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ORIGINAL ARTICLE

Physiological and psychological individual differences influence resting brain function measured by ASL perfusion

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Abstract Effects of physiological and/or psychological inter-individual differences on the resting brain state have not been fully established. The present study investigated the effects of individual differences in basal autonomic tone and positive and negative personality dimensions on resting brain activity. Whole-brain resting cerebral perfusion images were acquired from 32 healthy subjects (16 males) using arterial spin labeling perfusion MRI. Neuroticism and extraversion were assessed with the Eysenck Personality Questionnaire-Revised. Resting autonomic activity was assessed using a validated measure of baseline cardiac vagal tone (CVT) in each individual. Potential associations between the perfusion data and individual CVT (27 subjects) and personality score (28 subjects) were tested at the level of voxel clusters by fitting a multiple regression model at each intracerebral voxel. Greater baseline perfusion in the dorsal anterior cingulate cortex (ACC) and cerebellum was associated with lower CVT. At a corrected significance threshold of $p < 0.01$, strong positive correlations were observed between extraversion and resting brain perfusion in the right caudate, brain stem, and cingulate gyrus. Significant negative correlations between neuroticism and regional cerebral perfusion were identified in the left amygdala, bilateral insula, ACC, and orbitofrontal cortex. These results suggest that individual autonomic tone and psychological variability influence resting brain activity in brain regions, previously shown to be associated with autonomic arousal (dorsal ACC) and personality traits (amygdala, caudate, etc.) during active task processing. The resting brain state may therefore need to be taken into account when interpreting the neurobiology of individual differences in structural and functional brain activity.

Keywords MRI · Perfusion · Autonomic nervous system · Personality · Cerebral blood flow

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Introduction

Individual differences in psychological and physiological traits play a critical role in shaping complex human behaviors, successfully navigating social interactions, and adapting to our ever-changing environments. Such individual differences may also serve as important predictors of vulnerability to psychiatric disorders and/or physiological diseases. Identifying the biological mechanisms that

give rise to individual trait differences affords a unique opportunity to develop a deeper understanding of complex human behaviors, disease risk factors, and treatment.

Since the autonomic nervous system (ANS) represents the principal neural interface through which the brain and internal bodily organs interact, individual differences in ANS function may reflect the adaptive capacity to environment (Critchley 2009). An ANS imbalance in which the sympathetic system is typically hyperactive while the parasympathetic system is hypoactive is associated with various pathological and maladaptive conditions (Friedman 2007; Thayer and Lane 2007), and ANS function is believed to mediate a link between individual affective state and dispositions to disease such as cardiovascular disease (Thayer and Lane 2007).

In a similar way, personality dimensions describe individual differences in emotional response to a range of situations and are also known to influence the risk of psychiatric disorders (Canli 2004a) as well as somatic diseases such as cardiovascular diseases (Carney et al. 2005) and inflammatory disorders (Dantzer et al. 2007). The Five-Factor Model (FFM) is perhaps the most influential model of human personality and consists of extraversion, neuroticism, conscientiousness, agreeableness, and openness to experience. Among FFM, two of the dimensions, extraversion and neuroticism, are of particular interest because their effect on mental and physical health has been studied widely (Wright et al. 2006). Neuroticism is characterized as a pervasive sensitivity to negative or punishment cues in the environment. Individuals high in neuroticism have a greater tendency to experience negative emotions since they readily assess situations as threatening (DeYoung et al. 2010; Wright et al. 2006). Extraverts have a preference for seeking and engaging in social interactions and a tendency to experience positive emotions, which typically stem from sensitivity to positive or reward cues in the environment (DeYoung et al. 2010; Wright et al. 2006). Both ANS function and personality dimensions have been frequently studied as individual differences representing vulnerability to disease and ill health, particularly in the psychosomatic field (Lane and Wager 2009a, b).

Human neuroimaging studies have begun to reveal the neural substrates of inter-individual variability in both ANS function (Lane et al. 2009) and personality (Canli 2004a). Patterns of regional brain activity may serve as important markers of individual differences as well as disease liability and pathophysiology. Recent human functional neuroimaging studies have examined the relationship between brain activity and ANS activity induced by physical and/or cognitive tasks, and have demonstrated that the cortical components of the central autonomic network (CAN) such as dorsal anterior cingulate cortex (ACC) (Critchley 2005) and insula (Suzuki et al. 2009) are involved in the regulation of cognitive or emotionally driven ANS reactivity. The CAN consists of the functional units within the central nervous system that are involved in autonomic regulation (Thayer and Lane 2009), including the forebrain (ACC, insular, and ventromedial prefrontal cortices, the central nucleus of the amygdala, the paraventricular and related nuclei of the hypothalamus), midbrain (periaqueductal gray matter), and hindbrain [parabrachial nucleus, the nucleus of the solitary tract (NTS), the nucleus ambiguous, the ventrolateral medulla, and the medullary tegmental field]. Functional and anatomical brain studies also suggest a link between extraversion or neuroticism and particular brain regions involved in emotional processing/expression such as the basal ganglia, insula and ACC (Canli 2004b; Deckersbach et al. 2006; DeYoung et al. 2010; Kim et al. 2008; Kumari et al. 2004; O'Gorman et al. 2006; Wright et al. 2006). The brain areas related to ANS function and those associated with personality traits often overlap, suggesting that ANS and personality are closely connected to the characteristics of human behavior, and both are essential to consider in the context of individual differences.

While the influence of the above factors on task-induced brain activity has been studied extensively, few studies have examined the relationship between such factors and brain activity at rest. The relatively recent development of arterial spin labeling (ASL) perfusion imaging provides an endogenous and completely non-invasive method for the quantification of regional cerebral flow (CBF) with magnetic resonance imaging (MRI) (Aguirre et al. 2002; Detre et al. 1992; Parkes et al. 2004; Wolf and Detre 2007). Under this method, magnetically labeled arterial water is used as a freely diffusible endogenous tracer, and perfusion is quantified from regional changes in signal intensity caused by the inflow of blood labeled by a spatially selective radiofrequency (RF) pulse applied proximal to the brain. Although both the sensitivity and temporal resolution of ASL are generally lower than that of BOLD fMRI, ASL methods are quantitative and stable over time. In contrast to BOLD fMRI studies that remain the method of choice for mapping the neural response to brief tasks or events or more transient evoked responses, ASL fMRI is more useful for imaging the neural correlates of behavioral traits or states (Detre et al. 2009), as it demonstrates a lower inter-subject variability than BOLD (Tjandra et al. 2005). ASL also provides a quantitative measure of perfusion in absolute units, enabling the assessment of baseline differences between individuals as well as task-evoked changes. Regional ASL perfusion measures have been shown to correlate with personality traits (O'Gorman et al. 2006) and cortisol levels and heart rate during psychological stress (Wang et al. 2005).

Using ASL, we investigated resting markers of personality (extraversion and neuroticism) and the relationship

between resting brain activity and individual differences in baseline autonomic activity, measured by resting cardiac vagal tone (CVT) in healthy subjects. In contrast to task-related studies, few studies have investigated resting-state correlates of extraversion and neuroticism, and the correlation between individual traits in basal autonomic tone and resting brain activity has not been investigated. We hypothesized that perfusion in the regions responsible for affective processing will be associated with individual differences in neuroticism and extraversion, and that activity within regions of the CAN will correspond to inter-individual differences in resting CVT (Critchley 2005; Gianaros et al. 2004; Lane and Wager 2009a).

Methods

Subjects

The participant group consisted of 32 healthy subjects (16 females, mean age 29.4 years, range 20–53 years). All subjects had no history of head trauma and no current or previous psychiatric diagnosis. Several subjects were excluded from the study due to problems in perfusion quantification or autonomic measurement. ASL perfusion and CVT data for the remaining 27 subjects (14 females, mean age 30, range 20–53 years) and perfusion and personality data for 28 subjects (15 females, mean age 30 and range 20–53 years) were used for analysis. The personality traits of Extraversion and Neuroticism were assessed with the Eysenck Personality Questionnaire-Revised (EPQ-R) (Eysenck and Eysenck 1991).

Baseline ANS measures

Before the day of scanning, resting electrocardiographic (ECG) data were recorded for 5 min from each participant. ECG electrodes (Ambu Blue Sensor P, Denmark) were placed in right and left subclavicular areas and the cardiac apex, following skin preparation (Nuprep, Weaver & Co, USA) to reduce impedance and improve signal detection. The ECG was acquired at a sampling rate of >3 kHz using a commercially available biosignal acquisition system, which allows validated ANS parameters to be measured in real time (Neuroscope, Medifit Instruments, UK). Autonomic parameters were recorded according to the recommendations of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology Task Force (Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology 1996). To ensure volunteers were fully relaxed, the 5-min acquisition window of baseline ANS recording followed a 10-min period of rest after placement of the recording equipment. The Neuroscope has internal ‘‘voltage controlled oscillators” that detect positive phase shifts in the beat-to-beat R–R interval, a process called ‘‘phase-shift demodulation”. This phase-shift technique is based on unique non-invasive measures of cardiac vagal control (CVC) on ‘‘beat-to-beat” baroreceptor reflex physiology (Paine et al. 2009a). Most traditional CVC measures are based on ‘‘breath-to-breath” respiratory modulation, i.e., respiratory sinus arrhythmia (RSA) (Paine et al. 2009a). The baroreceptor reflex technique therefore has better face validity for smaller/beat-to-beat time windows in the study of CVC than do RSA measures. It also involves no inherent assumption of stationary activity (stationarity) compared with that of spectral analysis techniques. The phase-shift technique has been validated for humans using pharmacological blockade (Julu 1992) and is measured in standardized units on a Linear Vagal Scale (LVS).

To confirm the stability of the individual CVT at rest, CVT was re-measured 1 year after the first measurement in a sub-group of 17 of the 27 volunteers (11 females, mean age ± SD 29 ± 6.19 years [range 21–54]) on which CVT was initially assessed based on availability and consent. Test–retest reproducibility was assessed using a Bland–Altman plot analysis.

The link between personality factors (neuroticism and extraversion) and CVT was assessed with a Pearson correlation analysis in SPSS 16.

Imaging data acquisition and analysis

Imaging was performed with a 3-T GE Signa TwinSpeed HD MRI scanner (GE Medical Systems, Milwaukee, WI, USA). Resting ASL perfusion data were collected using a pseudo-continuous ASL tagging scheme with a 3D interleaved spiral fast spin echo (FSE) readout (Dai et al. 2008) with 8 spiral interleaves, repetition time (TR) = 5,500 ms, echo time (TE) = 25 ms, acquisition matrix = 64 × 64, slice thickness = 3 mm and field of view = 24 cm. The perfusion images were reconstructed with a matrix of 128 × 128, resulting in an effective resolution of 1.9 × 1.9 × 3 mm^3. The total scan duration for the ASL sequence was 6 min.

A post-labeling delay of 1.5 s was applied to reduce errors from transit time effects (Alsop and Detre 1998). The participants were not given an explicit task in the scanner, but simply instructed to relax and remain still with their eyes closed during the image acquisition.

The ASL perfusion images for each subject were skull-stripped using BET (FSL, FMRIB Analysis Group, Oxford, UK) and normalized using statistical parametric mapping (SPM5, Wellcome Dept of Cognitive Neurology). The normalized images were smoothed by a 6 × 6 × 6 mm^3 Gaussian filter. Potential associations between the perfusion

data and extraversion and neuroticism score and individual CVT at resting state were tested at the level of voxel clusters by fitting a multiple regression model at each intracerebral voxel with CamBA (Cambridge Brain Analysis, http://www-bmu.psychiatry.cam.ac.uk/software/), covarying for the effects of age and gender.

$$P = \mathrm{a1} * X + \mathrm{a2} * \mathrm{C1} + \mathrm{a3} * \mathrm{C2} + e$$

where P is the perfusion, X the independent variable (CVT or personality score), C1 and C2 the covariates (age and gender), and e is an error term.

This model was regressed repeatedly after random permutation of the independent variable (the vector of CVT or personality scores) across the group, and a preliminary null distribution of the coefficient a1 (standardized by its standard error) was derived by pooling the resulting estimates over all intracerebral voxels. After applying an initial voxelwise threshold, spatial clusters of significant voxels were defined and the cluster mass statistic was tested against the distribution of cluster mass values derived from the permuted maps. The significance thresholds were corrected for multiple comparisons by controlling the number of error clusters per image and the family-wise error (FWE) rate such that the expected number of false positive clusters in each analysis was <1 (equivalent $p < 0.01$, corrected) (Suckling and Bullmore 2004). Since the cluster mass statistic (the sum of suprathreshold voxelwise test statistics) was used, cluster extent thresholding was not necessary. The personality factors and CVT scores were not included as covariates in the initial analysis, but to assess the independence of their effects on perfusion, additional regression analyses were performed investigating the link between perfusion and CVT covarying for personality and between perfusion and personality, covarying for CVT in addition to age and gender.

Results

Personality score and baseline CVT value

The average Neuroticism score across 28 subjects was 8.2 ± 6.5 (mean ± SD) and the extraversion score was 16.9 ± 4.3 (Fig. 1). The average CVT value across 27 subjects was 9.2 ± 4.1 (Fig. 1). The baseline and follow-up CVT values from the 17 test–retest subjects are shown in Table 1, and the Bland–Altman plot is shown in Fig. 2. The difference in CVT between baseline and follow-up measurements all lie within ±2 SDs of the average difference between the measurements, suggesting good reproducibility and no systematic bias. The 95 % confidence interval ranged from −1.8 to 2.4. No significant correlation was seen between the CVT and personality scores ($p > 0.1$), and between neuroticism and extraversion scores ($p > 0.1$).

Baseline CVT value and regional cerebral perfusion

Perfusion in several brain regions correlated significantly with CVT. At a cluster-wise significance level of $p < 0.01$, corrected, individual CVT values were negatively correlated with resting perfusion in the right dorsal ACC and right cerebellum (see Fig. 3; Table 2). There were no brain areas where perfusion was positively correlated with baseline CVT. Figure 3 shows correlation plots for localized perfusion values extracted from significant clusters in

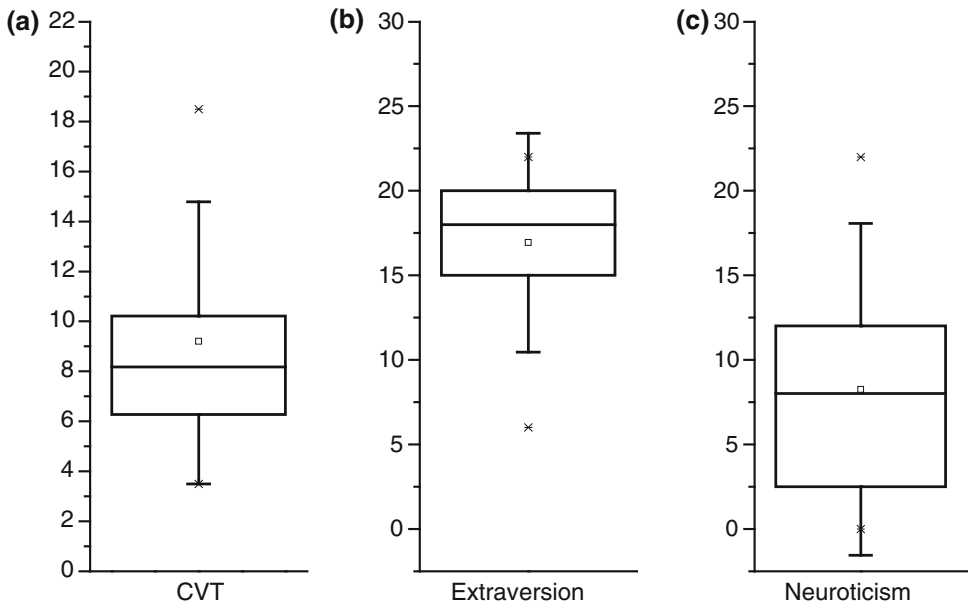

Fig. 1 The average mean ± SD. **a** CVT value (9.2 ± 4.1), **b** extraversion score (16.9 ± 4.3), and **c** neuroticism score (8.2 ± 6.5)

Table 1 CVT values from 17 subjects at baseline and after a follow-up interval of 1 year

CVT value (initial)	CVT value (1 year later)
10.18	11.71
14.68	12.9
18.5	14.93
7.23	7.94
6.76	8.44
3.49	6.73
5.73	6.43
17.57	12.09
13.52	14.72
5.9	8.73
4.63	7.11
9.83	12.15
2.39	6.8
17.59	12.98
8.4	8.2
9.84	7.34
7.88	7.22

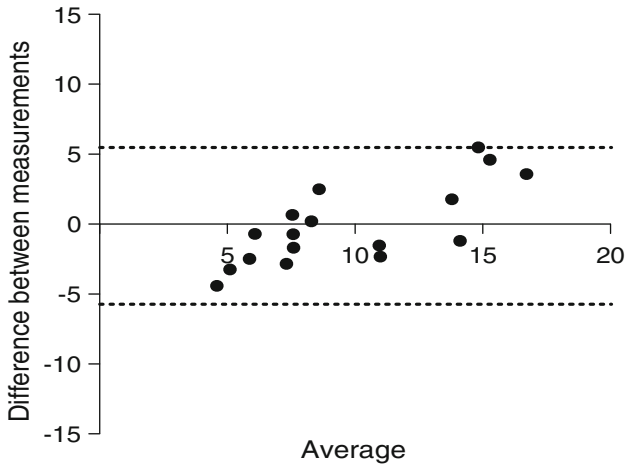

Fig. 2 Bland–Altman plot showing initial and follow-up CVT values. All points in the figure lie within ±2 SDs of the average of the difference between measurements suggesting good reproducibility and no systematic bias

the ACC and cerebellum decline, plotted against baseline CVT value.

Personality and regional cerebral perfusion

Significant positive correlations emerged between extraversion and perfusion in the brain stem, right caudate, superior frontal gyrus, mid-cingulate cortex, middle frontal gyrus, supramarginal gyrus, precentral gyrus, superior parietal gyrus, precuneus and supplementary motor area (Table 3; Fig. 4). There was no area where perfusion was negatively correlated with extraversion score ($p < 0.01$). Figure 4 also shows correlation plots for localized perfusion values extracted from significant clusters in the brainstem and caudate plotted against extraversion score.

Significant negative correlations were observed between neuroticism and perfusion in the left amygdala, bilateral insula, middle frontal gyrus, orbitofrontal cortex, temporal pole, cuneus, angular gyrus, precuneus, and supplementary motor area (Table 4; Fig. 5). There were no areas where perfusion was positively correlated with neuroticism ($p < 0.01$). Figure 5 shows correlation plots for localized perfusion values extracted from significant clusters in the amygdala and insula plotted against neuroticism.

Perfusion and CVT covarying for personality, and perfusion and personality covarying for CVT

Following the additional regression analyses, the clusters demonstrating a significant link between perfusion and neuroticism were unchanged after covarying for extraversion, but the correlation between perfusion and extraversion disappeared after covarying for neuroticism. The brain regions demonstrating a significant association between perfusion and both personality factors were largely unchanged after covarying for CVT.

Discussion

Using ASL, we investigated brain perfusion correlates of two fundamental personality traits, neuroticism and extraversion, and the association between individual traits in basal autonomic tone and resting brain perfusion. To our knowledge, this is first study using functional neuroimaging to investigate the neural correlates of inter-individual differences in the regulation of resting autonomic tone. Resting cerebral blood flow in the right dorsal ACC and cerebellum correlated negatively with parasympathetic tone (greater baseline arousal) across the groups, i.e., higher resting perfusion was associated with lower CVT. This result supports our hypothesis that differences in activity within regions of the CAN correspond to inter-individual differences in resting CVT. We also found that extraversion was positively correlated with resting perfusion in the caudate and mid-cingulate cortex, and neuroticism was negatively associated with perfusion in regions known to be responsible for affective processing including the amygdala, insula, and orbitofrontal cortex, consistent with our hypothesis.

Central influence on base autonomic tone

Our data show that resting dorsal ACC perfusion was greater in those with lower CVT. Transneuronal retrograde

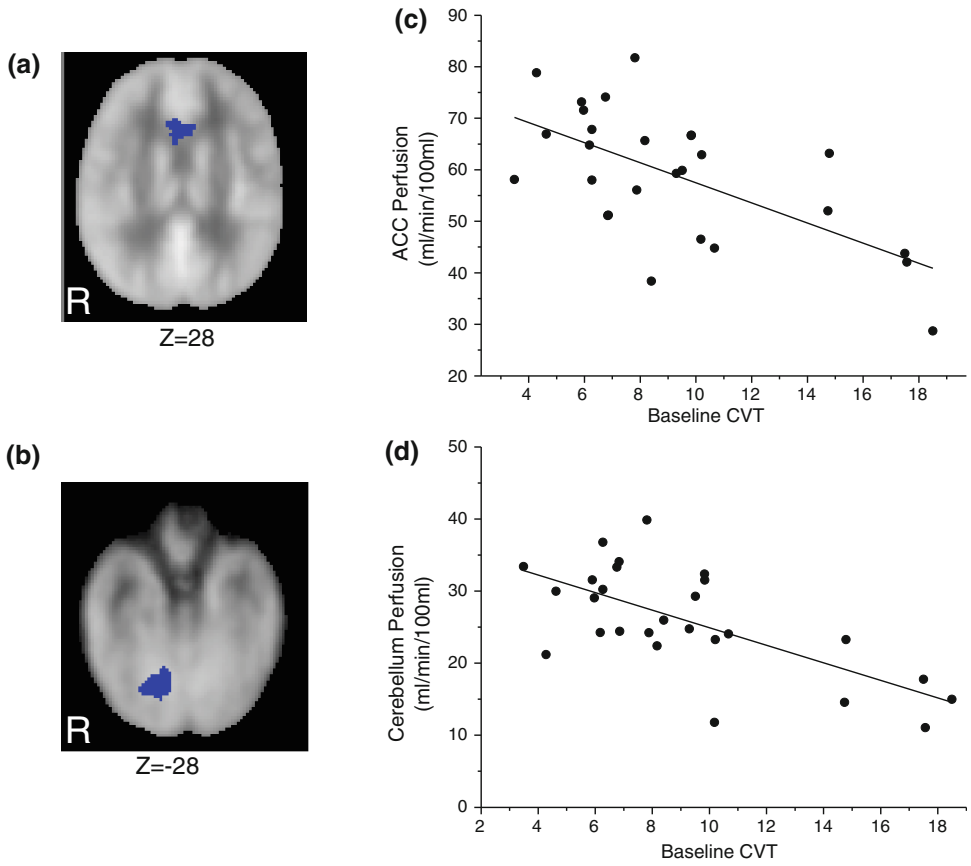

Fig. 3 Significant negative correlation between baseline CVT and perfusion. Axial perfusion images with clusters in **a** the ACC and **b** cerebellum overlaid in *blue* ($p < 0.01$). Perfusion extracted from significant clusters in **c** the ACC ($r = -0.63$) and **d** cerebellum ($r = -0.6$)

Table 2 Brain regions demonstrating a significant negative correlation between baseline CVT value and regional cerebral perfusion

Region	Number of voxels	Maximum standardized voxel statistic	Side	MNI coordinates		
Cerebellum	847	4.57	R	32	−52	−40
				12	−68	−44
				16	−52	−18
Anterior cingulate	288	3.92	R/L	2	18	22
				2	26	14
				−6	10	28

The standardized voxel statistic is given by a1/SE(a1), where a1 is the coefficient of the regression model between perfusion and CVT, and SE denotes the standard error

viral labeling provides firm evidence that the dorsal ACC acts as the representative region of supraspinal regulation of cardiac activities (Ter Horst et al. 1996). Dorsal ACC activity has also been shown to be associated with an increase in blood pressure and the sympathetic component of heart rate variability, sympathetic arousal as measured by papillary dilation, and skin conductance responses during mental (serial subtractions) and motor effort (isometric handgrip) tasks, working memory, and decision making (Critchley 2005; Nagai et al. 2004). Recently, Wager et al. (2009) reported that HR responses during social evaluative threat were mediated by increases in rostral dorsal ACC activation (rdACC) and de-activation in ventromedial prefrontal cortex (vmPFC). If the autonomic response is used as an index of arousal, these results suggest that the dorsal ACC may regulate the level of arousal in a variety of task-related conditions.

Arousal-related changes in the ACC activity have been observed in several PET studies in which the level of arousal varied from fully awake to deep sleep or general anesthesia, suggesting that dorsal ACC activity changes even in the absence of any overt cognitive activity (Paus 2001). Direct electrical stimulation of the ACC resulted in changes in autonomic tone (Devinsky et al. 1995), which is mediated by efferent connections with vagal nuclei and sympathetic columns in the thoracic spinal cord. Our data demonstrate that the greater the activity in the dorsal ACC, the greater the baseline arousal represented by lower CVT, suggesting a link between individual differences in the dorsal ACC activity and arousal level during the resting state.

In addition to the ACC, our data also suggest that cerebellar perfusion was greater at rest in those with lower CVT. Gianaros et al. (2004) observed similar findings during an active task using PET, which showed that a

Table 3 Brain regions demonstrating a significant positive correlation between extraversion score and regional cerebral perfusion

Region	Number of voxels	Maximum standardized voxel statistic	Brodmann area	Side	MNI		
Brainstem	227	4.66		L	−8	−32	−40
Cerebellum tonsil				L	−8	−50	−50
Caudate nucleus	329	4.86		R	12	14	−12
Extra-nuclear				R	16	34	4
					18	24	22
Superior frontal gyrus	941	5.62	6	L	−14	−5	63
Subgyrus				L	−30	−8	38
				L	−28	0	22
Mid-cingulate cortex	362	4.24	24	R	16	−6	46
Frontal gyrus, sub gyrus				R	26	−18	38
Corpus callosum				R	20	8	26
Middle frontal gyrus	324	3.97	6	L	−44	14	52
				L	−30	24	34
				L	−40	6	64
Supramarginal gyrus	910	4.96	40	R	60	−30	48
Precentral gyrus			6	R	60	0	38
Superior parietal gyrus			7	R	24	−48	72
Superior parietal gyrus	581	4.04	7	L	−30	−74	52
					−22	−70	40
					−30	−48	72
Precuneus	275	3.99	7	L	−8	−80	52
					−12	−74	42
					−6	−50	68
Supplementary motor area	389	3.89	8/6	R	12	14	56
Superior frontal gyrus					28	24	48
					10	20	72

The standardized voxel statistic is given by a1/SE(a1), where a1 is the coefficient of the regression model between perfusion and extraversion, and SE denotes the standard error

task-induced reduction in parasympathetic activity correlated with increased rCBF in the cerebellum. Brain injury studies also point to a possible role of the cerebellum in autonomic function. For example, Maschke (2002) demonstrated that patients with medial cerebellar lesions had little or no change in heart rate during a conditioned fear study, compared with healthy volunteers who showed significant increases in heart rate changes (i.e., increased arousal). Animal studies have also shown impaired conditioned HR responses after removal of the cerebellar vermis (Sebastiani et al. 1992), highlighting the role of the medial cerebellum in autonomic regulation. Our observation of an inverse correlation between perfusion in the right cerebellum and CVT provides further evidence that cerebellar activity may be involved in the regulation of autonomic tone during a resting state.

Lower baseline vagal tone has been reported in association with anxiety in a healthy population (Miu et al. 2009), depression (Rottenberg et al. 2007), PTSD (Sack et al. 2004), and autism (Ming et al. 2005), suggesting that these patient groups may be in a higher state of arousal in comparison to a control population even at baseline. Our previous data also showed that baseline CVT was negatively correlated with individual neuroticism scores such that higher neuroticism was associated with lower CVT (Paine et al. 2009a, b), a finding that was replicated in a cohort of 120 healthy volunteers (Farmer et al. 2009). Taken together with our current results, these reports suggest that individual differences in arousal are present in a normal population, and that this individual arousal state may be associated with the brain areas observed in the present study.

Variation in resting brain activity with extraversion and neuroticism

Extraversion

The positive association between extraversion and resting perfusion in the caudate is consistent with previous reports from studies of resting perfusion (O'Gorman et al. 2006),

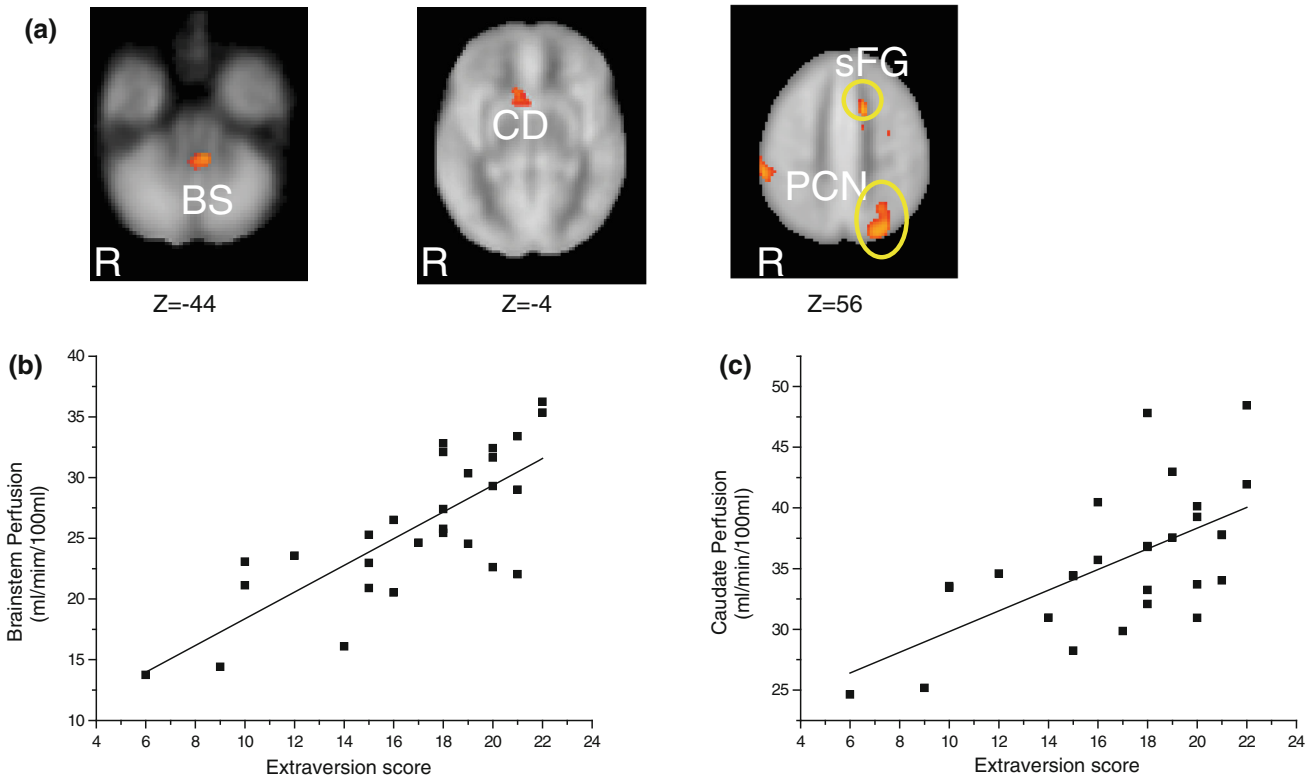

Fig. 4 **a** Axial perfusion images with clusters demonstrating a significant positive correlation with extraversion overlaid in *orange*. Perfusion extracted from significant clusters in **b** the brainstem ($r = 0.77$) and **c** caudate ($r = 0.63$). *BS* Brainstem, *CD* caudate, *sFG* superior frontal gyrus, *PCN* precuneus

regional cerebral glucose metabolism (Haier 1987) (Kim et al. 2008), and resting-state functional magnetic resonance imaging (R-fMRI) (Kunisato et al. 2011). The caudate comprises a part of the striatum related to reward processing (DeYoung et al. 2010). The striatum has a high level of D2-dopaminergic receptors. High levels of dopamine transmission have been related to greater sensitivity to incentive stimuli and also facilitate positive emotional and motivational experiences (Depue and Collins 1999), which comprise some of the descriptions for extraversion. Earlier neurobiological investigations revealed that detachment scores, which show negative correlation with extraversion scores, were negatively correlated with striatal D2 dopamine receptor or transporter availability (Farde et al. 1997). Tonic differences in dopamine levels may therefore contribute in part to observed differences in caudate perfusion.

Activity in the anterior and mid-cingulate cortex to positive stimuli has been demonstrated to correlate with extraversion during an emotional stroop attention task (Canli 2004a), suggesting that these areas might be related to attention to positive environmental signs in extraverts. Although the basis of the positive correlation between extraversion and resting perfusion in the superior frontal cortex (BA6), and precuneus is currently unknown, similar positive correlations have previously been reported in a R-fMRI study (Kunisato et al. 2011). The activity in superior frontal cortex also differs between extraverts and introverts on go/no-go task (Stahl and Rammsayer 2008). The correlation between extraversion and resting perfusion in superior frontal cortex may therefore reflect dis-inhibition related to extraversion. This correlation between perfusion and extraversion disappeared after covarying for neuroticism, suggesting that the individual differences of the brain areas above may be associated with the individual neuroticism tendency.

Neuroticism

A large body of neuroimaging studies has reported associations between the amygdala reactivity to affective, threatening stimuli and inter-individual variability in anxiety-related personality traits such as neuroticism (Hariri 2009). Subjects scoring higher in neuroticism have typically demonstrated an increased response in amygdala and medial frontal cortex to emotional conflict tasks (Haas et al. 2007). Amygdala functioning is also sensitive to the effects of central serotonin (Sadikot and Parent 1990), and

Table 4 Brain regions demonstrating a significant negative correlation between neuroticism score and regional cerebral perfusion

Region	Number of voxels	Maximum standardized voxel statistic	Brodmann area	Side	MNI		
Brainstem	227	4.66		L	−8	−32	−40
Cerebellum tonsil				L	−8	−50	−50
Caudate nucleus	329	4.86		R	12	14	−12
Extra-nuclear				R	16	34	4
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Superior frontal gyrus	941	5.62	6	L	−14	−5	63
Subgyrus				L	−30	−8	38
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Mid-cingulate cortex	362	4.24	24	R	16	−6	46
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Corpus callosum				R	20	8	26
Middle frontal gyrus	324	3.97	6	L	−44	14	52
				L	−30	24	34
				L	−40	6	64
Supramarginal gyrus	910	4.96	40	R	60	−30	48
Precentral gyrus			6	R	60	0	38
Superior parietal gyrus			7	R	24	−48	72
Superior parietal gyrus	581	4.04	7	L	−30	−74	52
					−22	−70	40
					−30	−48	72
Precuneus	275	3.99	7	L	−8	−80	52
					−12	−74	42
					−6	−50	68
Supplementary motor area	389	3.89	8/6	R	12	14	56
Superior frontal gyrus					28	24	48
					10	20	72

The standardized voxel statistic is given by a1/SE(a1), where a1 is the coefficient of the regression model between perfusion and neuroticism, and SE denotes the standard error

serotonin induces more excitation of hyperpolarized neurons (Cardenas et al. 1999). In vivo human PET studies have revealed that a decreased endogenous capacity for local 5-HT (serotonin, 5-hydroxytryptamine) reuptake is associated with increased amygdala reactivity (Rhodes et al. 2007). A functional polymorphism associated with relatively increased 5-HT signaling such as 5-HTTLPR (serotonin-transporter-linked polymorphic region) short allele, low MAOA (monoamine oxidase A) activity and 5-HT1A gene (HTreceptor1A)-1019G allele indirectly predict individual differences in anxiety-related traits (Hariri 2009).

The negative association between neuroticism and resting perfusion in the medial frontal cortex including ACC and insular cortex is consistent with previous reports of a link between neuroticism and regional cerebral glucose metabolism in the medial frontal gyrus (Kim et al. 2008) and insula (Deckersbach et al. 2006). One previous study investigating the link between ASL perfusion and personality scores did not observe any significant correlations between neuroticism and perfusion (O'Gorman et al. 2006), but this study examined an unselected sample of participants with a relatively narrow range of neuroticism scores. The previous study was also conducted at 1.5 T with an ASL sequence employing an echo planar imaging (EPI) readout, which is sensitive to magnetic susceptibility-induced field inhomogeneities in temporal and orbitofrontal regions, whereas the present study was conducted at 3 T with an ASL sequence employing a 3D FSE image readout and background suppression, resulting in perfusion images with reduced sensitivity to susceptibility artifacts. The significant correlations seen between perfusion and neuroticism in the present study but not previously may therefore arise from the increased sensitivity and the higher signal to noise ratio associated with the pCASL-FSE sequence at 3 T, especially in the temporal regions linked to neuroticism.

Temporal pole activity has been reported to be positively correlated with neuroticism score in healthy subjects looking at sad faces or empathizing with another person's

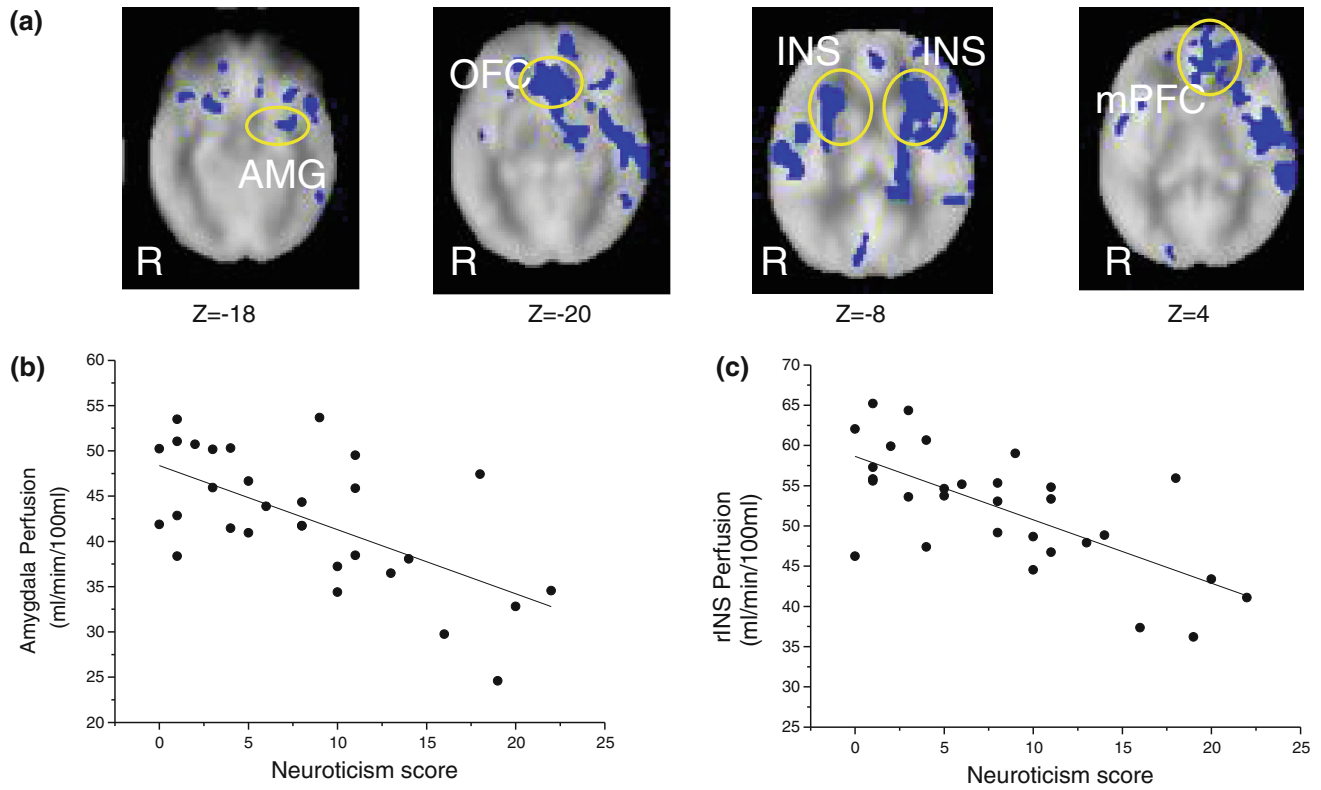

Fig. 5 Axial perfusion images with clusters demonstrating a significant negative correlation with neuroticism overlaid in *blue* (**a**). Perfusion extracted from significant clusters in **b** the amygdale ($r = -0.63$) and **c** right insula ($r = -0.66$). *AMY* Amygdala, *OFC* orbitofrontal cortex, *INS* insula, *mPFC* medial prefrontal cortex

mental state (Jimura et al. 2009, 2010), suggesting that temporal pole activity in particular may be associated with negative emotional processing in subjects with high neuroticism. Thus, the brain areas where the resting perfusion was negatively correlated with neuroticism score in this study are brain regions associated with negative affect and anxiety-like traits including neuroticism. Our data confirm that the resting brain activity in these areas differs between individuals in a manner dependent on their level of neuroticism. The insula cortex is also thought to be particularly relevant to anxiety states, which are characterized by physical changes such as increased heart rate and motor restlessness (Medford and Critchley 2010). We have recently demonstrated a significant positive correlation between brain activity in the anterior insula and neuroticism score during anticipation to visceral pain (Coen et al. 2011), supporting the association between insula activity and high neuroticism score.

Interestingly, the direction of the associations between extraversion and neuroticism with resting perfusion was opposite, i.e., extraversion showed only positive correlations with perfusion while neuroticism illustrated only negative correlations. This phenomenon has been reported previously in several studies of resting brain activity measured with regional cerebral glucose metabolism (Deckersbach et al. 2006; Kim et al. 2008) and R-fMRI (Kunisato et al. 2011). In particular, all these studies demonstrated lower resting brain activity and increased task-related activation in the brain areas related to negative emotion or anxiety such as amygdale and insula in subjects scoring high in neuroticism. Kim et al. (2008) speculated that it is possible that individuals with lower baseline levels of activity in this region may be more sensitive to stimulation, thereby accounting for the negative correlation between neuroticism and resting activity. To further explore this possibility, it would be useful to assess the relationship between personality traits and resting regional brain activity as well as task-related activation in the same subjects.

Although the close connection between ANS and personality was suggested in previous reports, in the present study CVT and personality were independently correlated to the different brain areas that have been related to ANS and personality, respectively. This lack of a direct association between CVT and personality, and the absence of overlapping effects on regional perfusion may be because the sample size of this study is not sufficient to examine an association between these three dimensions: ANS, personality and perfusion. Since many other factors will also affect the ANS and personality scores, this association may

be evident in a larger sample (Farmer et al. 2009). An alternative explanation for the lack of an association between ANS and personality is that the connection between these factors might be explained not by a brain area but by a brain circuit related to ANS control, but future studies employing a larger sample size would be required to investigate this possibility.

Limitation

Our study demonstrated the association of basal autonomic tone and personality on resting brain perfusion. However, the sample size (27 for CVT and 28 for personality) is relatively small and future studies investigating larger samples will be required to replicate our results. Furthermore, since both CVT and ASL perfusion are influenced by cardiac function, it is possible that the link between CVT and ASL perfusion could be confounded by cardiac effects in the local vasculature. In a healthy population, cerebral autoregulation processes maintain constant vascular flow despite alterations in cardiac output, but autoregulation has been observed to differ between men and women even in a healthy population (Deegan et al. 2010). In the present study, since gender was included as a covariate in the regression model, we believe the results are unlikely to be confounded by gender-related differences in autoregulation, but this effect could represent a significant confound in a patient population where autoregulation may be impaired. Future studies may be able to elucidate further the link between CVT, cardiac output, perfusion, vascular flow, and cerebral autoregulation.

Conclusion

The individual variability of resting cerebral perfusion depends on a number of physiological and psychological factors. The resting perfusion in brain areas related to autonomic arousal is strongly associated with baseline CVT tone. Extraversion was positively correlated with perfusion in the areas previously reported to relate to reward or motivation during active tasks, while neuroticism negatively correlated with perfusion in the regions associated with negative affect and anxiety during active tasks. These baseline inter-individual differences may be important when interpreting task-related activation in neuroimaging studies.

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