Negative brain: An integrative review on the neural processes activated by unpleasant stimuli

Luis Carretié *, Jacobo Albert, Sara López-Martín, Manuel Tapia

Facultad de Psicología, Universidad Autónoma de Madrid, 28049 Madrid, Spain

A R T I C L E   I N F O
Available online 23 July 2008

Keywords:
Emotion
Danger
Pain
Repugnance/disgust
Amygdala
Mediodorsal and pulvinar thalamic nuclei
Anterior insula
Ventricomedial prefrontal cortex
Anterior cingulate cortex
Visual cortex
Motor cortex
Striatum
Hippocampus

A B S T R A C T

Evolutionary pressure has led the nervous system to guarantee rapid and intense responses to negative events (dangerous, harmful or repugnant). Thus, the ‘negative brain’ (the set of neural mechanisms triggered by unpleasant or negative stimuli) is equipped with several specific characteristics. This review organizes the current data on the human negative brain in three blocks. Firstly, the “Input mechanisms” block describes those structures responsible for the rapid distribution of all sensory information. Secondly, the “Evaluation systems” block refers to the key pieces: those responsible for evaluating negative consequences of stimulation and deciding which response is the most appropriate for coping with them. Thirdly, the “Associated and output processes” block describes how evaluative elements may interact with other brain structures to modulate attention, store and recover situational information, activate defense/withdrawal motor programs (or plan new actions) and develop autonomic/motor actions to cope with the unpleasant event. Finally, an integrative summary that serves as a tentative model of the negative brain is provided.

© 2008 Elsevier B.V. All rights reserved.

1. Introduction

Life, in the course of its evolution, has had to deal with a considerable number and variety of hazards that put at risk the physical integrity and even the survival of organisms. The response to this permanent pressure has been the development of a wide variety of sophisticated and effective defensive and withdrawal strategies, ranging from claws or shells to camouflage or speed. In the case of humans, the main defensive tool is the brain. In fact, the human brain circuitry devoted to responding to and coping with dangerous, harmful or repugnant situations (which will all be referred to as ‘unpleasant’ or ‘negative’ throughout this review) is probably richer than that of any other life form.

Negative events require processing and response resources to be more intensely and urgently mobilized. This urgency would have obvious adaptive and evolutionary advantages: the consequences of a negative event are often much more dramatic than the consequences of ignoring or reacting slowly to neutral or even appetitive stimuli (Ekman, 1992; Ohman et al., 2000). Indeed, several studies indicate that negative events elicit more rapid and more prominent responses than neutral or positive events. Psychological research has shown that this ‘negativity bias’ is manifested through diverse response systems, including those related to cognitive, emotional, and social behavior (Cacioppo and Gardner, 1999; Taylor, 1991). Since non-negative events with an arousal value similar to that of negative events (the arousal dimension ranges from calming to arousing) do not trigger this bias, it is assumed that it is particularly explained by their valence (which ranges from negative or unpleasant to positive or pleasant). Valence and arousal are two affective dimensions widely considered to explain the principal variance of the emotional meaning (Lang et al., 1993; Russell, 1979; Smith and Ellsworth, 1985).

With respect to brain research, the existence of the negativity bias has received recent experimental support, since stronger or faster neural responses to unpleasant than to neutral and pleasant events have been reported (Carretié et al., 2001, 2003; D’Esposito et al., 2000; Ito et al., 1998; Kawasaki et al., 2005; Mourão-Miranda et al., 2003; Northoff et al., 2000; Pourtois et al., 2004, 2005; Smith et al., 2003; Williams et al., 2004). Interestingly, since evolutionary success requires the nervous system to guarantee a rapid and intense reaction even when recognition of danger clues is difficult and does not reach awareness (e.g., they are brief, occluded, or with poor contrast), the brain bias towards negative stimuli is manifested even when they are unconsciously perceived. Thus, in conditions of restricted awareness, the neural response to negative stimuli is higher than that of non-negative ones (Carretié et al., 2005; Liddell et al., 2005; Whalen et al., 1998; Williams et al., 2004). Studies on blindsight (i.e., a lesion that prevents conscious perception of visual stimuli) could provide convergent findings (e.g., de Gelder et al., 1999).
It is important to indicate at this point that circuitry that computes urgent utility (e.g., avoidance of a dangerous event) often diverges from the circuitry subserving deep identification and discrimination (LeDoux, 2000; Shizgal, 1999). Hence, the negativity bias would be in part supported by specific neural mechanisms that are less involved in non-negative situations. In the ‘urgency circuits’, rapidity is the key issue, at the cost of some precision. The opposite trend would apply to the ‘deep processing circuits’, where precision and accuracy are the main concerns, at the cost of speed. This dual strategy can be illustrated by considering the two different neural systems for processing visual information. One of them carries low-quality information (i.e., without high spatial frequencies and with poor color information) but rapidly provides, as explained later, visual information to areas important in the response to negative stimuli such as the ventromedial prefrontal cortex (VMPFC: Bar et al., 2006) or the amygdala (Vuilleumier et al., 2003). This system starts out in the magnocellular cells of the lateral geniculate nucleus (LGN) of the thalamus, and is often referred to as the ‘magnocellular pathway’. The other system is more accurate, but directs information exclusively to the visual cortex (Merigan and Maunsell, 1993), and allows a deep exploration of the stimulation. It is usually called the ‘parvocellular pathway’, in reference to the LGN cells in which it originates (e.g., Livingstone and Hubel, 1987). In fact, negative stimuli appear to preferentially make use of the magnocellular pathway to rapidly reach subcortical (Vuilleumier et al., 2003) and cortical processing areas (Carretié et al., 2007; Pourtois et al., 2005).

2. A definition of ‘negative brain’

We shall refer to the neural circuitry involved in the reaction to unpleasant events as the ‘negative brain’. This term intends to illustrate that structures activated by negative events deeply interact, as we are about to see, in order to achieve a unique objective (i.e., efficiently coping with unpleasant situations), so they may be considered a coherent goal-directed neural entity. But it is important to indicate here that the structures constituting the negative brain may participate in other affective (and non-affective) processes, so they are not exclusively activated by negative events; rather, they are preferentially activated by them.

In this regard, a relevant question is whether a ‘positive brain’ also exists (i.e., a set of neural structures that are preferentially activated by emotionally positive situations). Indeed, a set of neural circuits responding to positive events has been recently described (Burgdorf and Pansepp, 2006), and strong theoretical and experimental support has been provided for a segregation (at least partial) of neural circuits in charge of coping with negative situations and those activated in positive situations (see reviews in Cacioppo and Gardner, 1999; Davidson and Irwin, 1999; Lang et al., 1997). The ‘positive brain’ would even be dominant in certain situations, namely in those in which stimuli count with mild arousing content. Thus, an advantage in the processing of positive stimuli (‘positive offset’: Cacioppo and Gardner, 1999) is observed in response to soft emotional items such as positive, negative and neutral words or facial expressions (e.g., Carretié et al., 2008; Herbert et al., 2006; Kanske and Kotz, 2007; Kissler et al., 2006), which are less arousing than other stimuli such as affective pictures (Lang et al., 1998). However, when emotional stimuli are markedly arousing, and those with negative content clearly signal threat or pain, the ‘negative brain’ would dominate and the negativity bias would become evident (Cacioppo and Gardner, 1999).

The negative brain can be divided into three blocks of neural mechanisms (Rolls, 2000). First, one block (‘input mechanisms’) would be responsible for the initial distribution of sensory information to further levels of processing. A second block (‘evaluation systems’) includes those structures that would be in charge of assessing the risks or negative consequences derived from the situation and deciding on the most appropriate response for minimizing them. And third, a group of processes or tools by which evaluative systems can modulate attention, memory, action planning, and autonomic/motor execution to better cope with the negative event (‘associated and output processes’ block). The present review is organized in accordance with this three-block structure taking into account that, in this field, research in humans has focused almost exclusively on the visual modality.

3. Input mechanisms

Sensory information is initially distributed by the thalamus. The best-established line of distribution of visual information runs from the LGN of the thalamus to the visual cortex. The visual cortex then sends the processed information to the amygdala (e.g., Emery and Amaral, 2000), ventromedial prefrontal cortex or VMPFC (e.g., Bar et al., 2006) and insula (e.g., Gallese et al., 2004), the three evaluative structures of the negative brain, as we shall see later. In a parallel way, the thalamus sends direct projections to these evaluative structures. These direct connections from thalamus have not yet been well characterized, particularly with respect to latency-related issues (i.e., the moment in which they enter in action). Current data suggest that at least two thalamic nuclei, the pulvinar and the mediodorsal (MD), play a particularly important role in these connections. The pulvinar nucleus is clearly involved in visual processing, and several studies report on its connections with the amygdala (Romanski et al., 1997), insular cortex (Clascá et al., 1997; Romanski et al., 1997), and VMPFC (Cavada et al., 2000; Morecraft et al., 1992; Romanski et al., 1997). In humans, pulvinar lesions indicate that this nucleus plays a significant role in generating response to visual threat (Ward et al., 2005). Meanwhile, the MD nucleus, which is located at the hub of multiple transmission lines, probably also plays an important role in transmitting key signals necessary for an efficient defense response. In fact, it is also connected to the amygdala (Li et al., 2004), insula (Clascá et al., 1997), and VMPFC (Kuroda et al., 1998). In line with this proposal, studies in other species suggest that the MD intervenes in fear conditioning (Li et al., 2004), since its lesion impairs this type of learning. According to these data, the MD would participate in the encoding of stimuli, and provide this information to the structures with which it is connected. As a consequence, MD lesions produce emotional dysfunctions (see a review in Oyoshi et al., 1996). Other thalamic nuclei could also connect to evaluative systems, but data on thalamic behavior in response to emotional stimuli are still conspicuously scarce.

A key issue concerns whether thalamic nuclei mentioned above send the information to key elements of the negative brain in parallel to the information transmitted from the LGN to the visual cortex (i.e., whether visual information that reaches evaluative structures necessarily proceeds from the visual cortex or not). The important role of direct thalamo-amygddalar circuits in the response to negative stimuli is well-established in studies in animals (see a review in LeDoux, 2000), but data in humans are still scarce and inconclusive. There are data to suggest that, in fact, the pulvinar nucleus provides direct visual information to the amygdala that has not been processed previously by the visual cortex (de Gelder et al., 1999; Morris et al., 1999), but the interpretation of these scarce data could admit alternative explanations (see Vuilleumier, 2005). In any case, if the pulvinar (and/or MD and/or other thalamic nuclei) is finally found to send information not processed by the visual cortex to the amygdala, there is no reason to discard the possibility that, since it is also connected to other evaluative elements of the negative brain (such as the insular cortex or VMPFC), these cortical areas also receive this crude (magnocellular), but rapid, visual information. In fact, as explained below, VMPFC response latencies to negative events would be in line with this possibility.

4. Evaluation systems

According to current data, the elements making up the evaluative block of the negative brain (those in charge of evaluating the risks of the situation and deciding a response) are the amygdala, the anterior
insula, and the VMPFC. Evaluative elements share several characteristics. First, all of them receive direct sensorial inputs from sensory cortices or sensory nuclei. Second, they have direct access to output systems (later described). It should be indicated that these three elements are deeply interconnected (see Emery and Amaral, 2000 for amygdala-VMPFC mutual projections, Clascá et al., 1997 for those between the anterior insula and amygdala, and Cavada et al., 2000; Morecraft et al., 1992 for VMPFC and insula interconnections), so that all of them can modulate the activity of one another.

4.1. Amygdala

The amygdala is the most well-known element of the negative brain. This subcortical set of nuclei does not respond exclusively to negative emotional events (see, e.g., Balleine and Killcross, 2006; Hamann et al., 2004). However, when both positive and negative stimuli are presented, responses to the latter tend to be greater (see reviews in Calder et al., 2001; Phan et al., 2002; Phelps, 2006; Vuilleumier, 2005; Wager et al., 2003; Zald, 2003). Animal studies show that the lateral amygdala receives direct information from the thalamus, and also from sensory cortices, as previously explained (e.g., LeDoux, 2000). The former information is poor (magnocellular, in the case of visual inputs), but, since it is not processed by sensory cortices, it quickly reaches the amygdala. This short thalamo-amygdalar circuit permits the organism to react rapidly to danger. Indeed, the amygdala is connected to autonomic and motor executive structures that will be described later, such as the hypothalamus and periaqueductal gray (PAG) area (Emery and Amaral, 2000; LeDoux, 2000), and is capable of modulating the activity of sensory areas through its projections to auditory and visual cortices (Adolphs, 2004; LeDoux, 2000). As already indicated, some studies suggest that a pulvino-amygdalar direct transmission line (without the intervention of the visual cortex) exists in humans (de Gelder et al., 1999; Morris et al., 1999).

Despite the clear importance of the amygdala in the human defense circuitry, it is critical to stress that an intact amygdala appears not to be obligatory for basic fear or defense responses to be produced, at least in primates. Though it is often assumed that defense-related information necessarily passes through (and is distributed by) the amygdala, the fact is that there are experimental data showing that selective lesions of the amygdala (not affecting other temporal-lobe structures or fibers of passage coursing through the amygdala) do not extinguish fear responses to danger-related stimuli (see Izquierdo et al., 2005; Kalin et al., 2001). As we shall explain below, other evaluative elements may also receive sensory inputs, emotionally assess them and connect to executive structures without the collaboration of the amygdala.

4.2. Ventromedial prefrontal cortex

The prefrontal cortex hosts a rich variety of cognitive and affective functions, and therefore constitutes an area in which attention, memory, and different emotional processes interact. As in the case of amygdala, VMPFC responds also to non-negative stimuli (Burgdorf and Panksepp, 2006; O’Doherty et al., 2003). However, as explained below, data exist showing more intense and faster VMPFC responses to negative events. There is a broad consensus that the prefrontal areas mainly involved in the response to negative events are ventral (or orbitofrontal) and medial. We shall label the combination of the two areas as “ventromedial PFC” (VMPFC) (it should be indicated, however, that this same term is applied, by some authors, exclusively to the ventral part of the medial prefrontal cortex, and not to the sum of ventral and medial prefrontal cortices). The VMPFC seems not only to intervene, but indeed to constitute a key element, in the neural response to negative events. Thus, in primates, a lesion in the VMPFC produces impairments of defensive behavior similar (or even more severe) than those caused by amygdala lesions (Izquierdo et al., 2005). In this same line, several studies in humans have reported more intense VMPFC activation in response to negative events than in response to non-negative events (Carretié et al., 2006; Kawasaki et al., 2001, 2005; Northoff et al., 2000; Simpson et al., 2000), even when stimuli are unconscious or perceived (Carretié et al., 2005; Liddell et al., 2005).

Interestingly, this VMPFC response to negative events is produced very rapidly (100–150 ms from the stimulus onset: Carretié et al., 2005; Kawasaki et al., 2001; Northoff et al., 2000; Simpson et al., 2000). This VMPFC capability for fast activation is an interesting issue that has received attention from Neuroscience only recently. Important in the explanation of this capability is the fact that the VMPFC is equipped with groups of neurons specialized in processing sensory information. For example, this prefrontal area has neurons specializing in the identification of objects and faces (Tanibuchi and Goldman-Rakic, 2003). Several findings indicate that the VMPFC receives inputs from early stages of the visual cortex (e.g., V2: see Bar et al., 2006; Bar, 2003). As indicated in the previous section, direct visual input from the thalamus cannot be discarded on the basis of current data, since the pulvinar and MD nuclei of the thalamus (which send important and direct projections to the VMPFC) manage visual information. Some recent data even suggest that VMPFC response to visual stimuli may be more rapid than fusiform gyrus (a part of the visual cortex) response (Bar et al., 2006). In any case, key, significant elements of the visual scene can be rapidly extracted and detected by the VMPFC. Although the visual information that reaches the VMPFC has low-detail (also in this case, it is mainly magnocellular), it is sufficient for the development of rapid evaluation processes (Bar, 2003; Bar et al., 2006).

In relation to this, several studies suggest that the VMPFC is able to top-down regulate visual attention through its projections to the parietal and visual cortices (Armony and Dolan, 2002; Bar et al., 2006; Bar, 2003; Hopfinger and Mangun, 2001; Sarter et al., 2001). Along with these outputs to sensory cortices, the VMPFC sends projections to executive areas such as the hypothalamus, PAG, striatum and motor cortices (Cavada et al., 2000; Ongür and Price, 2000). Therefore, a clear parallel can be discerned between the amygdala and VMPFC with respect to their afferences and efferences.

4.3. Anterior insula

The anterior insula is a part of the insular cortex that is sometimes defined as a “visceral somatosensory cortex” (Adolphs, 2002). Data on the functional characteristics and anatomical connections of the human anterior insula are still quite scarce in comparison to those obtained for the other evaluative structures. However, it has been clearly identified as a central piece in the processing of negative stimuli and, as amygdala and VMPFC, it receives inputs from the thalamus (particularly, MD and ventromedial nuclei: Critchley, 2005; Shi and Cassell, 1998, but also from the pulvinar: Clascá et al., 1997) and from sensory cortices, mainly the gustatory and olfactory ones, but also the visual cortex (Gallese et al., 2004). Some degree of specialization is observed for the anterior insula, since it has been mainly associated with two particular classes of negative stimuli. On the one hand, those eliciting disgust (Calder et al., 2001); interestingly, viewing a third party’s facial expressions of disgust also elicits an enhancement in anterior insula activation (Adolphs, 2002). On the other hand, those eliciting pain (Peyron et al., 2000). As amygdala and VMPFC, the insular cortex sends outputs to executive areas once situation is evaluated, such as the motor cortex (Simonyan and Jürgens, 2005), the striatal system (Calder et al., 2000) or PAG (Critchley, 2005), as well as to the visual cortex (Rodman and Consuelos, 1994), suggesting a capability for modulating attention.

5. Associated and output processes

In this section, circuits by which the brain organizes and executes a response to the event that has been evaluated as negative, will be described. These circuits have been found to respond also to non-
negative events but, again, indices of their greater and faster responses to negative events have been reported.

5.1. Autonomic and motor execution

The goal of the neural processes described up to now is to produce rapid and efficient actions directed to avoiding or minimizing negative consequences associated with the unpleasant stimulation just perceived. In other words, the neural negativity bias leads also to a motor negativity bias, which has been proposed to be associated with the flight–fight response typically elicited by aversive stimuli (Pahlavan et al., 2000). Experimental findings support the existence of this motor bias (Coombes et al., 2005, 2006; Fox et al., 2000; Hansen and Hansen, 1988; Marsh et al., 2005; Ohman et al., 2001), showing the existence of more intense and/or more rapid motor responses to negative than to neutral or positive stimuli. However, behavior elicited by unpleasant events may present an important variety of forms, which range from the absence of visible movement (freezing) to agitated motor outputs (flight–fight) that depend on the situation, previous experience, the species’ idiosyncratic response and individual traits.

As indicated previously, the evaluative elements of the negative brain (amygdala, VMPFC and insula) are equipped with projections to motor executive areas and to areas responsible for triggering the autonomic changes that support motor execution. The autonomic response is dependent on the outputs from the amygdala, VMPFC and anterior insula to the hypothalamus (see Cavada et al., 2000; LeDoux, 2000; Ongür et al., 1998), dependent on the outputs from the amygdala, VMPFC and anterior insula to the hypothalamus (see Cavada et al., 2000). The dorsolateral PAG has been reported to be responsible for “flight and flight” behavior, while the ventral PAG triggers “freezing” behavior (De Oca et al., 1998). Second, the striatum (caudate nucleus and putamen) also receives inputs from the three evaluative elements: the VMPFC (Cavada et al., 2000; Ongür and Price, 2000), the insula (Calder et al., 2001), and the amygdala (Emery and Amaral, 2000). The striatum, an important element in the dopaminergic mesolimbic system, and also involved in other affective processes (such as reward-related processes, Burgdorf and Panksepp, 2006), possesses some important motor execution functions. Specifically, and according to recent proposals, the striatum activates motor programs (some of them innate) such as those associated with emotional expressions or withdrawal behaviors (Grillner et al., 2005), and has shown enhanced activation in response to unpleasant stimuli (Bercera et al., 2001). Third, there are experimental data showing higher activation of the primary motor cortex in response to sustained negative stimuli than in response to sustained neutral or positive stimuli (Carretié et al., 2006). Characteristically, the motor cortices (premotor, supplementary and/or primary) show enhanced activation in response to painful stimuli (Coghill et al., 1999; Lenz et al., 1998; Porro et al., 1998). It is important to point out that the motor cortices do not receive direct amygdalar projections (Emery and Amaral, 2000), but only VMPFC (at least to areas involved in eye, face and forelimb movement control: Cavada et al., 2000) and insular (at least to larynx areas: Simonyan and Jürgens, 2005), which suggests poorer motor “resolution” (i.e., the range of possible behaviors) in the motor output yielded by the amygdala than that yielded by the insula and, particularly, by the VMPFC.

5.2. Attention modulation

Once again, we shall refer here to the visual cortex, which is the most widely studied. The three evaluative elements of the negative brain send back projections to this sensory cortex: amygdala (Adolphs, 2004), VMPFC (Bar et al., 2006), and anterior insula (Rodman and Consuelos, 1994). Probably due to these back projections, several studies have found a greater activation of visual cortices in response to negative than in response to non-negative stimuli (Carretié et al., 2001, 2004, 2006, 2008; Fredrikson et al., 1993; Kosslyn et al., 1996; Lane et al., 1997; Mourão-Miranda et al., 2003; Pourtois et al., 2004, 2005). Interestingly, in studies where facial expressions are not employed as emotional stimuli (so that the face-specific, ventral visual areas are not necessarily required to act), this activation of the visual cortex in response to negative stimuli appear to involve dorsal visual areas (posterior middle temporal gyrus and/or parietal visual areas: Carretié et al., 2001, 2008; Lang et al., 1998; Kosslyn et al., 1996) to a greater extent than in the response to neutral or positive stimuli.

The main role of the dorsal stream, which preferentially receives magnocellular inputs (Maunsell, 1992), has been identified as the processing of motion and spatial location. However, it would seem that these are far from being its sole functions. For example, the processing of visual attributes ‘typically’ belonging to the ventral pathway, such as shape, has been found to be carried out in the dorsal stream of nonhuman primates (Sereno and Maunsell, 1998). In humans, data also exist showing high activation of dorsal stream areas (including the posterior middle temporal gyrus) in response to static visual stimuli presented with invariant spatial locations (Martin et al., 1995, 1996; Mummery et al., 1998). A possible explanation is that the dorsal stream is activated in response to visual stimuli with motor action-associated meaning, regardless of whether they are physically in motion or not. For example, static words associated with action elicit the activation of this stream (Martin et al., 1995, 1996; Mummery et al., 1998). Indeed, as we are stressing throughout the review, negative stimuli often demand defense or withdrawal motor actions.

5.3. Associated cognitive processes

The three evaluative elements are reciprocally connected to the hippocampal complex (amygdala: Pitkänen et al., 2000; VMPFC: Cavada et al., 2000; insula: Kondo et al., 2005), and form a circuit that is clearly involved in danger-related learning. Indeed, each of its elements has been found to intervene in fear conditioning (e.g., amygdala: Büchel and Dolan, 2000; hippocampus: Fanselow, 2000; VMPFC: Antoniadis and McDonald, 2006). It is crucial for the organism to rapidly learn to avoid or escape from certain events or contexts (the hippocampus is particularly involved in contextual fear conditioning). In fact, a single exposition to danger or pain is able, in certain situations, to elicit long-term behavioral changes (see a review in Wiedenmayer, 2004; see also Büchel and Dolan, 2000; Phillips and LeDoux, 1992). Through the rich interconnections between the hippocampal complex and evaluative structures of the negative brain, the latter are able to enhance hippocampal memory formation and storage (e.g., see data on the
amygdalar modulation of hippocampal function in Dolcos et al., 2004b; a similar modulation by VMPFC is probable due to its profuse outputs to the hippocampal complex: Cavada et al., 2000). E evaluative structures and hippocampus also intervene in the retrieval of emotional memories through the reactivation of representations in neocortical areas, such as the visual cortex (Fenike, 2005). As a result, emotional events and situations have been reported to be better remembered than neutral, anodyne information (Cahill and McGaugh, 1995; Dolcos and Cabeza, 2002; Dolcos et al., 2004a; Kensinger et al., 2002; Phelps et al., 1997).

The anterior cingulate cortex (ACC) has also been associated with the response to negative events (Vogt, 2005). The involvement of the ACC in attention (Bush et al., 2000; Cardinal et al., 2002; Posner, 1995; Sturm et al., 1999; Torok et al., 2002) and in the response to emotional stimuli (Carretí et al., 2004; Lane et al., 1998; Peoples, 2002; Ploghaus et al., 1999) makes this prefrontal region an optimum interface between cognitive and emotional processes. However, ACC should be considered a second term structure within the negative brain, since it receives main affect-related information from the amygdala, anterior insula, and VMPFC, while inputs from sensory cortices are weak (Morecraft et al., 1992; Cavada et al., 2000; Musil and Olson, 1988; Rodman and Consuelos, 1994). The ACC sends outputs to executive areas, both autonomic (Crichtley et al., 2005) and motor (Wenderoth et al., 2005), and it has been proposed as coming into play when rehearsed actions are insufficient for guiding behavior (Paus, 2001). Therefore, it may be activated by any of the evaluative elements whenever a non-programmed action is required. Finally, the dorsolateral prefrontal cortex (DLPFC) may also intervene in the response to negative stimulation (Grimm et al., 2006; Lorenz et al., 2003). There is a broad agreement, however, on the role of the DLPFC as the “cognitive face” of the prefrontal cortex, its involvement in emotional processes being produced, as in the case of ACC, as a second term element of the negative brain. The DLPFC’s activation during negative situations may reflect cognitive operations necessary for an effective response. Particularly, it is the main location of executive memory (Fuster, 2001), which is the long-term memory of behavioral sequences and plans or schemes of action, especially important for responding to danger: when exposed to a known unpleasant situation, the subject may need to retrieve previously employed (and stored) behavioral strategies to cope with it. But the DLPFC may also intervene in unfamiliar negative situations, since action planning (a cognitive function that includes estimates on possible consequences of alternative behaviors and is often necessary in threatening situations) also resides in this prefrontal area (Fuster, 2001). The VMPFC is the only evaluative element directly and reciprocally connected to the DLPFC.

6. Integrative summary: a model of the negative brain

Fig. 1 illustrates a possible model system that begins in the thalamus, where visual inputs are distributed to the visual cortex. From it, visual inputs are then sent to the three evaluative elements of the negative brain (amygdala, VMPFC and insular cortex). Additionally, existing data allow for hypothesizing that visual information may reach evaluative elements directly from thalamus. The main direct outputs from the thalamus to the evaluative elements appear to start out from the pulvinar and MD nuclei, which manage visual information. Experimental data on whether the thalamus sends initial visual information (not processed by the visual cortex) to the amygdala, VMPFC and anterior insula or, alternatively, whether it sends cortically-processed visual information re-entrant to the thalamus is still scarce in humans. However, short latencies found in VMPFC responses to negative stimuli (100–150 ms) point to the former possibility.

Once visual information reaches evaluative structures, they are capable of interacting with other brain areas in which information can be stored, or where previous experiences may be recovered (i.e., hippocampus, DLPFC and sensory cortices). Complex plans (on the sequences—and consequences—of behavior, for example) are also guaranteed thanks to connections between VMPFC and other prefrontal areas such as ACC and, again, DLPFC. Additionally, this decision on whether a response is necessary and, in case it is, what form this response should take, carried out by evaluative structures, is aided by their capability to modulate attention (i.e., all of them can directly regulate visual cortex activity).

Although amygdala, VMPFC and insula deeply interact and modulate each other to produce a final evaluation of the situation and a decision on the action to be taken or on the adjustment of ongoing actions, they may act autonomously. Lesions in any of them appear not to extinguish basic defense responses. This autonomy is favored by the fact that inputs and outputs from the amygdala, anterior insula and VMPFC overlap considerably (i.e., they are redundant in many aspects). However, the purpose of the existence of three potentially autonomous circuits is probably not only to minimize the consequences of lesions, but they actually appear to show some functional differentiation. First, it is reasonable to propose that the “resolution” (i.e., the range of possible outputs) of the evaluative/decision process is higher in the VMPFC circuit than in those of the amygdala or anterior insula, while speed of response is greater for the amygdala circuit. The anterior insula, on the other hand, seems to be specialized in disgust and pain situations, not intervening as much as the VMPFC and amygdala in fear or anger responses (reciprocally, the latter do not intervene as much as insula in responses to pain/disgust). This model includes some tentative or hypothetical elements that need to be confirmed or discarded once future research has provided additional data on the (many) scarcely studied elements of the negative brain, but it may constitute a useful tool for organizing current and forthcoming data on the neural response to unpleasant events.

Acknowledgements

This work was supported by the grant SEJ2005–08461-C02-01/PSIC from the Ministerio de Educación y Ciencia of Spain and CCG06-URM/SAL-0287 from the Comunidad de Madrid/Universidad Autónoma de Madrid.

References


