Systems/Circuits

The Autonomic Brain: An Activation Likelihood Estimation Meta-Analysis for Central Processing of Autonomic Function

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The autonomic nervous system (ANS) is of paramount importance for daily life. Its regulatory action on respiratory, cardiovascular, digestive, endocrine, and many other systems is controlled by a number of structures in the CNS. While the majority of these nuclei and cortices have been identified in animal models, neuroimaging studies have recently begun to shed light on central autonomic processing in humans. In this study, we used activation likelihood estimation to conduct a meta-analysis of human neuroimaging experiments evaluating central autonomic processing to localize (1) cortical and subcortical areas involved in autonomic processing, (2) potential subsystems for the sympathetic and parasympathetic divisions of the ANS, and (3) potential subsystems for specific ANS responses to different stimuli/tasks. Across all tasks, we identified a set of consistently activated brain regions, comprising left amygdala, right anterior and left posterior insula and midcingulate cortices that form the core of the central autonomic network. While sympathetic-associated regions predominate in executive- and salience-processing networks, parasympathetic regions predominate in the default mode network. Hence, central processing of autonomic function does not simply involve a monolithic network of brain regions, instead showing elements of task and division specificity.

Introduction

The autonomic nervous system (ANS) is involved in virtually every aspect of our daily life. The motor arm of the ANS regulates physiology within a variety of systems including respiratory, cardiac, vasomotor, digestive, and endocrine (Jänig, 2008). This ANS outflow calibrates bodily reactions with contextually adaptive behavior to meet the metabolic demands of motor, emotional, and cognitive challenges (e.g., Thayer and Lane, 2000; Critchley, 2005). Some of the most important integrative control centers for ANS functions are located in the brainstem and have been studied extensively in animals. Much less, however, is known about cerebral and cerebellar regions involved in autonomic regulation. Nevertheless, a central autonomic network (CAN) has been proposed based on observations from animal experiments using electrical stimulation and from tracer studies (Cechetto and Saper, 1990; Benarroch, 1993; Verberne and Owens, 1998; Saper, 2002).

Since the advent of noninvasive brain-imaging methods, a direct measurement of such regions has become possible in humans. A growing number of studies has investigated the role of these regions in autonomic control during cognitive, affective, and motor tasks, as well as during somatosensory and other modes of bodily stimulation. Based on some of their findings, the CAN has been approached from different perspectives. Some authors have highlighted the independent roles of single CAN regions, like the ventromedial prefrontal cortex (vmPFC), the anterior cingulate cortex (ACC), and the insula (Critchley et al., 2011), while others (Thayer and Lane, 2000) have emphasized similarities between the CAN and other theoretical constructs, like the anterior executive region of Devinsky et al. (1995) or the neural substrate of Damasio's "somatic marker hypothesis" (Damasio 1998). A comprehensive interpretation of the results obtained by imaging studies of autonomic CNS regions, however, is hampered by their large heterogeneity. Thus, a systematic review of neuroimaging studies assessing the CAN in humans seems timely.

We chose the meta-analytic activation likelihood estimation (ALE) method (Turkeltaub et al., 2002) to evaluate commonly activated regions across multiple studies. While a recent meta-analysis focused on assessing brain activity associated with heart rate variability (HRV) (Thayer et al., 2012), our aim was to perform a more comprehensive analysis, including all studies that had measured an autonomic outflow metric in conjunction with neuroimaging data. We evaluated the CAN across three task categories and two ANS outflow metrics. We also investigated the hypothesis that different subregions of the CAN are specifically involved in the sensory and motor control of the ANS when humans are responding to specific stimuli. Furthermore, the well-known dichotomy of a sympathetic and parasympathetic

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Table 1. Included ANS–fMRI studies with their stimuli and metrics

			Stimuli/tasks			Metrics		
	n	Foci	Affective	Somatosensory–motor	Cognitive	EDA	HFHRV	other
Fredrikson et al. (1995)	16	11				×		×
Hsieh et al. (1996)	4	10		×				×
Critchley et al. (2000a)	6	34		×	×			×
Critchley et al. (2000b)	6	13			×	×		
Redouté et al. (2000)	9	7						×
Williams et al. (2001)	11	4	×			×		
Ito et al. (2002)	11	12						×
Critchley et al. (2003)	6	32		×	×		×	
Kuniecki et al. (2003)	16	14	×					×
Nagai et al. (2004b)	8	38				×		
Petrovic et al. (2004)	7	2		×		×		
Williams et al. (2004)	22	10	×			×		
Critchley et al. (2005)	15	3			×			×
Kimmerly et al. (2005)	8	12						×
Knight et al. (2005)	9	13			×	×		
Lemche et al. (2006)	11	6				×		
Macey et al. (2006)	11	19					×	×
Nicotra et al. (2006)	14	6	×					×
Koelsch et al. (2007)	41	4	×				×	
Lagopoulos et al. (2007)	10	10	×			×		
Gamer et al. (2007)	14	5			×	×		
Marci et al. (2007)	10	12	×			×	×	×
Napadow et al. (2008)	7	13		×			×	
Wendt et al. (2008)	32	7	×			×		
Evans et al. (2009)	14	12			×			×
Harrison et al. (2009)	14	6						×
Kozel et al. (2009)	31	8			×	×		
Matsunaga et al. (2009)	12	16	×				×	
Mériau et al. (2009)	23	8	×			×		
Mobascher et al. (2009)	12	11		×		×		
Suzuki et al. (2009)	12	26		×				×
Urry et al. (2009)	26	2	×			×		×
Ziegler et al. (2009)	26	1						×
Fechir et al. (2010a)	16	22			×	×		×
Fechir et al. (2010b)	10	3						×
Harrison et al. (2010)	12	14	×					×
Piché et al. (2010)	14	2		×		×		
Goswami et al. (2011)	12	8		×			×	×
Maihöfner et al. (2011)	12	56		×				×
Nugent et al. (2011)	7	24		×	×		×	×
Beissner et al. (2012)	19	5		×				×
Gray et al. (2012)	21	11			×			×
Napadow et al. (in press)	18	39		×		×		×
Total	615	571	12	13	11	19	8	25

division of the ANS (Langley, 1903) that emanates from thoracolumbal and craniosacral regions of the CNS, respectively, is largely based on peripheral anatomy, but has been difficult to establish for higher centers of the CNS. Therefore, we aimed to resolve CAN subnetworks specific to these two important subdivisions of the ANS, and to gain insight into which subregions of the sympathetic and parasympathetic CAN subdivisions are associated with the performance of specific tasks or responses to specific stimuli.

Materials and Methods

Study selection. Our aims for the ALE meta-analysis were achieved by first identifying functional brain imaging studies of healthy subjects that had measured one or more peripheral autonomic signals. To identify relevant studies, we performed a literature search in Medline using a logical conjunction of the following three search terms: (1) a functional brain imaging modality, (2) the most relevant adjectives related to the autonomic nervous system, and (3) autonomic signals typically measured in a neuroimaging environment. Functional brain imaging modalities included positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI). For example, the search term for fMRI studies was "('fMRI' OR 'functional magnetic resonance imaging') AND ('autonomic' OR 'sympathetic' OR 'parasympathetic' OR 'vagal' OR 'vagus') AND ('heart rate' OR 'respiration' OR 'skin conductance response' OR 'skin response' OR 'pupil' OR 'skin temperature' OR 'blood pressure' OR 'electrogastrography')." In the other three searches, "fMRI" was replaced by one of the remaining imaging modalities (in full and abbreviation).

The literature search was performed on March 8, 2012, and identified 350 studies for fMRI, 125 for PET, 10 for MEG, and 90 for SPECT. All studies subsequently underwent a selection process consisting of reading the articles' methods sections and applying the following inclusion criteria: (1) functional brain images and autonomic measures were acquired in the same experimental session; (2) autonomic measures were used in the analysis for reasons other than physiological noise correction; (3) only healthy subjects were studied or their data were analyzed separately from patients'; (4) peak coordinates of group-level activations were reported; and (5) image acquisition included at least cerebral and cerebellar cortex and the analysis was not restricted to predefined regions of interest.

Following this selection process, 43 studies met the inclusion criteria (32 fMRI, 11 PET, no MEG, no SPECT) and are listed in Table 1. The

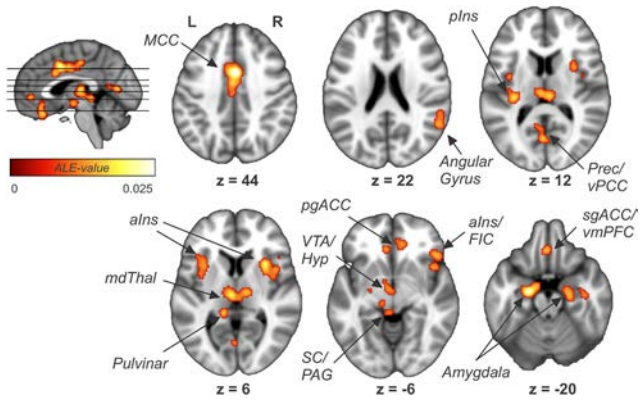

Figure 1. Results of the pooled analyses of all studies showing general brain regions involved in autonomic processing. Prec, Precuneus; vPCC, ventral posterior cingulate cortex; mdThal, mediodorsal thalamus; pgACC, pregenual ACC; VTA, ventral tegmental area; Hyp, hypothalamus; SC, superior colliculus; PAG, periaqueductal gray; FIC, frontoinsular cortex; L, left; R, right.

Table 2. ALE clusters of the pooled analysis of all studies

Anatomical region	Size (mm^3)	L/R	Max. ALE score	MNI coordinates (in mm) *x*	*y*	*z*
Midcingulate Cortex	7864	L/R	0.0283	2	10	40
Thalamus (medial– dorsal nucleus, pulvinar), Superior colliculus/ periaqueductal gray	6024	L/R	0.0191	−4	−16	8
Amygdala, hypothalamus, ventral tegmental area	4736	L	0.0271	−20	−6	−18
Anterior insula	3128	R	0.0193	32	18	6
Amygdala, hippocampal formation	2216	R	0.0160	20	−6	−18
Anterior insula	2040	L	0.0152	−36	22	0
Ventromedial prefrontal cortex, subgenual anterior cingulate cortex	1896	L/R	0.0168	−4	36	−24
Pregenual anterior cingulate cortex	1504	L/R	0.0143	−2	52	−2
Angular gyrus, supramarginal gyrus	1344	R	0.0144	56	−48	22
Ventral posterior cingulate cortex, precuneous cortex, lingual gyrus	1152	L/R	0.0169	−2	−64	10
Posterior insula	1064	L	0.0173	−32	−20	12
Frontoinsular cortex	1040	R	0.0151	46	32	−6

There were 43 studies, 616 subjects, 569 foci, 9.75 mm FWHM, and 1000 permutations. $p < 0.01$ is the cluster-forming threshold; $p < 0.05$ is the cluster threshold. L, Left; R, right.

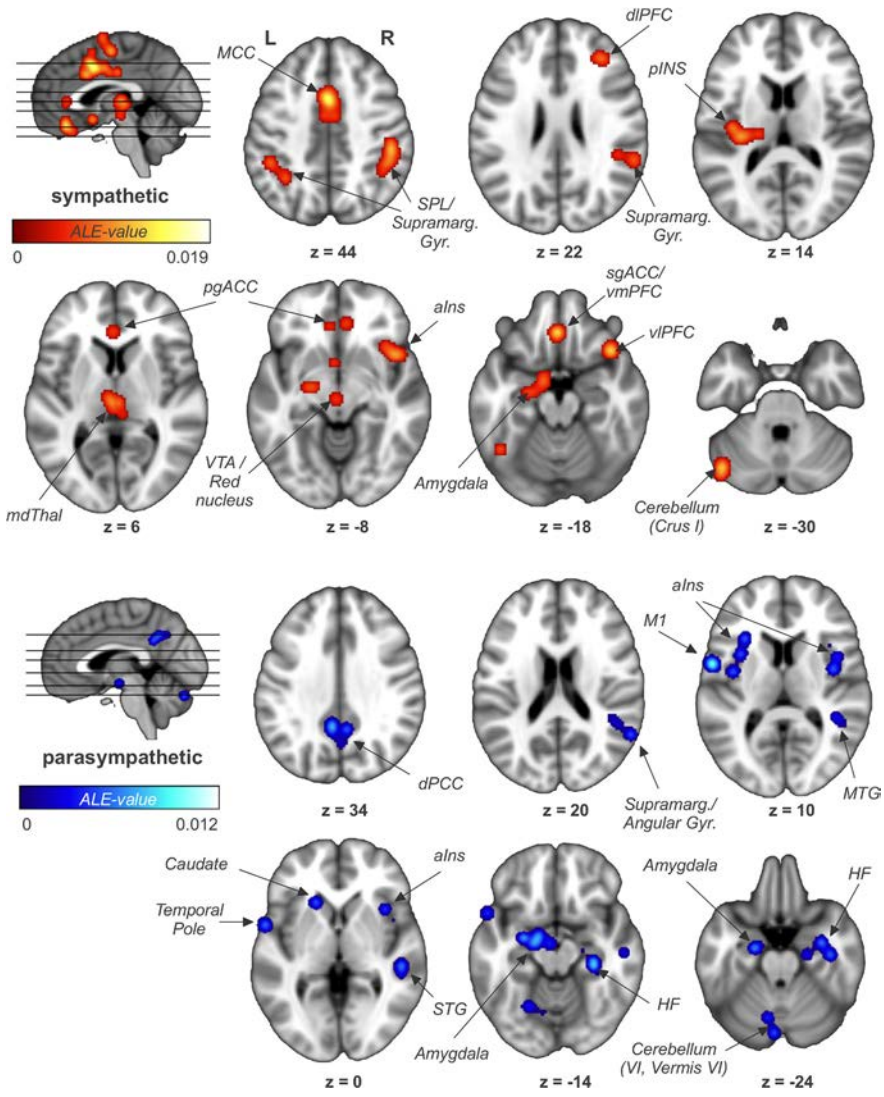

Figure 2. Brain areas associated with sympathetic and parasympathetic regulation as assessed by electrodermal activity and high-frequency heart rate variability. pgACC, Pregenual ACC; mdThal, mediodorsal thalamus; VTA, ventral tegmental area; M1, primary motor cortex; MTG, medial temporal gyrus; STG, superior temporal gyrus; L, left; R, right.

overall number of subjects was 615 (303 male, 252 female, 60 unclear from papers' descriptions) contributing 571 activation foci to the ALE analysis. Coordinates were extracted for each of these studies and entered into the ALE analysis.

The methods used to include autonomic recordings in the analyses of the functional imaging data were very diverse. However, the vast majority of studies either correlated time courses of autonomic signals directly with voxel time courses of the imaging data (23 studies) or used autonomic recordings to confirm that their stimuli modulated autonomic outflow (13 studies). The remaining seven studies either used parametric designs, where stimulus time courses were weighted by the intensity of the elicited ANS reaction, or conjunction designs, where the overlap of stimulus- and ANS-related activation clusters was assessed.

Tasks and divisions. Studies were categorized under two main aspects, namely, (1) tasks and stimuli (henceforth called "tasks") used to elicit an autonomic reaction and (2) the autonomic division predominantly driving the autonomic signal measured in the experiment (i.e., sympathetic or parasympathetic).

For the first aspect, three categories were formed: (1) "cognitive" for cognitively difficult or stressful tasks, like stroop, color word interference, or *n*-back tasks, but also deception or guilty knowledge tasks known to modulate the autonomic nervous system; (2) "affective" for emotional (appetitive or aversive) videos, pictures, music, or words, but also fear conditioning tasks; and (3) "somatosensory–motor" for handgrip tasks, tactile stimulation, acupuncture, and various pain induction methods.

For the second aspect involving the divisions of autonomic outflow, two categories were formed: (1) "sympathetic" for studies using electrodermal activity (EDA) or related metrics for skin conductivity (Venables, 1991), like galvanic skin response, skin conductance response, as well as their latencies and derivatives, and (2) "parasympathetic" for studies using the high-frequency spectral component of heart rate variability (HF-HRV) (Acharya et al., 2006). Although several metrics were used in the original studies, we chose to include only EDA and HF-HRV due to their clear interpretability in terms of representing the sympathetic and parasympathetic division of the autonomic nervous system: EDA is generally considered a purely sudomotor, sympathetic metric (Venables, 1991), whereas HF-HRV is regarded as a purely cardiovagal, parasympathetic metric (Acharya et al., 2006). It should also be mentioned that preejection period and muscle sympathetic nerve activity (MSNA) are unequivocal sympathetic measures, too, but no studies using these methods met our inclusion criteria. All studies were classified by two of the authors (F.B. and V.N.) and, if possible, allocated to one or more categories. This process yielded 11 studies for cognitive, 12 for affective, 13 for somatosensory–motor, 19 for sympathetic, and 8 for parasympathetic (Table 1).

To ensure independence of tasks and divisions (e.g., studies with cognitive tasks did not all cluster to include sympathetic metrics), the Freeman–Halton extension of the Fisher exact probability for a two-by-three contingency table was calculated. Its nonsignificance ($p = 0.30$) suggested meaningful independent analysis of tasks and divisions.

ALE. We used activation likelihood estimation (Turkeltaub et al., 2002), a voxel-based meta-analysis tool, to test for commonly activated regions across studies. All ALE-related calculations were carried out in GingerALE 2.3 (http://www.brainmap.org/ale/; Research Imaging Center, University of Texas, San Antonio, TX) using the nonadditive ALE algorithm (Turkeltaub et al., 2012). For conjunction analyses (see below, Conjunction analyses), we additionally used the FSLMATHS and CLUSTER tools of FSL 5.0.1 (http://fsl.fmrib.ox.ac.uk/; FMRIB, Oxford, UK).

Because some studies reported coordinates in Talairach space, whereas others (the majority) in Montreal Neurological Institute (MNI) space, coordinates reported in Talairach space by any included study were transformed to MNI space using the inverse of the icbm2tal transform (Lancaster et al., 2007), before the ALE analysis.

The ALE procedure consisted of the following steps: (1) modeling of single-study activation foci as peaks of three-dimensional Gaussian probability densities with subject-based full-width at half-maximum values (Eickhoff et al., 2009); (2) summation of probability densities to produce a statistical map estimating the likelihood of activation at each voxel; (3) thresholding of this ALE map based on the null hypothesis of a uniform distribution of foci; (4) correcting for multiple comparisons by permutation-based thresholding of the maximum cluster size (Friston et al., 1994).

We used a cluster-forming threshold of $p < 0.05$ and a cluster-level threshold of $p < 0.05$ for all tests except Analysis 1, where significantly higher power involved in combining all 43 studies allowed for a threshold

Table 3. ALE clusters associated with sympathetic and parasympathetic regulation

Anatomical region	L/R	Size (mm^3)	Max. ALE score	MNI coordinates (in mm)		
				x	*y*	*z*
Sympathetic						
Midcingulate cortex, paracingulate cortex, supplementary motor area	L/R	15,408	0.0190	0	10	40
Supramarginal gyrus, superior parietal lobule, primary somatosensory cortex	R	8624	0.0128	48	−26	46
Amygdala, subgenual anterior cingulate cortex, nucleus accumbens, caudate, hippocampal formation	L	4784	0.0114	−20	−8	−12
Ventromedial prefrontal cortex, pregenual/subgenual anterior cingulate cortex	L/R	4384	0.0129	−2	38	−18
Anterior insula, ventrolateral prefrontal cortex	R	3912	0.0125	44	18	−6
Thalamus (medial– dorsal nucleus), nucleus ruber, periaqueductal gray	L/R	3856	0.0094	−4	−16	6
Supramarginal gyrus, superior parietal lobule, primary somatosensory cortex	L	3432	0.0085	−44	−36	42
Secondary somatosensory cortex, posterior insula, putamen	L	3176	0.0099	−32	−20	14
Cerebellum (lobulus crus I)	L	3112	0.0122	−46	−66	−28
Dorsolateral prefrontal cortex	R	2984	0.0088	20	36	34
Parasympathetic						
Hippocampal formation	R	8416	0.0096	30	−22	−16
Amygdala, ventral tegmental area, hypothalamus	L	5784	0.0124	−20	−6	−18
Anterior insula, caudate	L	5376	0.0072	−40	0	12
Precuneus, dorsal posterior cingulate cortex	L/R	5360	0.0084	−6	−44	34
Primary motor cortex, temporal pole	L	5176	0.0115	−56	6	8
Medial temporal gyrus, superior temporal gyrus	R	4024	0.0071	50	−24	2
Supramarginal gyrus, angular gyrus	R	4008	0.0078	44	−38	14
Cerebellum (lobuli VI and vermis VI)	L	3960	0.0070	−10	−62	−20
Anterior insula	R	3752	0.0072	40	2	12

There were 19 studies, 296 subjects, and 172 foci, 9.57 mm FWHM, for EDA; 8 studies, 106 subjects, and 94 foci, 10.00 mm FWHM, for HF-HRV; and 1000 permutations. $p < 0.05$ is the cluster-forming threshold and the cluster threshold. L, Left; R, right.

of $p < 0.01$ to be used for cluster forming, providing for greater localizing power. The number of permutations was 1,000 for all calculations of simple ALE maps.

The following ALE meta-analyses were calculated. Analysis 1 is a pooled analysis of all studies, independent of their categorization to form a group map of brain areas generally involved in autonomic regulation. This can be considered a liberal interpretation of the CAN. Analysis 2 uses group maps for brain regions associated with activity in both the sympathetic and parasympathetic divisions of the ANS. Analysis 3 uses group maps for brain regions supporting ANS outflow for all three task categories (somatosensory–motor, affective, cognitive).

The results of Analysis 3 were calculated as a prerequisite for conjunction analyses (see below) and therefore not reported. In addition, for Analyses 1 and 2, we were interested in hemispheric differences, which we assessed by converting the thresholded ALE maps to *z* statistic maps and contrasting the original map with its right–left flipped version. A *p* value of 0.05 was considered significant. Note that we did not apply a correction for multiple comparisons to the laterality tests. This is because we had already established a significant activation in these regions, and the right–left difference is orthogonal to the bilateral effect per se.

Conjunction analyses. Using the results of the analyses detailed above, we also performed two conjunction analyses. These analyses used the conjunction null hypothesis (Nichols et al., 2005) and tested for brain areas that were activated in all conditions under consideration. We calculated the overlap of thresholded ALE maps, again applying a minimum cluster size of 100 mm^3. The two conjunction analyses were as follows: Analysis 4 used conjunction analyses for each task type and each ANS division to identify sympathetic and parasympathetic contributions to CAN modulatory regions observed for different tasks. Analysis 5 used a conjunction across all three task categories to identify regions mediating autonomic activity regardless of the task used to stimulate ANS outflow.

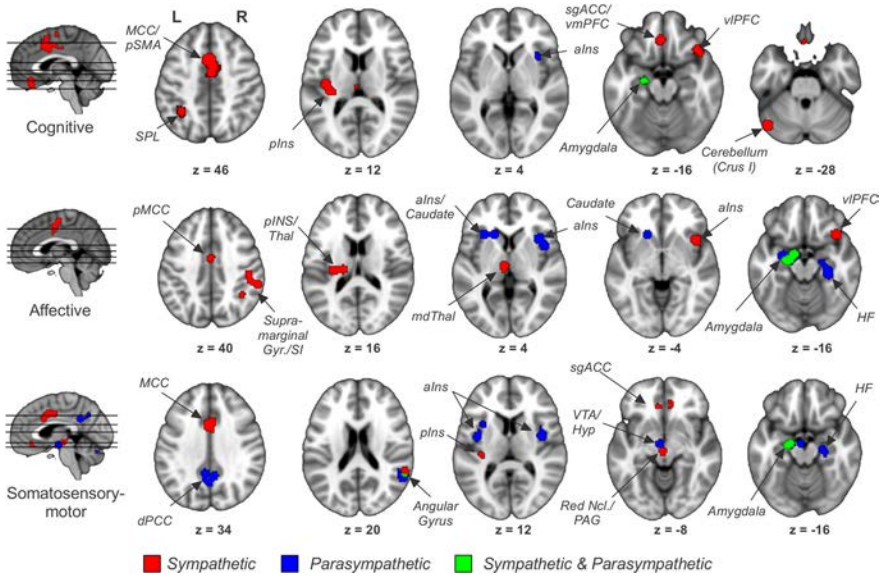

Figure 3. Conjunction analyses for three common task categories and the two ANS division to identify sympathetic and parasympathetic contributions to CAN modulatory regions observed for different tasks. pSMA, Presupplementary motor area; pMCC, posterior MCC; SI, primary somatosensory cortex; Thal, thalamus; mdThal, mediodorsal thalamus; VTA, ventral tegmental area; Hyp, hypothalamus; PAG, periaqueductal gray; L, left; R, right.

This provided a more specific interpretation of the CAN compared to Analysis 1.

Results

The pooled analysis of all studies (Analysis 1, 43 studies, 615 subjects, 571 foci) revealed a widespread network of cortical and subcortical regions consisting of ACC; midcingulate cortex (MCC); ventral posterior cingulate cortex; thalamus; bilateral anterior (aINS), left posterior (pINS), and right frontal insular cortices; vmPFC; bilateral amygdala; right hippocampal formation (HF); hypothalamus; midbrain and brainstem regions; and a lateral parietal area comprising parts of the right angular (AG)

Table 4. ALE clusters of the conjunction analyses for the three task types and the two ANS divisions showing sympathetic and parasympathetic contributions to CAN modulatory regions observed for different tasks

Anatomical region	L/R	Size (mm^3)	Max. ALE score	MNI coordinates (in mm)		
				x	*y*	*z*
Cognitive and sympathetic						
Midcingulate cortex, paracingulate cortex, supplementary motor area	L/R	7960	0.0120	−2	16	44
Anterior insula, frontal operculum, temporal pole	R	1752	0.0078	48	18	−6
Cerebellum (lobulus crus I)	L	1648	0.0106	−46	−64	−26
Secondary somatosensory cortex, posterior insula	L	1576	0.0092	−38	−12	12
Ventromedial prefrontal cortex, subgenual anterior cingulate cortex	L/R	1352	0.0088	−4	38	−16
Superior parietal lobule, supramarginal gyrus	L	1304	0.0077	−32	−48	42
Amygdala	L	656	0.0051	−22	−8	−16
Cognitive and parasympathetic						
Amygdala	L	480	0.0051	−22	−8	−16
Anterior insula	R	400	0.0054	34	20	4
Affective and sympathetic						
Amygdala	L	3184	0.0114	−20	−8	−12
Supramarginal gyrus, primary somatosensory cortex	R	2752	0.0089	48	−26	44
Posterior midcingulate cortex	L/R	2616	0.0084	4	0	48
Anterior insula, ventrolateral prefrontal cortex	R	2496	0.0103	38	24	−20
Secondary somatosensory cortex, posterior insula, putamen	L	1872	0.0084	−18	−16	18
Thalamus (mediodorsal nucleus)	L	968	0.0072	−6	−12	4
Supramarginal gyrus, angular gyrus, superior parietal lobule	R	624	0.0067	38	−46	36
Affective and parasympathetic						
Amygdala	L	3920	0.0124	−20	−6	−18
Hippocampal formation, amygdala	R	2840	0.0095	30	−22	−16
Anterior insula, caudate	L	2192	0.0071	−30	26	8
Anterior insula	R	2184	0.0071	44	12	6
Somatosensory–motor and sympathetic						
Midcingulate cortex	L/R	5392	0.0165	2	12	40
Amygdala, hippocampus	L	944	0.0082	−18	−8	−16
Supramarginal gyrus, angular gyrus	R	784	0.0080	58	−40	22
Supplementary motor area	L	704	0.0086	−10	4	62
Secondary somatosensory cortex, posterior insula	L	664	0.0086	−34	−20	14
Red nucleus, periaqueductal gray	L/R	624	0.0057	−2	−16	−8
Ventromedial prefrontal cortex, pregenual/subgenual anterior cingulate cortex	L	464	0.0061	−4	38	−12
Ventromedial prefrontal cortex, pregenual/subgenual anterior cingulate cortex	R	352	0.0059	8	42	−6
Somatosensory–motor and parasympathetic						
Precuneus, dorsal posterior cingulate cortex	L/R	2856	0.0076	−6	−42	32
Amygdala, ventral tegmental area, hypothalamus	L	2176	0.0083	−18	−8	−16
Anterior insula	R	1984	0.0072	40	2	12
Anterior insula	L	1304	0.0072	−40	0	12
Angular gyrus	R	1104	0.0063	58	−50	22
Hippocampal formation	R	1024	0.0055	22	−12	−20
Cerebellum (lobulus vermis VI)	R	144	0.0055	−2	−72	−24

There were 11 studies, 145 subjects, and 165 foci for cognitive stimuli/tasks; 12 studies, 230 subjects, and 107 foci for affective stimuli/tasks; 13 studies, 136 subjects, and 245 foci for somatosensory–motor stimuli/tasks; 19 studies, 296 subjects, and 172 foci for EDA; and 8 studies, 106 subjects, and 94 foci for HFHRF. L, Left; R, right.

and supramarginal gyrus (SMG) (Fig. 1; Table 2). Hemispheric differences were found for the amygdala (left > right).

Brain areas associated with sympathetic regulation (Analysis 2, 19 studies, 296 subjects, 172 foci) were ACC, MCC, paracingulate cortex, thalamus, right aINS, left pINS, vmPFC, left amygdala, left HF, right SMG, left primary (S1) and secondary (S2) somatosensory cortex, supplementary motor area (SMA), bilateral superior parietal lobule (SPL), ventrolateral (vlPFC) and right dorsolateral (dlPFC) prefrontal cortices, midbrain, and left cerebellum (Fig. 2; Table 3). No hemispheric differences were found.

In contrast, regions of parasympathetic regulation (Analysis 3, 8 studies, 106 subjects, 94 foci) comprised the dorsal posterior cingulate cortex (dPCC)/precuneus, bilateral aINS, left amygdala, right HF, right SMG/AG, left primary motor cortex, right medial and superior temporal gyri and left temporal pole, hypothalamus, midbrain, and left cerebellum (Fig. 2; Table 3). Here, once again, hemispheric differences were found for the amygdala (left > right).

We also investigated conjunctions of tasks and ANS divisions [Analysis 4, using foci for cognitive (11 studies, 145 subjects, 165 foci), affective (12 studies, 230 subjects, 107 foci), and somatosensory–motor (13 studies, 136 subjects, 245 foci), as well as foci reported for Analyses 2 and 3 above]. Regions associated with sympathetic outflow included MCC, right aINS, left pINS, vmPFC/subgenual ACC (sgACC), left SPL, left amygdala, and left cerebellum for cognitive tasks; MCC, right aINS, left pINS, right SMG/AG, left amygdala, and left thalamus for affective tasks; and MCC, left pINS, vmPFC/sgACC, right SMG/AG, left amygdala/HF, and periaqueductal gray for somatosensory–motor tasks (Fig. 3; Table 4). For parasympathetic outflow, we found right aINS and left amygdala to be associated with cognitive tasks; bilateral aINS, left caudate, left amygdala, and right HF with affective tasks; and dPCC, bilateral aINS, right AG, left amygdala, right HF, and ventral tegmental area for somatosensory–motor tasks.

Conjunction analysis of all task categories (Analysis 5) showed four regions to be consistently involved in autonomic regulation

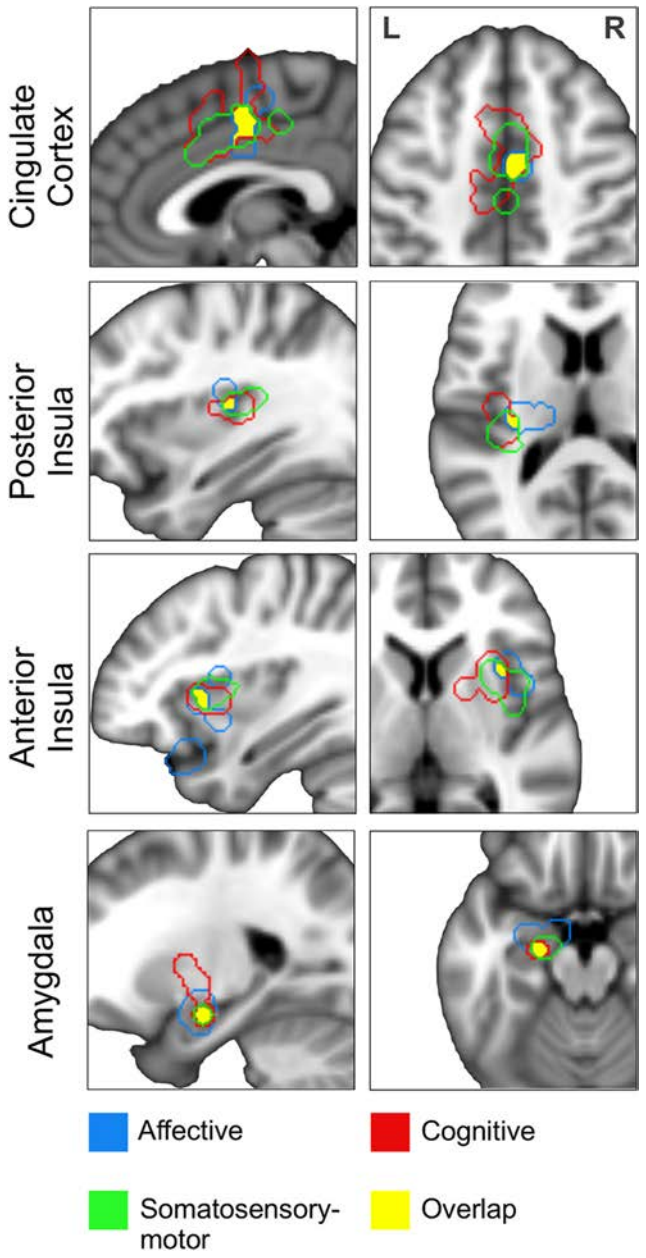

Figure 4. Core regions of the CAN as revealed by a conjunction analysis of autonomic modulatory regions across the three task categories. L, Left; R, right.

across tasks (Fig. 4), namely, the posterior MCC (MNI coordinates, $x = 4$, $y = 0$, $z = 48$), left amygdala (-22, -8, -16), right aINS (34, 20, 4), and left pINS (-32, -18, 12). It should also be noted that a cluster in the pregenual anterior cingulate cortex extending to the vmPFC was just under threshold for the affective task category and thus for the conjunction map across all tasks.

Discussion

Several regions identified by our human neuroimaging meta-analysis are fully consistent with a central autonomic network as proposed by many authors based on the results of animal experiments (Cechetto and Saper, 1990; Benarroch, 1993; Verberne and Owens, 1998; Saper, 2002). For instance, the results of the pooled analysis (Fig. 1) show anterior and midcingulate cortices, insula, ventromedial prefrontal cortex, mediodorsal thalamus, amygdala, HF, and hypothalamus as component regulatory areas of this network. Other regions, however, such as the angular gyrus, pulvinar, and precuneus, have been less often reported in this context and should be explored in more detail by future studies to better understand their role in regulating the ANS.

Separate analyses of the brain regions supporting sympathetic and parasympathetic regulation (Fig. 2) revealed largely divergent networks. Sympathetic regulation mainly involved prefrontal, anterior, and midcingulate, right ventral anterior insular and left posterior insular cortices, while parasympathetic regulation involved PCC, lateral temporal cortices, bilateral dorsal aINS, and HF. Importantly, the few regions that showed a dual role as both sympathetic and parasympathetic regulation centers included the left amygdala, right inferior parietal lobule, and a small area in right aINS, where the ventral sympathetic and dorsal parasympathetic clusters overlapped.

Concerning task specificity, our analysis revealed divergent networks for each task category (Fig. 3). We found a predominance of sympathetic regions in cognitive tasks consistent with the important role the sympathetic nervous system plays in cognitive stress (Anderson et al., 1991). Affective and somatosensory–motor tasks, in contrast, showed a more balanced contribution of sympathetic and parasympathetic regions. While each network had its distinctive features, we were more interested in the consensus regions mediating autonomic activity across tasks. As the pooled analysis (Fig. 1) detected any region reported by a sufficient number of studies, regardless of task, we conducted a conjunction analysis of the three task categories to identify a more specific set of regions. This analysis revealed four regions, which we posit to be the core of the central autonomic network (Fig. 4). They comprised the MCC, the right aINS, the left pINS, and the left amygdala. Among these, the amygdala was the only region with both sympathetic and parasympathetic regulatory function.

The amygdala is best known for its role in emotional processing, especially in the evaluation of aversive stimuli (Weiskrantz, 1956; LeDoux, 1992), which is consistent with a strong linkage to sympathetic regulation. More recent work has focused on determining the amygdala's role in regulation or modulation of cognitive functions, including attention, perception, and explicit memory (Ledoux, 2007). Its involvement in parasympathetic regulation, however, is an interesting and new finding that may reflect the need for balancing both increased sympathetic and decreased parasympathetic outflow in response to aversive stimuli. Furthermore, left lateralization of amygdala function, as noted in our results, has been shown before in the context of emotion processing (Morris et al., 1998; Wager et al., 2003), especially, when subjects were aware of the presented stimuli. Left dominance was also described by Thayer et al. (2012) in their meta-analysis of HRV-related brain activity.

The insula is a functionally heterogeneous structure and has been shown previously to consist of at least three functional subregions exhibiting differential connectivity with the cingulate cortex (Deen et al., 2011). Its involvement in autonomic functions and interoceptive feedback has been studied extensively (Critchley et al., 2000a; Craig, 2002). Our results suggest different autonomic roles for left and right, anterior and posterior, as well as dorsal and ventral portions of the insula. While the dorsal aINS was bilaterally associated with parasympathetic regulation, the right ventral aINS showed sympathetic predominance extending to the adjacent frontal operculum (Fig. 2). Interestingly, previous meta-analyses found that while dorsal aINS was associated with cognitive processing, ventral aINS was associated with affective/emotional processing (Kurth et al., 2010). Moreover, although no explicit lateralization was found in our analysis for regions other

than amygdala, the results of Analyses 2 and 4 support previous theories of functional specialization of the right anterior insula as a sympathetic regulatory center (Craig, 2005; Cechetto and Shoemaker, 2009). However, as some authors noted for the case of emotional responses (Hagemann et al., 2003; Wager et al., 2003), the hypothesis of a more generalized left/right dichotomy with respect to forebrain (and insular) (Craig, 2005) specialization in parasympathetic/sympathetic regulation is probably untenable.

Like the insula, the cingulate cortex is a functionally and structurally heterogeneous structure (Vogt et al., 1992). Three of the four major subregions that have been proposed to describe its different functions were found to be involved in autonomic regulation by our study, namely, the ACC, MCC, and PCC, with the largest cluster in the MCC. Anterior regions (ACC, MCC) were primarily associated with sympathetic, while posterior regions (PCC) were associated with parasympathetic outflow. Interestingly, the overlap of cingulate clusters between our different ANS-linked task categories was surprisingly small. The only region that was involved in ANS regulation for all tasks was the posterior MCC, an area usually reported in the context of cutaneous nociception (Vogt, 2005), response selection, and skeletomotor body orientation (Devinsky et al., 1995).

Our results can also be interpreted from the perspective of known large-scale brain networks. For instance, Fox et al. (2005) suggested in their influential paper that the activity of the brain at rest can be divided into a task-negative and a task-positive network that are temporally anticorrelated. The former is now widely known as the default mode network (DMN) (Raichle et al., 2001; Buckner et al., 2008); the latter consists of at least three subnetworks that vary in nomenclature. For example, Power et al. (2011) differentiated a dorsal attention network, a frontoparietal control network, and a cingulo-opercular task control system. Similarly, Seeley et al. (2007) differentiated the task-positive network into a central executive network (Selemon and Goldman-Rakic, 1988; Beckmann et al., 2005) and a salience network (Mufson and Mesulam, 1982; Seeley et al., 2007). As Figure 2 and Table 3 demonstrate, most of the DMN regions involved in autonomic processing (PCC, LTC, HF, and IPL) show a predilection toward parasympathetic regulation. A notable exception was the vmPFC, often considered a DMN region. However, the ventral portion of the vmPFC that contains a significant sympathetic regulation cluster has been suggested to belong to a separate "limbic" network rather than the DMN itself (Yeo et al., 2011). In stark contrast, most regions of the task-positive networks involved in autonomic regulation showed sympathetic predominance (dlPFC, vlPFC, aINS, MCC, and SPL). Together, these findings support divergent CAN subregions for regulating the sympathetic versus parasympathetic divisions of the ANS (Cannon, 1929; Recordati, 2003). The parasympathetic system prepares the body for internal physiological activity, thus the connection with the DMN, whose functional correlates are usually ascribed to self-referential cognition (Buckner et al., 2008). The sympathetic nervous system, in contrast, orchestrates bodily functions aimed at interacting with the external environment, which explains the colocalization of sympathetic regulatory regions with task-positive (sub)networks.

Interestingly, a linkage between DMN activity and autonomic regulation has been described in several previous studies (Nagai et al., 2004a; Wong et al., 2007; Dhond et al., 2008). Parasympathetic-modulatory brain regions were identified in our analysis by studies adopting HF-HRV, a cardiovagal metric. Previous studies have found that posterior portions of the DMN are particularly sensitive to physiological (cardiorespiratory) artifact correction algorithms (Khalili-Mahani et al., 2013), underscoring the important neurophysiological role of brain regions such as the PCC in cardioautonomic modulation.

In general, the interdependence of brain regions previously thought to subserve cognitive or executive associative brain functions with those found by our study as relating to central autonomic modulation raises several provocative possibilities. For instance, a nonnegligible component of the neuronal activity previously attributed in neuroimaging experiments to cognitive or executive control functions may instead (or in addition) signal medullary premotor nuclei underlying autonomic processing that calibrates bodily reactions with contextually adaptive behavior appropriate for these "higher" order functions (Thayer and Lane, 2000; Critchley, 2005).

Some limitations need to be discussed. Our meta-analysis did not differentiate between increases and decreases, or positive and negative correlations, of the PET and fMRI signals associated with sympathetic/parasympathetic activity. A more precise approach would be to form four categories, one for each combination of BOLD activation/deactivation and increase/decrease of the autonomic metric. However, given the low number of available studies, this would have precluded a meaningful meta-analysis at this time. Furthermore, our choice of EDA as the sympathetic metric and HF-HRV as the parasympathetic metric cannot rule out the possibility that some of our results were influenced by organ-specific autonomic systems (i.e., skin vs heart). Finally, although we chose to exclude studies from our meta-analysis that recorded brain imaging and ANS data in different experimental sessions (King et al., 1999; Dalton et al., 2005; Macefield et al., 2007; Wong et al., 2007; Burton et al., 2009; Sander et al., 2010; Gianaros et al., 2012), it should be noted that many of these studies reported brain areas (amygdala, cingulate, insular, and prefrontal cortices, etc.) consistent with our description of the central autonomic network.

In conclusion, our human neuroimaging meta-analysis identified a set of consistently activated brain regions, comprising the left amygdala, right anterior and left posterior insular, and midcingulate cortices that form the core of the CAN. The sympathetic and parasympathetic divisions have largely divergent regulatory networks differentially involved in affective, cognitive, and somatosensory–motor tasks.

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