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Research report

Neuroimaging the temporal dynamics of human avoidance to sustained threat

Michael W. Schlund [a,b,c,*], Caleb D. Hudgins [a], Sandy Magee [a], Simon Dymond [d]

[a] Department of Behavior Analysis, University of North Texas, Denton, TX PO Box 310919, USA
[b] Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA
[c] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[d] Department of Psychology, Swansea University, Singleton Park, Swansea SA2 8PP, United Kingdom

HIGHLIGHTS

- Many forms of human psychopathology are characterized by chronic avoidance.
- Functional MRI was used to examine human avoidance to a sustained threat.
- Frontal, limbic and striatal regions showed phasic rather than sustained activation.
- Learned avoidance was not associated with decreased threat-related activation.
- Increased experiential avoidance was associated with decreased threat-related activation.

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ABSTRACT

Many forms of human psychopathology are characterized by sustained negative emotional responses to threat and chronic behavioral avoidance, implicating avoidance as a potential transdiagnostic factor. Evidence from both nonhuman neurophysiological and human neuroimaging studies suggests a distributed frontal–limbic–striatal brain network supports avoidance. However, our understanding of the temporal dynamics of the network to sustained threat that prompts sustained avoidance is limited. To address this issue, 17 adults were given extensive training on a modified free-operant avoidance task in which button pressing avoided money loss during a sustained threat period. Subsequently, subjects underwent functional magnetic resonance imaging while completing the avoidance task. In our regions of interest, we observed phasic, rather than sustained, activation during sustained threat in dorsolateral and inferior frontal regions, anterior and dorsal cingulate, ventral striatum and regions associated with emotion, including the amygdala, insula, substantia nigra and bed nucleus of the stria terminalis complex. Moreover, trait levels of experiential avoidance were negatively correlated with insula, hippocampal and amygdala activation. These findings suggest knowledge that one can consistently avoid aversive outcomes is not associated with decreased threat-related responses and that individuals with greater experiential avoidance exhibit reduced reactivity to initial threat. Implications for understanding brain mechanisms supporting human avoidance and psychological theories of avoidance are discussed.

1. Introduction

Excessive threat reactivity accompanied by maladaptive forms of avoidance are prominent features of many forms of psychopathology, such as anxiety [1–7], and substance abuse disorders [8,9], which has increased recognition of avoidance as a transdiagnostic factor [6]. Despite its obvious survival advantages, well established, chronic avoidance can embed individuals within a struggle aimed at perseveration of the avoidance behaviors and routine, which only serves to minimize approach opportunities and perpetuate suffering. The mechanisms underpinning avoidance have been the focus of extensive behavioral research: avoidance is known to involve an instrumental response that modifies aversive, threatening emotional states, thoughts, and bodily sensations. When avoidance successfully prevents, reduces or otherwise modifies a threat or impending punishment it becomes strengthened through operant negative reinforcement. This process highlights an important and often unrecognized relation between avoidance-based decision-making and emotions and

* Corresponding author at: Department of Behavior Analysis, University of North Texas, PO Box 310919 Denton Texas 76203. Tel.: +1 940 565 2274.
E-mail addresses: Michael.Schlund@Unt.Edu (M.W. Schlund), Cdh0049@gmail.com (C.D. Hudgins), Sandy.Magee@Unt.Edu (S. Magee), s.o.dymond@swansea.ac.uk (S. Dymond).

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illustrates how avoidance can serve as an emotional regulation or coping strategy [6,10].

Several influential theories of avoidance hypothesize central roles for Pavlovian and instrumental learning processes in the maintenance of avoidance [11–15]. According to these accounts, fear is first conditioned to a cue (e.g., a light) that precedes the occurrence of an unconditioned aversive stimulus (e.g., brief shock) via Pavlovian conditioning. Avoidance is then negatively reinforced when it removes the fear-eliciting threat cue and cancels upcoming shock. In two-factor theory [11–14], the threatening cue elicits fear which is reduced or removed by the instrumental avoidance response and primarily serves to motivate ongoing avoidance. However, the emphasis placed on cue or threat removal as the negative reinforcer in avoidance research has not received extensive empirical support [16]. Alternatively, operant-based accounts of avoidance suggest that reductions in the frequency of contacting an unconditioned aversive stimulus can itself serve as a negative reinforcer, even in absence of a warning cue [13,16–19]. More recently, cognitive-based accounts such as expectancy theory have emerged that emphasize expectancies as a moderator of the interaction between Pavlovian and instrumental learning processes [15,20,21]. Expectancy theory proposes that avoidance learning is characterized by the formation of expectancies about the relation between avoidance and the probability of contacting the unconditioned aversive stimulus when the avoidance response is performed and withheld. Initially, fear and anxiety to the threat cue would be high whenever the expectancy of contact with the unconditioned aversive stimulus is similarly high. As avoidance becomes well learned and there is minimal contact with the unconditioned aversive stimulus, fear and anxiety in the presence of threat cues would diminish because the expectancy of contact with the unconditioned aversive stimulus would be low. In contrast to two-factor theory but consistent with operant based accounts, avoidance is hypothesized to be strengthened not by cue removal or reduction of fear or anxiety, but instead by the omission of the predicted unconditioned aversive stimulus.

One recently proposed nonhuman model of avoidance learning based on two-factor theory that may aid research on learned avoidance suggests each factor is represented by two distinct neural systems: one involves the amygdala for fear conditioning and the second involves the striatum for appetitive or instrumental conditioning of the avoidance response [22]. However, there is mounting evidence that implicates a much wider frontal–striatal–limbic network [23–30], with more recent evidence suggesting involvement of the hippocampus in supporting declarative memory of the cue-loss threat relation [29]. While the insula and amygdala appear to play central roles in threat recognition and affective responses, the evidence available also predicts the supporting network may recruit the bed nucleus of the stria terminalis (BNST) complex, which has been implicated in sustained fear in humans [31], and the substantia nigra, which has been demonstrated to play a role in fear memory consolidation [32].

In this investigation, our primary aim was to employ functional magnetic resonance imaging (fMRI) to characterize the temporal dynamics of regions implicated in threat processing and avoidance to a sustained threat that prompted sustained avoidance. We employed a whole-brain temporal assessment of activation modeled after approaches used in neurophysiological research on fear [31], pain [33], psychiatric dysfunction [34], working memory [35], approach-avoidance learning [29] and emotional responses [36,37]. This temporal analysis isolated the response profiles of regions in a way that enabled us to also evaluate core predictions from two-factor and expectancy theories. Two-factor theory predicts that prolonged threat that elicits fear and motivates sustained avoidance should be associated with sustained activation in threat and affective processing regions (amygdala, insula, BNST, substantia nigra). In contrast, expectancy theory predicts that once avoidance responding is learned, prolonged threat would motivate avoidance because of a low expectancy of contact with an aversive event and the absence of fear/anxiety to threat would predict minimal activation in threat and affective processing regions. Our secondary aim represents an extension of our prior research on how experiential avoidance, which is a known vulnerability factor associated with pathological avoidance, modulates brain activation in regions supporting avoidance [29].

Finally, our investigation sought to gain new insights into the neural mechanisms of intentional action and self-control [38] directed toward threat in a way that has translational value. We approached this goal by using a modified free-operant avoidance task coupled with fixed-ratio avoidance–extinction schedules. This schedule arrangement regularly alternated 16 s periods of fixed-ratio avoidance, where a fixed ratio button-pressing requirement completed under a time limit prevented money loss, with 16 s periods of extinction, which functioned as a safety condition devoid of threat. An important aspect of the task coupled with extensive pretraining prior to imaging is it models key aspects of chronic (well learned) avoidance present in many forms of psychopathology where direct action prevents contact with undesirable situations/emotions and the action is subsequently strengthened.

2. Method

2.1. Participants

Seventeen healthy, right-handed adults (7 men), aged between 18 and 28 years old ($M = 22.6$, $SD = 2.4$), participated. All reported being free of medications affecting either the central nervous or the autonomic system for at least 2 weeks and were without a personal history of psychiatric disorder. The University of North Texas Institutional Review Board for the Protection of Human Subjects approved this study. All participants provided written informed consent.

2.2. Assessment

Experiential avoidance measures were obtained using the *Acceptance and Action Questionnaire-2* (AAQ-2) [39], in which higher scores reflect greater pathology and cognitive inflexibility. Experiential avoidance is prevalent in many clinical disorders [9,40], particularly anxiety [41].

2.3. Procedure

2.3.1. Avoidance task

Subjects completed a cued, modified free-operant avoidance task (Fig. 1). The task consisted of a 16 s "Threat-Avoidance" context cued by a red background that alternated with a 16 s "Safety" context cued by yellow background. Fifteen threat-avoidance and safety contexts were presented. Contextual changes were based solely on the elapse of 16 s, regardless of performance. As shown in Fig. 1, trials began with a choice screen displaying two response buttons labeled "(1) and (2)" and ended with an outcome. It should be noted that while a discrete trial format was used, the number of trials completed within each context was self-paced and free to vary with response rates. Choice of one response button resulted in the removal of the unselected choice until after outcome delivery, preventing random switching between choices. A correct response in the threat-avoidance context involved selection of choice (1) followed by completion of a fixed-ratio 9 (FR 9) response-requirement in less than 8 s to prevent loss (a 1 s 'No Loss' prompt). Failure to choose or complete the response requirement in less than 8 s produced punishment (a 1 s 'Lose $0.20' prompt). Thus, prevention of

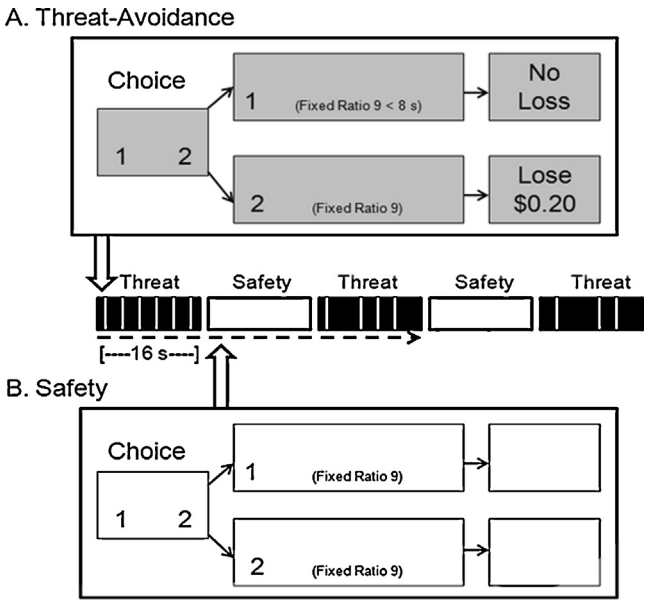

Fig. 1. Imaging task and behavioral performance. The self-paced modified free-operant avoidance task consisted of two cued, alternating 16 s contexts. In the threat-avoidance context (A) a correct initial choice and subsequent completion of a fixed-ratio 9 (FR 9) schedule of avoidance in less than 8 s avoided punishment (money loss). Selecting the alternative choice or failing to complete the FR 9 under the time limit resulted in punishment. In the safety context (B) a choice was presented but no responding was necessary. Contingencies were learned through trial and error prior to neuroimaging.

money loss served as a negative reinforcer that maintained selection of choice (1) and subsequent avoidance responding. During the safety context, selection of either choice and completion of the FR 9 produced no money gain or loss outcome (i.e., 1 s blank screen). After each outcome presentation, the choice screen was presented again, signaling the start of a new trial. It is important to note that consistent with all of our prior avoidance studies subjects were compensated (a) on an hourly basis and (b) earned/lost money based upon their task performance and task contingencies and (c) clearly informed that losses resulted in reduced compensation. Thus, monetary loses would have been framed against earnings and viewed as a real negative consequence.

Pretraining target performances occurred through trial and error learning several days before imaging. Task instructions highlighted the goal of avoiding money loss and choices available. Importantly, participants were not informed how to make choices or when, how often or how much to respond. Participants were pretrained under the threat-avoidance context to establish high rates of avoidance. Training continued until choice (1) was selected and loss avoided on over 90% of trials for two consecutive 3 min training session (sessions to criterion: $M = 2.23$; $SD = .56$). Next, participants were pretrained under the safety context to extinguish responding and ensure subjects had learned that responding was unnecessary and no money could be gained or lost in this context. Training continued until less than 30 responses were emitted over two consecutive 3-min training sessions (sessions to criterion: $M = 2.94$; $SD = 1.19$). The final stage involved completing a full version of the task at the end of training immediately prior to neuroimaging to ensure accurate and stable performances.

2.4. Image acquisition and processing

Functional MRI images were collected on a Siemens Trio 3T scanner. T_1 weighted anatomical volume images were collected for each subject using a MPRAGE sequence with a high-resolution isovoxel acquisition of 1 mm^3. Functional MRI data were gathered using a single shot echo planar imaging (EPI) sequence with a TR of 2 s, a TE of 20 ms, a 90° flip angle, 64×64 matrix size and field of view 24 cm, yielding voxels measuring 3×3 mm in plane. Forty-three contiguous 3 mm thick sections were obtained. The first two volumes were discarded to allow for equilibration effects. Data analysis was performed using SPM 8 (Wellcome Department of Cognitive Neurology, London UK, http://www.fil.ion.ucl.ac.uk/). Preprocessing procedures included reorientation, slice acquisition time correction, coregistration, within-subject realignment, spatial normalization to the standard Montreal Neurological Institute EPI template with resampling to $2 \times 2 \times 2$ mm voxel sizes, and spatial smoothing using a Gaussian kernel (6 mm full width at half-maximum). High pass filtering was applied to the time series of EPI images to remove any low frequency drift in EPI signal.

2.5. Statistical analysis

Analyses proceeded through three stages: whole-brain localization of sustained activation to sustained threat, whole-brain localization of early–late changes in activation during sustained threat along with time course verification, and correlation of brain activation with a measure of experiential avoidance. Based upon prior investigations, our regions of interest included dorsal, medial and inferior frontal regions, hippocampus, striatum, and regions associated with emotion such as the insula, amygdala, substantia nigra and bed nucleus of the stria terminalis (BNST). For each subject, a general linear model was utilized to evaluate regionally specific effects of task parameters on blood oxygenation level-dependent indices of activation. Motion parameters defined by the realignment procedure were also included in models as six separate regressors of no interest. Whole-brain localization of sustained activation during the 16 s sustained threat was revealed by convolving a 16 s boxcar function to the time series which produced a parameter estimate reflecting the magnitude of activation relative to an implicit baseline. Parameter estimates approximate percent change in the global mean BOLD signal for the imaging session. The resulting contrast images assessing sustained activation during the 16 s sustained threat were carried to a second level random effects analysis that employed a one sample *t*-test with a voxel-level false discovery rate (FDR) and whole brain correction for multiple comparisons thresholded at $p < .05$ and 30 contiguous voxels. Next, whole-brain localization of early versus late changes in activation during the 16 s sustained threat were examined by convolving two separate 6 s boxcar functions with early (0–6 s) and late (10–16 s) time periods. An early–late contrast image, reflecting absolute differences between parameter estimates, was produced to highlight regions with greater activation during the early time period relative to late time period. Similarly, a late–early contrast image was produced to highlight regions with greater activation during the late time period relative to early time period. To isolate voxels with significantly increased activation, contrast images were carried to separate second level random effects analyses that employed one sample *t*-tests with a voxel-level FDR and whole brain correction for multiple comparisons thresholded at $p < .05$ and 30 contiguous voxels. A more fine-grained and unbiased picture of changes in activation during the 16 sustained threat was pursued with a supplemental analysis that employed a Finite Impulse Response (FIR) model and a 2 s sampling rate. The FIR analysis generated parameter estimates for each voxel every 2 s over the 16 s sustained threat. The image series was carried to a second level random effects analysis that employed a repeated measures analysis of variance and inclusive making to restrict the analysis to regions highlighted in the early–late contrast (note: no significant difference were found for the late–early contrast). A voxel-level FDR and whole brain correction for multiple comparisons thresholded at $p < .05$ and 30 contiguous voxels

was utilized to identify regions that showed significant changes in activation (i.e., parameter estimates) over time. Modulation of brain activation by individual differences in response rate (total responses) and experiential avoidance was examined using a regression analysis and initial activation restricted to regions highlighted by the early–late contrast ($p < 01$ with 30 contiguous voxels; except where noted). Additionally, all regions reported survived an additional small volume correction implemented in SPM (using a 5 mm sphere). Regional time courses plotted reflect changes in activation in significant peak voxels. The location of voxels with significant activation was summarized by their local maxima separated by at least 4 mm, and by converting the maxima coordinates from MNI to Talairach coordinate space using conventional transformations [42], with resulting coordinates assigned neuroanatomic labels using the Talairach atlas. Statistical parametric maps displayed were overlaid onto a reference brain using MRIcron (http://www.sph.sc.edu/comd/rorden/mricron/).

3. Results

3.1. Behavioral

Fig. 2 plots the group mean total number of responses emitted every 2 s during each context. As expected, few responses were emitted during the safety context and sustained avoidance responding occurred throughout the threat-avoidance context, leaving little question about the motivating properties of money loss on avoidance, control exerted by the negative reinforcement contingency within the avoidance task during imaging and formation of an expectancy that avoidance responding would prevent loss [e.g., [24–26]]. Group means for successful avoidance of loss during imaging was 99.26% ($SD = 1.75$; *median* (M) = 100%). Paired t-test revealed no significant difference ($p > .05$) in number of responses between early and late threat periods. Furthermore, regression analyses revealed no significant relationship ($p > .05$) between levels of experiential avoidance and total number of responses, number of early responses or number of late responses. Collectively, these findings eliminate changes in responding as a contributing factor to results obtained in the main early–late contrast.

3.2. Neuroimaging

No brain regions exhibited sustained activation to the 16 s sustained threat at the statistical thresholds employed. However, as a control check, we used a more liberal uncorrected threshold and found marginally sustained activation in the cerebellum and motor and visual cortices (Fig. 2). Findings showing sustained but reduced activation are not unexpected given that the task was designed to motivate sustained responding and the extensive pretraining subjects received on the avoidance task prior to imaging.

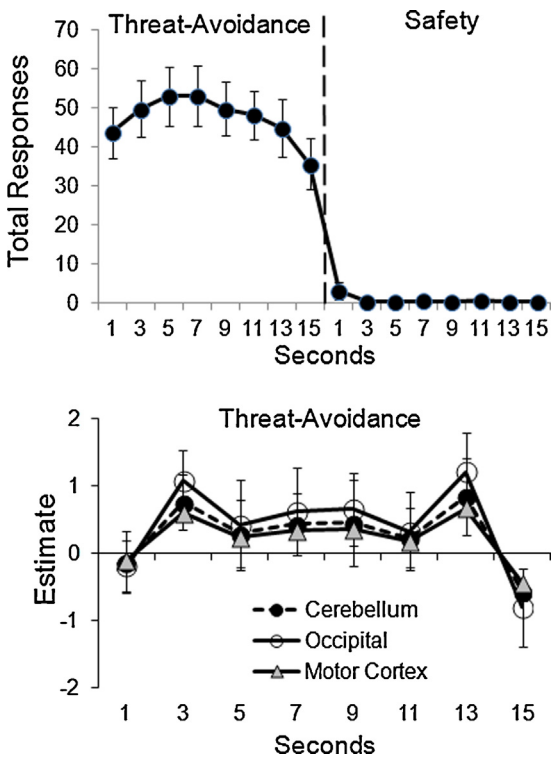

Fig. 2. Group behavioral performance during imaging. (Upper) Group mean total number of responses emitted in 2 s bins during a 16 s sustained threat. The threat-avoidance context prompted sustained avoidance responding which promptly diminished during the safety context. Bars represent 95% confidence intervals. (Lower) Brain activation was also marginally sustained in the cerebellum, occipital lobe and motor cortex during the 16 s sustained threat ($p < .05$, uncorrected; bars represent standard error).

Whole-brain temporal analysis revealed significant changes in activation during the sustained threat in targeted brain regions (Table 1). Significant effects observed in early–late contrast and fine grained analyses of changes in parameter estimates revealed phasic changes in activation in regions associated with emotion which included amygdala, insula, substantia nigra and in the vicinity of the BNST (Fig. 3). Similar phasic responses were observed in regulatory regions sensitive to the avoidance-outcome contingency which included DLPFC, inferior frontal regions, anterior and dorsal medial cingulate and striatum (Fig. 4).

Finally, rates of avoidance (i.e., total number of responses) and levels of experiential avoidance, a vulnerability factor associated with pathological avoidance, were shown to modulate activation in targeted regions during initial threat (Fig. 5). Rates of avoiding were found to be negatively correlated with right insula [$r = -.55$; $x = 38, y = 6, z = -4$] and dorsal anterior cingulate activation [$r = -.72$; $x = -8, y = 4, z = 42$] but positively correlated with amygdala activation [Left: $r = 58$; $x = -24$, $y = -8$, $z = -22$ and Right: $r = 55$; $x = 24$,

Table 1
Regions showing significant change over time.

Region	Left			F	Right			F
Insula	−42	14	−2	4.05	42	12	−4	4.48
BNST	−10	0	8	3.76	10	0	8	6.01
Substantia Nigra	−16	−26	−6	5.75	16	−24	−6	3.58
Amygdala	−22	−6	−10	4.37	22	−6	−10	7.88
Anterior Cingulate	–	–	–	–	0	42	13	4.03
Dorsal Anterior Cingulate	−4	20	34	10.06	–	–	–	–
Dorsal Lateral PFC	−34	44	24	5.51	34	44	24	3.97
Inferior Frontal	−28	28	−8	3.74	34	30	−6	4.78
Ventral Striatum	−16	14	−6	5.78	16	14	−6	5.15

$p < .05$ FDR corrected.

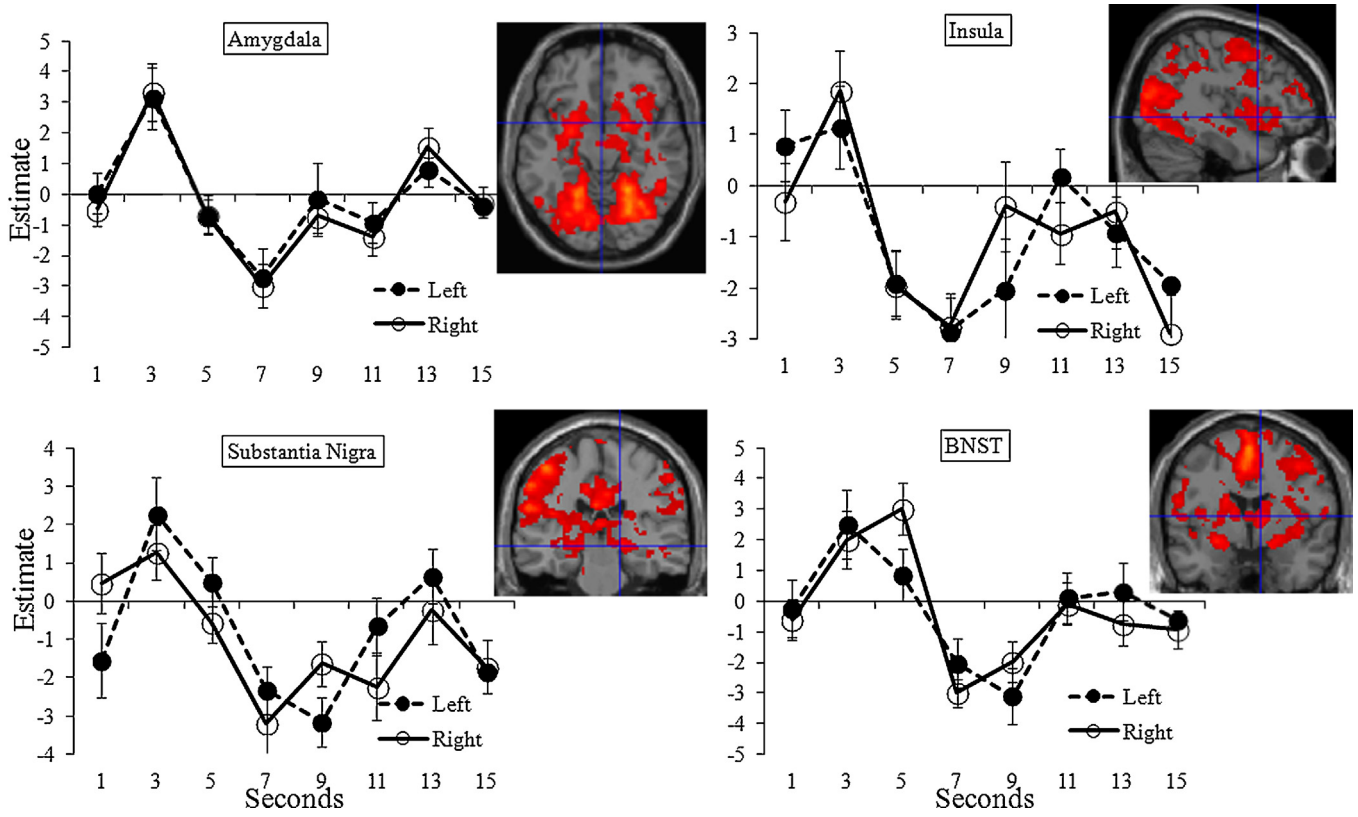

Fig. 3. Whole-brain temporal analysis reveals phasic response patterns. Parametric maps highlight regions with significantly greater activation during early as compared to late periods of a 16 s sustained threat in limbic and midbrain regions ($p < .05$ FDR corrected). Plots show results of a temporal analysis that highlights significant changes in parameter estimates (2 s bins) over the 16 s sustained threat ($p < .05$ FDR corrected). Bars represent standard error. Activation maps were overlaid on a normalized T1-weighted structural image displayed in neurological convention (left = left).

$y = -4$, $z = -24$]. Moreover, levels of experiential avoidance were negatively correlated with activation in the right insula [$r = -.63$; $x = -42$, $y = 10$, $z = -2$], hippocampus [Left $r = -.61$; $x = -18$, $y = -28$, $z = -8$ and Right $r = -.51$; $x = 18$, $y = -22$, $z = -6$] and left amygdala [$p < .05$, $r = -.42$; $x = -26$, $y = -4$, $z = -14$].

4. Discussion

Numerous clinical and basic research studies highlight an important interplay between avoidance-based decision-making and emotion. The primary aim of our investigation was to employ fMRI to characterize the temporal dynamics of avoidance neurocircuitry to a sustained threat that prompted persistent avoidance (sustained threat-avoidance). Our secondary aim was to advance our understanding of how experiential avoidance, which is a vulnerability factor implicated in the pathogenesis of avoidance, may modulate activation. Our findings provide several new insights into intentional human avoidance behavior which advances our understanding of brain mechanisms of human avoidance and emotion in ways that contribute to two-factor and expectancy theories of avoidance.

The present findings are largely consistent with results reported in prior human and nonhuman investigations that implicate frontal, limbic and striatal regions in aversion, avoidance learning and learned avoidance [22–24,26–29,43–46]. The contributions of the present investigation are the insights gained into the temporal patterns of brain mechanisms supporting avoidance and regions implicated in emotion and threat processing. Results of our whole-brain temporal analysis revealed sustained threat avoidance was associated with a phasic response in regulatory regions and regions associated with emotion which include the amygdala, insula, substantia nigra and bed nucleus of the stria terminalis complex. From the standpoint of avoidance as an emotional regulation strategy, the activation patterns observed point out that knowledge that one can actively alter an environment using avoidance to successfully prevent aversive outcomes does not suppress threat-related activation. Moreover, our temporal assessment revealed that continued avoidance to a sustained threat is not associated with sustained activation. One reason why may be that sustained avoidance ensures that aversive outcomes can be effectively prevented and this in turn alters the threatening nature of the context. One recent related study examining sustained fear has shown sustained activation in the BNST and phasic activation in the amygdala in contexts where unpredictable aversive events cannot be avoided [31]. In our case, avoidance that reliably kept unpredictable aversive events at bay may generate an inherently safe and reinforcing environment, with avoidance acquiring the function of a 'safety' behavior [e.g., [47]]. This view would account for why regions such as the insula, BNST and amygdala did not show a sustained response. It also predicts that under conditions with increasing contact, accomplished by degrading the avoidance contingency or scheduling non-contingent punishment, sustained responses would be more likely.

The phasic patterns of brain activation observed are also relevant to theories of human avoidance [11–15]. The increased activation we observed in limbic structures is consistent with the assertion of two-factor theory that conditioned threats may generate fear which initiates avoidance responding. However, we found sustained threat was associated with a reduction in activation in affective regions even though avoidance responding persisted. Findings highlighting reduced limbic activation over time but sustained avoidance runs counter to the two-factor theory position that threat elicited fear motivates continued

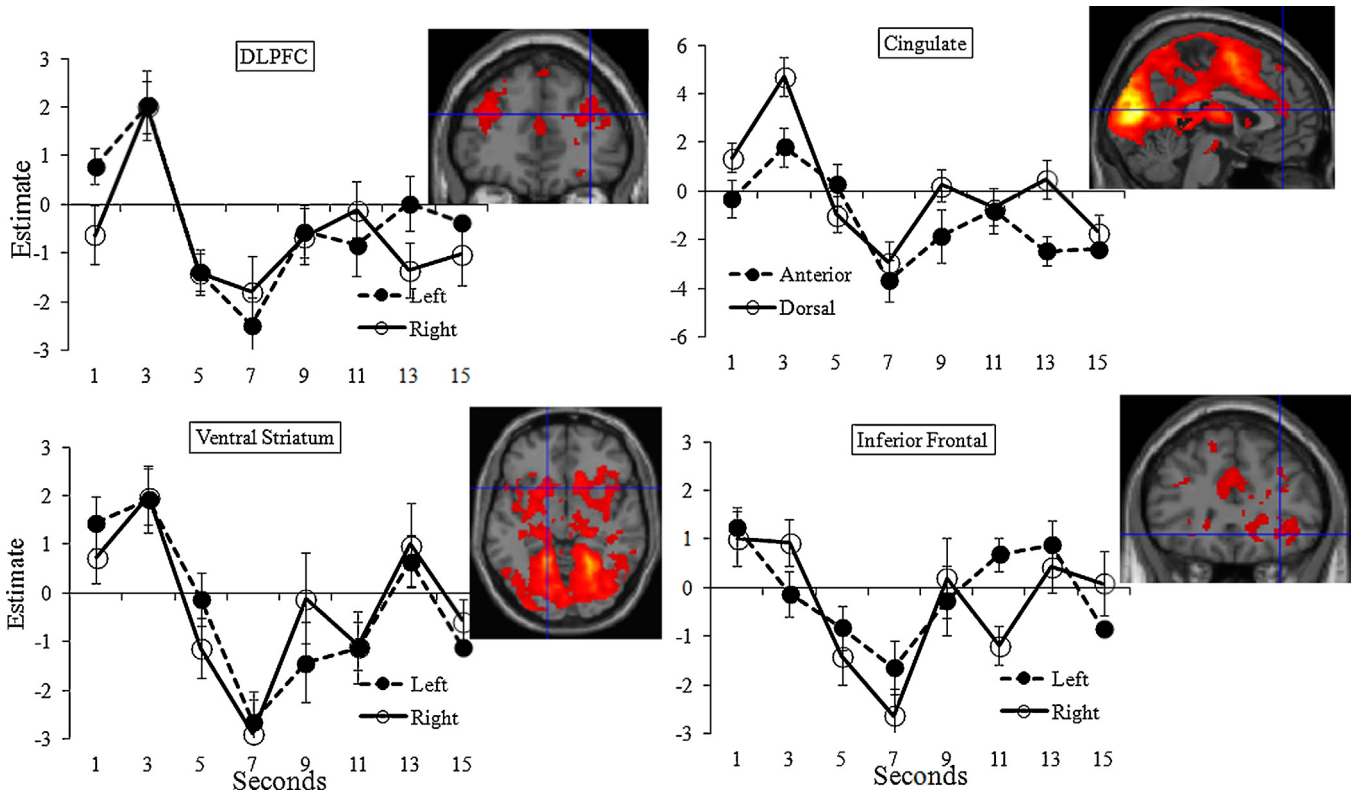

Fig. 4. Whole-brain temporal analysis reveals phasic response patterns. Parametric maps highlight regions with significantly greater activation during early as compared to late periods of a 16 s sustained threat in frontal and striatal regions ($p < .05$ FDR corrected). Plots show results of a temporal analysis that highlights significant changes in parameter estimates (2 s bins) over the 16 s sustained threat ($p < .05$ FDR corrected). Bars represent standard error. Activation maps were overlaid on a normalized T1-weighted structural image displayed in neurological convention (left = left).

avoidance. Our findings also runs counter to expectancy theory which would predict no activation during threat presentation because of the existing expectancy that avoidance has consistently prevented the aversive outcome. One plausible account is that two-factor theory and operant-based accounts of avoidance, which emphasize frequency reduction of aversive events, is that each position accounts for different facets of avoidance [5]. Initially, conditioned threats may elicit a prominent but transitory negative affective response that motivates avoidance. Potentially, this response cannot be overridden even by the explicit knowledge or expectancy that aversive events have consistently been avoided in the past. When the threat continues, avoidance is sustained not by fear/threat, but instead because it has produced a reduction in the frequency of contacting the aversive event in the past. In essence, the presentation of a threat may generate distress or fear sufficient to motivate initial avoidance and when the threat persists reductions in contact with the aversive event may maintain continued avoidance and negatively reinforce expectancies and related threat beliefs. By this view, avoidance works to temporarily alter the threatening/emotive properties of a cue as well as alter threat beliefs by severing its association with the aversive event [16].

Another contribution of our investigation were findings showing that magnitude of initial threat-related activation was negatively correlated with rates of avoidance and levels of experiential avoidance. These results are relatively consistent with prior findings relating avoidance-associated activation to experiential avoidance and anxiety. One prior study showed a negative correlation between experiential avoidance and activation in medial frontal gyrus, anterior cingulate and amygdala and between trait anxiety and activation in superior frontal gyrus and posterior cingulate [29]. Additionally, we observed that response rate was negatively correlated with amygdala activation, suggesting response rates may be predictive of amygdala reactivity. While both studies showed negative correlations, the regions implicated differ somewhat, which may reflect differences in amounts of avoidance learning (i.e., recently acquired vs. well learned). In any case, there exist several possible interpretations of the negative relations. Individuals with increased experiential avoidance may simply be less threatened by money loss as compared to other stimuli, such as undesirable and unwanted emotions. It is also possible that individuals with increased experiential avoidance who have extensive histories of avoidance based coping may possess some degree of resilience to threat or maintain a lower expectancy of contact or threat sensitivity when it is consistently found that avoidance is regularly successful. On the other hand, there is also a possibility that the activation patterns observed highlights a (subclinical) functional abnormality.

Currently, our knowledge about the neural substrates of human avoidance is based largely on nonhuman research involving direct aversive Pavlovian conditioning and trial and error learning of the avoidance response. However, it is a common clinical observation for fear and avoidance to have been similarly acquired through direct contact with an aversive event and trial and error learning. Although Rachman's [48] suggestion that fears can be acquired vicariously, via observational learning and verbal threat information (instructions), has generated considerable experimental support [49–52], it is noteworthy this observation has not motivated neurophysiological research on brain mechanisms supporting such 'indirect' pathways of fear and avoidance. This highlights a significant disconnect between neuroscience research and translational and clinical research and treatment of avoidance.

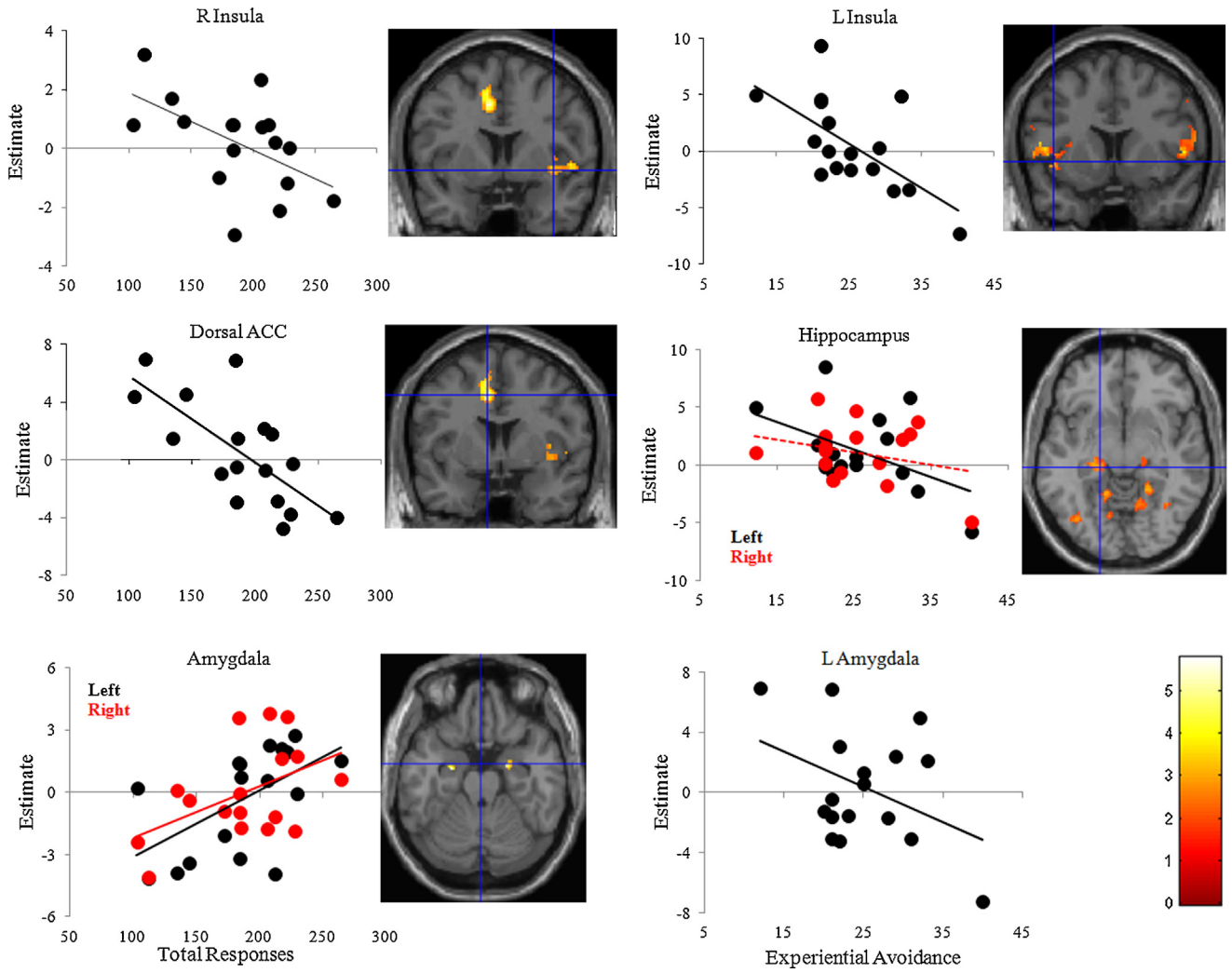

Fig. 5. Individual differences in response rate and experiential avoidance modulate brain activation. Within brain regions that evidenced significant changes in activation ($p < .05$ FDR corrected), plots show relations between response rate (left panel) and experiential avoidance (right panel) with initial threat-related activation ($p < .01$). Activation maps were overlaid on a normalized T1-weighted structural image displayed in neurological convention (left = left).

Some recent efforts are encouraging. For example, it is now known that fear acquired indirectly via observation or instructions is similar behaviorally to that acquired following direct aversive Pavlovian conditioning [49,50] and also results in both phasic and sustained limbic system activation [31,50,53]. An important goal for future investigations will be to determine whether brain mechanisms highlighted under experiential procedures (direct contact with aversive events and trial and error avoidance learning) generalize to avoidance established indirectly, such as through social transmission (instructions, modeling) and cognition (logical/relational inference) [5,49,54].

5. Conclusions

Chronic avoidance is a predominant feature of many forms of human psychopathology and substance abuse disorders, implicating avoidance as a transdiagnostic factor. The present findings contribute to a growing body of imaging research advancing our understanding of the brain network that supports human avoidance by highlighting the temporal dynamics of the network during a sustained threat. Results showed phasic response patterns in relevant brain structures, suggesting that learned avoidance does not mitigate initial threat-related responses and avoidance during sustained threat is not associated with sustained activation. Moreover, consideration of individual differences in levels of experiential avoidance did reveal that greater experiential avoidance was associated with reduced reactivity to initial threat. Collectively, the present findings aid in laying the foundation for further integrating ideas from two factor, operant and expectancy theories of avoidance in ways that enhance the translational value of avoidance as a transdiagnostic factor.

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