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Research report

Fear processing is differentially affected by lateralized stimulation of carotid baroreceptors

Elena Makovac [a,*], Sarah Garfinkel [b,c], Andrea Bassi [d], Barbara Basile [a], Emiliano Macaluso [a], Mara Cercignani [a,e], Giovanni Calcagnini [f], Eugenio Mattei [f], Matteo Mancini [g], Daniela Agalliu [d], Pietro Cortelli [h,i], Carlo Caltagirone [d], Hugo Critchley [b,c] and Marco Bozzali [a]

[a] Neuroimaging Laboratory, Santa Lucia Foundation, Rome, Italy
[b] Psychiatry, Brighton and Sussex Medical School, University of Sussex, Falmer, Brighton, United Kingdom
[c] Sackler Centre for Consciousness Science, University of Sussex, Falmer, Brighton, United Kingdom
[d] Department of Clinical and Behavioural Neurology, Santa Lucia Foundation, Rome, Italy
[e] Brighton & Sussex Medical School, Clinical Imaging Sciences Centre, University of Sussex, Brighton, United Kingdom
[f] Department of Technology and Health, Italian Institute of Health, Rome, Italy
[g] Department of Engineering, University of Rome "Roma Tre", Rome, Italy
[h] Neurological Clinic, Department of Neurological Sciences, Alma Mater Studiorum-University of Bologna, Bologna, Italy
[i] IRCCS Institute of Neurological Sciences of Bologna, Italy

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ABSTRACT

Information processing, particularly of salient emotional stimuli, is influenced by cardiovascular afferent signals. Carotid baroreceptors signal the state of cardiovascular arousal to the brain, controlling blood pressure and heart rate via the baroreflex. Animal studies suggest a lateralization of this effect: Experimental stimulation of the right carotid sinus has a greater impact on heart rate when compared to left-sided stimulation. We tested, in humans, whether the processing of emotional information from faces was differentially affected by right versus left carotid afferents. To achieve so, we used an automated neck suction device to stimulate the carotid mechanoreceptors in the carotid sinus (parasympathetic pathway) synchronously with functional magnetic resonance imaging (fMRI) acquisition whilst participants were engaged in an emotional rating task of fearful and neutral faces. We showed that both right and left carotid stimulation (CS) influenced brain activity within opercular regions, although a stronger activation was observed within left insula during right stimulation compared to left stimulation. As regards the processing of fearful faces, right, but not left carotid stimulation attenuated the perceived intensity of fear, and (albeit to a lesser extent) enhanced intensity ratings of neutral faces. Mirroring the behavioural effects, there was a significant expression-by-stimulation interaction for

Abbreviations: fMRI, Functional Magnetic Resonance Imaging; HRV, Heart Rate Variability; CS, Carotid Stimulation; RMSSD, Square root of the mean of the squares of differences between adjacent N–N intervals; VAS, Visual Analogue Scale; ITI, Inter-Trial Interval; BOLD, Blood Oxygenation Level Dependent; ROI, Region of Interest; FWE, Family Wise Error.

* *Corresponding author*. Neuroimaging Laboratory, Santa Lucia Foundation, IRCCS, Via Ardeatina 306, 00179 Rome, Italy.
E-mail address: e.makovac@hotmail.it (E. Makovac).

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right carotid stimulation only, when bilateral amygdala responses were attenuated to fear faces and amplified to neutral faces. Individual differences in basal heart rate variability (HRV) predicted the extent to which right carotid stimulation attenuated amygdala responses during fear processing. Our study provides unique evidence for lateralized viscerosensory effects on brain systems supporting emotional processing.

1. Introduction

Brain and body interact to support perceptions, thoughts and feelings (Critchley, Eccles, & Garfinkel, 2013; Critchley, Mathias, & Dolan, 2002; 2004). The processing of threat is coupled to physiological arousal via the autonomic nervous system, which facilitates evasive reactions, and enhances feelings of fear. Cardiovascular arousal is signalled to the brain by the activation of arterial baroreceptors, which respond to increased intraluminal pressure at systole. Vagus and glossopharyngeal nerves carry these signals to the brainstem where they trigger the baroreflex, lowering blood pressure by (parasympathetic) slowing of the next heartbeats and inhibiting (sympathetic) vasoconstriction within muscle vascular beds (reviewed Fadel, Ogoh, Keller, & Raven, 2003). Emotional challenges inhibit the baroreflex, allowing heart rate and blood pressure to rise together (Gianaros et al., 2009). This decreases heart rate variability (HRV), an index of cardiac parasympathetic effects (Thayer & Lane, 2000; Thayer, Hansen, Saus-Rose, & Johnsen, 2009), and a proposed signature of wellbeing and capacity for emotional regulation (Thayer & Brosschot, 2005; Thayer & Lane, 2000).

Thus, phasic baroreceptor firing informs the brainstem about the strength and rate of heartbeats. This information is also relayed up the neuraxis to insular cortex (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004) and amygdala (Cechetto & Calaresu, 1984, 1985). Natural fluctuations in baroreceptor activity can modulate memory encoding (Garfinkel et al., 2013), pain processing (Edwards, Inui, Ring, Wang, & Kakigi, 2008; Gray, Rylander, Harrison, Wallin, & Critchley, 2009) and appraisal of emotional stimuli (e.g., Garfinkel et al., 2014; Gray et al., 2012). Artificial stimulation of baroreceptors can be achieved using external neck suction (Cooper & Hainsworth, 2009) which increases transmural pressure within the carotid sinus, and enhances parasympathetic cardiovascular drive. Carotid stimulation (CS) can be applied to study the influence of baroreceptor afferent activity on psychological processes and underlying brain function.

Recently, CS was shown to decrease the perceived intensity of fearful faces and enhances the intensity of neutral faces via changes in amygdala activation (Makovac, Garfinkel et al, 2015). These findings endorse the role of the amygdala in the integration of viscerosensory information with fear processing (Garfinkel et al., 2014; Makovac, Garfinkel et al, 2015; Phelps & LeDoux, 2005) and extend previous evidence showing CS modulates amygdala and insula activity at rest, when engaged in a cognitive task, and during emotional challenges (Basile, Bassi, Calcagnini, Caltagirone, & Bozzali, 2013, Basile, Bassi, Calcagnini, Strano et al, 2013).

Animal studies suggest that perturbation of the right carotid sinus induces greater effects on heart rate when compared to left-sided stimulation (Greene, Brunner, & Shoukas, 1986; Worthen et al., 1972). In humans, there is some evidence for the superiority of right over left CS (Furlan et al., 2003; Tafil-Klawe, Raschke, & Hildebrandt, 1989). Heart rate slowing is observed to be greater during right, compared to left CS (Furlan et al., 2003; Tafil-Klawe et al., 1989), although other studies find no difference between the two sides (Williamson & Raven, 1993). In hypertensive individuals, therapeutic use of *baroreflex activation therapy* suggests that right-sided baroreflex activation elicits a more profound long term effect on blood pressure than bilateral or left-sided (de Leeuw et al., 2015). Such lateralization is proposed to have a basis in asymmetric cardiac innervation and baroreceptor inputs to brain (Hagemann, Randall, & Armour, 1975; Tafil-Klawe et al., 1989).

So far, there has been no assessment in humans of whether unilateral CS elicits differential psychological or neural responses. Motivated by observed bilateral CS effects on fear processing (Makovac, Garfinkel et al, 2015), we tested the hypothesis that unilateral right and left CS will have a different impact on cardiac activity, brain activations and behavioural responses during the appraisal of fearful and neutral faces. Specifically, we predict differential amygdala engagement, reflected in a greater impact of right CS on the subjective appraisal of fear. At both neural and behavioural levels, we expect to observe a significant emotion-by-CS interaction with right CS only, where amygdala's activity will decrease during fearful appraisal and increase during neutral appraisal. In accordance with this, we predict a decrease in fearful ratings and increase in neutral ratings during right CS, mirroring the results with our previous study using bilateral CS (Makovac, Garfinkel et al, 2015). Overall, we sought to gain greater insight into forebrain asymmetry in emotion (Davidson & Fox, 1982; Grimshaw & Carmel, 2014) and its putative basis in peripheral asymmetry within the autonomic nervous system (Craig, 2005; Craig, 2014).

2. Materials and methods

2.1. Participants

Twenty right-handed volunteers (11 females/9 males; mean age = 24.15 years; SD = 3.32; range, 20–31) with no neurologic,

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