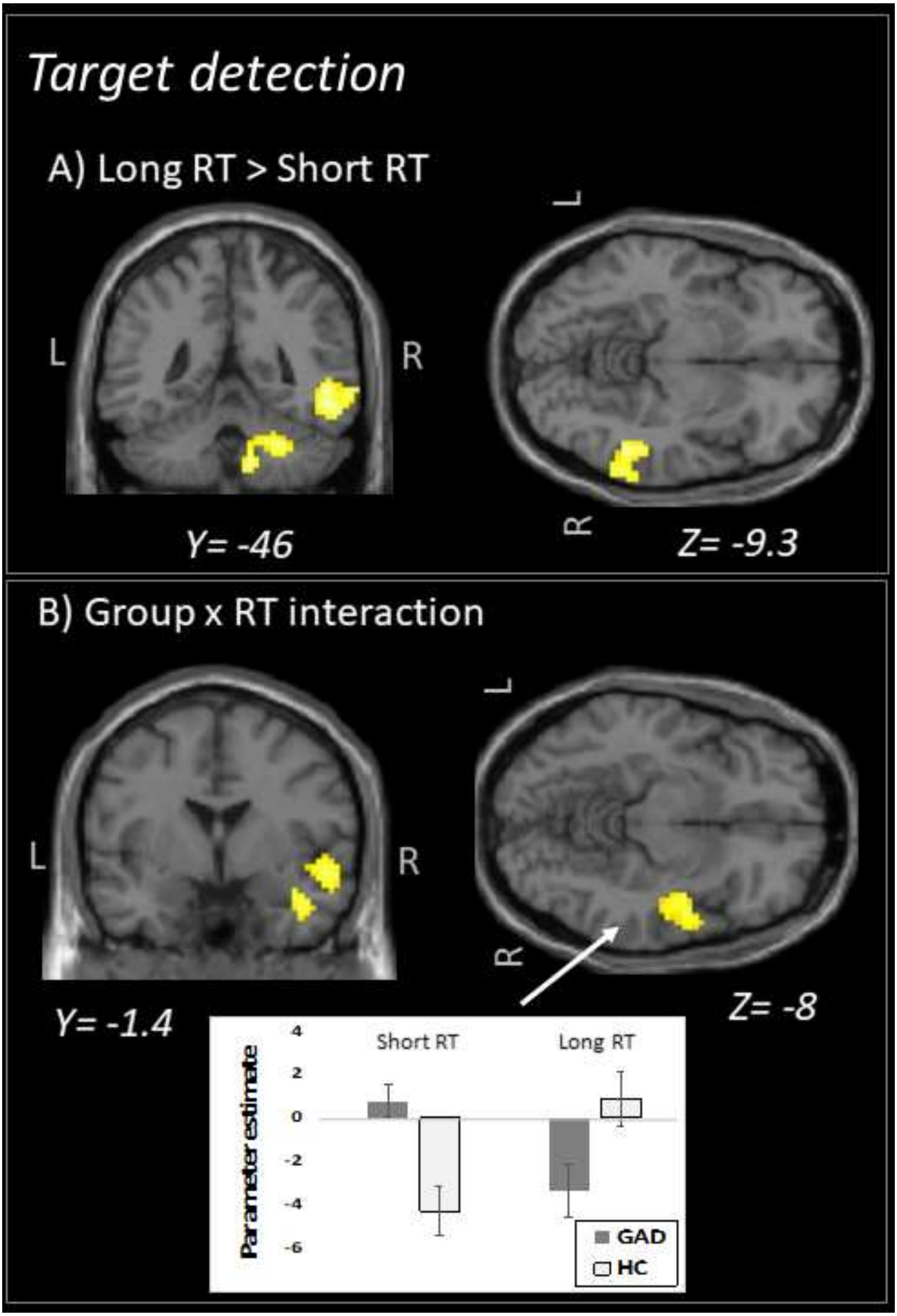

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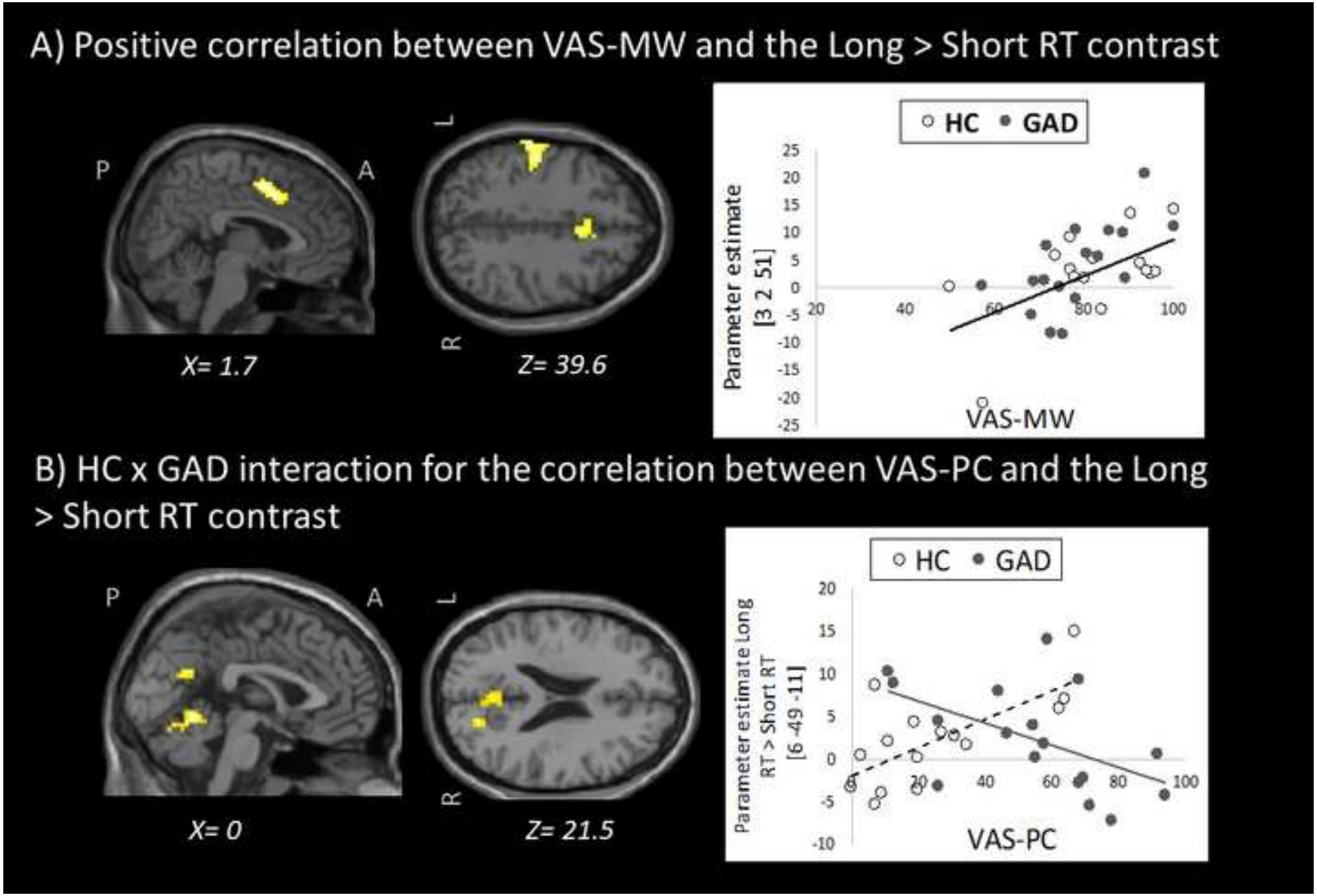

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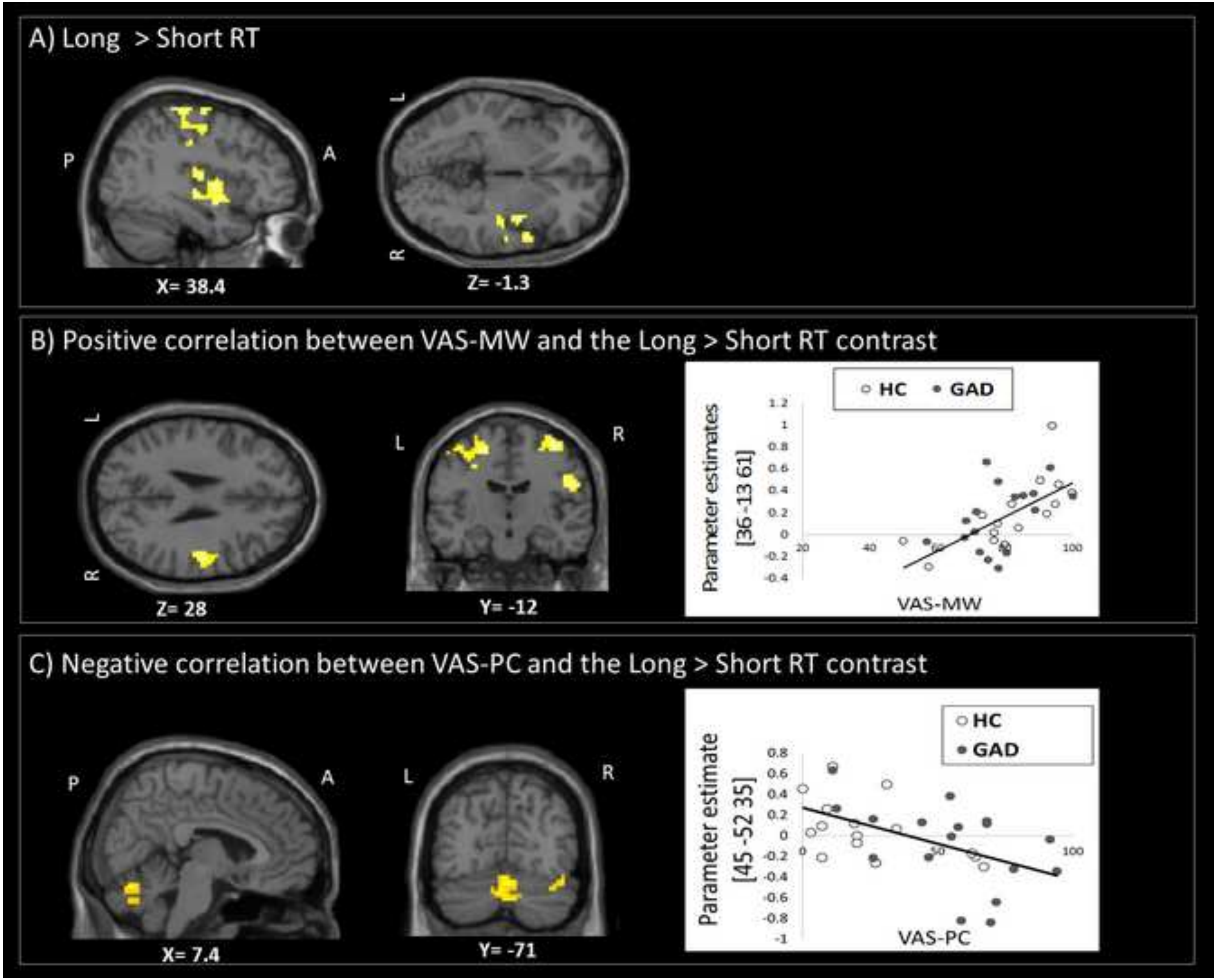

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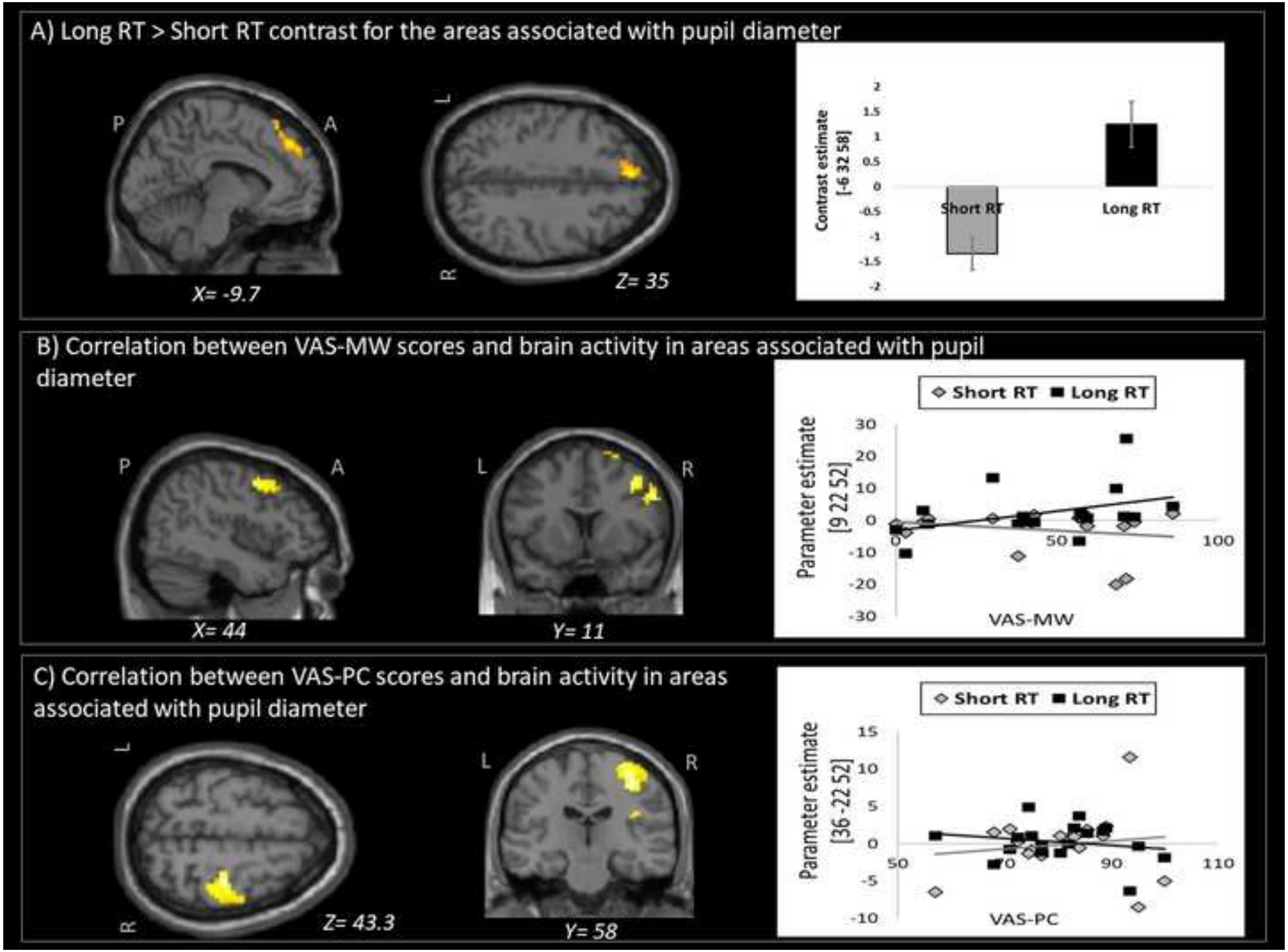

***Data and Code Availability Statement**

The anonymised datasets are available to individual scientists for non-commercial academic purposes upon direct request to the authors, consistent with the policy of, and subject to confirmation by, the Brighton and Sussex Medical School Research Governance and Ethics Committee. This is also compliant with data sharing requirements of the funder (Italian Ministry of Health).