Department of Information Engineering
University of Padova

Laboratory for Clinical Neuroscience
Centre for Biomedical Technology
Technical University of Madrid, Spain

Epilepsy Unit Department of Neurology, and Department of Neurosurgery
Hospital Ruber Internacional
Madrid, Spain

Institute of Neurology
UCL, Queen Square, London, UK

MASTER DEGREE THESIS

Intracranial electrophysiological recordings of human orbitofrontal responses to emotional stimuli

Student: **Michele Tessari**
1019398

Supervisor: Prof. **Alfredo Ruggeri**
Department of Information Engineering, University of Padova, Italy
Co-Supervisor: Prof. **Bryan Strange**
Laboratory for Clinical Neuroscience, CTB, Technical University of Madrid, Spain

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Summary

The orbitofrontal cortex involvement in processing facial expressions as its role in affective processing has been reported in numerous electrophysiological and functional neuroimaging studies. However, the literature does not provide precise data on the temporal course of emotional facial expressions processing. Intracranial event-related potentials were recorded in epileptic patients implanted with depth electrodes during a presurgical evaluation. Patients had to perform a gender judgement task while viewing fearful, happy and neutral high-spatial-frequency (HSF), low-spatial-frequency (LSF) and broadband face stimuli. Orbitofrontal responses were observed to all emotions and to all spatial frequency contents with latencies between 100 and 200 ms post-stimulus. This study shed light on the temporal course of the facial emotions information processing and on the involvement of the orbitofrontal cortex in the neural network recruited to process emotional information.

1. Introduction

Several studies have demonstrated an impairment of emotional recognition in several diseases, particularly frontotemporal dementia [1,2], Huntington's disease [3], right temporal lobe epilepsy [4] and schizophrenia [5]. Since this deficit may cause behavioural and social disorders, it is crucial to understand the neural processes involved in facial expression recognition.

Most evidence to date, from lesions and neuroimaging studies [6,7] as well as from neurophysiological studies in nonhuman primates [8], suggest that the orbitofrontal cortex (OFC) is crucial in emotional processing and reward-based decision-making processes [9,10,11]. Indeed, single-unit recordings in monkeys and functional magnetic resonance imaging (fMRI) studies in humans have shown that the orbitofrontal cortex participates in linking perception of stimuli to the guidance of behaviour [12], including the flexible execution of strategies for obtaining rewards and avoiding punishments as an organism interacts with its environment [13]. Furthermore, converging evidence indicates that the orbitofrontal cortex is involved in processing facial expressions, as its role in affective processing has been highlighted by numerous studies showing OFC responses to emotional faces, both in fMRI and intracranial EEG studies [14,15,16]. However, as noted in a recent review [15], the precise functions of the human orbitofrontal cortex are still enigmatic.

In addition, further neuroimaging studies have demonstrated the involvement of a complex neural network in specific facial expression processing. This network include limbic structures such the amygdala, which processes mostly threatening messages like fear or anger [17,18], paralimbic structures such the anterior cingulate, and other cortical areas such the ventral anterior insula, which is involved in disgust analysis [19,20], the superior temporal sulcus, the inferior occipital cortex, the middle fusiform gyrus, the somatosensory cortex and the orbitofrontal cortex itself.

Since most of these studies have used fMRI measures, which are based on relatively slow hemodynamic brain responses to emotional stimuli, information about the time course of emotional processing has been relatively scarce and the contribution of these

regions to recognition of different facial expressions and their specific role in emotional processing remain poorly described. The availability of detailed temporal information is necessary to obtain a more comprehensive picture of the functional properties of the emotional brain. Thus, fMRI measures need to be complemented with methods that provide insights into temporal parameters of emotional processing, such as event-related brain potential (ERP) or magnetoencephalographic (MEG) measures.

In the present study we benefited from a unique opportunity to record neural activity in the OFC of epileptic patients under pre-surgical evaluation with intracerebral EEG using depth electrodes. This technique combine very good spatial and temporal resolutions and is particularly well adapted to address such anatomical and temporal issues concerning human emotion processing. The fine spatio-temporal properties of OFC activity were assessed by performing direct recordings while the patients performed a gender judgement task (that is, an implicit facial expression detection).

We considered two basic and contrasting facial expressions (happiness and fear) versus neutral facial expressions and we set out to shed more light onto the properties of the OFC by hypothesizing that a modulation of the responses due to the factor emotion would have meant a specific involvement of the orbitofrontal cortex in emotional processing and by investigating whether these responses differ depending on the valence of the stimuli (positive versus negative).

Furthermore, some studies described the possibility that high and low spatial frequency information in visual images was processed by distinct neural channels [21]. In particular, these studies hypothesized the existence of a fast-pathway for fear processing that allows the amygdala to receive direct subcortical fear-related inputs from the thalamus, enabling crude but rapidly processed information about fear-related cues to bypass slower cortical processing in ventral visual pathways [22,23,24,25]. Since the orbitofrontal cortex receive projections (and project to) the amygdala, we searched for a potential modulation of the responses recorded in the orbitofrontal cortex due to the spatial frequencies of the images, to see how the orbitofrontal cortex is involved in the two different pathways of the visual information, the "standard" (slow) one and the fast one abovementioned.

2. Functional neuroanatomy of the orbitofrontal cortex

Over the last hundred years it has been learned more about the localisation of functions in the human brain than in the rest of recorded history. The early, poorly founded efforts of phrenology as practiced by Gall and his followers have been replaced by a corpus of solid neuroscientific evidence from experiments in other animals. This was made possible in part through the advent of human neuroimaging, though its interpretation needs to take into account the wealth of scientific evidence obtained also with different methods from both humans and other animals. The orbitofrontal cortex provides in many ways a good example of how functional neuroimaging and other neuroscientific research can advance our understanding of the functional role of a human brain region.

In this section we will focus on humans and macaques, because there are many topological, cytoarchitectural, and probably connectional similarities between macaques and humans with respect to the orbitofrontal cortex [26,27,28,29]. This brain region may be less well developed in rodents. Moreover, in primates the orbitofrontal cortex receives visual information from the inferior temporal visual cortex, which is a highly developed area for primate vision enabling invariant visual object recognition [30], and which provides visual inputs used in the primate orbitofrontal cortex for one-trial object-reward association reversal learning and for representing face expression and identity (see 2.3). To understand the functions of the orbitofrontal cortex in humans, the majority of the studies considered here were therefore performed with both macaques or humans.

Evidence from the connections, effects of damage, functional neuroimaging and neurophysiological studies is all necessary in order to understand cortical functions.

Some of the functions of the primate orbitofrontal cortex have been previously elucidated in a variety of experiments in non-human primates [30]. Some of the conclusions of this research are that the orbitofrontal cortex represents the changing and relative reward value of many different primary (unlearned) reinforcers such as taste and somatosensory stimuli; of many different secondary (learned) reinforcers

including olfactory and visual stimuli; and learns and rapidly reverses associations between secondary and primary reinforcers, that is it implements stimulus-reinforcement association learning, which is the type of learning that is involved in emotion [30].

2.1 Neuroanatomy

The primate orbitofrontal cortex occupies the ventral surface of the frontal part of the brain (see Fig.1) and can be defined as the part of the prefrontal cortex that receives projections from the **magnocellular, medial**, nucleus of the mediodorsal thalamus [31]. This is in contrast to other parts of the prefrontal cortex which receive projections from other parts of the mediodorsal thalamus, such the dorsolateral prefrontal cortex which receives projections from the **parvocellular, lateral**, nucleus of the mediodorsal thalamus; and the frontal eye fields (Brodmann's area 8) in the anterior bank of the arcuate sulcus which receive projections from the **paralamellar** part of the mediodorsal nucleus of the thalamus (in Fig.2 it is possible to see the structure of the thalamus). It is worth pointing out that magnocellular cells are large, fast-conducting neurons responsible for resolving motion and coarse outlines, while parvocellular neurons are sensitive to colour and more capable of discriminating fine details. In other words, parvocellular cells have greater spatial resolution, but lower temporal resolution, than the magnocellular cells, which operate with great speed at the expense of detail.

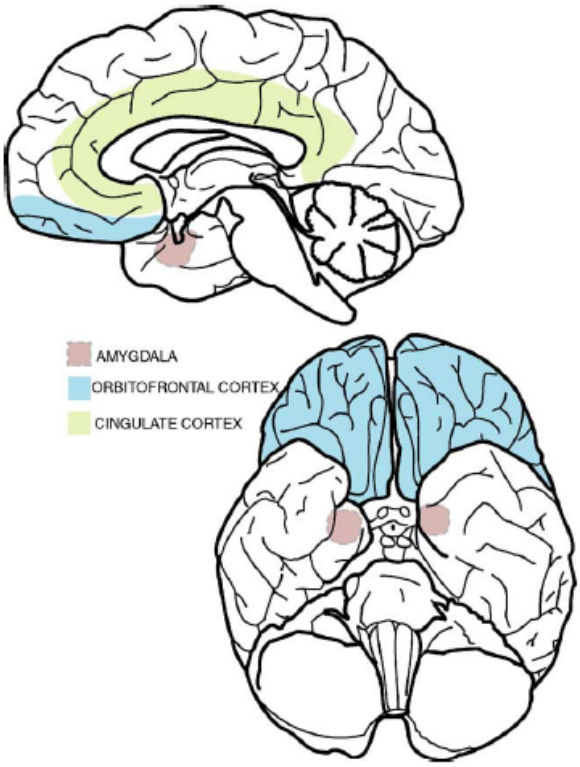

Figure 1: Some of the key brain structures implicated in emotion. The position of the amygdala, orbitofrontal cortex and cingulate cortex are shown on a midsagittal view (top) and on a ventral view (bottom) of the human brain.

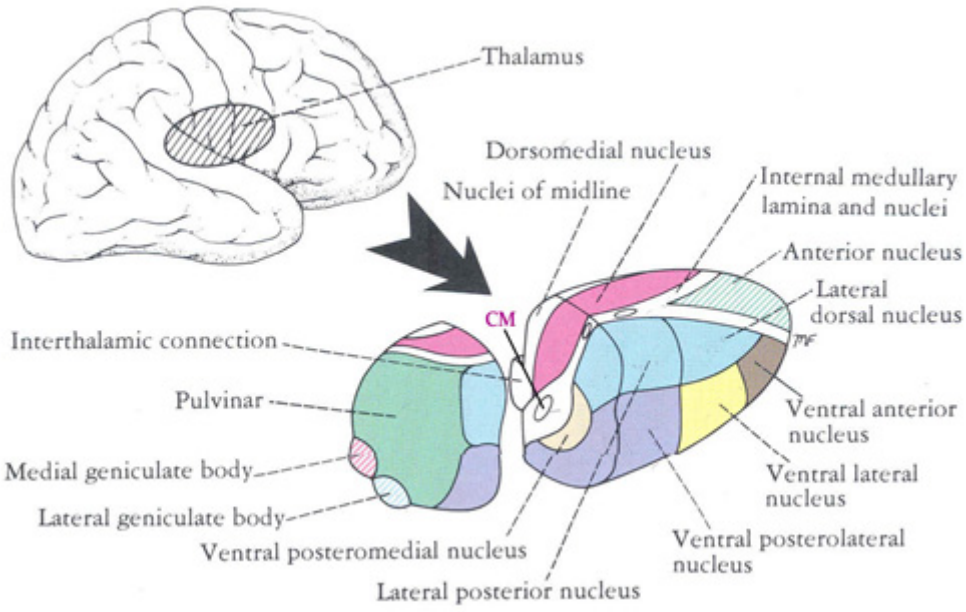

Figure 2: Human thalamus.

Brodmann [32,33] carried out one of the first comprehensive cytoarchitectural analyses of both the human and the primate (specifically that of the Cercopithecus monkey) brain and subsequently assigned unique numbers to different cytoarchitectonic areas (see Fig.3a). Unfortunately, Brodmann was less detailed in his investigations of the orbitofrontal cortex, and his cytoarchitectonical maps were restricted to mapping areas 10, 11 and 47 in the human brain. Moreover, the homologies between the human and primate regions were not fully worked out, in that in the primate map, area 11 is extended laterally and area 12 has taken over the medial area occupied by area 11 in the human map, while area 47 is not included at all in the non-human primate map. Clarification was provided by Walker [34], who investigated the monkey species Macaca fascicularis to try to resolve the inconsistencies present in Brodmann's maps. The orbitofrontal cortex turned out to be much less homogenous than specified by Brodmann. Walker therefore proposed to parcellate the primate orbital surface into five distinct areas (areas 10, 11, 12, 13 and 14; see Fig.3b). Areas 12 and 13 occupy the lateral and medial orbital surface, respectively, while area 14 is on the ventromedial convexity near the gyrus rectus. Further anterior, area 10 occupies the frontal pole, while area 11 occupies the remaining anterior orbital surface. Area 47 from the human map was still not included in Walker's map, and subsequently Petrides and Pandya [29] tried to reconcile the remaining inconsistencies between the human and monkey cytoarchitectonic maps by proposing to label the lateral parts of the orbitofrontal gyri as 47/12 (see Fig.3c). Another study (see Fig.3d) used nine different histochemical and immunohistochemical stains to further subdivide the orbitofrontal cortex into smaller subareas [26].

Another crucial cytoarchitectonic feature of the orbitofrontal cortices is the considerable variability between individuals. A study mapped the various orbital sulci in both humans and monkeys (Macaca mulatta) using magnetic resonance imaging of 50 right-handed humans (22 women and 28 men) and photographs of 50 post-mortem monkey brains [35]. Three main types of sulcal patterns were found in humans, with considerable variability even within each subtype. Generally, four main sulci were identified on the orbital surface: the olfactory, medial, lateral and transverse orbital sulci. These four sulci essentially subdivided the orbitofrontal cortex into four main gyri. The considerable

variability found in the orbitofrontal cortex can be further expressed in sulcal probability maps in standardised stereotaxic proportional space [36]. Overall, the considerable variability of human orbitofrontal cortex anatomy shows that there are significant differences between individuals. It also poses interesting methodological challenges for those who hope to normalise individual brains to a template brain in order to generalise about the functional anatomy of the human orbitofrontal cortex.

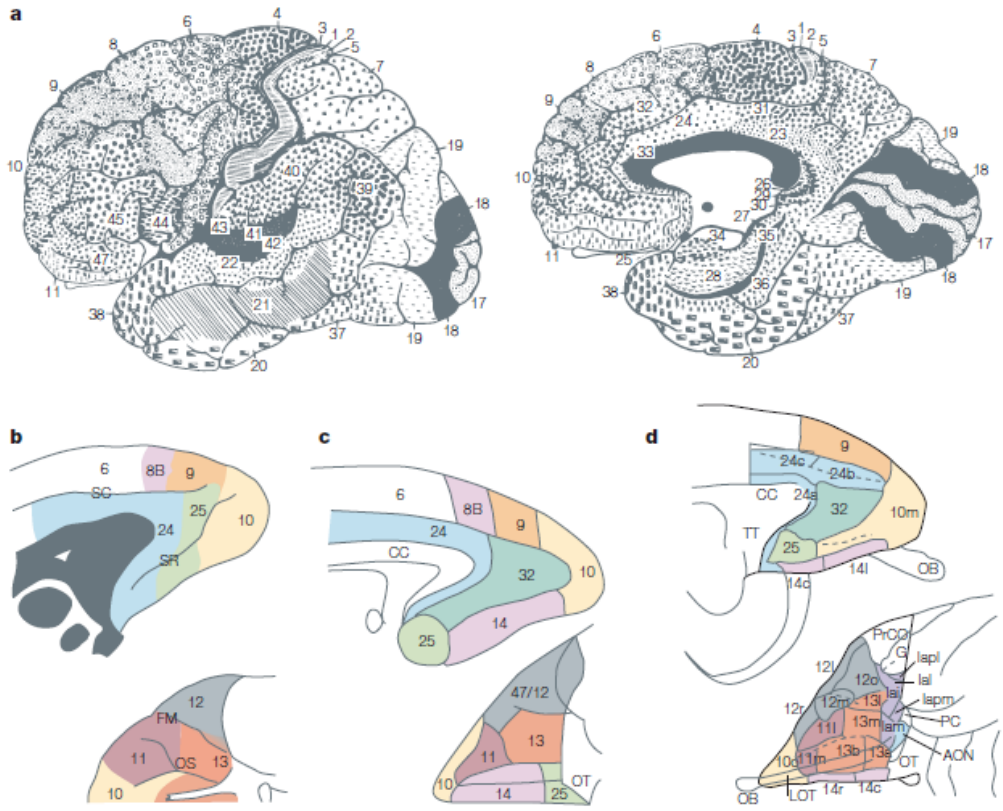

Figure 3: Cytoarchitectonic maps of human and monkey orbitofrontal cortices.
a) Brodmann's original cytoarchitectonic maps of the human brain with a ventral view of the brain on the left and a medial view of the cortical areas on the medial wall of the brain on the right. The complex cytoarchitecture of the orbitofrontal cortex was reduced to three areas, 11, 47 and 10.
b) Later investigations further subdivided the orbitofrontal cortex to reflect its heterogeneity, as first proposed in the maps of Walker. Views of the medial wall and ventral surface are shown for the monkey Macaca fascicularis. Walker proposed a further parcellation of the orbitofrontal cortex into five areas (areas 10, 11, 12, 13 and 14). FM, sulcus frontomarginalis; OS, sulcus orbitalis; SC, sulcus callosomarginalis; SR, sulcus rostralis.
c) Walker's nomenclature was then reconciled with that used in Brodmann's primate and human brains by Petrides and Pandya, with lateral parts of the orbitofrontal cortex designated area 47/12. CC, corpus callosum; OT, olfactory tubercle.
d) Even further subdivisions of the orbitofrontal cortex were subsequently proposed by Carmichael and Price. AON, anterior olfactory nucleus; G, gustatory cortex; Iai, intermediate agranular insula area; Ial, lateral agranular insula area; Iam, medial agranular insula area; Iapl, posterolateral agranular insula area; Iapm, posteromedial agranular insula area; LOT, lateral olfactory tract; OB, olfactory bulb; PC, piriform cortex; PrCO, precentral opercular cortex; TT, tenia tectum.

2.2. Connections

Part of the background for understanding neuronal responses in the orbitofrontal cortex is the anatomical connections of the orbitofrontal cortex [26,28,29]. The orbitofrontal cortex receives inputs from all the sensory modalities: gustatory, olfactory, somatosensory, auditory and visual (Fig.4) [30]. Visceral information is also received by the orbitofrontal cortex and all this sensory information makes the orbitofrontal cortex the perhaps most polymodal region in the entire cortical mantle with the possible exception of the rhinal regions of the temporal lobes. A schematic diagram that helps to show the stage of processing in different sensory streams of the orbitofrontal cortex is provided in Fig.4. Conceptually, the orbitofrontal cortex can be thought of as receiving from the ends of each modality-specific ‘‘what’’ cortical pathway. The orbitofrontal cortex is thus well placed for multimodal stimulus-reinforcement association learning [30].

2.2.1. Inputs

Rolls et al. [37] discovered a **taste** area with taste-responsive neurons in the lateral part of the macaque orbitofrontal cortex, and showed anatomically that this was the secondary taste cortex in that it receives a major projection from the primary taste cortex [38]. This region projects on to more anterior areas of the orbitofrontal cortex [38]. Taste neurons are also found more medially [30].

In the mid-orbitofrontal cortex, there is an area with **olfactory** neurons [39] and anatomically, there are direct connections from the primary olfactory cortex, orbitofrontal cortex (area 13) [26,40].

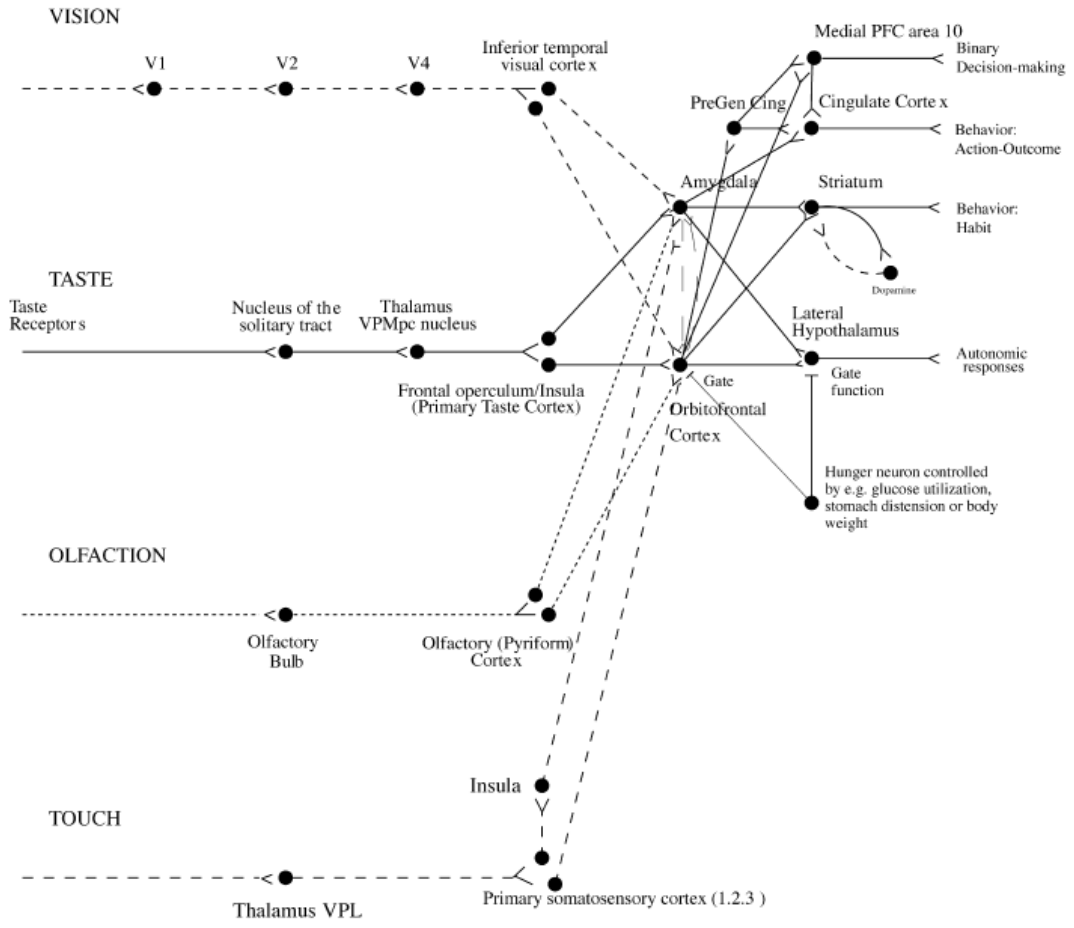

Figure 4: Schematic diagram showing some of the gustatory, olfactory, visual and somatosensory pathways to the orbitofrontal cortex, and some of the outputs of the orbitofrontal cortex, in primates. The secondary taste cortex, and the secondary olfactory cortex, are within the orbitofrontal cortex. V1: primary visual cortex, V4: visual cortical area V4; PreGen Cing: pregenual cingulate cortex. "Gate" refers to the finding that inputs such as the taste, smell, and sight of food in some brain regions only produce effects when hunger is present (Rolls, 2005). The column of brain regions including and below the inferior temporal visual cortex represents brain regions in which what stimulus is present is made explicit in the neuronal representation, but not its reward or affective value which are represented in the next tier of brain regions, the orbitofrontal cortex and amygdala, and in areas beyond these.

Thorpe et al. [41] found neurons with **visual** responses in the orbitofrontal cortex, and anatomically, visual inputs reach the orbitofrontal cortex directly from the inferior temporal cortex (where object and face identity are represented [42]), the cortex in the superior temporal sulcus (where face expression and gesture are represented [43]), and the temporal pole [44].

Auditory information is received in area 11 and 47/12 from area TA and area TAa in the superior temporal cortex [45].

Some neurons in the orbitofrontal cortex respond to oral **somatosensory** stimuli such as the texture of food [46] and anatomically there are inputs to the orbitofrontal cortex from somatosensory cortical areas 1, 2 and SII in the frontal and pericentral operculum, and from the insula [44].

Visceral information is received in the caudal orbitofrontal cortex (areas Ial and Iapm) from a region of the ventrolateral posteromedial thalamic nucleus [28].

There are also direct inputs from other brain structures. The most prominent of these brain structures is the **amygdala**, where a number of its nuclei including the lateral, basal and accessory basal, anterior, periamygdaloid and medial nuclei all project extensively to widespread areas of the orbitofrontal cortex [47]. Some of these projections and especially those from the basal nucleus of the amygdala are topographically organised. The connections are in almost all cases reciprocal, and there is some evidence that the orbitofrontal cortex projects more widely to the amygdala than vice versa [48]. In addition, as described above, the **insula** projects taste, olfactory, visceral, and somatosensory information widely to the caudal part of orbitofrontal cortex [49]. The projections from the **anterior cingulate cortex** to the orbitofrontal cortex are dense, with projections from nearly all parts of the anterior cingulate cortex [50]. Parts of the **posterior cingulate cortex** (areas 23 and 30) also project to the orbitofrontal cortex [50]. The **motor cingulate area**, 23c, also has strong reciprocal connections with the orbitofrontal cortex [48]. **Premotor area** F5 contains the representation of distal arm movement with neurons responding to goal-related motor acts and motivational visual stimuli, and has reciprocal connections with the lateral and caudal orbitofrontal cortex [30]. There are reciprocal connections with other **prefrontal areas** (areas 9 and 46) in extensive parts of the orbitofrontal cortex including areas 10, 11, 12 and 14 [44]. The **posterior hypothalamus** also projects to the prefrontal cortex [30]. The **hippocampus** has direct extensive ipsilateral topographic projections to primarily the medial orbitofrontal cortex [48]. The orbitofrontal cortex also receives inputs via the **mediodorsal nucleus of the thalamus**, pars magnocellularis, which itself receives afferents from temporal lobe structures such as the prepiriform (olfactory) cortex, amygdala, and inferior temporal cortex [28].These connections provide some routes via which the responses of orbitofrontal cortex neurons can be produced.

Within the orbitofrontal cortex, there are many intrinsic connections [28], and these may be part of what enables many orbitofrontal cortex neurons to have multimodal responses, as described below and elsewhere [30].

2.2.2. Outputs

The orbitofrontal cortex projects back to temporal lobe areas such as the **amygdala**. The orbitofrontal cortex also has projections to the **cingulate cortex**, the **ventral striatum** and head of the **caudate nucleus**, **medial prefrontal cortex** area 10, **entorhinal** and **perirhinal cortex** providing a route for reward information to reach the hippocampus, **preoptic region** and **lateral hypothalamus** (where neurons respond to the sight and taste of food, and show sensory-specific satiety), and the **ventral tegmental area**, and these connections provide some routes via which the orbitofrontal cortex can influence behaviour [30] and memory [51].

2.3 The functional role of the OFC in emotions processing

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 this brain region. Foremost this evidence has linked the orbitofrontal cortex to the study of emotion. In this section, first the orbitofrontal cortex is placed within the context of the current state of emotional research. Then follows a review of the evidence from lesions to the human orbitofrontal cortex, and from neurophysiological recordings and lesions to non-human primates.

2.3.1 What are "emotions"?

Emotion has for many years remained an elusive scientific topic, but recent years have seen a significant increase in research on emotion, leading to important new discoveries of the brain mechanisms involved. The main problem with scientific investigations of emotion has been one of definition. Ancient Greek and later Western philosophers have discussed emotion extensively, but with the emphasis almost exclusively on its cognitive evaluation, and a definition of emotion useful for scientific inquiry did not emerge. The field of emotion research began slowly to make headway with advances made by pioneering individuals such as Charles Darwin, who examined the evolution of emotional responses and facial expressions. In the 1880s, William James and Carl Lange independently proposed the idea that rather than emotional experience being a response to a stimulus, it is the perception of the ensuing physiological bodily changes which results in the emotional feelings . The James–Lange theory suggests that we do not run from the bear because we are afraid but that we become afraid because we run. These ideas, however, still did not address the question of what brain structures were involved in emotion, which only began with the detailed critique of the James–Lange theory by William Cannon in 1927 showing that surgical disruption of the peripheral nervous system in dogs did not eliminate emotional responses as would have been predicted by the James–Lange theory. Further investigations by Schachter and Singer

and others provided evidence that cognitive factors were essential for emotion, and that bodily states may merely modulate to some extent the intensity of whatever emotion is being produced by cognitive inputs. Nevertheless, the James–Lange theory was resurrected by Antonio Damasio [6] in the form of his somatic marker hypothesis, in which feedback from the peripheral nervous system controls the "decision" about the correct behavioural response rather than the "emotional feelings" as postulated in the James–Lange theory. An alternative to such bodily theories of emotions has been proposed by Larry Weiskrantz (1968), Jeffrey Gray (1975) and Edmund Rolls [8] who instead regard emotions as states elicited by rewards and punishments, i.e. by instrumental reinforcers. Emotional stimuli (primary and secondary reinforcers) are represented by different brain structures depending on the kind of reinforcer. The subsequent evaluation is a multistage process mediated by a number of specific brain structures, and the results of this evaluation then influence which behaviour is selected, which feelings are produced, and which autonomic responses are elicited.

2.3.2. Which brain structures are involved?

The early pioneering theories were built on a paucity of experimental data, and with the recent flourishing of emotion research, and especially given the ever increasing amount of primate neurophysiological and human neuroimaging data, we are finally in a much better position to evaluate which brain structures are crucial to emotion. The evidence points to the amygdala and the cingulate cortex as necessary for the proper emotional functioning of the primate brain. Furthermore, it has also become clear that in humans and other higher primates a very significant role is played by the orbitofrontal cortex. Some of the first evidence for this came from the case of Phineas Gage [52,53]. As described in this review, recent studies have shed further light on the functioning of the orbitofrontal cortex, and shown that the reward and punishment values of primary (unlearned) reinforcers such as taste, touch and pain, and visual and olfactory stimuli which become secondary (learned) reinforcers by association with a primary reinforcer, are represented in the orbitofrontal cortex. Strong reciprocal connections are found

between the orbitofrontal cortex and the amygdala, and the evidence suggests a similar role for the two brain areas, although the orbitofrontal cortex appears to be the more important for rapid emotion-related learning, and becomes relatively more important in humans and higher primates [8]. A number of other brain structures have been found to contribute to emotional processing in primates, including the hypothalamus, insula, nucleus accumbens, and various brainstem nuclei such as the periaqueductal grey [8]. These brain regions are closely linked with the orbitofrontal cortex, amygdala and anterior cingulate cortex, and are crucial for correct emotional processing. They are not, however, primarily concerned with decoding reinforcers and with stimulus-reinforcement association learning, but instead provide some of the necessary input and output systems for the multi-modal association regions such as the amygdala and the orbitofrontal cortex which are involved in representing and learning about reinforcers (see Fig.4).

2.3.3. Evidence from lesions of the human OFC

In humans, damage to the orbitofrontal cortex causes major changes in emotion, personality, behaviour and social conduct. Patients often show lack of affect, social inappropriateness and irresponsibility. It has been shown that patients are impaired at correctly identifying social signals including for example face and voice expression identification [54]. Analyses of the effects of lesions to the human orbitofrontal cortex show that they impair the patients in a variety of important ways related to emotion, stimulus-reinforcement association and reversal, and decision-making.

Rolls et al. [39] found that patients with lesions to the ventral part of the orbital surface were severely impaired on reversal tasks and on extinction tasks compared to control patients with damage elsewhere in the frontal or other brain regions. The patients with orbitofrontal lesions were unable to change their behaviour appropriately, but were nevertheless able to verbally report the change. Furthermore, high correlations were found between the performance on the reversal and extinction tests by patients with orbitofrontal lesions and the degree of disinhibited and socially inappropriate behaviour.

Most known cases of human orbitofrontal damage have occurred in adulthood, but also two cases of damage acquired in very early life were reported [55]. The two patients showed lifelong behavioural problems, which were resistant to corrective influences. But more importantly, the patients appeared completely to lack knowledge with about moral and societal conventions. Interestingly, other patients with late acquired orbitofrontal lesions have retained knowledge of such matters, even if they do not always act in accordance with this explicit knowledge. The lack of this moral knowledge and subsequent reckless behaviour in the two patients with early life damage to the orbitofrontal cortex is consistent with the hypothesis that the orbitofrontal cortex is crucial for stimulus-reinforcement learning [30]. The implication would seem to be that the orbitofrontal cortex is necessary for the development of personal moral-based knowledge based on the processing of rewards and punishments [56].

These results, along with several other studies on the effects of brain damage to the orbitofrontal cortex and other complementary neuroimaging results, provide evidence that at least part of the function of the orbitofrontal cortex in emotion, social behaviour, and decision-making is related to representing reinforcers, detecting changes in the reinforcers being received, using these changes to rapidly reset stimulus-reinforcement associations, and rapidly changing behaviour as a result. In summary, lesions to the human orbitofrontal cortex quite severely impair the detection of some reinforcers such as voice or face expression, responses to changing reinforcers, subjective emotion, emotional behaviour, social behaviour, and, as a consequence, some types of decision-making. This makes the orbitofrontal cortex a region of primary interest in the elucidation of the functional neuroanatomy of human emotion.

2.3.4. Evidence from neurophysiological studies in non-human primates

Much evidence from neurophysiological studies supports the hypothesis that the reward and punishment value of stimuli are represented in the orbitofrontal cortex, and that rapid stimulus-reinforcement association learning is implemented in the orbitofrontal cortex [8,30]. In the primate orbitofrontal cortex neurons have been found that code for

taste and olfactory stimuli [39]. Orbitofrontal cortex taste, olfactory, and visual neurons only respond to food when hunger is present, that is when the taste, smell and sight of the food are rewarding [57]. Evidence for stimulus-reinforcement learning has also been found in the macaque orbitofrontal cortex, where neurons can reverse the visual stimuli to which they respond in as little as one trial in a visual discrimination reversal task [41].

Further, there is a separate population of primate orbitofrontal cortex neurons that respond only when there is a mismatch between the expected reward value of a visual stimulus and the reward value that is actually obtained [41]. These error detection neurons are likely to play an important role in the behavioural changes that are required when reinforcement contingencies change[58]. In addition, there is evidence that some macaque orbitofrontal cortex neurons respond to faces, and this is likely to be important because face-reinforcement associations need to be learned and reversed for social interactions, and because face expression can itself be a reinforcer [8,30].

2.3.5. Evidence from neuroimaging studies

Neuroimaging offers important spatial information on neural activity in the human orbitofrontal cortex, which can serve to further elucidate the functional role of the subareas within this brain region. It is worth to remember though that functional neuroimaging has limitations in that there are many sometimes quite small populations of neurons with different responses to different types of stimulus or event in the orbitofrontal cortex and other brain regions which may not all be revealed by neuroimaging, which reflects the average metabolic demands of a brain region [8, 58]. Further, brain imaging does not address the issue of the information that is represented by virtue of the different tuning of individual neurons (which are the computing elements of the brain), and so does not provide the evidence on which computational models of brain function must be based. It is thus very important to consider the results of human functional neuroimaging in the light of what is known from complementary studies.

Kringelbach et al. [59] performed a meta-analysis based on the results from 87 neuroimaging papers published between 1994 and 2003, of which there were 48 PET studies and 39 fMRI studies. The meta-analysis revealed a distinction between the functions of medio versus lateral and posterior versus anterior areas in the sample of the 87 reviewed papers. The results of the meta-analysis thus confirm that there is some localisation of function within the orbitofrontal cortex in terms of its functional neuroanatomy.

Several studies included in the meta-analysis can be interpreted as evidence for a difference between medial orbitofrontal cortex areas involved in decoding and monitoring the reward value of reinforcers, and lateral areas involved in evaluating punishers which when detected may lead to a change in current behaviour.

Furthermore, the reviewed studies suggest that an increase in complexity of the representation and processing of rewards and punishers is mirrored by the posterior–anterior location of activation in the orbitofrontal cortex. Very abstract reinforcers such as loss of money appear to be represented further anterior towards the frontal pole [60] than posterior areas representing simple reinforcers such as taste [61,62] or thermal intensity [63]. This posterior–anterior trend is clearly demonstrated in the statistical results from the meta-analysis and is likely to reflect some kind of hierarchical processing in the orbitofrontal cortex. One trend is that the main effects of primary reinforcers such as odour and taste tend to be located in relatively more posterior areas of the orbitofrontal cortex, whereas correlations with subjective pleasantness and unpleasantness ratings tend to be more anterior, as exemplified by findings in a number of studies [60,61,62,64,65]. The meta-analysis thus demonstrates that the published studies do appear to show a posterior–anterior trend in the orbitofrontal cortex.

2.3.6. Face-selective processing in the orbitofrontal cortex

A type of visual information represented in the orbitofrontal cortex is information about faces. There is a population of orbitofrontal neurons that respond in many ways similar

to those in the temporal cortical visual areas [8,30,42]. The orbitofrontal face-responsive neurons, first observed by Thorpe et al. [41], tend to respond with longer latencies than temporal lobe neurons (140–200 ms typically, compared to 80–100 ms); also convey information about which face is being seen, by having different responses to different faces; and are typically rather harder to activate strongly than temporal cortical face-selective neurons, in that many of them respond much better to real faces than to two-dimensional images of faces on a video monitor [30]. Some of the orbitofrontal cortex face-selective neurons are responsive to face expression, gesture or movement [66]. The findings are consistent with the likelihood that these neurons are activated via the inputs from the temporal cortical visual areas in which face-selective neurons are found. The significance of the neurons is likely to be related to the fact that faces convey information that is important in social reinforcement in at least two ways that could be implemented by these neurons. The first is that some may encode face expression [66], which can indicate reinforcement. The second way is that they encode information about which individual is present [66], which by stimulus-reinforcement association learning is important in evaluating and utilising learned reinforcing inputs in social situations, e.g., about the current reinforcement value as decoded by stimulus-reinforcement association, to a particular individual.

This system has also been shown to be present in humans. For example, Kringelbach and Rolls [67] showed that activation of a part of the human orbitofrontal cortex occurs during a face discrimination reversal task. In the task, the faces of two different individuals are shown, and when the correct face is selected, the expression turns into a smile. (The expression turns to angry if the wrong face is selected.) After a period of correct performance, the contingencies reverse, and the other face must be selected to obtain a smile expression as a reinforcer. It was found that activation of a part of the orbitofrontal cortex occurred specifically in relation to the reversal, that is when a formerly correct face was chosen, but an angry face expression was obtained. In a control task, it was shown that the activations were not related just to showing an angry face expression. Thus in humans, there is a part of the orbitofrontal cortex that responds selectively in relation to face expression specifically when it indicates that behaviour should change, and this activation is error-related [67] and occurs when the error

neurons in the orbitofrontal cortex become active [41]. It has further been shown that there are impairments in the identification of facial emotional expression in a group of patients with ventral frontal lobe damage who had socially inappropriate behaviour [68]. The expression identification impairments could occur independently of perceptual impairments in facial recognition, voice discrimination, or environmental sound recognition. A comparison group of patients with brain damage outside the ventral frontal lobe region, without these behavioural problems, was unimpaired on the face expression identification test. It has further been shown that patients with discrete surgical lesions of restricted parts of the orbitofrontal cortex may have face expression identification impairments [54].

3. Intracranial recordings

3.1. On the use of depth electrodes

In the past, advances in the study of the human brain relied on a number of sources for scientific data. Seminal histological studies by Cajal, Golgi, Brodmann, Vogt, and others using animal brain tissue or human tissue obtained either post-mortem or during surgery provided invaluable information about brain structure at the micro- and macroanatomical levels. Brain function (as opposed to structure) was mainly inferred from clinical cases (such as the works of Wernicke [69] and Broca [70]) relating damaged brain structures to observed behavioural deficits. Further insight was provided by non-invasive recordings of electric and magnetic signals from the human scalp, namely electroencephalography (EEG) since Berger's seminal discovery [71], and later magnetoencephalography (MEG). A unique and important source of information regarding brain function was provided by neurosurgeons such as Penfield and others who recorded electrical activity or electrically stimulated the brains of neurosurgical patients during clinical procedures [72].Over the past few decades, technological advances have supplemented these tools with advanced neuroimaging methods that allow probing the structure and function of the living human brain in patients and healthy subjects in a non-invasive manner. These techniques have opened exciting new research fields that are now addressing the relationship between brain structure, function, and behaviour. Non-invasive tools can be largely classified into two categories on the basis of the type of information they provide: structural or functional.

- Structural tools such as computerized tomography (CT), magnetic resonance imaging (MRI), and diffusion tensor imaging (DTI) provide images that are static in time. The anatomical information can range from emphasizing, for example, grey matter, white matter, cerebrospinal fluid, blood vessels, or fibre tracks.

- Functional tools such as EEG, MEG, positron emission tomography (PET), and functional MRI (fMRI) provide information about the temporal dynamics of various physiological measures. These dynamics are most relevant because they allow examining the relationship between physiological measures in specific brain regions while the subject is engaged in various tasks and cognitive states that change in time.

However, given that the brain communicates and functions by electrical activity of individual neurons at millisecond resolution, all non-invasive techniques suffer from poor spatial and/or temporal resolution. [73]

Human depth electrodes recordings represent a relatively rare opportunity to observe the activity of single neurons and small assemblies of cells in humans, providing a unique opportunity to probe the human brain at high spatio-temporal resolution, which is otherwise unavailable. Depth electrode recordings are available in only a small subset of clinical situations, namely in patients with movement disorders or intractable epilepsy. Nonetheless, these recordings provide valuable information about the applicability of animal models to human neurophysiology and insights into the contributions of individual neurons to uniquely human cognitive processes.

Clinical application of depth electrodes is extremely challenging. It is justified exclusively by the necessity for each particular patient, and is applied under a strong ethical control. No invasive action is allowed if it is not justified for a given patient. Depth electrodes still have their own place for medically intractable forms of epilepsy, parkinsonism and brain tumours.

In patients with medically refractory epilepsy who are being considered for surgical treatment, invasive recording techniques are used in situations in which the surface EEG (recorded with scalp and sphenoidal electrodes) does not provide adequate localization of the epileptogenic focus or provides discordant localization in relation to other studies. These invasive techniques involve the surgical placement of intracranial electrodes in the subdural or epidural spaces or within the brain parenchyma. The rationale is to place recording electrodes close to brain regions thought to be generating seizures in order to

identify the epileptogenic region with certainty. Depth electrodes allow the direct recording of cerebral activity from the brain parenchyma into which they are implanted. The indications for depth electrode recordings are not agreed universally, but the method is particularly well suited to investigating seizures suspected of arising from deep structures such as the hippocampus, amygdala, and medial frontal lobe. Seizures arising from these areas may be difficult to localize with surface recordings because of the closed electric fields and attenuation of the activity by the time it arrives, if at all, at superficial electrode sites.

Rigid and flexible electrodes constructed of a variety of metals and containing a variable number of contacts have been used for chronic depth recordings; the recent availability of electrodes constructed of nonmagnetic materials has allowed post-implantation imaging with MRI to document the anatomic location of the electrodes. Modern placement of depth electrodes utilizing MRI- or computed tomography (CT)-guided stereotactic techniques allows accurate and safe implantation of the electrodes through cranial burr holes with the patient under local or general anaesthesia. The trajectory of electrode implantation depends on the location of the suspected epileptogenic focus and on the customary practices at the centre where the study is to be undertaken. [74]

In these epileptic patients, electrodes can be left into place for up to a couple of weeks, while the patients are waiting for spontaneous seizures to occur, in which case iEEG provide invaluable clues about the anatomical origin of their seizures onset. During those weeks, patients spend most of their time in their hospital room and they may agree to use some of this long spare time to perform cognitive tasks while their iEEG is continuously recorded. Needless to say, the selection of the electrode sites, as well as the duration of the implantations, are made solely on clinical grounds and without any reference to the cognitive protocols. Indeed, a disadvantage for studies of cognitive processes is that electrodes are in most cases implanted only in one brain region which is likely affected by pathological processes. In some cases, electrodes may be also implanted in areas "upstream" of the main target, or in cortical structures, but the implantation is always limited to a few sites (e.g. where the depth electrodes are inserted on their way to deeper brain nuclei) [75]. However, they provide a unique window to the human brain for those interested in the neural basis of human cognition.

And in addition to its value for research, the participation of patients in cognitive protocols can directly benefit them since such protocols help defining specific functional brain subregions close to the focus for which resection must be avoided because of their critical functional role. Such investigations could also help us to understand how for a given patient, his/her cognitive processes may interact with his/her brain activities involved in seizure induction, in an effort to develop with him/her cognitive strategies that could reduce the occurrence of seizures [76].

3.1.1. Types of signal and electrodes

Invasive procedures allow recording of the extracellular electrical activity from the brain at two levels of resolution—either at the level of action potentials emitted by individual (or very few) cells (single or multi units) or at the level of local field potentials (LFPs), which are the electrical signals resulting from the activity of large populations of cells near the electrode tip. Whereas the action potentials reflect the local processing and output of the cells, the LFP signal most probably reflects both action potentials and synaptic activity localized to the dendrites, thus corresponding better with the input to the cells. Depending on the type of implant, recording sessions can be conducted in the operating room (acute), the hospital ward (semi-chronic; between several days and two weeks or longer), or in a chronic manner. Acute recordings are performed during surgery and are therefore typically short (~15 minutes), whereas recordings from electrodes implanted semi-chronically can be longer (~30 minutes, across multiple sessions) because recordings are performed during the patient's stay at the ward. Several types of electrodes are commonly used:

- **Subdural strips/grids**. These are one- or two-dimensional arrays (strips or grids, respectively) of platinum-iridium or steel electrodes with a diameter of 2–4 mm and spaced several mm apart, although more dense arrays have been recently developed [77]. These electrodes are typically implanted under the dura, over the exposed cortex, and allow recording of the field potentials from the underlying brain tissue.

Implantation is usually semi-chronic, allowing recording over periods of several days/weeks.

- **Depth electrodes**. Unlike subdural electrodes, depth electrodes penetrate the brain parenchyma in order to target deep brain structures. These electrodes allow recording field potentials from contacts along the electrode shaft. Additionally, micro-wires can be inserted into the core of the shaft to allow recording of single/multi-unit activity from the tip of the electrode [78] or along the shaft. Another type of depth electrode is the hybrid depth electrode (HDE), which has high-impedance contacts for recording action potentials from single/multi units interspersed between low-impedance contacts for recording the electroencephalographic signal [79]. Using multiple, closely placed microwire tips (as in the case of stereotrodes or tetrodes) improves the yield and isolation of single from multi units [80].

- I**ntracortical electrodes**. These are electrodes that penetrate the cortex by a few millimetres and allow recording unit activity and LFP from superficial regions. The Utah array is a matrix of 10 × 10 electrodes that allows simultaneous recording from up to 100 channels [81] (Fig.6). A linear array multielectrode is a thumbtack-shaped array of 20–24 electrodes, separated by 75–200 μm, that are placed on the subdural cortical surface to allow recording of LFPs and unit activity from distinct cortical layers [82]. Another type of electrode is the neurotrophic electrode, which induces growth of cortical neurites into a recording chamber [83].

- **Microdialysis**. These are probes that allow measuring neurochemical concentration from brain dialysate samples and can be inserted via the lumen of depth electrodes or along the shaft [78]. These probes can be used in semi-chronic implantations for measuring levels of neurotransmitter release at different time points.

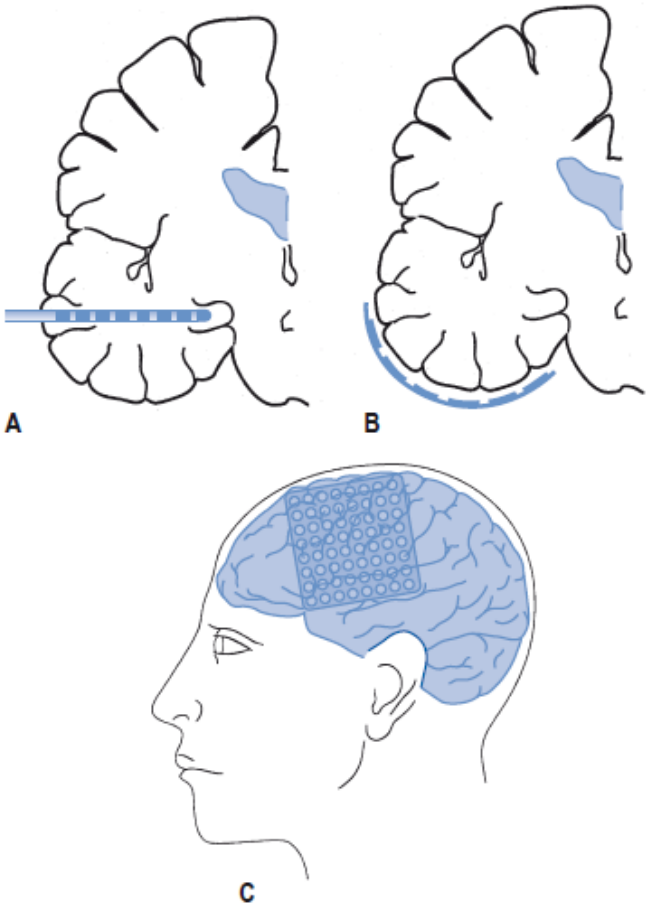

Figure 5: Various electrodes used for invasive recordings in the evaluation of epilepsy and the representative brain regions from which they record.
A: Depth electrode implanted to record from the medial and lateral portions of the temporal lobe.
B: Subdural strip electrode inserted to cover the subtemporal region.
C: Subdural grid covering the frontoparietal and superior temporal regions.

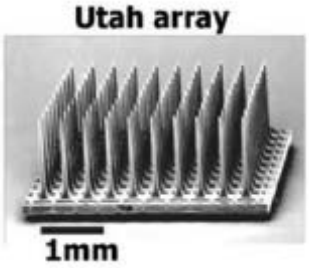

Figure 6: The Utah array intracortical electrode.

In addition to passive recording, some electrode types also allow electrical stimulation of the underlying tissue. This powerful combination makes it possible to stimulate one region while measuring activity in other regions and thus to examine the functional connectivity between them. In addition, stimulation allows the examination of causal links between neural activity in the stimulated region and overt behaviour.

3.1.2 Advantages of intracranial recordings

Because, fortunately, the population requiring such treatment is small and because those recordings require a complex combination of skills, there are relatively few reports of iEEG (intracranial EEG) during cognitive studies. Yet, if these constitute quantitatively a very minor stream of research within the more general field of human brain mapping, the spatio-temporal resolution of human intracranial studies make them very unique quality-wise, because they approach or go beyond the "gold standard" of human brain imaging, the "millimetre–millisecond" resolution [76]. Some of the advantages these techniques provide include:

- **Signal source.** Invasive techniques allow direct recording of the electrical activity from populations of cells or even individual cells while techniques such as fMRI or PET record surrogate signals (such as blood flow or metabolism rate), which are indirectly linked to the electrical activity of very large neural populations.

- **Spatial resolution.** The spatial resolution of human intracranial recordings ranges between two extremes. At one extreme, it is possible to record single and multi-unit activity from extracellular micro-electrodes. This is a rare situation that occurs typically for mapping purpose during a surgery. A handful of studies have used such micro-electrodes to describe specific changes of multi-units firing rates in relation to cognition. Needless to say, such micro-scale recordings, usually performed in the operating room, are technically extremely challenging and impose severe constraints

on the timing and design of the cognitive protocols. And, by far, the vast majority of human intracranial recordings do not have this cellular spatial resolution and measure instead meso-scale recordings, the LFPs, from surface strips or grids of electrodes or stereotactically placed depth electrodes in chronically implanted epileptic patients. Just as for scalp EEG, it is not straightforward to assess the spatial resolution of meso-scale iEEG. Each point of electrical contact between an electrode and the surrounding brain tissue records a weighted sum of activities: the sources of electric field present in the entire brain volume. But the weight of each source decreases with (is inversely proportional to) the square of the distance separating the source from the contact point [84]. This implies that parts of the brain far away from the electrode can theoretically have a significant influence in the signal it records, but this can only happen if those remote neural sources generate very strong electric fields relative to those created close to the electrode. Nevertheless, converging observations seem to indicate that the field created by neurons more than a centimetre away from a recording site contribute only for a negligible portion of the signal. Practically, the spatial resolution of iEEG depends both on the impedance and on the size of the electrical contacts along the electrodes; it also depends on the volume conduction properties in the piece of brain tissue around the electrode [76]. In general, targeting and localization of implanted recording electrodes is within ~1–2 mm. For comparison, source localization of EEG or MEG signals provides an effective spatial resolution that is an order of magnitude lower (~1 cm).

- **Temporal resolution.** In theory, the temporal resolution of iEEG is that of the electrophysiological phenomena it measures, that is, submillisecond. In practical, it is only limited by the sampling frequency of the acquisition boards. It is common to record local field potentials (LFP) with a sampling rate of 512 Hz or more, a rate that can for instance provide good descriptions of oscillatory signals at frequencies up to 150 Hz. When using micro-electrodes, the sampling rate can easily climb up to 30 kHz, which allows to sort spikes out and identify individual neurons within multi-unit activity. For comparison, the fMRI signal measures slow hemodynamic fluctuations that are on the timescale of seconds.

- **Signal-to-noise ratio (SNR).** Invasive recordings have higher SNR compared with scalp EEG and MEG. Non-invasive methods are more susceptible to artefacts (due to eye blinks and movement), and the signal is weaker because it has to pass the cranium and scalp before reaching the recording electrodes. The higher SNR provided by direct invasive recordings allows examination of high frequency bands that are unavailable from scalp recordings. The electrode is in close proximity to the source of activity, and so the amplitude of the signal is relatively high and various components of the signal (especially high-frequency activity) are therefore more robust than those recorded with surface electrodes.

- **Human cognition.** By far, the major advantage of invasive recordings in humans over similar recordings in animals is the possibility to address questions that are unique to human cognition and behaviour such as language, episodic memory, imagery, volition, and emotion. These aspects of human cognition clearly lack an experimental animal model and are unavailable at high spatio-temporal resolutions using non-invasive techniques.

Depth electrode recordings from brain parenchyma provide a sensitive means of recording, with negligible artefact, activity occurring in a limited volume of brain in the vicinity of the electrode. Although the sensitivity and clarity of the signal are heightened with depth recordings, the constricted “field of view” inherent in all intracranial techniques results in the risk that the recorded activity originated from afar and propagated to a brain region sampled by the implanted electrode. Thus interpretation of depth recordings must be performed within the larger context of data provided from other aspects of the evaluation [74].

4. Methods and signal acquisition

4.1 Stimuli

Faces of 139 different actors (70 male and 69 female) posing fearful, happy and neutral expressions were compiled from three different faces databases: Karolinska Directed Emotional Faces (KDEF) [85], Warsaw Set of Emotional Facial Expression Pictures (WSEFEP) [86] and the Radboud Faces Database (RaFD) [87]. All images were grey scaled, and enclosed in a rectangular frame excluding most of the hair and non-facial contours (Fig.7), in a 198 × 251 pixel array. Gaze direction of all stimuli was directly forward. Spatial frequency content in the original stimuli (BSF) was filtered using a high-pass cut-off that was >24 cycles/image for the HSF stimuli, and a low-pass cut-off of <6 cycles/image for the LSF stimuli (employing Matlab, The Mathworks, Natick, Massachusetts). Lastly, overall luminance was equated across different spatial frequencies.

The experimental design is an emotion by spatial frequency factorial design, with each factor having 3 levels. We therefore generated 139 identity unique faces for each of the 9 emotion and frequency conditions: broadband fearful (BF), happy (BH) and neutral (BN); low frequency fearful (LF), happy (LH) and neutral (LN); high frequency fearful (HF), happy (HH) and neutral (HN). For each patient, 135 actor/actress identities were randomly selected for presentation.

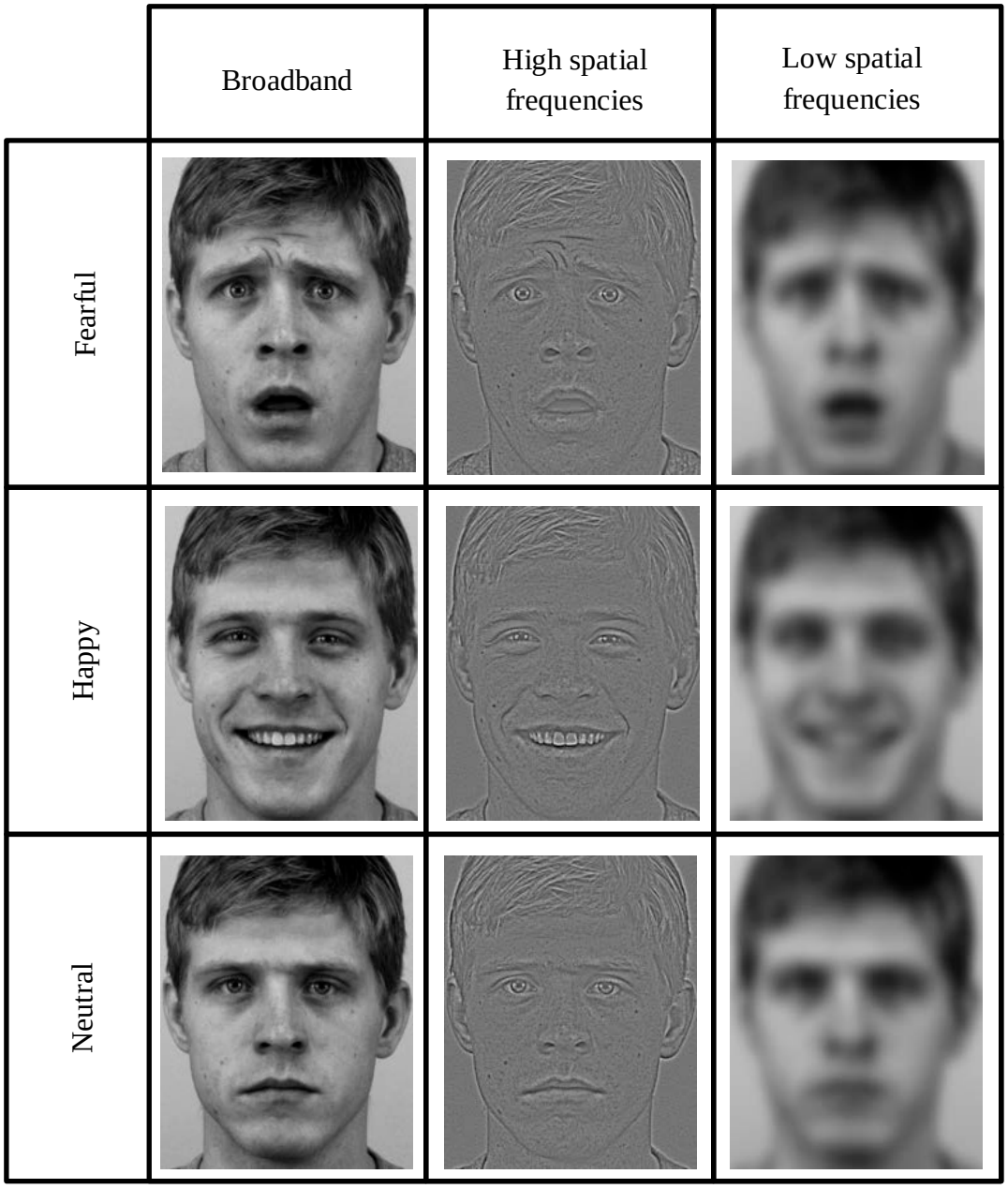

Figure 7: Experimental stimuli: examples of identity-unique broad (BSF), low (LSF) and high (HSF) spatial frequency neutral, fearful and happy faces.

4.2 Stereotactic electrodes implantation

A contrast enhanced MRI was performed preoperatively under stereotactic conditions to map vascular structures prior to electrode implantation and to calculate stereotactic coordinates for trajectories employing Neuroplan system (Integra Radionics, Burlington, USA). Dixi Medical (Besacon, France) Microdeep depth electrodes (multi-contact, semi-rigid, diameter 0.8 mm, contact length 2 mm, inter-contact isolator length 1.5 mm) (Fig.8) were implanted based on the stereotactic Leksell method [88].

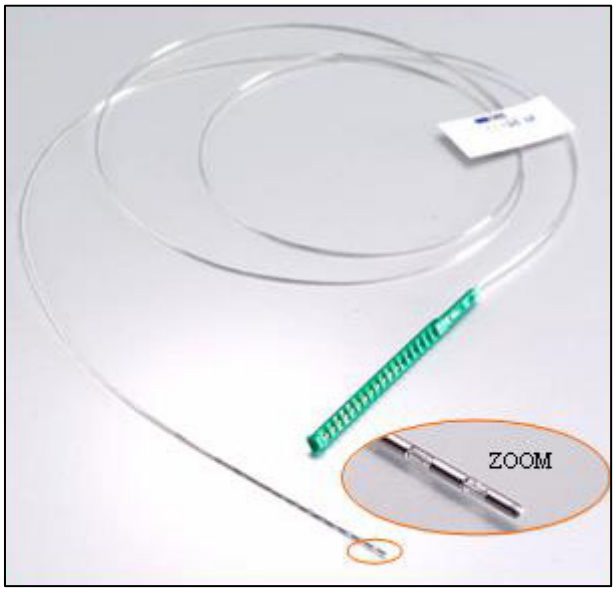

Figure 8: Microdeep® depth electrode (Dixi Medical).

4.3 Participants

Participants were 4 patients with medication-resistant epilepsy that had complex partial seizures whose foci could not be adequately localized by non-invasive methods such as scalp EEG. To aid localization, depth electrodes were surgically implanted under a clinical protocol for pre-surgical evaluation. Electrodes stayed in place chronically for 4-5 days, during which time the patient elected to participate in our research study. Implantation

sites were chosen solely on the basis of clinical criteria. Patients had normal or corrected-to-normal vision and had no history of head trauma or encephalitis. Preoperative structural magnetic resonance imaging (MRI) did not reveal any structural abnormalities in their orbitofrontal cortices. All patients signed informed consent. The study had full approval from the Hospital Ruber International Ethics Committee.

4.4 Procedure

Experiments were conducted during the second post-operative day (more than 24 hours after electrode implantation). All patients studied had been seizure free for the previous 12 hours. For each patient, and in each of the 2 experimental runs, 15 identities randomly selected from each condition (see 4.1) were centrally displayed on an LCD computer display for 500ms followed by a fixation cross for 3500 ms (visual angle 14.4°). Patients were required to perform a gender judgment task over the total 135 stimuli twice with a ten minutes lag between runs. The order of presentation of the stimuli was randomized independently for both runs. Patients were asked to remain as still as possible as they attended the centre of the screen, to avoid verbalizations and minimise eye-blinks. All patients appeared alert and attentive for the duration of all the experiment.

4.5 Data Acquisition

Ongoing intracranial EEG (iEEG) activity was acquired using an XLTEK EMU128FS amplifier (XLTEK, Oakville, Ontario, Canada). Stereotactic electrodes implanted on different parts of the brain besides the orbitofrontal cortex registered participants' neural activity. iEEG data were recorded at each electrode contact site at a 500 Hz sampling rate, with online bandpass filter between 0.1 Hz and 150 Hz. All recording sites were referenced to linked mastoid electrodes.

5. Electrodes contacts localization

To take advantage of the visibility of individual electrode contacts on computed tomography (CT) images, for each patient we co-registered the pre-electrode placement T1-weighted magnetic resonance images (pre-MRI) to post-electrode placement CT (post-CT) whole-brain volumes. MRIs were acquired on a 3.0T Signa HDx GE scanner (GE Healthcare, Waukesha, WI, USA).

To optimise this co-registration, both brain images were first skull-stripped. For CTs this was done by filtering out all voxels with signal intensities between 100 and 1300 HU. Skull stripping of the pre-MRI proceeded by first spatially normalising the image to MNI (Montreal Neurological Institute) space employing the "New Segment" algorithm in SPM8 (Statistical Parametric Mapping 8) [89]. The resultant inverse normalisation parameters were then applied to the brain mask supplied in SPM8 to transform the brain mask into the native space of the pre-MRI. All voxels in pre-MRI lying outside the brain mask and possessing a signal value in the highest 15th percentile were filtered out.

The skull-stripped pre-MRI was then co-registered and resliced to the skull-stripped post-CT. Next, the pre-MRI was affine normalized to the post-CT, thus transforming the pre-MRI image into native post-CT space. The two images were then overlaid, with the post-CT thresholded such that only electrode contacts were visible.

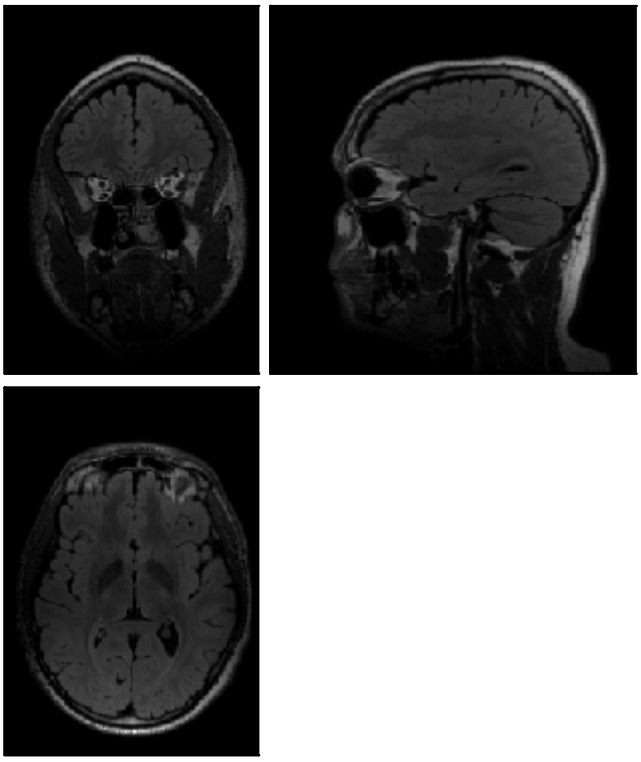

Figure 9: Coronal (top, left), sagittal (top, right) and axial (bottom) sections of the pre-MRI of a representative patient in SPM8.

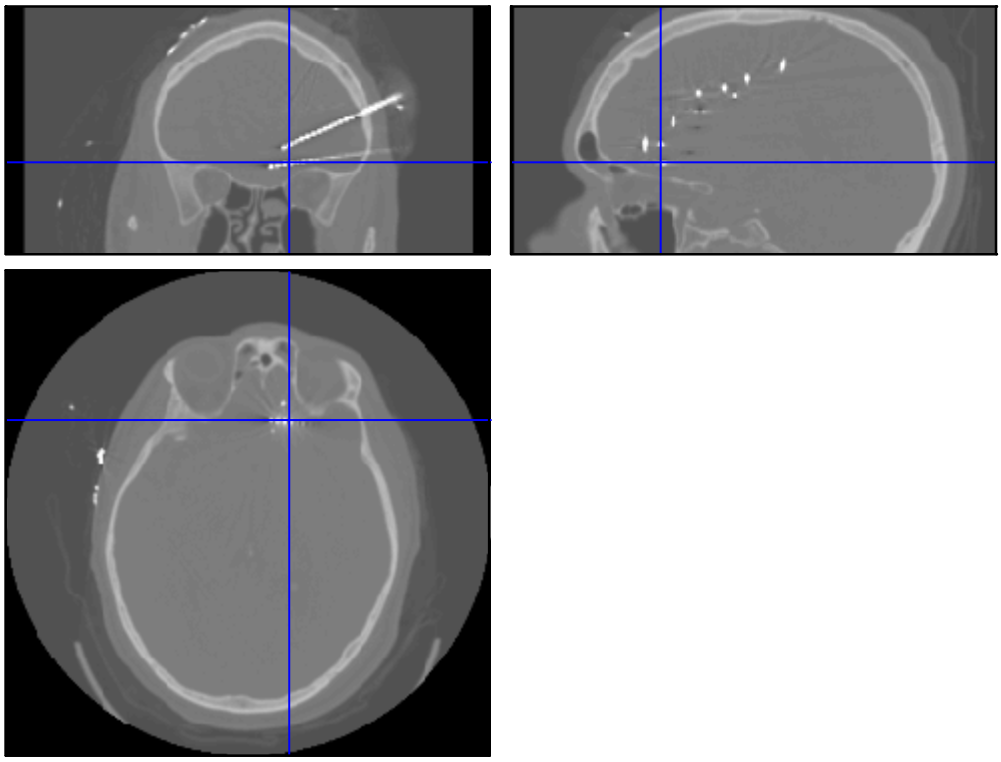

Figure 10: Coronal (top, left), sagittal (top, right) and axial (bottom) sections of the post-CT of a representative patient in SPM8. Crosshairs indicate a contact of a depth electrode implanted in the OFC.

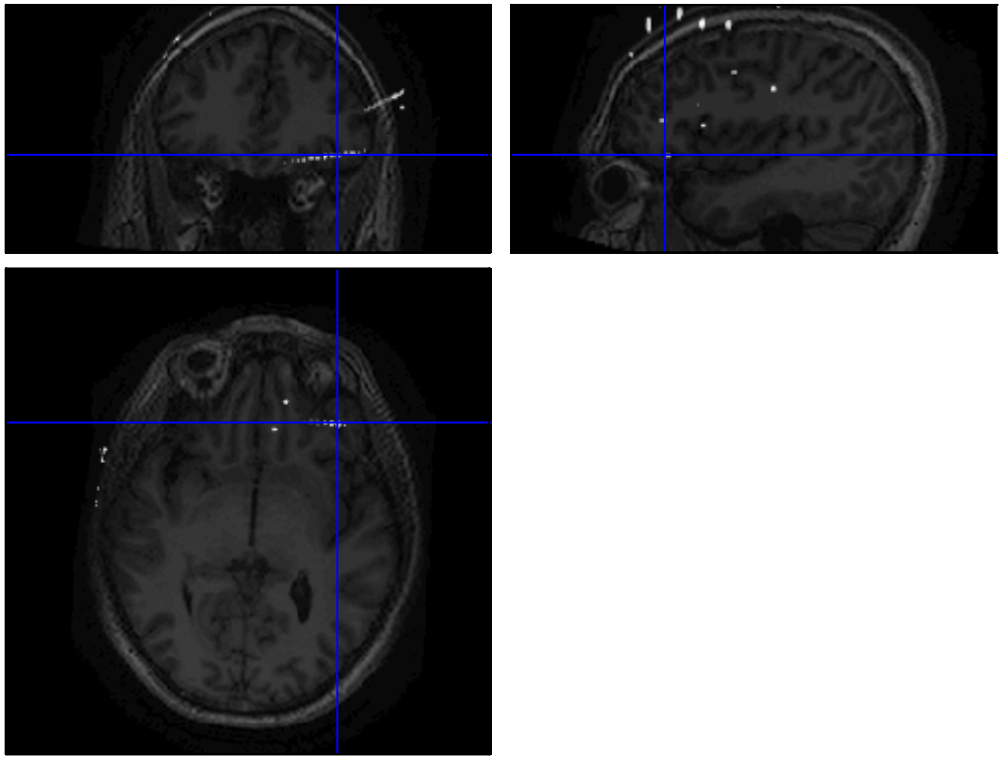

Figure 11: Coronal (top, left), sagittal (top, right) and axial (bottom) sections of the computed fusion of the pre-MRI with the post-CT of a representative patient in SPM8. Crosshairs indicate a contact of a depth electrode implanted in the OFC.

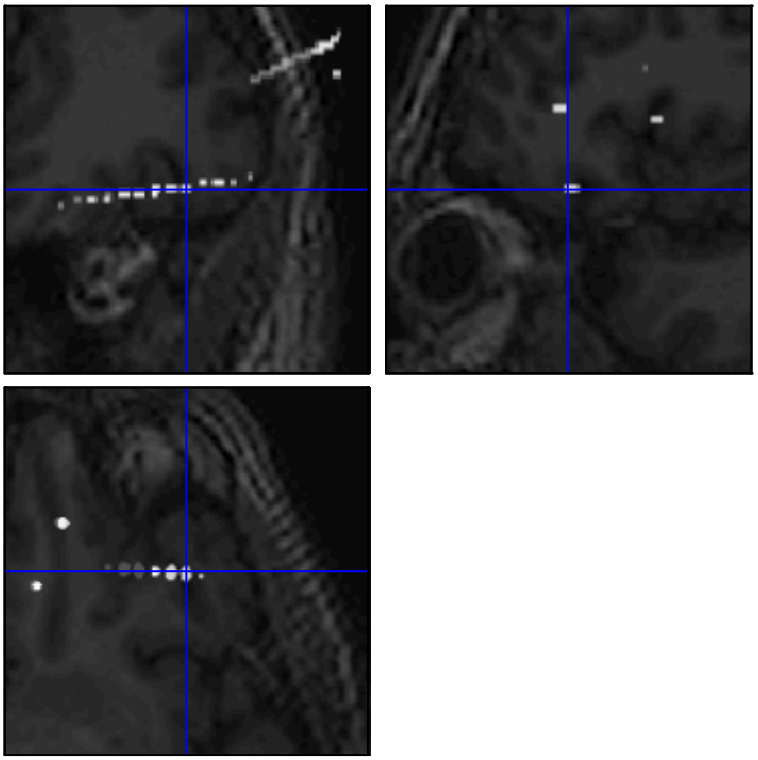

Figure 12: Zoom of the previous figure (Fig.11) in order to better localize the contact within the OFC.

6. Data analysis

Of the 4 patients with orbitofrontal electrodes who completed the task, 2 were excluded from the study because paroxystic epileptic discharges occurred in almost all of their trials and therefore they did not meet our criteria for spike-free trials (80%) (Fig.13). The paroxystic epileptic activity is characterized by patterns that stand out clearly on the background activity: sharp waves (transient, clearly distinguishable from background activity, with pointed peak at conventional paper speeds and a duration of 70-200 ms), spikes (same as sharp waves, but with duration of 20 to less than 70 ms), spike-and-slow-wave complexes (pattern consisting of a spike followed by a slow wave – classically the slow wave being of higher amplitude than the spike) multiple spike-and-slow-wave complexes (same as spike-and-slow-wave complex, but with 2 or more spikes associated with one or more slow waves) [90].

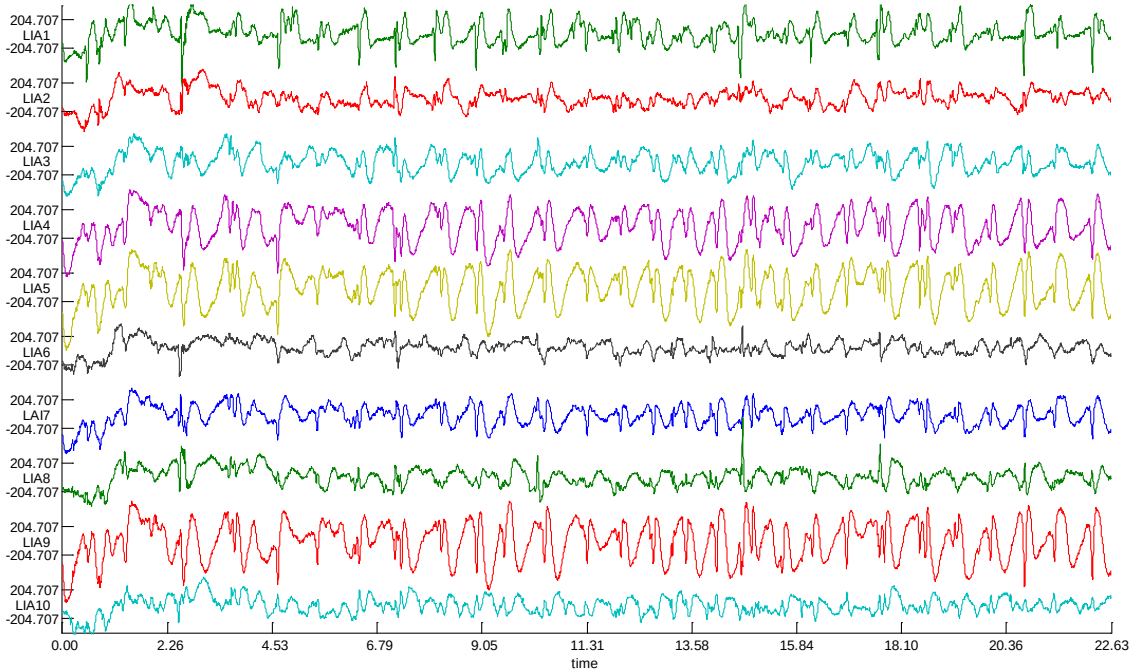

Figure 13: Paroxystic epileptic activity in one of the two excluded patients.

In the patients excluded, it was not possible to eliminate this epileptic activity by any method, either by using PCA (Principal Component Analysis) or ICA (Independent Component Analysis), without also deleting useful information.

In the remaining 2 patients the recorded signal did not present any epileptic abnormalities and their orbitofrontal cortices were therefore considered as not epileptogenic. Thus, we analysed data from two orbitofrontal cortices from two patients.

For each orbitofrontal contact, experimental condition, and patient, epochs from -200 to 800ms peri-stimulus time were extracted from continuous iEEG data. Epochs containing epileptiform activity or artefacts were rejected by trial-by-trial visual inspection, as were epochs corresponding to absent or multiple behavioural responses. Epochs were then detrended and band pass filtered at 1-30 Hz (Butterworth two-pass filter of order 4) and baseline corrected. For each experimental condition, data were then averaged across the two runs.

Data analysis was performed using the FieldTrip toolbox (Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Netherlands) [91] for Matlab (The Mathworks, Natick, Massachusetts).

7. Statistical analysis and results

Statistical analysis were performed on grand averaged single trial potential amplitudes from all orbitofrontal contacts in both patients.

First, we look for main effects of the factor "emotion". To do so, we collapsed the three emotional conditions across frequencies and we performed a three levels ANOVA (Analysis Of Variance) with within-subject factors of emotion (fearful, happy, neutral), applying it on contiguous 2 ms time-bins from 0 to 800 ms post-stimulus (Fig.14).

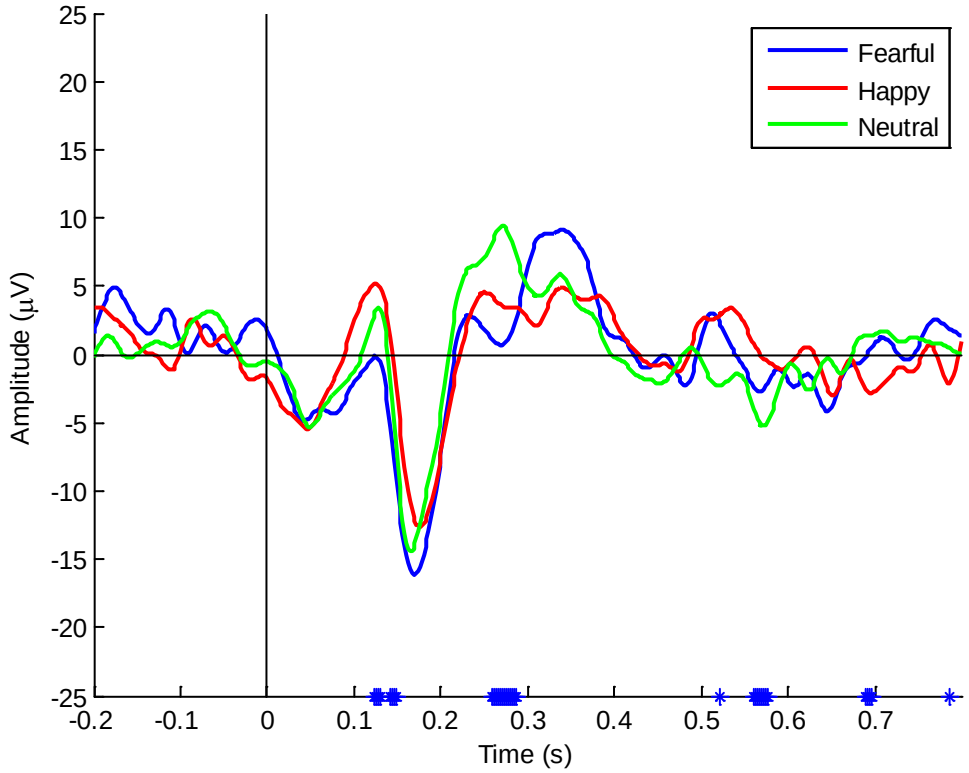

Figure 14: Grand averaged iERPs from the 2 patients to each emotional expression, collapsed over spatial frequencies. The blue dots on the Time axis indicate 2 ms time-bins in which appear a significant main effect of the factor "emotion" ($P < 10^{-5}$).

As can be seen in Fig.14, the effect of the factor "emotion" was significant and appeared specially at relatively early latencies between 100 and 200 ms and around 300 ms ($P < 10^{-5}$).

As significant main effects appeared, we wanted to see whether these effects were different depending on the frequency content of the images. We therefore performed another ANOVA for each emotional condition to test whether there was any significant interaction more than the main effects. The three ANOVAs were thus performed with within-subject factors of frequency (broadband, HSF, LSF) and applied on contiguous 2 ms time-bins from 0 to 800 ms post-stimulus (Fig.15-17).

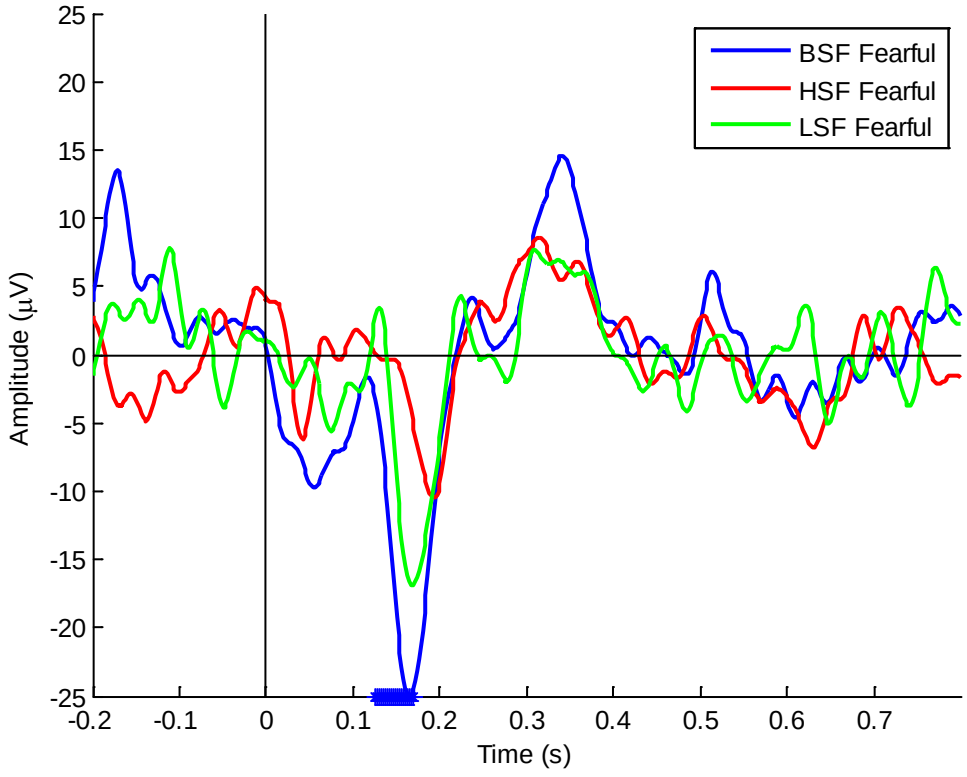

Figure 15: Grand averaged iERPs from the 2 patients to fearful faces, for the three different frequency contents. The blue dots on the Time axis indicate 2 ms time-bins in which appear a significant effect of the factor "frequency" ($P < 10^{-5}$).

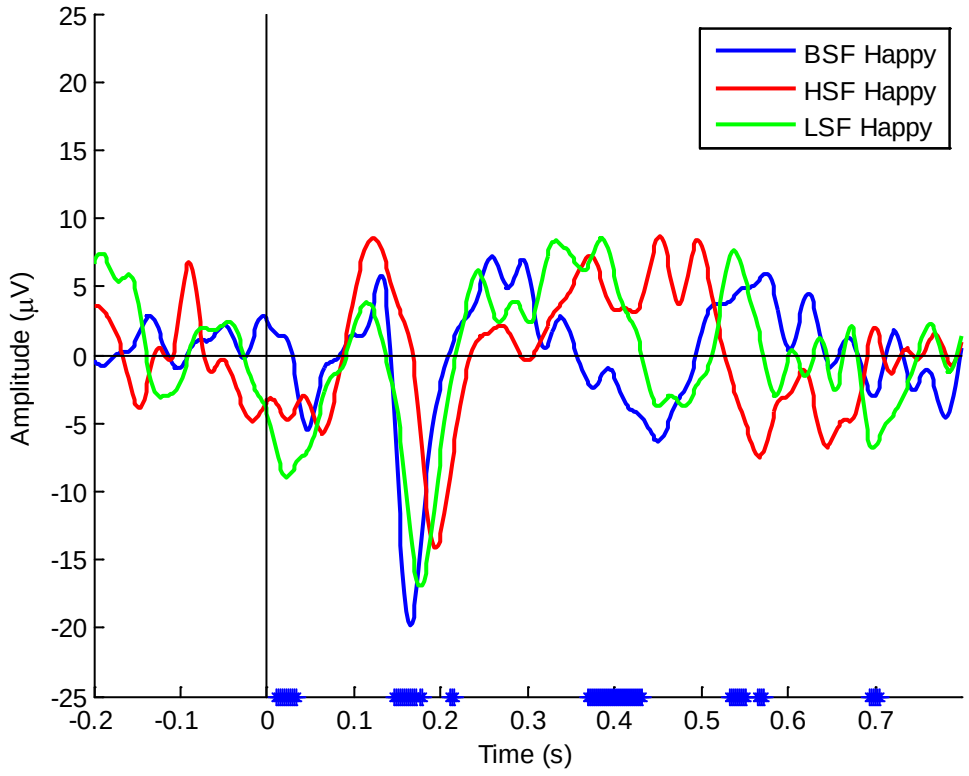

Figure 16: Grand averaged iERPs from the 2 patients to happy faces, for the three different frequency contents. The blue dots on the Time axis indicate 2 ms time-bins in which appear a significant effect of the factor "frequency" ($P < 10^{-5}$).

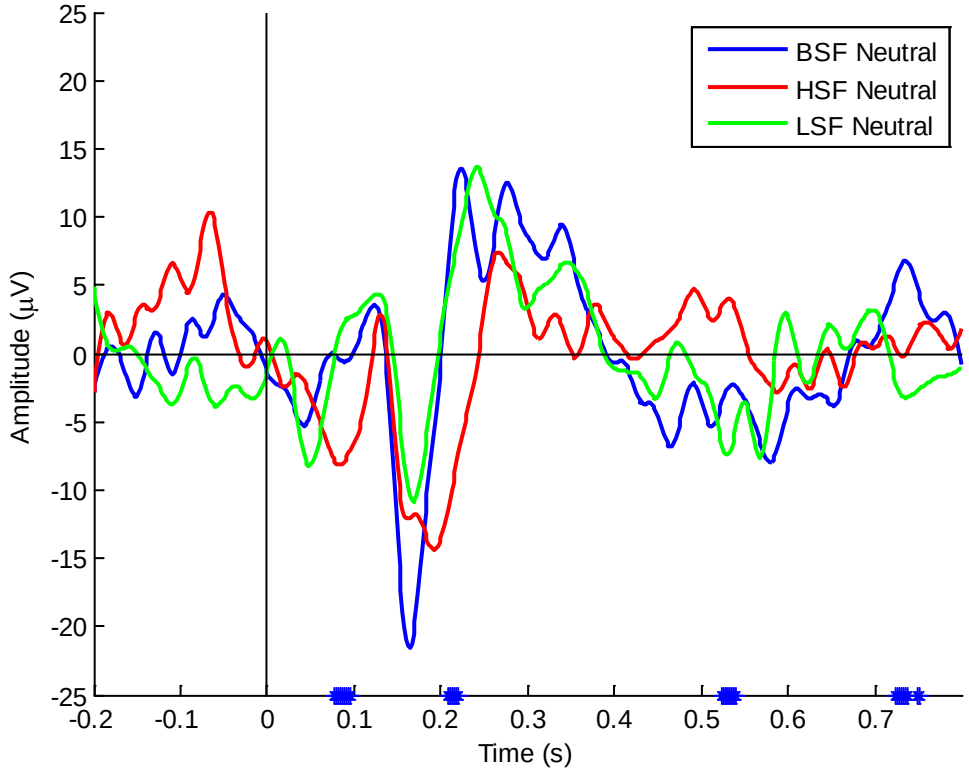

Figure 17: Grand averaged iERPs from the 2 patients to neutral faces, for the three different frequency contents. The blue dots on the Time axis indicate 2 ms time-bins in which appear a significant effect of the factor "frequency" ($P < 10^{-5}$).

We can see from the figures that there is a significant interaction between the two emotional conditions "Fearful" and "Happy" and the frequency content of the images between 100 and 200 ms ($P < 10^{-5}$), that is the interval in which the minimum polarization occurs for BSF and LSF. Moreover, comparing between the factor "frequency" for each emotional condition, it is possible to notice that the minimum polarization always occurs for broadband images. Finally, the minimum for the iERPs for the HSF condition always occurs slightly later compared to those for BSF and LSF conditions.

8. Discussion

In this study, human orbitofrontal responses show a prominent negative deflection starting as soon as 100 ms post-stimulus and reaching the minimum between 100 and 200 ms post-stimulus for every emotional condition. Our results contrast with the previous intracranial studies reporting late (500 ms) orbitofrontal responses to fearful faces [16]. However, these late orbitofrontal responses were obtained as results of a task that required specific attention to facial emotions, therefore probably involving different neural mechanism than those involved in implicit facial expression recognition. Rather, the results of our study are consistent with previous single-neuron recordings studies [14] showing short latency (120-160 ms) responses to aversive visual stimuli in ventral prefrontal cortex. This suggests that the orbitofrontal cortex may provide a rapid and coarse categorization of facial emotions, and not only the aversive ones. Moreover, human orbitofrontal responses in this study show statistically different responses ($P < 10^{-5}$) to different emotion conditions (fearful, happy and neutral). This is consistent with the hypothesis that distinct neural sub-systems within the orbitofrontal cortex specialise in the processing of specific emotions [93].

Furthermore, human orbitofrontal responses obtained in this study show shorter latencies than previous reports of rather late (200 ms) amygdala responses to facial expressions [94] or to complex emotional scenes (with standard photographs) [95]. The facts that connections of the amygdala with orbitofrontal areas are robust and bidirectional (see 2.2) and that we observed in the orbitofrontal region faster responses to emotional facial expressions than those recorded in the amygdala probably indicate that the orbitofrontal cortex does modulate activity in amygdala, and not vice versa (though the source of this activity is probably located in proximity of the temporal cortical visual areas, as studies report responses to emotional facial expressions with latencies of 80-100 ms in that area [30]. Further studies would be useful to better investigate this temporal-frontal-amygdala pathway for facial expressions information).

It has been demonstrated that face-selective neurons found in the orbitofrontal cortex [30] respond much better to real faces than to two-dimensional images of faces on a video monitor [92]. The fact that in our study the minimum polarization (i.e., the greater

response) always occur in response to broadband spatial frequency images when comparing between the frequency contents is probably due to the fact that broadband images are somehow perceived as more "real" than HSF and LSF images.

Finally, it is notable that the onset of emotional expression effects for HSF images is slightly delayed relative to the onset latencies observed for LSF and broadband images (Fig.15-17). This can be due to the fact that since HSF images contain only detailed information, they need more time to be processed. Another hypothesis can be that LSF images and a partially analysed version of the broadband images (comprised of the LSF components) are projected more rapidly from early visual areas to the orbitofrontal cortex, possibly by using the dorsal magnocellular pathway, while HSF information travel by a different, parvocellular pathway, as also proposed in a recent study by Bar et al. [96]. However, further studies are necessary to better demonstrate this hypothesis, since the differences in latency between the orbitofrontal responses to LSF and broadband images and those to HSF images obtained in our study appear very subtle.

9. Conclusion

In conclusion, this study provide unique, intracranial, temporal data about emotional facial expression processing in human orbitofrontal cortex. First, we found responses with latencies as short as between 100 and 200 ms, suggesting that orbitofrontal neurons can provide a rapid categorization of facial emotions. Second, we found significant differences between emotions in the time interval abovementioned (100-200 ms), suggesting that distinct neural sub-systems within the orbitofrontal cortex may be specialized in the processing of specific emotions. Third, we found a modulation of the responses by the frequency contents of the images presented as stimuli, and a slightly later responses for HSF images than for LSF and broadband images, probably indicating different mechanisms involved.

Further intracranial studies are needed to better shed light on the precise functions of the orbitofrontal cortex and to relate orbitofrontal activity to that in the areas and structures connected, in order to explore the existence of one or more neural networks comprising the orbitofrontal cortex and involved in processing emotional information.

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