**VIE VISIVE SOTTOCORTICALI E CORTICALI CHE VEICOLANO
LE INFORMAZIONI EMOTIVE FACCIALI AL GIRO FRONTALE
INFERIORE**

**SUBCORTICAL AND CORTICAL VISUAL PATHWAYS CONVEYING
FACIAL EMOTIONAL INFORMATION TO THE INFERIOR FRONTAL GYRUS**

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ABSTRACT

Face emotional perception, perhaps the most highly developed visual skill in humans, is mediated by a distributed neural system constituting by several cortical territories, such as occipital and temporal areas, and subcortical structures, such as the amygdala. Also, frontal areas, particularly the inferior frontal gyrus (IFG), have been demonstrated involved in the observation of emotional faces, especially during its explicit recognition. The anatomical pathways through which occipital and temporal areas interact with each other are well understood, but less detailed information is available regarding how these territories interact with IFG. To fill this gap, I studied the structural connectivity of 16 healthy subjects, using diffusion tensor imaging (DTI), concurrently the effective connectivity was studied by means of cortico-cortical evoked potentials (CCEPs) on data taken from an open-source dataset. I focused on the right hemisphere in according to literature and preliminary electrophysiological data.

DTI results showed that occipital and temporal areas, as well as the amygdala, are connected with IFG, throughout the inferior frontal occipital and uncinate fasciculi, respectively, both fasciculi whose lesion impairs the recognition of emotional faces. The analysis of the CCEPs indicates that the visual information reaches the IFG along the subcortical pathway at least faster than the visual information conveyed by the cortical route. These results suggest that explicit recognition of facial expressions we are observing needs of coarse subcortical information, endowed by emotional content, as well as of the cortical purely visual detailed one and that these two types of information would be integrated and maintained in time in IFG to realize a conscious experience of observed stimuli.

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1. INTRODUCTION

1.1. Face processing early models

Early models of face perception had separate processing pathways for the perception and recognition of various personal attributes from the face, particularly identity, emotion, and facial speech. These models were primarily based on Bruce and Young's model (Fig.1.1; Bruce & Young, 1986). The contrast between the mechanisms involved in recognizing identity and those involved in recognizing expression' and speech-related motions of the mouth was highlighted in Bruce and Young's influential cognitive model of face perception (Bruce & Young, 1986).
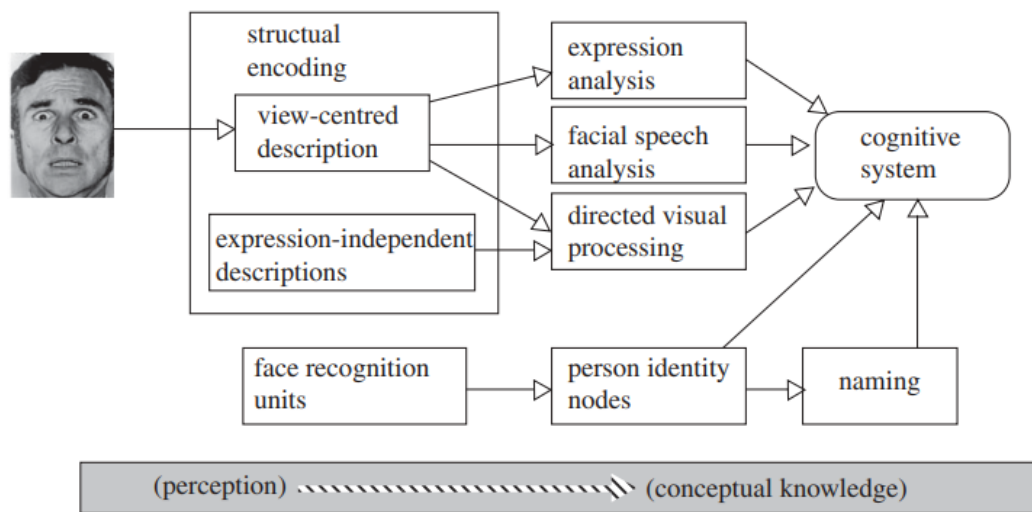
Figure 1.1 The face processing Bruce and Young's model (adapted from Atkinson & Adolphs, 2011)

Studies on behavior corroborate this distinction by demonstrating that identity and expression seem to be recognized relatively separately. For instance, repetitive priming and accustom ability make it easier to perform on processing faces' identities, but not

processing faces' expressions, which is a requirement for face perception tasks (Ellis et al., 1990; Young et al., 1986).

Several sources of evidence, including behavioral dissociations in speeded judgment tasks in healthy individuals and dissociations in task performance following brain injury, were used to support this aspect of early models of face perception. Nevertheless, no precise suggestions were made by these authors concerning the brain localization of these processes (Atkinson & Adolphs, 2011).

Lesion and monkeys' studies, first, and functional magnetic resonance studies (fMRI), subsequently, provided data useful to identify the cerebral region crucially involved in processing face visual stimuli.

1.1.1. Lesion and Monkeys' studies

The finding of patients with focal brain injury who had a selectively impaired ability to identify familiar faces, but a relatively unimpaired ability to distinguish other stimuli, originally revealed the presence of a specific neural system for face perception in the human brain. This syndrome is called prosopagnosia (Hecaen & Angelergues, 1962; McNeil & Warrington, 1993). Prosopagnosia is linked to lesions that are typically located bilaterally in the ventral occipitotemporal cortex (Benton, 1980; Damasio et al., 1982; Sergent & Signoret, 1992), while a few well-documented cases have been found after right unilateral lesions (De Renzi, 1986; Landis et al., 1986).

Studies on non-human primates also supported the existence of a distinct brain system for facial perception. Researchers have discovered neurons in the inferior temporal cortex and superior temporal sulcus of macaques that respond specifically to

faces using single-unit recording approaches (Desimone, 1991; Hasselmo et al., 1989; Perrett et al., 1982, 1984, 1985, 1990). Perrett and colleagues observed neurons that respond selectively to various gaze and profile angles when recording in the superior temporal sulcus and to the identity of faces when the recording is located in the inferior temporal convexity (Perrett et al., 1985, 1992). Accordingly, Hasselmo and co-workers by recording neurons in the superior temporal sulcus and the convexity of the inferior temporal gyrus discovered that only a low number of face-selective cells responded to either identification or expression (Hasselmo et al., 1989).

Many neurons in the superior temporal sulcus are also selectively activated to specific facial expressions and body postures, such as movements of the face, head, and body (Fig.1.2; Perrett et al., 1984; Perrett et al., 1985; Perrett et al., 1990; Perrett & Mistlin, 1990; Oram & Perrett, 1996).

(a)

A 20   A/P 0

CS

STS

IOS

PMTS

ITS   AMTS

(b)

Superior temporal sulcus

Inferior temporal sulcus

2.0–4.5P   5.0–6.5P   7.0–8.0P

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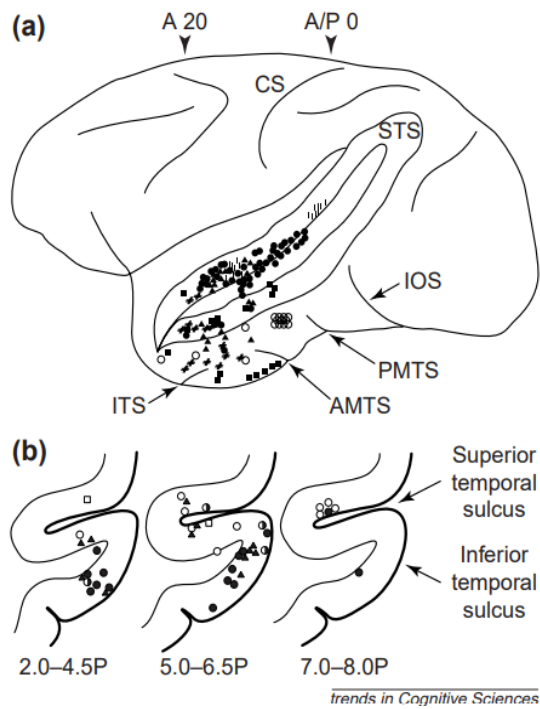
Figure 1.2 Abbreviations: A, anterior; AMTS, anterior middle temporal sulcus; CS, central sulcus; IOS, inferior occipital sulcus; ITS, inferior temporal sulcus; P, posterior; PMTS, posterior middle temporal sulcus; STS, superior temporal sulcus. (a) An overview of eight research (Perrett et al., 1992). Each symbol denotes a distinct researcher's body of work. (b) Neuronal locations that were selective for facial expressions (open circles), identity (closed circles), both expression and identity (half-filled circles), had an interaction between expression and identity (squares), or were selective for neither (squares) (triangles) (adopted from Haxby et al., 2000)

In summary, cells responding differently to various individuals did so across expression invariants and cells responding differently to various expressions did so over invariant individuals appear segregated in the inferior temporal cortex and the superior temporal sulcus, respectively. In other words, the perception of facial movement and static representations of dynamic elements of the face, such as expression and the angle at which the eyes and head are positioned, appears to be more represented in the superior temporal sulcus while the recognition of face identity appears to be more represented in the inferior temporal cortex (Haxby et al., 2000).

In line with these electrophysiological data, showing a relatively segregation of the dynamic and static aspects of face visual information, recently it has been proposed,

based on the monkey and human fMRI studies, the existence in the temporal cortex of two distinct pathways for processing these two components of facial stimuli (Bernstein & Yovel, 2015; Furl et al., 2012). The areas V2-V4 and the inferotemporal region are included in the first pathway, designated as the "ventral stream for faces" and involved in recognizing an individual's identity. The visual motion region MT, its satellites, and STS areas constituted the second route, designated as the "dorsal stream for faces" and crucial for recognizing emotional facial expressions.

In particular, several human investigations demonstrated responsiveness to dynamic faces and gaze movements in the STS accompanied by restricted or absence of activity in the inferotemporal cortex (Caruana et al., 2014; Ethofer et al., 2011; Fox et al., 2009; Mosconi et al., 2005; Schultz et al., 2013; Schultz & Pilz, 2009; Thompson, et al.,2007; Trautmann et al., 2009; Nummenmaa et al., 2010).

Furl and colleagues (2012) demonstrated that, in monkeys, consistent with human aforementioned results, the viewing of dynamic emotional expressions stimulated the anterior STS but not the inferotemporal cortex and, more interestingly, that the same anterior STS regions were still active, although less significantly when static emotional expressions were presented. The authors' interpretation of this data was that the same neural population responsible for encoding dynamic emotions was stimulated when static emotional expressions were observed because they "implied motion". Finally, the face dorsal pathway, conveys this emotional visual information to the pACC, anterior insula, and amygdala, where are cognition of each specific emotion occurs (Gerbella et al., 2019; Morecraft et al., 2012; Mufson & Mesulam, 1982).

1.1.2. fMRI human studies

A crucial improvement to find out what were the brain mechanisms below face perception and to identify in detail the visual areas involved in this processing was provided by fMRI studies on healthy human subjects. The previous fMRI studies have identified a face-responsive region in the lateral fusiform gyrus, designated as the face fusiform area (FFA), using either passive viewing tasks or tasks that focus attention on invariant aspects of the facial configuration.

These tasks included detecting the gender or profession (which requires recognizing identity) of shown individuals (Sergent et al., 1992) as well as simultaneous and delayed matching of similar or different photos of the same person (Clark et al., 1996; Haxby et al., 1994, 1999; Hoffman & Haxby, 2000; Ishai et al., 1999; Kanwisher et al.,1997). The size of the answer to faces in the fusiform face-responsive region is, nevertheless, diminished when focusing on a variable aspect of the face, specifically the direction of the eyes (Haxby et al., 2000). This demonstrates that rather than being essential to all aspects of face perception, this region may be more engaged in the perception of invariant features.

Other face-responsive areas have also been discovered by fMRI studies in addition to the FFA, which are typically and consistently found in the lateral inferior occipital gyrus (also known as the OFA) and the posterior superior temporal sulcus (pSTS) (Chao et al., 1999; Halgren et al., 2000; Haxby et al., 1999; Hoffman & Haxby, 2000; Kanwisher et al., 1997; Puce et al., 1998).

Early imaging research played a significant role in the development of a new face processing model by Haxby and co-workers, which has some similarities to Bruce and Young's model but places the various face processing components in distinct brain areas

(Haxby et al., 2000). In this model, face perception requires the coordinated involvement of several areas referred to as the "*core system*" and the "*extended system*" (Haxby et al., 2000).

The core system is made up of two processing streams that largely correspond to the aforementioned ventral and dorsal pathways for faces. The first stream runs from the inferior occipital cortex to the inferior temporal cortex and encodes generally constant facial features, where movable features of faces are represented. While the second one goes from the inferior occipital cortex to the superior temporal cortex, in which changing characteristics of facial features that come from movement that are presented. The so-called "extended face system" is composed of other brain regions distributed across the brain that support these core regions. They support requirements for processing faces in a task-dependent way.

These additional brain systems —including somatosensory prefrontal territories as well as subcortical structures like the amygdala— are involved in the processing of many types of relevant information obtained from other people's faces. For example, through these additional systems, one can learn more about another person, infer their mood, degree of interest, and intentions, focus their own attention on things that other people are interested in, and improve verbal communication.

The findings of functional imaging research make suggestions regarding which brain areas are used to process specific types of information for example some of these brain areas are a part of neural networks that carry out many cognitive tasks, including controlling spatial attention and understanding spoken language. Therefore, when these regions work together with extrastriate face-responsive regions to extract relevant

information from faces and thereby make it easier to recognize various facial characteristics, these regions become a part of the face perception system.

1.1.3. Feed-forward and interactive models of face perception

The Haxby model of face processing is primarily a hierarchical one, despite the assumption of bilateral linkages between modules and brain areas (Dricu & Frühholz, 2016). In line with this view, several fMRI studies in humans with lesions have demonstrated that processing of the shape and characteristics of faces is reflected in face-selective activity in the lateral occipital gyri (OFA), this area might also play a role in determining how different face characteristics relate to one another.

Furthermore, fMRI evidence has shown that OFA processes second-order relational or configural cues (Rhodes et al., 2009) and is involved in interpreting second-order relationship information from faces (Maurer et al., 2007). Also, recent TMS results and lesion studies are in line with the interpretation of Haxby's model, which maintains that the role of the OFA in face processing is limited to the initial encoding of information about specific structural properties of faces, information that is then fed forward to other face-processing regions like the FFA and STS (Dricu & Frühholz, 2016).

Nevertheless, the hierarchical model proposed by Haxby has been questioned from the very beginning. In fact, several studies do not support a strict feed-forward hierarchical model of face perception, in which the OFA acts as the primary and common source of input for other visual and non-visual cortical regions involved in face perception, such as the FFA, and pSTS. Otherwise, this research suggests a more

interactive paradigm in which multiple functionally and physically diverse brain areas interact to influence higher-level face perception skills. The nature of these interactions and the computations carried out by the various parts of the core face-processing network may also be influenced by the particular requirements of the task.

fMRI and human lesion studies demonstrated that lower-level face categorization abilities can be attained without OFA while higher-level face perception abilities appear to depend on an intact face-processing network that includes OFA and FFA and their connections to several extrastriate visual areas (Rossion, 2008). Recent studies demonstrate a direct relationship between the middle occipital gyrus (in this case not associated with OFA) and fusiform activity for low spatial frequency information related to facial identity, along with a distinct relationship between the inferior occipital gyrus and fusiform activity for high spatial frequency information related to facial identity (Atkinson & Adolphs, 2011). However, there is no evidence of a direct functional relationship between the middle and inferior occipital gyrus (Rotshtein et al., 2007).

In addition, TMS studies indicate a more pliable interaction between the OFA and other face-processing regions. Pitcher and colleagues (Pitcher et al., 2008), for instance, showed that the right OFA plays a crucial role in the early stages of processing — between 60 and 100 ms after the onset of the stimulus — in the discrimination of facial expressions of emotion. The ability of observers to match sequentially displayed faces with respect to emotional expression, as measured with a measure of accuracy, was disturbed in this study by repetitive TMS delivered over either the right OFA or right somatosensory cortex, regardless of the specific emotion. By the use of double-pulse TMS administered at distinct times to the right OFA and right somatosensory cortex, this study also revealed different critical intervals for the participation of these

regions in emotion discrimination: right somatosensory cortex involvement was localized to a window of 100–170 ms from stimulus onset, while right OFA involvement was localized to a window of 60–100 ms from stimulus onset. Thus, Pitcher and co-workers' study has demonstrated that the right somatosensory cortex plays a crucial role in enabling observers to distinguish between different faces based on emotional expressions.

Although lesion and fMRI studies and TMS results do not per se definitively support the more interactive model over a feed-forward hierarchical model of face perception, above mentioned, altogether present enough solid evidence to cast doubt on hierarchical feed-forward models (Atkinson & Adolphs, 2011). In particular, the results produced by combining electrophysiological, fMRI, TMS and lesion studies will be significantly more trustworthy than those obtained by using any one of these methods alone (Ruff et al., 2006).

In summarizing several studies demonstrate that the neural underpinnings of face perception do not merely implement bottom-up processing of the retinal images of faces and their features, but rather their operation reflects a complex interaction between mechanisms that extract various types of information from the retinal image at various points in time, the mechanisms that direct eye gaze and attention and the requirements of the task as well as environmental and social context. That is why recent research should focus on the active character of vision as well as the dynamic effects of task demands (Atkinson & Adolphs, 2011).

1.2 The perception of emotions in others

Seeing the expression on another's face provides information about the emotion that person is feeling and can evoke that emotion in oneself. The perception of emotional expressions is crucial for social interaction and during communicative behavior and has been found to evoke activity in brain regions not only associated with the perception of the face stimuli but also in those associated with experiencing own emotion (Haxby et al., 2000).

The face visual stimuli are thought process emotional information via two main mechanisms: the top-down and the simulation.

Top-down

The majority of brain regions that take part in basic emotions' recognition, such as the occipito-temporal cortices, amygdala, orbitofrontal cortex, basal ganglia and right parietal cortices, appear to process both the perceptual information and the emotional significance of a stimuli (Adolphs, 2002).

The analysis of socially and emotionally significant visual inputs starts in regions of the occipital and posterior temporal visual cortices. In fact, as described above, single-unit studies in monkeys, intracranial local field potential studies in neurosurgical human patients and functional imaging studies proved that face processing places a disproportionate amount of weight on cortical regions in the lateral sections of the inferior occipital gyrus, fusiform gyrus and superior temporal gyrus (Allison et al., 2000; Haxby et al., 2002)

Despite the fact that perceptual processing of faces primarily uses visual cortical regions and in line with the aforementioned two relatively distinct pathways for processing static and dynamic components of faces (Furl et al. 2012), the fusiform gyrus has been noted to be particularly involved in the representations of static features of faces and as a result contributes to the encoding of unity, while the temporal gyrus would appear to participate in the representation of dynamic features, thus in the encoding of facial expression and gaze direction (Adolphs, 2002).

In these latter cortical regions, the detailed perceptual representation of faces seems to take about 170 ms, however an unrefined representation of both gender and emotions occurs in shorter times in early visual cortex. In fact, an early activity that distinguishes between emotional facial expressions can be found in the midline occipital cortex as early as 80 to 110 ms. This suggests that there may be less refined perceptual pathways that run concurrently with pathways for the complete structural encoding of the event.In particular, these findings raise the hypothesis that subcortical inputs, maybe from the pulvinar and the amygdala, can influence how visual cortices respond to emotional stimuli (Adolphs, 2002; Halgren et al., 2000; Pizzagalli et al., 1999).

This subcortical route is thought to be a fast pathway conveying unconscious visual information; indeed it has been demonstrated that blindsight patients, that are patients who have lesions that cause the loss of functionality of the cortical pathway but maintain the functionality of the subcortical path unaltered, showed to the presentation of emotional stimuli specific autonomic responses, such as modification of the galvanic skin responsesand of the pupil diameter (Morris et al., 2001).

Concerning the amygdala, it is noteworthy that monkey and human anatomical studies suggest that this telencephalic structure can contribute to the recognition of

emotional signals through at least two groups of input: cortical projections from the visual neocortex and subcortical ones via the superior colliculus and the pulvinar. In line with the possibility that the amygdala receives information from both these pathways, electrophysiological studies in human showed that the first neuronal responses to emotional facial expressions in the amygdala were seen at around 120 ms, likely induced by subcortical inputs, while there are likely varied reactions based on the type of emotion at around 150 ms, likely produced by subsequent cortical inputs (Adolphs, 2002).

Many studies suggested that a crucial role in emotion recognition from speech and face is made by frontal territories including the orbitofrontal, especially the right one, and the ventro-lateral and the ventro-medial prefrontal cortices. Indeed, all these cortices, like the amygdala, react quickly to emotional visual stimuli. However, unlike the amygdala, these prefrontal regionsare activated especially when people performing cognitive activity that requires intentional awareness of the experienced emotions.

Accordingly, Hornak and co-workers discovered that patients with ventral frontal lobe injury andexhibiting socially unacceptable behaviour, showed impairments in the ability to recognise facial and vocal emotional expressionas well as in experiencing gown emotions (Hornak et al., 1996).

Electrophysiological recordings of two individuals who underwent epilepsy monitoring with depth electrodes implanted in the right prefrontal cortex allowed Adolphs and colleagues to collect further important data about this issue (Adolphs, 2002). In particular, the neuronal activity recorded from one patient revealed in the right prefrontal cortex the presence of response selectivity for faces versus objects at about 150 milliseconds or less respect the presentation of the visual stimuli. After right

prefrontal cortex surgery, the same patient's behavioural performance in classifying facial expressions of emotion was examined, and it showed a severe impairment that was significantly specific for expressions of fear. Another patient with a similar implant, in the right ventromedial prefrontal cortex, showed single-unit neuronal responsesafter the presentation of fearful and happy facial expressions, that differ, according to the two emotions presented, 120 ms following the stimuli presentation.

Altogether these findings,showing that prefrontal regions encode facial emotional information very quickly, suggested that these corticescanmodulate relatively early stage ofvisual perceptual processing via top-down mechanisms (Adolphs, 2002; Harmer et al., 2001; Narumoto et al., 2000).

It has been hypothesized that through these mechanisms, the prefrontal cortex and the amygdala can modulate the recognition of emotion by using at least three different ways. First, they may modify perceptual representations through feedback connections which may helpto categorise facial expressions more precisely and to shift attention to them. The existence of this mechanism is given by the finding that the amygdala modulates local field potentials in the temporal visual cortex on the basis of social or emotional information as well as visual attention (Adolphs, 2002; Anderson & Phelps, 2001). Second, these prefrontal areas as well as the amygdala, may produce associated knowledge and the retrieval of intellectual knowledge about the emotion by projecting to other areas of the neocortex and the hippocampal formation. Finally, these regions may elicit an emotional motor response via their connections to motor regions, the hypothalamus, and brainstem nuclei, generating a motor response specific for each emotional facial expression (Fig. 1.3).
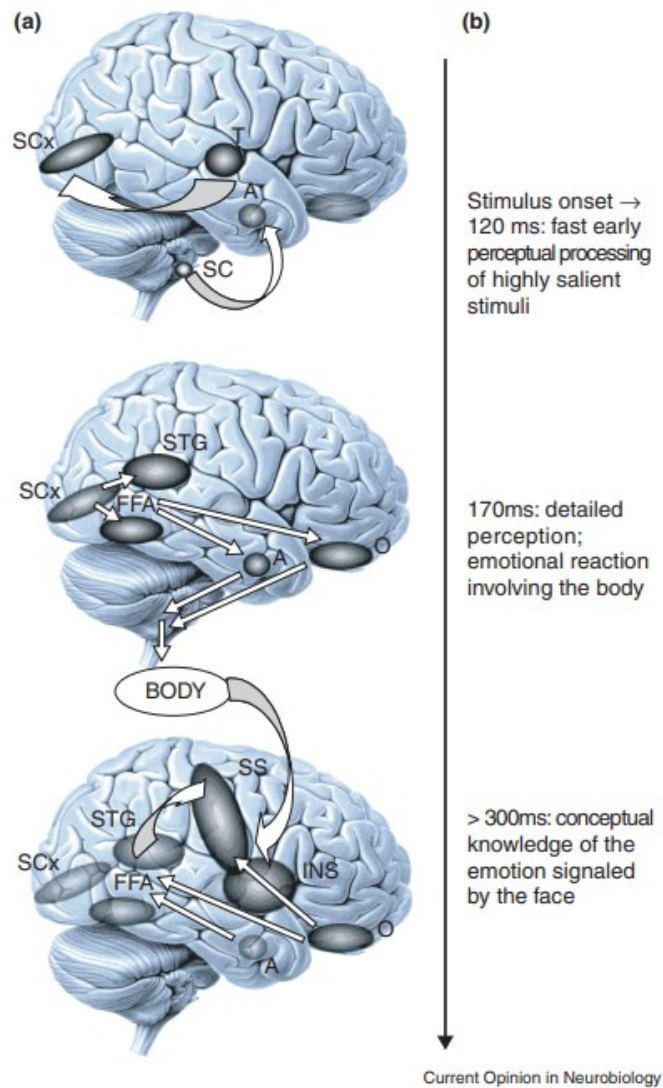
Figure 1.3. Time-dependent processing of emotional facial expressions. (a) At different times, the structures involved in emotion recognition. A, amygdala; FFA, fusiform face area; INS, insula; O, orbitofrontal cortex; SC, superior colliculus; SCx, striate cortex; SS, somatosensory cortex; STG, superior temporal gyrus; T, thalamus. (b) Time flow of emotion recognition, with the stimulus appearing first at the top, perception occurring next, and finally the emotion being recognised at the bottom. The same brain areas participate in various processing components at various times, making it difficult to localise the perception or recognition of the stimuli in space or time. Numerous of the techniques described here may also be used to distinguish emotion from other types of stimuli, such prosody (adapted from Adolphs, 2002).

Simulation

A relatively large number of lesion studies indicated that another cortical sector important for recognizing emotions are the frontal motor region and the somatosensory parietal ones. An explanation of the role of these sensorimotor territories in encoding face visual stimuli is that seeing emotional facial expressions causes the perceiver to experience an emotional reaction that mirrors the emotion displayed in the stimulus, and that the representation of this emotional response in the sensorimotor cortices then conveys information about the emotion (Rizzolatti & Sinigaglia, 2016).

In line with the existence of this mechanism to unconsciously infer the emotional state of others by simulating their affective states, fMRI studies have shown that when people view disgusting facial expressions is active the same region involved in one's perception of this emotion, that is the insular cortex (Calder et al., 2001; Phillips et al., 1997; Sprengelmeyer et al., 1998).

Even some lesion cases support the existence of this mechanism. In fact, a patient with an injury to the left insula and basal ganglia showed substantial deficits in both his capacity to identify disgust in others' emotions as well as his capacity to feel this motion (Adolphs, 2002). Similarly, in another patient with bilateral insula injury, in addition to significant temporal lobe damage, the ability to perceive and feel disgust from all sorts of stimuli was severely compromised (Calder et al., 2000). There is strong evidence that, in addition to the insula, the identification of disgust necessitates the health of the basal ganglia and other somatosensory-related cortices in the right hemisphere, suggesting a relatively broad brain network for processing this emotion (Adolphs, 2002).

Another region in which the simulation mechanism appears to be involved in perceiving the emotion expressed by others, is the pregenual anterior cingulate cortex (pACC). In fact, recent electrophysiological studies indicated that this sector of the cingulate cortex is involved in both the production and the observation of mirthful laughter (Caruana et al., 2017).

A further structure in which the simulation mechanism seems at the basis of the perception of emotion expressed by others is the amygdala; indeed, this structure has been demonstrated having a crucial role not only the perception of own fear but also in their cognition of it when expressed by others. Concerning the own expression of this emotion, Meletti and co-workers' on a large sample of drug-resistant epilepsy patients demonstrated that the electrical stimulation of the amygdala evoked the subjective sense of fear as well as the characteristic facial, physical, and verbal displays of this emotion (Meletti et al., 2006). Lanteaume and colleagues (2007) corroborated these findings as concerning the stimulation of the right amygdala but not for the left one, whose stimulation induced not only fear but also happy sensations.

Additional evidence of the crucial role of this structure in perceiving fear was described by Adolphs, he studied a patient with Urbach-Wiethe disease, a rare metabolic condition that causes a destruction of the bilateral amygdalae. This patient's fear experience was abnormal, particularly she exhibited an abnormally upbeat attitude when interacting with individuals and potentially dangerous situations. Even though she didn't feel fear the way most people do, she was able to explain what fear was, what should have made it happen, and even what to do in scary situations (Adolphs et al., 1994; Damasio, 1999; Gerbella et al., 2019).

Although some studies suggest that the amygdala does more than just encode fear (Murray & Wise, 2004), intracranial recordings in surgical patients revealed that the display of scared facial expressions causes faster and stronger amygdala activation than other facial expressions (Krolak-Salmon et al., 2004; Meletti et al., 2006; Méndez-Bértolo et al., 2016; Sato et al., 2011).

Electrophysiological research on monkeys supports the amygdala's function in processing fearful social cues, consistently with the connection of this structure with temporal and prefrontal regions encoding communicative stimuli including faces, the observer's gaze and vocalizations (Amaral & Price, 1984; Gerbella et al., 2014). Amygdala neurons respond not only to fearful faces but also to screams, suggesting that in this structure occurs an integration of multimodal fearful information (Kuraoka & Nakamura, 2007). The processing of fear by the amygdala regardless of the sensory channels conveying information to it is also observed in humans, where this structure became active both when listening to fearful voices (Dolan et al., 2001) and seeing fearful body expressions (Hadjikhani & de Gelder, 2003).

In conclusion, on one side, the amygdala is activated by the presentation of visual, auditory, natural, and social fearful stimuli, on the other one, its stimulation produces the normal visceromotor responses of fear accompanied by subjective feelings of the same emotion, revealing that the simulation mechanism in the amygdala allows a person to experience the fear that they observe in others (Gerbella et al., 2019).

1.2.1. A multi-stage model

Evidence from empirical investigations, across a range of perceptual modalities, strongly suggests that on the basis through which emotion is perceived —passive, incidental, and explicit —this information is processed by different brain mechanisms (Frühholz et al., 2012; Habel et al., 2007; Lane, 2008). For example, the assessment of emotion is dependent on immediately perceptible indicators (e.g., tone of voice, facial expressions) and it relies on brain areas like the posterior superior temporal sulcus as well as frontal areas involved in general cognitive functions like categorization and discrimination (Beer & Ochsner, 2006).

Dricu and Frühholz through the study of 102 experiments, observed distinct brain activity for each of the situations of perception of emotions (*incidental* perception, *passive* perception and *explicit* evaluation of emotional expressions) when triggered by the voice, body posture or face stimuli. Significant convergence was seen in seven bilateral clusters in trials comparing the assessment of emotional expressions.

The seven clusters are: inferior frontal cortex (IFC), posterior superior temporal sulcus (pSTS), dorsal medial frontal cortex (dMFC), amygdala (Amy), middle fusiform gyrus (MFG), and the visual association areas. In addition, there are significant activation in the left thalamus (Thal) and the left insula (Dricu & Frühholz, 2016).

Evaluating emotions from facial expressions alone showed remarkably similar activation. Explicitly evaluating vocal expressions of emotions triggered activation in bilateral pars triangularis of the IFC, dMFC, the left frontal operculum (fOp) and the right superior temporal gyrus (STG). While observing emotional reactions passively resulted in a considerable convergence in bilateral Amygdala, pSTS, inferior occipital gyri (IOG), pars orbitalis of the IFC, as well as the left MFG and the right precentral

gyrus. To end up the only incidental perception of facial expressions activated bilateral Amy, MFG and the left middle occipital gyrus. Summarizing, the study of Dricu and Frühholz shows that:

- *explicitly estimation* of another person's emotions engages brain regions involved in low- and high-level mindreading, including the *posterior superior temporal sulcus*, *inferior frontal cortex* and *dorsomedial frontal cortex*, as well as brain regions involved in the sensory processing of facial expressions, such as *the inferior occipital gyrus*, *middle fusiform gyrus* and *superior temporal gyrus*.

- during the *passive perception* of emotional expressions, only the sensory areas were continuously active.

- *explicitly evaluation* of both facial and voice expressions involves the activation of the mindreading brain areas.

As a result of their meta-analysis, Dricu and Frühholz proposed a multi-stage model (Fig.1.4) for processing the emotional expressions of others in which the explicit assessment of other people's emotional expressions begins in a network of brain areas that are trained to extract sensory data from visual and auditory signals: the visual association areas, MFG and IOG (visual), and the mSTG (auditory). These areas are active also during passive perception as well as incidental perception of emotional expressions, though to a much lesser extent.

Through a network of anatomical and functional connections, the outcome of this sensory processing is conveyed and integrated in the pSTS, which extracts representations about the observed expression generalizing across sensory inputs. For

the perception and comprehension of emotions, these two steps appear to be sufficient, because the relationship between sensory regions and the pSTS reveals a shared mechanism between actively analysing and passively observing other people's emotions.

The amygdala was the only structure recruited across all types of emotion perception, including explicit evaluation, incidental perception, and passive perception. This is not surprising given the subcortical region's lengthy tradition of connection with processing emotional versus neutral stimuli (Phelps & LeDoux, 2005). The amygdala, in particular, plays a critical role in decrypting emotional meaning from sound across a wide range of domains, such as verbal and nonverbal emotional expressions, as well as musical pieces (Frühholz et al., 2014; Frühholz & Grandjean, 2013; Pannese et al., 2015). Moreover, patients with amygdala injury have difficulty processing emotional voices, particularly when multimodal stimulation is used (Milesi et al., 2014), as well as overall reduced processing of emotional voices in the ipsilesional auditory cortex (Frühholz et al., 2015).

In the work of Dricu and Frühholz the explicit evaluation of emotions additionally recruits bilateral IFC in order to integrate information from sensoryprocessing regions with those that these frontal territories receive from the amygdala. The left and right IFC functions work together to access and select semantic representations of the emotional categories, keep potential choices in working memory, and prevent self-perspective while directing attentional resources toward the perceived individual. Following the suppression of one's own perspective, the right IFC starts a natural process of determining the perceived person's mental states, which is later completed in the dMFC (Apperly et al., 2004; Samson et al., 2005). The IFC, dMFC, and pSTS have developed strong structural (Frühholz et al., 2015; Sallet et al., 2013;

Seltzer & Pandya, 1989; Seltzer & Pandya, 1994) and functional linkages (Bzdok et al., 2013; Frühholz & Grandjean, 2012; Spunt & Lieberman, 2012) that would enable the essential information transmission between these regions at various levels of processing.
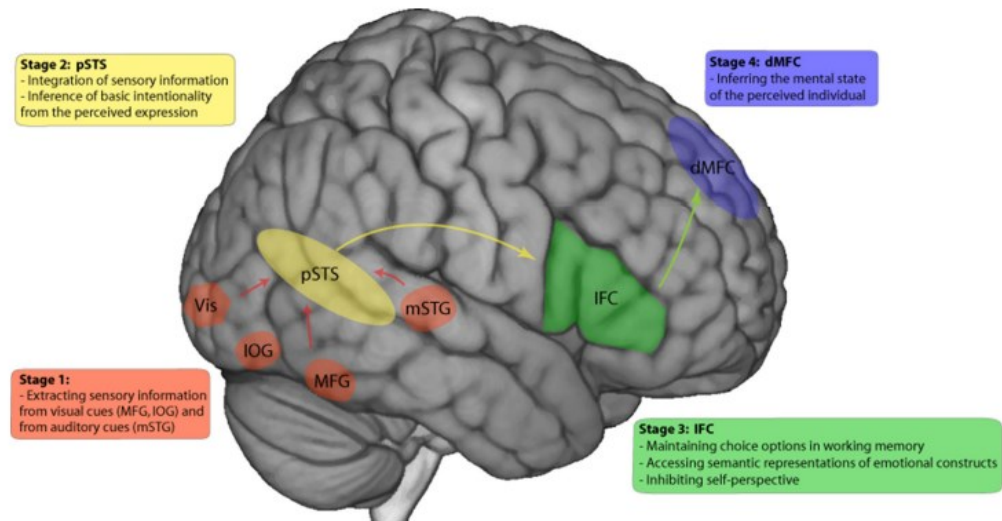
Figure 1.4. A multi-stage model for processing the emotional expressions of others. Vis = visual association areas, MFG = middle fusiform gyrus. IOG = inferior occipital gyrus. mSTG = middle superior temporal gyrus. Amy = amygdala. pSTS = posterior superior temporal sulcus. IFC = inferior frontal cortex. dMFC = dorsomedial frontal cortex (adapted from Dricu & Frühholz, 2016).

Wolf and colleagues demonstrated using tensor probabilistic component analysis that the mindreading network (during a naturalistic task) can be subdivided in *three* limited, statistically independent but functionally and temporally linked networks. As well as the Dricu and Frühholz's model, the *first* network component is made up of sensory processing regions, the *second* is made up of the pSTS, and the *third* network component is made up of the IFC and dMFC (Wolf et al., 2010). In this case, however, the authors noted some overflow between the components, such that some IFC activity and some pSTS activity were observed in the first and second components, respectively. The difficulty of precisely dividing the functional functions that each brain structure plays may be reflected in these spillovers, while at the same time, connections between

these structures that are both feedforward and feedback may change the temporal trajectories of their activity (Dricu & Frühholz, 2016).

In conclusion, it is important to note that despite these factors, it seems that mindreading is still a significant part of explicit emotional expression evaluation based on visual cues. This indicates that coherently theories, which include consistent links between circumstances, feelings, and acts, represent the knowledge of observers about emotions. Following that, observers employ this understanding to interpret the actions and signals of others, such as facial expressions, in a manner comparable to rational reasoning in other fields (Ong et al., 2015).

Based on the above-described model many authors then hypothesize that when deciding which emotions to display, we not only perceive others' expressions but also activate brain areas that are crucial for accurately estimating another person's mental condition.This finding has several theoretical and practical implications for the research on emotional expressions (Brüne, 2005; Goldmann, 2008; Sharp et al., 2011; Wood, 2014). First it supports the hypothesis that even straightforward paradigms of emotion recognition would voluntarily stimulate brain areas involved in mindreading. Second these results could contribute to a better understanding of interpersonal perception, e.g., how initial impressions are formed.

Studies have demonstrated that people may be perceived quickly and accurately, based on a small number of cues. Temporary aspects of another person, such as emotional expressions, are unconsciously extrapolated into defining personal attributes when two people first meet. This may reflect the impromptu mindreading techniques underlying even the most basic emotion assessment activities.

1.3. Hemispheric lateralization

Studies on patients showed that the lesions can result in impaired facial expression recognition on a variety of tasks, particularly those that have biological importance or motivational relevance and have implications for clinical practice, involved especially the right hemisphere (Tippett et al., 2020).

Although these results are in line with numerous investigations showing laterality effects in the representation of emotions (Gainotti, 1969, 1972; Rosadini & Rossi, 1967; Terzian & Cecotto, 1959), the topic remains controversial because different lateralization models of emotion processing were created to explain the meaning of the observed asymmetries. One of the first researchers, to propose a direct link between emotional processing and the right hemisphere, discovered that the presence of a unilateral right-sided lesion was associated with a reduction or paralysis of emotional expression, implying that emotional processing was localized within the right hemisphere (Borod et al., 1998).

Over the last 20 years, there has been a surge of interest in the neocortex's role in emotional processing. As a result, *two major hypotheses* for explaining the relationship between the right cerebral hemisphere and emotion have been proposed. According to the *right-hemisphere hypothesis*, the right hemisphere is dominant for emotional expression and perception despite of valence. In the *valence hypothesis*, the right hemisphere is dominant in negative/unpleasant emotions, while the left hemisphere is dominant in positive/pleasant emotions.

Supporting the *right-hemisphere hypothesis*, Terzian & Cecotto (1959) and Rosadini & Rossi (1967) were the first to describe differences in emotional behaviour in patients undergoing left and right drug inactivation. These authors reported that

injection of sodium amylate into the left carotid artery produced a "depressive-catastrophic reaction" (characterized by a depressed attitude with crying outbursts), while right hemisphere inactivation wasfollowed by a "euphoric-manic" reaction. Initially, these different emotional reactions were attributed to the disruption of opposite aspects of mood neural mechanisms. The authors proposed that depressive-catastrophic reactions could be attributed to the inactivation of a centre for positive emotions on the left, while euphoric-manic reactions could be attributed to the disruption of a centre for negative emotions on the right.

Gainotti (1969, 1972, 2019), a few years later made partly similar, in particular he described the presence of "catastrophic reactions" in patients with damaged brain in the left hemisphere (aphasics) and of "indifference reactions" in patients with severe right brain damage. Gainotti interpreted these findings differently, viewing catastrophic reactions as a type of response that, while intense, was psychologically appropriate to a tragic event like a brain injury, whereas indifference reactions in patients with severe right hemisphere lesions were viewed as an abnormal or inappropriate reaction to a dramatic event. To explain these differences Gainotti (1972) proposed that the right hemisphere may be dominant for emotion processing, just as the left is for language, and that inappropriate emotional responses, such as indifference, following injury would occur only as a result of lesions in the right hemisphere.

Gainotti's data were found to be consistent with subsequent results obtained in healthy subjects by Wittling (Wittling, 1990) and in patients with brain damage by Heilman et al. (Heilman et al., 1978) Morrow et al. (Morrow et al., 1981), and Zoccolotti et al. (Zoccolotti et al., 1982, 1986). These researchers specifically demonstrated that data on hemispheric lateralization were coherent with differences in autonomic activity modulation as a function of the activated hemisphere during a

specific behavioural task in healthy subjects and as a function of the lesioned hemisphere in pathological subjects.

Recent preliminary electrophysiological results of Caruana and colleagues (Caruana et al. in preparation) on implanted drug-resistant epileptic patients, showing a greater numerosity of responses in the right hemisphere than in the left one after the presentation of stimuli consisting in emotional faces, support the idea of *right hemisphere hypothesis* have a counterpart also for emotion recognition.

Wittling (1990) studied blood pressure changes in healthy subjects while watching movies with high emotional content, revealing the presence of specific changes in the right hemisphere, that occurred in conjunction with increases in systolic and diastolic pressure; these increases were in direct contrast to what was recorded as a result of increased activity in the left hemisphere, whose increase corresponded, that is, to a decrease in cardiac activity. In line with these observations, Heilman et al. (1978), Morrow et al. (1981) and Zoccolotti et al. (1982, 1986) demonstrated how patients with right brain damage also presented response reduced cutaneous galvanic in response to painful or distressing emotional stimuli.

Other authors later partially revised Gainotti' s model, proposing a dominant role for the right hemisphere in processing negative emotions and the left hemisphere in processing positive emotions, in accordance with the *valence hypothesis*. Additional authors, such as Etcoff (1986), have proposed specific observations for the smile, pointing out how this facial expression differed from others not only because of its positive emotional valence, but also because it represents the facial expression that is emotionally easiest to reproduce voluntarily, as well as the one most used for approach and social communication. He stated that in the case of smiling, there is a predominant

role of the left hemisphere for the intentional control of the facial expressive apparatus, as opposed to the right hemisphere being more involved when smiling occurs automatically, involuntarily, and spontaneously.

Gainotti et al. (1993) advanced a somewhat similar interpretation, based on Leventhal's (Leventhal, 1974, 1982) distinction between "automatic" and "conceptual" emotional levels, according to which the right hemisphere would be preferentially involved in spontaneous emotional expression and the left hemisphere during intentional control of the emotional expressive apparatus. This hypothesis is consistent with the findings of Ross and Pulusu (Ross & Pulusu, 2013) who demonstrated the difference in muscle activation between spontaneous and automatic facial emotional expressions; specifically, these authors demonstrated that spontaneous facial expressions originate on the left side of the face, which is controlled by the right hemisphere, whereas voluntary expressions (related to social communication and associated display rules) originate on the right side of the face.

1.4. Aim of the thesis

In this thesis tractography and effective connectivity analysis has been performed to analyse a series of territories activated during the observation of emotional faces. These territories are defined by overlapping the BOLD activations reported by Dricu and Frühholz's (2016) in their meta-analysis of 102 imaging studies in which healthy subjects observed and listened emotional expressions and preliminary electrophysiological data (gamma band activity, 50-150Hz), analysed by Caruana and co-workers, obtained from 31 epileptic patients during the passive observation of emotional expressions. While the activation showed by Dricu and Frühholz's are

bilateral, the intracranial recordings of Caruana and colleagues showed noticeable rightward lateralization. In completely agreement to these latter results, also Babo-Rebelo and co-workers have obtained more significant responses from the right hemisphere during the analysis of intracerebral EEG from 11 epileptic patients viewing a stimulus sequence beginning with a neutral face with direct gaze, that could avert or remain direct, while the emotion changed to fearful or happy (Babo-Rebelo et al., 2022). For all this evidence, in the present thesis I focused on studying the connectivity of the right hemisphere.

Using this approach, I identified territories located exclusively in the right hemisphere and corresponding to V4, lateral fusiform gyrus (FusLat), mediotemporal area (MT), the posterior superior temporal sulcus (pSTS), the anterior temporal pole (TP), the amygdala and the inferior frontal gyrus (IFG). Although it is well known what are the anatomical pathways through which these occipital and temporal territories interact one to another, less detailed information is available concerning how these territories interact with the IFG, the main region, in according to Dricu and Frühholz's study, for the explicit recognition of the emotional faces.

To fill this gap, in the present thesis first, I aimed to identify, by using the tractography method, the anatomical pathways conveying visual information to this prefrontal sector. Second using a meta-analysis based on intracortical stimulations at low frequency performed in epileptic patients (The Functional Brain Tractography project, F-TRACT; https://f-tract.eu/), I aimed to elucidate the temporal dynamics of the visual information flow along the anatomical pathways identified in the tractography study.

Overall, the results of the present thesis aim to provide a detailed description of the directionality, latency, velocity, and amplitude of neural signals transferred along

anatomical pathways that convey facial visual information to IFG, resulting in a more detailed framework of the network through which the explicit recognition of emotional faces occurs.

2. MATERIALS AND METHODS

The structural connectivity of 16 healthy subjects, 12 from University of Parma database and 4 from Human Connectome database, was analyzed using the diffusion tensor imaging (DTI), concurrently the effective connectivity was studied by means of cortico-cortical evoked potentials (CCEP). In this second case, data were taken from an open-source dataset, F-TRACT.

2.1. Diffusion tensor imaging (DTI)

2.1.1. Scanning Protocols

Data from 12 healthy humans (5 Males, 7 Females, range age 21– 35, mean age 28) were acquired in a 3T MR scanner (GE MR750) equipped with a dedicated 8 channel head-coil at Parma University Hospital.

The sequence protocol included a structural T1 weighted BRAVO sequence for anatomical reference, with TR/TE 57501/3.96 ms, 0.5 × 0.5 × 0.9 mm3 voxel, and a diffusion spin echo single shot echo planar imaging (EPI) sequence, with TR/TE 56586/82.4 ms, 2 × 2 × 2 mm3 isotropic voxel, 64 diffusion directions with an effective b value of 1000 s/mm2 and 8 images with an effective b value of 0 s/mm2 both in anterior–posterior phase encoding direction and in the reverse phase encoding direction. To assess whether our results were replicable also in data with smaller voxel size, additional four subjects (2 Males and 2 Females, range age 26–35, mean age 30.5) from the WU-Minn dataset of the Human Connectome Project (Van Essen et al., 2013) were included in our analysis. These additional subjects (numbers 102 816, 102 311, 128 935,

and 100 610) have been acquired with a 3 T MR scanner (Siemens) and the sequence protocol included a structural T1 weighted BRAVO sequence for anatomical reference, with TR/TE 2400/2.14 ms, 0.6999 × 0.6999 × 0.6999 mm3 voxel, and a diffusion spin-echo single shot EPI sequence, with TR/TE 5520/89.5 ms, 1.25 × 1.25 × 1.25 mm3 isotropic voxel, 96 diffusion directions with an effective b value of 3010 s/mm2 90 diffusion directions for each shell defined with b-values of 1000, 2000, and 3000 s/mm2, plus 18 images with an effective b value of 0 s/mm2, scanned along two phase encoding directions (L/R and R/L).

2.1.2. Diffusion data analysis

The diffusion images were analysed with the FMRIB Software Library (FSL) tools (version 5.0.9) (Glasser et al., 2013; Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). First, employing the reversed phase data, raw images were corrected for head motion and distortions induced by eddy currents and difference in the susceptibility distribution within the brain using the FSL's tools TOPUP (Andersson et al., 2003; Smith et al., 2004) and EDDY (Andersson & Sotiropoulos, 2016). Then, diffusion tensor estimate was carried out with FSL's BEDPOSTX tool, which enables to model multiple fiber crossing within each voxel of the brain (Behrens et al., 2003; Behrens et al., 2007).

Subsequently, a probabilistic tractography analysis was executed with FSL's PROBTRACKX tool (using curvature threshold = 0.2, number of sample = 5000) (Behrens et al., 2003; Behrens et al., 2007). For each tract, the streamlines were seeded from two mask images, constituted by spherical region of interest (ROI), testing the

structural connection from seed A to seed B and vice versa (from B to A): the final output is the sum of the connectivity distributions resulting from the two analyses.

To compare and average the resulting tracts, the assessment was performed in the Montreal Neurological Institute 152 (MNI 152) space (Grabner et al., 2006). Each voxel of the resulting images contained the value of the total number of streamlines crossing in voxel, producing maps of connectivity distribution showing the most probable pathway between the selected seeds: to reduce false negative and false positive rate and obtain the best tractography reflection of tracers in monkey studies (Azadbakht et al., 2015), a threshold of 10% on the maximum number of streamlines reported by PROBTRACKX was chosen.

Subsequently, to highlight the repeatability in the different subjects of the streamlines of the tracts found, each tract was binarized, the binarized tract of the different subjects added one to another and then, their sum averaged. The value obtained is proportional at the number of the voxels in which the streamlines are present in at least the 60% of the examined subjects.

2.1.3. Identification of the White Matter Tracts

In order to identify at which fasciculi belonging the white matter tracts observed, we overlap our results with the white matter tracts (Rojkova et al., 2016) of the atlas present in the Tractotron tool in BCBToolkit software (http://toolkit.bcblab.com/; Foulon et al., 2018). A threshold of 10% on the maximum number of streamlines was used also for the tracts of the BCBTToolkit.

2.1.4. ROIs' location

The ROIs included the following occipital, temporal and prefrontal territories: V4, FusLat, MT, pSTS, TP, amygdala and IFG (pars triangularis). The ROIs consisting of spheres of 5 mm of radius located at the MNI coordinates corresponding to the center of gravity of the intracranial recording sites of Caruana and co-workers (in preparation) observed within the activation of the metanalysis of Dricu and Frühholz's (see Figure 2.1 and Table 1). Each ROI has been created by using MARSBAR tool of SPM software.
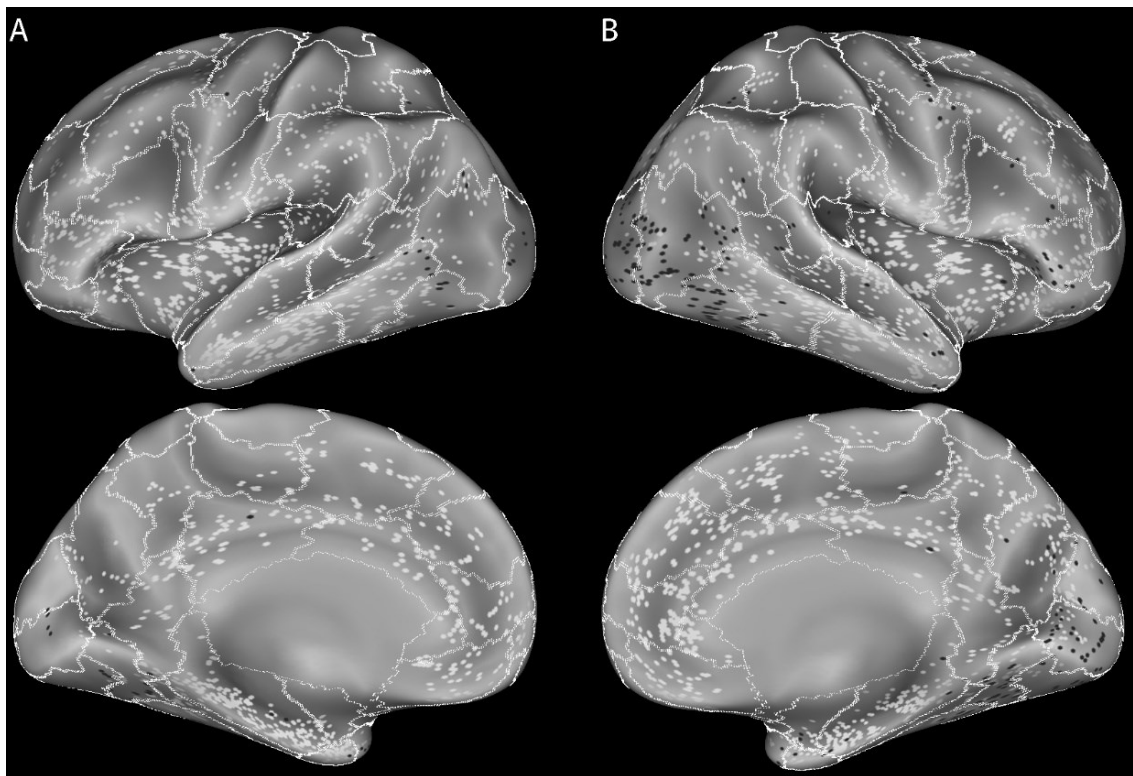
Figure 2.1. The picture represents the preliminary results obtained from a cohort of 31 drug-resistant epileptic patients (35 hemispheres: 14 right, 13 left, 4 bilateral) undergoing sEEG investigation for a pre-surgical evaluation. Data were collected from 5211 recording sites (2938 right). During the task, patients were requested to passively observe static pictures depicting emotional expression (Ekman series; 500ms with 500ms intertrial). Sites showing a significant increase of gamma band activity (50-150 Hz) are depicted in black, while unresponsive sites are colored in white. Results are presented in an inflated version of the fs_LR brain template, using Caret software. White borders represent the subdivision Lausanne60 (see below section 2.2)

Table 1. Coordinates of seeds used in human probabilistic tractography studies and given in MNI standard coordinates

Region	x	y	z
V4	25	-82	-10
Lateral fusiform	41	-40	-22
MT	42	-68	4
pSTS	39	-60	5
TP	30	10	-38
Amygdala	30	-1	-18
IFG	41	83	-8

2.2. F-TRACT

All the CCEPs used for the analysis of effective connectivity were downloaded from the dataset open access f-tract.eu. The Functional Brain Tractography (F-TRACT) project aims to improve understanding of large-scale human brain connectivity through low-frequency intracortical stimulations performed in epileptic patients who are candidates for resective surgery. The European Research Council Funded F-TRACT through a Consolidator Grant awarded to Olivier David, team leader at the Grenoble Institute of Neuroscience in France. F-TRACT began in August 2014 and will conclude in July 2019. Its continuation was supported until the end by the Human Brain Project (March 2023).

The data were collected using single-pulse direct electrical stimulation at low frequency (< 5 Hz) of cortical regions in 780 patients, suffering from focal drug-resistant epilepsy, who were explored using intracranial electrodes for a presurgical evaluation. For each patient, a preoperative anatomical MRI (T1 contrast) and an image with SEEG electrodes (T1 MRI or CT scan) were obtained in order to position SEEG electrodes.

For each individual stimulation, several electrophysiological parameters are evaluated, including: the probability defined as the percentage of the single pulse electrical stimulation (SPES) inducing CEEPs (%), onset latency (milliseconds/ms), peak latency (milliseconds/ms), amplitude (millivolt/mV), duration (milliseconds/ms), integral (millivolt/mV), axonal delay(milliseconds/ms), and axonal velocity (meters per second/ m/s). All the features have been estimated separately for patients younger than 15 y.o. (group "0-15") and patients older than 15 y.o. (group "15-100"). Subsequently, all results collected from adjacent sites are averaged together to give a single value for each area of interest.

The areas of interest are obtained by combining results from previously validated templates that differ primarily in the granularity of the parcellation, so that the data can be analyzed using the parcellation with the best grain for the researcher's needs. Among the templates, Lausanne2008 33, Lausanne2008 60, Lausanne2008 125, Lausanne2008 250 and Lausanne2008 500, which segment the entire cortical surface into approximately 33, 60, 125, 250, and 500 areas.

First, we projected on the fs_LR template (Caret software) the ROIs used in the DTI study. Next, we imported the different templates (Lausanna 33, 60, 125, and 250) into Caret, and for each parcel we created the corresponding edges. At this point, we compared the different edges with our ROIs, selecting the parcel that best suited them (Fig. 2.2).
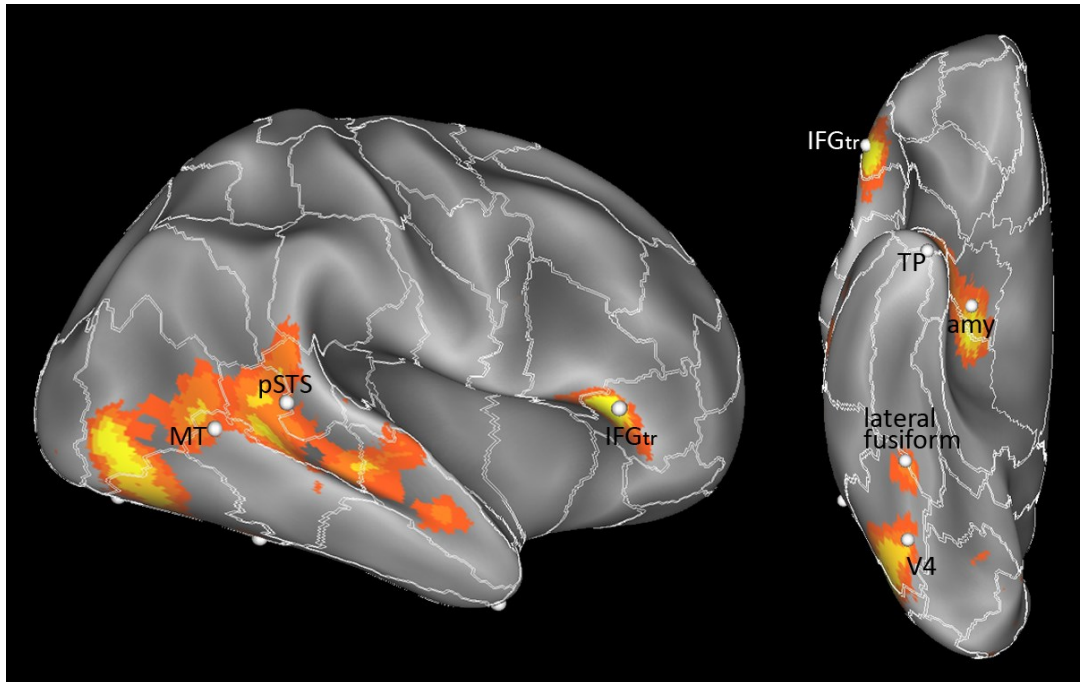
Figure 2.2 Overlap of Dricu and Frühholz' meta-analysis areas with the parcellation of Lausanne60 on the inflated surface of the FS_LR brain template and the ROIs

The SPES data from the F-TRACT dataset related to the IFGtr was then exported so to project the results of the averaged CCEPs for each of the Lausanne60 areas onto the template and thus discover the connectivity values between the pars triangularis and each of the other areas in the template.

We used four sets of CEEPs' features: (1) the probability of the effective connectivity between areas (probability); (2-3) features that extract the dynamical properties of the signal (onset latency and peak latency) and (4) feature that extracts the strength of connections (amplitude). Onset latency is the latency of the first sample with an amplitude exceeding the significance threshold, peak latency is the latency of the first peak above the significance threshold, while amplitude is referred to as the amplitude of the first peak above the significance threshold.

In our pipeline, we first analyzed the afferent probability, to identify the probability of afferent connections from all brain regions to IFGtr, and then we analyzed the peak latency, the onset latency and the amplitude, relative to the regions where the DTI was performed. To conclude, the data were exported and displayed on fs_LR template on CARET software.
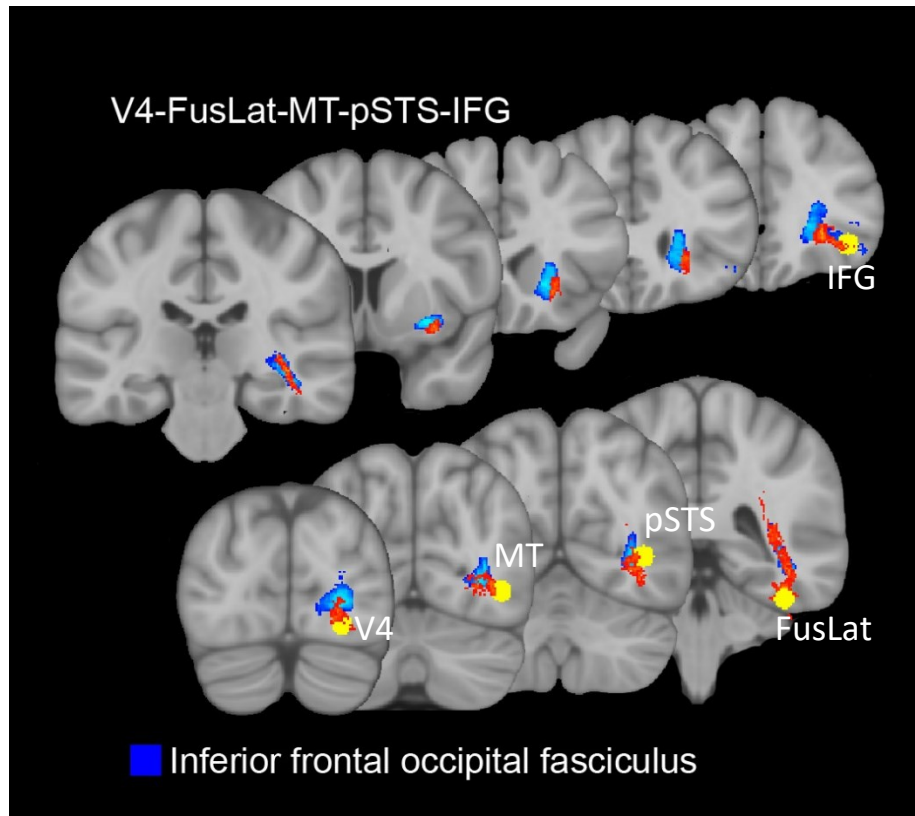
3. RESULTS

3.1. Diffusion Tensor Imaging

White Matter Tracts Connecting IFG withV4, MT, lateral fusiform, and pSTS

Figure 3.1.A shows the connectivity of IFG with V4, MT, lateral fusiform, and pSTS, based on the average of the streamlines obtained from our dataset. IFGis connected to all the aforementioned visual areas in all of the subjects of our dataset. More specifically, ball-and-stick analysis from our dataset showed connections between IFG and the V4MT, lateral fusiform, and pSTS in 12 of 12 subjects and 4 of 4 subjects from Human Connectome dataset.
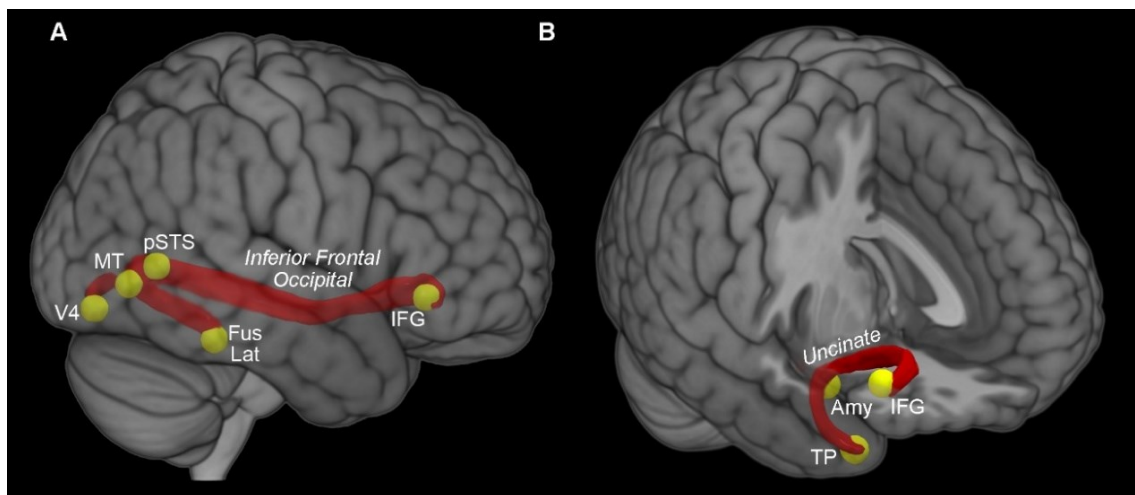
Figure 3.1. the inferior frontal occipital (A); the uncinate fasciculus (B)

The white matter tract connecting IFGwithV4, MT, lateral fusiform, and pSTS overlaps with the IFOF (Fig. 3.2.).

Figure 3.2. the inferior frontal occipital fasciculus (IFOF) is showed in blue, the ROIs in yellow and the tract resulting from DTI analysis in red

White Matter Tracts Connecting IFG with TP

Figure 3.1.B shows the connectivity of IFG with TP, based on the average of the streamlines obtained from our dataset. IFGis connected to all the TP in the majority of the subjects of our dataset. More specifically, ball-and-stick analysis from our dataset showed connections between IFG and TPin 10 of 12 subjects and 4 of 4 subjects from Human Connectome dataset. The white matter tract connecting IFGwithTPoverlaps with the uncinate fasciculus (Fig.3.3).

White Matter Tracts Connecting IFG with amygdala

Figure 3.1B shows the connectivity of IFG with amygdala, based on the average of the streamlines obtained from our dataset. IFGis connected to all the amygdala in most of the subjects of our dataset. More specifically, ball-and-stick analysis from our dataset showed connections between IFG and amygdala in 10 of 12 subjects and 4 of 4 subjects from Human Connectome dataset.

The white matter tract connecting IFG with amygdala overlaps with the uncinate fasciculus (fig. 3.3.).
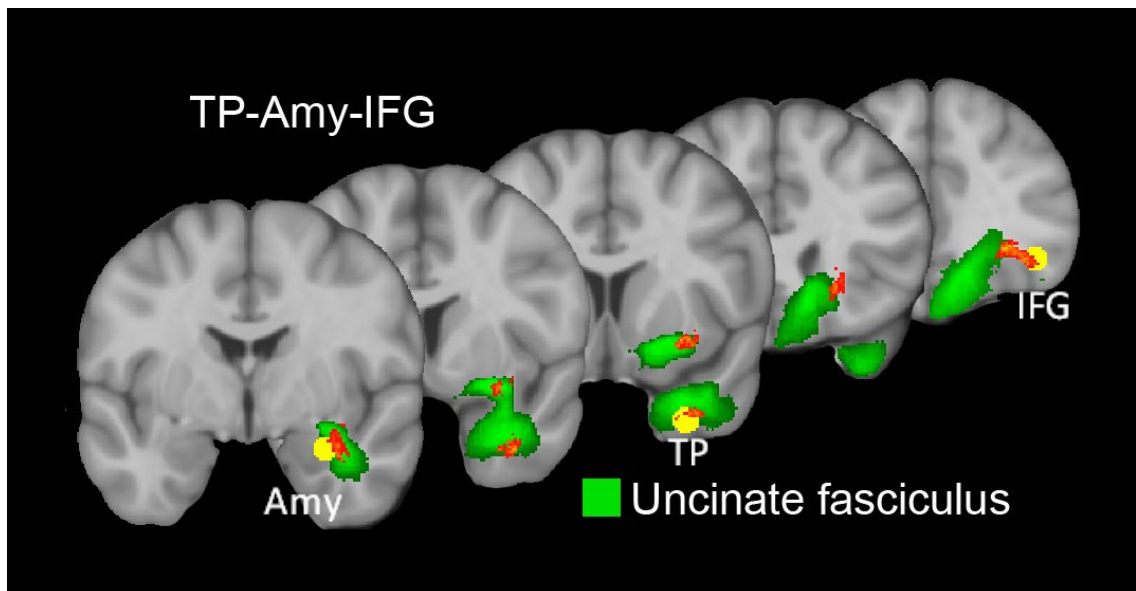
Figure 3.3. the uncinate fasciculus (UF) is showed in green, the ROIs in yellow and the tract resulting from DTI analysis is red

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3.2. F-TRACT

Concerning the probability, we found a strong connectivity between IFG_triangularis and the putamen (100%), IFG (pars triangularis and opercularis: 90% and 80% respectively), the caudate nucleus (80%), and the anterior insula (70%). The only one that re-enters in Dricu and Frühholz's meta-analysis is the IFG (Fig. 3.4).
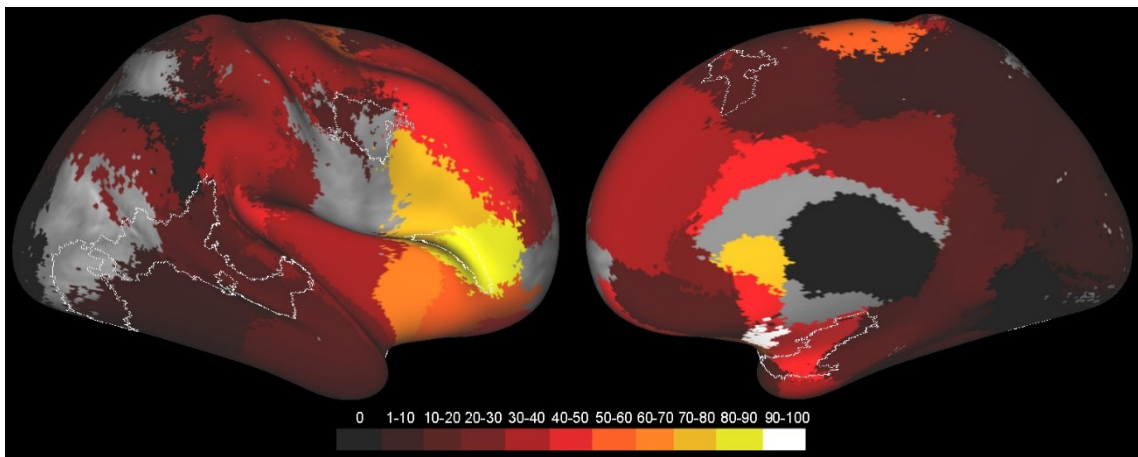
Figure 3.4 Overlap of probability map of IFGtr with the parcellation of Lausanne60 on the inflated surface of the FS_LR brain template. Gray areas are the brain regions for which data are not available. Scale bar represents the percentage of the connections' probability.

Regarding the regions in which DTI was carried out (see above) the results of the probability are the following: fusiform_1 corresponding to V4 (10%), inferior temporal_2 corresponding to MT (10%), middle temporal_2 corresponding to lateral fusiform (20%), middle temporal_1 corresponding to pSTS (20%) and the temporal pole (20%). Of note, the amygdala shows the strongest connectivity (50%) (Fig.3.5).
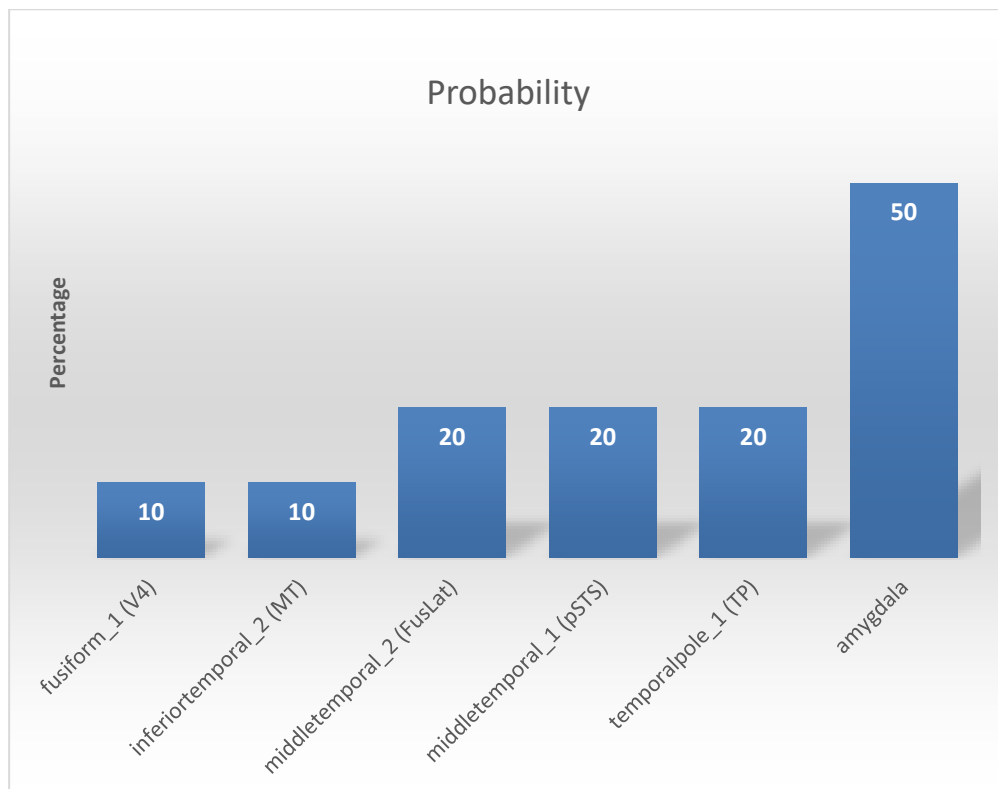
Figure 3.5 Connections' probability of the analyzed areas expresses in percentage

Onset latency, peak latency and amplitude were analyzed only in the areas where DTI was performed. Specifically, the earliest onset latencies are in inferior temporal_2 corresponding to MT (50 ms), amygdala (60 ms), and middle temporal_1 corresponding to pSTS (70 ms) while longest are in the temporal pole (80 ms), middle temporal_2 corresponding to lateral fusiform (100 ms) and fusiform_1 corresponding to V4 (110 ms) (Fig. 3.6).
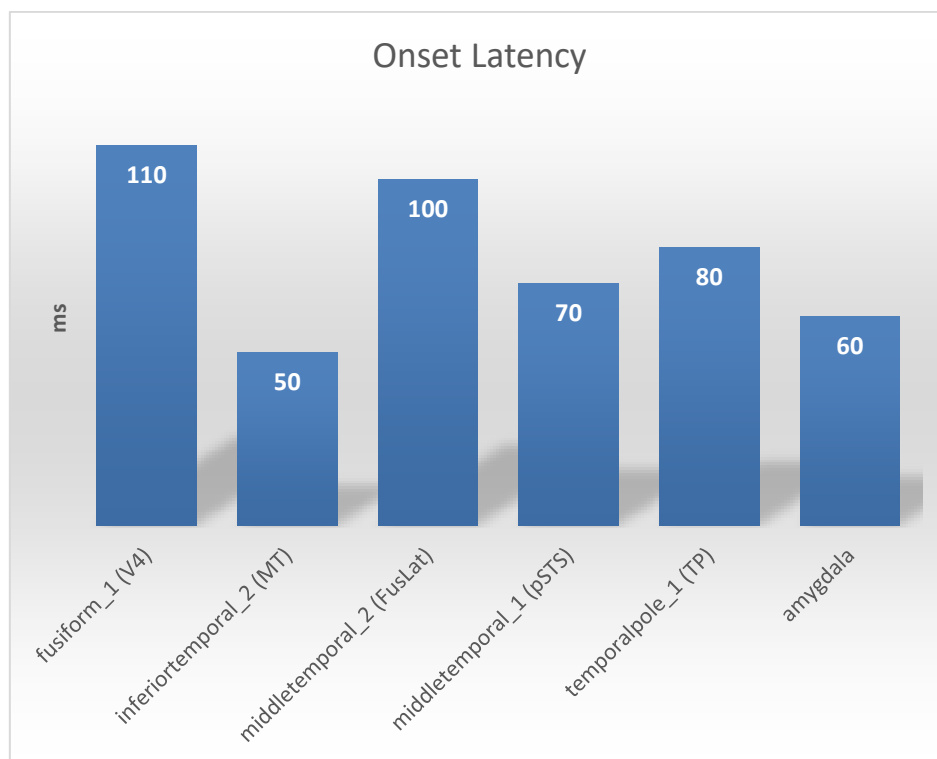
Figure 3.6 Onset latency of the analyzed areas expresses in ms

Peak latency results are in line with onset latency ones, therefore the peak zone in the inferior temporal_2 corresponding to MT (60 ms), in the amygdala (70 ms) and middle temporal_1 corresponding to pSTS (70 ms) is earlier, whereas longer in the temporal pole (90 ms), in middle temporal_2 corresponding to lateral fusiform (110 ms) and in fusiform_1 corresponding to V4 (120 ms) (Fig. 3.7).
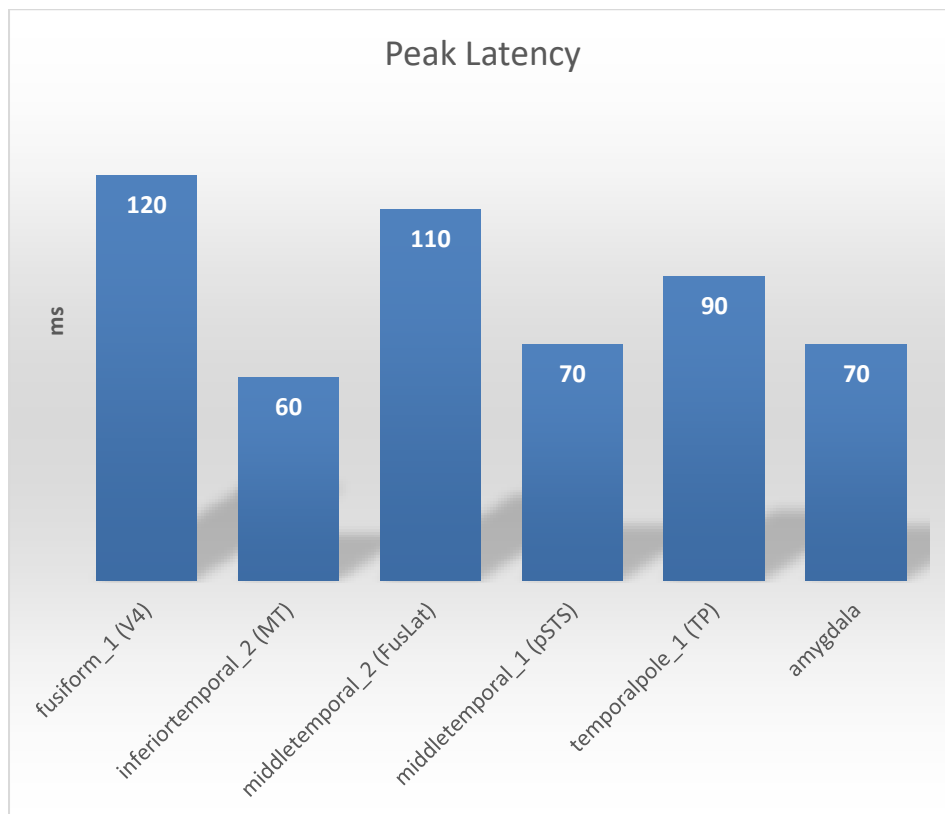
Figure 3.7 Peak latency of the analyzed areas expresses in ms

Amplitude data are the following: fusiform_1 corresponding to V4 (7 mV), inferior temporal_2 corresponding to MT (6 mV), middle temporal_2 corresponding to lateral fusiform (7 mV), middle temporal_1 corresponding to pSTS (6 mV), the temporal pole (6 mV) and the amygdala (8 mV) (Fig. 3.8).
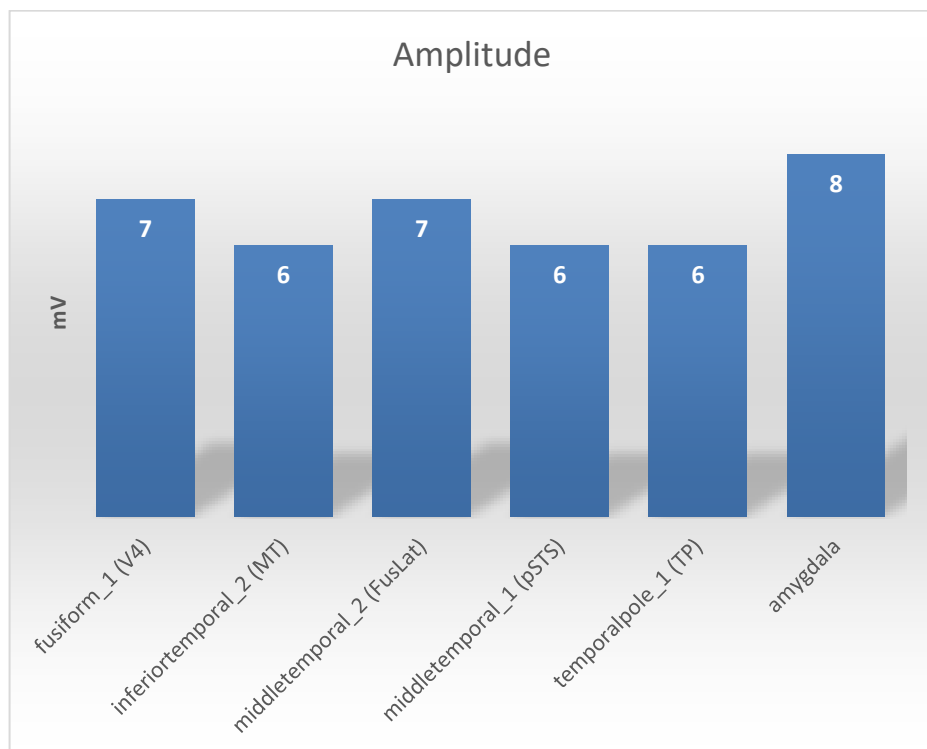
Figure 3.8 Amplitude of the analyzed areas expresses in mV

4. DISCUSSION

The results of this thesis show that the cortical anatomical pathway connecting visual regions to the IFG is the IFOF, in line with anatomical studies (Catani & Thiebaut de Schotten, 2008) showing that this fasciculus represents the main anatomical route connecting visual regions with the prefrontal cortex. Furthermore, it has been shown that the amygdala, which is the main target of the subcortical pathway for emotion perception, is directly connected via the uncinate fasciculus to the IFG. Although it was already known that the orbitofrontal cortex (Papinutto et al., 2016) was connected to the amygdala the present result showed the presence of a direct connection of this subcortical structure with the IFG.

4.1. The Uncinate and Inferior Frontal Occipital fasciculi

The Uncinate Fasciculus (UF) is a hook-shaped cortico-cortical white matter pathway that provides bidirectional connectivity between the orbital and medial prefrontal cortex, and the anterior portions of the temporal lobe, including the temporal pole, perirhinal cortex and amygdala (Petrides & Pandya, 2007; Schmahmann et al., 2007; Thiebaut de Schotten et al., 2012). Disruption of the UF is seen in a range of neurological and psychiatric conditions that are characterized by altered social behavior, including autism spectrum disorder (Kumar et al., 2010; Pugliese et al., 2009), frontotemporal dementia (Mahoney et al., 2014; Whitwell et al., 2010), psychopathy (Craig et al., 2009; Sundram et al., 2012), and social anxiety disorder (Baur et al., 2013; Phan et al., 2009). By virtue of its connectivity, the UF has been suggested to underpin a "*temporo-amygdala-orbitofrontal network*" (Catani et al., 2013) or "*anterior temporal*

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system" (Ranganath & Ritchey, 2012), potentially critical to the regulation of social and emotional behavior (Von Der Heide et al., 2013) .

In line with the results of the present thesis, there is preliminary neuropsychological evidence that lesions impacting the right UF (rUF) can lead to impaired emotion recognition (Fujie et al., 2008; Ghosh et al., 2012; Mike et al., 2013; Oishi et al., 2015). In addition, in a recent study it was demonstrated that the right UF microstructure, quantified via fractional anisotropy, is linked to facial expression decoding skills and facial emotion discrimination abilities (Coad et al., 2020). Interestingly, in Alzheimer's patients the poor recognition of facial emotions, especially the negative ones, has been correlated with the mean diffusivity of the UF and not correlation was observed with the other fiber tracts analyzed, that are the inferior longitudinal fasciculus and the IFOF (Takahashi et al., 2020) .

As mentioned above, the occipital and temporal areas found by Caruana and co-workers involved in emotional recognition are connected with the IFG throughout the IFOF. The IFOF begins in ventral occipital lobe and terminates in ventral and lateral aspects of frontal cortex (Catani & Thiebaut de Schotten, 2008). The IFOF is a mysterious tract, not identified in non-human primates but only in humans using diffusion imaging techniques (Schmahmann & Pandya, 2007). This has led some researchers to suggest that it may be specific to humans (Catani, 2007). Electrical stimulation of this tract during neurosurgery consistently results in semantic errors (Duffau et al., 2008) providing strong evidence that this tract plays a significant role in semantic memory. However, there is a hint that it may also play some role in face processing as one study reported reduced structural integrity of the right IFOF (rIFOF) in congenital prosopagnosia (Thomas et al., 2008). In addition, two studies found a relationship between damage to the rIFOF and emotion recognition impairments

(Genova et al., 2015; Philippi et al., 2009). The alteration of the fractional anisotropy of the rIFOF is also correlated to autism severity, in agreement with the notion that autistic people showed an evident impairment in the recognition of the others' emotions when engaged in communicative behaviour (Kilroy, et al., in press).

The evidence of the literature, showing that both lesion or alteration of the rUF and rIFOF impair the recognition of emotional faces, suggests that along these fasciculi two, at least partially, different typologies of information are conveyed, both crucial for exploiting this function. Functional studies suggest that the cortical pathway conveys pure visual information, that is the semantic aspects of the observed faces, whereas the subcortical route a visual information endowed by emotional content. Since the target of these anatomical pathways is, in both cases, the rIFG, known to have a crucial role in the explicit recognition of an observed or listened emotion (Dricu & Frühholz, 2016), a working hypothesis is that this prefrontal territory is critical for exploiting this function through the integration and the processing of these two typologies of visual information. Future studies are needed to better elucidate this issue.

In line with my hypothesis, the effective connectivity data showed that through the subcortical pathway the visual information, in term of CCEPs, reaches the IFG with a latency comparable to that by which is conveyed via the cortical pathway and with greater amplitude. Thus, contrary to the classical view, indicating that during the observation of emotional faces the main role of the prefrontal cortex and amygdala interactions is the top-down modulation of amygdala activity, the present data suggest that this subcortical structure represents, in addition to occipital and temporal areas, a main source of visual information to the IFG. This interpretation is in complete agreement with electrophysiological data which show that in the amygdala the responses after the presentation of stimuli consisting of emotional faces occur with a

latency of 120 ms, thus earlier to that observed in the prefrontal cortex in which the same trigger responses with a latency of 170ms (Adolphs, 2002). Additional analyses of the preliminary electrophysiological data presented in this thesis (Caruana et al. in preparation) will allow to test of this hypothesis more carefully.

4.2. The subcortical pathway and the Amygdala

Over the last decade, there has been growing evidence that subcortical structures are important for perceptual and cognitive functions. In addition, several lines of evidence, suggest that the subcortical face-processing route does not simply respond to top-down cortex influence. On the contrary, it appears to modulate cortical face procession (Johnson, 2005).

The subcortical face-detection system involves the superior colliculus, pulvinar and amygdala. The anatomical stage revealed that the most likely network included cortical, subcortical, and medial connections to the amygdala, providing evidence for the existence of a forward pulvinar-amygdala connection that operates in parallel with cortical-amygdala connections. This adds functional support to anatomical evidence for the pulvinar-amygdala link (Day-Brown et al., 2010; de Gelder et al., 2012; Rafal, et al., 2015).

Anatomically, rebuilt white matter streamlines from the superior colliculus to the pulvinar to the amygdala form only a small portion of the total streamlines from the pulvinar to the amygdala (Rafal et al., 2015; Tamietto et al., 2012). The medial pulvinar is functionally linked to the amygdala as well as several cortical regions involved in cognitive and affective functions (Bridge et al., 2016).

In a study of McFadyen and co-workers (McFadyen et al., 2017), magnetoencephalography was used to measure neural activity while human participants discriminated the gender of neutral and fearful faces filtered for low or high spatial frequencies. They used dynamic causal modelling to show that the most likely underlying neural network consisted of a pulvinar-amygdala connection that was unaffected by spatial frequency or emotion, and a cortical-amygdala connection that conveyed high spatial frequencies. They showed that the pulvinar-amygdala connection transmits a wide range of spatial frequencies quickly, indicating a network of subcortical pathways to the amygdala, which most likely includes the superior colliculus. In addition, pulvinar's effect on amygdala activity precedes that of the visual cortex (Tamietto & de Gelder, 2010). Finally, they propose that if the subcortical route is viewed as playing a generalized rather than a specialized role in face processing, it may explain why emotional responses to different spatial frequencies have produced contradictory results. Thus, they suggest reframing "coarseness", in "unfiltered". In line with McFayden study and our data, a recent fMRI experiment showed that the observation of emotional laughter activates both cortical and subcortical regions, including the superior colliculus, medial pulvinar and right amygdala (Lombardi et al., 2022) .

Clinical studies of patients with blindsight, a disease provoked by V1 lesion and that causes loss of function of the cortical pathway but unaltered functionality of the subcortical one, suggest that the cortex is mainly involved in the conscious perception of observed stimuli while the subcortical structures is deputed to an unconscious perception accompanied by the production of the autonomic changes associated to the viewing of emotional stimuli (Gerbella et al., 2019). In fact, these patients when faced with the presence of emotional stimuli, although showing no awareness of the stimuli

visual they observe, are subject to autonomic-type changes, such as alterations in the pupillary diameter and skin electrical conduction. In line with these studies, Lombardi and coworkers (2022) showed that the brain activations during laughing observation involved also subcortical structures, such as the hypothalamus, that are crucial to produce autonomic and visceral responses and connected to the amygdala (Lombardi et al., 2022).

In line with the TP-amygdala connections observed in the present thesis, monkey studies showed that higher-order visual association cortices in the anterior temporal lobe are the primary source of visual input to the amygdala, specifically to the basolateral nucleus, that makes the amygdala a convergence zone for highly processed sensory data meaningful to object and face processing (Pessoa & Adolphs, 2010). In fact, also the prefrontal cortex's medial and orbital territories and in a weaker manner the lateral prefrontal regions project to this amygdala nucleus (Ghashghaei et al., 2007). These amygdala's extensive connections with the cortex result in additional integrative functions. Affective visual information processing receives a great contribution by the amygdala because it has extensive connections also with other subcortical structures. Because of this, the amygdala's influence on behavior can be mediated by a variety of pathways (Pessoa & Adolphs, 2010). Our data showing that amygdala could modulate via bottom-up interaction not only the visual cortices but also the IFG, support the idea that this structure enhances sensory processing during affectively significant item processing via both direct (amygdala-visual cortex) and indirect (amygdala-prefrontal cortex-visual cortex) pathways. As a result, there are multiple parallel paths for visual information processing, resulting in significant temporal dispersion of evoked responses and allowing 'high-level' regions to respond with short latencies. Every processing step adds about 10 milliseconds to the latency (Nowak & Bullier, 1997). The 'cost' of

utilizing such bypassing stages may be that initially only coarse grain information about a visual item is available. This is coherent with a coarse-to-fine processing strategy in which the stimulus's more global contents are processed before finer details (Sripati & Olson, 2009; Sugase et al., 1999).

Considering the aforementioned data and results of the present thesis, the initial processing of visual information occurs concurrently along parallel channels, resulting in'multiple waves' of activation across the visual cortex and beyond (Rudrauf et al., 2008). Visual stimuli with affective and motivational significance can thus participate in multiple brain sites, including the amygdala, OFC, anterior insula, and anterior cingulate cortex, which can direct processing toward these behaviorally relevant items (Pessoa & Adolphs, 2010).

4.3. Inferior frontal gyrus

In according to Dricu (Dricu & Frühholz, 2016) and Caruana (Caruana et al., in preparation), two others meta-analyses found that in addition to the amygdala, the superior temporal sulcus and the middle and superior temporal gyri (MTG; STG), also the IFG is involved in the observation of emotional facial expressions (Fusar-Poli et al., 2009; Sabatinelli et al., 2011).

Accordingly, lesion studies have shown that damage of this prefrontal territory impairs the recognition of facial expressions (Uono et al., 2016). Previous research has shown a positive correlation between accurate facial emotion recognition and functional outcomes including social adjustment and mental health (Kohler et al., 2010; Kret & Ploeger, 2015; Uljarevic & Hamilton, 2013) and are characterized by unusual brain

anatomy genetically inherited (Crespi & Badcock, 2008).Several studies showed gender disparities in social cognition (Ruigrok et al., 2014) and facial expression recognition (Kret & De Gelder, 2012), according to differences in this brain structure. Individual variations in expression recognition may be also linked to specific genotypes involved in the formation of this brain region (Lin et al., 2012). Anger and melancholy are specifically encoded by caudal areas of the left and right IFG (Uono et al., 2016). In several illness (e.g., schizophrenia, psychopathy, autism spectrum disorder and acquired brain injury) dysregulation of the activity of this specific region may play a role in modulating the encoding of anger and sadness from other people's faces.

According to some theories, the IFG contains mirror neurons that fire when we watch and perform particular activities, and matching these representations enables us to comprehend each other's actions (Gallese et al., 2004; Rizzolatti et al., 2001). A recent study showed that in autistic people during the observation of hand actions and facial expressions there is a selective hypoactivation of the right IFG (Kilroy et al., 2021). Accordingly with this latter result and with the classical theory of the right hemisphere dominance for emotions, many studies showed a crucial role of the right IFG (rIFG) respect to the left one in processing visual information related to emotional faces. In fact, damage of the rIFG reduces the ability to perceive emotional expressions from the area around the eyes, according to a study showing anatomical double dissociations between cognitive and emotional empathy (Shamay-Tsoory et al., 2009). Uono and co-workers discovered that the capacity to identify facial expressions in six different emotion categories is correlated with the grey matter volume of the rIFG (Uono et al., 2016). Earlier fMRI research has demonstrated that the mimicking of observed facial emotions enhanced IFG activity especially on the right (Carr et al., 2003; Hennenlotter et al., 2005; Pfeifer et al., 2008). Along with these earlier

discoveries, Uono and co-workers suggested that rIFG's larger volume reflects improved facial imitation, which makes it easier to recognise facial expressions (Uono et al., 2016).

In line with previous study (Catani et al., 2002) the results of the present thesis showed that the STS region has a direct relationship to the IFG. These results are consistent with the hypothesis that this STS-IFG interaction may be used to accomplish motor mimicry (Hamilton, 2008) and with lesion symptom studies showing that both these regions are crucial for recognising another person's facial expressions (Adolphs et al., 2000; Dal Monte et al., 2013).

In addition to the IFG also the anterior insula and adjacent inferior frontal operculum (IFO) have all been proven to be recruited when watching videos of other people's facial expressions (Jabbi & Keysers, 2008). This finding agrees with our data, indicating that the rIFO, similarly to rIFG, receives emotional visual information from both the amygdala, via uncinate, and visual areas, via IFOF. The IFO, according to neuroimaging research, is thought to be a component of a neural network that processes facial expressions, but its exact function in the recognition of emotional faces is yet unknown (Iarrobino et al., 2021). Nevertheless, Iarrobino and co-workers suggested a crucial role of the IFO in emotion discrimination, indeed they tested the effects of r-IFO and l-IFO on the ability of healthy volunteers to distinguish between basic facial expressions using cathodal (inhibitory) tDCS while participants took part in an emotion discrimination task.In particular, in line with the arousal hypothesis, assuming that high arousal emotions (e.g., anger, fear and happiness) are processed by the right hemisphere while low arousal emotions (e.g., sadness and disgust) are processed by left hemisphere (Gainotti, 2019), they specifically investigated whether and how the processing of facial expressions conveying high or low arousal emotions is selectively modulated by the two

IFO. While cathodal tDCS applied to l-IFO altered recognition of a low arousal emotion (such as sadness), it had no effect on the recognition of a high arousal emotion (such as rage; Iarrobino et al., 2021).

5. CONCLUSION

Our data indicate that the visual information reaches the rIFG along the subcortical pathway at least faster than the visual information conveyed by the cortical route, suggesting that the explicit recognition of the facial expressions we are observing, which is largely dependent on rIFG, needs of coarse subcortical information as well as the cortical detailed one. The subcortical pathway would provide coarse or unfiltered visual information but endowed of the emotional content of the observed stimuli whereas the cortical route, in parallel, would provide to rIFG visual information more faithful of the image that we are observing. Both information in the IFG would be integrated and maintained in time, accordingly to the well-known role of the prefrontal cortex in working memory, to realize a conscious experience of the observed stimuli.

An additional, not mutually exclusive, hypothesis is that the subcortical pathway has a role in the attentional modulation, through an increase of the salience of the visual stimuli we are observing, crucial for improve the explicit emotions recognition especially in some situations such as those characterizing by a high cognitive load (Johnson, 2005).

Further functional studies of these two pathways will be needed to assess the correctness of these two hypotheses.

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