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Reduced startle reflex and aversive noise perception in patients with orbitofrontal cortex lesions

Alessandro Angrilli[a,b,*], Marta Bianchin[a], Silvia Radaelli[a], Giannettore Bertagnoni[c], Marco Pertile[d]

[a] *Department of General Psychology, University of Padova, Via Venezia 8, 35131 Padova, Italy*
[b] *CNR Institute of Neuroscience, Section of Padova, Italy*
[c] *Department of Neuroscience, San Bortolo Hospital, Vicenza, Italy*
[d] *Department of Mechanical Engineering, University of Padova, Italy*

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Abstract

In the present study, the primary emotional response represented by the acoustic startle reflex was investigated in a group of six male patients, selected with lesions of the orbitofrontal cortex, and twenty matched healthy controls. Accurate neuropsychological assessment and lesion mapping showed relatively spared cognitive functioning in the patient group, most of the lesions being confined to the bilateral polar orbitofrontal cortex. Patients had significant inhibition of startle amplitude, together with a reduced self-evaluated perception of the unpleasantness of the acoustic probe stimulus. Results add to current literature on the circuit of the human startle reflex, by suggesting cortical–limbic down-regulation of the orbitofrontal cortex on the main startle pathway, probably at the level of the activating reticular system. The orbitofrontal cortex, together with the amygdala, is confirmed to represent the main center organizing both primary and secondary learned aspects of emotions.

Keywords: Startle reflex; Orbitofrontal cortex; Frontal cortex; Emotion; Amygdala; Human

1. Introduction

The prefrontal cortex, especially the subregion termed orbitofrontal cortex (OFC) is the highest order associative cortical region of the brain. Lesions of the dorsolateral prefrontal cortex are typically associated with a number of deficits in high level cognitive processes (Stuss & Benson, 1984), whereas lesions confined to the orbital and ventromedial frontal cortex are rare, and produce mainly behavioral and emotional impairment which resembles some psychiatric disorders such as psychopathy and depression (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Angrilli, Palomba, Cantagallo, Maietti, & Stegagno, 1999; Damasio, Tranel, & Damasio, 1990; Stuss & Benson, 1984). However, within the emotional domain, the specific role of OFC[1] with respect to deeper limbic structures such as the amygdala – the main subcortical organizer of emotional fear responses – is not clear. In principle, the amygdala seems to be mainly involved in primary psychobiological aspects of emotional responses (Bechara, Damasio, Damasio, & Lee, 1999; LeDoux, 1995), and the OFC in learning social behaviors and

* Corresponding author at: Department of General Psychology, University of Padova, Via Venezia 8, 35131 Padova, Italy. Tel.: +39 049 827 6692; fax: +39 049 827 6600.
E-mail address: alessandro.angrilli@unipd.it (A. Angrilli).

[1] To avoid confusion, it is necessary to clarify briefly the controversial definition and boundaries of the OFC. In most cases, it is a matter of definition, but this confusion has been increased by the poorly defined functional role and subdivision of this associative cortex. Depending on author, the OFC corresponds to ventromedial PFC only (Anderson & Tranel, 2002), Brodmann's areas (BA) 11, 12, 13, 25, or includes the lateral BA 47 and polar frontal cortex BA 10 (Krawczyk, 2002; Rolls, 1999) and anterior cingulate BA 24 and 32 (Öngür & Price, 2000). A survey of literature (Stuss & Benson, 1984) reasonably divides the prefrontal cortex (PFC) into dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (anterior BA 24 and 32) and orbitofrontal cortex (OFC). The OFC in turn may be divided into two subdivisions, ventromedial PFC (BA 11, 12, 13, 25) and polar PFC (BA 10 and rostral BA 9, Ramnani & Owen, 2004). In the present study, all patients had lesions mainly in the polar subdivision of the OFC.

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in complex secondary aspects of emotions (Adolphs, 1999). However, given the close bidirectional connection between the anterior temporal pole, which includes the amygdala, and the ventromedial-orbitofrontal cortex (Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003; Rolls, 1999,2004), this functional distinction may be unrealistic (Adolphs, 1999; Damasio, 1995).

Among the primary emotional responses under subcortical control is the startle reflex, an automatic defensive response elicited by intense, sudden stimuli, such as thunder or lightning, which is highly preserved and very similar in all mammals (Anthony, 1985). A large body of literature has shown how this primary reflex, elicited by aversive noxious stimulation is increased by fearful or anxiogenic background emotional states (Grillon & Davis, 1995; Lang, Bradley, & Cuthbert, 1990). Studies on rats have shown that both the startle reflex and its modulation depend on amygdala facilitatory efferents operating on the main circuit of the acoustic startle response in the reticular system (Davis, 1992a,b; Davis, Hitchcock, & Rosen, 1991). Notwithstanding differences in emotion circuits among species, a few studies on neurological patients have substantially confirmed the relevance of the amygdala on the startle reflex in humans. In fact, in the rare case of a patient with a selective lesion of the right amygdala, we have previously shown an overall impairment of the startle reflex, especially for the response contralateral to the lesion site, and a loss of the typical startle modulation elicited by an aversive emotional background (Angrilli et al., 1996).

With respect to the amygdala and subcortical structures, much less well known is the role and influence of the frontal associative cortex relevant for emotions on the startle reflex. This research issue is in fact more critical and demanding, as animals have a small, functionally reduced prefrontal cortex, and are therefore expected to differ substantially from the final target represented by humans. Starting from the observation of the insensitivity to punishment and aversive stimuli, and the reduced emotional autonomic response typically exhibited by patients with frontal damage (Angrilli et al., 1999; Critchley et al., 2003; Damasio et al., 1990) we hypothesized that, as in patients with lesions of the amygdala, those with limited focal lesions of the orbitofrontal cortex would show a reduced startle response and reduced perception of the unpleasantness of the startle probe.

2. Method

2.1. Participants

Six male patients (mean age = 25.83, S.D. = 5.4, range = 20–35) with polar OFC lesions following a traumatic brain injury, participated in the study after we obtained their informed consent. All subjects were former in-patients from the neurological rehabilitation program of the San Bortolo Hospital in Vicenza.

All patients had suffered a traumatic brain injury, five as a consequence of a car accident (frontal closed head injury), and patient RS (see Table 1) as a consequence of a skiing accident (frontal skull fracture). Although head trauma may involve diffuse lesions, only patients with detectable lesions in the polar frontal cortex were selected for this study, with the help of the author G.B. (a neurologist). Since it is difficult to collect a sample with very confined lesions, a double criterion was planned to guarantee a selection of a homogenous sample of patients: lesion location at the polar OFC, and limited cognitive deficits, which are more typically associated with dorsolateral prefrontal cortex lesions. Patients were therefore administered a battery of neuropsychological tests assessing both general cognitive ability and frontal lobe functioning (see Table 1).

Patients with large lesions involving the dorsolateral prefrontal cortex or with more than two significantly impaired neuropsychological functions were excluded from selection. Neuropsychological screening revealed attention deficits on the Trial Making Test B in four patients, on the Tower of London in two, on the Wisconsin Card Sorting Test in one (Table 1).

From each patient, MRI or CT scans were collected and their lesions were mapped onto standard brain templates (Damasio & Damasio, 1989) in order to obtain an average map of group lesion. The final map was obtained through (1) scanning of the radiograph, (2) manual mapping of the lesion onto a standard template by means of Photoshop 6.0, (3) alignment of template sections into a 3D representation of the brain with a Matlab program, (4) combination of all individual lesion maps into a colored unitary map, (5) projection of the average lesion on the lateral surface of the brain (Fig. 1A and B) and on a specific coronal section at the level of the maximum extension of the group lesion (Fig. 1C). The final maps of the lesions confirmed the validity of the criterion based on the selection of a homogenous sample of patients. All patients had lesions in the polar subdivision of the orbitofrontal cortex, including the rostral portion of the superior and inferior frontal gyri, corresponding to the whole Brodmann's area 10 and the rostral portion of area 9 (polar frontal cortex according to Ramnani & Owen, 2004). In a few patients, the lateral portion of Brodmann's areas 9, 45 and 46 were also involved (Fig. 1A–C). Lesions were bilateral, typical of closed

Table 1
Performance of each patient on main tests used for neuropsychological assessment (values represent *z*-scores compared with normative data—an absolute *z*-score > 2 indicates significant impairment in that test) and raw data of the three variables associated to startle reflex

Patients	BI	BR	RS	S.D.	VM	ZD
Neuropsychological measures						
Raven	−1.16	0.92	0.5	1.32	0.93	0.65
Tower of London	2.19	0.27	−0.27	3.25	0.81	0.27
WCST	1.44	3.2	1.15	−0.68	−0.32	0.42
TMT A	1.54	−0.59	−0.57	−0.87	2.16	1.01
TMT B	7.96	2.13	−0.87	−0.43	2.32	3.83
TMT B–A	8.44	2.93	−0.85	0.07	1.32	3.86
Selective attention test	−1.12	−1.26	0.06	0.66	–	0.07
Phonemic fluency	−1.89	−0.89	−0.85	0.21	−0.28	0.09
Semantic fluency	−0.74	−0.34	0.9	1.13	−0.21	0.33
Story memory	0.62	−1.13	−1.31	1.16	−0.25	1.05
Startle variables						
Self-perceived unpleasantness	4	8	3	3	3	6
Mean amplitude (μV)	1.823	0.166	1.649	3.004	0.132	0.013
Latency (ms)	85	76	65	78	73	58