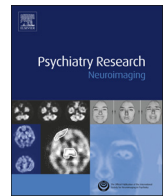




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Distress tolerance to auditory feedback and functional connectivity with the auditory cortex

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ABSTRACT

Distress tolerance is the capacity to withstand negative affective states in pursuit of a goal. Low distress tolerance may bias an individual to avoid or escape experiences that induce affective distress, but the neural mechanisms underlying the bottom-up generation of distress and its relationship to behavioral avoidance are poorly understood. During a neuroimaging scan, healthy participants completed a mental arithmetic task with easy and distress phases, which differed in cognitive demands and positive versus negative auditory feedback. Then, participants were given the opportunity to continue playing the distress phase for a financial bonus and were allowed to quit at any time. The persistence duration was the measure of distress tolerance. The easy and distress phases activated auditory cortices and fronto-parietal regions. A task-based functional connectivity analysis using the left secondary auditory cortex (i.e., planum temporale) as the seed region revealed stronger connectivity to fronto-parietal regions and anterior insula during the distress phase. The distress-related connectivity between the seed region and the left anterior insula was negatively correlated with distress tolerance. The results provide initial evidence of the role of the anterior insula as a mediating link between the bottom-up generation of affective distress and top-down behavioral avoidance of distress.

1. Introduction

Distress tolerance (DT) is the capacity to withstand negative physical, psychological, and/or affective states in pursuit of a goal (Daughters et al., 2016; Leyro et al., 2010; Simons and Gaher, 2005). DT is a broad concept that encompasses other variables such as experiential avoidance of negative emotional and somatic states, emotional suppression or regulation, disengagement, anxiety sensitivity, and personality-based persistence (Leyro et al., 2010). The concept of DT is highly relevant to psychiatry, as low DT may be a cognitive-affective risk factor for the development and maintenance of different types of psychopathology, such as substance use, anxiety, mood, and personality disorders (Leventhal and Zvolensky, 2015; Leyro et al., 2010). Low DT may bias an individual to avoid experiences that induce stress or other negative internal states, or to avoid experiences that are expected to induce these states; for example, individuals with substance use disorders may be motivated to use the substance to avoid experiencing emotional and/or physical pain (Baker et al., 2004; Koob, 2013). In fact, low DT has been associated with a higher frequency and severity

of substance use and an increased likelihood of treatment dropout and relapse among substance users (Ali et al., 2015; Brown et al., 2002; Brown et al., 2009; Daughters et al., 2005a; Daughters et al., 2005b; Strong et al., 2012). Furthermore, DT level may also relate to how a substance user can tolerate drug abstinence during a quit attempt (Magidson et al., 2013). The relevance of DT to psychiatry is underscored by the rise of psychosocial and cognitive-behavioral interventions, including mindfulness meditation, designed to strengthen coping skills and improve DT (Bornovalova et al., 2012; Brown et al., 2008; Hsu et al., 2013; Kapson et al., 2012; Liu et al., 2013; McHugh et al., 2014).

In the laboratory, DT may be quantified based on self-reported perceptions or behavioral measures. These measures include physical DT (e.g., breath holding duration) and cognitive/affective DT. A well-used manipulation of cognitive/affective DT is the Computerized Paced Auditory Serial Addition Task (Lejuez et al., 2003). Originally, consecutive numbers were presented aloud at a fixed pace by the administrator, and the participant was asked to continually sum the two most recent numbers. The PASAT was initially designed to measure

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information processing (Gronwall and Sampson, 1974) although it also tests attention, concentration, and working memory performance (Tombaugh, 2006). Incidentally, the PASAT elicited affective stress, negative affect, and early task termination (Tombaugh, 2006); thus, it was redesigned and reconceptualized as a behavioral measure of DT (Lejuez et al., 2003). In the redesigned version, participants play practice trials then they are given an opportunity to continue playing a final set of trials (i.e., DT phase) to earn points, or to quit at any time. Unbeknownst to the participant, the DT phase automatically terminates after a predetermined amount of time (e.g., 10 min). The length of time the participant chooses to persist on the DT phase is a behavioral measure of distress tolerance (Lejuez et al., 2003).

The PASAT as a measure of DT has been shown to increase self-reported negative mood such as anxiety, difficulty concentrating, irritability and frustration (Brown et al., 2002; Lejuez et al., 2003). Low DT persistence on this measure has been related to a variety of psychiatric problems, such as borderline personality disorder (Gratz et al., 2006), binge eating (Eichen et al., 2017), and depressive symptoms among adults with problematic alcohol use (Gorka et al., 2012). Neuroimaging studies using the auditory and computerized visual versions of the PASAT have reported activation in the anterior cingulate, bilateral frontal (e.g., superior and middle frontal gyri) and parietal areas (e.g., superior temporal gyrus), anterior insula, superior temporal gyri, and motor areas (e.g., supplementary motor area, premotor cortex, and cerebellum) (Audoin et al., 2003; Lazeron et al., 2003; Lockwood et al., 2004; Staffen et al., 2002). This fronto-cingulo-parietal pattern of activation is consistent with the cognitive control network, which underlies a broad range of executive functions (Niendam et al., 2012). However, the version of the PASAT in these studies was used to test working memory and attention, not specifically to elicit distress or measure DT.

Recently, Daughters et al. adapted a version of the PASAT-C to study the neural mechanisms of DT during functional magnetic resonance imaging (fMRI) among healthy and substance using participants (Daughters et al., 2016). This version was divided into an easy phase designed to control for cognitive and motor functioning, a titrated latency test phase to determine skill level, a distress phase designed to elicit affective distress, and a distress tolerance phase to measure DT (i.e., latency in sec to task termination). Compared to healthy participants, substance users had less activity in the bilateral middle frontal and inferior frontal gyri during the distress phase. A psychophysiological interaction (PPI) analysis using the right middle frontal gyrus as the seed region of interest showed that DT was positively correlated with the connectivity between the seed region and the right ventromedial prefrontal cortex/subgenual anterior cingulate cortex among substance users but not healthy subjects during the distress phase. Their results support the idea that substance users have impaired ability to cognitively regulate emotions during distress via top-down mechanisms (Daughters et al., 2016).

Neuroimaging research can shed light on how the brain integrates a cognitive challenge like the PASAT with an affective/limbic response, and related studies have shown distinct neural bases for bottom-up generation (i.e., automatic) and top-down regulation (i.e., cognitive) of emotions (Ochsner and Gross, 2005; Ochsner et al., 2009). A better understanding of individual differences in this functional integration, as it relates to DT, can provide guidance and quantitative support for the development and efficacy of DT-related interventions. Individual differences in emotional avoidance relate to the experience of anxiety and distress to physical discomfort (Feldner et al., 2003), suggesting that certain individuals will experience more distress than others in response to the same environmental stimulus. Likewise, there may be individual differences in the ability to control arousal, attention, and the behavioral response to distress based on top-down cognitive control strategies (Garnefski et al., 2001; Gross and John, 2003; Siegle et al., 2006). The previous fMRI PASAT DT study investigated a top-down mechanism by which the middle frontal gyrus (part of the cognitive

control network) may help regulate affective distress (Daughters et al., 2016). However, the bottom-up processing of positive versus negative auditory feedback pertaining to how affective distress is generated and where this information is processed in the brain—especially during efforts to tolerate the distress—remains poorly understood.

The purpose of the present study was to investigate the bottom-up processing of aversive stimuli and its relationship to DT persistence. As in previous distress tolerance PASAT tasks, in our version of the PASAT the primary performance feedback was auditory (Daughters et al., 2016; Strong et al., 2003). The auditory stimuli were either pleasant, positive feedback (i.e., during the easy phase) or aversive, negative feedback (i.e., during the distress phase). The secondary auditory cortex (i.e., the planum temporale) has been described as a computational hub, engaged in the analysis of complex sounds, including both speech, music, tones, and sound patterns, that directs further processing in other brain regions (Griffiths and Warren, 2002). A recent study shows that the auditory association cortex is functionally connected to limbic/paralimbic (e.g., insula) somatosensory, visual, motor-related, and attentional regions, and suggests the auditory cortex plays a central role in the affective processing of auditory information (Koelsch et al., 2018). In addition, the auditory cortex has a leftward asymmetry for gray matter volume and functional activation to sounds (Devlin et al., 2003; Steinmetz, 1996). The leftward asymmetry of the planum temporale may be related to the leftward asymmetry of anatomical connectivity in the arcuate fasciculus (Takao et al., 2011), which could support stronger functional connectivity to other brain areas. Thus, to complement and expand on previous work, we investigated the role of the planum temporale in the bottom-up generation of affective distress among healthy subjects. The interoceptive awareness of affective distress is believed to be represented in the insula (Craig, 2002). The insula plays an important role in the integration of emotion, cognition, and the identification of salient events (Seeley et al., 2007; Uddin et al., 2014), and it is thought to connect the awareness of affective distress to cognitive control brain regions (Craig, 2002; Garavan, 2010; Paulus and Stein, 2010). This suggests that the insula may be a critical brain region in the regulation of distress and the determination of distress tolerance thresholds. Thus, it was hypothesized there would be task-based functional connectivity between the left planum temporale and the insula, and that this connectivity would be associated with PASAT DT persistence across individuals.

2. Methods

2.1. Participants

Healthy, right-handed adults aged 18–55 years were recruited from the local community. Participants completed a phone interview and laboratory-based screening session to determine eligibility. Exclusion criteria included significant health problems including a history of head trauma or seizures, current diagnosis of Axis I psychiatric disorder, presence of conditions that would make MRI unsafe, a positive urine drug screen for psychoactive drugs or medications (iCup, Alere Toxicology Services Portsmouth, VA), a positive breath alcohol screen (Alco-Sensor III, Intoximeters Inc St. Louis, MO), and among women—a positive urine pregnancy screen (QuickVue+, Quidel Corporation San Diego, CA). Participants provided informed consent and this protocol was approved by Duke University's Institutional Review Board. This research was carried out in accordance with the Code of Ethics of the World Medical Association.

2.2. Paced Auditory Serial Attention Task (PASAT)

Participants completed a modified version of the Paced Auditory Serial Attention Task for fMRI (Daughters et al., 2016). A series of single-digit numbers appeared in the center of the screen one at a time and players had to add the current number to the previous number, and

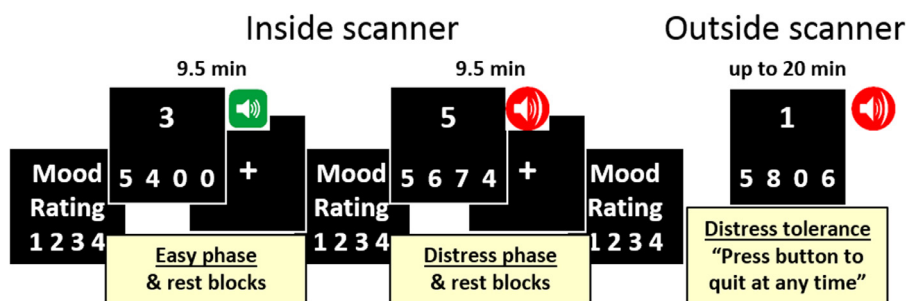


Fig. 1. Design of the modified Paced Auditory Serial Addition Task for fMRI (PASAT-M). During the easy phase, a pleasant bell sound played after each correct answer. During the distress phase, an aversive buzzer sound played after each incorrect and late answer.

indicate their response using an MR-compatible response box. Four response options (i.e., correct and incorrect sums) were displayed along the bottom of the screen. On each trial, numbers appeared onscreen for 3 sec. The modified PASAT-M consisted of an easy and a distress phase that were administered during fMRI. Each phase consisted of six 60 sec task blocks, beginning and alternating with seven 30 sec rest blocks. Participants received auditory feedback via MR-compatible headphones. See Fig. 1.

During the easy phase, participants had 2 sec to respond to each trial. Two response options (i.e., the correct sum and an incorrect value) were displayed along the bottom of the screen along with 2 null options (represented by “0”). Correct, on-time responses were followed by a 750 msec pleasant bell sound. Missed responses resulted in a “Respond Faster!” message onscreen for 1 sec and incorrect responses received no feedback.

During the distress phase, participants had to respond 75% faster than their average response time calculated from trials during the easy phase. Four response options (i.e., the correct sum and three incorrect values) were displayed along the bottom of the screen. Correct, on-time responses received no feedback. Late and incorrect responses were followed by a 750 msec aversive buzzer sound. Missed responses resulted in a “Respond Faster!” message onscreen for 1 sec. The easy phase was always presented before the distress phase to calculate the average response time and to avoid carry-over effects of stress and negative affect.

The distress tolerance (DT) phase was identical to the distress phase except that the message “Press esc to end the task” appeared across the top of the screen and participants could end the task at any time. This phase was conducted immediately after the MRI scan (began within 5 min post-MRI) and was completed in an adjacent room. The task lasted a maximum of 20 min. The duration (in min) before quitting the task was the primary behavioral measure of DT.

Participants earned points for each correct, on-time response during the easy phase and lost a point for every incorrect, late response during the distress phase. Point totals were revealed after the entire task was completed. During the DT phase, they earned points for each correct, on-time response and the number of points they earned went towards a \$2.50 bonus.

Participants were given explicit instructions about the points and financial bonus in each phase, and that they had to respond faster, on average, in the distress and DT phases than in the easy phase.

2.3. Mood rating scales

As part of the PASAT, a mood rating scale was presented onscreen before the easy phase, in-between the easy and distress phase, and after the distress phase. Participants were instructed to rate the extent to which they were experiencing each emotion right now on a scale from 1 (“not at all”) to 4 (“extremely”). Emotions were *irritable*, *bored*, *frustrated*, *happy*, *angry*, *stressed*, *excited*, and *motivated to perform well*. Negative mood was calculated as the mean ratings of *irritable*, *frustrated*,

angry, and *stressed* at each time point.

2.4. Image acquisition and preprocessing

Images were acquired on a 3T General Electric MR750 scanner (Milwaukee, WI) equipped with 50 mT/m gradients. A high-resolution T1 anatomical image was collected using a three-dimensional fast spoiled gradient recalled echo (3D-SPGR) sequence (TR = 8.156 ms, TE = 3.18 ms, field of view = 25.6 cm², matrix = 256 × 256, flip angle = 12°, 166 slices, and slice thickness = 1 mm).

During the resting-state scan and PASAT task, blood oxygen level-dependent (BOLD) signal was measured using a gradient-recalled inward spiral pulse imaging sequence (SENSE spiral) (TR = 2000 ms, TI = 0, TE = 32 ms, flip angle = 77°, acquisition matrix = 64 × 128, field of view = 25.6 cm², number of slices = 34, and slice thickness = 4 mm resulting in 4 × 4 × 4 mm voxels). The resting-state scan consisted of 150 volumes for a duration of 5 min. Participants were asked to keep their eyes open during the resting-state scan and were shown a blank screen. The PASAT scan consisted of 2 runs (easy phase and distress phase) with 285 volumes each for a duration of 9 min 30 sec per run. The first four image volumes were removed to allow for stabilization of the MR signal. An infrared camera attached to the head coil was used to monitor alertness.

Functional images were preprocessed using Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience www.fil.ion.ucl.ac.uk). Images were slice-time corrected, spatially realigned to the first volume, coregistered to the T1 anatomical image, resliced to 2 mm voxels, and normalized to the Montreal Neurological Institute (MNI) template. Images were spatially smoothed with 5 mm full width half-maximum Gaussian kernel.

2.5. Resting-state functional connectivity

A resting-state functional connectivity analysis was conducted using the Conn v17.f toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) (www.nitrc.org/projects/conn). Preprocessed functional and normalized anatomical images were entered into Conn and a region of interest (ROI) seed-to-voxel analysis was performed using the left planum temporale (based on the Harvard-Oxford template) as seed ROI. Six movement regressors were included as covariates of no interest.

2.6. Task-based BOLD activation

Block-design analyses of the fMRI data were conducted using SPM12. The task block was the regressor of interest, constructed as a boxcar convolved with the canonical hemodynamic response function. Images were high-pass filtered and 6 movement regressors were included as covariates of no interest. The easy and distress phases of the PASAT were concatenated and first-level fixed effects contrasts were created for easy > rest, distress > rest, [distress > rest] > [easy > rest], and easy and distress.

2.7. Task-based functional connectivity

A generalized psychophysiological interaction (gPPI) routine was implemented using the Conn v17.f toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) (www.nitrc.org/projects/conn). PPI assesses functional connectivity between brain regions in a task-dependent manner, and gPPI is configured to accommodate more than two task conditions within the same model (McLaren et al., 2012). Specifically, the difference in connectivity strength between the distress phase and the easy phase was investigated between a seed region of interest (ROI) and all other voxels in the brain. The left planum temporale was chosen as a seed ROI because of its role in auditory processing and the task-related activation in this region. The gPPI model includes three regressors: psychological (i.e., easy > rest and distress > rest), physiological (i.e., the BOLD time course from the seed region for easy > rest or distress > rest), and the psychophysiological interaction (i.e., the interaction between the psychological and physiological regressors).

2.8. Data analysis

Self-report mood data was analyzed in SPSS v24 (Corp, Released 2017). Self-reported mood scores during the PASAT were analyzed with a repeated-measures ANOVA with Bonferroni-corrected pairwise comparisons. PASAT performance was analyzed with paired-sample *t*-tests. Group random effects in the neuroimaging data were analyzed using one-sample *t*-tests. Significance threshold for the task-based activation, resting-state and task-based functional connectivity analyses was set at $p < .001$ uncorrected and cluster extent of >100 voxels (cluster-level extent family-wise error (FWE) $p < .01$) to adjust for multiple comparisons; no masking was applied to the neuroimaging analysis. Lastly, the behavioral measure of PASAT DT was correlated with the difference in task-based functional connectivity (distress > easy) between the seed ROI and all other voxels in the brain. Significance threshold for this correlation was set at $p < .001$ uncorrected and cluster-level extent false discovery rate (FDR) $p < .05$. Neuroimaging figures were created using MRIcron (www.mccauslandcenter.sc.edu/mricron/). Figures are shown using neurological convention.

2.9. Procedure

Participants underwent an initial eligibility screening session. During this session, prospective participants played a practice version of the PASAT. Participants had to perform the easy phase with 75% accuracy to remain eligible for the study (2 prospective participants were excluded for this reason). Participants were allowed to practice the task up to 3 times to meet criterion.

Eligible participants were scheduled for a 1-hr MRI session followed immediately by a 1-hr behavioral session. Upon arrival to the MRI scan, participants submitted a breath sample to test for alcohol (all participants tested negative). During the MRI, participants completed the PASAT, followed by the behavioral PASAT DT outside the MRI scanner.

These procedures were part of a larger study that included other measures of distress tolerance and transcranial magnetic stimulation sessions conducted after the first MR session. The results of these procedures will be described elsewhere. Participants were compensated up to \$300 for completion of the entire study.

3. Results

3.1. Participants

Thirty participants completed all aspects of the study; however, 2 were removed due to equipment malfunction and 1 was removed due to excessive head motion (relative mean displacement > 1 mm in the xyz planes). The final sample consisted of 27 participants; this sample is missing one participant's behavioral data from the PASAT distress

phase. Twenty of the participants were female and 7 were male. The average age was 29.8 ± 11.6 (M \pm SD) and average years of education was 16.6 ± 2.3 . The racial distribution was 17 non-Hispanic Caucasian, 1 Hispanic Caucasian, 1 Asian, 6 African-American, and 2 other/mixed race.

3.2. Mood ratings

During the PASAT, the average negative mood scores (*irritated, frustrated, angry, and stressed*) significantly increased across 3 time points (pre-PASAT easy, post-PASAT easy/pre-PASAT distress, post-PASAT distress) from 1.16, to 1.34, to 1.8 ($F(2,24) = 13.5, p < .001$). Follow-up pairwise comparisons revealed significant increases from time 1 to time 2 ($p = .012$), and from time 2 to time 3 ($p < .001$).

The scores for *motivation to perform well* and average positive mood (*happy and excited*) did not significantly vary across the three time points.

3.3. PASAT performance

During the scan, participants made correct responses to the PASAT easy phase in $84 \pm 6\%$ of the trials (resulting in a pleasant sound), and made incorrect responses to the PASAT distress phase in $65 \pm 18\%$ of the trials (resulting in an aversive sound). There were more instances of feedback sounds in the easy phase than in the distress phase ($t(25) = 5.5, p < .001$). Reaction times on all trials were similar between the PASAT easy phase and the distress phase (940 msec vs 900 msec, respectively; $t(25) = 2.0, p > .05$). Across subjects, the number of DT trials were evenly distributed and ranged from 1 to 20 min (20–401 trials; M \pm SD 219 ± 134 trials). The number of DT trials completed after the fMRI scan positively correlated with the DT percent correct (Spearman's rho = .645, $p < .001$). Neither the number of DT trials completed nor the percent correct correlated with education level across participants.

3.4. Imaging

3.4.1. Resting-state functional connectivity

The resting-state functional connectivity scan revealed functional connections between the left planum temporale seed region and all other voxels in the brain. At rest, the left planum temporale is positively functionally connected to the bilateral auditory cortex and superior temporal gyri, as well as the bilateral supplementary motor area, pre- and postcentral gyri, posterior insula, and putamen. At rest, the left planum temporale is negatively functionally connected to the bilateral lateral occipital cortex, precuneus, and frontal poles. See Fig. 2 and Table 1.

3.4.2. BOLD activation

Patterns of BOLD activation revealed brain regions activated by the performance of the PASAT. During the task, the easy and distress phases together activated the bilateral middle frontal gyri, bilateral superior parietal lobes, and the medial supplementary motor area extending into the paracingulate and anterior cingulate cortex. Additional activation was elicited in the bilateral anterior insula, thalamus, putamen, occipital cortex, cerebellum, and brainstem. Notably, activation was elicited in the bilateral Heschl's gyrus and planum temporale. See Fig. 3 and Table 2. Compared to the easy phase, the distress phase elicited less activation in the right precuneus, supramarginal gyrus, and lingual gyrus. There were no significant regions where the distress phase elicited more activation than the easy phase. See Table 2.

3.4.3. Task-based functional connectivity

The task-based functional connectivity analysis revealed brain regions that were more functionally connected to the planum temporale seed region during performance of the PASAT. Compared to rest, the

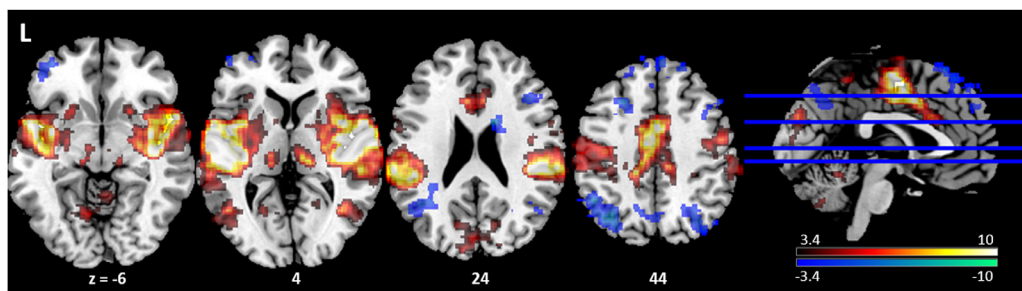


Fig. 2. Resting-state functional connectivity of the left planum temporale, defined by the Harvard-Oxford Cortical Atlas. Significance threshold $p < .001$ uncorrected and cluster extent of >100 voxels. Color bars represent t scores. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1

Resting-state functional connectivity with the left planum temporale seed region. Significance threshold $p < .001$ uncorrected and $K_E > 100$ voxels (2 mm^3).

	MNI coordinates	Cluster size (# voxels)	Peak t value
<i>Positive connectivity</i>			
L&R auditory cortex	-48 -22 6	31380	22.44
Heschl's gyrus			
Planum temporale			
Superior temporal gyrus			
Central opercular cortex			
Parietal opercular cortex			
L&R Supplementary motor area			
Anterior cingulate			
L&R precentral gyrus			
L&R postcentral gyrus			
L&R posterior insula			
L&R putamen			
L thalamus			
R thalamus	6 -18 0	367	9.33
R lateral occipital cortex	40 -62 4	355	7.60
Middle temporal gyrus			
L Middle temporal gyrus	-48 -62 4	388	7.23
Lateral occipital cortex			
R cerebellum	26 -46 -30	3303	8.79
L cerebellum	-26 -48 -52	123	5.04
<i>Negative connectivity</i>			
L lateral occipital cortex	-32 -68 44	2131	6.92
Angular gyrus			
R lateral occipital cortex	36 -78 48	1008	6.01
L superior frontal gyrus	-24 20 46	410	6.83
Middle frontal gyrus			
Medial superior frontal gyrus	0 30 64	1572	6.73
L&R Frontal pole			
L frontal orbital cortex	-52 26 -12	336	5.42
Frontal pole			
L frontal medial cortex	-10 46 -18	155	5.34
Frontal pole			
L precuneus cortex	-6 -72 50	360	5.17
L cerebellum	-24 -72 -40	164	5.88
R white matter	14 6 24	232	6.70

Table 2

Task activation results for the PASAT easy and distress phases. Significance threshold $p < .001$ uncorrected and $K_E > 100$ voxels (2 mm^3).

	MNI coordinates	Cluster size (# voxels)	Peak t value
<i>Easy and distress</i>			
L&R precentral gyrus	-44 -2 36	21118	13.69
L&R middle frontal gyrus			
L&R supplementary motor cortex			
L&R paracingulate cortex			
L&R anterior cingulate cortex			
L opercular cortex			
L anterior insula			
L Heschl's gyrus & planum temporale			
L superior parietal lobule			
L supramarginal gyrus			
L lateral occipital cortex			
L&R occipital pole			
L thalamus			
L&R cerebellum			
L&R brainstem			
R superior parietal lobule	28 -56 42	2376	11.67
R supramarginal gyrus			
R lateral occipital cortex			
R frontal operculum cortex	36 14 8	795	9.16
R anterior insula			
R thalamus	10 -12 4	300	7.00
R white matter	28 -22 -6	100	6.60
R Heschl's gyrus & planum temporale	48 -16 2	664	6.31
R superior temporal gyrus			
R supramarginal gyrus			
<i>Easy > Distress</i>			
R precuneus cortex	10 -64 50	679	6.84
R lateral occipital cortex			
R supramarginal gyrus	40 -38 42	170	5.83
R superior parietal lobule			
R lingual gyrus	10 -66 -8	157	5.72
R occipital fusiform gyrus			
<i>Distress > Easy</i>			
No surviving clusters			

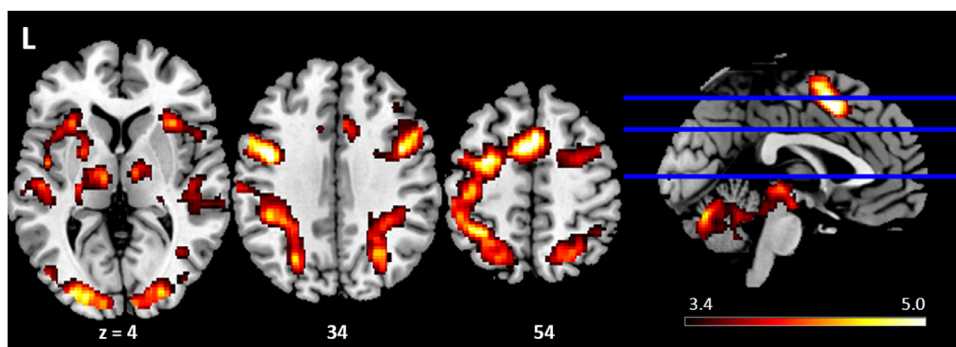


Fig. 3. BOLD activation of the easy and distress phases of the PASAT. Significance threshold $p < .001$ uncorrected and cluster extent of >100 voxels. Color bar represents t scores. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Task-based functional connectivity results for the PASAT easy and distress phases. Significance threshold $p < .001$ uncorrected and $K_E > 100$ voxels (2 mm^3).

	MNI coordinates	Cluster size (# voxels)	Peak t value
<i>Main effect of easy: positive connectivity</i>			
L paracingulate	-6 50 -4	137	4.96
L precuneus	-12 -60 28	123	5.21
<i>Main effect of easy: negative connectivity</i>			
R supramarginal gyrus	42 -32 24	446	8.49
L supramarginal gyrus	-60 -30 34	258	5.82
R lateral occipital cortex	42 -54 4	364	6.42
R precuneus	6 -50 50	558	5.47
R superior parietal lobule			
R inferior frontal gyrus	58 14 22	194	5.82
L inferior frontal gyrus	-42 18 20	107	5.32
R middle frontal gyrus	48 24 30	116	4.93
R anterior insula	34 14 8	112	5.59
L anterior insula	-28 22 -02	130	5.66
R anterior insula	34 14 8	112	5.59
R paracingulate	6 20 48	162	4.74
L middle temporal gyrus	-50 -60 -2	160	5.95
<i>Main effect of distress: positive connectivity</i>			
R Heschl's gyrus & planum temporale	50 -18 2	136	5.65
L Heschl's gyrus & planum temporale	-42 -26 8	118	5.67
<i>Main effect of distress: negative connectivity</i>			
R&L precentral gyrus	36 -20 44	7529	8.91
R&L postcentral gyrus			
R&L precuneus cortex			
R parietal operculum			
R central opercular cortex			
R putamen			
R&L supplementary motor area			
R posterior insula			
R&L mid-cingulate			
L postcentral gyrus	-58 -10 22	2000	7.04
L precentral gyrus			
L parietal operculum			
L central opercular cortex			
L putamen			
L posterior insula			
R lateral occipital cortex	52 -60 0	748	7.21
R middle temporal gyrus			
L lateral occipital cortex	-46 -66 6	191	6.08
<i>Main effect of distress > easy</i>			
R&L superior frontal gyrus	-6 28 42	1016	6.45
R&L paracingulate gyrus			
R middle frontal gyrus	46 20 30	961	6.85
R inferior frontal gyrus			
L inferior frontal gyrus	-44 18 26	696	7.66
L middle frontal gyrus			
L anterior insula	-30 18 2	226	6.19
R anterior insula	38 26 -6	276	5.45
L supramarginal gyrus	-48 -44 46	123	6.00
R supramarginal gyrus	50 -32 44	236	6.23
L superior parietal lobe	-26 -55 40	234	5.95
<i>Main effect of easy > distress</i>			
R putamen	30 -8 4	392	6.88
L putamen	-28 4 2	626	6.67
L posterior insula			
L&R precentral gyrus	-4 -16 42	863	6.47
L&R postcentral gyrus			
L&R supplementary motor area			
L&R paracingulate gyrus	2 40 -10	124	5.35

easy phase showed positive connectivity between the seed region and the left ventromedial paracingulate and precuneus; and showed

negative connectivity with the bilateral supramarginal gyrus, inferior frontal gyrus, anterior insula, and dorsomedial paracingulate. Compared to rest, the distress phase showed positive connectivity between the seed region and the bilateral Heschl's gyrus and planum temporale; and showed negative connectivity with regions of the sensorimotor network, including the bilateral pre- and post-central gyrus, supplementary motor area, putamen and posterior insula. See Table 3.

Compared to the easy phase, the distress phase showed stronger connectivity between the seed region and the bilateral superior, middle, and inferior frontal gyri, dorsomedial paracingulate cortex, anterior insula, and supramarginal gyri; and showed weaker connectivity with the bilateral pre-/postcentral gyri, supplementary motor area, ventromedial paracingulate cortex, and putamen. See Table 3 and Fig. 4.

The behavioral measure of PASAT DT was subsequently included as a covariate of interest in the distress > easy phase contrast. As hypothesized, there was a negative correlation between the left planum temporale seed region and the left anterior insula during the distress > easy phase (MNI coordinates of peak voxel = -34, 20, 0; $K_E = 58$; peak t value = 5.10; $r^2 = .55$). See Table 3 and Fig. 5.

4. Discussion

The goal of this study was to investigate the generation of cognitive/affective distress induced by auditory negative feedback. We administered a mental arithmetic task (i.e., PASAT) with an easy and distress phase, which differed in cognitive demands and positive versus negative auditory feedback. The final phase consisted of a behavioral measure of distress tolerance (DT) duration. The PASAT increased self-reported negative mood and activated the auditory cortices and fronto-parietal regions consistent with the cognitive control network (Niendam et al., 2012). At rest, the left secondary auditory cortex (i.e., planum temporale) was positively associated with sensorimotor regions; however, task-based functional connectivity between the planum temporale and the rest of the brain revealed that distress weakened connectivity with the sensorimotor cortices and ventromedial paracingulate cortex, and strengthened connectivity with fronto-parietal regions and the anterior insula. This suggests that the distress phase recruited more cognitive control and was more emotionally salient than the easy phase. Lastly, in support of our hypothesis, distress-related functional connectivity between the left planum temporale and the left anterior insula negatively correlated with DT duration across participants. Lower DT was associated with a larger difference in functional connectivity (distress > easy). This suggests a stronger association between auditory processing of negative feedback and emotional processing in the anterior insula is related to a faster action to quit a distressing task. This may be due to increased bottom-up awareness of the distress, a stronger influence of negative affect over behavior, or an impaired ability to ignore or suppress the awareness of the distress. Altogether, this study provides additional support for the use of the PASAT to elicit cognitive/affective distress in healthy participants and demonstrates a role for the anterior insula in distress tolerance.

4.1. The role of the anterior insular cortex

The anterior insular cortex (AIC) plays a fundamental role in interoception (i.e., the conscious awareness of the internal state of the body) and the AIC is believed to follow a posterior to anterior integration of primary interoceptive awareness to subjective emotional interpretation, respectively (Craig, 2009). Activation in the AIC is elicited by monitoring one's own emotions (Zaki et al., 2012) and is associated with signals from the autonomic nervous system (e.g., pupil dilation or heart rate deceleration) that prepare the individual to respond to changes in internal and external demands (Ullsperger et al., 2010). The AIC also plays a role in task-level control, performance monitoring (including error-related feedback), and focal attention capture (i.e., when environmental information becomes available to

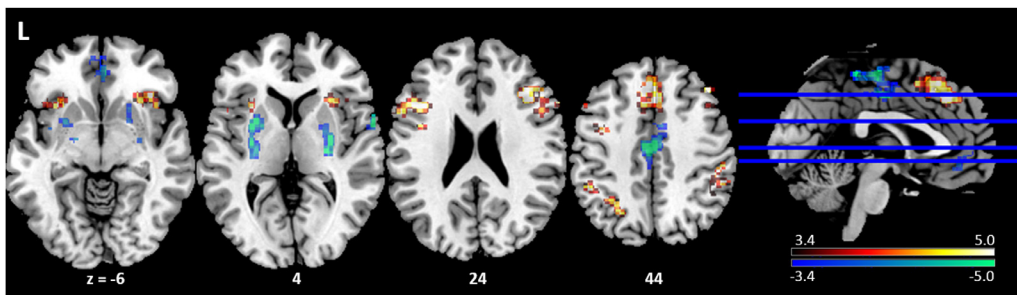


Fig. 4. Task-based functional connectivity (i.e., generalized psychophysiological interaction) between the left planum temporale seed region and all other voxels in the brain. Shown is the contrast for distress > easy phase of the PASAT. Significance threshold $p < .001$ uncorrected and cluster extent of >100 voxels. Color bars represent t scores. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

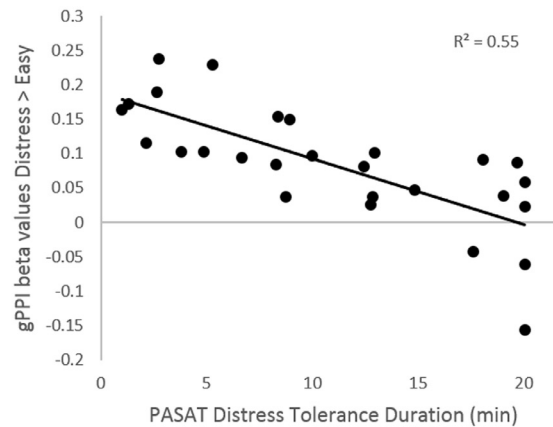
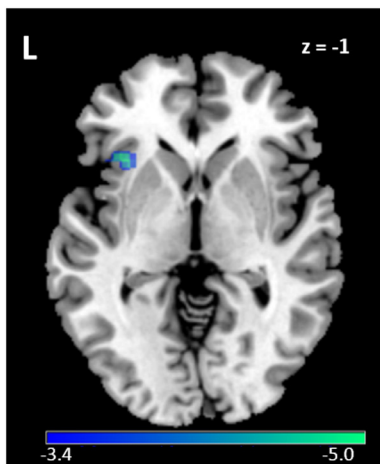


Fig. 5. Correlation between PASAT distress tolerance duration and the task-based functional connectivity (distress > easy phase) between the left planum temporale and all other voxels in the brain. Significance threshold $p < .001$ uncorrected and cluster extent of false discovery rate (FDR) $p < .05$. Color bar represents t scores. The scatterplot shows the extracted beta values from the left anterior insula plotted against the distress tolerance duration in min. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

awareness) (Nelson et al., 2010). In the distress phase of the PASAT, incorrect and late responses were met with aversive auditory feedback, thus alerting the participants' attention to the error. Given the role of the AIC, the distress-related connectivity between the planum temporale and the bilateral AIC may have been related to this auditory feedback. Although, it is also possible that participants made more commission errors during the distress phase and were aware of incorrect responses before the auditory feedback. In either case, response errors are salient events that elicit an orienting response subserved by the AIC (Ullsperger et al., 2010).

The AIC, along with functional connections to the anterior cingulate and other regions, compose the salience network, which is sensitive to unexpected or arousing stimuli and integrates external sensory information with internal emotional signals (Seeley et al., 2007; Uddin et al., 2014). The existence of this network is consistent with the idea that the insula represents the limbic sensory cortex and the cingulate is the limbic motor cortex, linking emotions to motivation to approach or escape a stimulus (Craig, 2009). In fact, the AIC may be the hub where bottom-up sensory signals meet volitional top-down control relevant for goal-directed behavior (Nelson et al., 2010). In this case, the bottom-up processing of affective distress from the auditory cortex, and the top-down cognitive decision making related to terminating the DT phase of the PASAT. Based on the accumulated evidence, it is reasonable that the AIC would play an integral role in the awareness of affective distress and setting a subjective distress tolerance 'threshold' to help determine when an individual will act to escape or alleviate distress.

A promising application for this line of research is the use of real-time fMRI to train individuals to volitionally activate or deactivate the AIC based on BOLD magnitude neurofeedback (Caria et al., 2010; Caria et al., 2007). Importantly, individual participants who successfully increased left AIC activation rated aversive pictures more affectively negative, and there was a positive correlation between left AIC activation and negative valence ratings of aversive pictures (Caria et al., 2010), suggesting that individuals can learn to control their cognitive/

affective engagement with aversive stimuli. Future research could adapt real-time fMRI to help guide or test the effectiveness of therapeutic interventions designed to improve emotional regulation and/or distress tolerance duration. A complementary approach would be the manipulation of cortical activation via transcranial magnetic stimulation to test the role of the insula in the awareness of distress; for example, see (Malik et al., 2017).

4.2. Relevance to psychiatry

The results of this study are relevant to psychiatry, in particular, augmented interoceptive signals in the AIC are thought to mediate the tendency to perceive certain interoceptive sensations as dangerous or threatening among individuals with high anxiety sensitivity (Paulus and Stein, 2006). High anxiety sensitivity is a transdiagnostic symptom, occurring across psychiatric disorders such as generalized anxiety disorder, panic disorder, post-traumatic stress disorder (Olatunji and Wolitzky-Taylor, 2009), and substance use disorders (Grant et al., 2004). In particular, the role of the insula in interoceptive awareness has been implicated in tobacco use disorder. Smokers who have suffered strokes affecting the insula have sometimes reported a sudden loss of the urge to smoke (Abdolahi et al., 2015; Gaznick et al., 2014; Naqvi et al., 2007; Suner-Soler et al., 2012), but also see (Bienkowski et al., 2010; Suner-Soler et al., 2017). This underscores the role of the insula as the hub between interoceptive awareness (e.g., of nicotine withdrawal symptoms or affective distress) and goal-directed behavior (e.g., lighting a cigarette). Indeed, many tobacco users report smoking to alleviate negative affect, which may or may not be related to nicotine withdrawal symptoms (Kassel et al., 2003; Morissette et al., 2007).

The relationship between interoception, negative affect and substance use is generalizable to other drugs of abuse, and individuals with anxiety disorders and low distress tolerance may be at increased risk of substance abuse and addiction (Morissette et al., 2007). This raises the

question of whether chronic substance use could sensitize users to affective distress or whether substance users ‘self-medicate’ at the expense of other cognitive coping mechanisms and are subsequently less able to engage alternative coping mechanisms when drugs are not available. Thus, substance users—and other individuals high in anxiety sensitivity—may have increased bottom-up awareness of distress as well as diminished top-down control of distress. While the present study suggests that healthy individuals with low DT have stronger bottom-up functional connectivity with the AIC, previous work suggested diminished top-down control between the middle frontal gyrus and ventromedial prefrontal cortex in cocaine/tobacco users (Daughters et al., 2016). Future research can further clarify this relationship by investigating the role of anxiety sensitivity on the neural mechanisms of DT.

4.3. Comparison to other studies

We used a modified version of the PASAT previously used by Daughters et al. (2016). One important modification was the lengthening of the maximum PASAT DT phase from 10 to 20 min. This resulted in an even distribution of DT durations with less of a ceiling effect caused by individuals whose DT durations met the maximum time limit. This distribution may have contributed to the correlation we observed between DT duration and task-based functional connectivity to the AIC. However, we did not replicate the distress > easy phase BOLD activation shown previously. In their exploratory whole-brain analysis, Daughters et al. reported healthy participants had distress-induced activation in the auditory cortex, insula, anterior cingulate, precentral gyrus, and supplementary motor area; and deactivation in the precuneus, middle frontal gyrus, lingual gyrus, caudate, and middle temporal gyrus (among other regions) (Daughters et al., 2016). Other studies have investigated the neural mechanisms underlying cognitive/affective stress using other paradigms (Dedovic et al., 2009a). Overall, these studies have shown that stress is associated with changes in cerebral blood flow in the orbitofrontal cortex and anterior cingulate (Dedovic et al., 2009a). One paradigm similar to the PASAT is the Montreal Imaging Stress Task (MIST), which is a computerized mental arithmetic test with social evaluative threat components (i.e., negative verbal feedback regarding performance errors) (Dedovic et al., 2005). The mental arithmetic in this task has also been associated with increased activation in fronto-parietal regions (Dedovic et al., 2005; Dedovic et al., 2009b; Wheelock et al., 2016), consistent with the cognitive control network. The MIST has been shown to increase cortisol release in some individuals, and these individuals showed stress-induced activation in the AIC, anterior cingulate, and dorsomedial prefrontal cortex (Dedovic et al., 2009b). Also, a positive correlation between trait anxiety and stress-induced activation in the insula, dorsomedial prefrontal cortex, and posterior cingulate has been revealed (Wheelock et al., 2016). In all, these studies demonstrate the recruitment of the cognitive control network and other regions in the prefrontal cortex and insula during cognitive stress compared to a non-stress control condition.

In the current study, there was a small extent of distress-induced deactivation in the precuneus, supramarginal gyrus, and lingual gyrus, but no distress-induced activation. In the original version of the PASAT-M, a latency phase was included prior to the distress phase, thereby increasing the duration of stress exposure. Further, the rate of number presentations increased from the easy to the distress phase (Daughters et al., 2016), whereas in the current study, numbers were presented at a fixed rate with a shorter response time limit in the distress phase. Perhaps the faster presentation rate increased attentional demands to an extent that was measurable by greater BOLD activation. Despite the lack of difference in BOLD activation, our results showed different patterns of connectivity with the planum temporale between the easy and distress phase, suggesting a selective recruitment of different cognitive areas during the performance of each phase of the task.

In our version, there was no difference in auditory cortex activation between the distress and the easy phase, so this does not fully account for the differences in functional connectivity during the two phases. To our knowledge, this is the first study to investigate the role of the auditory cortex in distress tolerance, although a recent study investigated the functional connectivity of the auditory cortex while participants listened to joyful, fearful, or neutral music (Koelsch et al., 2018). A psychophysiological interaction analysis using the left planum temporale as a seed region revealed stronger task-based functional connectivity during fearful than joyful music with the middle/posterior cingulate, orbitofrontal cortex, middle frontal gyrus, inferior frontal gyrus, precentral sulcus/premotor cortex, and temporo-parieto-occipital area, among other regions. Koelsch et al. concluded that the auditory cortex plays a central role in the affective processing of auditory information. Altogether, this line of research reveals important functional connections between the auditory cortex and the prefrontal cortex during the emotional processing of auditory information.

4.4. Limitations

There are several limitations to the present study. Most of the sample was female, which limits the generalizability and the small sample size precludes a preliminary assessment of sex differences. PASAT performance is affected by math ability and general intellectual ability (Deary et al., 1991; Tombaugh, 2006), and we report a positive correlation between the DT duration and the number of correct trials. It is possible that math ability was a better predictor of the number of trials completed than DT in general; however, previous work did not find a relationship between PASAT performance and distress tolerance (Daughters et al., 2016). A financial incentive was offered to help motivate DT persistence, but was kept low (\$2.50) to avoid overly-influencing participants’ behavior. The strength of influence of the value of this incentive is unknown but potentially important. Participants’ hearing was not tested during the screening session and auditory differences could have affected the BOLD response, although no participants reported problems with hearing the auditory feedback in the scanner. Another limitation was that the participants’ made more correct answers during the easy phase of the PASAT than incorrect answers during the distress phase, which resulted in more instances of auditory feedback in the easy phase. While there was no difference in auditory activation between phases, differences in auditory feedback should be minimized in future studies. Related, trial events occurred at fixed intervals that precluded separate analyses of events (e.g., response, auditory feedback); future versions of the task can include variable intervals to allow for more precise modeling of events. Lastly, self-reported negative mood increased pre- to post-easy phase, although this phase was not intended to induce distress. Future studies should include more objective measures of physiological arousal (i.e., skin conductance, cortisol levels) to complement the self-report measures.

Despite these limitations, this study sheds light on the generation of auditory feedback distress and its relationship with the anterior insula. While these results are based on a nonclinical sample of healthy adults, future studies could apply this basic research to psychiatric conditions related to low distress tolerance, and use a mixed event-/block-related design to permit a more thorough examination of trial events.

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Author's contributions

M.A.A., S.B.D., T.J.S., and L.G.A. contributed to the conception and design of the study. M.A.A. conducted the analyses, data interpretation, and drafted the manuscript. S.B.D., T.J.S., and L.G.A. also contributed to the interpretation of the data and helped revise the manuscript. All authors gave approval for the version to be published.

Competing interests

The authors have no conflicts of interest to report.

Ethics approval

The Institutional Review Board of Duke University School of Medicine approved this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2018.10.003](https://doi.org/10.1016/j.psychres.2018.10.003).

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