UNIVERSITA' DEGLI STUDI DI PADOVA

Sede Amministrativa: Università degli Studi di Padova

Dipartimento di Psicologia Generale

SCUOLA DI DOTTORATO DI RICERCA IN SCIENZE PSICOLOGICHE

INDIRIZZO PSICOBIOLOGIA

CICLO XX

FROM EMOTION TO DECISION: ROLE PALYED BY THE PREFRONTAL CORTEX

Direttore della Scuola: Ch.mo Prof. Luciano Stegagno

Supervisore: Ch.mo Prof. Alessandro Angrilli

Dottorando: Marta Bianchin

DATA CONSEGNA TESI

31 gennaio 2008

Emotions are about the life of an organism, its body to be precise,
and their role is to assists the organism in maintaining life.
- AR Damasio, 1999 –

To Enrico and Emma

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List of Abbreviations

5-HT serotonine
AC alternating current
ACC anterior cyngulate cortex
Ach acetylcoline
BA Brodman's area
CT computed tomography
DA dopamine
DC direct current
DLPFC dorsolateral prefrontal cortex
E-DIS Experience Seeking
EEG electroencephalogram
EMG electromyography
EOG electrooculogram
ERN error related negativity
ERP event related potential
E-TAS Thrill and Adventure Seeking
fMRI functional magnetic resonance imaging
FRN feedback related negativity
HP high pass
IAPS International affective picture systm
I-DIS Disinhibition
IGT Iowa Gambling Task
I-TAS Boredom Susceptibility
Kt time constant
LP low pass
MFN medial frontal negativity
MRI magnetic resonance imaging

MSEC multiple source eye correction

NA noradrenaline

NRPC nucleus reticularis pontis caudalis

OFC orbitofrontal cortex

PET positron emission tomography

PFC prefrontal cortex

pOFC polar orbitofrontal cortex

SAM self assessment manikin

SCR skin conductance response

SPECT single photon emission computed tomography

SPN stimulus preceding negativity

SSS sensation seeking scale

STAI State trait anxiety inventory

TA trait anxiety

VMPFC ventromedial prefrontal cortex

1. The Prefrontal Cortex

The physiology of the cerebral cortex is organized in hierarchical manner. At the bottom of the cortical organization, sensory and motor areas support specific sensory and motor functions. The prefrontal cortex (PFC) constitutes the highest level of the cortical hierarchy dedicated to the representation and execution of actions (Fuster, 2001).

The PFC can be subdivided in three major regions: *a*) ventral, *b)* orbital, and *c)* dorsolateral. The ventral (VMPFC) and orbital (OFC), regions are involved in emotional behavior. The dorsolateral (DLPFC) region supports the cognitive control and the temporal organization of behavior, speech, and reasoning. This function of temporal organization is served by several subordinate functions that are closely interdependent. A recent study (Fuster, 2001; Öngür and Price, 2000) states that much of the prevalent confusion in the PFC literature derives from two common errors: first is considering PFC subregions specialized in one particular prefrontal function while opposing or neglecting others; second is localizing any of these functions within a discrete portion of PFC.

The PFC is one of the last territories of the neocortex which develops, in evolution as well as in ontogeny. In general term, the entire OFC is dedicated to the memory, planning or execution of actions. All the integrative functions of the PFC operate within the broad biological context of the sensory-motor cycle of integrations that link the organism with it’s environment at all levels of the nervous system. The PFC closes that cycle at the top of cortical hierarchy by integrating in the time the domain cognitive representation of perception and action as required by goal-directed behavior.

1.1 Anatomy and Connections

The PFC is the association cortex of the frontal lobe. In primates, it comprises areas 8, 9, 10, 11, 12, 13, 24, 32, 46 and 47 according to the cytoarchitectonic map of Brodmann (see Jerison 1994), recently update for the monkey by Petrides and Pandia (1994) (Fig. 1.1). Phylogenetically is one of the latest cortices to develop, having attained maximum relative growth in the human brain where it constitutes nearly one-third of the neocortex.

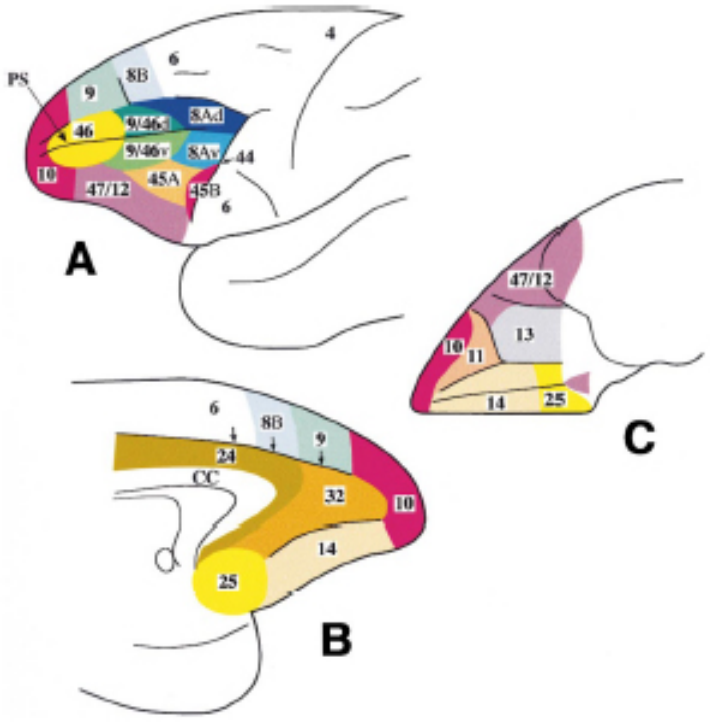


Fig 1.1 **Cytoarchitectonic Map of the Monkey' Frontal Cortex.** (A) Lateral view. (B) Medial view. (C)Inferior (orbital) view. CC, corpus callosum; PS, principal sulcus. From Petrides and Pandya (1994), modified by Fuster (2001).

Furthermore, the PFC undergoes late development in the course of ontogeny. In the human, by myelogenic and synaptogenic criteria, the PFC is clearly late-maturing cortex (Huttenlocher, 1990; Huttenlocher and Dabholkar,

1997). Imaging studies indicate that, in the human, prefrontal areas do not attain full maturity until adolescence (Paus et al. 1999; Sowell et al., 1999). This is consistent with the behavioral evidence that these areas are critical for those higher cognitive functions that develop late, such as language, social interaction, and reasoning.

The profuse variety of connections of the PFC is obviously related to the variety of the information it integrates. The PFC is connected with brainstem, thalamus, basal ganglia and the limbic system. Much of the connectivity with subcortical structures is reciprocal. Especially well organized topologically are the connections between the PFC and the thalamus (Fuster, 1997).

The functional role of the afferent connections of the PFC can be broadly inferred from the functions of the contributing structures. In the aggregate, the afferent connections from the brainstem, the diencephalons and the limbic system convey to the PFC information about the internal environment, the level of arousal, the drive and motives of the animal, and the visceral concomitants of emotion. Especially relevant for the behavioral integrative functions of the PFC are its afferents connections from the amygdala and the hypothalamus. The PFC is connected with other associative cortices, but is not connected directly with primary sensory or motor cortices (Fuster, 2001). Each of the major prefrontal regions is connected with itself and with the other two (Pandya and Yeteran, 1985). Some of the cortico-cortical connectivity of the PFC is interhemispheric, and almost all of it is reciprocal and topologically organized. In general, connection between association cortices both originate and terminate in upper cortical layers, especially II and III (Andersen et al., 1985). Those connections presumably constitute the structural frame of cognitive networks (Fuster, 1995).

1.2 The Orbitofrontal cortex

The cortex of the orbital surface of the frontal lobe is a large and heterogeneous region wich covers the medial wall and the ventral surface of the frontal lobe. Although the organization and the function of this region was historically poorly understood, recently anatomical and physiological studies have substantially expanded our knowledge. Today it can be recognized that the region as a whole receives highly processed sensory afferents, provides cortical influence on over visceral functions, and participates in high-level cognitive and emotional processes. Several terms have been used to refer to parts of this region (i.e. orbitofrontal, anterior cingulate, polar frontal cortex).

To avoid confusion, it is necessary to clarify briefly the controversial definition and boundaries of the OFC. In most case, 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 and Tranel, 2002), Broadman's areas (BA) 11, 12, 13, 25, or includes the latgeral BA 47 and polar frontal cortex BA 10 (Krawczyk, 2002; Rolls, 1999) and anterior cingulate BA 24 and 32 (Öngür and Price, 2000). A survey of literature (Stuss and Benson, 1984) reasonably divides the PFC into dorsolateral prefrontal cortex (DLPFC) , medial prefrontal cortex (anterior BA 24 and 32), and 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 and Owen, 2004).

The OFC has extensive connection with other parts of the brain, including the mediodorsal nucleus of the thalamus, several sensory areas or systems, virtually all limbic structure and areas, the ventromedial striatum, the hypothalamus and brainstem. In addition there are intrinsic cortico-cortical connections which are sufficiently structured that they allow the definition of distinct networks within the OFC.

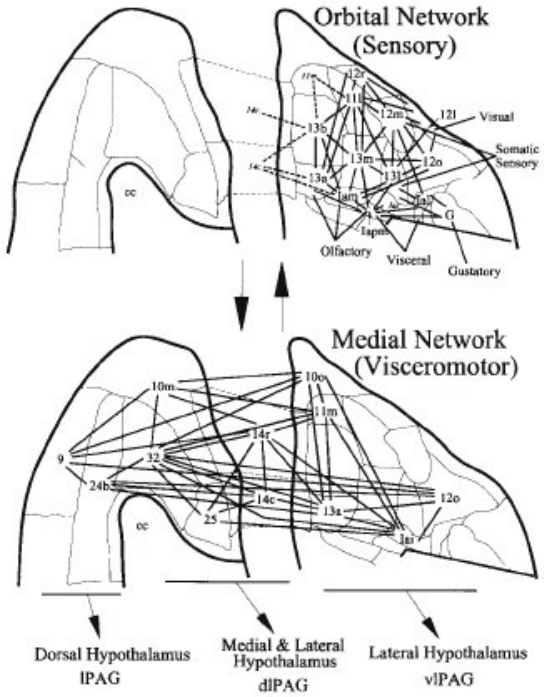


Fig 1.2. **Summary of cortico-cortical connection within the OFC,** which forms the basis for the division of the area into an "orbital" network and a "medial" network. PAG, periacqueductal gray; dlPAG, dorsolateral column; vlPAG, ventrolateral column (Öngür and Price, 2000)

OFC can be divided into two groups of networks, one restricted to the orbital cortex and the other involving the medial cortex and some orbital areas (Fig 1.2). Although the network are distinct, there are several points of interaction, especially through areas near the ventromedial corner of the frontal lobe. The orbital network receive several sensory inputs and appears to function as a system for sensory integration. The medial network project to the hypothalamus and perieaqueductal gray, and appears to function as a visceromotor system (An et al., 1998; Öngür et al., 1998).

The medial network projects primarily to the ventromedial striatum, including the medial caudate nucleus, the accumbens nucleus and the ventral putamen, and is also interconnected with the dorsomedial and caudal part of mediodorsal thalamic nucleus. In contrast, the orbital network projects to a

central region of the striatum, in the lateral caudate nucleus and in the ventromedial putamen, and is interconnected with the more central part of the mediodorsal thalamic nucleus. The striatal and the thalamic regions are connected through the ventral pallidum, although the pallidal projection of the central striatum has not been demonstrated in detail (Öngür and Price, 2000).

1.3 Functions of the OFC

Behavioral study suggests that OFC participates in the guidance of emotional behavior. Many of the behavioral effects of OFC lesions are remarkably similar to those seen following amygdala lesions, indicating that both of these structures are involved in circuits controlling emotional and social behavior (Kling, 1972). In a review, Nauta (1971), posited that the prefrontal cortex is informed about most of sensory stimuli impinging on the sensory organs of the body, and that the OFC uses these information to obtain the most desiderable and rewarding outcomes for the organism. Nauta emphasized that the visceral sensory inputs and visceromotor outputs are particularly important in this regard since they provide information about the status of the internal milieu and generate bodily reactions to alter that status. These bodily reactions are then relayed to the prefrontal cortex as new information on the state of the body, forming a loop where the OFC is constantly monitoring and altering that state. Based on these ideas, Nauta suggested that animals with lesion of the prefrontal cortex experience an “interoceptive agnosia” – an inability to determine how the body is reacting when faced with contrasting behavioral options. Since the organism is deprived of the “navigational marker” it would normally use to decide which action is the most desirable, this agnosia then leads to a variety of emotional and social deficits.

These ideas of Nauta received important support from clinical studies in humans. Observations about lesions of the OFC have a long history, starting with Harlow's report on his famous patient Phineas Gage.

1.4 Effects of Prefrontal lesions

Individual with PFC lesions are typically described as dishinibited, socially inappropriate, misinterpreting other's moods, impulsive, unconcerned with the consequences of their actions, irresponsible in everyday life, underestimating the seriousness of their condition and showing a pour sense of initiative (Rolls et al., 1994; Séguin, 2004).

One of the most famous patients described in the literature was Phineas Gage. Gage was working with explosives, a charge was accidentally set off and projected a tamping rod to his head, through his frontal lobe but spared vital brain centers. Although Gage survived the blast, he became irritable, short-tempered, obnoxious, irresponsible, and could no longer hold a job or provide for himself. Nonetheless, neurocognitive functions were purportedly intact. A recent reconstruction of the lesion site (Fig. 1.3) suggests that the lesion were mainly located in the orbitofrontal and ventromedial frontal lobes (Damasio et al., 1994).

Eslinger and Damasio in 1985 presented the case of a patients who showed severe disturbance of higher cognition after bilateral frontal lobe ablation. The patient E.V.R., had a bilateral orbitofrontal meningioma removed leaving OFC damage. Comparison of his behavior before and after this incident demonstrate the profound disability that is occurred with such damage and highlights the selective nature of the deficits caused by this type of lesion. Importantly, E.V.R.'s behavior counters traditional views of frontal syndromes, which maintain that such damage will impair intellectual faculties revealed by the standard neurological frontal test batteries. E.V.R. had been a successful student, accountant, and husband prior the surgery; however, he changed dramatically after surgery.

He was described as having been a role model to his sibling and had received consistent promotion at work as comptroller. After the surgery he began to have great difficulties holing a job and was repeatedly fired from jobs due to tardiness and general disorganization. His marital life deteriorated and he went trough two divorces. He developed idiosyncratic behaviors such as a refusal to dispose of broken appliances, out of date newspapers, and food containers. Other abnormalities included excessive time spent preparing for work and attending personal hygiene. He also showed evidence of profoundly impaired decision-making. Very soon after the surgery he entered into an unwise business partnership and had to declare bankruptcy. He also took extreme amounts of time to make decision of minor importance such as choosing a restaurant. Importantly E.V.R. had largely intact knowledge and normal problem solving abilities on laboratory tasks. Intelligence tests revealed that he was well within the normal range. He also able to reason and decide normally on problems that presented social or ethical dilemmas, but despite these abilities, a prominent feature of the disorder was his inability to carry this intact knowledge into action in his everyday activities.

This dissociation of inappropriate behavior from intact knowledge is also seen in adults with acquired sociopathy due to frontal lobe injury. In these cases frontal lobe damage results in impaired social behavior despite adequate performance on social and moral judgment scales (Anderson et al., 1999).

In a further study of patients E.V.R., Saver and Damasio (1991) suggested that differences between his intact laboratory test performance on social knowledge tasks and the disordered situation in his actual life may be due to the fact in the laboratory that he did not need to decide among the option that he had generated. Interestingly, when pressured to make a choice of action in a laboratory moral reasoning task, E.V.R. was unable to do so effectively. This study indicates that E.V.R.’s disorder was largely limited to instance requiring a decision.

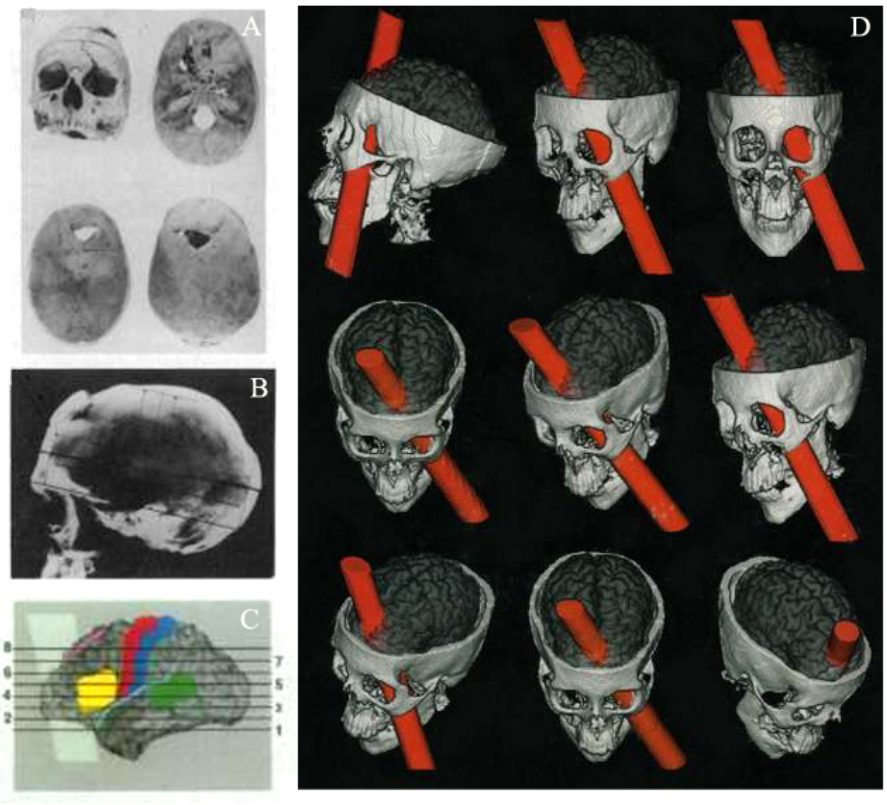


Fig. 1.3 (A) Photographs of several **views of the skull** and (B) **of the skull x ray of Phineas Gage**. (C) Lateral view of the brain. Normal brain filled with the live possible rods. The best rod is highlighted in solid white [exept id (D) where is shown in red]. D. **Computerized reconstruction of the the lesion incurred by Phineas**. (Modified from Damasio et al., 1994).

Other case studies involving frontal lobe dementia patients indicate similar problems consistent with orbitofrontal cortical loss. Case studies of several elderly frontal lobe dementia patients indicate that they have difficulties living independently, but may refuse to accept other living arrangements that would improve their situation (Schindler et al., 1995). Patients needing medications for other health problems chose not to take medication despite awareness of their symptoms. Such descriptions provide additional evidence of the dissociation of knowledge of appropriate conduct from its real-world implementation.

Frontal patients' problems often manifest themselves in financial decision making. In a laboratory study, Goel and colleagues (1998) addressed the

financial planning deficits of patients with PFC damage. These patients were asked to generate a long-term financial plan allowing for buying a house, pay for children education, and retiring comfortably. Each of these events was to be accomplished during specified points in life. Verbal protocols were taken while the subject decided what should be done with the finances. The task situation was poorly defined, requiring subjects to spend time structuring the problem before generating solution. Results showed that patients spent longer on the structuring phase and less time generating solution than controls. This time allocation was probably not due to the patient fatiguing or running out of time, as they tended to finish the task quickly. The authors concluded that a judgment deficit existed in which the patients generally believed that they had provided acceptable solutions, despite using less solution time and generating fewer viable solution. Another important aspect of this study that may be particularly relevant to orbitofrontal-damaged patients is the fact that the frontal-damaged group tended to spend decreasing amounts of time working on the long term future goals. This behavior is consistent with results that suggest that such patients have deficits in foreseeing future long-term consequences (Bechara et al., 2000a). A limitation of the patients of Goel and colleagues (1998) is that many had both dorsolateral and orbitofrontal damage, making it difficult to get a pure sense of how the ventral and medial regions of the frontal lobes operate in the performance of the task. Regardless, much of patients' behavior demonstrated a laboratory equivalent of patients' inability to successful financial plans and allocate resources wisely for future use and indicates that problems may lie in excessive planning without action, much like the characterization of other frontal patients.

Several studies about decision and risk-taking challenge the notion that OFC patients are risk-taking in responding, and suggest that their impairments instead may stem from impulsivity (Miller and Milner, 1985; Miller 1985, 1992). These studies indicated that frontal-damage patients tend to take risk in order to gain rewards, regardless of whether their strategy is profitable.

2. Theories on Emotion

2.1 Two fathers of affective neuroscience

In 1872, Charles Darwin published a groundbreaking book -The Expression of the Emotions in Man and Animals (1872). It was the culmination of 34 years of work on emotion and made two important contributions to the field. The first was the notion that animal emotions are homologues for human emotions - a logical extension of Darwin's early work on evolution. Darwin sought to show this by comparing and analyzing countless sketches and photographs of animals and people in different emotional states to reveal cross-species similarities. He also proposed that many emotional expressions in humans, such as tears when upset or baring the teeth when angry, are vestigial patterns of action. The second contribution was the proposal that a limited set of fundamental or "basic" emotions are present across species and across cultures (including anger, fear, surprise and sadness). These two ideas had a profound influence on affective neuroscience by promoting the use of research in animals to understand emotions in humans and by giving impetus to a group of scientists who espoused the view that different basic emotions had separable neural substrates. Around ten years later James, in his seminal paper entitled "What is an Emotion?" (1884), controversially proposed that emotions are no more than the experience of sets of bodily changes that occur in response to emotive stimuli. So, if we meet a bear in the woods, it is not the case that we feel frightened and run; rather, running away follows directly from our perception of the bear, and our experience of the bodily changes involved in running is the emotion of fear. Different patterns of bodily changes thereby code different emotions. Similar ideas were developed in parallel by Carl Lange in 1885 (see Lange and James 1967), providing us with the James-Lange theory of emotions. The James-Lange theory was challenged in the 1920s by Cannon on several

grounds: total surgical separation of the viscera from the brain in animals did not impair emotional behavior; bodily or autonomic activity cannot differentiate different emotional states; bodily changes are typically too slow to generate emotions; and artificial hormonal activation of bodily activity is insufficient to generate emotion. Recent research has cast doubt on Cannon's claims. Emotional responses can be distinguished (at least partly) on the basis of autonomic activity (Ekman et al., 1983); emotions were less intense when the brain was disconnected from the viscera in Cannon's studies; and some artificial manipulations of organ activity can induce emotions - for instance, intravenous administration of cholecystokinin (a gastric peptide) can provoke panic attacks (Harro and Vasar, 1991). The James-Lange theory has remained influential. Its main contribution is the emphasis it places on the embodiment of emotions, especially the argument that changes in the bodily concomitants of emotions can alter their experienced intensity. Most contemporary affective neuroscientists would endorse a modified James-Lange view in which bodily feedback modulates the experience of emotion.

2.2 The Cannon-Bard theory

Cannon's criticism of the James-Lange theory arose from his investigations with Bard of the effects of brain lesions on the emotional behavior of cats. Decorticated cats were liable to make sudden, inappropriate and ill-directed anger attacks - a phenomenon that Cannon and Bard labeled "sham rage". Cannon and Bard argued that if emotions were the perception of bodily change, then they should be entirely dependent on having intact sensory and motor cortices. They proposed that the fact that removal of the cortex did not eliminate emotions must mean that James and Lange were wrong. On the basis of data such as these, Cannon and Bard proposed the first substantive theory of the brain mechanisms of emotion (Bard, 1928; Bard and Rioch, 1937). They argued

that the hypothalamus is the brain region that is involved in the emotional response to stimuli and that such responses are inhibited by evolutionarily more recent neocortical regions. Removal of the cortex frees the hypothalamic circuit from top–down control, allowing uncontrolled emotion displays such as sham rage. Cannon and Bard's work illustrates the benefits of two important methodologies in affective neuroscience. First, the use of animal emotions as human homologues, as proposed by Darwin. And second, the use of surgical brain lesions to understand emotions, based on the logic that any changes after surgery must reflect processes that involved the lesioned part of the brain.

2.3 The Papez circuit

In 1937, James Papez proposed a scheme for the central neural circuitry of emotion - now known as the Papez circuit. Papez proposed that sensory input into the thalamus diverged into upstream and downstream - the separate streams of thought and feeling. The thought stream was transmitted from the thalamus to the sensory cortices, especially the cingulate region. Through this route, sensations were turned into perceptions, thoughts and memories. Papez proposed that this stream continued beyond the cingulate cortex through the cingulum pathway to the hippocampus and, through the fornix, to the mammillary bodies of the hypothalamus and back to the anterior thalamus via the mammillothalamic tract. The feeling stream, on the other hand, was transmitted from the thalamus directly to the mammillary bodies, allowing the generation of emotions (with downward projections to the bodily systems), and so via the anterior thalamus, upwards to the cingulate cortex. According to Papez, emotional experiences were a function of activity in the cingulate cortex and could be generated through either stream. Downward projections from the cingulate cortex to the hypothalamus also allowed top–down cortical regulation of emotional responses.

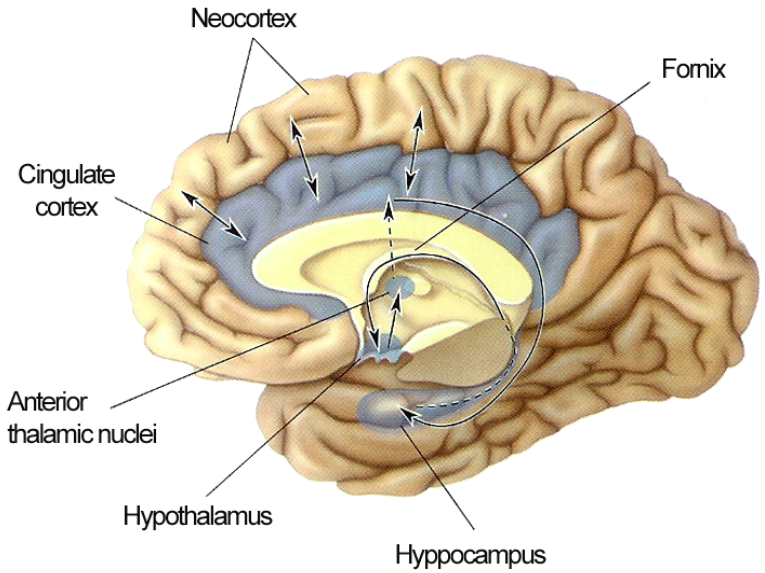


Fig 2.1. **Papez circuit.** (Modified from Bear et al., 1999).

A more broadly supported anatomical model of the brain regions that are involved in emotion was proposed by Paul MacLean in 1949. MacLean's model elaborated on Papez's and Cannon and Bard's original ideas and integrated them with the knowledge provided by the seminal work of Kluver and Bucy. In 1937, Kluver and Bucy had shown that bilateral removal of the temporal lobes in monkeys led to a characteristic set of behaviours (the Kluver-Bucy syndrome) that included a loss of emotional reactivity, increased exploratory behaviour, a tendency to examine objects with the mouth, hypersexuality and abnormal dietary changes, including copraphagia (eating of faeces). These studies indicated a key role for temporal lobe structures in emotion; MacLean viewed the brain as a triune architecture(MacLean, 1970). The first part is the evolutionarily ancient reptilian brain (the striatal complex and basal ganglia), which he saw as the seat of primitive emotions such as fear and aggression. The second part is the old mammalian brain (which he originally called the "visceral brain"), which augments primitive reptilian emotional responses such as fear and also elaborates the social emotions. This brain system includes many of the components of the Papez circuit - the thalamus, hypothalamus, hippocampus and cingulate cortex

(see fig 2.1) - along with important additional structures, in particular the amygdala and the PFC. Finally, the “new” mammalian brain consists mostly of the neocortex, which interfaces emotion with cognition and exerts top-down control over the emotional responses that are driven by other systems. MacLean’s essential idea was that emotional experiences involve the integration of sensations from the world with information from the body. In a neo-Jamesian view, he proposed that events in the world lead to bodily changes. Messages about these changes return to the brain where they are integrated with ongoing perception of the outside world. It is this integration that generates emotional experience. MacLean proposed that such integration was the function of the visceral brain, in particular the hippocampus, and three years later he introduced the term ‘limbic system’ for the visceral brain (MacLean, 1952). MacLean’s limbic system concept survives to the current day as the dominant conceptualization of the “emotional brain”, and the structures that he identified as important have been the focus of much of the research in affective neuroscience since his original publication. However, the notion of the limbic system has more recently been criticized on both empirical (LeDoux, 1995) and theoretical grounds (Calder et al., 2001).A number of the limbic system structures — the hippocampus, the mammillary bodies and the anterior thalamus - seem to have a much smaller role than MacLean imagined. Some of them seem to be more involved in higher cognitive processes such as declarative memory. Nevertheless, other brain regions identified by Cannon and Bard, Papez and MacLean seem to be integral to emotional life - notably, the “reptilian brain” (the ventral striatum and the basal ganglia) and the limbic structures of the amygdala, hypothalamus, cingulate cortex and PFC.

Other brain regions (the thalamus, nucleus accumbens, ventral pallidum, hippocampus, septum, insula, somatosensory cortices and brain stem) have also been implicated in the processing of emotion; however, detailed discussion of these areas is beyond the scope of this review (but see below for a discussion of the insular cortex and its potential involvement in disgust). The amygdala The

original work on Kluver–Bucy syndrome (Kluver and Bucy, 1937) involved surgical removal of almost the entire temporal lobes in monkeys. However, Weiskrantz (1956) showed that bilateral lesions of the amygdala were sufficient to induce the orality, passivity, strange dietary behaviour and increased exploratory tendencies of the syndrome. Removal of the amygdala also permanently disrupted the social behaviour of monkeys, usually resulting in a fall in social standing (Rosvold et al., 1956).The aspiration lesions used in these early studies were anatomically inexact. However, more recent studies involving ibotenic acid lesions have provided similar results, albeit with less severe Kluver–Bucy behaviours (Murray et al., 1996; Meunier et al., 1996).This line of research established the amygdala as one of the most important brain regions for emotion, with a key role in processing social signals of emotion (particularly involving fear), in emotional conditioning and in the consolidation of emotional memories.

2.4 The motivational organization of emotion: *Lang's model on emotion*

Lang and colleagues (1998) proposed that the evolutionary foundation of emotion has a simpler, two-factor motivational organization. That is, affects organized by brain systems that adaptively respond to two basic types of stimulation, appetitive or aversive. This biphasic organization of emotion has been proposed by many theorists (Konorski, 1967; Dickinson and Dearing, 1979). Osgood and colleagues (Osgood et al., 1957), using the semantic differential that the emotional descriptors were primarily distributed along a bipolar dimension of affective valence – ranging from attraction and pleasure to aversion and displeasure. A dimension of activation – from calm to aroused – also accounted for substantial variance. Similar conclusion have been drawn by

other investigators based on verbal reports (Mehrabian and Russel 1975; Russel, 1980; Tellegen, 1985), as well as facial expression (Schlosberg, 1952).

The view of Lang and colleagues merges these lines of theoretical development. They postulated that two motivational systems exist in the brain, appetitive and defensive, and that each can vary in terms of activation and arousal (Lang et al., 1998). The varying emotional states, observed and reported, reflect these basic motive systems. That is, the motive system determines the general behavioral strategy, defense or appetitive acquisition. The specific and autonomic patterns of affective responding are tactical, in that they are formed by behavioral context.

The behavior of very primitive organisms can be wholly characterized by two responses: direct approach to appetitive stimuli and withdrawal from aversive stimuli. This modest behavioral repertoire cannot however, implement the many sub-goals of human being nor effectively deal with the perceptually rich, complex environment in which we live. Emotional behavior in human are more adaptive and creative, and less predictable than those of less evolved species. In human being, the presume indices of emotional expression include responses in three reactive systems (Lang, 1978): (a) expressive and evaluative language; (b) physiological changes mediated by the somatic and autonomic systems; (c) behavioral sequelae, such as patterns of avoidance or performance deficits.

Lang's group developed a set of calibrate pictures system - International Affective Pictures System (IAPS; Lang et al., 2005) – which includes normative ratings of the pleasure and arousal associated with each picture, obtained from groups of naïve subjects. Research has demonstrated that these photographic images evoke a broad range of emotional reactions, varyin in intensity, and involving both pleasant and unpleasant affect (Greenwald et al., 1989; Lang et al., 1993).

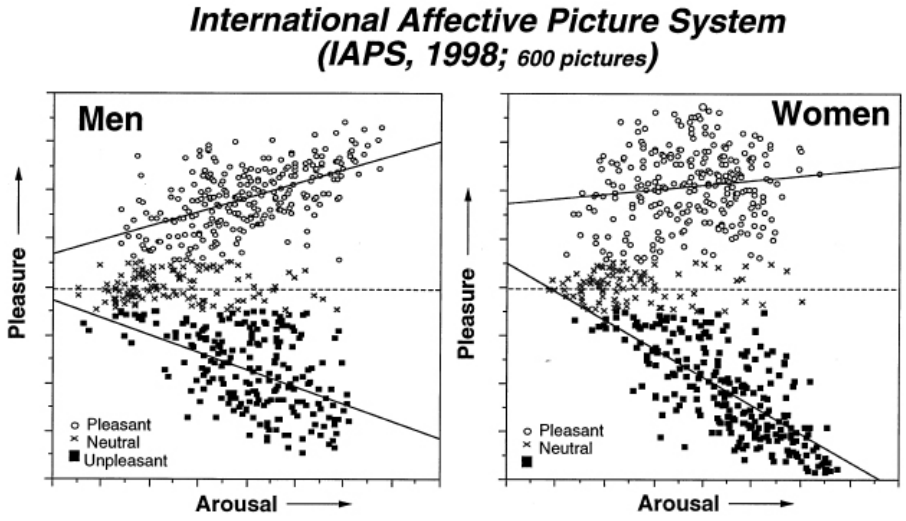


Fig 2.2. **Distribution of pictures from IAPS** standardization sample of mes and women, plotted in a two-dimensional affective space, defined by rating of pleasure (y-axis) and arousal (x-axis) for each stimulus (lang et al., 1998)

A number of physiological systems covary significantly with pleasure or arousal, as defined by evaluative judgments. When valence ratings are ranked from the most to the least unpleasant for each subject, facial muscle activity during picture viewing is strongly related to differences in affective valence; corrugator ("frown") electromyographic (EMG) activity increases linearly as pictures are rated as more unpleasant; conversely, zygomatic ("smile") EMG activity increases with judged pleasantness. Heart rate is also responsive to differences in affective valence; unpleasant pictures generally prompt marked deceleration during viewing, whereas greater acceleration is obtained when viewing pleasant pictures. Other evoked responses vary with changes in rated arousal, rather than affective valence. Skin conductance activity covaries positively with judged arousal, increasing monotonically with increases in rated arousal, regardless of picture valence. The slow cortical response evoked directly by the picture stimuli is also directly correlated with stimulus arousal; both pleasant and unpleasant arousing pictures prompt a marked positive-going slow wave (Cuthbert et al., 2000). This positive slow wave is sustained for nearly the entire viewing period, whereas the slow-wave response to neutral pictures is

distinctly more negative. These measures, then, index the intensity or activation level of the current motivational state, rather than its direction (i.e., appetitive or defensive). Behaviors elicited in the context of emotional picture perception also covary with motivational parameters. When first exposed to a new picture, reaction time responses to probes are significantly slower for emotionally arousing, compared to neutral pictures (Bradley et al., 1992). These data suggest that new activating images may require more attentional resources at encoding. Choice viewing behavior also covaries with arousal. When normal subjects are placed in a free-viewing context, unpleasant pictures are viewed as long as pleasant pictures, and both are viewed for a longer duration than non-arousing, neutral pictures. As might be inferred from the popularity of “slasher” movies, or the habitual slowing of traffic at a roadside accident, normal subjects allocate more processing time to arousing, intense images, regardless of valence. This relationship does not occur if pictures evoke very high levels of distress; when phobics view pictures specific to their fear, a palpable reduction in viewing time is found, consistent with their general avoidant behavior pattern (Hamm et al., 1997). As the phobia data imply, relationships between specific measures can vary widely for individuals, and to some extent between particular groups.

Gender effects are clear: pleasantness ratings covary more closely with facial muscle activity in female than male subjects; on the other hand, skin conductance changes are more closely correlated with arousal ratings in male than in female subjects (Lang et al., 1993). Overall, however, motivational variables of affective valence and arousal predominate in organizing the picture perception data. A factor analysis of various affect self-report, physiological, and behavioral measures resulted in a strong two-factor solution, with pleasantness ratings, heart rate, and facial muscles loading on a first, valence factor and arousal and interest ratings, viewing time, skin conductance, and cortical slow-wave electroencephalographic (EEG) activity loading highly on a second, arousal factor. The cross-loadings for all measures are very low. Thus, affects are built around motivational determinants. The motivational states elicited by these

affective cues (and the somatic, cortical, and autonomic substrates of their perception) are assumed to be fundamentally similar to those occurring when organisms stop, look, and listen, sifting through the environmental buzz for cues of danger, social meaning, and incentives to appetite.

2.4.1 The motivational circuits in the brain

The psychophysiological reactions, patterns of regional blood flow in occipital cortex, and behavioral responses that are all evoked by picture viewing reflect (in their organization) the engagement of neural structures in appetitive or defensive motivation systems.

Input normally passes from the sense organs to the sensory cortex and then from sensory-specific nuclei of the thalamus to the amygdala. Efferent to the amygdala, the aversion circuit branches, with each path apparently governing separate response outputs. Direct projections to the nucleus reticularis pontis caudalis modulate the startle response, potentiating the reflex in the context of nociceptive and fear-conditioned stimuli (Davis, 1989, 1997; Davis et al., 1987; Fendt et al., 1994). Autonomic response (e.g., blood pressure change) is dependent on an intact pathway through the hypothalamus (LeDoux, 1990), whereas somatic components require an intact midbrain (i.e., periaqueductal central gray). Furthermore, the ventral central gray is the fear “freezing” path, whereas the dorsal gray is a critical part of the fight/flight action circuit (Fanselow et al., 1995, Depaulis and Bandler, 1991). Taken together, the neurophysiological findings suggest that the amygdala is a key site in the defensive motivational system; structures “downstream” from the amygdala are implicated in the different types of defense behaviors. Some of these same neural structures are active in appetitive motivation; other nuclei are specific to the appetitive system, mediating different outputs or inhibiting defense responses. The startle reflex, for example, is exaggerated in defensively motivated rats. It is,

however, reduced in the context of signals that specifically indicate the animal is safe from painful shock (Falls and Davis, 1995). Other work shows that startle is reduced in the presence of a stimulus that has previously been paired with a primary reward (Schmid, 1995). Neither startle reduction in “safe” environments nor the inhibition found in the context of reward require amygdala activation. “Pleasure attenuated startle” does depend, however, on an intact nucleus accumbens (Koch et al., 1996). “The finding that the mesolimbic dopamine system is involved in this phenomenon suggests that other parts of the complex limbic–striatal–pallidal circuitry that governs reward-related behavior might also be relevant for the reduction of the acoustic startle response in the presence of a stimulus that predicts reward” (Koch and Schnitzler, 1997; Robbins and Everitt, 1996).

2.5 The amygdala: social signals of emotion and fear conditioning

One of the first studies of human amygdala lesions showed that amygdala damage can lead to impairments in the processing of faces and other social signals (Jacobson, 1985). This finding builds on single-unit recording studies in animals that have shown that amygdala neurons can respond differently to different faces (Leonard et al., 1985) and can respond selectively to dynamic social stimuli such as approach behavior (Brothers et al., 1990). Later studies (Adolphs et al., 1994; Young, 1995) indicated that the processing of emotional facial expressions, especially fear, was particularly impaired in humans with amygdala lesions (Calder et al., 1996, Angrilli et al., 1996). This involvement of the amygdala in the processing of facial expression has been supported by functional neuroimaging studies. Morris and colleagues, using positron emission tomography (PET) (Morris et al., 1996), and Breiter and colleagues, using functional magnetic resonance imaging (fMRI) (Breiter et al., 1996), showed selective brain activation in the amygdala in response to the presentation of

fearful faces. The amygdala is also selective for certain emotions, especially fear, in vocal expressions (Scott et al., 1997). Such activation of the amygdala by fearful faces occurs even when the faces are presented so quickly that the subject is unaware of them (Whalen et al., 1998; Morris et al., 1998), or are presented in the blind hemi-field of patients with blind-sight (Morris et al., 2001). Nevertheless, there is evidence that amygdala activation can be modulated by attention. Pessoa and colleagues, for example, showed that the amygdala did not respond differentially to emotional faces when attentional resources were recruited elsewhere, indicating that emotional processing in the amygdala is susceptible to top–down control (Pessoa et al. 2002).

In fear conditioning, meaningless stimuli come to acquire fear-inducing properties when they occur in conjunction with a naturally threatening event such as an electric shock. For example, if a rat hears a tone followed by a shock, after a few such pairings it will respond fearfully to the tone, showing alterations in autonomic (heart rate and blood pressure), endocrine and motor (for example, freezing) behavior, along with analgesia and somatic reflexes such as a potentiated startle response. Fear conditioning has been extensively studied (mostly in animals), prototypically by Blanchard and Blanchard (1972), and more recently and extensively by LeDoux and colleagues (1995), among many others. This body of research has highlighted the roles of two afferent routes involving the amygdala that can mediate such conditioning. The first is a direct thalamo-amygdala route that can process crude sensory aspects of incoming stimuli and directly relay this information to the amygdala, allowing an early conditioned fear response if any of these crude sensory elements are signals of threat. This echoes psychological ideas about emotion activation, notably Zajonc's position regarding emotions without cognition (Zajonc, 1996). The second route is a thalamo-cortico-amygdala pathway that allows more complex analysis of the incoming stimulus and delivers a slower, conditioned emotional response. Fear conditioning in humans has been less extensively studied. However, there have been a number of important findings. One study, by Angrilli

and colleagues (1996), described a man with extensive right amygdala damage who showed a reduced startle response to a sudden burst of white noise. The patient also seemed relatively immune to fear conditioning, as this startle response was not potentiated by the presence of aversive slides to provide an emotional backdrop — a technique that reliably potentiates startle in healthy subjects. Another study, by Bechara and colleagues (1995), described a patient with bilateral amygdala damage who again failed to fear-condition to aversive stimuli, but who could nevertheless report the facts about the conditioning experience. By contrast, another patient with hippocampal damage successfully acquired a conditioned fear response but had no explicit memory of the conditioning procedure - indicating that fear conditioning depends on the amygdala. Morris and colleagues showed that the amygdala was activated differentially in response to fear-conditioned angry faces that had been previously paired with an aversive noise, compared with angry faces that had not been paired with noise (Morris et al., 1998). In line with LeDoux's ideas (Morris et al., 1999), there is also evidence from functional neuroimaging that such conditioning to faces operates by a subcortical thalamo-amygdala route. Finally, as well as its role in fear conditioning, the amygdala has also been implicated in appetitive conditioning (Gallagher et al., 1990).

2.6 Startle reflex modulation

The startle response has proven to be a convenient defensive reflex for testing the above hypotheses. In most mammals, an abrupt sensory event will prompt a chained series of rapid flexor movements that cascade throughout the body (Landis and Hunt, 1939). This startle reaction appears to be a primitive defensive reflex that serves a protective function, avoiding organ injury (as in the eyeblink), and acting as a behavioral interrupt (Graham, 1979), clearing processors to deal with possible threat. Abruptness is the key to startle elicitation;

the risetime of the eliciting stimulus should be instantaneous. In human subjects, sudden closure of the eyelids is one of the first, fastest (occurring within 25–40 msec after startle stimulus onset), and most stable elements in the reflex sequence, and this blink component is measured in the studies reported here. Electromyograph electrodes placed just beneath the eye (Anthony, 1985; Lang et al., 1990) sense the bioelectric potentials produced by orbicularis oculi contraction, allowing one to measure the onset latency and magnitude of this muscle activity. Although strong stimuli generate larger and more reliable reflexes, high stimulus intensity is not necessary to evoke a reaction. According to the motivational priming hypothesis, the defensive startle reflex should be of significantly greater amplitude (and faster) when the aversive motivational system is active, e.g., as in a fear state. Alternatively, if appetitive system activation predominates, as in states of pleasure, the startle reflex should be attenuated. Evidence for defense system priming of the startle reflex has been found in both animal and human studies of fear conditioning. This was first examined systematically by Brown and colleagues (1951), who compared reflex responses to startle probes presented to male rats during neutral or shock-conditioned stimuli at extinction. Results conformed to expectation: animals did indeed react more forcefully when the startle stimuli were presented during fear-conditioned signals (Ross 1961; Spence and Runquist 1958).

As already noted, appetitive priming of the startle reflex in animals has also been demonstrated, i.e., probe reflex responses are attenuated both during “safety” signals and in the presence of stimuli associated with reward (Koch and Schnitzler, 1997). Several studies have confirmed reliable potentiation of the blink response in humans following simple shock exposure or as a function of learned associations that parallel the modulatory patterns previously obtained with rats (Hamm et al 1993; Grillon and Davis 1995). In brief, the blink response to a startle probe is generally larger after subjects experience electric shock, and selectively larger to startle probes presented during exposure to a shock-conditioned stimulus than to probes presented during exposure to an unshocked

control stimulus. Wide use has been made of startle probes in the assessment of human attention.

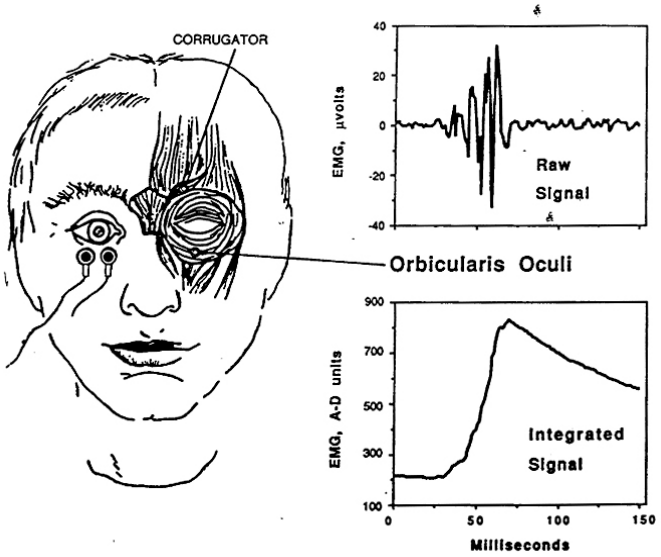


Fig 2.3. Left. Illustration of the placement of the electrodes for measuring activity over the orbicularis oculi muscle when assessing startle blink response. *Right.* The resulting raw EMG recorded (top) and the rectified, integrated signal from which the magnitude of the blink is scored (bottom) (Lang *et al.*, 1990).

Probe studies of picture perception have generally employed binaural startle stimuli in the range of 90–100 dB; however, lower intensities (sufficient to reliably evoke startle) also produce affective startle modulation (Cuthbert et al., 1996). Furthermore, significant affective modulation has been shown with monaural acoustic probes. In the monaural case, emotional pictures appear to be differentiated most reliably by probes presented to the left (presumably conferring an advantage in right brain processing) compared to the right ear (Bradley et al., 1991, 1996). Affective modulation of startle is observed for picture stimuli regardless of whether the startle probe is visual, acoustic, or tactile (Bradley et al., 1990; Hawk and Cook., 1997), suggesting that modality-specific processes are not primary in these modulatory effects. Furthermore,

affective modulation is not confined to visual percepts; when the foreground stimuli consist of short, 6-sec sound clips of various affective events (e.g., sounds of lovemaking; babies crying; bombs bursting), and the startle probe is a visual light flash, the same affect–reflex effect is obtained (Bradley et al., 1994). Other researchers have found startle potentiation in subjects smelling unpleasant odors (Miltner et al., 1994; Ehrlichman et al., 1995), supporting the view that affective reflex modulation is broadly motivational and thus consistent across affective foregrounds of differing stimulus modality.

3. Damasio's model on emotion

Taking together Lang's and Damasio's theories on emotion, both models agree in suggesting that learning processes play a key role for responses to emotional stimuli and social situation. In addition, both authors postulate a network organization of the emotion underlying brain structures.

Damasio's theories are based upon the standard neuroscientific conceptualization of brain functions, a framework which originally derived from work on the visual system. Essentially, objects in the external environment cause patterns of activation of retinal receptive cells, and these retinal patterns are processed serially and in parallel to extract the visual aspects of the environment that we perceive. Patterns in the external world correspond with patterns of nerve cell activity in the brain, and these brain patterns are termed cognitive representations. So thinking is done by means of patterns of nerve cell activation.

Damasio suggested that while the senses of vision, hearing, touch, taste smell function by nerve activation patterns correspond to the state of the external world; emotion are nerve activation patterns that correspond to state of the internal world. If we experience a state of fear, our brain will record this body state in nerve cell activation patterns obtained from neural and hormonal feedback, and this information may be used then to adapt behavior appropriately.

Emotion are based on internal body environment which act as inputs into the brain, just as visual or auditory information is an input to the brain from the external environment. Indeed, in evolutionary terms, the brain is primarily an organ for homeostasis – a centre which collect and collates feedback on body state, and acts to maintain constancy of the internal milieu.

3.1 The Somatic Marker Hypothesis

Damasio's hypothesis attributes the inability to make advantageous decision in real-life to a defect in an emotional mechanism that rapidly signals the prospective consequences of an action, and accordingly assists in the selection of an advantageous response option. The hypothesis specifies a number of structures and operations required for the normal operation of decision-making. Patients with ventromedial prefrontal lesions, deprived of this emotional signal, rely on a reasoned cost-benefit analysis of numerous and conflicting option involving both immediate and future consequences. The impairment degrades the speed of deliberation, and also the adequacy of the choice, i.e. patients may choose disadvantageously.

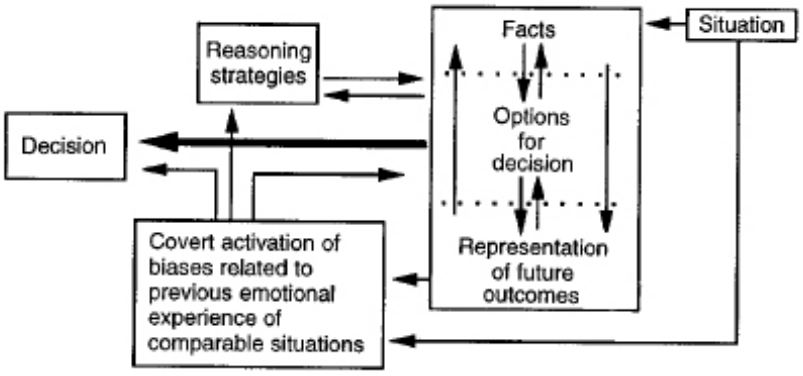


Fig. 3.1. **Diagram of the steps involved in Decision-Making** proposed by Bechara and colleagues (1997)

Bechara and Damasio (2005) defined emotion as a collection of change in body and brain system that responds to specifics contents of one's perceptions, actual or recalled, relative to a particular object or event. The specific object or event that predictably caused an emotion is designated as an "emotionally-competent stimulus". The responses toward the body proper enacted in a body (somatic) state involve physiological modifications. These modifications range

from changes in internal viscera that may not be perceptible to an external observer (e.g. endocrine release, heart rate, smooth muscle contraction) to change in the musculoskeletal system that may be obvious to an external observer (e.g., posture, facial expression, specific behavior such as freezing, flight and fight). The responses aimed at the brain lead to the central nervous system release of certain neurotransmitters, an active modification of the state of somatosensory maps and to a modification of the transmission of signals from the body to somatosensory regions. The ensemble of all these enacted responses in the body proper and in the brain constitutes an emotion. The ensemble of signals as mapped in somatosensory regions of the brain itself provide the essential ingredients for what is perceived as feeling (Damasio, 1999, 2003).

3.2 Testing the Somatic Marker Hypothesis

An extensive line of studies began in the early 1990s by Damasio and colleagues investigating gambling decisions in patients with medial orbitofrontal damage. This series of studies, like those of Miller et al. (1985, 1992), was targeted at demonstrating real-world decision making deficits of frontal patients in an laboratory setting. The patients had localized damage to a medial region of the ventral frontal lobes (Damasio, 1995; Bechara et al., 2000b). The resulting experiments used a technique known as the Iowa Gambling Task (IGT). As in previous studies (Rolls et al., 1994; Miller and Milner, 1985; Miller 1985) the subject's goal was to maximize a number of reward points, or facsimile money in this case, while encountering ways of making large or small gains and being lightly or heavily penalized. Subjects could either take risks or play conservatively. These studies generally capture the real world financial behavior of orbitofrontal-damaged patients, who characteristically make decisions that have disastrous financial implications (Eslinger and Damasio, 1985; Rolls et a., 1994). The original version of the gambling task was a pure measure of the

behavioral differences demonstrated by medial orbitofrontal patients compared to normal controls (Bechara et al., 1994). The task was intended to simulate real-world financial decision making in these patients by examining their performance during a card game in which the decisions made would determine their degree of financial success. Subjects were given a 'loan' of facsimile money and told that they should try to maximize their profit total as they performed the task. Subjects selected one card at a time from a set of four decks and were stopped after making 100 selections. Two of the card decks were disadvantageous in the long run and two were advantageous. This was accomplished by a preset reward schedule in which disadvantageous decks paid a total of 100$ per selection; however, unpredictably interspersed within the decks were cards that paid the reward, but also required that subjects pay a penalty. The penalties in the disadvantageous decks were varied in terms of their frequency and magnitude, but ultimately selecting 10 cards from either of these decks, resulted in a net loss. Alternatively the advantageous decks paid only 50$ for each selection; however they included penalties that were lower in magnitude, resulting in a net gain over the course of 10 choices made from these decks. Thus choosing from disadvantageous decks was risky and unprofitable overall, while choosing the advantageous decks was conservative and profitable overall. Subjects could not calculate the precise frequencies of rewards and punishments, so they had to rely on developing a general sense of which decks were advantageous or disadvantageous over many trials. Results indicated that medial orbitofrontal damaged patient's chose more from the disadvantageous decks, while control subjects chose more from the advantageous decks. Thus, medial orbitofrontal damage performed poorly when faced with immediate gains and sporadic losses. Other work suggested that the impairment was not due to misrepresentation of reward or punishment magnitudes, but was instead due to a lack of ability to accurately predict future outcomes. In a subsequent study, physiological responses were measured by taking skin conductance measures related to appropriate and inappropriate decisions in the gambling task (Bechara

et al., 1996). Subjects in this version performed the gambling task while researchers recorded skin conductance responses (SCRs), a measure of autonomic arousal. Recordings were taken after the obtaining of rewards alone, rewards along with penalties, and prior to the selection of a card. Results indicated that both medial orbitofrontal patients and normal controls generated post-selection SCRs both to reward cards and to those indicating reward and penalty. Control subjects also began to show SCR activity prior to selecting from a disadvantageous deck as they became familiar with the outcomes, while medial OFC patients showed no such SCR activity at any time during the course of the experiment. This finding was interpreted as an evidence that a physiological marker, indicated by the anticipatory SCR, may serve a critical function in making decisions that involve risk. The authors raised the possibility that the medial OFC is critical in linking outcome knowledge to biological responses from the body, and in addition may relay biological signals regarding outcomes through other connected structures such as the amygdala and hippocampus, leading to an emotional reaction associated with certain decision options. A further investigation of the gambling task indicated that there is a typical time course for learning the appropriate strategies and that it is disrupted in medial OFC damaged patients (Bechara et al., 1997). Skin conductance measures were again recorded. During this administration of the task, subjects had to report their knowledge about the decks after the first 20 trials and every 10 trials after that. Typically subjects preferred cards from the disadvantageous decks for the first several trials prior to encountering a penalty. During this time, labeled the pre-punishment phase, subjects showed no anticipatory SCR activity. After encountering penalties from the disadvantageous decks, the normal subjects began to show anticipatory SCRs, while the patients did not. At the time of the first questioning, 20 trials into the task, no subject knew what the appropriate decision strategy was. This period was labeled pre-hunch. Half-way through the task, normal subjects verbalized a hunch that the disadvantageous decks were riskier than the others and continued to show anticipatory SCR activity when

considering a choice from these decks. In contrast, the patient group did not express a hunch at this time and failed to show anticipatory SCRs. This period of the task was labeled the hunch period. Just over three quarters of the way through the task, most of the normal controls were able to report why the disadvantageous decks were poor choices, while the advantageous decks were sensible choices; this period was labeled conceptual. All controls continued to show anticipatory SCR activity to the disadvantageous decks and continued to choose predominantly from the advantageous decks. Interestingly, even those control subjects who did not reach the conceptual phase continued to choose advantageously. Meanwhile half of the medial OFC patients reached the conceptual knowledge period and could accurately describe the advantages of profitable decks and the disadvantages of the risky ones; however, they continued to choose regularly from the disadvantageous decks, while showing no anticipatory SCRs. This study again demonstrated the dissociation of knowledge and behavior in OFC damaged patients, even indicating a double dissociation in some subjects. In addition to the gambling task, Damasio and colleagues (1990) have tested the autonomic activation responses of medial OFC damaged patients. Subjects in the task viewed sets of socially relevant pictures while SCR's were recorded. Subjects were medial OFC damaged patients, non-orbitofrontal brain damaged controls, and normal controls. Subjects viewed target slides depicting nudes, mutilation scenes, and disasters, all intended to elicit SCRs, as well as neutral stimuli lacking social significance. In an active condition, subjects were to give a verbal description of the scene, or a subjective impression, while in a passive condition no responses were required. Results indicated abnormal SCRs from the medial OFC patients for the passive condition only. In the active condition these patients showed appropriate SCR activity, suggesting that there may be an insensitivity to social implications if pictures do not undergo a threshold degree of processing. In a later study (Bechara et al., 1999) this hypothesis was suggested as being a possible basis for the slightly lower SCR activity of medial OFC patients compared to control subjects during gambling

task performance. Interestingly, one of the verbal reports from a medial OFC patient indicated that the subject suspected that they should have had certain feelings toward some of the target slides; however those feelings were absent. In terms of the overt and covert forms of processing referred by Bechara and colleagues (1997) the fact that the SCR activity was abnormal in the passive condition would correspond to the lack of a covert somatic state dependent on intact medial OFC, while the normal SCR present in the active condition could be due to the conscious processing necessary to respond verbally to the emotionally charged pictures.

The Somatic Marker Hypothesis of Damasio and colleagues (Damasio, 1995; Tranel et al., 2001) was aimed specifically at explaining the behavior of patients who had sustained damage to their medial OFC and serves as an explanation of the results of the gambling task and variations upon it. Such patients include E.V.R., who had relatively intact intellectual capacities, yet displayed disastrous decision deficits.

3.3 Induction of somatic state

Damasio used the term “somatic” (from Greek word “soma”, i.e. body) referring to collection of body-related responses that hallmark an emotion. somatic state can be induced from primary inducers and secondary inducers (Damasio, 1995).

Primary inducers are innate or learned stimuli that cause pleasurable or aversive states. Once present in the immediate environment, they automatically and obligatorily elicit a somatic response. Example of primary inducers include the encounter of a fear object, or a stimulus predictive of fear object. Primary inducers are also concepts or knowledge that through learning can automatically and obligatorily elicit emotional responses, such as hearing that you have won a prize or a lottery ticket, or that your life savings have been lost in a market crash.

Humans also automatically, involuntarily, and obligatorily elicit a “pleasure” response when they uncover a solution to a problem. This “aha” reaction to solving a puzzle is also an example of primary inducers.

Secondary inducers, on the other hand, are entities generated by the recall of a personal or hypothetical emotional event, i.e., “thoughts” and “memories” of the primary inducer, which when brought to working memory elicit a somatic state. Examples of secondary inducers include the emotional response elicited by the memory of encountering a snake, or the memory of losing a large sum of money. The imagination of being attacked by a bear, winning an award, or losing a large sum of money, are also examples of secondary inducers.

Evidence suggests that, in a normal brain, primary and secondary inducer processing can be elicited by the same stimulus and at the same time. Looking at a picture of a baby with a tumor growth may quickly and automatically trigger an emotional response (serving as a primary inducer), but at the same time, it may generate thoughts (e.g., picturing one’s own child in this situation) that operate as a secondary inducer (Bechara et al., 2003). The operations of the primary and secondary inducer systems are difficult to disentangle in a normal brain, and can best be brought to light in patients with lesions in structures critical for the processing of primary or secondary inducers (Bechara and Damasio, 2005). Furthermore the normal development of secondary inducers is contingent upon the normal development of primary inducers, i.e., if the processing of primary inducers were abnormal, then secondary inducer processing would be abnormal too. However, once secondary inducers have been acquired normally, the induction of somatic states by secondary inducers becomes less dependent on primary induction (Bechara et al., 2003).

The physiological steps that lead to the normal development of somatic states representations are the following:

1) The amygdala is an important *trigger* structure for somatic states from primary inducers. It couples the features of primary inducers, which can be processed subliminally via the thalamus (LeDoux, 1996; Morris et al., 1999) or explicitly

via early sensory and high-order association cortices, with the somatic state associated with the inducer. This somatic state is evoked via effector structures such as the hypothalamus and autonomic brainstem nuclei that produce changes in internal milieu and visceral structures along with other effector structures such as the ventral striatum, periacqueductal gray (PAG), and other brainstem nuclei, which produce changes in facial expression and specific approach or withdrawal behaviors. Several lines of animal and human studies support this functional role of the amygdala in triggering somatic states from primary inducers (Bechara et al., 2003).

2) Once somatic states from primary inducers are induced, signals from these somatic states are relayed to the brain. Signals from activated somatic states lead to the development of somatic state patterns in brainstem nuclei, and in somatosensory cortices (e.g., insular/SII, SI cortices, and cingulate cortices). After a somatic state has been triggered by a primary inducer and experienced at least once, a pattern for this somatic state is formed. The subsequent presentation of a stimulus that evokes thoughts and memories about a specific primary inducer will then operate as a secondary inducer. Secondary inducers are presumed to re-activate the pattern of somatic state belonging to a specific primary inducer and generate a fainter activation of the somatic state than if it were triggered by an actual primary inducer. For example, imagining the loss of a large sum of money (secondary inducer) re-activates the pattern of somatic state belonging to an actual prior experience of money loss (primary inducer). However, the somatic state generated by the imagination of losing a large sun of money is fainter than one triggered by an actual experience of money loss.

3) Provided that somatic states associated with secondary inducers develop normally, generating somatic states from secondary inducers is dependent on cortical circuitry in which the Ventromedial Prefrontal Cortex (VMPFC) plays a critical role. The VMPFC is a *trigger* structure for somatic states from secondary inducers. It serves as a convergence–divergence zone, which neuron ensembles can couple a certain category of event based on memory records in high order

association cortices to the effector structures that execute the somatic state, and to the neural patterns related to the non-conscious or conscious *feeling* of the somatic state.

In other words, the VMPFC couples knowledge of secondary inducer events to somatic state patterns related to "what it feels like" to be in a given situation. However, in some instances, the VMPFC couples knowledge of secondary inducer events to covert response effectors at the level of the basal forebrain or brainstem only. The anticipatory SCRs acquired during the pre-hunch period of our experimental gambling task are an example of this instance (Bechara et al., 1997). In this case, consciously pondering on which deck to choose from (a secondary inducer) elicits a covert somatic response, which is an expression of the *bias* process that leads the subject to choose the correct deck without any awareness of why the choice was made. Several lines of studies support the notion just presented, that the VMPFC is a trigger structure for somatic states from secondary inducers (Bechara et al., 2000; Bechara et al., 2003; Bechara et al., 2002).

3.4 The "body loop" mechanism of somatic markers

In one chain of physiological events, an appropriate somatic state is actually re-enacted in the body proper, and signals from its activation are then relayed back to subcortical and cortical processing structures, especially in the insular and SII and SI cortices. This anatomical system is described as the "body loop" because it engages the body.

A large number of channels convey body information to the central nervous system (spinal cord, vagus nerve, humoral signals). Evidence suggests that the vagal route is especially critical (Bechara, 2002). The enacted somatic state can then act at conscious or non-conscious level and influence activity in regions involved in *body mapping*, (i.e., holding patterns of somatic states that

help generate *feelings*), regions involved in the triggering of somatic states (e.g., amygdala and VMPFC), so that the threshold for triggering subsequent somatic states is increased or decreased, and regions involved in *working memory* (e.g., dorsolateral prefrontal cortex and other high order association cortices), so that a particular representation is strengthened or weakened. Indeed, the somatic marker hypothesis has posited that somatic states operate on decision making and working memory (Damasio, 1994).

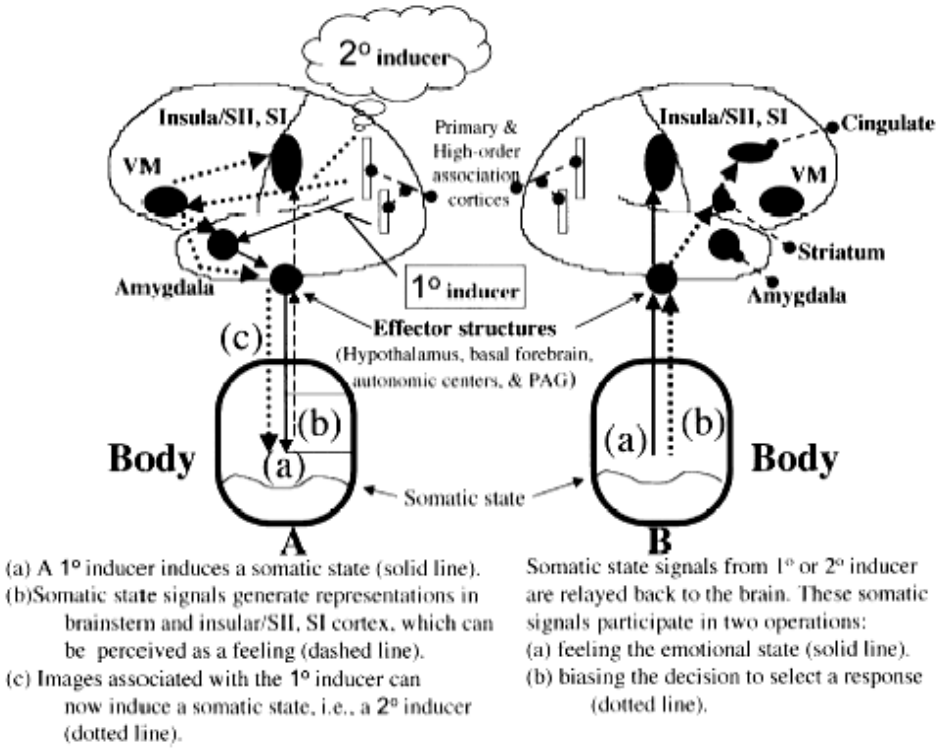


Fig. 3.2. Simple diagrams illustrating the **"body loop"** and **"as if loop"** chain of physiologic events. In both "body loop" and "as if loop" panels, the brain is represented by the top black perimeter and the body by the bottom one (Bechara et al., 2002).

The influence of somatic state signals on the contents displayed in working memory helps endorse or reject "objects" and "response options" (i.e., secondary inducers) brought to mind during the pondering of a decision, i.e., they help *bias* the options and plans for action; and finally, somatic state signals influence activity in regions concerned with motor responses and behavioral actions (e.g., striatum and anterior cingulate/supplementary motor area, SMA).

They interfere with response selection and thus render the occurrence of a given behavior more likely or less likely.

Bechara and Damasio (2005) propose that the biasing action of somatic states on response selection is mediated by the release of neurotransmitters in the telencephalon (i.e., the cerebral cortex) and the diencephalon, which includes the basal ganglia and thalamus. The cell bodies of all major neurotransmitter systems (e.g., dopamine, DA; serotonin, 5-HT; noreadrenaline, NA; and acetylcholine, Ach) are located in the brainstem; the axon terminals of these neurotransmitter neurons synapse on cells and/or terminals all over the telencephalon. When somatic state signals are transmitted to the cell bodies of these neurotransmitter neurons, the signaling influences the pattern of neurotransmitter release at the terminals. In turn, evidence from cellular physiology shows that neurotransmitters modulate synaptic activity by rendering the triggering of action potentials as more likely or less likely (see Mogenson, 1987). Thus changes in neurotransmitter release induced by somatic state signals modulate the synaptic activities of telencephalic neurons subserving behavior and cognition, thereby providing a mechanism for somatic states to exert a biasing effect on behaviors (e.g., selection of a response over another), feelings, and cognitive patterns.

During the deliberation of decisions, the mental representation of a future event triggers a somatic state, no matter how faint, which may be consciously perceived as a good or bad feeling, or processed unconsciously (Damasio, 1994; Overskeid, 2000). When somatic states from primary or secondary inducers cannot be detected as changes in physiological parameters within the body proper, they can at least be detected as changes in the activity of different neurotransmitter systems. Indeed, the anatomy of these neurotransmitter systems is consistent with this hypothesis, i.e., there are multiple direct and indirect connections between the amygdala and the VMPFC, and the neurotransmitter nuclei within the brainstem (Blessing, 1997; Nauta, 1971). Because after somatic states have been expressed they form patterns in nuclei of the brainstem and insular/SII, SI cortices, one possible chain of physiologic events is to by-pass the

body altogether, activate directly the insular/SII, SI cortices, and or the brainstem nuclei holding covert patterns of somatic states. In other words, instead of having somatic states expressed in the body, we propose that the activation of representations of somatic states in the brainstem and/or the cortex can induce changes in neurotransmitter release, without engaging the body. This anatomical system is described as the “as if body loop” because the somatic state is not re-enacted in the body. Although somatic signals are based on structures representing the body and its states, from the brain stem and hypothalamus to the cerebral cortex, the somatic signals do not need to originate in the body in every instance. Somatic states can in fact be “simulated” intra-cerebrally in the “as if body loop.” Thus the neural system mediating the activation of somatic states involves several neural regions: (a) the VMPFC, (b) the amygdala, (c) the somatosensory cortices (insular/SII, SI), (d) the basal ganglia, anterior cingulate, and brainstem nuclei, and the humeral and neural pathways that signal body states to the central nervous system.

3.5 Other proposal for the aberrant emotional and social behavior of patients with frontal lobe lesion s

Frontal lobe damage has long been linked to emotional/personality changes such as euphoria, irresponsibility, lack of affect and lack of concern for the present or future (Stuss and Benson, 1986). In addition, frontal lobe damage has been linked to impairments in social behavior. Patients with frontal lobe lesions have been describe as presenting diminished social awareness and a lack of concern for social rules (Stuss et al., 1996; Damasio, 1994). Frequently, increased levels of aggression and aberrant behavior are reported both when lesions are acquired early in life and when they occur in adulthood (Burges and Wood, 1990; Price et al., 1990; Grafman et al., 1996).

Probably the best documented case of a patient with emotional and behavioral changes following lesions to the OFC is the patient E.V.R. (see Eslinger and Damasio, 1985; Damasio, 1994). Damasio proposed that an impairment in a somatic marker system caused the aberrant social behavior.

Five other major proposal have been offered to the account for the aberrant emotional and social behavior of patients with frontal lobe lesions.

Rolls proposed that the inappropriate social behavior shown by patient E.V.R. may be related to a dysfunction in altering behavior appropriately in response to a change in reinforcement contingencies (Rolls, 1996). He suggested that the OFC is associated with rapid stimulus-reinforcement association learning, and the correction of these associations when they become inappropriate.

Grafman interpreted the patient's impairment in term of an inhability to access social schema knowledge stored in the frontal lobes (Grafman, 1994; Grafman et al., 1996). Social schema knowledge is thought to inhibit aberrant behavior. Patients with OFC lesions who cannot access to social schema knowledge fail to inhibit aberrant behavior, such as physical thereat and aggression. Dimitrov and colleagues (1996) found that some patients with frontal lobe lesions showed atypical performance on a task investigating ability to rate solutions to social problems according to their effectiveness. However, the patients who showed atypical performance were also those with the lowest IQs and poorest performance on the Wisconsin Card Sorting Test. It is thus unclear whether generalized intellectual or executive difficulties might explain their impaired performance on the experimental task. Moreover, Saver and Damasio (1991) found that, contrary to Grafman's hypothesis, E.V.R. showed intact knowledge on task such as the cartoon prediction test (O'Sullivan and Guilford, 1976) and the moral judgment interview (Colby and Kohlberg, 1987).

Baron-Cohen (1995) interpreted the patient's impairment in terms of damage to the neural circuit mediating Theory of Mind. Theory of Mind is defined as the ability to represent the mental states of other individuals who,

because of OFC damage, cannot represent the mental state others will be unable to modulate their emotional and social behavior. In line with this, Price and colleagues (Price et al., 1990) reported two cases who performed poorly on a test of visual perspective taking, and a SPECT neuroimaging study reported that the OFC was implicated in Theory of Mind processing (Baron-Cohen et al., 1994). However, it is unclear whether visual perspective taking requires the representation of mental states.

Brothers (1995, 1997) interpreted her patients' impairment in term of a social editor that is specialized for processing other social intentions. The editor encourage the rest of the brain to report on features of the social environment; effectively it focuses attention on stimuli, such as faces and expressions, that are particularly important in social interactions. The editor is considered a unitary system specialized for responding to social signals of all kinds, a system that would ultimately construct representation of the mind. Brother specifically argues against the idea of dissociable systems for what she terms "cold social cognition" (attribution of believe, Theory of Mind) and "hot social cognition" (processing the emotional expressions of others).

3.6 Recent study about decision making

The Iowa Gambling Task (IGT) was developed to simulate real-life financial decision (Bechara et al., 2004). In contrast to other task in which all necessary information is avalaible for making each decision (Elliot et al., 1999; Paulus et al., 2001; Rogers et al., 1999) the IGT is based on a long exploratory learning processes to evaluate long-term risk anticipation in decision making. Moreover, IGT performance is strongly influenced by emotional factors related to reward and penalties. The neural underpinning of the IGT has not yet been fully clarified. Poor performance of this task has been associated with lesions involving the VMPFC (Bechara et al., 1994, 1996, 1999) or amygdala (Bechara

et al., 1999, 2003). Recent lesion studies suggests the involvement of more extensive structures including the DLPFC for the IGT (Clark et al., 2003; Maners et al., 2002). Evidence from neuroimaging studies is limited. Using positron emission tomography (PET), Ernst and colleagues (2002) demonstrated widespread activations including the orbitofrontal, dorsolateral, prefrontal, and anterior cingulate cortices in healthy subjects. However, PET evaluates the summation of brain activity over a period of time (typically >1 minute), during which the IGT requires multiple cognitive components and should elicit complex emotional reactions. Hence, the most important component of the IGT -the anticipation of the long-term consequences associated with risky decision making- may not be appropriately highlighted by PET.

Fukui and colleagues (2004) used functional magnetic resonance imaging (fMRI) to assess the neural responses to risk anticipation during the IGT. They found evidence showing the significance of the VMPFC for the IGT performance: only the VMPFC showed significantly differential activations between the risky and the safe decisions, and the net scores of the IGT was significantly correlated with the magnitude of the medial prefrontal activity during risky decisions. From their point of view, the IGT capture more emotional components of decision making than do other conventional cognitive decision making tasks. In fact, the anterior part of the VMPFC was found to be activated in various emotion-eliciting experimental paradigms (Lane et al., 1997a,b). A limited number of studies have specifically focused on the anticipatory component of decision making (Breiter et al., 2001; Knutson et al., 2001a,b). In these studies, subcortical activation, particularly those of the nucleus accumbens, where demonstrated in addition to medial prefrontal or orbitofrontal activations. The differences would be depend from differences in the tasks used.

In a recent fMRI study, Daw and colleagues (2006) demonstrated that frontopolar cortex and intraparietal sulcus are preferentially active during exploratory decisions. In contrast, region of striatum and ventromedial prefrontal cortex exhibit activity characteristic of an involvement in value-based

exploitative decision making. Their results suggests a model of action selection under uncertainty that involves switching between explorative and exploitative behavioral modes, and provide a computationally precise characterization of the contribution of the key decision-related brain systems to each of these functions.

Their findings of brain regions implicated in exploration -and particularly in relation to prefrontal, high level control structure (Miller and Cohen, 2001)- is consistent with a theory in which exploration is accomplished by overriding an exploitative tendency, but is in trouble in the explanation of uncertainty bonus schemes, which more tightly entangle exploration and exploitation. Such anatomical separation would be unlikely under these latter schemes, because they work by choosing action with respect to an unified value metric that simultaneously prizes both information gathering and primary reward. Just such an exploration-encouraging value metric has previously been suggested to explain why dopamine neurons respond to novel, neutral stimuli (Kakade and Dayan, 2002); such anomalous responses in an otherwise typically appetitive signal remain puzzling in view of our failure here to find either behavioral or neural evidence for such an account.

A fighter pilot monitoring cockpit indicators, a stock-exchange trader checking prices, and a gambler playing blackjack in a casino all evaluate quickly whether events are good or bad and use them to make rapid decisions. There is still evidence for neural processing in humans that is not only fast enough to reflect this evaluation but also is directly related to choice behavior. Gehring and Willoughby (2002) reported the observation of neurophysiological activity with characteristic that are consistent with its involvement in rapidly evaluating the motivational impact of events and in guiding choice behavior. They reported the observation of neural activity that occurs within 265 ms after outcome stimuli that inform human participants about gain and losses in a monetary gambling task. A negative-polarity event-related brain potential (ERPs), probably generated by a medial-frontal region in or near the cingulate cortex; this medial frontal negativity (MFN) was greater in amplitude when participant’s choice

between two alternatives resulted in a loss than when it resulted in a gain. The sensitivity to losses was not simply a rejection of detecting an error; gains did not elicit the medial-frontal activity when the alternative choice would have yielded a greater gain, and losses elicited the activity even when the alternative choice would have yielded a greater loss. Choices made after losses were riskier and were associated with greater loss-related activity than choices made after gains. It follows that medial-frontal computations may contribute to mental states that participate in higher level decisions, including economic choices. The MFN responded to the motivational impact of the outcome event, not to the response- or error-feedback information. Moreover, its response to the preceding outcome mirrored the pattern of risk taking in behavior.

Their data suggest that a rapid assessment of the motivational impact of an event participates in the evaluation of outcomes and that this processing is particularly sensitive to losses. In decision-making behavior, such processing could affect non-normative decision making by mediating the role that outcome events play in choices. Studies of higher level decisions have shown that "losses loom larger than gains," meaning that the aversion to a loss of a certain magnitude is greater than the attraction to a gain of the same magnitude (Kahneman and Twersky, 1979). Consistent with this finding, studies of emotion have shown that affective responses are faster and stronger to proximate negative events than to positive ones (Cacioppo and Gardner, 1999; Taylor, 1991). In particular, the processing represented by the MFN could contribute to the experience that Kahneman (1999) refers to as "instant utility," which is the momentary mental state resulting from the continuous evaluation of events along a good-bad dimension. Such a computation can contribute to decision making by influencing the emotional state that individuals anticipate will occur upon making a choice (Mellers, 2000), or it may affect the emotional state that drives behavior at the moment of the choice itself (Loewenstein, 2000).

As for the neural circuitry that produces the MFN, the results of Gehring and Willoughby suggest that the ACC is likely to contribute to the MFN. The

medial-frontal scalp distribution of the MFN is consistent with an ACC origin, and the dipole localization modeling further supports an ACC locus. Moreover, the loss-related processing that gives rise to the MFN and the relation between the MFN and risky behavior are both consistent with evidence for a close functional relationship between the affective and behavioral control functions of the ACC (Bush et al., 2000; Paus, 2001), and in particular with evidence for a sensitivity of ACC activity to reductions in reward or to penalties (Knutson et al., 2000).

4. Emotion modulation: *role played by the OFC*

4.1 Experiment 1: Reduced startle reflex and aversive noise perception in patients with OFC lesions

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 *et al.*, 1999; Angrilli *et al.*, 1999; Damasio *et al.*, 1990; Stuss & Benson, 1984). However, within the emotional domain, the specific role of OFC 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 (LeDoux, 1995; Bechara *et al.*, 1999), and the OFC in learning social behaviors and 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 (Rolls, 1999), 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 stimuli is increased by fearful or anxiogenic background emotional states (Grillon & Davis, 1995, Lang *et al.*, 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 et al., 1991; Davis, 1992 a, b). 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 also 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 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 (Critchley et al., 2003; Damasio et al., 1990; Angrilli et al., 1999) 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.

4.1.1. Participants

Six male patients (mean age= 25.83, SD= 5.4, range= 20-35) with OFC lesions following a traumatic brain injury event, participated in the study after their signing the 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 4.1.1) 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 a leading neurologist.

		Patients					
		BI	BR	RS	SD	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

Tab. 4.1.1. 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).

Since it is difficult to collect a sample from very confined lesions, a double criterion was planned to guarantee a selection of a homogenous sample of patients: lesion location on 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 4.1.1). Patients

with large lesions involving also 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 4.1.1).

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 (Figs. 4.1.1 C and B) and on a specific coronal section at the level of the maximum extension of the group lesion (Fig. 4.1.1 C). 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 orbital and medial subdivision of the orbitofrontal cortex, including the rostral portion of the superior and inferior frontal gyri, corresponding to the whole of Brodmann area 10 and the rostral portion of area 9 (polar frontal cortex according to Ramnani and Owen, 2004). In a few patients, the lateral portion of Brodmann areas 9, 45 and 46 were also involved (Figs. 4.1.1 A-B-C).

Lesions were bilateral, typical of closed head injuries, with a slight greater involvement of the right polar orbitofrontal regions (Fig. 4.1.1 C). The ventromedial prefrontal cortex and anterior cingulate were essentially intact in our samples.

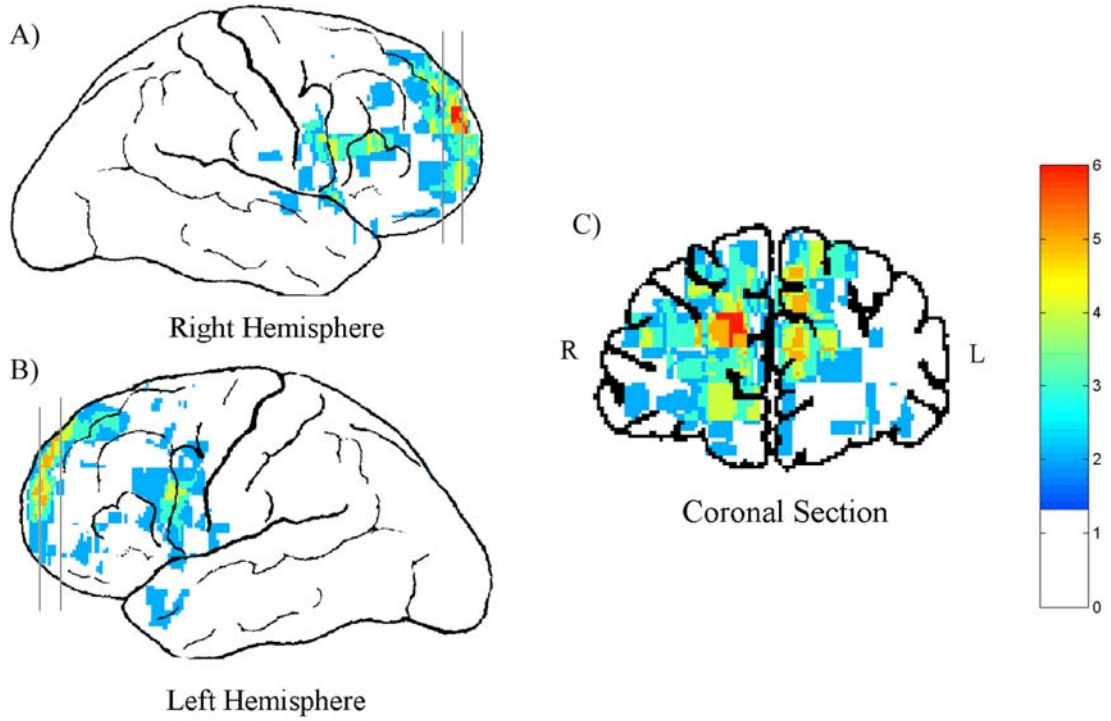


Fig 4.1.1. **Map showing average cortical lesion of patients**. Color code lesion density, i.e. areas with two (blue), three (green), four (yellow), five (orange) or six (red) overlapping lesions. Right (A) and left (B) lateral viewing of group lesion, and coronal section (C) of OFC at the level of maximum lesion density.

Data collected from OFC patients were compared with those from a group of twenty healthy matched male controls (mean age= 23.55, *SD*= 2.6, range= 20-28), with no history of neurological disease, head injury, drugs abuse, alcoholism, stroke or psychiatric disorders (statistic for age factor*:* $t_{(24)}$= 0.16, *ns*). All participants provided their written informed consent to the study.

4.1.2. Procedures

Eight acoustic startle stimuli were presented to subjects through closed headphones during a rest condition with open eyes. The startle probe consisted of an unexpected 100dBA burst of white noise of 50 ms duration, with instantaneous rise time. At the end of the startle session, participants were asked how much unpleasant the loud noises were in the headphones on a 0-10 scale. Inter-stimulus interval was randomly varied between 11000 and 14000 ms.

The eyeblink component of the startle response was measured by recording EMG activity over the orbicularis oculi muscle of the left eye, with two 6 mm Ag/AgCl electrodes placed below the lower eyelid at a distance of 10 mm from each other, and one ground electrode placed on the left subclavicle fossa. The raw EMG signal was amplified with a gain of 10000 and filtered with a 16 Hz high pass and a 340 Hz low pass. The signal was also rectified and integrated with a 100-ms time constant integrator. Activity from the orbicularis oculi muscle was sampled at 250 Hz 0.5 s before and 1 s after the startle probe. Raw startle data were visually inspected to detect and reject rare artifacts and, after averaging all accepted trials, the latency of the greatest peak found in the 20-100 ms time interval was used to set a 20-ms window centered on the peak (see, for analysis, also Angrilli et al., 1996).

Data acquisition and analyses were performed with a LabVIEW software (National Instruments) according to Angrilli (1995). Within the 20 ms peak-adjusted time window, the mean value of the integrated startle and peak latency, as well as noise unpleasantness, were tested for group statistical effects by means of one-tailed Student t-test for independent samples.

4.1.3 Results

Analysis of the mean startle amplitude revealed a significant smaller response in OFC patients compared with controls ($t(24)= 3.84$, $p<0.001$ one-tailed; OFC patients, mean= 1.13 μV DS= 1.22 μV; controls, mean= 10.37 μV, DS= 5.77 μV).

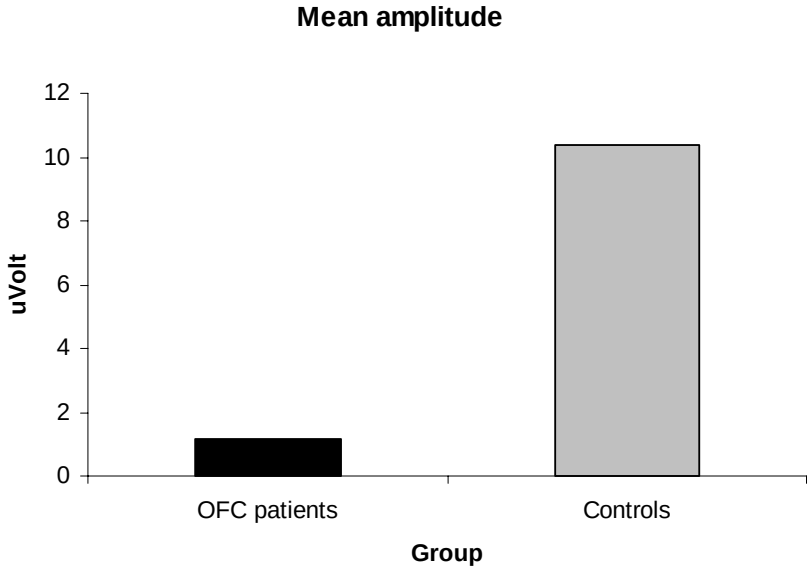


Fig. 4.1.2. **Amplitude of startle response** in OFC patients and controls. Startle response was recorded from integrated EMG of left orbicularis oculi in a 20-ms time window centered on mean individual peaks.

Analysis of startle peak latency showed no difference between the two groups (OFC patients, mean= 72.50 ms DS= 9.64 ms; controls, mean= 70.15 ms, DS= 3.48 ms).

After the experimental session, each participant was asked how unpleasant the loud noise heard in the headphones was. Statistical analysis revealed significant differences between groups in self-perceived unpleasantness ($t(24)= 1.95$, $p<0.03$ one-tailed): OFC patients perceived the white noise as less unpleasant than controls (OFC patients, mean= 4.50 DS= 2.07; controls, mean= 6.45, DS= 2.16).

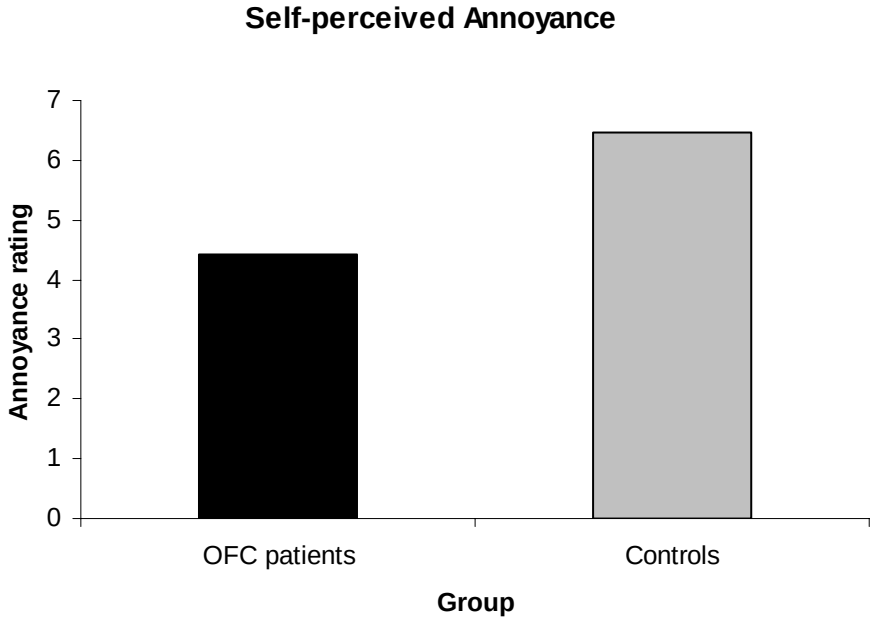


Fig. 4.1.4. **Self report of unpleasantness** of 100-dB acoustic probe eliciting startle reflex in OFC patients and in matched controls. Evaluation was collected soon after startle recording session on a 0-10 scale.

4.1.4 Discussion

Animal neurophysiological models of human emotional responses have been effective in studying amygdala and fear responses (LeDoux, 1995; Davis,1992 a, b) but they are necessarily less reliable when studying the influence of the prefrontal cortex on emotions, mainly because the frontal cortex is extremely small in rats and cannot be functionally compared with the corresponding human cortical region. On one hand, past investigations with rats found that lesions of the OFC, especially in early infancy, resulted in severe alteration of defensive responses and social behavior (Pellis *et al.*, 2006) - a result which is consistent with human studies (Adolphs, 1999; Anderson *et al.*, 1999) on infant lesions of the orbital part of the prefrontal cortex. On the other hand, studies in rats have found essentially no effects of lesions of the medial

prefrontal cortex on the startle reflex and its modulation (Gewirtz *et al.*, 1997; Rosen *et al.*, 1992). Thus, results on rats provide limited evidence that the OFC is relevant for secondary learned emotional behaviors but not for primary emotional responses represented by the startle reflex.

Unlike animal studies, clinical and scientific observations of more severe disorganization of behavior and emotions in adult patients with OFC damage, associated with the evidence of a reduced arousal level and activation modulation (Angrilli *et al.*, 1999; Bechara *et al.*, 1999; Damasio *et al.*, 1990), led us to hypothesize an impaired startle response and reduced perception of the aversiveness of the startle probe in these patients. In the present sample of patients selected for lesions limited mainly to the polar OFC, our hypothesis was confirmed, as we found a marked depression of the startle response, no substantial difference in startle latency, and a significant decrease in the perceived unpleasantness of the acoustic startle probe. The burst of 100-dB white noise used to elicit the defensive blink reflex was typically perceived as moderately unpleasant by controls, and in particular it was evaluated very aversive by healthy subjects with heightened startle, whereas our patients did not find this noise aversive - a result which is consistent with the concurrent reduction of the primary startle reflex, and with literature showing, the reduction of emotion-related skin conductance responses, especially to negative stimuli, and insensitivity to punishment and monetary loss in prefrontal lesion patients (Angrilli *et al.*, 1999; Damasio *et al.*, 1990; Tranel & Damasio, 1994). Similar results on reduced startle amplitude have recently been observed in humans suffering from Traumatic Brain Injury (TBI) (Saunders *et al.*, 2006). Although results from TBI patients are consistent and support our present data, unfortunately lesion location was not made in the above study. Since traumatic brain injuries typically include a mixture of lesions which may involve the frontal, temporal, occipital cortex and several other brain regions, in some patients the lesion may spare the orbitofrontal cortex in others, the anterior temporal lobe with the amygdala may also be involved. Therefore, results

obtained from TBI patients in the absence of lesion mapping are ambiguous, and may imply either lesions of the amygdala or the absence of any lesion of the OFC. However, in addition to the problem of obtaining lesion map from patients, it is necessary to clarify what subdivision of the orbitofrontal cortex was investigated by other authors (see note 1). Indeed, there are three PFC subregions considered to be important for the modulation of emotional arousal in humans: the most inner and caudal ventromedial prefrontal cortex (Bechara *et al.*, 1999; Damasio *et al.*, 1990) which is closely connected with the hypothalamus and amygdala; the anterior cingulate (Tranel & Damasio, 1994; Angrilli *et al.*, 1999), an important portion of the limbic system connecting the anterior thalamus and the reticular system with the rest of the cortex; and the polar orbitofrontal cortex, apparently less directly involved in the integration of cortical-subcortical afferents compared with the other two, deeper frontal regions (see, for frontal regions and their connections, Barbas et al., 2003; Krawczyk, 2002; Ramnani and Owen, 2004; Rolls, 1999).

Our results also provide some indications on the neural circuit of the human startle response. Although this circuit in rats is essentially subcortical and is well-known and described (Davis *et al.*, 1991; Davis, 1992 a, b), in humans it is still relatively unknown. Indeed, in rats, the acoustic startle involves a main pathway going from the ear to the ventral cochlear nucleus, the motoneurons of the spinal cord, the body muscles eliciting the jump reflex and cage acceleration (Davis *et al.*, 1991). The central node where afferents, for example from the secondary circuit controlled by the amygdala, are directly connected the main circuit, is the nucleus reticularis pontis caudalis (NRPC). The amygdala contains neurons which are highly sensitive to the rapid sensory changes that typically characterize the startle probe, and exerts a facilitation effect on the reflex itself by acting directly on the NRPC (Davis, 1992 a, b). The startle reflex in humans is also modulated by their more complex emotional background (Grillon & Davis, 1995; Lang *et al.*, 1993), and the human amygdala is able to modulate both the primary reflex and the emotional background related response (Angrilli *et al.*,

1996). Subsequent studies on more numerous samples of patients with larger lesions (temporal lobectomy) involving the amygdala have confirmed its role in the human startle reflex (Buchanan *et al*., 2004; Funayama *et al.*, 2001; Kettle *et al.*, 2006).

Past studies indicate that the prefrontal cortex subregions represented by the ventromedial cortex, anterior cingulate and polar orbitofrontal cortex, can modulate the autonomic nervous system top-down but they also include fundamental crossing pathways for the bottom-up modulation of all cortical arousal (Angrilli *et al.*, 1999; Critchley *et al.*, 2003; Damasio *et al.*, 1990; Stuss & Benson, 1984; Tranel & Damasio, 1994), from the ascending reticular activating system and the two main diffuse neurotransmitters involved, serotonin and noradrenalin. This interpretation fits observations made by means of retrograde tracers of direct bidirectional connections between the OFC/medial prefrontal cortex on one hand, and hypothalamus, amygdala and lower brainstem on the other hand (Barbas et al., 2003). These connections allow fast efficient cortical control of arousal modulation and autonomic activity. It is probability that these direct pathways run parallel and synapse with the reticular formation at some levels. The present study shows that, within the prefrontal cortex, an important role is played by the polar OFC, a superficial cortical region placed more anteriorly with respect to the anterior cingulate and ventromedial prefrontal cortex, which is in itself sufficient to produce severe impairment of the primary avoidance emotional response represented by the startle reflex. Thus, although for some psychophysiological domains of emotional responses, the amygdala and medial prefrontal cortex seem to play different roles (Bechara *et al.*, 1999), for the modulation of the primary defensive startle reflex, in addition to the amygdala, also the OFC plays a crucial role in the direct modulation of the startle response.

To our knowledge, results of the present study have shown the influence of human polar OFC on the startle response for the first time - finding which adds to current literature on the human startle reflex circuit but is also important

psychobiological theories of emotions and for psychiatry. As an example from the last mentioned field, the observation of reduced prefrontal gray matter (Raine et al., 2000) and reduced startle reflex to aversive stimuli (Patrick et al., 1993) in criminal psychopaths, together with the results of the present study, provide further support to the use of OFC lesions as a valid neurological model of human psychopathy (Anderson et al., 1999; Blair & Cipolotti, 2000; Damasio et al., 1990).

4.2 Experiment 2: Emotion modulation of the startle reflex in OFC patients

Converging evidence from lesions of the orbitofrontal cortex in both non-human primates and humans as well as neurophysiological recordings in non-human primates has led to a number of theories on the functional role of these regions. In humans, damage to the prefrontal cortex causes major changes in emotion, personality, behaviour and social conduct. Patients often show lack of affect, social inappropriateness and irresponsibility (Hornak et al., 2003; Rolls et al., 1994 ; Bechara et al., 1994, 1999). Most literature shows that prefrontal lesions induce both cognitive and emotional deficits (Kringelbach & Rolls, 2004; Blair and Cipolotti, 2000). The cognitive deficits associated with frontal lobe lesions are well known, and many neuropsychological tests have been developed and standardized to measure the specific functions supported by this anatomical structure. More recently, there has been an increasing interest in emotional deficits originating from frontal cortex damage. The behavioural and emotional alterations are so pervasive that they also affect most everyday activities and social functioning. In fact, patients are often completely impaired in finding and keeping a job, and generally in social skills and decision planning (Bechara et al., 1997, Angrilli et al., 1999). Despite this evidence, it is commonly argued that the lack of such capabilities is a consequence of the cognitive deficits typically observed in frontal lobe syndromes. Unfortunately, given the large extent of most brain lesions, many patients show both the classical frontal lobe deficits and emotional impairment, and patients with dissociation between the two functions are rare. There is agreement on the fact that patients with pure emotional deficits have more limited lesions, at the level of the orbitofrontal cortex, which spare the dorsolateral areas. Damasio (Bechara et al., 1997; Damasio et al., 1990; Tranel & Damasio, 1994) first advanced a coherent hypothesis based on the evidence of a lack of autonomic response to emotional stimulation in patients with ventromedial frontal damage. According to the hypothesis, autonomic activation

provides the covert information (implicit knowledge) related to past emotional experiences, which is necessary to find a solution (decision) in complex everyday situations.

Processing of emotions, especially negative emotions, appears to be mediated by a system encompassing the limbic system and the orbitofrontal cortex (Adolphs, 2002). Within this temporofrontal system, it has been suggested that discrete neural systems mediate different emotions (Adolphs, 2002; Adolphs, et al., 1996). Neuroimaging, clinical, and experimental studies suggest that there may be hemispheric asymmetry in the processing of different emotions, leading to a view that the right hemisphere is dominant either for all emotions or for negative emotions specifically (Saunders et al., 2006).

The startle paradigm provides an indirect, implicit and sensitive measure of emotional experience. In animal as well as in human research the most effective index used to measure the aversiveness of an emotional state is the startle reflex, an immediate and progressive flexor movement of the muscles involving the entire body. From an evolutionary point of view the startle reflex constitutes an integral part of avoidance responses. Individuals' startle responses, when viewing emotional material are sensitive to valence (Lang et al., 1990). Furthermore, the startle reflex is automatic and independent of conscious behavior and voluntary control. Unlike facial expression it is unaffected by demand characteristics and subject reporting (Bradley et al., 1999). The amplitude of the usual eye-blink induced by a loud noise is typically 'potentiated' by unpleasant emotional states. In humans, research on emotions has shown startle potentiation in a variety of aversive conditions, such as during shock-expectancy as compared with a safe, neutral condition (Grillon and Davis, 1995), during fear imagery in comparison with neutral and pleasant imagery (Vrana, 1995), expecting unpleasant stimuli versus neutral ones (Haerich, 1994), or when viewing emotive slides (Bradley et al., 1993).

Only a few studies have used the startle probe procedure to examine emotional experience in brain-injured populations (e.g. Saunders et al., 2006,

Angrilli et al., 1996). The normal pattern of startle magnitude and a lack of potentiation to unpleasant pictures has been reported in one patient with a right amygdala lesion (Angrilli et al., 1996). These studies suggest an important role for the right amygdala, in particular, in negative emotional states, although they remain inconclusive with regard to the role of the orbitofrontal cortex in emotion modulation. It should be noted that a considerable number of patients reported as "VMPFC damaged patients", including the famous Phineas Gage (Damasio et al., 1994) or EVR (Bechara et al., 1994), actually had medial prefrontal damage in addition to the orbitofrontal ones (Bechara et al., 1996). The functional relationship between OFC and medial frontal cortices remains to be elucidated (Fukui et al., 2005).

The aim of the present study was to investigate the role of the orbitofrontal cortex in emotion processing. For this purpose we studied a group of patients with localized lesions to the orbitofrontal cortex with sparing of most of the dorsolateral areas. All patients showed a pure emotional impairment, without relevant cognitive deficits. We expected in these patients an emotionally altered startle response pattern compared to the normal 'potentiation-inhibition' pattern of the control group.

4.2.1. Participants

Eighteen male patients (mean age=26.44 years, SD=6.16 , range=18-37) with OFC lesions following a traumatic brain injury event, participated in the study after their signing the 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, 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 leading neurologist .

Since it is difficult to collect a sample from very confined lesions, a double criterion was planned to guarantee a selection of a homogenous sample of patients: lesion location of 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 4.2.1).

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 six patients, on the Tower of London in two, on the Wisconsin Card Sorting Test in one (Table 4.2.1).

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 (procedure was describe in par. 4.1.1)

		Neuropsychological Tests												
		MMSE	Span*	Tower of London*	Semantic Incidental Memory*	Raven Progressive Matrices*	Fonemic Fluency*	Semantic luency*	Selective Attention Matrices*	Story memory*	WCST perseverations*	TMT A*	TMT B*	TMT A-B*
Patients	AM	30	1.87	1.65	-0.9	0.78	0.83	0.86	0.66	0.62	1.95	-0.5	0.41	0.87
	SZ	29	0.88	-0.6	0.1	0.65	-0.8	0.19	0.66	-0.2	-0.5	1.68	1.01	0.07
	SZ	28	-1.1	-1.9	-1.3	0	-1.6	-0.7	0.36	-1.7	-2.7	2.54	5.62	5.55
	AG	30	-0.1	1.37	0.1	0.92	-2.4	-1.4	0.22	-1.2	-0.5	-0.7	0.77	1.09
	GS	30	-0.1	1.1	0.1	1.05	-1.8	-1.4	0.96	0.29	-0.4	-0.1	0.38	0.47
	RN	27	-0.1	-4.9	-1.8	0.51	-1.6	-0.5	-0.5	-1.6	0.81	1.4	0.93	-0.3
	MP	29	0.88	2.2	-1.3	0.78	-1.4	-1.1	0.96	0.73	-0.4	1.07	-0.63	-0.3
	AC	29	0.88	0	-1.3	-0.3	-3.3	0.33	-1.1	0.62	-0.7	0.35	3.42	2.71
	AB	28	1.87	0.28	-0.4	0.38	-2.9	-0.2	-2.2	0.39	-0.8	0.75	1.32	0.75
	PZ	29	0.88	1.1	0	0.51	-0.4	-0.3	2.58	0.63	-0.5	1.92	-2.97	1.37
	ML	28	1.87	0.28	0.57	2.85	0.09	0.86	-1	0.51	0.04	1.68	1.36	0.49
	AB	24	-0.1	-0.8	-2.3	-0.7	-2.3	-1.9	0.97	0.33	-0.6	0.81	3.3	3.26
	IB	30	-0.1	2.19	-0.4	-1.2	-1.9	-0.7	-1.1	0.62	1.44	1.54	7.96	8.44
	RB	28	-0.1	0.27	-1.3	0.92	-0.9	-0.3	-1.3	-1.1	3.2	-0.6	2.13	2.93
	SR	30	-0.1	-0.3	-2.8	0.5	-0.9	0.9	0.06	-1.3	1.15	-0.6	-0.87	-0.9
	DS	29	-0.1	3.25	-1.8	1.32	0.21	1.13	0.66	1.16	-0.7	-0.9	-0.43	0.07
	MV	30	1.87	0.81	-0.4	0.93	0.46	-1	-2	-0.3	-0.3	2.16	2.32	1.32
	DZ	29	-0.1	0.27	-1.8	0.65	0.09	0.33	0.07	1.05	0.42	1.01	3.83	3.86

Tab. 4.2.1. 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).

Lesions were bilateral, typical of closed head injuries, with a slightly greater involvement of the right polar orbitofrontal regions (Fig. 4.1.1). The ventromedial prefrontal cortex and anterior cingulate were essentially intact in this sample.

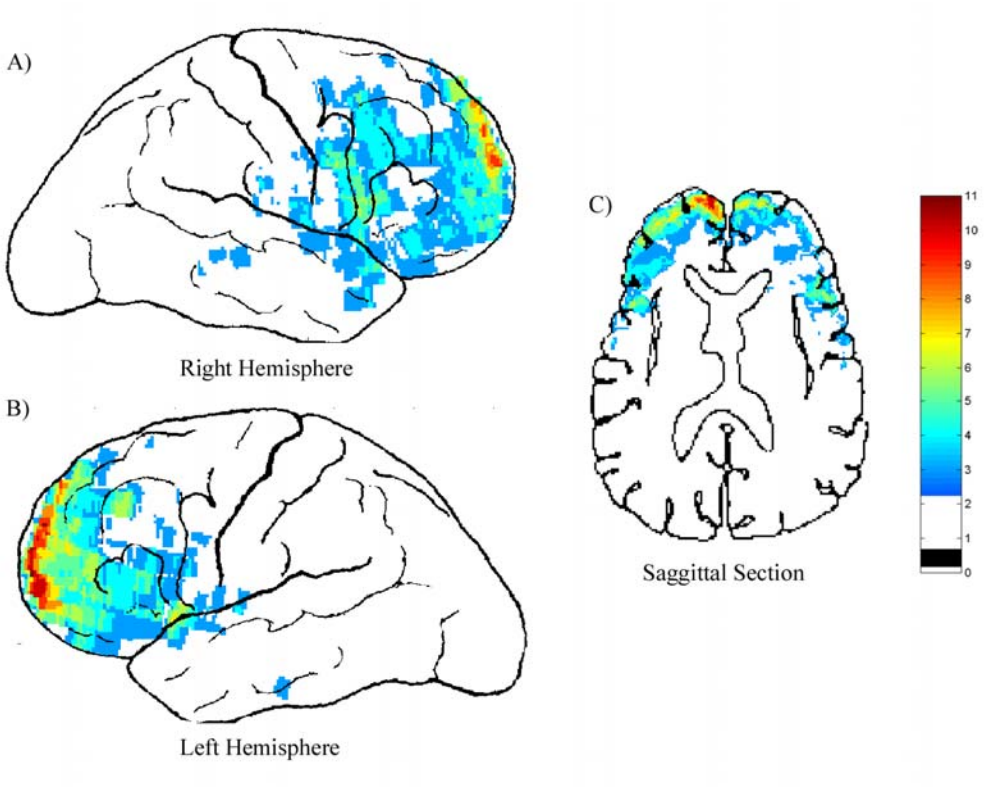


Fig 4.1.1. **Map showing average cortical lesion of patients**. Right (A) and left (B) lateral viewing of group lesion, and saggital section (C) of OFC at the level of maximum lesion density.

Data collected from OFC patients were compared with those from a group of thirty-eight healthy male controls (mean age 24.52 years, SD=3.41 , range=18-32) with no history of neurological disease, head injury, drugs abuse, alcoholism, stroke or psychiatric disorders (statistic for age factor: $t_{(54)}$=1.584; p=0.119; ns). All participants provided their written informed consent to the study.

4.2.2. Stimuli

Sixty digitized pictures were selected from the International Affective Picture System (I.A.P.S, CSEA, 1999; Lang et al., 1999). Pictures were divided into three groups according to normative ratings of emotional valence and arousal on a nine-point scale. Groups included pleasant pictures (positive condition: mean valence = 7.55; mean arousal =7.05) representing happy people, naked women, sport scenes; neutral pictures (neutral condition: mean valence = 4.89; mean arousal =2.52), household objects and city views; unpleasant pictures (negative condition: mean valence = 2.11; mean arousal = 6.46) of aimed guns, war scenes and blood/injuries. Pictures were selected starting from a priori ratings of arousal and valence (Lang et al., 1999). Such ratings were scored on a nine-point scale (Self Assessment Manikin, SAM; Bradley and Lang; 1994).

Each slide was projected for 6 s, and the inter-stimulus interval varied randomly between 5 and 8 s. Startle probes were presented randomly on half of the trials in each valence category.

The acoustic startle stimulus consisted of a 50ms presentation, 100dBA burst of white noise with instantaneous rise time. This stimulus was presented over matched headphones, whenever planned, 4 s after picture onset.

Upon arrival, participant were given general information about the experiment, and their written informed consent was obtained. Subject were then seated in a comfortable chair and physiological sensors were attached. The participants was instructed to view each picture as it appears on the screen. Furthermore participants was instructed that brief noises heard over the headphones could simply be ignored. At the end of the first session was asked to participants how unpleasant brief noises over the headphones was perceived as annoy. During a second session, startle-free, self-report of pleasure and arousal of each picture was measured using the Self Assessment Manikin (SAM; Bradley & Lang, 1994). At the end of the study, participants were debriefed and thanked.

During a following session, about one week later, patients were screened with a neuropsychological battery, to investigate their cognitive function.

4.2.3. Physiological recording and data analysis

Physiological recording and data analysis were described in par. 4.1.2 (p. 53).

4.2.4. Results

A significant Group Main Effect ($F(1, 54)=4.375$, $p<0.05$) was observed, indicating that OFC group showed a lower startle response amplitude for all the Conditions.

The significant Group x Condition interaction ($F(2,108)=5.512$, $p<0.005$) provide an interesting information on OFC response pattern compared to controls. As expected (Bradley et al, 2001) control group showed a valence-related pattern response: startle reflex magnitude varied as function of specific unpleasant content, in particular Post Hoc Newman-Keuls comparisons revealed that controls discriminated between neutral and unpleasant condition ($p<0.05$) and between pleasant and unpleasant ($p<0.005$).

OFC Group showed an atypical response pattern: Post hoc Newman-Keuls comparisons pointed out that patients did not discriminate between pleasant and unpleasant conditions ($p=0.792$), conversely, they had an enhanced response to neutral vs emotional conditions (pleasant vs neutral, $p<0.05$; neutral vs unpleasant, $p<0.05$). These results indicated that OFC group showed a lack of potentiation during unpleasant slides view.

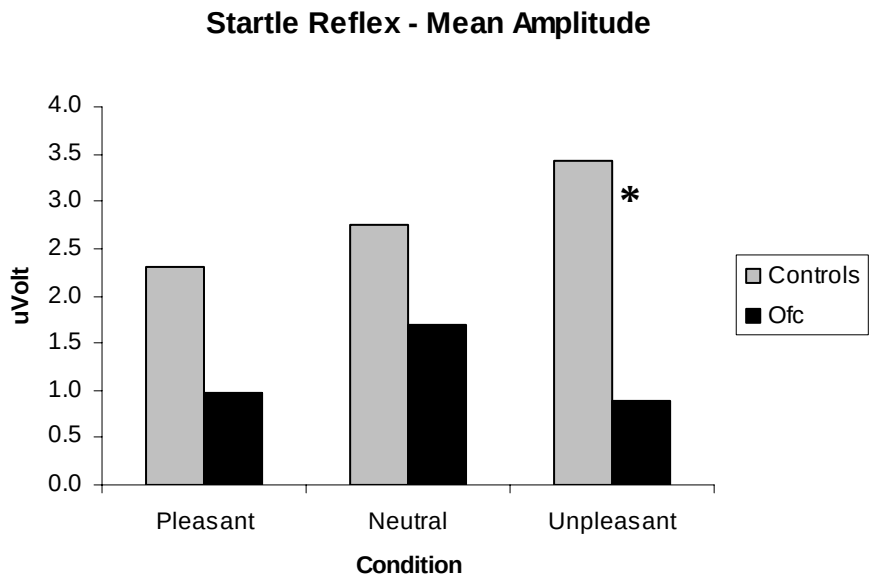


Fig. 4.2.1. **Mean amplitude of the startle reflex** in OFC patients and Controls for all the conditions. Controls showed a normal inhibition/potentiation of the startle reflex; OFC patients showed an inhibition during viewing of unpleasant stimuli..

No significant effects were found for Latency analysis. These results indicated that there were no differences between groups for latency measures.

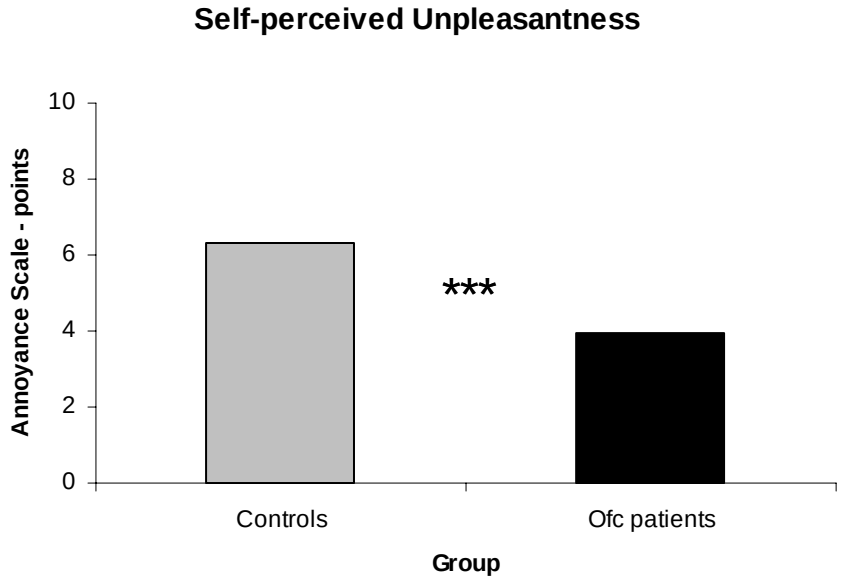


Fig. 4.2.2. **Self report of unpleasantness** of 100dB acoustic probe eliciting startle reflex in OFC patients and in matched controls. Evaluation was collected after picture-viewing session on a 0-10 scale.

After experimental session participants were asked how unpleasant brief noises over the headphones were perceived. t-test showed significant differences between groups in self-perceived annoyance ($t(54)=-3.828$, $p<0.005$): patients perceived the white noise as less unpleasant than controls did.

Analysis of self-perceived arousal pointed out a significant Group x Condition interaction ($F(2,108)= 7.525$, $p<0.001$). Post Hoc Newman-Keuls comparisons revealed that control group showed, as expected (Lang et al., 1999), an higher self-rating for emotional-content slides vs neutral (pleasant vs neutral, $p<0.05$; neutral vs unpleasant, $p<0.01$; pleasant vs unpleasant, $p=0.504$). On the other hand OFC group self-rating showed a different pattern, in particular they evaluated unpleasant slides as less activating than pleasant ($p<0.05$). Furthermore patients estimated unpleasant slides as less activating than controls ($p<0.005$).

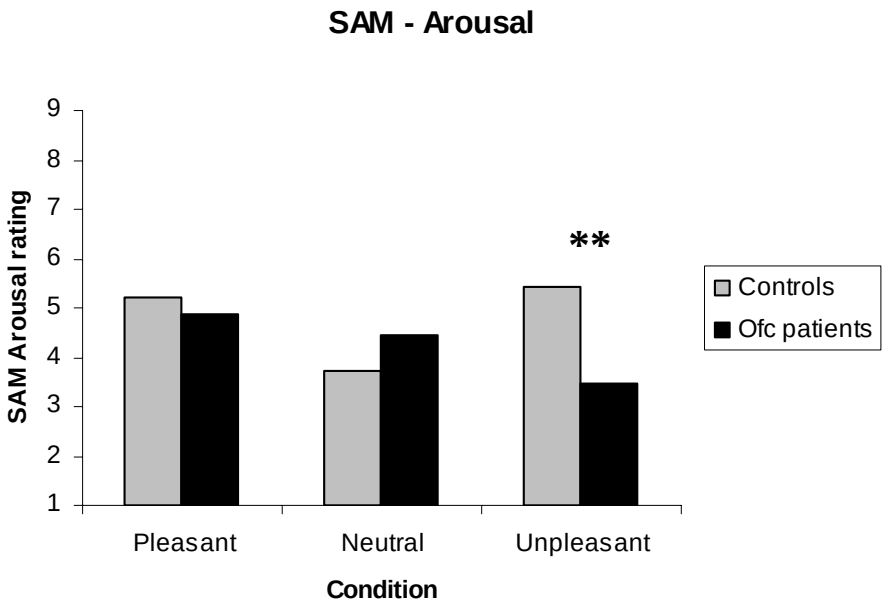


Fig. 4.2.3. **Self Assessment of slides arousal** in OFC patients and matched controls. SAM evaluation was collected during a second viewing session startle free.

Analysis of emotional valence revealed a Condition Main Effect, as both groups showed lower ratings to increasing unpleasantness ($F(2,108)= 3.572$, $p<0.05$), and a Group Main Effect ($F(1,54)= 17.428$, $p<0.00001$) in which OFC patients showed lower valence ratings with respect to controls for all the conditions.

4.2.5 Discussion

For the first time in this work we demonstrated the contribution of pOFC in primary emotional responses (startle) and secondary learned emotional behaviors (emotional modulation of the startle reflex), and the role of this associative cortex in negative/aversive stimuli elaboration. In this studies there are three main findings. First, like in the first experiment, OFC patients showed an overall reduction of the startle reflex in comparison with healthy control group. Second, startle potentiation induced by a negative emotional background, as seen in control group, was not only missing in OFC patients, but even inhibited. Controls' responses were in accordance with other studies (Bradley et al., 1993). Third, as OFC patients showed a reduced startle reflex, they either evaluated startle probe less annoying than controls did. As in previous study pOFC patients showed an overall reduction of the startle reflex, a lower self-perceived aversiveness of startle noise with respect to controls, demonstrating that OFC play a key role in the top-down control of the startle reflex. Moreover these data extend our knowledge about functions of OFC in modulation of the startle reflex by unpleasant context.

Despite large effort in defining the alterations of high level functioning of these areas, we still don't have sufficient knowledge about the relationship between OFC and basic autonomic functions. Our results contribute on making specific hypothesis about that. It's known that OFC is a part of the limbic system, which is composed by several structures that work together in a very

strictly integrated way. It's known that OFC has several connections both bottom-up and top-down with sub-cortical structures (Öngür et al., 1998; Öngür and Price, 2000), and following OFC lesion several emotional behavioural deficits have been observed (e.g. Bechara et al, 2000a; Fellow and Farah, 2005a,b). In other words, it seems that aversive brain system (Lang et al., 1990), which is normally activated by negative context, following OFC lesions is specifically inhibited. Thus, OFC could be responsible of aversive system regulation. Patients' response pattern, during pleasant and neutral pictures viewing, did not differ from controls' pattern. These indicates that aversive and appetitive system are independent. Moreover, we can observe that there is a circular linking between complex elaboration level and behavioral somatic and subjective responses: OFC patients showed not only reduction of overall startle reflex, but also evaluated startle probe as less annoying than control did. These results suggest that the cognitive emotional evaluation of the startle probe annoyance is coherent with the physiological reaction, that means that the return pathway of the sensation to the cortical elaboration level is intact, but clearly dampened. Results about emotional valence and arousal ratings are in accordance with the hypothesis that OFC plays a pivotal role in emotional driving specifically under aversive context. In sum, we can assert that these patients showed a specific main deficit for unpleasant experiences.

In a series of experiments Bechara and colleagues (Bechara et al., 2000) concluded that VMPFC patients did not show impairment in working memory, have a normal recall of emotional events, and that deficits of these patients are not related to an impairment of emotion retrieval. Furthermore, they found that patients have a less intense experience of emotion, and proposed that if the experience of emotion (like punishment) would be more intense, these patients could overcome the failure to re-experience the emotional state of punishment, and therefore improve the decision making capacity.

Our results conversely demonstrate that OFC is crucial in emotion processing, and in particular in encoding of emotional negative stimulation.

These findings support the idea that OFC patients have a specific impairment in elaboration of negative feedback (lack of frustration of punishment), already at a basic level, that unavoidably inhibits their retrieval process. Lesions of the OFC interfere with the normal processing of somatic/emotional signals, but leave other cognitive functions minimally affected. This damage leads to pathological impairments in decision making process which seriously compromise the efficiency of everyday-life decisions. Damasio and colleagues demonstrated, by means of SCRs, that patients with PFC lesions showed an impairment in anticipation emotional processes that guide decision making.

Results of this experiment, therefore, clarify the role of the OFC, and explain, at a basic level, behavioural deficits described by Damasio (Damasio et al., 1990; Tranel and Damasio, 1994): specific deficits in primary emotion processing would compromise adequate punishment and reward processing. Taken together these data are consistent with the view that mood, affect, and emotions have a primary role in decision making. That could explain pseudo-psychopathic syndrome, often observed in PFC patients, and there sensitivity to rewards that seems not compensated by the fear/processing of punishments.

5. Decision making and emotion: *encoding and retrieval*

5.1 Experiment 3: Risk anticipation and feedback processing in a gambling task

Risk anticipation is an important cognitive/emotional component of decision making. The Iowa Gambling Task (IGT, Bechara et al., 1994), which is the most widely used risk-anticipation task in clinical studies, has been demonstrated to be sensitive to lesions involving the ventromedial prefrontal cortex or amygdala. Making advantageous decision by weighing differently on their risks and benefits based upon previous experiences is an important ability for survival; however, this process would rely not only on cognitive but also on emotional substrates. The IGT was developed to simulate real life financial decisions. In contrast to other task in which all necessary information is available for making each decision (e.g., Elliot et al, 1999; Rogers et al., 1999). The IGT is based on a long exploratory learning process to evaluate long-term risk anticipation in decision making. Moreover, IGT performance is strongly influenced by emotional factors related to reward and penalties. Despite the above mentioned properties, the neural underpinning of the IGT has not yet been fully clarified.

A limited number of studies have specifically focused on the anticipatory component of decision making (Kukui et al., 2005; Breiter et al., 2001; Knutson et al., 2001a,b). In a series of study of Bechara and colleagues, physiological measures were obtained by skin conductance responses (SCRs) to the advantage and disadvantageous decisions (Bechara et al., 1996). Normal subjects develop anticipatory sympathetic arousal before selecting high-risk options. The observation of a conjunction between absent anticipatory arousal and maladaptive behavioural strategies, in ventromedial/orbitofrontal patients, has

led to a hypothesis that cerebral representation of anticipatory arousal biases behaviour and guides strategic decision making (Damasio, 1994; Bechara et al., 1996; Critchley et al., 2001). This behavioural bias may be dissociated from explicit, conscious knowledge about risk. Healthy subjects show a preference for low risk decision and show increased amplitude of anticipatory SCR to high risk options before developing explicit awareness of the most advantageous behavioural strategy (Bechara et al., 1997). Thus, anticipatory arousal is an index of implicit risk-related learning that may directly influence behaviour. Critchley and colleagues (2001) showed that OFC activity increases with increasing outcome uncertainty. They reported that activity during the delay period before the outcome of reward-related decisions in brain areas implicated in the control of social and emotional behaviour. Moreover, activity in anterior cingulate during this period was modulated by both outcome risk and anticipatory arousal, with discrete regions of cingulate reflecting both. Their findings support a role for anterior cingulate and OFC in integrating cognitive processing of uncertainty with adaptive changes in bodily state that may serve to prospectively bias behaviour.

Fukui et al. (2004), in a fMRI study, demonstrated that medial frontal gyrus is activated during risk anticipation. They found a significant correlation between the task performance and the magnitude of brain activity during risky decision at level of medial frontal gyrus.

The aim of the present study was to investigate the neural basis of the anticipation components of Decision Making by means of ERPs, and the feedback related component of IGT. The use of evoked potentials will provide information both on the temporal dynamics of cortical activity which precedes and follows a choice, and the spatial localization of the processes which are activated in healthy subjects and impaired in neurological patients. We expect, in line with the hypothesis of an implicit elaboration of the decision, that the readiness potential which precede the choice by one second, shows responses correlated with the success/failure of the decision. Additional hypotheses which

will be tested focus on the potentials evoked after the choice, these latter components show the elaboration of the stimuli which mark winning/losses.

5.1.1. Participants

Sixteen healthy right-handed males participated to the study (mean age= 24.62, SD= 3.1, range= 20-30; school attendance= 14.18), with no history of traumatic brain injury, neurological diseases, psychiatric disorders, substance abuse, alcohol abuse, or stroke. All participants received information about the aim and procedures of the experiment, and signed the informed consent. Participants received monetary payment based on the final budget obtained on the gambling task.

5.1.2. Experimental task

Task consisted in a modified version of the IGT, adapted for ERPs analysis and PC presentation. Each subject performed a decision making task with feedback for which they obtained monetary gain or loss. The task goal was to maximize the profit from a loan of play money. Subjects are required to make a series of 150 free picks from one of four decks (A, B, C, and D). Each selection was followed by an immediate showdown of a reward (winnings) or a penalty (losses). The reward/penalty schedules were predetermined: decks A and B yielded an immediate rewards but carried a risk of much higher long-term penalties, which will resulted in total loss in long run (disadvantageous decks); decks C and D yielded immediate low reward but smaller long-term penalties, which will resulted in long-term gain (advantageous decks). After the task, subjects were asked about which decks they thought were advantageous, in order to assess if subjects understood the rules of the game.

We developed a computerized version of the IGT , the differences from the original task were as follow:

(1) play money was converted from dollars to euros (subjects started from a budget of 2000 €);

(2) subjects are required to make 150 free picks (50 more than the original;

(3) characteristics of feedback (advantageous decks: +100, +50, -25, -75; disadvantageous decks: +1000, +600, -200, -300)

On the PC desk four card decks were displayed. Subjects are instructed to picks from a deck with the left button of mouse with right forefinger. After participants pressed one of the four decks compared an immediate feedback and budget were updated. To familiarize themselves with the task were trained with a short version of the game. Each deck contained 50 cards, if a participant selected all the 50 cards, deck disappeared. The task ended when subject had selected 150 cards or when two of the four decks were finished.

On the basis of the description from Bechara and colleagues (1994, 1997) reports, participants were told that the game required a long series of selections from the four decks and that, in selecting cards, they could choose from any of the decks and alternate between the decks. The participants were told that the object of the task was to win as much money as possible. They were not told that the task consisted of 15 trials. Moreover subjects were instructed to consider the four decks presented on the desk as real decks.

5.1.3. Data acquisition and reduction

EEG data were continuously recorded in DC mode, with a low-pass filter set to 150 Hz, sampling rate of 500 Hz. EEG was measured by means of 38 tin electrodes (see fig 5.1.1), using SynAmps amplifiers (NeuroScan Labs, Sterling, USA), 31 mounted on an elastic cap (ElectroCap) according to the International 10–20 system (Oostenveld and Praamstra, 2001); the other seven electrodes were

applied below each eye (Io1, Io2), on the two external canthii (F9, F10), on the Nasion (Nz) and on the mastoids (A1, A2). A1 was used as an on-line recording reference for the EEG channels, and then data were off-line converted to the average reference.

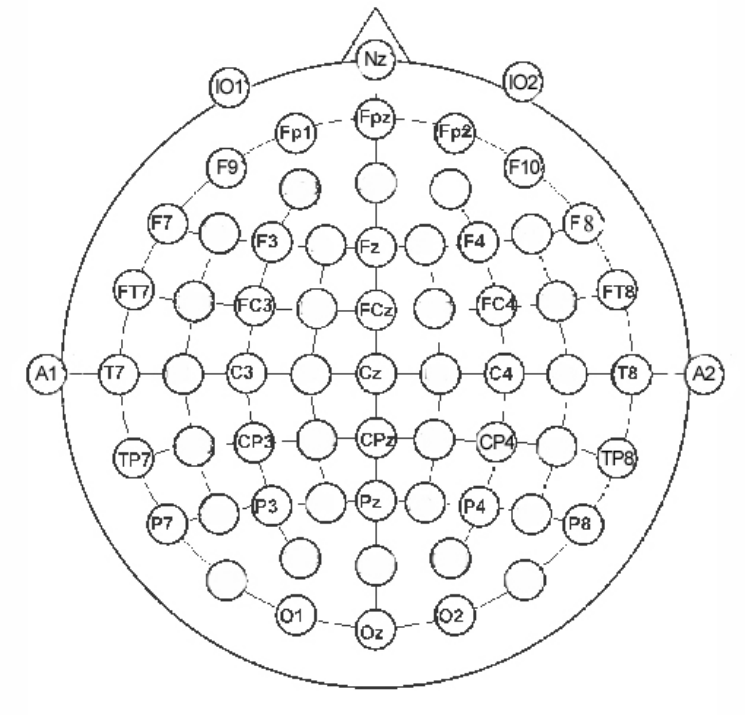


Fig. 5.1.1. Schematic representation of **38 electrodes disposition** according to the International 10–20 system (Oostenveld and Praamstra, 2001).

A calibration of eye-movements was performed at the beginning of the experiment in order to correct for ocular artifact, made trough the method MSEC (Berg & Scherg, 1994). This method is based on the assumption that the potential measured by an electrode is the linear sum of contributions (source components) from brain and eye sources and determines independently source vectors for eye and brain activity. Together with the temporal information of each vector, a source component is defined. For eye movements these source components are

estimated on the basis of empirical data taken from the individual eye movement calibration performed prior to the experimental session.

Eye correction is then accomplished by subtracting from artifact contaminated data the source components of the electrooculogram (EOG), but at the same time specifying the contribution of brain source components and leaving those unaltered. As a result of the MSEC method, the EOG electrodes can be analyzed as EEG electrodes in the artifact-free corrected data. This procedure allow to use also data from EOG electrodes which provide important information on orbitofrontal brain activity. After eye artifact correction each trial was visually inspected and eventually excluded, if there were remaining artifacts of different source (muscle potentials, large drifts, etc.).

5.2.3. Data analysis

Analysis were conducted in two temporal periods: before stimulus, for anticipation components (1000 ms back from the mouse click), and after monetary feedback simulus, for feedback prossessing components.

For anticipation component analysis time window and electrode clusters for statistical analysis of ERP data were chosen on the basis of prior assumptions about risk anticipation, regions of interests, and by means of visual inspection of grand mean waveform. Two time period were analyzed before deck choosing, from -1000 ms to -500 ms, and from -500 ms to 0 ms. Electrodes were clustered into nine groups/regions of interest for statistical pourpose with three spatial factors of three levels each: gradient (anterior, central, and posterior), and laterality (left, central, right). Each quadrant comprised three electrodes: anterior left (AxLx: F7, F8, FT7), anterior central (AxCx: IO1, Nz, IO2), anterior right (AxRx: F9, F10, FT8), central left (CxLx: F3, FC3, C3), central central (CxCx: Fz, FCz, Cz), central right (CxRx: F4, FC4, C4), posterior left (PxLx: A1, TP7, P7), posterior central (PxCx: O1, Oz, O2), posterior right (PxRx: A2, TP8, P8).

Data were submitted to repeated measures analysis of variance (ANOVA), repeated measures factors were decks contingency (Condition, 2 levels: advantageous, disadvantageous), Gradient (3 levels: Ax, Cx, Px), and Lateralization (3 levels: Lx, Cx, Rx).

For feedback related potentials, time window and electrode clusters were chosen on the basis of prior assumptions about risk anticipation, regions of interests, and by means of visual inspection of the grand mean waveform. Three time periods were analyzed: 220-260 ms (P200), 310-330 ms (N260), 370-410 ms (late P300). Electrodes were clustered into six groups/regions of interest to perform statistics with two spatial factors of three levels each: antero-posterior asymmetry and laterality. Each quadrant comprised two electrodes: anterior left (AxLx: IO1, FP1), anterior central (AxCx: Nz, FPz), anterior right (AxRx: IO2, FP2), posterior left (PxLx: C3, CP3), posterior central (PxCx: Cz, CPz), posterior right (PxRx: C4, CP4). One additional two-electrode cluster was analyzed separately, according to literature (Gehring and Willoughby, 2002; Hajcak et al., 2006), and included electrodes Fz, FCz. Data were submitted to repeated measures analysis of variance (ANOVA), repeated measures factors were Feedback (2 levels: gain, loss), Gradient (2 levels: Ax, Px), and Lateralizatio (3 levels: Lx, Cx, Rx). In the central frontal cluster (Fz, FCz) a repeated measures analysis of variance (ANOVA) was conducted, repeated measures factor was Feedback (2 levels: gain, loss).

5.1.4. Results

Behavioral data

According to previous reports (Bechara et al., 1994; Fukui et al., 2005) we subdivided trials into blocks consisting of 20 trials each. For each block the number of disadvantageous selections (Decks A and B) and advantageous selections (Decks C and B) was counted. For the analysis we divided mean picks into three period (Fig. 5.1.2): *1)* first period, firstv40 trials); *2)* second period, trials 41-80; *3)* third period, trials 81-120. After a exploring period (first 40 trials), subjects learned to avoid the disadvantageous decks, and to prefer advantageous decks.

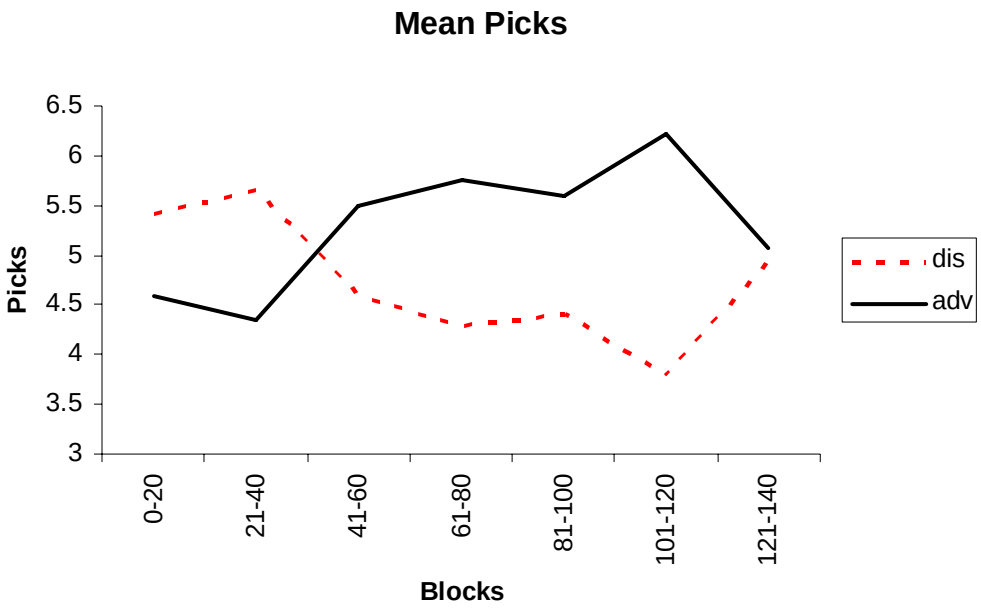


Fig. 5.1.2. **Means of the total number of cards selected** from advantageous versus disadvantageous decks in each block of 20 cards. It is shown that subjects learned to avoid disadvantageous decks and to prefer good decks.

Anticipatory event-related potentials

Based on behavioral data, the first forty trials (first period, in which subjects had not yet learned to avoid the disadvantageous decks) were excluded from the analysis of Anticipatory ERPs.

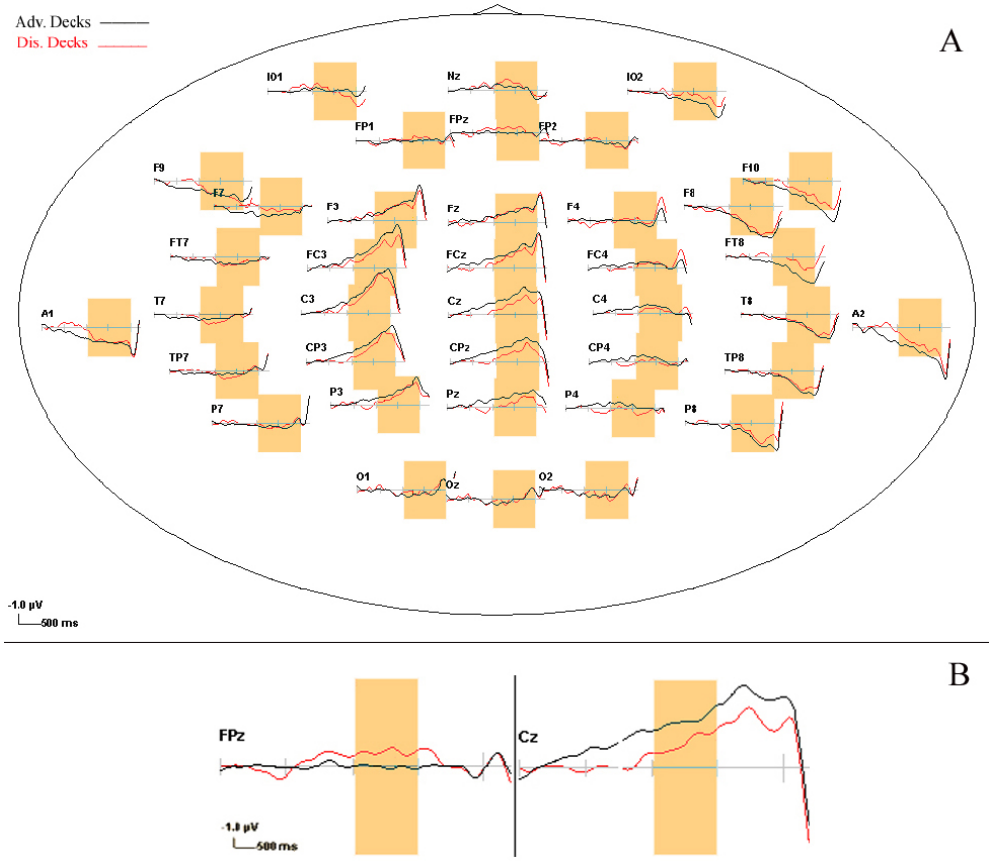


Fig. 5.1.2. **A) Grand Average of anticipatory ERPs** of all electrodes in topographic arrangement. The two analyzed epochs is evidenced. **B) Waveform at FPZ and Cz**. The first considered epoch is evidenced. It is shown that subjects exhibited a greater negativity for the disadvantageous condition (in red) compared to the advantageous one (in black).

Analysis on the anticipatory ERPs in the first epoch (-500 ms to -0 ms before pick) showed a Condition Main Effect ($F_{(1,15)}=12.346$, $p<0.005$). Subjects showed a greater anticipatory component before risky picks than safe ones.

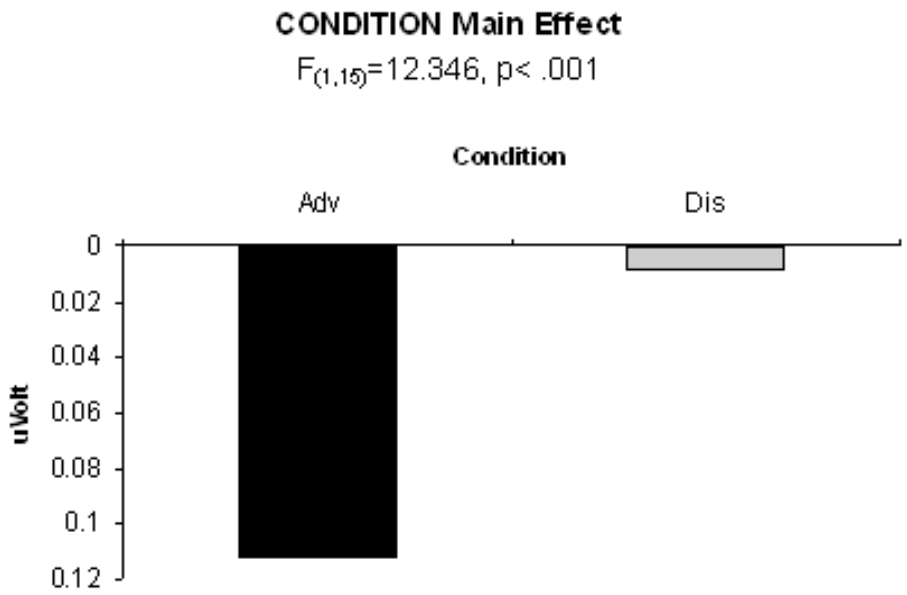


Fig. 5.1.4 **Mean amplitude of anticipatory potential** in the first epoch (from -1000 to -500 ms). Subjects showed a greater negativity before risky choices than safe ones.

In the second epoch (-1000 ms to -500 ms before pick), the Condition Main Effect showed a tendency toward statistical significance in the same direction ($F_{(1,15)}=4.109$, $p=0.06$, higher negativity before risky choice than safe ones).

Analysis showed, for both epoch considered, significant Lateralization Main Effect (-1000 ms-500 ms: $F_{(2,30)}=4.733$, $p<0.05$; -500 ms -0 ms: $F_{(2,30)}=13.419$, $p<0.001$), and Gradient Main Effect (-1000 ms-500 ms: $F_{(2,30)}=5.806$, $p<0.01$; -500 ms -0 ms: $F_{(2,30)}=8.691$, $p<0.01$). Subjects showed a greater negativity in central cluster compared to the others.

Feedback-related potentials

Analysis of feedback related potentials were conducted on all the stimuli, differently from the prestimulus analysis, learning of contingency were not considered.

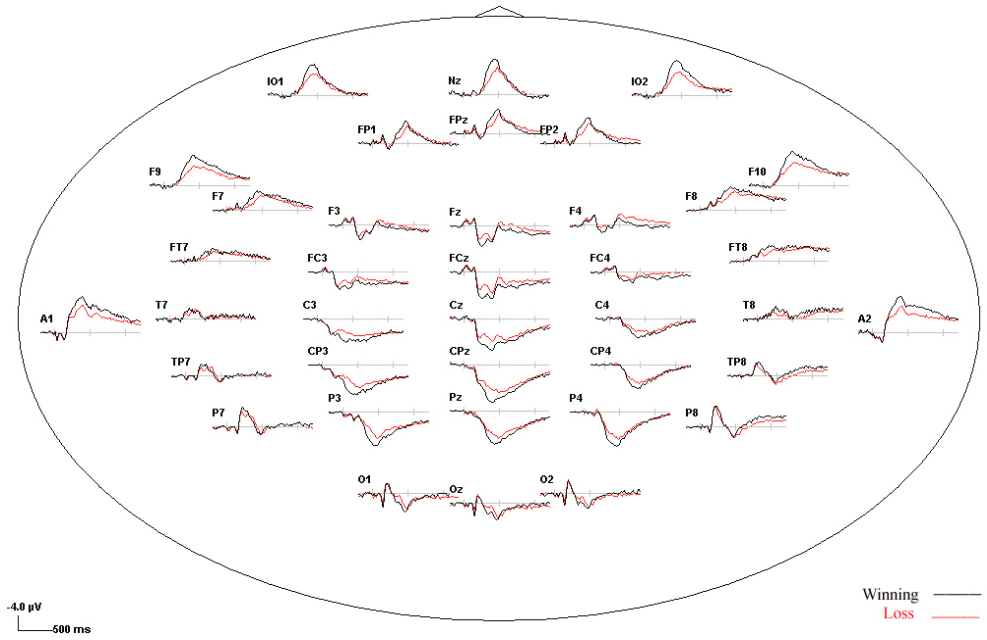


Fig. 5.1.5. **Grand Average of feedback related potentials** of all electrodes in topographic arrangement.

Analysis of P200 amplitude showed significant Feedback x Gradient x Lateralization interaction ($F_{(2,30)}$=9.540, p<0.001). Subjects showed a greater positivity for winnings than for losses (Condition Main Effect: $F_{(1,15)}$=6.339, p<0.05). Analysis of the frontal-central cluster (Fz-FCz, Fig. 5.1.6) showed significant Feedback Main Effect ($F_{(1,15)}$=20.397, p<0.001), in the same direction.

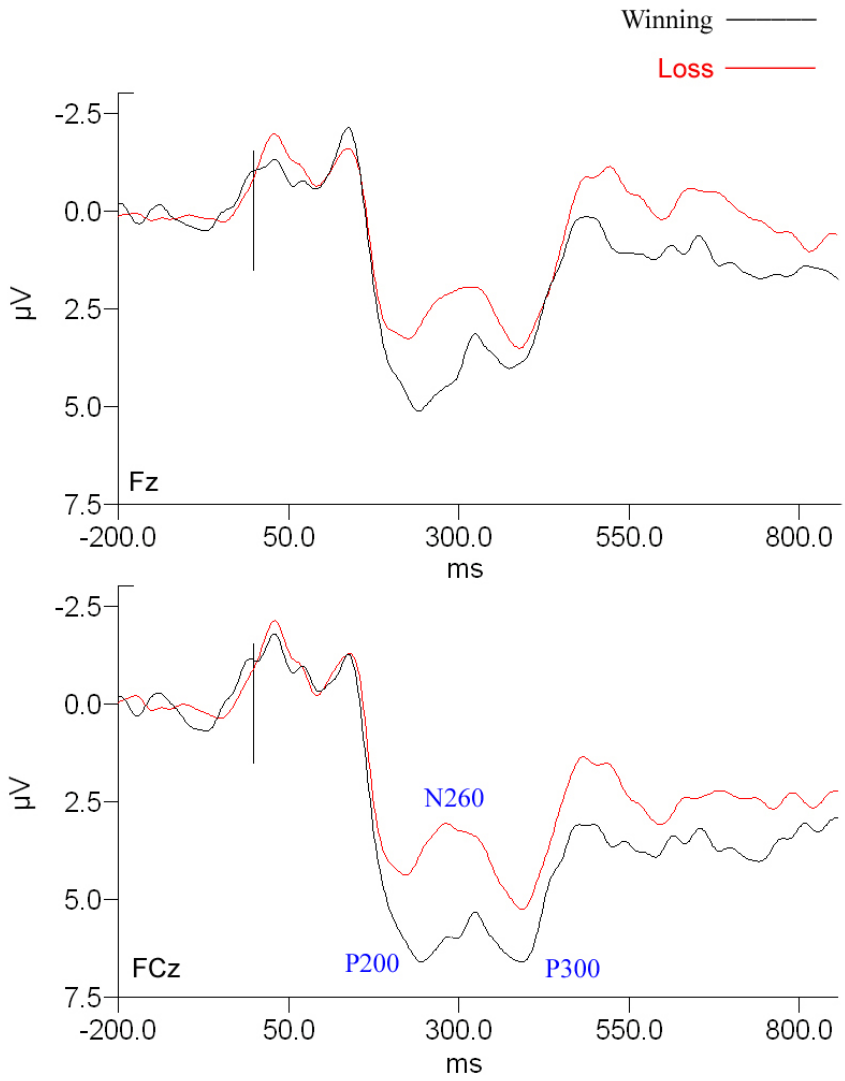


Fig. 5.1.6. **Waveform at Fz** (upper panel) **and FCz** (lower panel). Winning in black, losses in red. It is shown that subject exhibited greater positivity when they received a reward (winnings) than when received a punishment (losses).

Analysis of N260 amplitude showed significant Feedback x Gradient x Lateralization interaction ($F_{(2,30)}$=8.812, p<0.001). Analysis of the frontal-central cluster (Fz-FCz, Fig. 5.1.6) showed significant Feedback Main Effect ($F_{(1,15)}$=26.608, p<0.001), subjects showed a greater negativity for losses compared to winnings.

Significant Feedback x Gradient x Lateralization interaction ($F_{(2,30)}$=5.821, $p<0.01$) was also observed for late P300 amplitude. Analysis of the frontal-central cluster (Fz-FCz, Fig. 5.1.6) showed significant Feedback Main Effect ($F_{(1,15)}$=8.18, $p<0.05$), subjects showed a greater positivity for winnings compared to losses.

5.1.5. Discussion

The present study was designed to investigate the neural basis of the anticipation components of Decision Making, and feedback related components of winnings and losses, by means of ERPs.

In this experiment for the first time, we distinguished the capability of subjects to encode and elaborate monetary rewards and punishment through the ERPs evoked by the feedback stimulus, from their capability to retrieve stored memories on advantageous and disadvantageous decks, through the anticipatory potentials.

Consistent with our hypothesis, anticipatory potentials amplitude were found to be larger in anticipation of risky choice, rather than safe choice. These results in part confirm the somatic marker hypothesis, and enlarge findings of Damasio and colleagues (Damasio, 1994; Bechara et al., 1996). Moreover our findings demonstrate the important role of emotion in taking decision.

A recent study about stimulus preceding negativity (SPN, Poli et al., 2007) in anticipation of affective pictures showed, that the SPN amplitude was larger in anticipation of emotional (high arousing) rather than neutral pictures. This effect was only significant for high arousal pictures, especially relevant for the survival of individuals (Bradley et al., 2001). In line with these findings our results suggest that there were an emotional processing of decision, in particular demonstrated that risky choice were processed as more arousing than safe ones. Thus these anticipatory potentials seems not to reflect a generic affective

anticipation but rather the motivational engagement ascribed to affective stimulus anticipation. Emotional anticipation is an essential regulating factor of human behavior, enabling anticipation of positive outcomes and avoidance of danger. This findings demonstrated that decisions of everyday life behavior is guided by emotional (somatic) signals, which help individuals in the choice of alternative actions and possibly help us to survive.

Results about feedback processing showed higher positivity following winnings than losses. Recent studies, that utilized ERPs to examine how evaluative process is implement in the brain following feedback, identified a negative deflection at fronto-central recording sites that peaks approximately 250 ms following the presentation of negative feedback (i.e., Gehring and Willoughby, 2002; Hajcak et al., 2006). Functionally it appears to reflect a process involved in evaluating the motivational significance of ongoing event. Our results showed, for the window of feedback related negativity, significance in the same direction. All these authors considered three peaks around 200-400ms as independent, and attribute the evaluation of feedback only to negative peak, named feedback related negativity. This viewing could be incorrect, because this complex clearly showed the same time-course, and this would reflect the same process.

Like anticipation (implicit retrieval), which reflect what subjects learned, feedback assumes an emotional valence (encoding), and contribute to learn from experiences, to create representation of future outcomes, and consequently to guide decisions. From this point of view it make sense to interpret feedback processing in terms of emotion processing.

In the cognitive literature (Kok, 1997), stimulus evaluation, target identification, and other recognition processes are associated with positive ERPs components, e.g. P300, that are specifically evoked by emotional stimuli. Any studies (Herbert et al., 2007; Cuthbert et al., 2000; Mini et al., 1996) highlighted that for the P300 complex showed a pronounced effect of emotional content, and in particular that pleasant stimuli showed an higher P300 than unpleasant. In the

same way, if we consider feedback related potential like a positive complex, that may reflect the emotional and cognitive elaboration of monetary gain, we can conclude that this complex reflect the activation of motivational system in the brain. It is interesting to speculate that whereas in the monkey the evaluative system may be relatively sensitive to the apparently objective value of the rewards (Amiez et al., 2005), in the human, this system may be predisposed to classified outcomes into two categories: those outcomes that indicate that a goal has been satisfied and those that not. A possibility is that feedback related complex could reflect a double elaboration process of emotional stimuli. For both arousing condition (pleasant/gain and unpleasant/loss) there is an arousal elaboration, but while in pleasant stimuli processing, subjects spend more attention because stimulus is more interesting and pleasant (I'm happy because I won!); when subjects has to elaborate an unpleasant stimulus (in this case a loss/punishment), there would be a tendency to avoidance and thereby an higher tendency to cortical negativity.

5.2 Experiment 4: Anxiety trait, risk anticipation, and feedback processing in a gambling task

Decision making deficit has been related to a number of psychiatric and neurological pathologies. Although the investigation of the neuroanatomical and electrophysiological correlates of decision making is still at the beginning, it would increase our knowledge in a field which is central for the understanding of criminal psychopatic behavior, major depression, bipolar disorder, drug addiction, risk-taking behavior of adolescents, compulsive gambling. Research in this topic could lead to an advance also in other fields which are thought to be far from psychology, such as decision planning in the economic-financial domain.

Damasio and colleagues theorized that the somatic marker hypothesis may provide a powerful explanation for many symptoms of psychopathy, including impulsivity, irresponsibility, and failure to follow a life plan. Schmitt and colleagues instead (1999) have interpreted Bechara's results (1994) as mainly related to the level of anxiety rather than to psychopathy (indeed there is an inverse relationship between psychopathy and anxiety levels), and this latter would be predictive of response choices.

Recently a "risk-as-feeling" hypothesis, which highlights the role of affect experienced at the moment of decision making, has been proposed (Loewenstein et al., 2001). Accordingly, anticipated outcomes are translated into different body states based on previous experiences. They showed that emotional reaction to risk situation often diverge from cognitive assessment of those risk. When such divergence occurs, emotional reactions often driven behaviour. This would process critically depend on the OFC, insula, amygdala, and anterior cingulate cortex. Given the importance of hyperarousal and related autonomic changes in anxiety, anxious patients may show an altered pattern of aversive somatic markers during the assessment stage of decision making, as well as during the experience of outcome.

IGT is a decision-making task simulating uncertainty of premises and outcomes, as well as reward and punishment in controlled laboratory conditions (Bechara et al., 1994). IGT has proven extremely valuable in studies of the effects of personality in decision-making. For instance, some timely studies that approached the influence of personality on decision-making found that sensation-seeking positively correlats with the frequency of advantageous choices (Reavis and Overman, 2001), whereas negative emotionality negatively correlats with the frequency of choices from high-punishment decks (Peters & Slovic, 2000). These studies suggests personality differences, particularly those associated with emotional reactivity such as trait anxiety, and might provide a partial explanation for the high variance of IGT performance in healthy volunteers (Bechara and Damasio, 2005).

Anxiety may strongly affect the capability of individuals to make a decision under conditions perceived as risky. To date, decision making is a complex psychological construct influenced by both cognitive and emotional factors and whose the anatomical substrates are still under investigation. In agreement with recent studies, we assume that negative emotions and anxiety may play an important influence on decision making. To our knowledge characteristics of decision making in anxiety disorders have not yet been systematically examined; however a number of investigations report on cognitive substrates of anxiety, the most widespread substrate being attentional bias toward threat (Mogg and Bradley, 1999). An obvious difficulty in the study of anxiety is the heterogeneity of disorders placed under the classification of anxiety disorders (Ernst and Paulus, 2005). Nonetheless, several theoretical models on genetic of anxiety have been proposed which focus on the interaction between cognition, affect, physiology, and behaviour (see Wilken et al., 2000). The association of specific stimuli with adverse affective experiences is a critical determinant of hyperarousal (Dowden and Allen, 1997) and anxious apprehension (Nitschke et al., 1999), which occur across anxiety disorders. Accordingly, the neural substrates engaged in the processing of aversive stimuli have been implicated in

the pathophysiology of anxiety. These include limbic (amygdala, ventral striatum) and paralimbic structures (OFC, insula, anterior cingulate).

One approach for examining the effect of anxiety on decision making processes is to study individuals with high trait anxiety, which can defined as a general predisposition to respond anxiously (Spielberger, 1966; Spielberger and Smith, 1996; Endler and Kocovski, 2001). High trait anxiety can be used to examine the effect of elevated levels of anxiety on the stimuli processing and on action selection. Subjects with high trait anxiety are at risk of a number of different psychiatric conditions (Comeau et al., 2001; Willinger et al., 2002), including the full spectrum of anxiety disorders (Bennet and Stirling , 1998). Investigating subjects with high trait anxiety represents a unique opportunity to examine the neural systems which are important for mediating increased levels of anxiety and might, in addition, provide insight into processes that could be responsible for the development of anxiety disorders.

Functional neuroimaging studies on anxiety that compared high trait anxiety subjects (or subjects with anxiety disorders) with healthy subjects, have revealed a neural circuitry that involves orbitofrontal cortex (Grachev and Apkarian, 2000), inferior prefrontal cortex (Rauch et al., 1997), insular cortex (Liotti et al., 2000), hippocampus (Ploghaus et al., 2001), medial prefrontal cortex (Simpson et al., 2001a,b), and adjacent anterior cingulate cortex (Chua et al., 1999). The components of this neural circuitry involve many of many structures which underlies to decision making. Specifically, functional neuroimaging studies have shown that decision making is at cortical level dependent on the activation of inferior prefrontal cortex (Ernst et al., 2002; Paulus et al., 2001), ventromedial and ventrolateral frontal cortex (Elliott et al., 1999, 2000; Rogers et al., 1999), anterior cingulate (Elliott et al., 2000), insula (Critchley et al., 2001), and parietal cortex (Paulus et al., 2001).

With the present experiment we hypothesized that high and low trait anxiety (TA) subjects show a different activation in risk anticipation, in particular we expected that individuals high in trait anxiety show higher

readiness potential for risky choices. Additional hypotheses were tested concerned the potentials evoked after the choice. These latter components show the elaboration of the stimuli which mark winnings/losses.

5.2.1. Participants

In order to investigate psychobiological basis of decision making in people with high vs low trait anxiety, we administered the German version of State and Trait Anxiety Inventory, form Y (STAI-Y, Spielberg, 1983) to 120 students of the Univerity Julius Maximilian of Würzburg. Eighteen subjects were selected from this group, based on distribution of the sample: 9 subjects low TA (mean age= 24.22, SD= 2.68) with STAI Trait rating lower than 25° percentile (STAI Trait= 34.11, SD= 4.91); 9 subjects high TA (mean age= 23.33, SD= 2.12, statistic for age factor: $t_{(16)}$=0.78, p=0.447, ns) with STAI Trait rating higher than 75° percentile (STAI Trait= 50.22, SD= 4.12, statistic for STAI- Trait factor: $t_{(16)}$= -7.543, p<0.00001).

Subject had no history of traumatic brain injury, neurological diseases, psychiatric disorders, substance abuse, alcohol abuse, or stroke. All participants received information about the aim and procedures of the experiment, and signed the informed consent. Participants received monetary payment based on the final budget obtained on the gambling task.

5.2.2. Experimental task

Task was the same described in the previous experiment (par 5.1.2).

To control the stability of selection criterion STAI Trait was administered again soon before gambling. Before the experimental task were administered also the STAI- state and the German Version of Sensation Seeking Scale V (SSS,

Zuckerman, 1971; Beauducel et al., 2003), for personality trait assessment. Following the task STAI- State eas administered again.

5.2.3. Data Acquisition and reduction

EEG data were continuously recorded in AC mode, with a Kt of 10 sec sampling rate of 1000 Hz. EEG was measured by means of 33 tin electrodes (see fig 5.2.1), using a BrainAmp MR EEG amplifier, BRAIN VISION RECORDER software (Brainproducts, Munich, Germany), 26 electrodes were mounted on an elastic cap, according to the International 10–20 system (Oostenveld and Praamstra, 2001); the other seven electrodes were applied below each eye (Io1, Io2), on the two external canthii (F9, F10), on the Nasion (Nz) and on the mastoids (A1, A2).

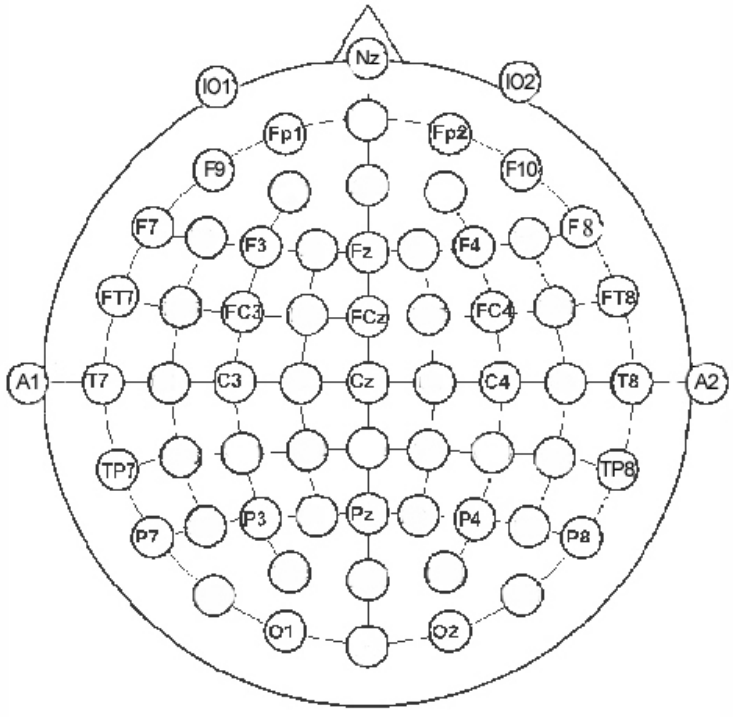


Fig. 5.2.1. Schematic representation of **33 electrodes location** (with labels) according to the International 10–20 system (Oostenveld and Praamstra, 2001).

A1 was used as on-line recording reference for all EEG channels, and data were off-line converted to average reference.

A calibration of eye-movements was performed at the beginning of the experiment in order to correct for ocular artifacts, by using the method MSEC (Berg & Scherg, 1994). For further details about method see paragraph 5.1.3.

5.2.4. Data analysis

Analyses were performed on two temporal periods: before decks choosing, for anticipation components (1000 ms back from the mouse click), and after card picking for monetary feedback processing components.

In the analysis of anticipation component the time, window and electrode clusters for statistical analysis were chosen on the basis of prior assumptions about risk anticipation, regions of interest, and visual inspection of grand mean waveform. Two time intervals were analyzed before deck choosing, from -1000 ms to -500 ms, and from -500 ms to 0 ms. Electrodes were clustered into nine groups/regions of interest for statistical purpose with two spatial factor: gradient (anterior, central, and posterior), and laterality (left, right). Each quadrant comprised two electrodes: anterior left (AxLx: FP1, IO1), anterior right (AxRx: FP2, IO2), central left (CxLx: FC3, C3), central right (CxRx: FC4, C4), posterior left (PxLx: A1, O1), posterior right (PxRx: P8, O2). Data were submitted to repeated measures analysis of variance (ANOVA), repeated measures factors were decks contingency (Condition, 2 levels: advantageous, disadvantageous), Gradient (3 levels: Ax, Cx, Px), and Lateralization (2 levels: Lx, Rx).

In the analysis of monetary-feedback related potentials, time window and electrodes were chosen on the basis of prior assumptions about risk anticipation, regions of interest, and by means of visual inspection of the grand mean waveform. Three time intervals were analyzed: 210-250 ms (P200), 250-320 ms (N260), 330-390 ms (late P300). Analysis were conducted on three frontal

electrodes in the central line: Fz, FCz, and Cz. A repeated measures analysis of variance (ANOVA) was conducted, repeated measures factor were Electrode (3 levels), and Feedback (2 levels: gain, loss).

5.2.5. Results

Questionnaires assessment

STAI-Trait administered before task showed, agreement with earlier test administered for group selection, significant difference between groups (mean of low TA= 34.11, mean of high TA= 46.78, $t_{(16)}$= -4.43, p<0.001).

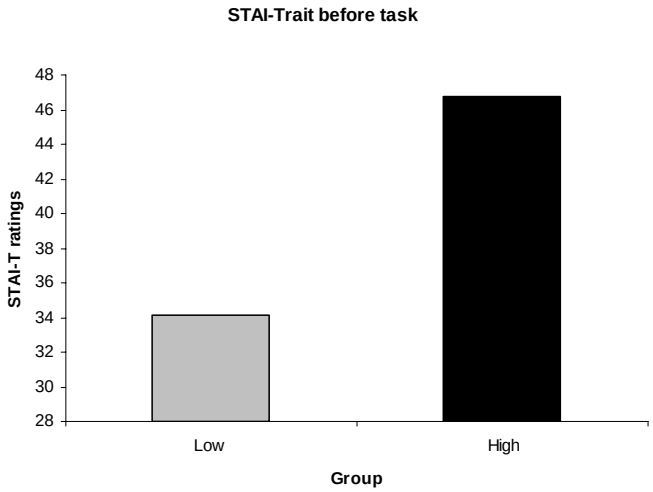


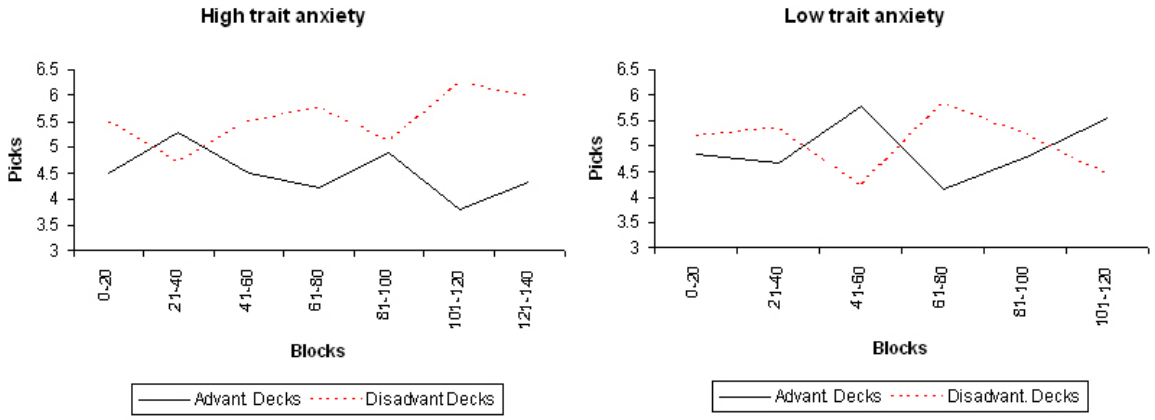
Fig. 5.2.2. **STAI-Trait ratings** of subjects Low (in grey) and High (in black) in trait anxiety, administered before experimental session.

Also STAI- State ratings showed significant difference between groups both before ($t_{(16)}$= -3.79, p<0.01), and after the task ($t_{(16)}$= -2.88, p<0.01).

Analysis of SSS-V sowed no statistical difference between groups (statistic for Sensation Seeking: ($t_{(16)}$= -0.50, p=0.623, ns).

Behavioral data

As in the previous experiment we subdivided trials into blocks consisting of 20 trials each (Fig. 5.2.2).



*Graf. 5.2.2. N***umber of card picks selected** from advantageous versus disadvantageous decks in each block of 20 cards, in subjects with high TA (left) and low TA (right).

Both group reported to have comprehended the contingency of decks, but both did not show the expected behaviour: subjects did not learn to avoid disadvantageous decks.

Anticipatory event-related potentials

Based on first experiment, the first forty trials (first period, in which subjects had not yet learned to avoid the disadvantageous decks) were excluded from the analysis of anticipatory ERPs.

Analysis of the first epoch (from -1000 ms to 500 ms, before choice) resulted in a Group x Condition x Gradient x Lateralization interaction with a tendency toward statistical significance ($F_{(2,32)}=2.814$, $p=0.07$).

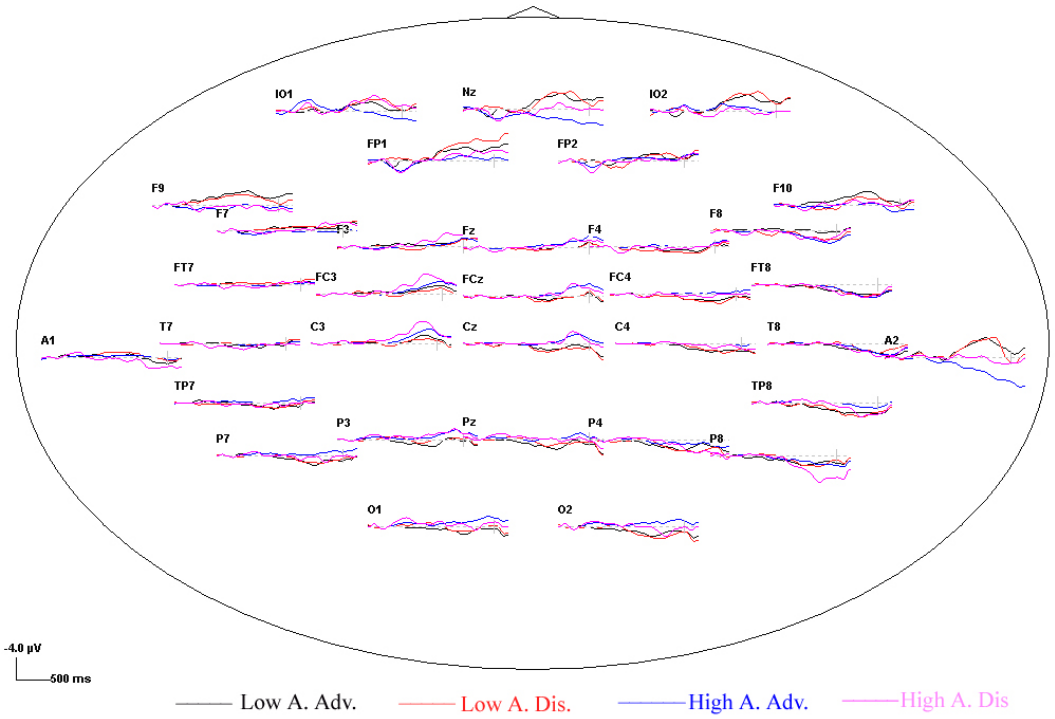


Fig. 5.2.3. **Grand Average of anticipatory ERPs** of all electrodes in topographic arrangement.

The analysis of pattern (EEG-Voltage Maps, Fig. 5.2.4) showed an interesting effect in subjects high TA: they showed a greater early positivity compared to low TA, in particular before risky choices. This would reflect an inhibition of response, when they decided to pick from disadvantageous decks. Subjects low TA, as expected, showed higher negativity before risky choice than for safe ones.

In the second epoch (-500 ms to -0 ms before pick), analysis did not show any statistical effect. Pattern show a trend in the same way of previous.

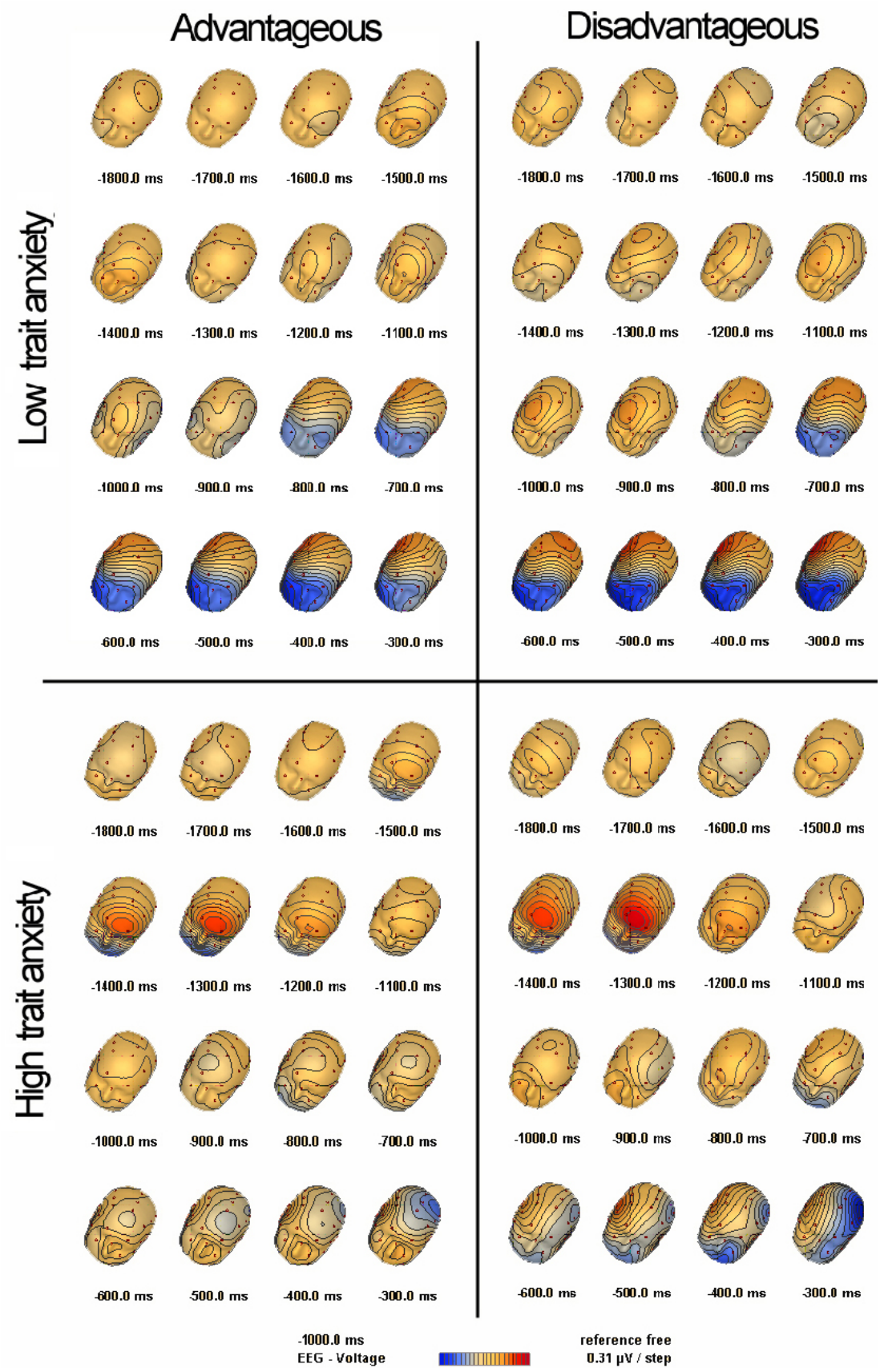


Fig. 5.2.4. **EEG-Voltage maps** in both group low in trait anxiety (upper panels) and high in trait anxiety (lower panels), for both conditions (advantageous on left, and disadvantageous on right).

Feedback-related potentials

Analysis of P200 wave showed significant Feedback Main Effect ($F_{(1,16)}$=24.009, p<0.001), and Feedback x Electrode interaction ($F_{(2,32)}$=34.171, p<0.00001). Subjects showed greater positivity for winnings than for losses. Post Hoc Newman-Keuls comparisons showed significant differences between conditions (p<0.001), winnings elicited higher positivity than losses.

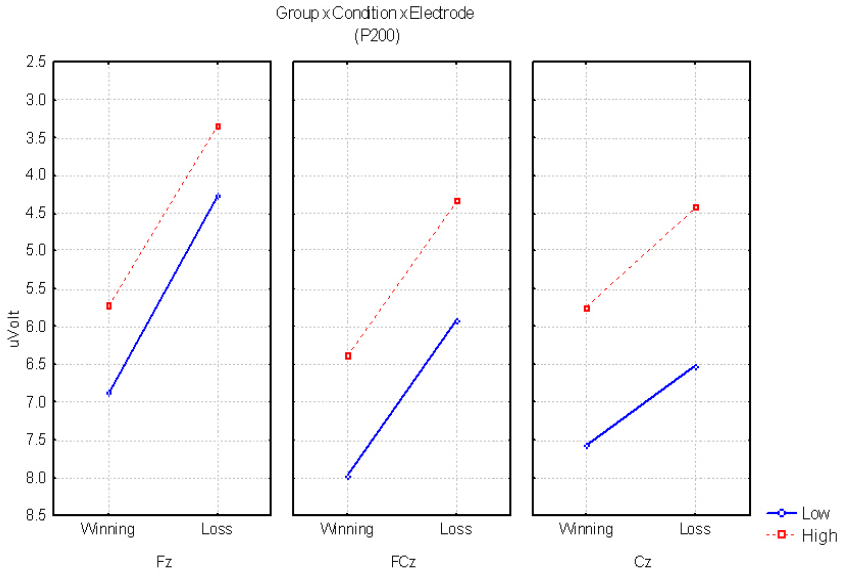


Fig 5.2.5. **P200 amplitude** in low TA (in blu) and high TA (in red), for the two conditions (winnings and losses) in the three considered electrodes (Fz, FCz, and Cz).

Analysis of N260 wave revealed significant Group x Feedback x Electrode interaction ($F_{(2,32)}$=5.932, p<0.01), Feedback x Electrode interaction ($F_{(1,16)}$=23.940, p<0.001), Electrode Main Effect ($F_{(2,32)}$=10.725, p<0.001), and Feedback Main Effect ($F_{(1,16)}$=23.94, p<0.001). Both groups showed higher positivity for winnings than for losses (Post Hoc Newman-Keuls, p<0.01), at particular they showed higher negativity in Fz compared to the other electrodes (Post Hoc Newman-Keuls, p<0.01).

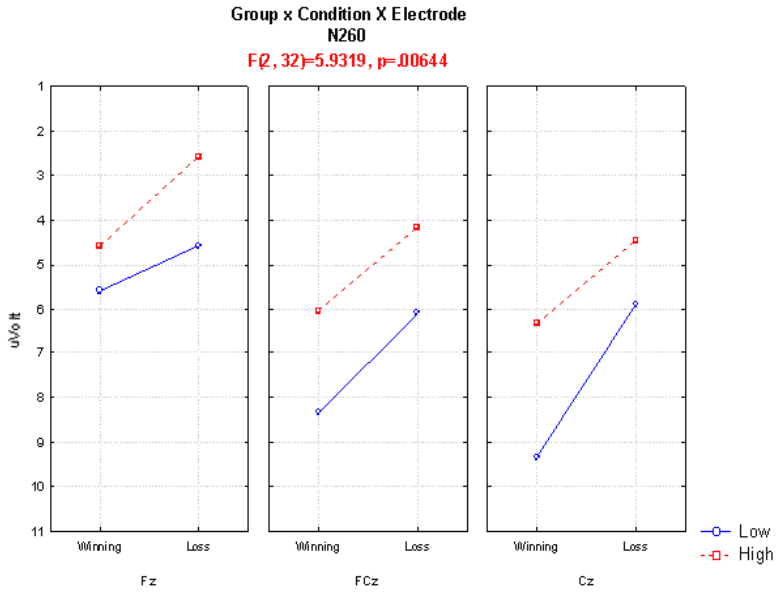


Fig 5.2.5. **N260 amplitude** in low TA (in blu) and high TA (in red), for the two conditions (winnings and losses) at Fz, FCz, and Cz.

Analysis of late P300 wave showed significant Feedback Main Effect ($F_{(1,16)}$=13.441, p<0.005), Electrode Main Effect ($F_{(2,32)}$=16.764, p<0.00001), and Feedback x Electrode interaction ($F_{(2,32)}$=5.425, p<0.01). Both groups showed greater positivity for winnings than for losses.

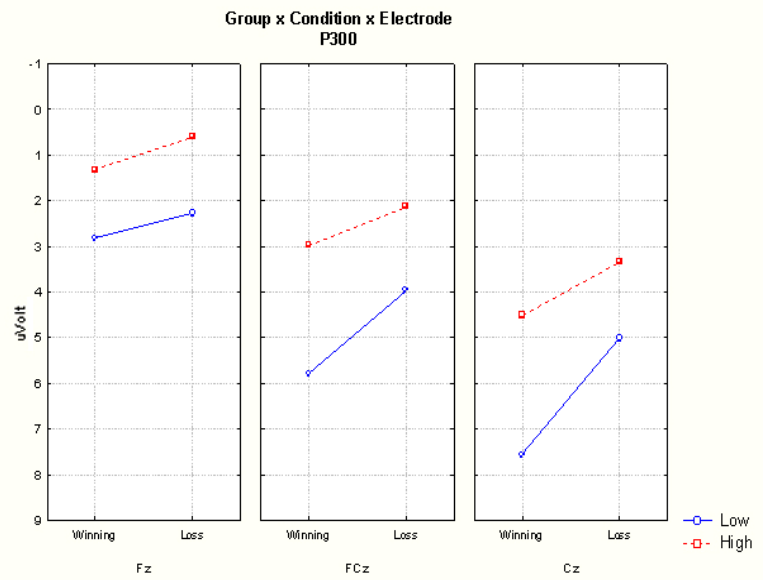


Fig 5.2.5. **Late P300 amplitude** in low TA (blu) and high TA (red), for the two conditions (winnings and losses) in the three considered electrodes (Fz, FCz, and Cz).

5.2.6. Discussion

The present study was designed to investigate the role of anxiety trait in anticipation components of Decision Making, and feedback related components of winnings and losses, by means of ERPs.

Results showed that both groups elaborate the feedback in the same way. Low TA subjects showed an higher global positivity, compared to high TA. Both groups revealed feedback processing pattern comparable to subjects of the previous experiment. Despite this apparently normal processing, subjects showed a dysfunctional choice behavior, presumably caused by a dysfunctional retrieval of stored information. This interpretation is supported by anticipatory potentials data, which represent retrieval: subjects exhibited a risk processing, but they can not adjust their behaviour in order to take right decision. Indeed, both group showed a differentiated pattern response compared with prior findings. Subjects with low TA did not show significant differences between conditions, and did not learn to avoid risky decks. These subjects, presumably showed the same behavior of patients described by Bechara and colleagues (e.g., Bechara et al., 2000a).

Subjects with high TA, instead, showed an overall cortical positivity. Birbaumer (1999) defined slow cortical potentials as negative or positive polarization of the EEG. Functionally, they constitute a threshold regulation mechanism for local excitatory mobilization (negative slow cortical potentials) or inhibition (positive slow potentials) of cortical networks. From this view the observed positivity, measured in high TA, especially before risky choice, probably reflect an inhibition of action. Anxious subjects be frightened by the perception of the risk and are unable to enact proper strategies in decision making behaviour under stressful situations. Therefore, it seems that anxiety affect selectively retrieval processes.

Risk-taking decisions could be considered as the product of complex interactions of several cognitive factors, including availability of cognitive resources, memory processing and the reflection of decision strategies. Recent

research has suggested that mood exerts its influence on all these factors (see e.g., Nygren et al., 1996; Hockey et al., 2000). In related to risk taking decisions, researchers (Drevets and Raichle, 1998; Matthews et al., 1995; Teasdale, 1993), suggested that the affective states of an individual would activate information similar affective meaning in one's memory for the retrieval. This mechanism allows the individual to retrieval relevant information from memory in a short time for decision making; but it would also biased the memory retrieval and distorted the cognitive processes during judgment (Schwarz and Bless, 1991).

Individual differences in the tendency to experience particular emotions play a strong role in shaping cognitive processes associated with decision making (Lerner and Keltner, 2000). Emotions serve as salient forms of information by signalling the presence of particular threats to be avoided or rewards to be acquired (Maner et al., 2007). Emotion, in turn, promote cognitive responses facilitating the avoidance of threat and the acquisition of rewards (Maner et al., 2005). Among different factors's guiding one's decision making processes the ability to take risk might be the most crucial factor influencing individuals overt behaviour, as in real life situations most judgements require to deal with risky situation or dilemmas. Kenneth and Lee (2003) hypothesized that positive affective states increase the risk-taking tendency, and that individuals with positive mood prime would be vulnerable to access thoughts about the positive aspects of the risky situations than does those in neutral mood. On the other hand people in negative mood would be more conservative and less willing to take risk.

People in negative mood tend to perceive the world as a threatening place and thus would be more likely to carefully process information in order to avoid potential loss. Leith and Baumeister(1996) conversely, found that a range of induced negative states (such as anxiety and anger) increased the choice of risky/disadvantageous options. This could explain why subjects high TA were not able to avoid risky decks notwithstanding cortical inhibition that preceded

choices. High anxious people would experience risky decision particularly negative and that could affect their capability to take advantageous decisions.

In particular, the possibility that neural activity in some cognitive-processing areas is suppressed during intense emotional states suggests mechanisms by which extreme fear or severe depression may interfere with cognitive performances. Drevets and Raichle (1998) suggested that activities of several cortical areas necessary for cognitive functioning (e.g., anterior cingulate and the dorsolateral prefrontal cortices) decreased during experimentally induced or pathological affective states. This suggests that changes in brain activity accompanying intense emotional states may affect the quality of decision making. With respect to our data this view suggests that taking risky decision under uncertainty could induce, in high AT subjects a negative mood. This involves an overload of prefrontal/emotional circuits by inducing a less efficient retrieval processing, and wrong choices.

For a series of contingent reasons (data was collected in Germany, subjects were recruited out of refectory during summer and were contacted again two months later) we collected data from a small sample and that implied we did not found significant effects. Maybe collected data from a control group with controlled level of anxiety would helped us to interpreted data (we cannot compare these data with those from previous experiment because of different nationality of sample and different recording apparatus). Probably with a bigger sample we would find higher power of statistics. However, in this experiment for the first time, we distinguished the two important processes which characterized decision making (encoding and retrieval), and highlighted how anxiety could affect retrieval process necessary for taking advantageous decision.

5.3 Experiment 5: Sensation Seeking, risk anticipation, and feedback processing in a gambling task

A number of researchers have proposed that sensation seeking and impulsivity are complex and multidimensional traits (Arnett, 1994; Dickman, 1993; Zuckerman, 1979). The concept of a sensation seeking personality trait was developed by Zuckerman (1979, 1994) to account for differences in people's willingness to participate in risky activities across a wide range of behaviours. Sensation seeking is ‘‘a trait defined by the seeking of varied, novel, complex and intense sensations and experiences, and the willingness to take physical, social, legal and financial risks for the sake of such experience.’’ (Zuckerman, 1994, p 27).

Impulsivity, on the other hand, can be conceptualized as a lack of reflectiveness and planning, rapid decision making and action, and carelessness (Schalling, 1978). Sensation seeking and impulsivity are related, leading some researchers to combine them into a single construct (e.g., Zuckerman, 1996). Sensation seeking incorporate two aspects: a tendency to enjoy and pursue activities that are exciting, and openness to trying new experiences that may or may not be dangerous. Impulsivity is an aspect of behaviour which adds important color to everyday life.

The concept of impulsivity covers a wide range of “actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable outcomes”. As such it plays an important role in normal behavior, as well as, in a pathological form, in many kinds of mental illness such as mania, personality disorders, substance abuse disorders and attention deficit/hyperactivity disorder (Eveden, 1999).

The Sensation Seeking Scale has gone through a number of stages in its development and currently Sensation Seeking Scale reached the version number VI. The SSS-VI consists of four sub-scales; Thrill and Adventure Seeking (E-TAS), Experience Seeking (E-DIS), Boredom Susceptibility (I-TAS) and

Disinhibition (I-DIS). Since its development the SSS-VI and the four sub-scales have been found to be very reliable (Zuckermanet al., 1978) and to be associated with a wide range of behaviours. These include recreational activities such as mountaineering, scuba diving and adventure travel (e.g. Cronin, 1991; Fowler et al., 1980; Gilchrist et al., 1995) pro-social risk taking among groups such as fire fighters, police and bomb disposal experts (e.g. Goma-i- Freixanet, 1995; Glicksohn and Bozna, 2000; Levenson, 1990) and anti-social risk takers such as criminals, drug users and risky drivers (e.g. Horvath and Zuckerman, 1993; Rosenbloom, 2003). Zuckerman (1994) argues that this format is valid for this questionnaire and that participants do not report any difficulty making the necessary choices. However, the forced-choice format means that some potentially useful information is lost as it does not provide any indication of the extent to which participants agree or disagree with the items, and it also assumes participants' responses are adequately reflected in the choice available[1].

Most of previous studies on decision making focused on considerable changes after brain injuries, considering that individual differences in decision making related to covert somatic activities (Bechara et al., 1999; Garpenstrand et al., 2001; Hariri et al., 2002). In their study Suzuki and colleagues (2003), considering that variation in affective physiological responses within a normal population demonstrated that a variation in covert physiological appraisal underlies individual differences in decision making.

Zermatten and colleagues (2005) measured the links between various dimensions of impulsivity and decision maiking. They hypothesized that lack of premeditation would be related to disadvantageous decisions on the IGT. Their results showed that a lack of premeditation was the impulsivity facet that was most related to decision making performance on the IGT, and influenced by

[1] In this experiment we adopted the Italian standardization of the Sensation Seeking Scales VI introduced by Galeazzi and colleagues (2003).

somatic markers. They proposed that premeditation may correspond to decision making processes, influenced by somatic (or emotional) markers.

Thus the purpose of the present study was to examine the effects of sensation seeking factor on the decision making processes and behavior. We expected a lack of inadequate planning in high sensation seekers, specifically related to disadvantageous decks. In particular we hypothesized that high sensation seekers showed a different anticipation pattern, compared to low sensation seekers.

5.3.1. Participants

In order to investigate psychobiological basis of decision making in high vs low sensation seekers, we administered the Italian version of SSS-VI (Galeazzi et al., 2003) to 250 students of the University of Padova. Thirty subjects were selected from this group, based on normative distribution: 15 low sensation seekers (mean age= 22, SD= 2.038) with SSS-VI rating lower than 25° percentile (e-tas=17.3; e-dis= 64.4; i-tas=36; i-dis=62.2, see par. 5.3.3.); 15 High sensation seekers (mean age= 23.27, SD= 2.344, statistic for age factor: $t_{(28)}$=1.548, p=0.133, ns) with SSS-VI rating higher than 75° percentile (e-tas=26; e-dis=96.7 ; i-tas=60; i-dis=97).

Subject had no history of traumatic brain injury, neurological diseases, psychiatric disorders, substance abuse, alcohol abuse, or stroke. All participants received information about the aim and procedures of the experiment, and signed the informed consent. Participants received monetary payment based on the final budget obtained on the gambling task.

5.3.2. Experimental task

Decision making task was the same described in the prior experiment (par 5.1.2).

STAI trait and STAI state, were administered before gambling, for personality trait assessment. Following the session, STAI- State were administered again.

5.3.3 Data acquisition and reduction

EEG data were continuously recorded in DC mode, with a low-pass filter set to 150 Hz, sampling rate of 500 Hz. EEG was measured by means of 38 tin electrodes (see fig 5.3.1), using SynAmps amplifiers (NeuroScan Labs, Sterling, USA), 31 mounted on an elastic cap (ElectroCap) according to the International 10–20 system (Oostenveld and Praamstra, 2001); the other seven electrodes were applied below each eye (Io1, Io2), on the two external canthii (F9, F10), on the Nasion (Nz) and on the mastoids (A1, A2). A1 was used as an on-line recording reference for the EEG channels, and then data were off-line converted to the average reference.

A calibration of eye-movements was performed at the beginning of the experiment in order to correct for ocular artifacts, trough the method MSEC (Berg & Scherg, 1994). This method is based on the assumption that the potential measured by an electrode is the linear sum of contributions (source components) from brain and eye sources and determines independently source vectors for eye and brain activity. Together with the temporal information of each vector, a source component is defined. For eye movements these source components are estimated on the basis of empirical data taken from the individual eye movement calibration performed prior to the experimental session.

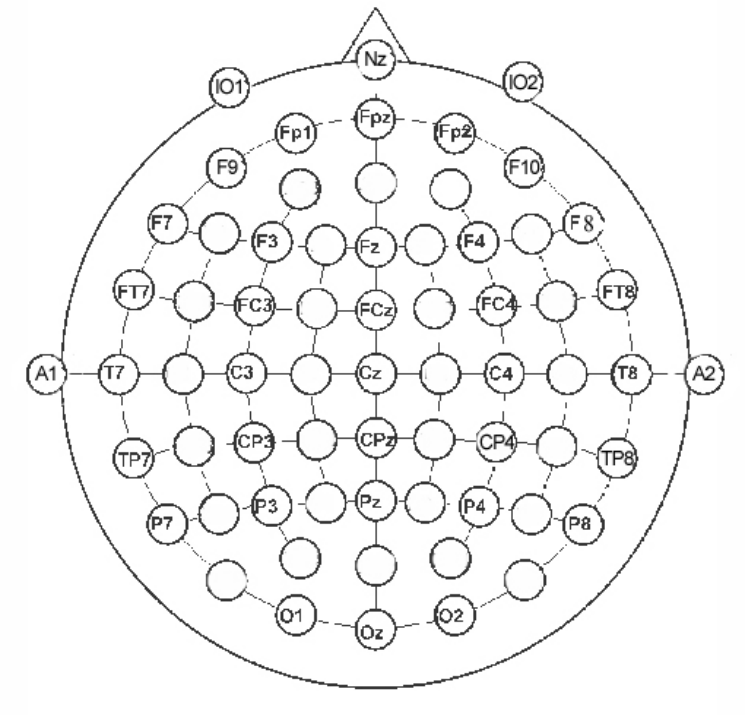


Fig. 5.3.1. Schematic representation of **38 electrodes location** (with label) according to the International 10–20 system (Oostenveld and Praamstra, 2001).

Eye correction is then obtained by subtracting from artifact contaminated data the source components of the electrooculogram (EOG), but at the same time specifying the contribution of brain source components and leaving those unaltered. As a result of the MSEC method, the EOG electrodes can be analyzed as EEG electrodes in the artifact-free corrected data. This procedure allow to use also data from EOG electrodes which provide important information on orbitofrontal brain activity. After eye artifact correction each trial was visually inspected and excluded, if there were remaining artifacts of different source (muscle potentials, large drifts, etc.).

5.3.4 Data analysis

Analysis were conducted in two temporal periods: before stimulus for anticipation components (1000 ms back from the mouse click), and after monetary feedback stimulus, for feedback processing components.

For anticipation component analysis, time window and electrode clusters for statistical analysis of ERP data were chosen on the basis of prior assumptions about risk anticipation, regions of interests, and by means of visual inspection of grand mean waveform. Two time period were analyzed before deck choosing, from -1000 ms to -500 ms, and from -500 ms to 0 ms. Electrodes were clustered into nine groups/regions of interest for statistical purpose with three spatial factors of three levels each: gradient (anterior, central, and posterior), and laterality (left, central, right). Each quadrant comprised three electrodes: anterior left (AxLx: F7, F8, FT7), anterior central (AxCx: IO1, Nz, IO2), anterior right (AxRx: F9, F10, FT8), central left (CxLx: F3, FC3, C3), central central (CxCx: Fz, FCz, Cz), central right (CxRx: F4, FC4, C4), posterior left (PxLx: A1, TP7, P7), posterior central (PxCx: O1, Oz, O2), posterior right (PxRx: A2, TP8, P8). Data were submitted to repeated measures analysis of variance (ANOVA), repeated measures factors were decks contingency (Condition, 2 levels: advantageous, disadvantageous), Gradient (3 levels: Ax, Cx, Px), and Lateralization (3 levels: Lx, Cx, Rx).

For feedback related potentials, time window and electrode clusters were chosen on the basis of prior assumptions about risk anticipation, regions of interests, and by means of visual inspection of the grand mean waveform. Three time periods were analyzed: 250-300 ms (P200), 320-360 ms (N260), 370-410 ms (late P300). Electrodes were clustered into six groups/regions of interest to perform statistics with two spatial factors of three levels each: antero-posterior asymmetry and laterality. Each quadrant comprised two electrodes: anterior left (AxLx: IO1, FP1), anterior central (AxCx: Nz, FPz), anterior right (AxRx: IO2, FP2), posterior left (PxLx: C3, CP3), posterior central (PxCx: Cz, CPz), posterior

right (PxRx: C4, CP4). One additional two-electrode cluster was analyzed separately, according to literature (Gehring and Willoughby, 2002; Hajcak et al., 2006), and included electrodes Fz, FCz. Data were submitted to repeated measures analysis of variance (ANOVA), repeated measures factors were Gradient (2 levels: gain, loss), Feedback (2 levels: Ax, Px), and Lateralization (3 levels: Lx, Cx, Rx). In the central frontal cluster (Fz, FCz) a repeated measures analysis of variance (ANOVA) was conducted, repeated measures factor was Feedback (2 levels: gain, loss).

Following data reduction and artifact inspection, 3 low sensation seekers and one high sensation seeker, were excluded from the analysis (because of too many artifacts, EEG data was unusable: trials artifact-free were less than 10%).

5.3.5 Results

Questionnaire assessment and Behavioural data

Analysis of STAI trait and STAI state showed no significant differences between groups.

According to previous experiment (Par 5.1) we subdivided trials into blocks consisting of 20 trials each. For each block the number of disadvantageous selections (Decks A and B) was counted, and advantageous selections (Decks C and B). For the analysis we divided mean picks into three period (Fig. 5.1.2): *1)* first block, 40 trials; *2)* second block, trials 41-80; *3)* third block, trials 81-120.

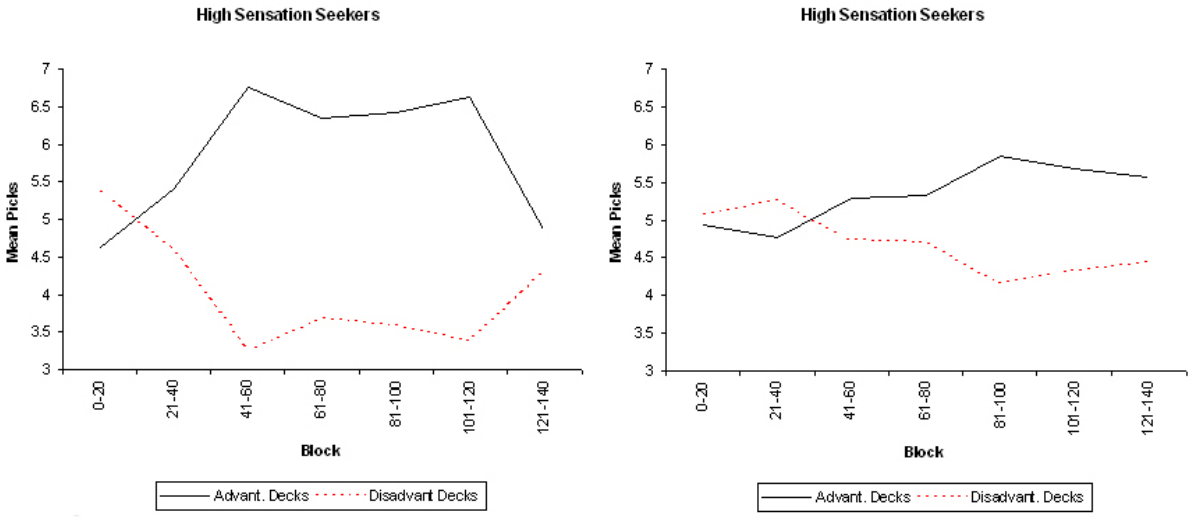


Fig. 5.3.2. **Means of the total number of cards selected** from advantageous versus disadvantageous decks in each block of 20 cards, in high sensation seekers on left and in low sensation seekers on right.

Analysis showed significant Blocks main effect ($F_{(2,22)}$= 6.836, p<0.01) After an exploring period (pre-punishment), low sensation seekers learned to avoid the disadvantageous decks, and to prefer advantageous ones, in fact Post Hoc Newman-Keuls showed significant differences between first block and two others (p<0.01) and no differences between the last two blocks. High sensation seekers did not to learn to avoid disadvantageous decks ($F_{(2,26)}$= 1.439, p=0.255, ns), and showed perseveration in risky behavior (Fig. 5.3.2).

Anticipatory event-related potentials

Based on first experiment and behavioral data, the firs forty trials (pre-punishment period, in which subjects had not yet learning to avoid the disadvantageous decks) were excluded from the analysis of Anticipatory ERPs.

Analysis of the first epoch (from -1000 ms to -500 ms, before choice) showed a Group x Condition x Gradient x Lateralization interaction with a tendency toward statistical significance ($F_{(4,92)}$=2.256, p=0.069).

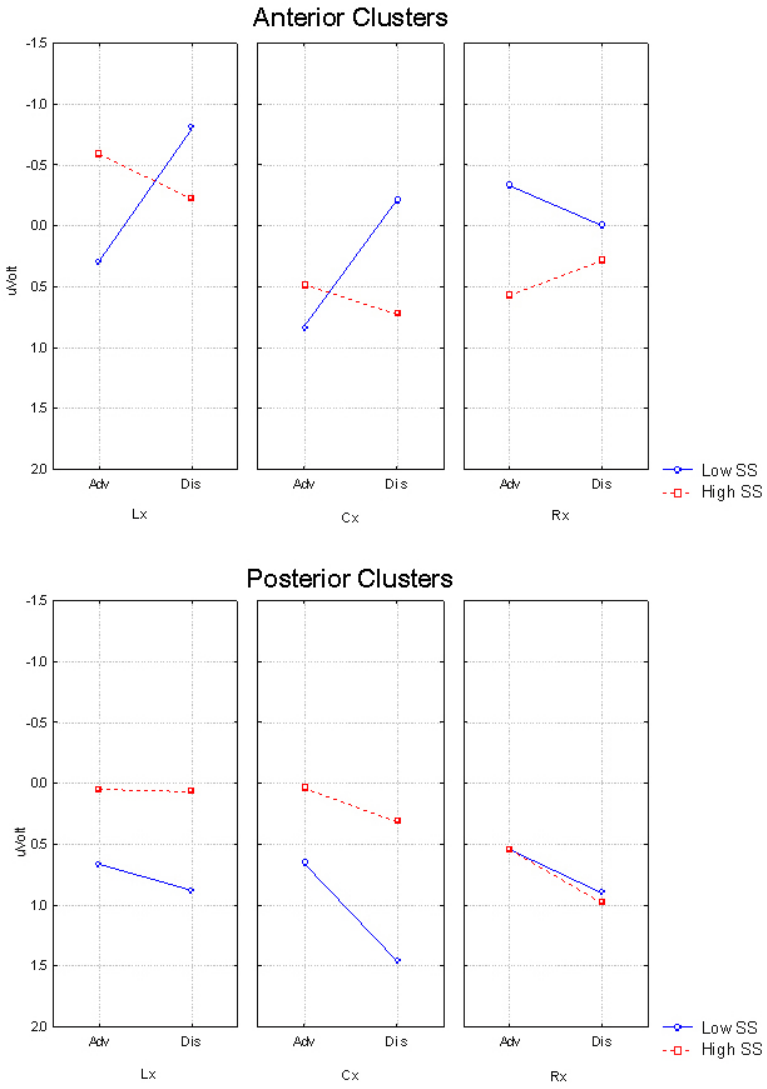


Fig. 5.3.3. **Mean amplitude of the anticipatory potential** in the first epoch in anterior clusters (upper panel), and in posterior clusters (lower panel). Low sensation seekers in blue, and high sensation seekers in red.

As shown in Fig. 5.3.3, in the anterior clusters high sensation seekers showed an inversion (higher negativity for advantageous than for

disadvantageous) compared to low sensation seekers. Moreover, high sensation seekers showed a smaller differences between conditions.

Analysis of the second epoch (from -500 ms to 0 ms, before choice) indicates a significant Group x Condition x Gradient x Lateralization interaction ($F_{(4,92)}$=2.107, p<0.01).

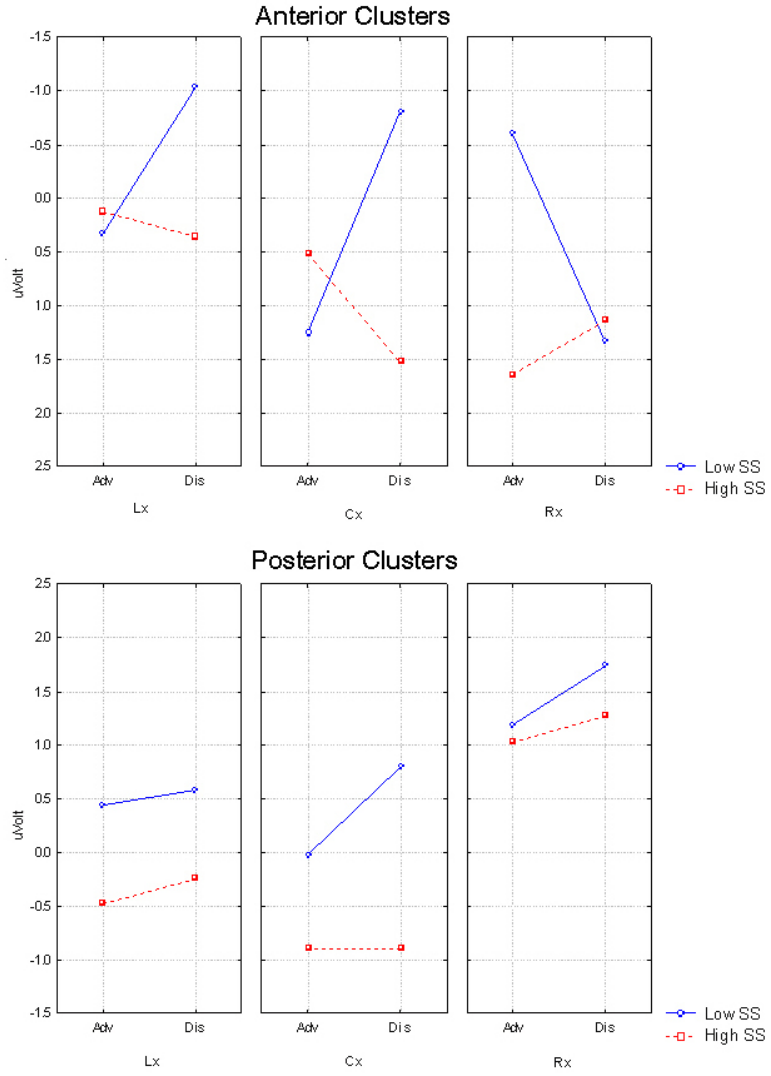


Fig. 5.3.3. **Mean amplitude of the anticipatory potential** in thesecond epoch in anterior clusters (upper panel), and in posterior clusters (lower panel). Low sensation seekers in blue, and high sensation seekers in red.

Post Hoc Newman-Keuls confirmed significance in the same direction of the prior analysis, significant differences between anterior and posterior clusters were found. In this interval, in the anterior clusters, the inversion of high sensation seekers compared to low sensation seekers was more evident. Overall, low sensation seekers showed higher negativity before disadvantageous choices than before safe ones. High sensation seekers, on the contrary, showed higher negativity before advantageous than risky choices.

Feedback-related potentials

Analysis of P200 amplitude showed significant Gradient Main Effect ($F_{(1,24)}$=80.09, p<0.00001), Lateralization Main Effect ($F_{(1,48)}$=17.58, p<0.00001) Feedback x Gradient interaction ($F_{(1,24)}$=19.36, p<0.001), Feedback x Lateralization interaction ($F_{(2,48)}$=24.30, p<0.00001), and Feedback x Gradient x Lateralization interaction ($F_{(2,48)}$=6.20, p<0.01).

Analysis of the central frontal cluster showed a significant Feedback Main Effect ($F_{(1,24)}$=12.95, p<0.005). Subjects overall showed a greater positivity for winnings than for losses.

Analysis of N260 amplitude showed significant Gradient Main Effect ($F_{(1,24)}$=104.59, p<0.00001), a Lateralization Main Effect ($F_{(2,48)}$=10.63, p<0.001), Feedback x Gradient interaction ($F_{(1,24)}$=28.29, p<0.0001), Feedback x Lateralization interaction ($F_{(2,48)}$=8.41, p<0.0001), Gradient x Lateralization interaction ($F_{(2,48)}$=27.40, p<0.00001), Feedback x Gradient x Lateralization interaction ($F_{(2,48)}$=4.78, p<0.05), and Group x Feedback x Gradient x Lateralization interaction ($F_{(2,48)}$=3.61, p<0.05). Both groups showed higher negativity for losses than for winnings (Post Hoc Newman-Keuls comparisons, p<0.01).

Analysis of the central frontal cluster revealed significant Feedback Main Effect ($F_{(1,24)}$=8.19, p<0.01), and Group x Feedback interaction ($F_{(1,24)}$=11,

p<0.001). Subjects overall, exhibited greater positivity for winnings than for losses, Post Hoc Newman-Keuls comparisons pointed out that high sensation seekers showed a significant difference between gain and loss.

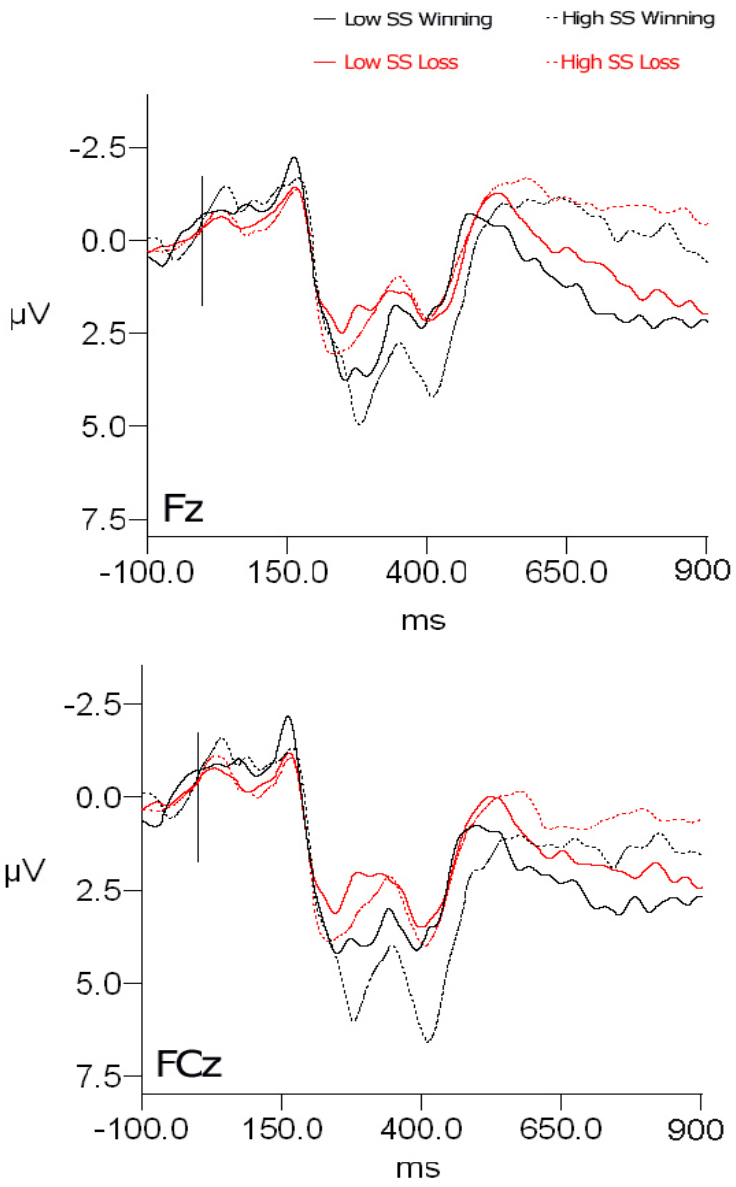


Fig. 5.3.4. **Waveform at Fz and FCz** (Frontal Central Cluster). Winnings in black, losses in red; low sensation seekers: solid line, high sensation seekers: dashed line. Subject exhibited a greater positivity when they received a reward than when received a punishment.

Analysis of late P300 amplitude showed significant Gradient Main Effect ($F_{(1,24)}$=74.07, p<0.00001), a Lateralization Main Effect ($F_{(2,48)}$=4.37, p<0.05), Feedback x Gradient interaction ($F_{(1,24)}$=7.02, p<0.05), Feedback x Lateralization interaction ($F_{(2,48)}$=7, p<0.01), Gradient x Lateralization interaction ($F_{(2,48)}$=14.9, p<0.00001), and Group x Feedback x Gradient x Lateralization interaction ($F_{(2,48)}$=3.61, p<0.05).

Both groups showed higher negativity for losses than for winnings (Post hoc Newman-Keuls, p<0.01).

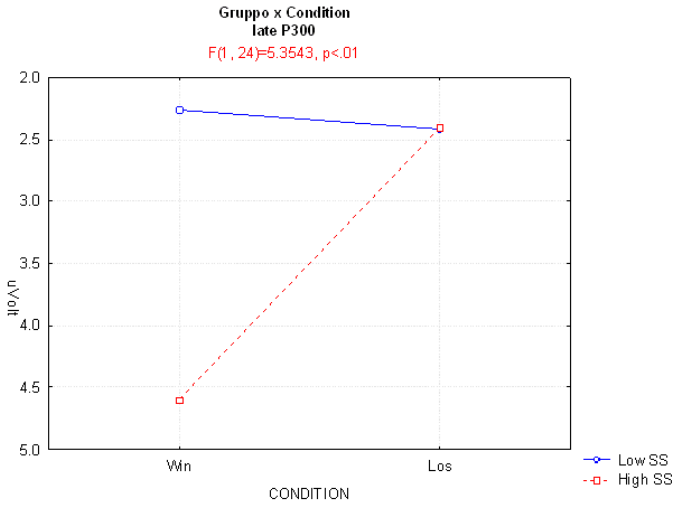


Fig. 5.3.5. **Late P300 amplitude** in low sensation seekers (in blu) and in high sensation seekers (in red), for the two conditions (winnings and losses) in the central cluster (Fz, FCz).

Analysis of the central frontal cluster revealed a a tendency toward statistical significance of the Feedback Main Effect ($F_{(1,24)}$=3.83, p=0.062), and a significant Group x Feedback interaction ($F_{(1,24)}$=5.354, p<0.05). Post Hoc Newman-Keuls showed in high sensation seekers a significant difference between winnings and losses (Fig. 5.3.5): high sensation seekers had higher positivity for winnings compared with losses conditions (p<0.01).

5.3.6 Discussion

The present study was designated to investigate the influence of the trait sensation seeking in decision making, assessed by a version of the IGT.

Results indicate three main findings. First high sensation seekers did not learn to avoid risky decks. Second, high sensation seekers, compared to low sensation seekers, showed a complete inversion of anticipatory patterns, showed higher anticipatory potentials before risky than safe choices. Third, high sensation compared to low sensation seekers, showed higher positivity for winnings than losses, and this was particularly evident in prefrontal recording sites.

Humans and other animals have developed more or less efficient ways to manage the seeking of instant gratification whenever the immediate outcomes of a choice are less advantageous than the future prospects. Impulsivity is defined as the preference for a small, immediate with respect to large, delayed reward (Kalenscher et al., 2006). One specific aspects of impulsiveness is the inability to tolerate long delays for reinforcer achievement, or preference for smaller more immediate rewards over larger but delayed rewards (Logue, 1995). Wittmann and Paulus (2007) proposed that impulsive individuals experience time differently, that is with a higher cost. Impulsive individuals are frustrated by delayed rewards more strongly with respect to do self-controlled individuals. In other words, they fail to weight the pros and cons of their actions and to postpone immediate gratifications; so their behavior is almost always guided by negative or positive events present at the moment. When pleasurable or aversive events are confronted in one's immediate circumstances, appropriate somatic states are generated via activation of sub-cortical circuitry, and these emotions are implicitly stored for future occurrences of the same stimuli. The OFC, in particular, is critical for activating feeling or emotional states from stored experiences about rewarding or punishment events that are not actually present in current perception (Bechara et al., 1999).

According with this view, decision making behavior of high sensation seekers could reflect this inability to evaluate future outcomes in the right way. Feedback related potentials showed that high sensation seekers hyper-process gains compared with low sensation seekers, this could reflect a general increased reward seeking and immediate gratification (delayed discounting) behavior. This kind of encoding influence the retrieval processes, that become dysfunctional and supports disadvantageous strategies. At cortical level this was particularly evident in the orbitofrontal recording sites, where the anticipation potentials and differences between conditions, were higher, and where the differences between groups was clearer. These results further supports the central role of the OFC in emotion processing and in risk taking behavior.

Lissek and colleagues (2005) proposed that the mutually inhibitory relation between aversive and appetitive states (Albert and Ayers, 1997; Bull, 1970; Davis and Kreuter, 1972; Dickinson and Pearce, 1977) lends plausibility to the involvement of both systems (appetitive and aversive) in the generation of motivational antecedents of risky behaviors. More specifically, enhanced appetitive arousal in response to intense and risky stimulus events among high sensation seekers may dampen levels of anxiety associated with exposure to physical danger, leaving them with mostly positive arousal during these sensory experiences. Conversely, stronger anxiety elicited during the anticipation and actual experience of intense and risky activities among low sensation seekers may prevent positive arousal (e.g., excitement) that otherwise accompany participation in such activities, leaving subjects with mostly aversive experiences of these stimulus events. The aversive motivational component of sensation seeking is not the equivalent of trait anxiety but may rather serve as a latent predisposition for anxiety that manifests only in the presence of stress. This conception of sensation seeking is consistent with the fact that correlation between anxiety and sensation seeking are not found when using broad trait anxiety scales and emerge only when using measures of anxious reactivity to situations involving physical threat (for a review, see Zuckerman, 1979).

Similarly, in present results as well as, in prior experiment (see cap 5.2), experiment of Lissek and Powers (2003), trait anxiety did not differ between low- and high-sensation seeking groups. Indeed, low sensation seekers group showed a different pattern, with respect to high trait anxiety group (described in previous experiment), and, take together data about STAI trait, evidenced that SSS did not measure the dimension of high sensation avoidance, tipically associated to anxious trait. The null association between broad trait anxiety and sensation seeking may result from the fact that low sensation seekers organize their lives in ways that protect them from physical risk and sensory overload. Results also suggest that the decision to participate in risky activities among high sensation seekers may be facilitated by the relative absence of apprehensive anticipation. This explanation of the differential participation in dangerous activities among those high and low on sensation seeking contrasts Zuckerman's explanation, which focuses exclusively on differences in the appetitive motivational system (i.e., those high but not low on sensation seeking are appetitively motivated to approach intense and risky sensory experiences).

6. Conclusions

The aim of the present work was to investigate the role of OFC in emotion processing to clarify its key role in emotion modulation, and how emotions guide decision making. Moreover, we were interested in risk anticipation process, an important cognitive/emotional component of decision making, and how personality traits influence risky choices and economic decisions.

In the first two studies the influence of OFC lesions in emotion processing and startle modulation was investigated. Results provided evidence that within the prefrontal cortex, an important role is played by the polar OFC, which is in itself sufficient to produce severe impairment of the primary avoidance emotional response represented by the startle reflex. Our results also provide some indications on the neural circuit of the human startle response. Several studies indicated that the prefrontal cortex subregions represented by the ventromedial cortex, anterior cingulate and polar orbitofrontal cortex, can modulate the autonomic nervous system top-down but they also include fundamental crossing pathways for the bottom-up modulation of all cortical arousal (Angrilli *et al.*, 1999; Critchley *et al.*, 2003; Damasio *et al.*, 1990; Stuss & Benson, 1984; Tranel & Damasio, 1994), from the ascending reticular activating system and the two main diffuse neurotransmitters involved, serotonin and noradrenalin. The present study shows that an important role in startle modulation is played by the polar OFC, which is in itself sufficient to produce severe impairment of the primary avoidance emotional response represented by the startle reflex. Thus, although for some psychophysiological domains of emotional responses, the amygdala and medial prefrontal cortex seem to play different roles (Bechara *et al.*, 1999), for the modulation of the primary defensive startle reflex, in addition to the amygdala, also the OFC plays a crucial role in the direct modulation of the startle response. Our results showed, for the first time, that pOFC plays a fundamental role in emotion modulation and especially in negative emotion processing. In other word, a specific impairment in negative

emotional responses (e.g. punishment) would be at the basis of affective and behavioral alterations that affect OFC patients' everyday activities and social functioning (e.g. finding and keeping a job, and generally engaging in social skills and decision planning).

The literature contains a few descriptions of neurological patients affected by severe social and emotional impairment, with no neuropsychological deficits (Saver and Damasio, 1991). There is agreement on the fact that patients with pure emotional deficits have more limited lesions, at the level of the OFC, which spare the DLPFC, typically associated to cognitive function (Angrilli at al., 1999). Damasio and colleagues (Bechara et al., 1997; Damasio et al., 1990; Tranel and Damasio, 1994) first advanced a coherent hypothesis on the evidence of a lack of autonomic response to emotional stimulation in patients with VMPFC lesions. According to this hypothesis, autonomic activation provides the covert information (implicit knowledge) related to past emotional experiences, which is necessary for finding a solution in complex everyday situations. In a series of experiments, Bechara and colleagues (Bechara et al., 2000) concluded that VMPFC patients did not show impairment in working memory, and impaired recall of emotional events, and that deficits of these patients are not related to an impairment of emotion retrieval. They suggested that lesions to VMPFC impair the ability to re-experienced an emotion from recall of an appropriate emotional event. Consequently the failure of VMPFC patients to acquire anticipatory SCRs, coupled to their decision making impairment, is in part due to their inability to re-experience the emotion of similar past and stored fearful situations. Conversely, our results demonstrate that OFC is crucial in emotion processing, and in particular in the encoding of emotional negative events. These findings support the idea that OFC patients have a selective impairment in the elaboration of negative feedback (lack of frustration of punishment) already at a basic level, and this deficit would block their capacity of emotional retrieval. Lesions of the OFC interfere with the normal processing of somatic/emotional signals, but leave other cognitive functions minimally

affected. This damage leads to pathological deficit in decision making process which in turn affects the efficiency of everyday-life decisions. Our interpretation is consistent with the view that mood, affect, and emotions have a primary influence in decision making.

The theory of the “somatic marker” is supported by several behavioral and neuropsychological data (Damasio, 1994), but it mainly relies on the observation of reduced skin conductance emotional responses in patients with prefrontal damage. In the last decade studies on decision making received increasing attention from neuroscientists, nevertheless no-one so far investigated the two important components which characterize decision making: encoding and retrieval of economic salient stimuli (i.e. winning/losses). In particular despite the high importance of anticipation processes in decision making, there are only a few studies on this aspect, which were mainly performed by fMRI.

We implemented a gambling task to investigate the neural basis of the anticipation components of Decision Making, and the feedback related components of winnings and losses, by means of ERPs. The paradigm was designed to measure, through the ERPs, the capability of subjects to encode and elaborate monetary rewards and punishments evoked by the feedback stimulus, but also to quantify their capability to retrieve stored memories on advantageous and disadvantageous decks, through the anticipatory potentials.

With the exception of a few theories on decision making (Janis and Mann, 1977; Mann, 1992), most current theories on choice processes use a cognitive perspective. These theories assume that decisions derive from an assessment of the future outcomes with various options and alternatives through some type of cost-benefit analyses. Some of these theories have pointed on emotion as a critical factor in decision making, but mostly as a consequence of a decision (e.g. the disappointment or regret experienced after some risky decisions) rather than as reactions arising directly from the decision itself in the occurrence of a planned act. The somatic marker hypothesis proposes that individuals make

decisions not only by assessing the severity of outcomes and their probability of occurrence, but also and primarily in terms of their emotional quality.

Adaptive behavior requires an ability to make advantageous decisions by predicting the likelihood of future success based upon previous experience. During learning, normal subjects develop anticipatory arousal before selecting high-risk options, and adopt the more advantageous low risk strategy. Healthy subjects and low sensation seekers showed a preferences for low risk decisions and larger anticipatory potentials preceding high risk options. Thus anticipatory arousal is an index of risk-related emotional processing that may directly influence behavior. Prefrontal recording sites, compared to more posterior ones, showed increased amplitude both during preparation for action (before decks picking) and during feedback processing. Taken together data of the present work suggest that OFC region is involved in anticipatory responses as well as in the representation of outcomes. Thus activity within this region is implicated in mediating cognitive and behavioral dimensions of anticipation.

The findings that high AT subjects showed a normal processing of feedback together with cortical inhibition leading to disadvantageous strategy in taking risky decisions, supports the idea that decision making is mediated by two separate processes: encoding of monetary outcome (feedback processing) that provides the covert information (implicit knowledge), and retrieval of learned associations (measured through anticipation processes), both necessary for optimal decisions. Moreover these findings support the hypothesis that negative affective states and emotional individual differences influence decision making in everyday-life.

The OFC is a cytoarchitectonically heterogeneous area that has not yet well characterised in humans (Carmichael and Price, 1994; Price et al., 1996). In monkeys, the literature regarding the anatomical connectivity and the effects of lesions involving of the orbital surface of the prefrontal cortex points to a specialization in emotion-related functions (Carmichael and Price, 1995; Damasio and Van Hoesen, 1983). The innervations of the OFC is primarily with

limbic or paralimbic structures that have been implicated in emotional processing, such as the amygdala, the lateral hypothalamus, the ventral striatum, and the lateral orbital cortex (Carmichael & Price, 1995; LeDoux, 1987). OFC is also an area where cerebral blood flow (CBF) is elevated in pathological emotional states. Both CBF (Drevets et al., 1992) and glucose metabolism (Drevets et al., 1995) are elevated in this region in depressed subjects with familial major depression syndrome (Drevets and Raichle, 1998). Deactivation of the medial orbital cortex has been observed during experimental conditions involving language or visuo-spatial processing. Drevets and Raichle (1998) observed metabolic activation of this region when actively reading words as compared with passively viewing words, and when monitoring moving visual objects for changes in either colour, shape, or velocity as compared with passively viewing the same visual objects (Shulman et al., 1996). CBF reductions in areas implicated in emotional processing may thus relate to an attentional mechanism in which the neural processing resources become increasingly allocated in this region following attentional demand. Suppression of afferent transmission to regions related to emotional processing may account for the observations of some patients suffering from mildly to moderately severe major depressive episodes, in whom their dysphoria is less pronounced when they become busy with word-related tasks, whereas it worsens when they are no longer distracted by work. Similarly, in the course of bereavement, grief can be temporarily interrupted by occupation with attentionally demanding cognitive activities required to solve word-related tasks. This phenomenon may be analogous to the experience that mild somatosensory pain is no longer noticeable when one is actively engaged in social interaction, task performance, or problem solving, but returns during relaxation from such activities. This suppression of mild pain could reflect a manifestation of somatosensory gating. It might be hypothesised that afferent neural information to areas subserving emotional processing is suppressed, or “gated” , when task demands require heightened attention to cognitive operations unrelated to emotions.

Research investigating the influence of trait anxiety on risk-taking produced very interesting and relevant results. However, to date the literature focussed on judgment of probability instead of actual decision making behaviour. In past paradigms subjects were typically asked to assess how likely is the occurrence of positive or negative events, and what is their perceived relevance. The reason for such a separate assessment of probability and utility is that TA may affect decision making because of bias in probability judgment. Gasper and Clore (1998) argued that high TA individuals have an attentional bias toward threatening information (see Broadbent and Broadbent, 1988; MacLeod and Cohen, 1993), which, in turn, produces a biased risk perception. Butler and Matthews (1987) provided evidence for a generalized tendency of TA individuals to over-estimate risks. They related scores on the STAI State to probability judgement for situations involving both positive and negative outcomes. Whereas anxiety state was consistently related to risk over-estimation in situation specific outcomes, TA predicted a generalized over-estimation of risk for all the outcomes.

Sensation seeking is perhaps one of the most investigated trait in risk taking research. Recently, Zuckerman (1994) added to original aspects of sensation seeking, such as physical and social risks, also legal and financial risks. The psychological explanation for individual differences in observed risk-taking is based on sensation seekers' need for high arousal which can be provided by varied, novel, complex and intense experiences. Zuckerman reported that in controlled tasks with hypothetical gamblers, high sensation seekers tend to bet more money and higher odds with respect to low sensation seekers. Our results confirmed that high sensation seekers tended to take more risks than low sensation seekers did. Moreover, high sensation seekers showed a hyper-processing of winnings, and exhibited greater anticipatory negative potentials before safe than risky choices. Feedback potentials had bilateral distribution, but were higher in prefrontal EEG sites. It is interesting to note that anticipation components showed group differences in prefrontal sites (in prefrontal clusters

sensation seekers showed a reversed pattern compared to low sensation seekers), confirmed the important role of OFC in decision making processes.

Convergent functional neuroimaging studies (Elliot et al., 1997 ; Paulus et al., 2004) have repeatedly demonstrated that OFC is active during flexible modification of stimulus-reward associations. Several studies reported increased risk taking (rather than impulsivity) in patients with frontal lobe damage (Clark et al., 2003; Manes et al., 2002; Mavaddat et al., 2000). Lesion in this region, as discussed above, may disrupt emotional responses to rewards/punishments which motivate behavior and guide decisions (Floden et al., 2007). Our results suggest that blunted reaction to negative outcomes or failure to use negative feedback impairs decision making. Sensation seekers indeed showed an hyper-processing of positive outcomes/winnings to detriment of negative ones, a non-adequate anticipation of risk, and consequently a dysfunctional decision making behavior. These findings suggest that sensation seeking is related to the reward (emotion)-based aspects of decision making (risk taking) rather than to a simple response disinhibition.

Emotion are pervasive in every instant of human life. Several theories in neuroscience, psychology, and sociology acknowledge its central role in explaining human behavior. Although some economists have recognized the role of emotions in explaining human behavior, the overall significance of emotions have been virtually ignored in economics literature, especially in an ecological context.

Perhaps economists have ignored the role of emotions in decision-making because emotions had a checkered history in psychology and neuroscience; there was disagreement on how to define them, disagreement on what they are for, and what processes they involve. Furthermore, according to a popular and superficial notion spread in modern culture, rational reasoning forms the basis of cognitive decisions; “emotions have no IQ” and can only interfere with optimal cognitive judgments.

In financial context, emotional reactions to market news, as well as "concerns" about future investments induce somatic states. However, stored rewards/punishments influence the feeling and triggering of subsequent affective responses and drive future economic decisions (Bechara and Damasio, 2005). Markets economy favors conditions where investors take risks. There is probably an evolutionary advantage to taking risks. The work of Schultz and colleagues (2000) provides a good biological explanation for why we take risks. If an animal received an unexpected (or unlikely) reward, the activity of dopamine neurons increases. Perhaps the greater release of dopamine after an unexpected reward is what prompts the risk taking. Without it, the organism would not explore new resources for food and consequently might starve to death. By analogy, "… without the dopamine signal to take a risk, modern investors would probably keep all their money under the mattresses" (Zweig, 2002). This suggests that risk taking in economic investment is modulated by somatic/emotional states. Background somatic states related to past market news (e.g., a market loss) exert an influential role on the operation of the somatic marker circuitry and subsequent decisions and risk taking behaviors. There are several conditions under which somatic states that guide decisions can be altered by background emotions and moods (e.g. when the market conditions are not stable vs uneventful). This model offers several predictions of human economic choice, but its validation is only at preliminary stages, and studies are currently aimed at testing various predictions from this model.

Results of present dissertation supports this view, as they highlighted how outcomes encoding (capacity to react emotionally) and retrieval processes (leading to decision taking) interact in behavioural risky choice, and showed the neural mechanisms underlying emotion elaboration and decision making processes.

Emotions are a major factor in the interaction between environmental conditions and human decision processes, with these emotional systems (underlying somatic state activation) providing valuable implicit or explicit

knowledge for making fast and advantageous decisions. Thus the somatic marker framework on decision-making is anchored to the emotional side of humans as opposed to the construct of homo economicus (Bechara and Damasio, 2005). Although the view of maximizing utility in the decision-making is pervasive and has a useful benchmark function, human decision-makers seldom conform to it. The process of deciding advantageously is not just logical but also emotional.

7. References

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My last remaining task is to acknowledge the people that have contributed to the work described in this dissertation. This dissertation is the result of three years of work whereby I have been accompanied and supported by many people. It is a pleasant aspect that I have now, the opportunity to express my gratitude for them.

I would like to thank my supervisor Prof. Alessandro Angrilli, for his scientific, but also human, support. He stimulated me to start and carry out my work and to write this dissertation. Thanks for the scientific and methodological discussions that was very important for my scientific and professional training.

I would also like to tank: Dr. Giannettore Bertagnoni for help with patients recruiting; all the stuff of the Department of Biological Psychology, Clinical Psychology, and Psychotherapy, for their hospitality and helpfulness during my period in Würzburg; Sandro Bettella and Marco Pertile for technical support; and all the Psychophysiology Research Group.

Un sentito ringraziamento va a coloro che mi hanno aiutata fornendo le *variabili* necessarie come il cibo, la formazione, i geni, i soldi, l'aiuto, il consiglio, l'amicizia. Particolarmente, ma non esclusivamente: grazie a Mamma, Sara, Enrico, Emma, Luca, e Giovanni, senza di loro tutto ciò non sarebbe stato possibile; grazie a Elisa e Simone per l' immancabile sostegno e l'amicizia che sanno superare i chilometri e il tempo; grazie a Silvia e Simona per il supporto e la bella amicizia che questo dottorato ha contribuito a far nascere e crescere.

This study was supported by a Ph.D. fellowship from CARIPARO foundation