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Right ventromedial prefrontal lesions result in paradoxical cardiovascular activation with emotional stimuli

Max J. Hilz,[1,4] Orrin Devinsky,[1] Hanna Szczepanska,[1,2] Joan C. Borod,[2,3] Harald Marthol[1,4] and Marcin Tutaj[1,5]

[1]Department of Neurology, New York University, [2]Department of Neurology, Mount Sinai School of Medicine, [3]Department of Psychology, Queens College and The Graduate Center of the City University of New York (CUNY), New York, NY, USA, [4]Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany and [5]Department of Neurology, Jagiellonian University Medical College, Cracow, Poland

Correspondence to: Orrin Devinsky, MD, Comprehensive Epilepsy Center, New York University School of Medicine, 403 East 34th Street, 4FL; New York, NY 10016, USA
E-mail: od4@nyu.edu

Ventromedial prefrontal cortex (VMPFC) lesions can alter emotional and autonomic responses. In animals, VMPFC activation results in cardiovascular sympathetic inhibition. In humans, VMPFC modulates emotional processing and autonomic response to arousal (e.g. accompanying decision-making). The specific role of the left or right VMPFC in mediating somatic responses to non-arousing, daily-life pleasant or unpleasant stimuli is unclear. To further evaluate VMPFC interaction with autonomic processing of non-stressful emotional stimuli and assess the effects of stimulus valence, we studied patients with unilateral VMPFC lesions and assessed autonomic modulation at rest and during physical challenge, and heart rate (HR) and blood pressure (BP) responses to non-stressful neutral, pleasant and unpleasant visual stimulation (VES) via emotionally laden slides. In 6 patients (54.0 ± 7.2 years) with left-sided VMPFC lesions (VMPFC-L), 7 patients (43.3 ± 11.6 years) with right-sided VMPFC lesions (VMPFC-R) and 13 healthy volunteers (44.7 ± 11.6 years), we monitored HR as R–R interval (RRI), BP, respiration, end-tidal carbon dioxide levels, and oxygen saturation at rest, during autonomic challenge by metronomic breathing, a Valsalva manoeuvre and active standing, and in response to non-stressful pleasant, unpleasant and neutral VES. Pleasantness versus unpleasantness of slides was rated on a 7-point Likert scale. At rest, during physical autonomic challenge, and during neutral VES, parameters did not differ between the patient groups and volunteers. During VES, Likert scores also were similar across the three groups. During pleasant and unpleasant VES, HR decreased (i.e. RRI increased) significantly whereas BP remained unchanged in volunteers. In VMPFC-L patients, HR decrease was insignificant with pleasant and unpleasant VES. BP slightly increased ($P = 0.06$) with pleasant VES but was stable with unpleasant VES. In contrast, VMPFC-R patients had significant increases in HR and BP during pleasant and not quite significant HR increases ($P = 0.06$) with only slight BP increase during unpleasant VES. Other biosignals remained unchanged during VES in all groups. Our results show that VMPFC has no major influence on autonomic modulation at rest and during non-emotional, physical stimulation. The paradoxical HR and BP responses in VMPFC-R patients suggest hemispheric specialization for VMPFC interaction with predominant parasympathetic activation by the left, but sympathetic inhibition by the right VMPFC. Valence of non-stressful stimuli has a limited effect with more prominent left VMPFC modulation of pleasant and more right VMPFC modulation of unpleasant stimuli. The paradoxical sympathetic disinhibition in VMPFC-R patients may increase their risk of sympathetic hyperexcitability with negative consequences such as anxiety, hypertension or cardiac arrhythmias.

Keywords: cardiovascular autonomic system; emotion; prefrontal cortex; somatic markers; valence hypothesis

Abbreviations: BP = blood pressure; HR = heart rate; RRI = R–R interval; VMPFC = ventromedial prefrontal cortex; VMPFC-L = left-sided VMPFC lesions; VMPFC-R = right-sided VMPFC lesions

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Introduction

The ventromedial prefrontal cortex (VMPFC), comprising the orbitofrontal and medial prefrontal cortices, constitutes a functional neurophysiological entity that integrates sensory information and emotional stimuli (Phillips *et al.*, 2003; Rolls, 2004). The VMPFC contributes to regulating emotional and cognitive processes (Damasio, 1994; Phillips *et al.*, 2003; Rolls, 2004), including decision-making and guiding appropriate appetitive or aversive modes of behaviour oriented towards advantageous future outcomes (Bechara *et al.*, 1994; Damasio, 1994). Patients with VMPFC lesions often manifest an altered emotionality and may present a syndrome of 'acquired sociopathy', composed of, for example, inappropriate affect, poor frustration tolerance, irritability, impaired decision-making and psychosocial dysfunction (Barrash *et al.*, 2000). The VMPFC is also involved in mediating autonomic responses to emotional stimuli, such as changes in skin conductance (Damasio, 1994; Phillips *et al.*, 2003), heart rate (HR) (Critchley *et al.*, 2000; Damasio *et al.*, 2000; Phillips *et al.*, 2003), or blood pressure (BP) (Critchley *et al.*, 2000; Phillips *et al.*, 2003).

Mediation of emotional-autonomic interaction by the VMPFC is not well understood. The autonomic effects of the VMPFC seem to differ between the left and right hemisphere and to depend on the quality of emotional stimuli (Damasio, 1994). Patients with VMPFC lesions show a reduction of somatic markers (i.e. autonomic responses) accompanying the decision-making process and indicating the behavioural relevance of an emotional stimulus (Bechara *et al.*, 1994, 1996; Damasio, 1994). For example, these patients fail to trigger anticipatory skin conductance responses when contemplating a decision in the gambling task (Bechara *et al.*, 1996, 2000).

Animal studies confirm that emotional–autonomic interactions mediated by the medial prefrontal cortex depend on the level of emotional stimulation (Verberne *et al.*, 1987; Frysztak and Neafsey, 1994) and differ for sympathetic and parasympathetic modulation (Frysztak and Neafsey, 1994). Lesion studies in rats suggest that the VMPFC does not affect resting BP and HR (Verberne *et al.*, 1987) or parasympathetic-mediated bradycardia but is essential for sympathetic cardiovascular activation to stressful stimuli (Frysztak and Neafsey, 1994). In contrast, medial prefrontal cortex stimulation induces cardiovascular depressor and sympathoinhibitory responses in rodents (Neafsey, 1990; Owens and Verberne, 2000).

The side of VMPFC activation seems to modify autonomic responses. In healthy persons and in patients with unilateral VMPFC lesions, the left and right VMPFC have different modulatory effects on emotional-autonomic interaction. Anticipatory skin conductance response during the gambling task is preserved in patients with left-sided VMPFC (VMPFC-L) lesions but absent in patients with right-sided VMPFC (VMPFC-R) lesions (Tranel *et al.*, 2002). Yet, skin conductance changes are still preserved in response to actual reward or penalty, confirming that autonomic modulation by VMPFC depends on the quality of emotional stimuli (Damasio, 1994; Bechara *et al.*, 1996). Healthy persons who recalled and re-experienced life episodes marked by sadness, happiness, anger or fear, had similar HR increases with all emotions but PET showed varying activations and deactivations in the VMPFC and other brain regions (Damasio *et al.*, 2000). There was right orbitofrontal activation during happiness, bilateral activation during sadness, and bilateral deactivation during fear (Damasio *et al.*, 2000). Orbitofrontal cortex blood flow during mental arithmetic and isometric exercise covaried positively with rises in BP, but negatively with HR increases, whereas more medial parts of the prefrontal cortex also covaried negatively with BP (Critchley *et al.*, 2000).

Other studies support an asymmetrical processing of emotion by the left and right VMPFC (George *et al.*, 1996). Broad generalizations about lateralization of emotional function remain controversial (Devinsky and D'Esposito, 2004), but several lines of evidence suggest that the right hemisphere is more involved in emotional perception and expression (Ross, 1997), especially for negative emotions (Borod *et al.*, 1986; Meadows and Kaplan, 1994; Mandal *et al.*, 1999), whereas the left hemisphere is more engaged in processing positive emotions (Dimond *et al.*, 1976).

Similarly, studies in brain-damaged patients have shown greater involvement of the right than left hemisphere in regulating autonomic arousal to emotional stimuli (Heilman *et al.*, 1978; Morrow *et al.*, 1981; Meadows and Kaplan, 1994). Moreover, there are hemispheric differences in the modulation of the cardiovascular autonomic system. In epilepsy patients, the right hemisphere mediates predominantly sympathetic cardiovascular activation whereas the left hemisphere is more involved in cardiovagal control (Hilz *et al.*, 2001).

It remains unclear to what extent the left and right VMPFC itself or other hemispheric structures involved in autonomic control account for changes in autonomic modulation during emotional stimulation. Although a relationship among emotional stimulation, VMPFC activation, and cardiovascular autonomic activity (e.g. HR or BP changes) has been established, its nature remains uncertain

Table 1 Clinical characteristics of the 13 patients participating in the study

Patient no.	Age (years)	Gender	Lesion side	Lesion aetiology	Seizure type	Medication
1	47	Female	Left	Neurosurgery due to therapy-refractory epilepsy	CPS	Cbz, Tpx
2	64	Female	Left	Meningioma	CPS, GTC	Cbz
3	48	Male	Left	Arteriovenous malformation	CPS	Ltg
4	55	Female	Left	Arteriovenous malformation	CPS, GTC	Fbm, Clb
5	61	Male	Left	Abscess	CPS	Phy
6	46	Male	Left	Head trauma	CPS, GTC	Ltg
7	49	Male	Right	Head trauma	CPS, GTC	Ltg
8	52	Female	Right	Arteriovenous malformation	SPS, CPS	Ltg
9	31	Female	Right	Abscess	CPS, GTC	Cbz, Tpx
10	49	Female	Right	Neurosurgery due to therapy-refractory epilepsy	CPS, GTC	Obz, Vpa
11	26	Male	Right	Head trauma	CPS, GTC	Ltg
12	39	Male	Right	Ischaemic stroke	SPS, CPS	Obz, Lev
13	55	Male	Right	Meningioma	CPS	Tpx, Lev, Pri

SPS = simple partial seizures, CPS = complex partial seizures, GTC = generalized tonic–clonic seizures; Ltg = lamotrigine, Fbm = felbamate, Clb = clobazam, Cbz = carbamazepine, Tpx = topiramate, Obz = oxcarbazepine, Vpa = valproic acid, Lev = levetiracetam, Pri = primidone, Phy = phenytoin.

(Critchley *et al.*, 2000; Damasio *et al.*, 2000). Some investigators believe that the VMPFC may be involved only in emotional processing whereas autonomic cardiovascular changes might be mediated by other cerebral structures. Alternatively, VMPFC might directly contribute to HR increases or be activated in response to HR changes to inhibit excessive HR rises. VMPFC activation could also be a cortical representation of peripherally occurring HR changes or result from perceiving the cardiovascular arousal (Critchley *et al.*, 2000; Damasio *et al.*, 2000; Pollatos *et al.*, 2005).

Animal, but not human, studies suggest that medial prefrontal cortex exerts an inhibitory effect on HR and BP with non-stressful stimuli (Owens and Verberne, 2000). The distinct roles of the left and right VMPFC in modulating cardiovascular responses to non-arousing emotional stimuli (e.g. happiness with calmness and relaxation or sadness without arousal and crying) have not been studied in humans. Based on previous studies, we hypothesize that the left and right VMPFC will have distinct effects on cardiovascular responses to non-stressful emotions and that cardiovascular responses will differ as a function of positive or negative stimulus valence.

We, therefore, studied whether HR and BP responses to standardized, non-stressful visual emotional stimuli associated with little or no arousal (Borod *et al.*, 1986; Meadows and Kaplan, 1994) differ between patients with left- or right-sided VMPFC lesions and healthy persons, and whether responses depend on the positive or negative valence of the stimulus.

Material and methods

Study participants

We studied 13 patients (6 female, 7 male), aged 26–64 years (mean 47.8 ± 11.3) with isolated unilateral ventromedial prefrontal lesions of the brain, documented by computed tomography and MRI studies. As control persons, 13 education-, sex-, and age-matched healthy volunteers (7 female, 6 male), aged 25–62 years (mean 44.7 ± 11.6), also participated in the study. All the patients were recruited from the outpatient population at the NYU Comprehensive Epilepsy Center. Six patients (three female, mean age 54.0 ± 7.2) had a left-sided lesion, and seven patients (three female, mean age 43.3 ± 11.6) had a right-sided lesion. The lesions were due to head injury (three patients), arteriovenous malformation (three patients), an abscess (two patients), meningioma (two patients), epilepsy surgery due to medication-refractory seizures of unknown origin (two patients), and ischaemic stroke (one patient). Nine patients (four with left-sided and five with right-sided lesion) had undergone brain surgery at least once in their lifetime. The surgeries had been limited to the frontal lobes in all but one patient, who had had a tailored resection of the anterior temporal lobe. All patients had been suffering from complex partial seizures, and at the time of enrolment, all of them were treated with antiepileptic drugs at stable doses. Satisfactory control of seizures had been achieved in all patients, who had all been seizure-free for at least 6 months prior to this study (Table 1). All participants, except for one patient with right-sided lesion, were right-handed.

Participants with a history of psychiatric disorder, with a history of alcohol or other substance abuse, suffering from diseases that might affect autonomic regulation (e.g. myocardial ischaemic disease, arterial hypertension, diabetic or other neuropathies, or neurodegenerative diseases of the central nervous system), and/or who were taking drugs that might interfere with autonomic function (e.g. antihypertensive, antiarrhythmic, or neuroleptic agents) were excluded from the study. All participants were asked not to consume nicotine, caffeine or alcohol for at least 12 h before testing. The study protocol was approved by the Institutional Review Board of New York University School of Medicine, and each participant gave informed written consent.

Procedures

All procedures were performed in a quiet room with an ambient temperature of 24°C and stable humidity. We took a short history and explained to the patients details of the testing procedures. As anxiety has been shown to particularly influence cardiovascular autonomic function (Piccirillo *et al.*, 1997), we attempted to rule out or assess differences in state- and trait-anxiety between the patient groups and the volunteers in order to determine any

possible influence of differing levels of anxiety on cardiovascular autonomic control. We therefore determined each participant's level of state- and trait-anxiety (i.e. the anxiety state at the time of study and the level of preexisting, long-term trait-anxiety), using the Spielberger State-Trait Anxiety Inventory (Spielberger *et al.*, 1983). Patients were seated in a comfortable armchair and the monitoring instruments were attached to them. To ensure a stable cardiovascular resting state, the participants rested in the sitting position for at least 40 min prior to commencing the experiment.

Cardiovascular recordings

R–R-intervals (RRI) were measured using a standard 5-lead electrocardiogram with superficial skin electrodes attached to the chest under the right and left clavicles, over the right and left costal arch, and over the fifth intercostal space at the left midclavicular line. Blood pressure was continuously recorded from the left radial artery at the wrist positioned at heart level by means of non-invasive applanation tonometry (Colin Pilot, Colin, San Antonio, TX, USA). The tonometer consists of an array of 32 equally spaced piezoresistive pressure transducers, an automated positioning system, signal conditioning, and initial as well as intermittent calibration by oscillometric cuff measurements of the brachial artery BP (Kemmotsu *et al.*, 1991). End-tidal carbon dioxide levels ($ETCO_2$) were monitored using infrared spectrometry via nasal cannulae (Colin Pilot, Colin, San Antonio, TX). Transcutaneous oxygen saturation ($SatO_2$) was measured at the right index finger by means of a pulsoximeter (Nellcor, Pleasanton, CA, USA). Respiratory frequency was recorded with a calibrated two-belt chest-abdomen inductance plethysmograph (Respitrace Calibrator®, Ambulatory Monitoring, Ardsley, NY, USA).

Baseline recordings and autonomic function tests

To control for possible cardiovascular autonomic dysfunction that might bias the results of emotional stimulation, for each participant, the basal cardiovascular autonomic status was assessed under resting conditions and in response to standard tests of autonomic function.

Heart rate variability at rest. During the resting period, we recorded 5-min time series of HR and analysed heart rate variability (HRV) by calculating the mean of the RRI, the RRI standard deviation (RR-SD), and the root mean square of successive differences between adjacent RRIs (RMSSD) (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). RMSSD reflects mainly parasympathetic modulation of HR, whereas RR-SD reflects sympathetic and parasympathetic HR modulation (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Heart rate variability during deep breathing. The participants were then asked to breathe deeply for 2 min at a frequency of 6 cycles per minute, as this frequency has been shown to produce maximal HRV in healthy individuals (Ewing and Clarke, 1982; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). For each breathing cycle, we compared the increase in RRI during expiration (E) with the decrease in RRI during inspiration (I) by calculating the E–I difference as the average of the differences between the maximal and the minimal RRI from the three cycles with the greatest difference. From these three cycles, we also calculated the E/I ratio as the averaged ratio of the maximal and the minimal RRI (Ewing and Clarke, 1982; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Valsalva manoeuvre. Participants were asked to blow into a mouthpiece connected to a modified BP manometer and to maintain a pressure of approximately 40 mmHg for 15 s. We calculated the Valsalva ratio (VR), which is defined as the ratio of the highest RRI within the first 20 s after and the lowest RRI during the manoeuvre (Ewing and Clarke, 1982). For each subject, the value was calculated as the mean of two Valsalva manoeuvres.

Active standing. After a subsequent resting period of at least 5 min in the sitting position and after another 5 min of baseline recordings, participants were asked to actively stand up. BP and RRI were measured continuously during the 5 min before standing and during 3 min in the upright position. The arm wearing the BP cuff was maintained at the level of the heart. According to Ewing (Ewing and Clarke, 1982), we assessed HRV during standing as the 30:15 ratio (i.e. the ratio between the highest RRI around the 30th heart beat and the lowest RRI around the 15th heart beat after standing-up). Additionally, we calculated the differences between the lowest systolic (BP_{sys}) and diastolic (BP_{dia}) BP values during standing and the BP_{sys} and BP_{dia} values averaged over the 5-min period in the sitting position, prior to standing.

Spectral analysis of resting heart rate and blood pressure variabilities. In addition, we assessed the contribution of the sympathetic and parasympathetic systems to HR and BP modulation by evaluating R-R interval and BP variability by means of power spectral analysis, using an autoregressive algorithm with a linear detrending option and model order estimation according to Akaike information criteria (Burr and Cowan, 1992). The spectral analysis was applied on a 3-min segment with most stable respiration derived from the 5-min time series that we used for calculation of HRV parameters. We identified peaks of oscillations in the low frequency (LF: 0.04–0.14 Hz) and high frequency (HF: 0.15–0.50 Hz) ranges. LF oscillations of RRI at rest are considered to be mediated by combined sympathetic and parasympathetic activity, whereas there is a predominance of sympathetic activity during stressful conditions (Saul *et al.*, 1991; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). In contrast, LF fluctuations of the BP signal are mostly related to fluctuations in sympathetic outflow (Saul *et al.*, 1991; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). HF oscillations in RRI are associated with respiratory sinus arrhythmia and reflect parasympathetic activity (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), whereas fluctuations of the BP signal in the HF range are primarily a mechanical consequence of respiration-induced fluctuations in venous return (Saul *et al.*, 1991; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). We normalized the powers of RRI oscillations (LFnu, HFnu) as percentage values by dividing the LF or HF power by the sum of the LF and HF powers and multiplying by 100 (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Because the LF and HF powers of the RRI and BP signals showed a skewed distribution, the powers were transformed into natural logarithms.

Responses to visual emotional stimulation

To assess cardiovascular function and responses to visual stimuli with emotional content, we presented the study participants with a standard set of slides (Buck, 1978), consisting of two slides considered pleasant (a laughing family and a mother picnicking with a child), two slides considered unpleasant (a starving child and a crying mother holding an injured child in her hands), and two slides considered neutral (two landscapes). The slides had been validated in previous studies (Buck and Duffy, 1980; Borod *et al.*, 1983) and used with patients with unilateral brain damage (Borod *et al.*, 1985) to study changes in facial expression, prosodic intonation, and the ability to express emotion in words. We presented the images via a slide projector (Sony Caramate) on a screen positioned slightly below eye level, directly in front of the subject, at a distance of ~3 m. Participants were asked to focus on a fixation point in the centre of a blank slide prior to presentation of each stimulus. To ensure stability of the cardiovascular system before the next stimulus, there was a 1-min recovery interval after each slide presentation.

All six slides were presented in a randomized order for 20 s each. After 20 s of slide presentation, participants were asked to describe their feelings elicited by each slide to confirm whether it had induced a response consistent with the intended emotion. In addition, participants were required to rate their response to the slide on a 7-point Likert scale, ranging from 'extremely unpleasant' (1), to 'moderately unpleasant' (2), 'slightly unpleasant' (3), 'neutral' (4), 'slightly pleasant' (5), 'moderately pleasant' (6), and 'extremely pleasant' (7). Cases where a pleasant slide was rated as 'neutral' or 'unpleasant', where an unpleasant slide was rated as 'neutral' or 'pleasant', or where a neutral slide was rated as 'extremely unpleasant' or 'extremely pleasant' were not included in the analysis.

To determine the effects of emotional stimulation, we compared the mean values of the cardiovascular parameters recorded during the presentation of each slide to the mean values of these parameters recorded during the 20-s period immediately preceding the stimulation.

Data acquisition and analysis

All data were digitized by a custom-made analogue-to-digital converter at a sampling rate of 300 Hz, fed to a Macintosh PowerBook computer (Apple Inc.) and manually cleaned from artefacts by linear interpolation (Bernardi *et al.*, 1995; Brys *et al.*, 2003). A computer program identified all QRS complexes in each sequence and located the peak of each R-wave. Values for systolic, diastolic, and mean BP were derived from the continuous BP waveform. Time series were created for all parameters and stored for off-line analysis (Bernardi *et al.*, 1995).

During both visual stimulation and the intervals preceding presentation of each slide, we calculated mean values and the standard errors of the mean (SEMs) for all signals.

Statistical analysis

To assess the effects of positive, negative, and neutral emotional stimulation within each of the three groups (i.e. healthy subjects and patients with left- or right-sided VMPFC lesions), we compared the average of the values recorded during presentation of the two pleasant slides, the average of the two unpleasant slides, and the average of the two neutral slides to the average of the corresponding baseline values that preceded the presentations (Meadows and Kaplan, 1994; Herpertz *et al.*, 1999), using a two-tailed paired *t*-test. To compare responses (i.e. the change from baseline values to values during slide presentation) to stimulation among the three subject groups, one-way analyses of variance and Tukey *post hoc* comparisons were used.

Among the three groups, we compared the Likert scale scores of the participants' self-reported emotional response ratings and their Spielberger State-Trait Anxiety Inventory scores via the Kruskal–Wallis test with Dunn's post-test whenever a significant *P*-value occurred.

The level of statistical significance was set at $P < 0.05$. A commercially available statistical program was used for data analysis (GraphPad Prism 4®, GraphPad Software Inc., San Diego, CA, USA).

Results

Baseline measurements

State anxiety scores, depicting anxiety levels at the time immediately preceding the testing procedure, did not differ significantly among the three groups (controls = 32.5 ± 2.1 versus left-sided = 34.8 ± 2.4 versus right-sided = 35.4 ± 3.4; Kruskal–Wallis: $P = 0.84$). In contrast, the trait-anxiety scores describing the participants' feelings, in general, were higher in the patients with right-sided lesions (45.9 ± 3.0) than in the patients with left-sided lesions (36.2 ± 3.6) or in healthy persons (36.6 ± 1.7; Kruskal–Wallis: $P = 0.049$).

At baseline, there was no difference in any of the biosignal values among healthy persons, patients with VMPFC-R lesions, and patients with VMPFC-L lesions (ANOVA: $P > 0.05$; Table 2).

Baseline spectral powers of RRI and BP oscillations in the LF and HF ranges did not differ significantly among healthy persons, patients with VMPFC-R lesions, and patients with VMPFC-L lesions (ANOVA: $P > 0.05$; Table 2).

There were no significant differences among the groups in autonomic RRI modulation as assessed by the standard deviation and RMSSD at rest, the E/I ratio and E-I difference during metronomic breathing, the VR, the 30:15 ratio, and changes in BP_{sys} and BP_{dia} upon standing up (ANOVA: $P > 0.05$; Table 3).

Emotional responses to pleasant, unpleasant, and neutral slides (7-point Likert scale)

Emotional response ratings obtained on the 7-point Likert scale with 20-s presentations of pleasant slides did not differ among the healthy persons, patients with left VMPFC lesions, and patients with right VMPFC lesions (Kruskal–Wallis: $P > 0.05$; Table 4). As with the pleasant slides, the emotional response values obtained on the 7-point Likert scale with 20-s presentations of unpleasant slides and neutral slides did not differ among the three groups (Kruskal–Wallis: $P > 0.05$; Table 4). Two healthy subjects rated one of the pleasant slides as 'neutral', and one patient with a left VMPFC lesion rated one of the pleasant slides as

Table 2 Mean values of cardiovascular and respiratory parameters assessed in healthy persons, and patients with left-sided and patients with right-sided ventromedial prefrontal lesions at baseline

Parameters	Controls	VMPFC-L	VMPFC-R	ANOVA
RRI (ms)	863.2 ± 27.8	856.4 ± 47.8	963.0 ± 19.1	n.s.
ln LF_{RRI} (ln ms^2)	5.9 ± 0.3	5.7 ± 0.8	6.6 ± 0.3	n.s.
ln HF_{RRI} (ln ms^2)	5.1 ± 0.3	4.6 ± 0.7	6.0 ± 0.5	n.s.
$LFnu_{RRI}$ (%)	65.4 ± 6.6	71.6 ± 8.0	58.8 ± 10.4	n.s.
$HFnu_{RRI}$ (%)	34.6 ± 6.6	28.4 ± 8.0	41.2 ± 10.4	n.s.
BP_{sys} (mmHg)	111.8 ± 4.8	117.3 ± 3.1	15.8 ± 7.9	n.s.
ln LF_{BPsys} (ln $mmHg^2$)	1.4 ± 0.5	1.6 ± 0.5	1.6 ± 0.4	n.s.
BP_{dia} (mmHg)	62.9 ± 3.8	68.4 ± 4.9	66.4 ± 4.8	n.s.
ln LF_{BPdia} (ln $mmHg^2$)	1.1 ± 0.4	1.1 ± 0.2	1.3 ± 0.5	n.s.
BP_{mean} (mmHg)	80.5 ± 4.0	85.1 ± 4.0	84.0 ± 5.6	n.s.
ln LF_{BPmean} (ln $mmHg^2$)	1.5 ± 0.4	1.2 ± 0.4	1.2 ± 0.5	n.s.
Resp (min^{-1})	14.8 ± 0.5	12.1 ± 1.5	14.2 ± 0.9	n.s.
TV (ml)	346.0 ± 90.3	342.8 ± 96.6	359.0 ± 102.6	n.s.
$ETCO_2$ (mmHg)	35.3 ± 1.6	34.2 ± 8.5	37.3 ± 1.3	n.s.
$SatO_2$ (%)	98.3 ± 0.7	97.6 ± 1.2	99.8 ± 0.6	n.s.

n.s., non-significant differences (one-way analysis of variance); VMPFC-L/VMPFC-R, patients with left-sided/right-sided ventromedial prefrontal cortex lesions; RRI, R-R interval (ms); BP_{sys}, BP_{dia}, BP_{mean}, systolic, diastolic and mean blood pressures (mmHg); ln LF_{RRI}, ln HF_{RRI}, ln LF_{BPsys}, ln LF_{BPdia}, ln LF_{BPmean}, spectral powers of RRI (ln ms^2) and BP (ln $mmHg^2$) transformed into natural logarithms; $LFnu_{RRI}$, $HFnu_{RRI}$, normalized LF and HF spectral powers of RRI (%); Resp, respiration rate (min^{-1}); TV, tidal volume (ml); $ETCO_2$, end-tidal CO_2 (mmHg); $SatO_2$, oxygen saturation (%).

Table 3 RRI variability at rest (RRI-SD, RMSSD), during metronomic deep breathing (I/E, I–E), Valsalva manoeuvre (VR) and R-R interval and blood pressure responses to active standing from the sitting position (30:15, ΔBP_{sys}, ΔBP_{dia}) assessed in healthy persons, patients with left-sided and patients with right-sided ventromedial prefrontal lesions

Parameters	Controls	VMPFC-L	VMPFC-R	ANOVA
RRI-SD (ms)	34.0 ± 4.8	35.3 ± 10.5	46.9 ± 5.4	n.s.
RMSSD (ms)	26.3 ± 5.4	25.9 ± 9.5	36.1 ± 10.7	n.s.
I/E (1)	1.35 ± 0.06	1.26 ± 0.05	1.29 ± 0.06	n.s.
I–E (ms)	362.7 ± 53.2	296.1 ± 69.1	288.2 ± 47.9	n.s.
VR (1)	1.63 ± 0.08	1.98 ± 0.27	1.61 ± 0.16	n.s.
30:15 ratio (1)	1.34 ± 0.05	1.28 ± 0.08	1.30 ± 0.04	n.s.
ΔBP_{sys} (mmHg)	−11.6 ± 4.7	−7.8 ± 5.4	−12.9 ± 5.3	n.s.
ΔBP_{dia} (mmHg)	−4.9 ± 3.3	−2.9 ± 1.9	−6.7 ± 2.8	n.s.

n.s., non-significant differences (one-way analysis of variance); VMPFC-L/VMPFC-R, patients with left-sided/right-sided ventromedial prefrontal cortex lesions; RRI-SD, standard deviation of RRI; RMSSD, root mean square of successive differences between adjacent RRIs; I/E, inspiratory/expiratory ratio, I–E, inspiratory–expiratory difference of RRI during metronomic (6 cycles/minute) deep breathing; VR, Valsalva ratio; ΔBP_{sys}, ΔBP_{dia}, the greatest systolic and diastolic blood pressure falls during 3 min standing.

'unpleasant'. Five healthy subjects categorized their feelings as 'extremely pleasant' for seven of the neutral slides. The same rating was given by one patient with a VMPFC-L lesion to both of the neutral slides and by three patients with a right-sided lesion to four neutral slides.

When talking about their feelings regarding the pleasant slides, all participants described their emotional responses as 'pleasant', 'feeling happy', 'feeling relaxed', etc. It is interesting to note that these reactions were not associated with laughter. All participants described their emotional responses to the unpleasant slides as 'unpleasant', 'feeling sad', 'feeling depressed', etc. Interestingly, none of the participants wept during the stimulation. When presented with the two slides of emotionally neutral content, all participants characterized their emotional responses as 'neutral' or 'pleasant'.

Cardiovascular responses to 20 s stimulation with pleasant, unpleasant and neutral slides

R–R intervals

Among the three groups, pleasant stimulation induced significantly different changes in RRI (ANOVA: $P = 0.0001$). While there was a similar RRI increase in healthy persons (by 72.0 ± 9.5 ms) and in patients with left-sided lesions (by 68.2 ± 16.8 ms; $P > 0.05$), the patients with right-sided lesions had an RRI decrease by 117.4 ± 35.3 ms, which differed significantly from the RRI changes in both the healthy persons and the patients with left-sided lesions ($P < 0.001$).

With unpleasant stimulation, the changes in RRI showed a trend towards a difference between the three groups (ANOVA: $P = 0.09$). Similar to the pleasant stimulation,

Table 4 Emotional responses to pleasant, unpleasant, and neutral visual stimuli rated on a 7-point Likert scale*

Stimulation	Controls	VMPFC-L	VMPFC-R	Kruskal–Wallis
Pleasant	5.92 ± 0.2	6.40 ± 0.3	5.92 ± 0.5	n.s.
Unpleasant	1.42 ± 0.2	1.00 ± 0.0	1.08 ± 0.1	n.s.
Neutral	5.40 ± 0.2	5.20 ± 0.3	5.10 ± 0.4	n.s.

n.s., non-significant differences (Kruskal–Wallis test); VMPFC-L/VMPFC-R, patients with left-sided/right-sided ventromedial prefrontal cortex lesions.
*From 'extremely unpleasant' (1), 'moderately unpleasant' (2), 'slightly unpleasant' (3), 'neutral' (4), 'slightly pleasant' (5), 'moderately pleasant' (6), to 'extremely pleasant' (7).

healthy participants showed an RRI increase by 246.4 ± 112.8 ms and patients with left-sided lesions had an increase by 75.4 ± 3.2 ms, whereas patients with right-sided lesions had an RRI reduction by 101.3 ± 33.5 ms.

Moreover, there were significant changes within the control group and the group of patients with right-sided lesions. In the healthy persons, RRI increased significantly (i.e. HR actually slowed from baseline) with pleasant (842.9 ± 32.0 versus 928.8 ± 40.0 ms; *t*-test: $P = 0.0002$) and unpleasant (843.2 ± 31.7 versus 1089.0 ± 131.5 ms; *t*-test: $P = 0.03$; Fig. 1), but not neutral (854.6 ± 39.5 versus 855.9 ± 40.7 ms; *t*-test: $P = 0.85$) stimulation.

In the patients with left-sided lesions, RRI increase (i.e. HR decrease) was not significant with pleasant (881.8 ± 52.4 versus 977.2 ± 59.2 ms; *t*-test: $P = 0.12$) and unpleasant (869.9 ± 51.0 versus 943.0 ± 53.3 ms; *t*-test: $P = 0.06$) VES (Fig. 1), and absent with neutral VES (903.3 ± 44.0 versus 902.3 ± 51.1 ms; *t*-test: $P = 0.93$).

In patients with right-sided lesions, RRI decreased (i.e. HR actually increased) significantly in response to pleasant slides (964.0 ± 20.7 versus 847.4 ± 43.4 ms; *t*-test: $P = 0.02$), but not quite significantly for unpleasant slides (942.6 ± 23.0 versus 854.8 ± 42.3 ms; *t*-test: $P = 0.06$; Fig. 1). In contrast, RRI remained unchanged during the presentation of neutral slides (952.2 ± 28.4 versus 948.0 ± 31.3 ms; *t*-test: $P = 0.57$).

Blood pressure

In controls, BP_{sys} did not change with happy, sad (Fig. 2) or neutral stimulation.

In patients with left-sided lesions, there was an almost but not quite significant BP_{sys} increase (108.9 ± 5.4 versus 111.6 ± 5.0 mmHg; *t*-test: $P = 0.06$) with pleasant stimulation, and no change in BP_{sys} with unpleasant stimulation (110.6 ± 5.3 versus 111.2 ± 6.2 mmHg; *t*-test: $P = 0.80$) (Fig. 2) or neutral stimulation (114.0 ± 5.8 versus 113.5 ± 6.4 mmHg; *t*-test: $P = 0.74$).

In right-sided lesions, BP_{sys} increased significantly with pleasant (121.0 ± 7.4 versus 130.8 ± 6.7 mmHg; *t*-test: $P = 0.008$), but not significantly with unpleasant (121.4 ± 8.7 versus 127.5 ± 7.5; *t*-test: $P = 0.37$) (Fig. 2) or neutral (117.4 ± 8.2 versus 118.0 ± 8.8 mmHg; *t*-test: $P = 0.80$) stimulation.

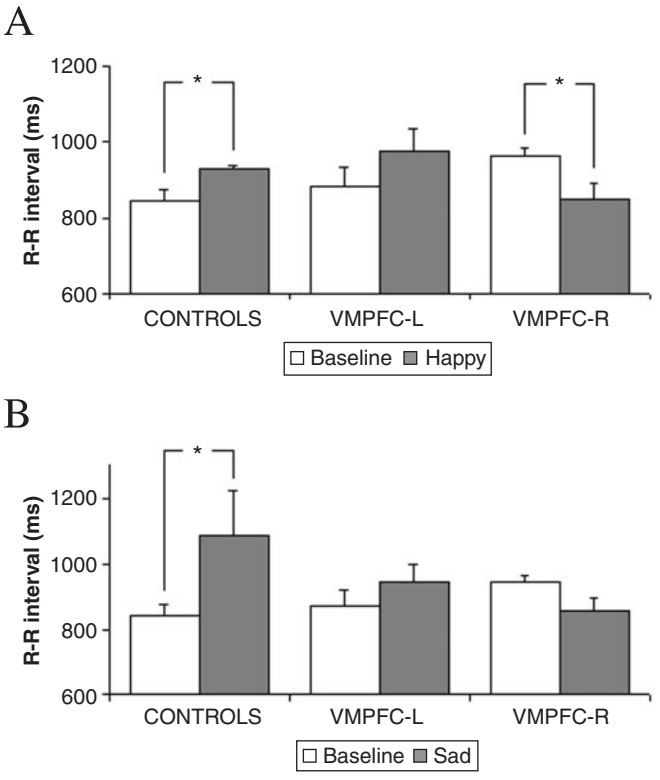

Fig. 1 Effects of pleasant (**A**) and unpleasant (**B**) emotional stimuli on RR interval in healthy subjects, patients with left ventromedial prefrontal cortex lesions (VMPFC-L) and patients with right ventromedial prefrontal cortex lesions (VMPFC-R). Significant differences from baseline preceding the presentation of emotional stimuli are indicated by $*P < 0.05$.

BP_{dia} and BP_{mean} did not change significantly in any of the three groups during pleasant, unpleasant (Fig. 2) or neutral stimulation.

Additional measures

Respiratory frequency, tidal volume, end-tidal CO_2, and oxygen saturation did not change with pleasant, unpleasant, or neutral stimulation in any of the three groups.

Discussion

In healthy persons, HR decrease with stable BP during non-stressful pleasant or unpleasant VES suggests that VMPFC interaction with emotional–autonomic modulation depends on stimulus intensity

Our healthy participants exhibited a significant decrease in HR with positive and negative, but not with neutral VES, whereas BP remained unchanged. The HR decreases during pleasant and unpleasant VES are consistent with previous studies (Davison *et al.*, 1991; Meadows and Kaplan, 1994; Bradley *et al.*, 2001), although some authors have found increased HR during happiness (Damasio *et al.*, 2000;

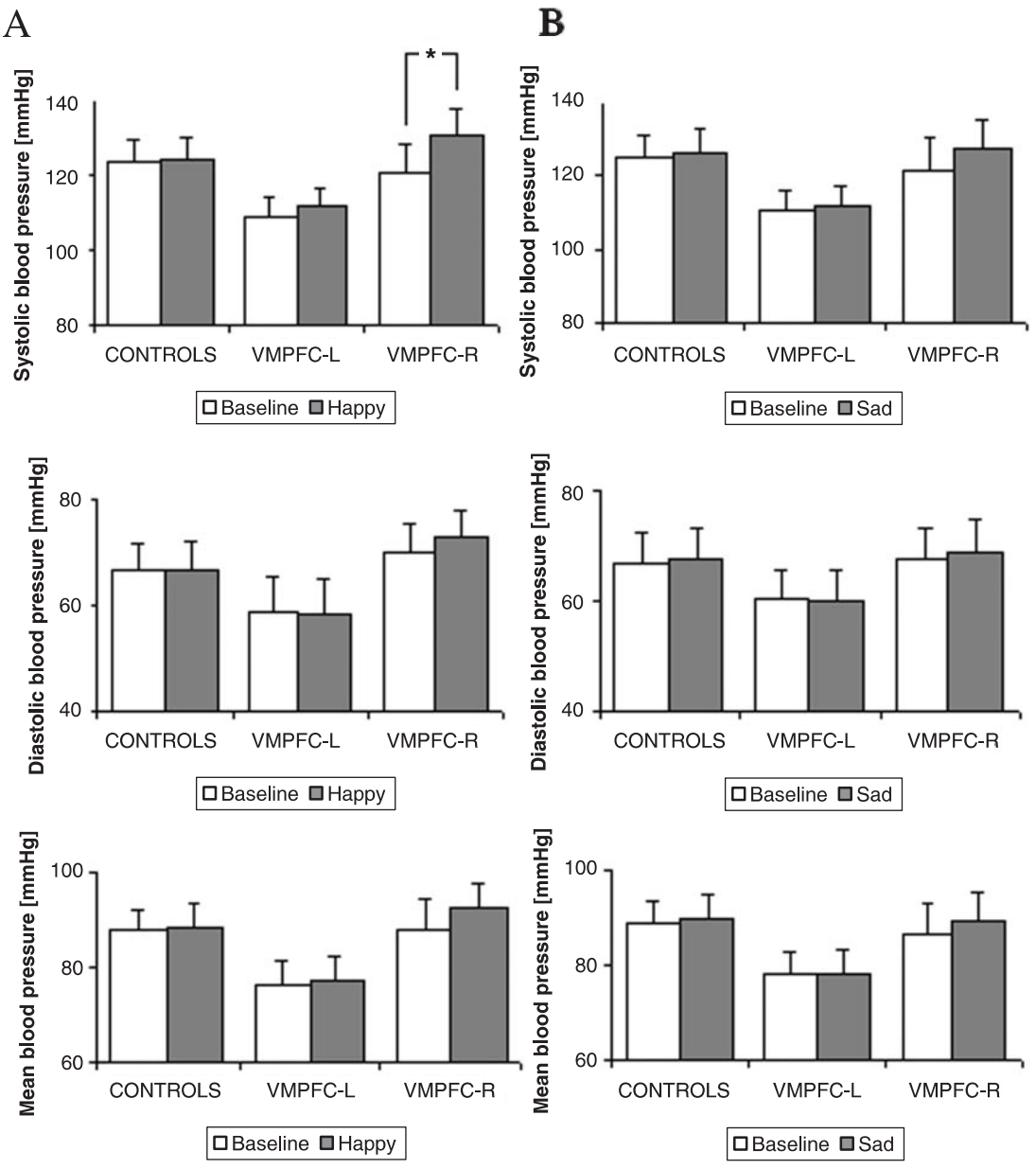

Fig. 2 Effects of pleasant (**A**) and unpleasant (**B**) emotional stimuli on systolic, diastolic and mean blood pressure in healthy subjects, patients with left ventromedial prefrontal cortex lesions (VMPFC-L) and patients with right ventromedial prefrontal cortex lesions (VMPFC-R). Significant differences from baseline preceding the presentation of emotional stimuli are indicated by $*P < 0.05$.

Labouvie-Vief *et al.*, 2003) and vagal withdrawal during sadness associated with crying (Sakuragi *et al.*, 2002). These discrepancies may be attributed to differences in the emotional stimuli and in the nature of the emotional states induced.

Emotions can be classified in a 2D affective space according to the valence (positive versus negative) and the degree of emotional arousal (relaxation versus arousal) (Bradley *et al.*, 2001). Both pleasant and unpleasant emotions can increase or decrease HR and BP depending on the arousal associated with particular emotional states (Bradley *et al.*, 2001). For example, joy, laughing and crying are associated with emotional arousal (Gross *et al.*, 1994). However, in our participants, happiness was associated with feelings of calm and relaxation, not laughter or mirth. Similarly, sadness experienced by our participants was not accompanied by weeping. Since our positive and negative VES were associated with a low level of emotional arousal, they both also resulted in similar cardiac autonomic responses. Moreover, in contrast to our experimental procedures, in the studies reporting increased HR during positive emotions, happy feelings were evoked by recall of autobiographical memories (Damasio *et al.*, 2000; Labouvie-Vief *et al.*, 2003). Yet, the process of recalling previously acquired information, even emotionally neutral, is itself associated with increased HR (Jennings *et al.*, 1990).

This response is preserved in amnesics (Diamond *et al.*, 1996), supporting a basic phenomenon associated with cognitive activity such as recalling information from memory. Also, experiencing personally-relevant emotions can elicit greater autonomic responses than viewing emotionally laden pictures or movies (Waldstein *et al.*, 2000).

Whereas our healthy controls had HR decreases but stable BP during non-stressful pleasant and unpleasant VES, healthy persons undergoing more stressful mental arithmetic and isometric exercise have shown BP increases that covaried positively with and HR increases that covaried negatively with orbitofrontal activity (Critchley *et al.*, 2000). Thus, HR decreases with unchanged BP in our healthy participants likely reflect different processing of our non-stressful stimuli versus Critchley *et al.*'s (2000) more stressful stimuli. Stimulus-specific VMPFC involvement is also supported by Damasio *et al.*'s (2000) findings (*see above*): different right and left orbitofrontal activation or deactivation during happy, sad, or fearful stimulation. Finally, animal studies suggest that the VMPFC mediates cardiovascular depressor responses with non-stressful stimulation (Owens and Verberne, 2000) but is essential for cardiovascular activation with stressful stimulation (Frysztak and Neafsey, 1994). Our findings therefore support the concept of a stimulus- (i.e. valence- or intensity-) specific VMPFC activation or deactivation (Critchley *et al.*, 2000; Damasio *et al.*, 2000).

In healthy persons, VMPFC buffers HR and BP responses to non-stressful VES, very likely by increasing cardiovagal outflow

Whereas animal studies suggest sympathoinhibitory responses during non-stressful medial prefrontal cortex stimulation (Neafsey, 1990; Owens and Verberne, 2000), the increased HR but stable BP in our healthy controls is more consistent with an increase in vagal tone than a decrease in sympathetic activity. Reduced sympathetic outflow lowers HR and BP. Increased parasympathetic outflow mainly lowers HR and has only a limited secondary effect on BP via cardiac output reduction (Spyer, 1999). Therefore, during non-stressful pleasant or unpleasant VES, there appears to be a shift of sympathovagal balance towards more prominent cardiovagal activity.

Left VMPFC lesions account for a shift in sympathetic–parasympathetic modulation towards enhanced sympathetic outflow

The findings in patients with VMPFC-L lesions, with only slight non-significant HR decreases during pleasant and unpleasant VES and slight BP increases during pleasant VES, confirm the attenuating role of the VMPFC on cardiovascular autonomic modulation in animals with non-stressful stimuli (Neafsey, 1990; Owens and Verberne, 2000). The less prominent HR and BP responses in patients with left-sided lesions than in controls also support a primary parasympathetic mediation of cardiovascular responses to left VMPFC activation. Zamrini *et al.* (1990) and our group (Hilz *et al.*, 2001) observed a shift of the sympathovagal balance towards more sympathetic outflow after left-hemisphere anaesthetization. In our patients with VMPFC-L lesions, the attenuated HR decrease and slight BP increase during pleasant VES can be ascribed to a similar shift towards sympathetic activation. Left-sided VMPFC lesions may compromise normal interaction with other left-hemisphere centres of autonomic control (e.g. insular cortex, amygdala, and hypothalamus; Benarroch, 1997) and thereby slightly enhance sympathetic activation with increased BP and buffered decrease of HR. Hence, the left VMPFC may serve as both an evaluative site in determining autonomic responses to emotional stimuli but also a modulator of other left-hemispheric, predominantly parasympathetic, autonomic centres (Benarroch, 1997).

Right-sided VMPFC lesions disinhibit HR and BP moderation and suggest a hemisphere-specific VMPFC interaction with emotional–autonomic processing

In contrast to our healthy participants or patients with left-sided lesions, patients with VMPFC-R lesions had no HR or BP decreases but had significant HR and BP increases during pleasant VES and an almost significant HR increase ($P = 0.06$) during unpleasant VES.

In animals, the electrical activation of the prefrontal cortex inhibits the sympathetic cardiovascular system and reduces BP, HR and peripheral resistance (Neafsey, 1990; Owens and Verberne, 2000; Owens and Verberne, 2001). The HR and BP increase in patients with VMPFC-R lesions suggests a disinhibition of sympathetic outflow which is not seen after VMPFC-L lesions. This can be explained by specializations of the left and right VMPFC to most potently influence ipsilateral autonomic centres. VES in patients with left VMPFC dysfunction results in less 'buffering' of HR and BP than in controls as the left VMPFC interacts less with primarily left-hemispheric centres upregulating parasympathetic control. With right VMPFC lesions, one might expect less sympathetic outflow during VES due to reduced interactions with right-hemispheric, primarily sympathetic centres. Instead, the HR and BP increases suggest a disinhibition of sympathetic centres. This 'paradoxical' HR and BP increase suggests hemisphere-specific VMPFC effects on the emotional–autonomic interaction. Such hemisphere-specific VMPFC interactions with emotional–autonomic modulation are supported by findings that healthy persons re-experiencing stressful emotions of differing valences show similar HR changes—suggesting similar arousal—but varying activations and deactivations of the left and right VMPFC (Damasio *et al.*, 2000).

In humans, VMPFC lesions have no major effect on resting autonomic modulation or adjustment to non-emotional stimuli

Autonomic activity at rest and during non-emotional autonomic challenge was similar among our three groups. Animal lesion studies also demonstrated that the VMPFC does not influence resting BP or HR (Verberne *et al.*, 1987). Our findings show that autonomic adjustment to mild physical challenge, such as metronomic breathing, a Valsalva manoeuvre, or active standing, is not compromised in patients with unilateral VMPFC lesions. Abnormal cardiovascular responses in these patients obviously depend on emotional activation. The VMPFC is more important for emotional processing than for autonomic modulation and VMPFC lesions only alter autonomic responses to an emotional trigger.

Unilateral VMPFC lesions alter emotional-autonomic interaction but have no major effect on the emotional perception of non-stressful stimuli

The altered HR and BP responses of patients to pleasant and unpleasant, but not to neutral stimuli, confirm the notion that in humans, cardiovascular effects of VMPFC dysfunction primarily manifest during emotional activation. However, VMPFC lesions had little effect on instantaneous emotional perception as ratings of emotional responses to the neutral, pleasant, and unpleasant VES were similar among our three groups. Further, the similar state anxiety scores among the three groups suggest that the autonomic differences in patients with left- and right-sided VMPFC lesions were not related to anxiety levels just before VES. Together, these findings support a primary role of VMPFC in cognitive-emotional rather than autonomic processing of stimuli.

Increased trait-anxiety levels seem to facilitate cardiovascular disinhibition in right-sided VMPFC lesions

In contrast to state anxiety scores, trait-anxiety scores were significantly higher in patients with right-sided lesions (45.9 $\pm$ 3.0) than in patients with left-sided lesions (36.2 $\pm$ 3.6) or healthy participants (36.6 $\pm$ 1.7). This finding confirms previous reports of asymmetrical processing of emotion by the left and right VMPFC (George *et al.*, 1996; Damasio *et al.*, 2000) and of anxiety being more common in persons with right-sided than VMPFC-L lesions (Damasio, 1994). Our data indicate that the right VMPFC is more important than the left for mitigating cardiovascular responses to emotional stimuli but also for moderating anxiety. Thus, the trait-anxiety scores support the concept of the right hemisphere being more involved in emotional perception and processing than the left (Ross, 1997).

Patients with right VMPFC lesions have been described as being insensitive to the future consequences of their behaviour (Bechara *et al.*, 1994; Damasio, 1994). This insensitivity has also been expressed as a lack of emotional and autonomic arousal during anticipation of consequences (Tranel *et al.*, 2002). However, these patients show skin conductance responses to some pleasant emotions (e.g. those associated with monetary reward) (Damasio, 1994; Bechara *et al.*, 1996). Such diametrical autonomic responses to emotions of different intensity or valence (Bechara *et al.*, 1994, 1996; Damasio, 1994; Tranel *et al.*, 2002) suggest instability of the interaction between emotional processing and autonomic control in patients with right VMPFC lesions.

Patients with right VMPFC lesions may manifest increased trait-anxiety and may have reduced judgement for future consequences of their behaviour because there is instability of autonomic responses with a lack of somatic markers that should normally consolidate coherent experiences of emotional autonomic interaction (Bechara *et al.*, 1994, 1996, 2000; Damasio, 1994). Instability of somatic markers with emotional stimulation may create insecurity and higher levels of anxiety, which secondarily affect cardiovascular autonomic function (Piccirillo *et al.*, 1997). Thus, higher trait-anxiety levels could magnify the excitatory cardiovascular responses to VES in the patients with right VMPFC lesions.

Sympathetic hyperexcitability associated with anxiety (Piccirillo, 1998) and frequent perception of HR increases to non-arousing stimuli of daily-life may promote unpleasant emotions or inadequate emotional responses (Critchley *et al.*, 2000; Pollatos *et al.*, 2005). Patients with right VMPFC lesions may therefore suffer a pathologically reinforcing cycle of: (i) altered somatic markers (e.g. tachycardia with stimuli that are not stressful to healthy persons), (ii) biased interoceptive perception of these markers, and (iii) subsequently higher trait-anxiety (Critchley *et al.*, 2000; Pollatos *et al.*, 2005). In patients with right VMPFC dysfunction, disinhibition of cardiovascular responses to non-stressful stimuli and altered emotional interoception with higher trait-anxiety may contribute to the emotional instability, impulsiveness, even criminal behaviour, (Anderson *et al.*, 1999; Gainotti, 2001) or other aspects of 'acquired sociopathy' described in these patients (Barrash *et al.*, 2000).

Stimulus valence has a limited effect on HR and BP responses to non-stressful VES

In our healthy controls and particularly in patients with right VMPFC lesions, HR and BP responses were more prominent with pleasant than unpleasant VES. In addition to hemisphere-specific sympathoinhibitory (right VMPFC) and cardiovagal activating (left VMPFC) effects, the hemispheres differ in how they process positive and negative affective information (Dimond *et al.*, 1976; Borod and Madigan, 2000; Damasio *et al.*, 2000; Waldstein *et al.*, 2000; Tranel *et al.*, 2002). The valence hypothesis, supported by

neuroimaging studies, holds that the left prefrontal cortex dominates in processing positive pleasant emotions and appetitive behaviours, whereas the right prefrontal cortex dominates in modulating negative emotions and aversive behaviours (Davidson, 1995; Davidson and Irwin, 1999; Damasio *et al.*, 2000).

Patients with left hemisphere lesions tend to experience negative emotions, such as sadness (Morris *et al.*, 1996; Paradiso *et al.*, 1999), whereas patients with right hemisphere damage are more prone to experiencing positive emotions, such as euphoria or mania (e.g. Starkstein *et al.*, 1989). Our patients with right VMPFC lesions may have generated more prominent HR and BP increases with positive than negative VES because their intact left VMPFC, which processes positive emotions, was relatively overactive. The valence concept is also supported by the slightly, though not significantly, more pronounced HR changes in patients with left VMPFC lesions during unpleasant (P = 0.06) than pleasant VES (P = 0.12), providing some support for preserved right-hemispheric processing of negative emotions.

However, with our non-stressful stimulation, the influence of stimulus valence only resulted in minor HR and BP differences. Therefore, we conclude that VMPFC modulation of emotional autonomic responses depends mainly on the degree of arousal associated with the stimulus rather than the valence of the stimulus (Bradley and McCanne, 1981).

Limitations of our study

Several factors should be considered while interpreting our results. Changes in respiration, end-tidal carbon dioxide level, and haemoglobin saturation can affect the cardiovascular system. However, these parameters were similar across our three groups and did not change during any of the induced emotional states. Heterogeneity of lesion extent and aetiology could also have affected our results. We highly selected patients for those with lesions exclusively or almost exclusively involving VMPFC. Thus, lesion extent and location were very similar between left and right VMPFC groups (Table 1).

Finally, possible differences in emotional perception between men and women should be considered (Brody and Hall, 1993). However, it is unlikely that different HR and BP responses in patients with left and right VMPFC lesions were due to gender differences in emotional perception (e.g. Borod and Madigan, 2000) as numbers of men and women were similar in each study group.

Conclusions

Our HR and BP findings with non-stressful pleasant and unpleasant VES suggest that in healthy persons, VMPFC interaction with emotional autonomic modulation depends on stimulus intensity and yields mainly parasympathetically mediated decrease in HR while stressful stimulation appears to increase HR and BP. Pleasant or unpleasant VES in left VMPFC lesions results in somewhat higher BP and less decrease in HR than in healthy persons suggesting that left VMPFC lesions are associated with relatively augmented sympathetic activity. The 'paradoxical' HR and BP increases seen during VES in right VMPFC lesions support the concept of a hemispheric VMPFC specialization with mediation of parasympathetic activation by the left and inhibition of sympathetic outflow by the right VMPFC.

VMPFC lesions do not significantly affect resting autonomic activity or autonomic adjustment to non-emotional, physical stressors. Although VMPFC lesions do not appear to affect the emotional perception of non-stressful emotional stimuli, right VMPFC lesions are associated with higher levels of trait-anxiety. The findings confirm the stabilizing effects of the right VMPFC on anxiety and emotional processing. They suggest a possible positive feedback between increased trait-anxiety and compromised emotional autonomic interaction with instability or inconsistency of somatic markers, resulting, for example, in increased HR and BP with daily-life, non-stressful emotions. Thus, increased trait-anxiety may contribute to emotional instability or impulsiveness, frequently observed in patients with right VMPFC lesions. Although the emotional valence of non-stressful stimuli had limited effects on cardiovascular responses, subtle signs suggest left-hemispheric dominance of cardiovascular modulation (right VMPFC lesions) in response to positive stimuli. This is consistent with the aspect of the valence hypothesis pertaining to left-hemisphere dominance for processing and responding to positive stimuli. Similarly, there was a slight right-hemispheric dominance in mediating cardiovascular response to unpleasant stimuli (left VMPFC lesions). However, the similar HR and BP responses with pleasant or unpleasant VES indicate that valence of non-stressful stimuli has less influence on VMPFC emotional-autonomic processing and somatic responses than do stimulus intensity and levels of arousal (Bradley and McCanne, 1981; Sakuragi *et al.*, 2002).

Finally, reduced parasympathetic modulation in patients with left VMPFC lesions and—even more—the sympathetic disinhibition in patients with right VMPFC lesions during common stimuli, which are non-arousing to healthy individuals, may have significant and long-term clinical relevance. Patients with reduced parasympathetic outflow and increased sympathetic activity or even sympathetic hyperexcitability are at higher cardiovascular risk including, e.g. the development of arterial hypertension or cardiac arrhythmias (e.g. Oppenheimer *et al.*, 1991; Hilz *et al.*, 2002). In patients with prefrontal cortex lesions, sympathetic hyperexcitability may not only contribute to behavioural abnormalities but may also constitute a significant risk factor for myocardial damage (Oppenheimer *et al.*, 1991) and even sudden death (e.g. Samuels, 1993; Critchley *et al.*, 2005). In animal studies, increased sympathetic tone has resulted in diffuse cardiac damage with myocytolysis, characterized by muscle cell

vacuolation and necrosis, and by monocytic infiltration and haemorrhage (Oppenheimer *et al.*, 1991). In humans, sudden death may result even from minimal brain lesions (Black and Graham, 2002). Therefore, our findings of altered HR and BP responses, even with non-stressful stimuli, suggest that patients with VMPFC lesions, particularly right-sided ones, should be monitored for psychiatric disorders and studied further to assess their risk for cardiovascular abnormalities, such as hypertension, arrhythmias, or electrocardiographic abnormalities.

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