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Cortical and Cerebellar Modulation of Autonomic Responses to Loud Sounds

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Abstract

Detecting unexpected environmental change causes modulation of autonomic activity essential for survival. Understanding the neural mechanisms associated with responses to loud sounds may provide insights into the pathophysiology of Post-Traumatic Stress Disorder (PTSD), since individuals with PTSD exhibit heightened autonomic responses to unexpected loud sounds. We combined fMRI with **autonomic** psychophysiological assessment to investigate **central** and peripheral reactivity to loud tones in 20 healthy participants. Activity in anterior insula, pregenual anterior cingulate cortex, anterior mid-cingulate cortex, supplementary motor area, supramarginal gyrus, and cerebellar lobules VIII-IX was associated with both tones and concomitant skin conductance responses. Since regions signaling unexpected external events modulate autonomic activity, heightened loud tone autonomic responses to in PTSD may reflect sensitization of this "salience" network.

Descriptors: functional magnetic resonance imaging, unconditioned response, heart rate, skin conductance, saliency, autonomic nervous system

The ability to accurately detect potentially meaningful environmental events is essential for adaptive behavior, because it facilitates rapid and efficient engagement of executive functions needed to regulate attention, working memory and behavioral responses. For instance, if the phone rings on one's desk, engagement with any ongoing task will be interrupted and attention can be redirected towards the phone. This *orienting response*, which involves a complex set of adjustments, is elicited by changes in the sensory environment signaling novel, unexpected, or otherwise salient events (Corbetta, Patel, & Shulman, 2008; Öhman, Hamm, & Hugdahl, 2007).

Recent human neuroimaging studies have substantially increased our understanding of the neural processing of salient stimuli. Modulation of activity in insula, temporoparietal junction, cingulate cortex, supplementary motor area, and inferior frontal gyrus has been observed in response to a variety of novel or unexpected visual, auditory, and tactile stimuli, including abstract shapes, transitions between the sound of running water and croaking frogs (Downar, Crawley, Mikulis, & Davis, 2000), successive movements of musical symphonies (Sridharan, Levitin, Chafe, Berger, & Menon, 2007), pitch changes of a buzzing sound (Downar, Crawley, Mikulis, & Davis, 2001), and sequential presentation of everyday sounds such as rising tones or chimes (Downar, Crawley, Mikulis, & Davis, 2002). It has been postulated that interactions among these brain regions constitute a “salience” network that mediates detection and involuntary orienting attention to unexpected events (Corbetta, et al., 2008; Menon & Uddin, 2010). However, little is known about the functional relationship between activity in this salience network and concomitant autonomic responses. It is well established that salient events can induce short-term electrodermal and cardiovascular responses (Dykman, Reese, Galbrecht, & Thomasson, 1959). Along these lines, there is a long history of using autonomic activity as a measure of orienting to environmental changes (Boucsein, 2012).

Central functional magnetic resonance imaging (fMRI) and peripheral autonomic recording of skin conductance (SC) and HR have been used to measure responses to intermittent, sudden loud tones. The loud tone procedure is a standardized technique used to assess autonomic reactivity that has minimal behavioral, cognitive and emotional demands, requiring only that participants sit quietly and listen (Table 1). It has been shown to have clinical utility because of its ability to reliably discriminate Post-Traumatic Stress Disorder (PTSD) from healthy participants (Carson et al., 2007; Metzger et al., 1999; Orr, Lasko, Shalev, & Pitman, 1995; Orr et al., 2003; Orr, Solomon, Peri, Pitman, & Shalev, 1997; Shalev, Orr, Peri, Schreiber, & Pitman, 1992; Shalev et al., 2000; Shalev, Peri, Orr, Bonne, & Pitman, 1997). In addition, there is evidence that the increased HR responses to loud tones observed in PTSD is an acquired, rather than preexisting, feature of the condition (Orr, et al., 2003; Shalev, et al., 2000). Moreover, this heightened HR response appears to normalize with clinical improvement (Griffin, Resick, & Galovski, 2012).

Findings from studies investigating neural responses to auditory stimuli (Downar, et al., 2000, 2001, 2002; Sridharan, et al., 2007) suggest that loud tones should generate activity in regions mediating salience processing, including insula, cingulate cortex, supplementary motor area, temporoparietal junction, and inferior frontal gyrus. Of these, temporoparietal junction, insula, and cingulate cortex are known to modulate electrodermal responses to unconditioned auditory stimuli (Knight, Nguyen, & Bandettini, 2005; Knight, Waters, King, & Bandettini, 2010; Raine, Reynolds, & Sheard, 1991). Given that SC responses primarily reflect sympathetic activity (Boucsein, 2012), one might also expect to see relationships between neural activity in these regions and HR, to the extent that HR is influenced by sympathetic as well as parasympathetic activity (Critchley, Corfield, Chandler, Mathias, & Dolan, 2000; Critchley et al., 2003).

The present fMRI study explores the neural mechanisms of SC and HR reactivity during the aforementioned loud tone procedure in healthy participants as a first step towards clinical

investigations. Despite compelling evidence for autonomic sensitization in PTSD from studies using measures of peripheral psychophysiological activity, the neural basis of this sensitization is unknown. Identifying the neural basis of this pathophysiological process could inform the development of new diagnostic tests and possibly more effective therapeutic interventions. The present study also provided a test of whether 95 dB tones, the intensity level used in our previous work, are sufficiently loud to generate reliable and detectible SC and HR responses in the presence of fMRI system auditory noise.

Methods

Participants

Participants were 20 medication-free participants (60% females), recruited by advertisement, without any current mental disorder as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I, First, Spitzer, Gibbon, & Williams, 1997). All participants were free of major medical or neurological illness, including current or past traumatic brain injury and substance dependence.

Within seven days prior to scanning, participants completed the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), Brief Symptom Inventory (BSI; Derogatis & Melisaratos, 1983), and the Trait portion of the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970). Standard tests for assessing cognitive performance were administered using the Hogrefe Test System 4 (Hogrefe, 2006) and included the Viennese Matrices Test (Formann & Piswanger, 1979), an adapted version of the Raven Progressive Matrices (Raven, 1947), the Test of Word Power (Schmidt & Metzler, 1992), and the d2 Test of Attention (Brickenkamp & Zillmer, 1998). Immediately prior to scanning, participants completed the State portion of the STAI. All measures had been previously translated into German and validated. Demographic and psychometric information is presented in Table 2. The study protocol was approved by the

Institutional Review Board of the Canton of Zurich, Switzerland. All participants provided written informed consent according to the Helsinki Declaration.

Task Procedures

A screening test performed outside the MRI system verified that participants could hear 1000 Hz tones presented binaurally at 25 dB. Experimental procedures were adapted for use in the fMRI environment, but otherwise were similar to those used in previous studies of PTSD (Carson, et al., 2007; Metzger, et al., 1999; Orr et al., 1998; Orr, Lasko, Metzger, & Pitman, 1997; Orr, et al., 1995; Orr, et al., 2003; Orr, Solomon, et al., 1997; Shalev, et al., 1992; Shalev, et al., 2000; Shalev, et al., 1997). Stimuli were created using Audacity software **(http://audacity.sourceforge.net)** and consisted of 1000 Hz, 500 ms pure tones. The rise and fall times of the tone onset and offset were set at 0 ms, reflecting the selected software setting. **Actual rise and fall times as measured from the amplifier were 1 ms and less than 1 ms, respectively.** Stimuli were presented binaurally through MRI compatible insert earphones (Model S14, Sensimetrics Corp., Malden MA) at a 95 dB sound pressure level. Although the published peripheral psychophysiological work used only 15 tone presentations, we presented eleven additional tones, for a total of 26, in order to test whether larger trial numbers could improve detection sensitivity for associations between neural activity and autonomic responses. Standard noise-attenuating headphones (Resonance Technology, http://www.mrivideo.com), customarily used during fMRI scanning, were placed over the earphone inserts to attenuate gradient auditory noise. Following a 10 min resting baseline period, 26 tones were presented with inter-trial intervals varying between 27 and 52 sec. Participants were instructed to keep their eyes open while listening to the tones. The procedure was implemented using E-Prime Professional 2.0 and E-Prime Extensions for fMRI (Psychology Software Tools, Inc., Sharpsburg, PA).

Data Acquisition

Peripheral Psychophysiology

Peripheral psychophysiological data were obtained with a Biopac modular instrument system (Biopac Systems, Inc., Goleta, CA). SC was recorded with an MRI-compatible electrodermal activity amplifier (EDA100C-MRI) using disposable radiotranslucent Biopac electrodes (EL509) filled with Biopac Isotonic Electrode Gel (Gel101) placed on the hypothenar surface of the participant's nondominant hand in accordance with published guidelines (Fowles et al., 1981). Inter-beat intervals were recorded with a pulse plethysmograph and amplifier modified for MRI (PPG100C-MRI). The tachometer output provided a continuous measure of HR (in beats per min, BPM) that reflected the immediately preceding inter-beat interval and was updated with each successive heartbeat. Psychophysiological analog signals were digitized at 1000 Hz by an analog-to-digital converter (MP150). Analog amplifier low pass cut-off frequencies were 1 Hz for the EDA100C-MRI and 3 Hz for the PPG100C-MRI. Eyeblink responses were not recorded due to the technical challenges associated with recording facial electromyogram in the MRI environment.

fMRI

A General Electric Signa HD.xt TwinSpeed 3.0T MR system, located at the Center for MR-Research at the University Children's Hospital Zurich in Switzerland, was used to estimate brain activity using a gradient echo-planar imaging (EPI) sequence with repetition time = 2500 ms, echo time = 28 ms, 64 × 64 matrix, flip angle = 70°, and field of view = 22 x 22 cm. Whole brain coverage was obtained with 42 axial slices (thickness = 3.4 mm, and in-plane resolution = 3.44 × 3.44 mm). A high-resolution anatomical scan (using a three-dimensional spoiled gradient-echo sequence with repetition time = 9.9 ms, echo time = 2.9 ms, field of view = 25.6 cm, flip angle = 8°, inversion time = 600 ms, 172 axial slices, thickness = 1.0

mm, and in-plane resolution = 1.00 × 1.00 mm) was collected to facilitate spatial normalization of the EPI data.

Data Analysis

Scoring of Peripheral Psychophysiological Data

Peripheral psychophysiological data processing followed our previously published methods (Orr, et al., 2003). SC and HR response scores were calculated for each tone presentation by subtracting the mean level during the 1 sec interval preceding tone onset from the highest level within the 1 - 4 sec interval following tone onset. Artifactual SC and HR responses were determined by visual inspection of each participant's data, and corrected values were imputed using predictions from a regression to the remaining valid values (Gelman & Hill, 2007). Square root transformations were applied to all responses to reduce heteroscedasticity (Orr, et al., 2003). A measure of relative habituation for SC and HR responses was calculated from the slope of the regression equation $Y = bX + a$ for the subsets of trials 2 - 15 and trials 2 - 26, where *Y* represents the square root of the response score and *X* represents the log trial number (Orr, et al., 2003). Locally weighted scatterplot smoothing (LOESS) was used for fitting non-linear, piecewise polynomial curves for SC and HR responses. Habituation of autonomic responses was tested using repeated measures ANOVA for SC and HR responses across trial blocks (trials 1 - 5, 6 - 10, 11 - 15 for the first 15 trials; trials 1 - 5, 6 - 10, 11 - 15, 16 - 20, 21 - 26 for all 26 trials), with trial block as the within-subject factor. A measure of absolute habituation for SC response was determined by counting the number of trials prior to reaching a criterion of two successive non-response trials ≤ 0.05 μS for untransformed data. Cohen's effect sizes (*d*) were calculated for autonomic response magnitudes.

fMRI Analysis

Preprocessing of the EPI time series included: (1) rigid body realignment for head motion correction, (2) slice timing correction, (3) rigid body co-registration of EPI with high resolution anatomical data (4) spatial normalization to the Montreal Neurological Institute (MNI) anatomical space, and (5) spatial smoothing (10mm full width at half maximum). Statistical modeling of the loud tone-related effects involved a summary statistics approach. At the first level, for each participant, blood oxygen level dependent (BOLD) contrast signal variance was predicted with a set of regressors using a general linear model. The total signal variance was decomposed into components associated with both the tone presentation and associated autonomic responses, with the inter-trial intervals serving as an implicit baseline for comparison. The tone regressor was constructed by first generating an event vector with duration of 0 sec and then convolving it with the SPM canonical hemodynamic response function resulting in a regressor allowing parameter estimates proportional to tone-related neural activity per event. Trial-specific SC and HR response scores were used to form orthogonalized parametric modulators of tone-related neural activity, thereby reflecting unique sources of variance beyond that accounted for by the tone regressor. Note that the term 'modulate' is used in this context without implying direction or causality. These regressors, together with other regressors that modeled residual movement-related signal modulation, the mean signal for the session, and a discrete cosine transform basis set that modeled the low frequency, presumably artifactual, signal modulations at frequencies lower than 0.008 Hz, jointly comprised the full model for each participant. The parameter estimates for each regressor were calculated from the fit of the model to the data using classical restricted maximum likelihood algorithms.

Parameter estimates from the tone regressor were assumed to represent activity associated with tone perception and other variance sources shared with the SC and HR responses, where parameter estimates from the SC and HR response parametric modulators represented unique autonomic activity responses associated with the tones.

At the second-level, voxel-wise, mixed-effect, repeated measures analysis of variance (ANOVA) was used to model contrast images representing the activity associated with the tones and the SC and HR parametric modulators for each participant. In separate one-way ANOVAs, additional regressors were included to model parametric modulation by psychometric scores.

In accordance with our previous peripheral psychophysiological work, primary analyses were based on 15 tone presentations and secondary analyses were performed for all 26 tones. A paired t-test was used to contrast estimates derived from the tone and parametric modulator regressors for the first 15 compared to all 26 tones.

In order to investigate habituation of the neural tone response, additional regressors were included on the first level to model linear, quadratic and cubic temporal effects. Habituation of tone-related activity was further explored by visual examination of effects related to tone onsets in each of five trial blocks (trials 1 - 5, 6 - 10, 11 - 15, 16 - 20, and 21 - 26).

For the whole-brain analyses, the critical threshold for interpreting voxel-wise estimates of loud tone, SC or HR responses was $p < 0.05$, family-wise error (FWE) corrected, providing strong protection from Type I errors. Cohen's effect sizes (*d*) were calculated for neural responses. SPM8 was used for fMRI statistical analyses (Wellcome Trust Centre for Neuroimaging, 2009).

Results

Peripheral Psychophysiological Results

The primary analyses examined responses to the first 15 tone trials. Group means and standard deviations (SD) for SC and HR pre-tone levels, mean response magnitude scores, response slopes, and number of trials required to reach the SC non-response criterion are shown in Table 3. Group means for the time course of SC and HR responses to tone

presentations are presented in Figure 1A. Group mean of square root SC and HR responses by trial are presented in Figure 1B. There were no significant sex differences in average SC and HR pretone levels, response magnitudes, response slopes, or number of trials to reach the SC non-response criterion (ts ≤ 1.2, ps ≥ 0.268). Repeated measures ANOVA revealed a main effect of trial block for SC responses ($F(2, 38) = 3.89$, $p = 0.029$) with higher SC responses in trials 1-5 compared to trials 6-10 ($t\,(19) = 2.14$, $p = 0.046$) and trials 11-15 ($t\,(19) = 1.97$, $p = 0.064$); the trial block main effect was not significant for HR responses ($F(2, 38) = 0.26$, $p = 0.772$). Results of analyses of SC and HR responses for all 26 tone trials are reported in Supplemental Table S1 and Supplemental Figure S1.

fMRI Results

Neural Response to Loud Tones

Our first model examined the total neural response to loud tones. The primary analyses examined responses to the first 15 tone trials. A comparison of neural responses to the first 15 tone trials with neural responses to the full 26 trials revealed no significant differences. Increased neural activity was observed in the salience network, including anterior insula, pregenual ACC, anterior MCC, supplementary motor area, and temporoparietal junction (Figure 2A). Increased activity was found in the anterior and posterior cerebellar vermis (coordinates: -5, -64, -6; 12, -46, -44), caudate nucleus (coordinates: -12, 9, 16), and hypothalamus (coordinates: -2, -12, -9). As expected, increased neural activity was observed in auditory areas, including medial geniculate body (MNI: 17, -27, -2; $p < 0.001$, uncorrected), and primary and secondary auditory cortices (Figure 2A). Neural activity was not significantly associated with BDI depression, BSI global severity index, state or trait anxiety scores. There was no significant habituation of the neural response to 15 tones. However, there was significant habituation in bilateral anterior insula (coordinates: -35, 21 -5;

41, 21, -3) and right superior temporal gyrus (60, -24, 0) when considering 26 trials ($p < 0.05$, FWE-corrected; Supplemental Figure S2).

Loud Tone Response Partitioned Into Changes Related to Tones, SC, and HR Responses

Our second model partitioned the neural response into components representing: (1) activity changes related to tones along with any variance shared with SC or HR responses, (2) changes uniquely associated with SC responses, and (3) changes uniquely associated with HR responses. As above, the primary analyses focused on results for the first 15 tone trials. A comparison of neural responses to the first 15 tone trials with neural responses to the full 26 trials revealed no significant differences regarding tone, SC, or HR components. For the tone component, activity was observed in primary and secondary auditory cortices (Table 4, Figure 2B). For the SC component, anterior insula, pregenual ACC, anterior MCC, supplementary motor area, supramarginal gyrus of the temporoparietal junction, and posterior cerebellar vermis were positively modulated by SC responses (Table 5, Figure 2B). The association of neural activity with SC responses was relatively consistent in each participant (Supplemental Figure S3). In addition, activity in subcortical regions, including caudate nucleus, parahippocampal gyrus, and supramammillary body and paraventricular nucleus of the hypothalamus, was positively modulated by SC response (Table 5). Activity in the dentate gyrus of the hippocampal formation (coordinates: 26, -40, 7) was negatively modulated by SC responses (for 15 tone trials: $t_{Contrast}(38) = -2.83$, $d = 0.91$, $p = 0.002$, uncorrected; for 26 tone trials: $t_{Contrast}(38) = -5.84$, $d = 1.90$, $p < 0.05$, FWE-corrected), suggesting a role for the hippocampus in habituation of SC responses. For the HR component, no areas showed activity modulation by HR responses; this was also true when using an uncorrected critical threshold of $p < 0.05$.

Discussion

As expected, tone-related activity was observed in a network including anterior insula, pregenual ACC, anterior MCC, supplementary motor area, and temporoparietal junction, regions that are all believed to play crucial roles in the detection of salient stimuli that can be nested in a complex environmental sensory stream (Downar, et al., 2000; Menon & Uddin, 2010) and may require subsequent modulation of the state of cognitive control mechanisms (Corbetta, et al., 2008). Along with the posterior cerebellar vermis, activity in these regions was associated with SC responses (Figure 3).

The mean SC and HR response magnitudes for the 15 tone presentations were within the range typically observed for healthy comparison groups (cf. Table 1 and 3) included in PTSD studies (Carson, et al., 2007; Metzger, et al., 1999; Orr, et al., 1995; Orr, et al., 2003; Orr, Solomon, et al., 1997; Shalev, et al., 1992; Shalev, et al., 2000; Shalev, et al., 1997). This suggests that fMRI environment characteristics, including high background acoustic noise and reclined participant posture, have no substantial impact on autonomic reactivity to loud tones. Because the neural activity pattern associated with 15 tones was similar to that observed for 26 tones, the shorter procedure, as used in previous studies of peripheral psychophysiological reactivity to loud tones, seems suitable for use in fMRI studies of neural responses to loud tones.

As has been observed in other studies involving novel or unexpected auditory events (Downar, et al., 2000, 2001, 2002; Sridharan, et al., 2007), we found loud tone-related modulation of neural activity in regions (Figure 3) believed to either mediate salience detection or facilitate access to executive attention systems (Corbetta, et al., 2008; Menon & Uddin, 2010). This study's finding of a positive association between loud tone-related activity in right anterior insula, bilateral anterior MCC, and the supramarginal gyrus, and SC response magnitude is in agreement with Knight et al. (2005), who presented both: (1) startling, 500ms white noise stimuli at 100 dB levels which elicited unconditioned SC responses, and (2)

various, novel, 2-10 sec duration auditory stimuli designed to elicit orienting SC responses. However, the present study also found tone-related activity in right pregenual ACC and bilateral supplementary motor area. Activity in pregenual ACC was previously found to be related to SC responses to faces expressing fear, anger, or disgust (Williams et al., 2005). Blunting of SC responses to brief, loud noises, including unwarned hand-claps close to participant's ears, was observed in participants with lesions in ACC (Tranel & Damasio, 1994). A relationship between neural activity and SC responses to different kinds of stimuli, including emotional faces, gambling tasks, motor tasks, or electrical shock was observed in anterior insula (Critchley, Elliott, Mathias, & Dolan, 2000; Critchley, Mathias, & Dolan, 2001; Gamer, Bauermann, Stoeter, & Vossel, 2007; MacIntosh, Mraz, McIlroy, & Graham, 2007), pregenual ACC (Williams, et al., 2005), anterior MCC (Milad et al., 2007; Williams, et al., 2005), and supplementary motor area (Gamer, et al., 2007). The coupling of activity in these regions to SC responses to simple unconditioned stimuli, as represented by the loud tones used in the present study, supports the role of these regions in mediating autonomic responses to stimuli that are salient by virtue of their intensity and unexpectedness, but free from cognitive or emotional content and complexity.

The anterior insula is believed to play a key role in detection of the sorts of unexpected, but salient, stimuli (Menon & Uddin, 2010) that might generate signals in anterior insula by direct inputs from sensory or association cortex (Bamiou, Musiek, & Luxon, 2003; Uddin et al., 2010). Anterior insula may also receive afferent, stimulus-related physiological information (Craig, 2002, 2009; Critchley et al., 2005). Evidence from tracer studies demonstrating direct projections from anterior and posterior insula to autonomic brainstem nuclei (Flynn, Benson, & Ardila, 1999), and from stimulation studies for cardiovascular responses (Oppenheimer, Gelb, Girvin, & Hachinski, 1992; Yasui, Breder, Saper, & Cechetto, 1991) suggests that insula efferents modulate autonomic activity.

The salience network model predicts strong functional coupling of the anterior insula with the ACC and MCC in order to engage networks mediating attention, working memory, and other higher order cognitive processes (Menon & Uddin, 2010; Sridharan, Levitin, & Menon, 2008). There is also compelling evidence from animal studies for an essential role of ACC, and to a less extent anterior MCC, in modulating autonomic activity by receiving projections from baroreceptors and, in turn, sending projections to subcortical autonomic nuclei, including lateral hypothalamus, periaqueductal grey, and dorsal motor nucleus of the vagus (Vogt, Aston-Jones, & Vogt, 2009; Vogt & Derbyshire, 2009). Electrical stimulation of the subgenual ACC in rodents drives depressor cardiovascular responses including bradycardia (Burns & Michael Wyss, 1985; Fisk & Wyss, 2000). In contrast, pregenual ACC stimulation appears to increase heart rate (Vogt & Derbyshire, 2009). In human imaging studies, activity in pregenual ACC and anterior MCC was related to cardiovascular arousal elicited by cognitive and behavioral stressor tasks (Critchley, Corfield, et al., 2000; Critchley, Elliott, et al., 2000; Critchley, et al., 2003; Gianaros et al., 2005; Gianaros, Onyewuenyi, Sheu, Christie, & Critchley, 2012). The positive association we observed between tone-related activity in pregenual ACC and anterior MCC, and SC responses is in agreement with the proposition that pregenual ACC and anterior MCC, but not subgenual ACC activity, drive sympathetic output (Medford & Critchley, 2010). The failure to find a relationship between tone-related activity in pregenual ACC or anterior MCC, and HR responses in this study may reflect Type II error, as discussed in the limitations section. Alternatively, the HR acceleration observed in relationship to loud tones may reflect decreased parasympathetic, rather than increased sympathetic, output. Thus, pregenual ACC and anterior MCC activity could be related to SC changes, primarily reflecting sympathetic influences. In contrast, no such relationship was observed for HR responses to loud tones, reflecting its sensitivity to both parasympathetic and sympathetic influences.

Supplementary motor cortex, receiving projections from the anterior MCC (Morecraft & Van Hoesen, 1992), is thought to be involved in evoking motor responses to salient stimuli (Menon & Uddin, 2010). Because neither stimulation nor anatomical studies indicate direct projections from supplementary motor cortex to subcortical autonomic regions, the association we found between loud tone-related neural activity in pre-supplementary motor cortex and SC responses might be mediated through anterior MCC activity (Morecraft & Van Hoesen, 1992).

The temporoparietal junction seems to be central to the reflexive direction of attention to novel, salient stimuli (Corbetta, et al., 2008). Although the entire temporoparietal junction showed responses to loud tones, we observed a positive association with SC responses primarily in the inferior parietal lobule, including the supramarginal gyrus, in agreement with other animal (Sequeira, Ba-M'Hamed, & Roy, 1995) and human studies (Gianaros, et al., 2005).

Taken together, our findings suggest that autonomic responses to intermittent auditory stimuli, such as loud tones presented in task-free situations, are modulated by specific structures within the cortical salience network. It may be that salient stimulus characteristics, such as type and intensity level, shape a primary autonomic orienting response through insular processes, whereas higher-order cognitive processes, such as interaction with emotion in cingulate cortex and attention mechanisms in inferior parietal lobule, further modulate autonomic activity resulting in final cardiovascular and electrodermal responses.

We also observed modulatory effects in the posterior cerebellar vermis. This structure shows activity following stimulation of secondary, and to a lesser extent, primary auditory cortex, presumably mediated by cortico-pontine projections originating in the superior temporal gyrus (Brodal, 1972). Lobule IX of the cerebellum regulates visceral motor function (Bradley et al., 1990; Bradley, Pascoe, Paton, & Spyer, 1987; Bradley, Paton, & Spyer, 1987) and receives auditory and vestibular inputs. It may be influenced by the sorts of auditory

stimuli used in our experiment, possibly playing an error detection role for unexpected auditory or vestibular events.

Dentate gyrus activity was associated with habituation of SC responses to loud tones. This is consistent with evidence from animal studies suggesting inhibitory influences of hippocampus on electrodermal activity (Yokota, Sato, & Fujimori, 1963). The present study did not find evidence for relationships between cortical or cerebellar regions and SC response habituation. It might be that SC response habituation results more from desensitization mechanisms related to repeated stimulus presentation within regions of the salience network than from active inhibition by other cortical structures.

Our failure to detect neural concomitants of HR responses to loud tones may partly reflect Type II error resulting from the relatively rapid habituation of the HR response in situations involving more than 15 tone trials. Subsequent studies should address this issue by: (1) increasing the sample size, (2) using louder tones in order to optimize the contrast-noise ratio by increasing the magnitude of neural and HR responses (Raskin, Kotses, & Bever, 1969), and (3) applying more liberal significance thresholds to *a priori* identified regions-of-interest when determining within- and between-participants effects related to the relationship between neural and autonomic responses (Vul, Harris, Winkielman, & Pashler, 2009). Another limitation originates from the potential for variability of tone intensity due to varying tightness of the soft insert earphones in the auditory meatus. Although technically challenging, measuring within-ear sound pressure levels may be pursued in future fMRI studies. The somewhat restricted variability of autonomic responses in this small healthy sample may also limit the ability to identify associations with neural activity in certain brain regions. Finally, the design of this study does not allow determination of whether regional activity changes reflect SC response generation or sensory feedback processes.

With respect to the likely clinical significance of these findings, it is notable that atypical task-related activity has been reported in PTSD for each of the cortical regions

mentioned above, including anterior insula during anticipation of negative pictures (Aupperle et al., 2012), and pregenual ACC (Shin et al., 1999), anterior MCC (Lindauer et al., 2004), and supramarginal gyrus (Bremner et al., 1999) during recollection of traumatic events. Our findings suggest that salience network functional alterations might underlie heightened SC responses to loud tones observed in PTSD (Shalev, et al., 1992; Shalev, et al., 1997). Therefore, these results may motivate future clinical studies examining the neural substrates underlying stress-related sensitization during the development of PTSD following a traumatic event. This is of particular relevance because there is currently no established procedure using fMRI measurements that can reliably generate physiological responses known to be associated with the development of PTSD. The loud tone procedure coupled with fMRI may allow for the identification of the mechanism(s) underlying sensitization processes associated with the pathogenesis of this disorder. Current treatments for PTSD are relatively non-specific. For example, although a particular drug may target a particular neurotransmitter and thereby modulate specific classes of synaptic activity, it can have widespread regional influences across different brain structures due to the spatial distribution of the receptors. With technical advances, it is hoped that future treatments will become capable of selectively influencing the function of particular brain structures. Identifying the brain structures involved in stress-related sensitization would provide potential targets for intervention, as well as for the development of more sensitive and specific physiologically-based diagnostic tests.

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Table 1. *Results of Peripheral Psychophysiological Studies Using the Loud Tone Procedure*

		Healthy Participants				
		SC Reactivity to 15 Tones			HR Reactivity to 15 Tones	
Study	N	Mean Response √μS (SD)	Response Slope (SD)	Trials to reach non-response criterion (SD)	Mean Response √BPM (SD)	Response Slope (SD)
Shalev et al. (1992)	19	0.36 (0.20)	-0.23 (0.18)	7.90 (5.50)	1.30 (0.60)	0.20 (0.70)
Orr et al. (1995)	19	0.62 (0.37)	-0.32 (0.17)	9.90 (5.10)	1.00 (0.50)	-0.29 (0.56)
Shalev et al. (1997)	28	0.30 (0.21)	-0.14 (0.13)	5.96 (4.92)	1.52 (0.84)	
Orr et al. (1997)	74	0.46 (0.30)	-0.21 (0.22)	8.40 (5.50)	1.10 (0.60)	0.01 (0.58)
Metzger et al. (1999)	13	0.50 (0.40)	-0.36 (0.26)	6.40 (4.20)	1.30 (0.40)	
Shalev et al. (2000)	166	0.21 (0.21)		2.70 (4.30)	1.70 (0.90)	
Orr et al. (2003)	53	0.60 (0.44)	-0.25 (0.20)	9.60 (5.10)	1.11 (0.51)	-0.07 (0.57)
Carson et al. (2007)	49	0.70 (0.50)	-0.31 (0.28)	10.50 (4.60)	1.20 (0.80)	0.00 (0.78)
Weighted Means		0.40	-0.15	6.37	1.39	-0.01

SC: Skin conductance; HR: Heart rate; μS: micro Siemens; BPM: Beats per minute; SD: Standard deviation

Table 2. *Demographic and Psychometric Sample Characteristics (N = 20)*

	Mean	SD
Age (Years)	26.3	5.3
Education (Years)	17.3	3.7
EHI: Right Handedness	8.8	2.9
EHI: Left Handedness	2.0	2.8
Cognitive Performance		
d2: Total Number of Items processed (Processing Speed)	554.5	63.3
d2: Total Number of Errors (Accuracy)	7.8	6.5
WMT: Total Number of Correct Responses (Non-Verbal Intelligence)	16.1	4.7
WST: Number of Recognized Words (Verbal Intelligence)	32.1	3.1
BDI: Depression	3.7	2.3
BSI: Global Severity Index	0.1	0.2
STAI: State Anxiety	30.8	5.2
STAI: Trait Anxiety	29.8	9.5

SD: Standard deviation ; EHI: Edinburgh handedness inventory; d2: d2 Test of Attention; WMT: Viennese Matrices Test; WST: Test of Word Power; BDI: Beck Depression Inventory; BSI: Brief Symptom Inventory; STAI: State-Trait Anxiety Inventory

Table 3. *Peripheral Physiological Responses to Loud Tones*

SC	Mean	SD	*p*	*d*
Pretone Level (μS)	9.80	9.77	-	-
√ Mean Response (√ μS)	0.38	0.42	< 0.001	0.91
Response Slope[a]	-0.02	0.05	0.033	-0.53
Trials to Reach Non-Response Criterion	4.80	5.41	0.001	0.90
HR				
Pretone Level (BPM)	64.00	9.31	-	-
√ Mean Response (√ BPM)	1.42	0.41	< 0.001	3.41
Response Slope[b]	0.02	0.09	0.294	0.24

[a]$R^2 = 0.40$. [b]$R^2 = 0.01$

SD: Standard deviation; SC: Skin conductance; HR: Heart rate; μS: Micro Siemens; BPM: Beats per minute

Table 4. *Neural Responses to Loud Tones Controlling for Parametric Modulation by SC or HR Responses*

	MNI coordinates			Analysis	
Region[a]	x	y	Z	*t*	*d*
L Primary Auditory Cortex	-50	-21	6	5.50	1.79
R Primary Auditory Cortex[b]	57	-17	7	4.75	1.54

[a] Regions with a whole-brain FWE-corrected *p*-value less than 0.05 are reported (peak-level)

[b] Significant at a critical threshold of $p < 0.001$, uncorrected

Table 5. *Neural Responses to Loud Tones Parametrically Modulated by SC Responses*

Region[a]	MNI coordinates			Analysis	
	x	y	Z	*t*	*d*
L Anterior Insula	-38	9	9	5.75	1.87
R Anterior Insula	35	8	11	5.94	1.93
L Pregenual Anterior Cingulate Cortex	-9	44	17	5.07	1.65
R Pregenual Anterior Cingulate Cortex	14	44	12	7.19	2.33
L Anterior Mid-Cingulate Cortex	-11	20	35	6.00	1.95
R Anterior Mid-Cingulate Cortex	11	18	26	5.79	1.88
R Supplementary Motor Area	5	6	53	8.39	2.72
L Supramarginal Gyrus	-59	-23	24	5.43	1.76
R Supramarginal Gyrus	65	-38	33	6.14	0.94
L Middle Frontal Gyrus	-27	53	7	5.83	1.89
R Superior Parietal Lobule	17	-42	50	7.66	2.49
L Calcarine Gyrus	-12	-65	17	6.48	2.10
R Cerebellum (Lobule IX Vermis)	5	-41	-47	5.58	1.81
L Caudate Nucleus	-12	9	17	5.66	1.84
R Caudate Nucleus	12	11	1	5.62	1.82
L Parahippocampal Gyrus	-24	-38	-9	5.40	1.75
Supramammillary Body of the Hypothalamus[b]	0	-11	-9	6.71	2.18

[a] Regions with a whole-brain FWE-corrected *p*-value less than 0.05 are reported (peak-level)

[b] Cluster extends to bilateral paraventricular nuclei

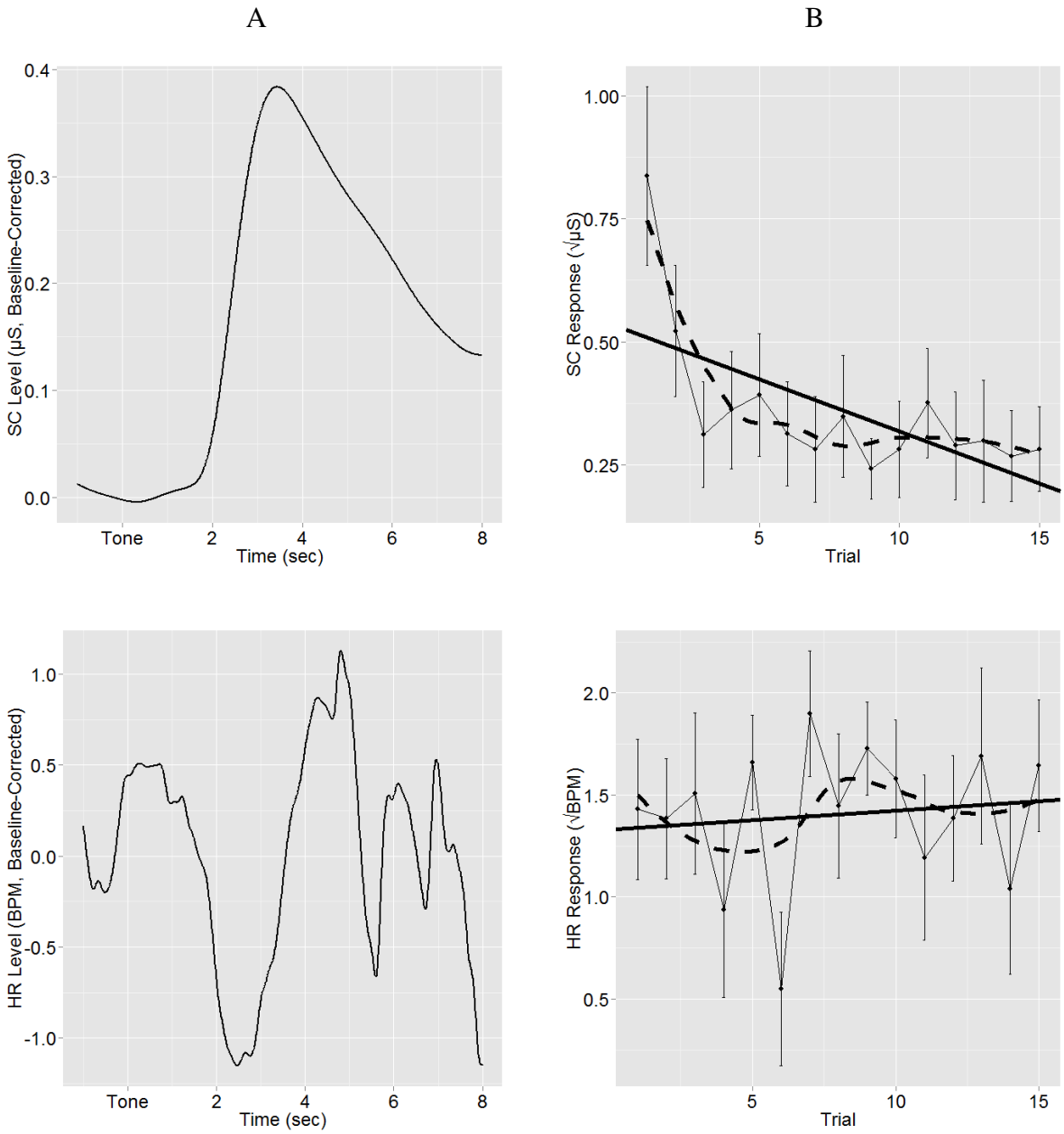

Figure 1. (A) Group means for time course of SC and HR responses to tone presentations (baseline-corrected and smoothed). (B) Group mean SC and HR responses (square root) by trial. Error bars represent standard errors. The thick solid line represents a fitted linear regression line, the thick dashed line shows the locally weighted scatterplot smoothing (LOESS) curves. SC: Skin conductance; HR: Heart rate; µS: Micro Siemens; BPM: Beats per minute

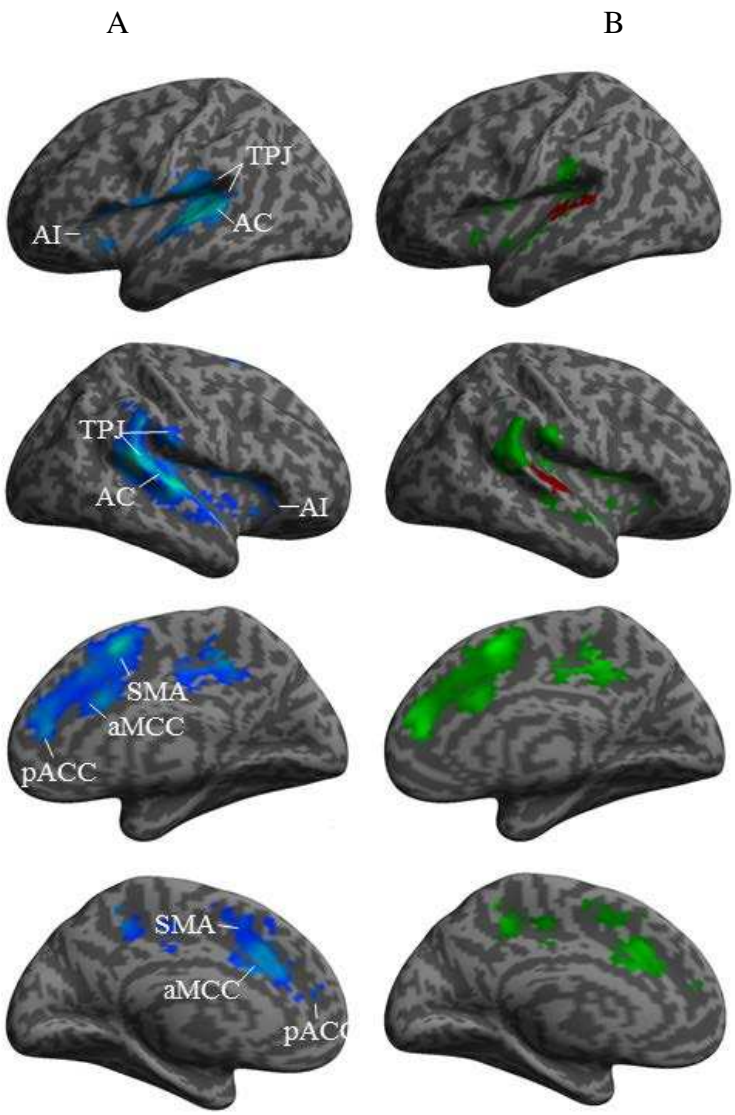

Figure 2. The total neural response to loud tones can be decomposed into activity changes not exhibiting autonomic modulation and activity changes modulated by autonomic responses: (A) Total activity response to loud tones (blue). (B) The components of total activity response remaining following orthogonalization of skin conductance and heart rate responses with respect to the tone onset (red), and the component of total activity response uniquely associated with skin conductance changes (green). Auditory network: Auditory cortex (AC). Salience network: anterior insula (AI), pregenual anterior cingulate cortex (pACC), anterior mid-cingulate cortex (aMCC), supplementary motor area (SMA), temporoparietal junction (TPJ).

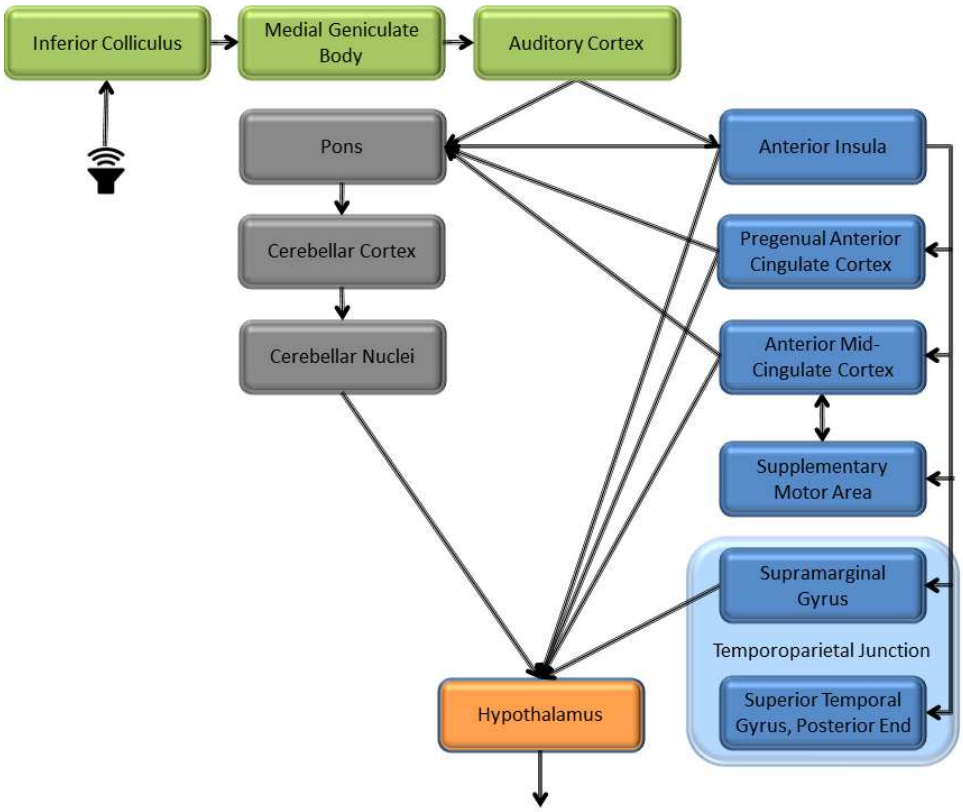

Figure 3. A theoretical network associated with the generation of autonomic responses following loud tone presentations based upon the present results. Auditory signals generated by sudden, loud tones influence "auditory" regions (green) and the anterior insula, whose activity reflects stimulus saliency. Signal generated in the anterior insula modulate autonomic activity through: (a) direct projections to hypothalamus (orange), and (b) projections to other cortical areas within the salience network (blue), including pregenual anterior cingulate cortex, anterior mid-cingulate cortex, supplementary motor area, and supramarginal gyrus within the temporoparietal junction. Pregenual anterior cingulate cortex, anterior mid-cingulate cortex, and supramarginal gyrus, in turn, influence autonomic activity through direct projections to subcortical autonomic nuclei. Supplementary motor area can indirectly influence autonomic activity through modulation of the anterior mid-cingulate cortex. Signals generated in the auditory cortex also influence cerebellar nuclei through pontine projections. Cerebellar cortex (grey), in turn, influences autonomic activity through projections to hypothalamus.