

UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA

**Dipartimento di Medicina e Chirurgia
Dottorato di Ricerca in Neuroscienze
- Ciclo XXVIII -**



TITOLO

Interactions between emotions and decision making: a SEEG study with focus on the role of the cingulate cortex.

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Anno Accademico 2014-2015

L'émotion est un mouvement de l'âme.
Paul Claudel

Acknowledgements

This work would not have been possible without the precious help of Dr Vadym Gnatkovsky, so a big Thanks!!!

I wish to thank Profs Guido Cavaletti and Paola Marmioli for their competence and tact and Dr Stefano Francione who imparted to me knowledge of his field of expertise.

I also wish to thank Prof Costanza Papagno, Alberto Pisoni, PhD and Federica Pelle, PsyD for their valuable indications, the latter also for the moral support. I thank, too, Dr Roberto Mai as well as the équipe of neurophysiology technicians for their help, with a particular mention to Antonio Menna for his constant assistance.

Last but not least, I am thankful for the energy, confidence, perspicacity and smile of Dr Joseph Negreanu who contributed a lot to this effort.

Finally, I am grateful to my parents who are always by my side.

ABSTRACT

Introduction

Depending on their content, negative or positive, emotions can promote or slow down the cognitive functions.

The anterior cingulate cortex has been classically subdivided in two major regions with distinct functions: a dorsal-cognitive division and a rostral-ventral affective division. Recent evidence, however, does not support this traditional differentiation but indicates that both subdivisions of the anterior cingulate make important contributions to emotional processing.

Aim of the study

The project consisted on performing an analysis of the cerebral activity (mainly in the gamma band: 30Hz-140 Hz) during a protocol of alternating tasks which necessitated the taking of simple decisions, either within an emotionally neutral and within an emotionally negative context, with the aim

- (i) to compare the performance in an emotionally-negative condition with the performance in an emotionally-neutral condition,
- (ii) to search the electrophysiological responses of the cerebral areas implanted, implicated in the cognitive and in the emotional control in the different conditions,
- (iii) to compare the frequency modulations of the different subregions of the cingulate cortex implanted in the different conditions.

Patients and methods

The study was realized with 6 adult patients (female/male: 3/3) undergoing invasive presurgical evaluation for epilepsy surgery by stereo-electroencephalography (SEEG) in the Claudio Munari Epilepsy Surgery Center, Niguarda Hospital. Monopolar SEEG data were converted to the format of the software Elpho-SEEG developed in LabView, in the Besta Institute. A total of 1365 contacts were analysed. Contacts exploring lesional areas and those showing ictal paroxysmic abnormalities were excluded. Frequency changes between the range 1-150 Hz were included in the study.

Results

Behavioural results

For patient 3, reaction time (R-T) was not associated with the emotional content of the pictures but rather with the complexity of the Raven matrices; furthermore the mean reaction time, as well as the total number of erroneous responses, progressively decreased from the first to the last task, indicating learning mechanisms/adaptability, independently of the emotional valence of the associated pictures. This finding could be due either to the low arousal per se of the negative

images and to the fact that it is difficult to induce highly disturbing emotions in a "non-ecological" condition in the lab.

Patients 1 and 2 exhibited either slower R-T or more errors in during the accomplishment of the Raven task of the condition (base-condition) that followed the negative one.

Finally, 3 patients did more errors and showed a faster (patient 4) or slower (patients 5, 6) reaction time in the Raven task of the negative condition compared to the other two ones. Interestingly, patient 4 spontaneously reported that his bad performance was strictly related to the negative-pictures distracters, while patient 5 reported that the negative pictures had very high (negative) valence and arousal, with some pictures provoking to her nausea/vomit and extreme sadness, so a huge effort was required in order to stay on to the task.

Frequency modifications

Analysis of frequency modulations during the exposure (3sec) to the negative images compared with the affectively neutral conditions, showed a power increase in the anterior aspect of midcingulate cortex, the pregenual aspect of anterior cingulate cortex, the short gyri of insula, the supplementary motor area, the frontal antero-mesial cortex as well as the temporal pole.

With regard to the cingulate subdivisions, exposure to negative pictures compared with exposure to both neutral images and fixation cross induced an activation of the aMCC, mainly around 70 Hz. When focusing exclusively on the 3 subjects who exhibited a worst performance - more errors committed along with longer or faster Reaction-Time - during the Raven trial in the negative condition, (a) there was an activation of the pregenual aspect of anterior cingulate cortex and the anterior aspect of midcingulate cortex during the exposure to the negative images comparing with the exposure to both the neutral pictures and the fixation cross; (b) there was an activation of the posterior aspect of midcingulate cortex and a deactivation of anterior cingulate cortex during the accomplishment of the Raven trial in the negative condition compared with its accomplishment respectively in the neutral and in the base condition.

Interestingly, only the short gyri of insula (anterior insular cortex), but not the long gyri, were activated during the exposure to the negative pictures.

Furthermore, in bilateral implantations, the homologous cortical regions of both cerebral hemispheres were activated and deactivated strictly within the same frequency range.

Our results are in line with the existing human imaging studies focusing on empathy for other's aversive events that have highlighted the role of cingulate cortex and insula, structures involved in the direct pain experience. Furthermore, we provide evidence that dorsal cingulate cortex codes emotional processing. Moreover, our results support the suggestion that "second-hand" experience of pain follows only an anterior activation pattern of the insular cortex.

INDEX

| | |
|---|-------------|
| Setting the scene | pag. 6-7 |
| Introduction | pag. 8-20 |
| - Emotion | pag. 8-11 |
| - Emotion-cognition interaction | pag. 11-20 |
| Cingulate cortex | pag. 21-28 |
| StereoEEG | pag. 29-35 |
| Intracranial EEG and human cognition | pag. 36-42 |
| Aim of the study | pag. 43 |
| Patients | pag. 44-50 |
| Methods | pag. 51-59 |
| Results | pag. 60-78 |
| - Behavioural results | pag. 60 |
| - Frequency analysis results | pag. 61-72 |
| - Summary of frequency analysis results | pag. 73-74 |
| - Further results | pag. 75-78 |
| Discussion | pag. 79-96 |
| Conclusion | pag. 97 |
| References | pag. 98-115 |

“The question is not whether intelligent machines can have any emotions, but whether machines can be intelligent without any emotions”

(Minsky M, *The society of mind*, 1986)

The feeling of what happens

The mind itself is unconscious, but we perceive it consciously by looking inwards. It is this capacity for looking inwards (for introspection or self-awareness) that is the most essential property of mind.

The elementary background state of consciousness represents “you”, the most basic embodiment of “your self”: “this is me, I am this body, and right now I feel like this”. This aspect of consciousness, therefore, not only represents your self, it also tells you how you are doing.

Thus, the function of consciousness is not only intrinsically introspective, it is also intrinsically evaluative; it imparts value, it tells us whether something is good or bad, and it does that by making things feel good or bad. Consciousness is not only what you feel, it is what you feel about something.

Damasio therefore concluded that consciousness consists of more than mere awareness of our inner states; rather it consists of fluctuating couplings of the current state of the self with the current state of the object world. Each unit of consciousness forges a link between the self and the objects. These momentary units of conscious time are probably generated by the rhythmical oscillations, for instance the 40 Hz oscillations that characterize visual awareness. This is how we generate “the feeling of what happens” that provided the title of Damasio’s book.

(Damasio A, *The feeling of what happens*, 1999;

Solms M and Turnbull O, *The brain and the inner world*, 2002)

The archaeology of mind

At its lower levels of organization (at the level of core consciousness) the primal self (to use Panksepp’s terminology) is a brainstem structure; it is essentially the inner source of awareness that is the source of the experience of being alive. But it is mistake to think of this source of consciousness in purely sensory terms. Although it is true that the inner surface of core consciousness perceives the current state of the body, it is nevertheless fundamentally a motor system. There are two reasons for this: first, the fundamental purpose of consciousness is the perception of emotion; second, the sole purpose of perception is the guidance of action. This is to say that the self guides action on the basis of evaluation.

At the level of the organization of the basic-emotion command systems, such evaluations have an obligatory outcome: they trigger stereotyped motor programs (reflexes and instinctual behaviors). In this level of core consciousness there are four basic-emotion command systems - they represent the connections that link certain feeling states with certain classes of perception -: the Seeking (and associated pleasure-lust) system, the Rage (or anger-rage) system, the Fear (or fear-anxiety) system and the Panic (or separation-distress) system. These systems, when activated, trigger “pre-prepared” motor programs.

At this primitive level of organization the self, therefore, is still essentially a passive mechanism, it lacks choice, free-will. From the neuroscientific point of view, ironically perhaps, the essence of free-will appears to be the capacity of inhibition, the capacity to choose not to do something. What distinguishes human beings more than anything else from their nearest primate relatives is the development of a higher level self system which is organized fundamentally in inhibitory mechanisms, which have their physical locus in the prefrontal lobes.

[\(Panksepp J, The archaeology of mind, 2012\)](#)

Coming to feel as another person feels

Throughout our lives there is virtually no moment in which we don't feel. Our feeling, though, goes further than our personal experience and observation. The feelings of the people that surround us are contagious. Introspectively, this emotional contagion appears to occur outside the sphere of rational thinking. People tend to automatically mimic the facial expressions, vocal expressions, postures and behaviors of those around them and thereby to feel a pale reflection of others' emotions as a consequence of such feedback.

To understand the actions of other individuals we need to map them onto our own body's motor programs. To understand their emotions, we need to map them onto our own visceral feelings. It turns out that as we observe the behavior of other individuals our brain appears to share a rich mosaic of neural activity with the observed individual, including representations of his bodily actions, feelings, facial expressions. Shared circuits become spontaneously activated while we witness what other people experience.

[\(Keysers C, The empathic brain, 2011\)](#)

Neurons that fire together, wire together - and wire people together, one might add. The brain has to connect visual, auditory, somatosensory and premotor areas together because the brain has to plan actions based on what it sees, hears and feels.

Empathy is then the inevitable consequence of Hebbian plasticity in these connections.

INTRODUCTION

The functioning of the human mind has often been characterised as a battle between opposing forces: reason, rational and deliberate, versus emotion, impulsive and irrational. This way of thinking can be traced back to Plato, who described the human soul as divided into emotion (what we feel), cognition (what we know) and motivation (what we want), and has been further developed by philosophers such as René Descartes (*Les passions de l'âme*) and David Hume (*A treatise of Human Nature*).

Emotion

“What is an emotion?” is not only the title of one of the most widely cited articles on emotion (James, 1884) but it is also a current conceptual question on emotion research that seems to correspond to a never ending attempt to define emotion (Frijda, 2007; Kleinginna and Kleinginna, 1981; Russell and Barrett, 1999; Scherer, 2005).

For instance, let us consider the definitions offered by two of the most influential scholars of current research on the emotional brain, Damasio and LeDoux. LeDoux (1994, p 291) highlighted the fact that emotions cannot be unconscious when stating that “in my view, emotions are affectively charged, subjectively experienced states of awareness. Emotions in other words are conscious states”. According to Damasio (1998, p 84) “the term emotion should be rightfully used to designate a collection of responses triggered from parts of the brain to the body, and from parts of the brain to other parts of the brain, using both neural and humoral routes”. Therefore Damasio certainly does not exclude the possibility that what he calls an emotion can be unconscious. Distinguishing between emotion and feeling, Damasio (1998, p 84) also stated that “the term feeling should be used to describe the complex mental state that results from the emotional state”. It is likely that such a mental state is conceptually closer to what Ledoux called an emotion, although Damasio called it a feeling rather an emotion.

Moreover, Brehm (1999) argued that emotion can be reduced to motivational states. Motivation is typically considered as being related to emotion and as its constituent is often considered as being expressed in action tendencies (e.g. approach or avoidance) that indeed motivate a change in the relation between the individual and the event (Frijda, 1986); however most authors agree on the need to distinguish between the two constructs (Frijda, 2007).

Is there a minimal consensus for a definition of emotion? A review of recent major models of emotion indicates that there is indeed consensus on four key criteria: (a) emotions are multicomponent phenomena (the major theories acknowledge the existence of five components:

appraisal, expression, autonomic reaction, action tendency and feeling); (b) emotions are two-step processes involving emotion elicitation mechanisms that produce emotional responses; (c) emotions have relevant objects; (d) emotions have a brief duration in contrast to other affective phenomena (e.g. moods, preferences, dispositions, affective styles).

Indeed, it seems existing a consensus in defining the emotion as an event-focused, two-step, fast process consisting of relevance-based emotion-elicitation mechanisms that shape a multiple emotional response (i.e. action tendency, autonomic reaction, expression and feeling)

([The Cambridge Handbook of Human Affective Neuroscience, section I](#)).

Therefore, emotion is crucial for orchestrating a wide range of physiological reactions that allow the organism to adjust to the environment. A modulation of action tendencies, and of the current focus of thoughts, is a defining component of many, if not most, emotions.

Thus, an experience of emotion is a state of mind the content of which is at once affective (pleasant or unpleasant) and conceptual (a representation of the individual relation to the surrounding world) ([Barrett et al, 2007](#)).

Primary emotions (basic, innate, pre-organized) (anger, disgust, fear, joy, sadness, surprise) depend on limbic system circuitry, the amygdala and the anterior cingulate cortex being the prime players. Secondary emotions (e.g. shame, gratitude, guilt, etc) occur once we begin experiencing feelings and forming systematic connections between categories of objects and situations, on one hand, and primary emotions, on the other. Structures in the limbic system are not sufficient to support the process of secondary emotions; the network must be broadened and it requires the agency of prefrontal and of somatosensory cortices.

Traditional studies on the neural mechanism of emotion adopted a locationist approach, which asserted that each basic emotion faculty has its own specialized neural circuitry that is architecturally distinct, inborn and shared with other animals ([Panksepp, 2004](#)). Early neuroimaging results were indeed congruent with this assumption, for example amygdala for fear ([Adolphs et al, 1995](#)), insula for disgust ([Wicker et al, 2003](#)), orbitofrontal cortex for anger and subgenual anterior cingulate cortex for sadness ([Murphy et al, 2003](#)).

However, several recent meta-analyses and reviews favored the constructionist approach, which suggests that a set of interacting brain regions involved in the basic psychological operations of both emotional and non-emotional processing are activated during emotion experience and perception ([Lindquist and Barrett, 2012](#); [Lindquist et al., 2012](#)). Yet co-activation of different brain regions does not necessarily mean connectivity between them, so the brain connectivity results would be critical for examining this approach.

Emotion is also an interpersonal communication system that elicits response from others (Decety, 2010). Thus, emotions can be viewed both as intrapersonal and interpersonal states; the construct of empathy entails both such dimensions.

Empathy can be defined as the process to generate an isomorphic affective state in the self to understand another individual's emotional state or condition while realizing that it is the other who causes this affective state (Decety and Svetlova, 2012; Engen and Singer, 2012).

Empathy is a major emotion in terms of pro-social cooperation and formation of bonding between persons. Indeed, emotion plays a crucial role in human social cognition. Perceiving and interpreting other people's emotion status is one of the most important steps during social interaction.

According to Decety (2010), human empathy is constituted by three macrocomponents: affective arousal, emotion understanding and emotion regulation.

The essential neural components of affective arousal are amygdala, hypothalamus, hippocampus and orbitofrontal cortex (OFC), the amygdala and OFC with reciprocal connection with the superior temporal sulcus (STS) underlying rapid and prioritized processing of the emotion signal. Emotion understanding develops later, and begins to be really mature around the age of 2–3 years; this component largely overlaps with theory-of-mind-like processing and draws on the ventromedial (vm) and medial (m) prefrontal cortex (PFC). Emotion regulation enables the control of emotion, affect, drive and motivation; this component develops throughout childhood and adolescence, and parallels the maturation of execution functions. The dorsolateral PFC, the anterior cingulate cortex (ACC) and the vmPFC, via their reciprocal connections with the amygdala and widespread cortical areas including the STS, play a primary role in self-regulation. This model supports the influential hypothesis of “shared-networks”, which states that empathic experiences are subserved by activation of the same neural networks which are activated in the first-person experience of an affective state (Decety J, *The social neuroscience of empathy*, 2009). Viewing facial expressions, for instance, activates the shared circuit for the observation and execution of facial expressions, in which three main regions are involved: the temporal cortex, which provides a visual description of the observed facial expressions, the premotor cortex which is part of the cold-motor, higher order cognitive control system, and the cingulate cortex that is part of the hot-motor, affective, emotional system (*see appendix, p. 18*). The activation of the hot-motor control system in the midline of the brain is stronger for emotional facial expressions compared to the observation of movements of the face that carry no emotional content. The brain appears to simulate the movements of the face through the cold-motor system, whether the

movement is emotional or not. If the facial expression signals a bodily emotion such as disgust or pleasure, information is exchanged between the premotor cortex and the insula triggering a representation of similar visceral feelings. We now not only feel what the face is doing but also what the person is feeling inside and we share this pleasure or disgust. Premotor areas mirror the actions of other people and may enable us to perceive other individuals' goals and motivations from their perspective. The insula, on the other hand, mirrors the visceral state of other people and may enable us to share their emotions. Given that the insula also receives direct input from visual areas, two routes may converge toward emotional contagion. One directly triggers the representations of feelings based on the sight of the emotional facial expression and one does so indirectly by first translating the visual description into a motor representation in the hot and cold motor system and then triggering the representation of corresponding feelings through connections between these motor systems and the insula ([Keysers C, The empathic brain, 2011](#)). Indeed, when an empathic person says "I feel for you", this is actually the case in neurological terms.

Emotion - cognition interaction

"Brains can have many interesting steps in the circuits mediating stimulus and response, and still have no mind, if they do not meet an essential condition: the ability to display images internally and to order those images in a process called thought"

([Damasio A, Descartes'error, 1999](#)).

A classical dichotomy between cognition and emotion equated the first with rationality or logic and the second with irrational behaviors. The idea that cognition and emotion are separable, antagonistic forces competing for dominance of mind has been hard to displace despite abundant evidence to the contrary. For instance, it is now known that a pathological absence of emotion leads to profound impairment of decision making. Behavioral observations of this kind are corroborated at the mechanistic level: physiological studies and network simulations suggest that top-down signals from prefrontal cortex realize cognitive control, in part by either suppressing or promoting emotional responses controlled by the amygdala, in a way that facilitates adaptation to changing task demands ([Barbas, 2013](#)). Behavioral, anatomical, and physiological data suggest that emotion and cognition are equal partners in enabling a continuum or matrix of flexible behaviors that are subserved by multiple brain regions acting in concert ([Barbas, 2013](#)).

Furthermore, emotions have been described as states elicited by reinforcers, and are thought to have evolved as an efficient means of influencing behaviour ([Rolls, Emotion explained, 2005](#)). It

makes sense, therefore, that the neural regions involved in modulating what we do (decision making) share remarkable overlap with those involved in modulating how we feel (emotion regulation) (Mitchell et al, 2011). Indeed, the brain regions that are associated with intact decision-making are sensitive to stress-induced changes.

Meta-analyses that summarize the neuroimaging literature on mental categories such as emotion, the self, memory, etc. confirm that brain regions show little psychological specificity and a combination of large-scale distributed networks contribute to emotions, thoughts, and body feelings, although these mental states differ in the relative contribution of those networks (*see following figure and table 1*).

Conjunction for body feelings, emotions and thoughts

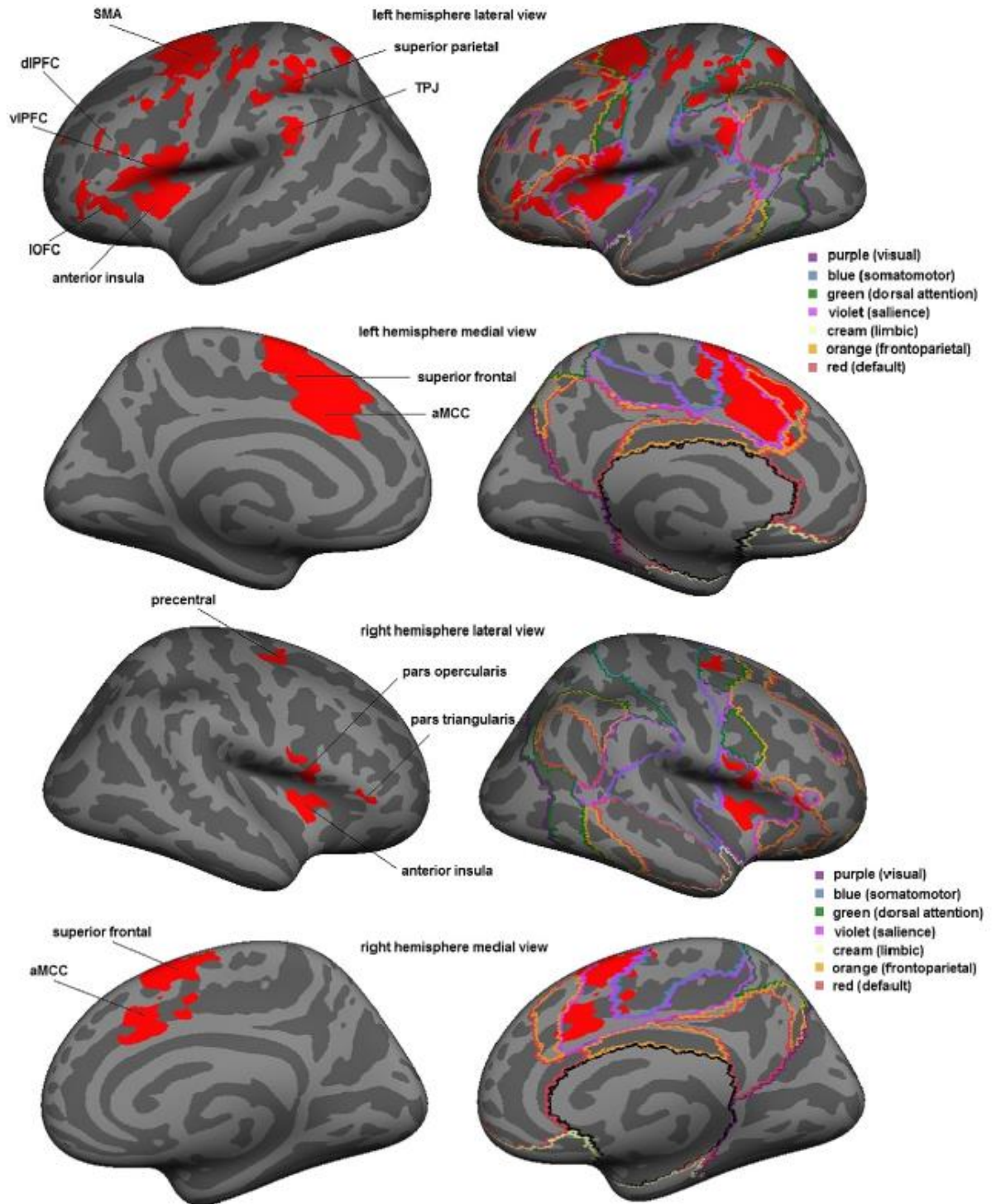


Table 1
Overview of seven networks of interest.

| Network | Brain regions | Task domains | Psychological description and hypotheses |
|---|---|--|---|
| "limbic network" (Yeo et al., 2011) | bilateral anterior temporal lobe, medial temporal lobe, subgenual anterior cingulate cortex, medial and lateral orbitofrontal cortex (although Yeo et al.'s network only covers the cortex, we also hypothesize that the basal ganglia including the caudate, putamen, globus pallidus and central nucleus of the amygdala will be a part of this network). | <ul style="list-style-type: none"> emotion and affect (Lindquist et al., in press; Andrews-Hanna et al., 2010) autobiographical memory (Spreng & Grady, 2010) | <p>core affect generation: engaging visceromotor control of the body to create core affective feelings of pleasure or displeasure with some degree of arousal.</p> <p>Hypothesis: Body feeling and Emotion > Thought</p> |
| "salience network" (Seeley et al., 2007) or "ventral attention network" (Yeo et al., 2011; Corbetta & Shulman, 2002) or "cingulo-opercular network" (Vincent et al., 2008) | bilateral anterior midcingulate cortex (aMCC), anterior insula (AI) and mid-insula, frontal operculum, and parts of the pars opercularis and temporoparietal junction | <ul style="list-style-type: none"> cognitive control (Cole & Schneider, 2007) stimulus-driven control of attention (Corbetta & Shulman, 2002) set maintenance (Dosenbach et al., 2006) maintaining sub-goals (Fincham et al., 2002) anxiety (Seeley et al., 2007) representation of the body (Craig, 2009) pain (Lamm et al., 2010) | <p>body-directed attention: using representations from the body to guide attention and behavior. This ingredient might use changes in the homeostatic state of the body to signal salient events in the environment and regulate behavioral responses.</p> <p>Hypothesis: Body feeling and Emotion > Thought</p> |
| "default network" (Dosenbach et al., 2008; Vincent et al., 2008; Yeo et al., 2011) | medial prefrontal cortex, parts of the pars triangularis, retrosplenial area, posterior cingulate cortex/precuneus, medial temporal lobe (hippocampus, entorhinal cortex), bilateral superior temporal sulcus, parts of the anterior temporal lobe (ATL), and angular gyrus | <ul style="list-style-type: none"> autobiographical memory (Spreng & Grady, 2010) prospection (Spreng & Grady, 2010) theory of mind (Spreng & Grady, 2010) moral reasoning (Greene et al., 2001) context-sensitive visual perception (Bar, 2004) spontaneous thought (Andrews-Hanna et al., 2010) emotion (Lindquist et al., in press; Andrews-Hanna et al., 2010) semantics, phonology, sentence processing (Binder et al., 2009) | <p>conceptualization: representing prior experiences (i.e., memory or category knowledge) to make meaning of sensations from the body and the world in the moment.</p> <p>Hypothesis: Thought and Emotion > Body feeling</p> |
| "frontoparietal network" (Dosenbach et al., 2008; Vincent et al., 2008; Yeo et al., 2011) or "executive control network" (Seeley et al., 2007) | bilateral dorsolateral prefrontal cortex (dlPFC), inferior parietal lobe, inferior parietal sulcus, and aspects of the middle cingulate cortex (mCC) | <ul style="list-style-type: none"> task-switching (Crone et al., 2006) alerting to a stimulus after a cue (Fan et al., 2005) planning (Fincham et al., 2002) rule-specific processing (Sakai & Passingham, 2006) working memory (Sakai & Passingham, 2003) | <p>executive attention: modulating activity in other ingredients to create a unified conscious field during the construction of a mental state (e.g., selecting some conceptual content when meaning is made of sensations and inhibiting other content; selecting some sensations for conscious awareness and inhibiting others).</p> <p>No specific hypothesis formulated</p> |
| "dorsal attention network" (Corbetta & Shulman, 2002; Yeo et al., 2011) | bilateral frontal eye fields, dorsal posterior parietal cortex, fusiform gyrus, area MT+ | <ul style="list-style-type: none"> top-down control of visuospatial attention (Corbetta et al., 2002) | <p>visuospatial attention: modulating activity in an ingredient for processing visual content in particular (e.g., selecting which visual sensation is selected for conscious awareness and inhibiting others).</p> <p>No specific hypothesis formulated</p> |
| "somatomotor network" (Yeo et al., 2011) | precentral and postcentral gyri (sensorimotor cortex), Heschl's gyrus (primary auditory cortex) cortex, posterior insula | <ul style="list-style-type: none"> audition (Morosan et al., 2001) somato-visceral sensation (Eickhoff et al., 2006) | <p>exteroceptive sensory perception: representing auditory and tactile sensations</p> <p>No specific hypothesis formulated</p> |
| "visual network" (Yeo et al., 2011) | occipital lobe | <ul style="list-style-type: none"> vision (Engel et al., 1994) | <p>exteroceptive sensory perception: representing visual sensations</p> <p>No specific hypothesis formulated</p> |

Taken from *States of mind: Emotions, body feelings, and thoughts share distributed neural networks*
Oosterwijk et al *NeuroImage*, 62, 2110–2128, 2012.

- The default mode network (DMN), mainly comprised of the posterior cingulate cortex, precuneus, medial prefrontal cortex and bilateral inferior parietal lobe, was first defined by Raichle and colleagues based on the observation that this set of brain regions showed higher energy consumption during the resting-state compared with when performing tasks (Raichle et al, 2001). The regions in this network are usually deactivated during task execution (Laird et al, 2009; Shulman et al, 1997), and their activities are anti-correlated with task positive regions during the resting-state (Fox et al, 2005). This network is thought to be necessary for constructing a situated conceptualization that creates a body state, emotion or thought (Oosterwijk et al, 2012). The hypothesis that the DMN supports conceptualization is consistent with the role of the DMN in mental state attribution (Mitchell et al, 2005), emotion experience (Lindquist et al, 2012), recollection of the autobiographical past (Addis et al, 2007; Spreng and Grady, 2010), spontaneous thought (Andrews-Hanna et al, 2010) and semantic and conceptual processing (Binder et al, 2009; Visser et al, 2010). In fact, what unites these disparate domains is the process of conceptualization – in which representations of prior experiences are brought to construct representations of the past, the future, or the present moment (Oosterwijk et al, 2012). The default mode regions are necessary to give meaning to others' actions, to make meaning of one's own core affective state, to recall prior experiences during instances of memory and spontaneous thought, and to represent the meaning of concepts by simulating category instances (Lindquist et al, 2012).

- The salience network generally comprises of the bilateral anterior insula and the anterior cingulate cortex, and was first distinguished from other task-positive networks by Seeley and colleagues (Seeley et al, 2007). The salience network is involved in bottom-up detection of salience events and plays a key role in switching between large scale networks to facilitate the access of resources from attention and working memory (Menon and Uddin, 2010). In any situation where people are presented with evocative or behaviorally relevant information, the salience network will guide the direction of attention based on body sensations, irrespective of whether people are directed to experience an emotion or objectively think about the situation.

- The somatomotor network activity, in the study of Di et al (2015) on resting state networks, was positively covaried with the functional connectivity between the motor network regions, in line with studies showing that performing of a motor task is accompanied by both the activations of the motor areas and increase in functional connectivity between them (Zhuang et al, 2005). The authors underlined that the functional connectivity decreased between regions from different brain systems when the motor network activity increased, especially between the DMN and the fronto-parietal regions and between the DMN and the visuomotor regions.

- The frontoparietal network plays an executive role by modulating activity in other functional networks (e.g. prioritizing some information and inhibiting other information) to help construct an instance of a mental state (Oosterwijk et al, 2012). Brain areas within this network tend to have increased activity during “top-down control” of attention (Corbetta and Shulman, 2002), as in memory maintenance (Cole and Schneider, 2007), rule representation (Crone et al, 2006) and planning (Fincham et al, 2002). Oosterwijk et al (2012) found common involvement of an aspect of the frontoparietal network across body states, emotions and thoughts, suggesting that all these mental states involve executive attention; the authors argued that activity within this network may reflect the cognitive control needed to instantiate the processes of conceptualizing the core affect (=the basic psychological element; Russell, 2003).
- The dorsal attention network plays a similar role with the frontoparietal network by directing attention, in particular, to visual information, while the visual network processes exteroceptive visual sensations.
- The limbic network supports the brain's ability to generate and/or represent somatovisceral changes that are experienced in the core affect that is common to every mental state (Oosterwijk et al, 2012) - many philosophers and psychologists have proposed that every moment of mental life has some affective aspect (Wundt, 1897, 1998) that can be described as a combination of hedonic pleasure and displeasure with some degree of arousal (Russell and Barrett, 1999; Barrett and Bliss-Moreau, 2009).
- Finally, a recent work (Amft et al, 2015) using meta-analytic connectivity modeling (MACM) identified a robust network, partially overlapping with the default mode network, formed by regions associated with social and affective processing. The identified regions are thus considered to form the “extended” social-affective default (e-SAD) network. The respective regions are located in the anterior cingulate cortex, posterior cingulate cortex/precuneus, dorsomedial prefrontal cortex (dmPFC), bilateral temporo-parietal junction, bilateral ventral basal ganglia, left anterior middle temporal sulcus/gyrus, bilateral amygdala/hippocampus and ventromedial prefrontal cortex (vmPFC). These findings are in line with an activation likelihood estimation (ALE) meta-analysis performed by Schilbach et al (2012) that provided evidence for a shared neural network that underlies emotional processing, social and unconstrained cognition, which localizes to the anterior medial prefrontal cortex and precuneus. The authors argued that a ‘common denominator’ may exist in cognitive terms, which could consist in introspective processes; by making use of these, we may become aware of our own or others’ states, equally relevant for social cognition, emotional processing and unconstrained thought (Schilbach et al, 2008).

In summary, recent theoretical views propose that affective and cognitive mechanisms are processed in shared underlying neurocircuitry, with emotion and cognition highly interacting by accessing identical brain regions in broadly overlapping neural networks to guide behavior (Duncan and Barrett, 2007; Pessoa, 2008, 2010; Banich et al, 2009; Pessoa and Adolphs, 2010; Shackman et al, 2011). However, the precise nature of this integration and its underlying neuroanatomy are still unclear.

An influential conceptualization of how emotions affect decision making is Damasio's somatic marker hypothesis (SMH; Damasio, 1994, 1996). The SMH proposes that signals from the body help to regulate decision-making in situations of complexity and uncertainty. During decision-making, somatic signals (e.g. heart rate, skin conductance, tonic), the so-called somatic markers, arise from the periphery or the representation of the periphery and indicate an emotional reaction to the response option. Accordingly, for each response option a somatic state is generated and stored in memory. The SMH proposes that the somatic markers are represented and regulated in the emotion circuitry of the brain. When a particular situation arises that is similar to a previously experienced situation, information regarding the possible response options and their likely outcomes is reactivated. This information is associated with the somatic responses to the given situation and assists decisions by encouraging the rejection of disadvantageous choices and endorsement of advantageous ones. According to the SMH, the reactivation of the somatic responses is evoked on two different pathways. First, these somatic responses can actually be elicited and projected to the somatosensory cortex (making up the so-called "body loop"). Second, the representation of the somatic-affective response can be directly activated in somatosensory brain regions without eliciting peripheral bodily responses (the so-called "as-if body loop").

Emotion has not only transient effects on cognitive processing, by influencing initial perceptual processes and attention paid to emotional stimuli or to details surrounding emotional events, but also long-lasting effects, which will eventually lead to better memory for those events. Emotional information also impacts other higher level processes, such as working memory and decision making, which are essential to goal-directed behaviour.

Emerging evidence concerning the impact of emotion on working memory and the associated neural correlates comes from studies in which emotional stimuli are presented as task-irrelevant distractors (Denkova et al, 2010; Dolcos et al, 2008; Dolcos and McCarthy, 2006).

Distraction challenges our ability to maintain focus on goal-relevant information and thus may impair cognitive performance. The existence of neural mechanisms that allow for privileged access of emotional information to processing resources raises the possibility that emotional information

may also be a very potent distraction, particularly when task-irrelevant. The outcome of task-irrelevant emotional distraction depends on dynamic interactions between neural systems that allow the ability to stay focused on task-relevant information and systems involved in the processing of emotional information that may compete with the available processing resources. Possibly as a result of their salience, emotional distractors may produce a bottom-up impact on processing of goal-relevant information by reallocating processing resources (Vuilleumier et al, 2001) and impairing performance.

In fact, according to the “salience hypothesis,” modulation of attentional processes may also depend on emotional salience of task-irrelevant stimuli. For example, previous studies have indicated that negative, relative to neutral, emotional stimuli are associated with impairment of accuracy and slower of reaction time (RT) during goal-directed attentional control processes (Vuilleumier et al, 2001; Blair et al, 2007). In more detail, slowing of cognitive processes takes place when negative emotional stimuli anticipate goal-directed behavior requiring a low level of attentional control. However the disadvantageous outcomes of this bottom-up impact of emotional distraction can be mitigated by “top-down” interventions from cognitive control regions, which are engaged to regulate emotional responses and cope with emotional distraction (Dolcos et al, 2006; Pessoa, 2008).

On the other hand, some studies have reported facilitation of attentional processes during emotional interference. In a recent meta-analysis (Cromheeke et al, 2014), where the discrepant findings on the influence of affective processing on cognitive control were synthesized, four main findings emerged: (i) several brain regions at both the cortical (e.g. inferior frontal gyrus, dorsolateral prefrontal cortex, inferior parietal lobule, subgenual anterior cingulate cortex) and subcortical level (anterior insula, putamen, and amygdala) consistently responded to an emotional challenge within a cognitive control setting; (ii) two regions were consistently involved in the integration of emotion and cognition, namely bilateral subgenual anterior cingulate cortex and precuneus; (iii) tasks where emotional stimuli served as distractors yielded increased activation in dorsolateral prefrontal cortex and parietal cortex when compared with tasks where emotion was relevant for the task at hand; (iv) behavioral performance patterns were associated with both similar and distinct regions; although the activity in the superior frontal gyrus was increased irrespective of performance, clusters in ‘emotional’ regions (e.g., amygdala, subgenual anterior cingulate cortex) were only found if performance was impaired, however, the direct contrast between improved and impaired performance did not reveal any significant regions.

The following table lists some of the cognitive phenomena that have shown affective influences (taken from Clore and Huntsinger, 2007).

A sample of the cognitive phenomena influenced by affect^a

| Cognitive phenomenon | Influence |
|------------------------------|---|
| Semantic priming | Participants in positive moods are more likely than those in negative moods to activate semantically related concepts (e.g. doctor–nurse) from memory |
| Global superiority effect | The general tendency to process incoming information in a global manner is empowered by positive mood and inhibited by negative mood |
| Heuristic processing | People in positive moods are more likely than those in negative moods to use judgment heuristics. In a persuasion context, for example, participants in positive moods are equally persuaded by strong and weak appeals, whereas those in negative moods are persuaded more by strong appeals |
| False memories | When presented with a list of words (e.g. bed, rest) that implies a non-presented critical lure (e.g. sleep), participants in positive moods are more likely than those in negative moods to recall incorrectly having seen the critical lure (show false memories). |
| Schema-guided memory | When presented with a situation that activates a schema (e.g. eating out at a restaurant), people in positive moods are more likely than those in negative moods to use the schema to fill in the blanks when recalling details of the situation (e.g. ordering dessert) |
| Retrieval-induced forgetting | Retrieval-induced forgetting occurs when rehearsal of a subset of previously observed material inhibits memory for non-rehearsed material; research indicates that this tendency is empowered by positive moods and inhibited by negative moods |
| Stereotyping | Participants in positive moods tend to rely more on stereotypes to guide their thinking about members of various social groups than do those in negative moods, who tend to rely on individuating information |

Understanding the mechanisms by which cognition, to its turn, affects emotion is the focus of a recently emerging field that investigates the neural underpinnings of cognitive control of emotion. Emotion regulation is, in fact, an important coping mechanism in the face of emotional stressors. Because emotion regulation strategies have a substantial impact on one's emotional experience, leading to different behavioural, cognitive and neural results (Gross, 2008), they are an important part of emotion-cognition interactions.

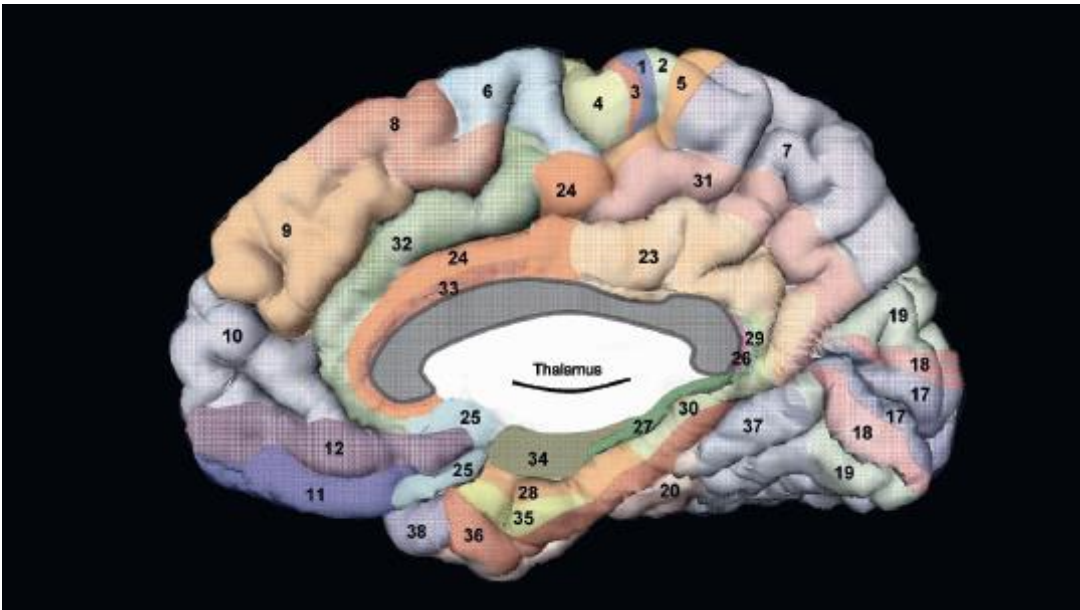
Non conscious emotion regulation is an important part of our behaviour that, similar to conscious forms of emotional control, undergoes ontogenetic transformations. Although emotions are displayed very early in ontogeny, the ability to control them is not fully developed in early childhood and adolescence (Dolcos et al, 2011). An important aspect related to the impact of cognition on emotion processing is the capacity to deploy cognitive control in order to resist momentary emotional distraction and, on a long run, the ability to cope with longer lasting emotions and feelings. Emotional stimuli benefit from enhanced processing due to their ability to "capture attention" and reallocate processing resources. A series of investigations (Denkova et al, 2010; Dolcos et al, 2008) provided evidence that coping with task-irrelevant emotional distraction entails increased activity in and interactions between brain regions involved in basic emotion processing (e.g. the amygdala) and brain regions associated with cognitive control (particularly lateral and medial prefrontal cortex). In a study by Mitchell et al (2008), amygdala activity was positively correlated with activity in anterior cingulate gyrus, posterior cingulate, and middle temporal cortex, while it was negatively correlated with activity in dorsolateral and dorsomedial prefrontal regions (superior frontal gyrus, middle frontal gyrus) and parietal regions, when

emotional distracters (positive and negative IAPS pictures - International Affective Pictures System) interfered with a cognitive task (a shape identification task).

The ability to voluntarily modulate responses to emotional information through the use of cognitive strategies, e.g., through shifting attention away from irrelevant or unwanted emotional material, is indeed a crucial part of cognitive emotion regulation ([Ochsner and Gross, 2005](#); [Schweizer et al, 2013](#)). This ability seems to be impaired in stress-related psychiatric disorders such as borderline personality disorder (BPD) and (complex) post traumatic stress disorder (PTSD).

Appendix

The brain areas that control the voluntary movement of the face are different from those that cause the emotional generation of facial expressions. The premotor cortex and primary motor cortex are part of the voluntary “cold” motor system: to fake a smile without generating the emotion we utilize these two cortical areas. The “cold” system also controls the facial motor program for masticating, blowing the nose, articulating, etc. In parallel to this system, regions around the cingulate sulcus produce involuntary emotional behaviour: the wrinkling of the nose when smelling something awful, the contraction of the face when feeling pain, the laughter when hearing something funny. The fact that the “hot” and “cold” motor programs are stored in separate cortical locations means that we can not willingly activate the emotional smile motor system ([Keysers C, The empathic brain, 2011](#)).



For most of the past century the cingulate cortex was viewed as a uniform functional entity. Broca (1878) defined the cingulate gyri as belonging to the limbic lobe, while Papez (1937) and McLean (1954, 1990) viewed cingulate cortex as a single functional entity and emphasized its role in emotion. Brodmann (1909), Vogt (1919), Rose (1927) and von Economo (1929) showed that as many as 40 cytologically unique areas comprised the cingulate gyrus, while functional studies proposed a single overarching function throughout most of the past century.

It is generally agreed that Brodmann established the dual model of the cingulate gyrus with anterior and posterior divisions, while in the early 1970s a dual model of cingulated function was introduced: anterior cingulate cortex (ACC) was differentiated from posterior cingulate cortex (PCC) on the basis of cytoarchitecture and patterns of projections, as well as distinct functional properties. This view proposed that ACC is involved in executive functions while PCC is involved in evaluative processes, but the past two decades of research have shown that this view of cingulate cortex is seriously at odds with neurobiological observations and needs substantial revision.

Indeed, with the advent of more precise methods for studying anatomical connectivity, cytoarchitecture and function, it becomes now clear that cingulate cortex encompasses numerous specialized subdivisions that subserves a vast array of cognitive, emotional, motor, nociceptive and visuospatial functions.

Anterior Cingulate Cortex (ACC)

Among prefrontal cortices it has the strongest connections with the rest of the prefrontal cortex, and is well suited to allocate attentional resources, as is widely reported ([Medalla and Barbas, 2009](#),

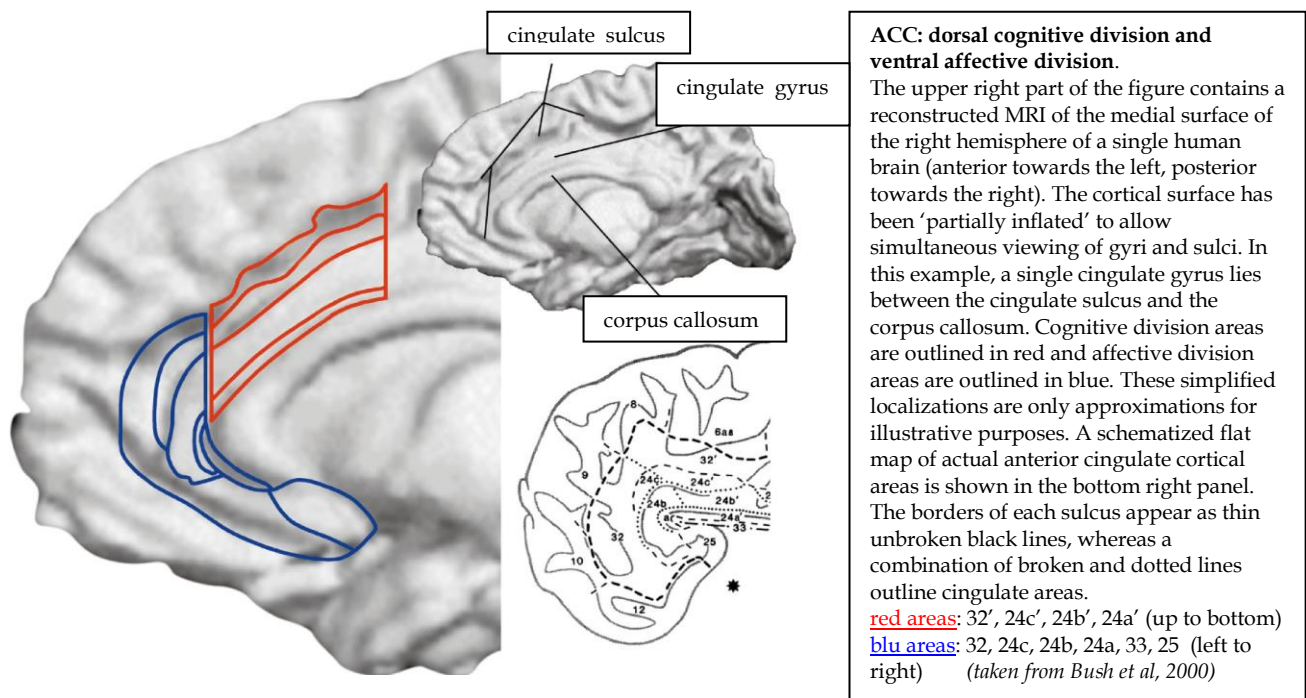
2010; Rushworth et al, 2007). The ACC has robust connections with the orbitofrontal cortex, perhaps providing the contextual information necessary to interpret signals in the environment and contribute to emotional arousal. In addition, ACC receives strong monosynaptic projections from the hippocampus and has bidirectional connections with medial temporal cortices, in pathways that are thought to convey contextual information (Barbas et al, 2013). Interestingly, the ACC is the primary effector to brainstem autonomic structures through projections to hypothalamic and spinal autonomic centers (Barbas et al, 2003). These features suggest that the ACC is the primary effector of emotional expression, linking motor control, cognition and drive (Barbas, 2000; Paus, 2001; Shackman et al, 2011).

Furthermore, the area 24c projects to the facial motor nucleus to regulate the muscles of facial expression. This notion fits quite well with the role of area 24c in emotion because the muscles of facial expression are the only group that explicitly transmits information about emotional states; it does not appear to be an accident that the head representation of the rostral cingulate motor subregion is located in area 24c (Vogt, 2009).

Indeed, the ACC has its own specializations (Pourtois et al, 2010). Human neuroimaging research has consistently implicate the ACC in situations that involve conflict between a goal-directed response and a distracting alternative (Botvinik et al, 2007; Sheth et al, 2012), in the evaluation of action outcomes, in the processing of pain (Ranville et al, 2002; Williams et al, 2003; Shackman et al, 2011), in the witnessing of pain in others (Singer et al, 2004; Botvinik et al, 2005), in aversive learning, in studies of motivation (Paus 2001; Pessoa 2009), in processing “social” information (processing elicited by, about or directed towards others; Amodio and Frith, 2006; Apps et al, 2012), in rewards (Doya, 2008), attention and salience (Davis et al, 2005), in emotional response inhibition (Albert et al, 2012), in error detection (Rushworth et al, 2007), while it includes at least two motor regions that are active during movement (Paus, 2001). Moreover, the more rostral ACC is particularly important for the integration of visceral, attentional and affective information (Vogt, 2005) and it is active during autonomic arousal (Critchley et al, 2000).

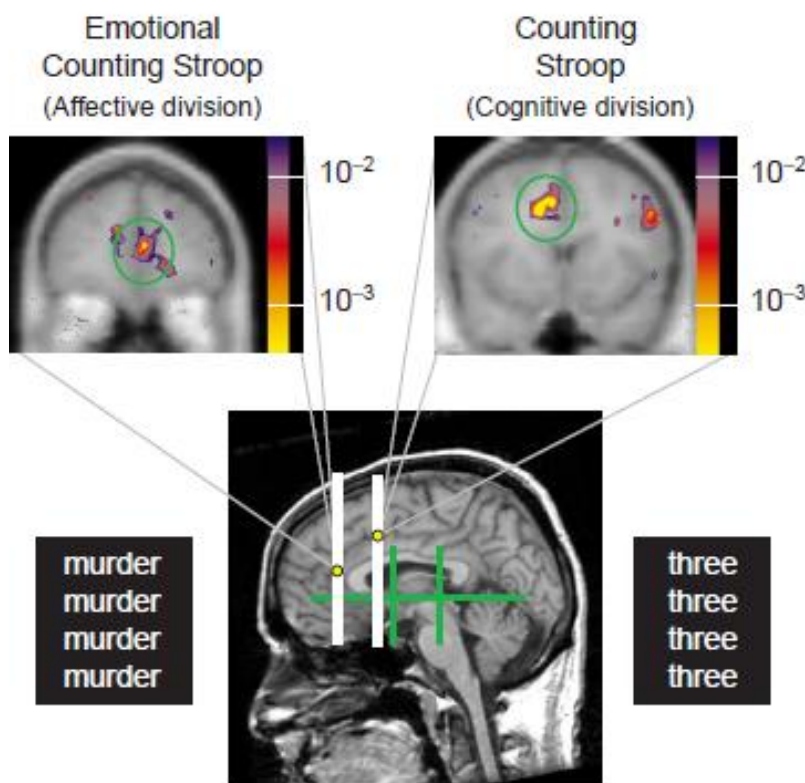
Classically, two major subdivisions with distinct functions have been described: a dorsal-cognitive division (areas 24b'-c' and 32') and a rostral-ventral affective division (rostral areas 24a-c and 32, and ventral areas 25 and 33) (Bush et al, 2000, *see following figure*). The cognitive subdivision is part of a distributed attentional network; it maintains strong reciprocal interconnections with lateral prefrontal cortex (BA 46/9), parietal cortex (BA 7), and premotor and supplementary motor areas. Various functions have been ascribed to the dorsal-cognitive division, including modulation of attention or executive functions by influencing sensory or response selection (or both), monitoring competition, complex motor control, motivation, novelty, error detection and working memory,

and anticipation of cognitively demanding tasks. The affective subdivision, by contrast, is connected to the amygdala, periaqueductal gray, nucleus accumbens, hypothalamus, anterior insula, hippocampus and orbitofrontal cortex, and has outflow to autonomic, visceromotor and endocrine systems. The rostral-ventral affective division is primarily involved in assessing the salience of emotional and motivational information and the regulation of emotional responses.



The cognitive division has been activated by cognitively demanding tasks that involve stimulus-response selection in the face of competing streams of information, including Color Stroop (*see appendix, p. 26*) and Stroop-like tasks, divided-attention tasks, verbal- and motor-response selection tasks and many working-memory tasks. The affective division has been activated by affect-related tasks, including studies of emotional processing in normal healthy volunteers and symptom provocation studies in a number of psychiatric disorders (anxiety, simple phobia and obsessive-compulsive disorder). It has also been activated repeatedly by induced sadness in normal subjects and in individuals with major depression.

Notably, a direct comparison of two versions of the Counting Stroop task (one involving cognitive interference, the other emotional words) activated the two ACC subdivisions differentially (*see following figure, taken from Bush et al, 2000*).



Emotional and Cognitive Counting Stroops modulate different ACC divisions.

Subjects were instructed to report by button press the number of words in each set, regardless of their meaning. Neutral trials contained single semantic category common animals (e.g. 'dog' written three times). Interference trials contained number words that were incongruent with the correct response (e.g. 'three' written four times). In contrast, during the interference portion of the Emotional Counting Stroop, emotionally valenced words were substituted for the number words (e.g. 'murder' written four times). In addition, a different set of emotionally neutral words was used for comparison. The Emotional Counting Stroop activated the affective division, whereas the cognitive version of the Counting Stroop activated the cognitive division. Examples of the interference portions of the two tasks are displayed beneath the scan data (for example, the correct answer would be to press button number '4' to indicate four items in the display).

Recent evidence, however, do not support the traditional differentiation of dorsal and rostral ACC for cognitive and emotional function, respectively (Bush et al, 2000; Devinsky et al, 1995) but indicate that both subdivisions of the ACC make important contributions to emotional processing (Albert et al, 2012; Beckmann et al., 2009; Etkin et al., 2011; Vogt, 2005).

Unfortunately, often the MCC is labeled as dorsal ACC and the actual ACC as rostral ACC. Midcingulate cortex (MCC), for example, represents the posterior part of areas 24 and 32 (Vogt et al, 2003).

Consequently, the use of ACC as a "catch-all" terminology, has led many to inaccurately discuss the functional properties of the MCC in relation to the functional and anatomical properties of the ACC (Apps et al, 2013).

Mid Cingulate Cortex (MCC)

According to Vogt (2009), a leading expert on the anatomy and functions of the cingulate cortex, MCC is not simply a transition cortex with a linear increase in the number of layer IV neurons from the anterior to the posterior aspect of the cingulate structure, as it has been proposed, but it is qualitatively different from ACC.

In terms of connections, MCC receives more inferior parietal and less amygdala input than does the more anterior cingulate cortex and MCC contains the cingulate motor areas (Vogt et al, 2003). MCC provides a cognitive interface with skeletomotor systems via projections to the spinal cord, striatum, supplementary/pre-supplementary motor areas (SMA/pre-SMA).

The role of MCC in punishment and avoidance is stressed by a substantial literature on acute nociceptive stimulation (Vogt et al, 2003). Moreover, MCC is critical to decisions selecting between pain and reward outcomes; midcingulotomy lesions can disrupt reward-guided response selection (Williams et al, 2004).

Posterior Cingulate Cortex (PCC)

The PCC has connections via parahippocampal areas with the hippocampus which is involved in episodic memory (Rolls, 2008), and with parietal regions involved in the representation of space, which is usually a component of an episodic memory (Rolls, 2015).

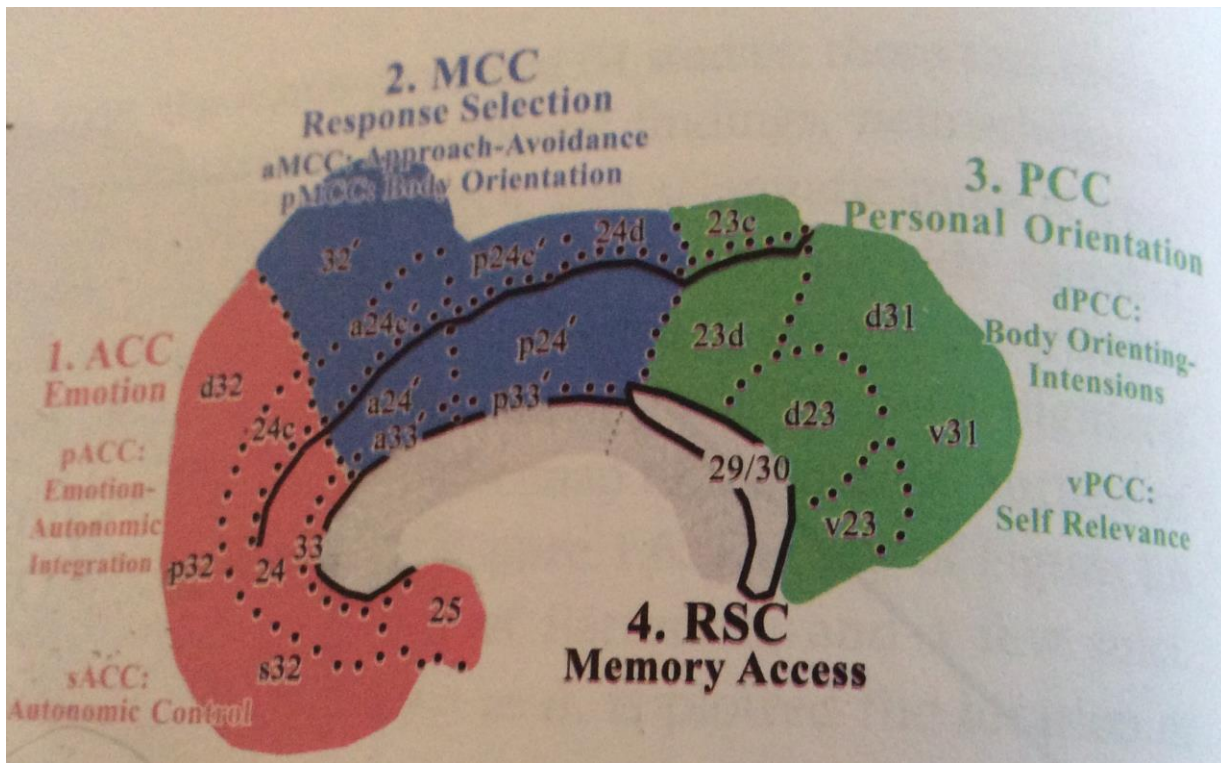
Although the major projection of the inferior parietal cortex is to PCC and RSC, it does extend with equal density into posterior MCC and minimally into anterior MCC; no parietal projections were observed to pregenual ACC and this is pivotal to differentiating the functions of PCC and ACC. Previous research suggests that healthy individuals commonly show negative correlations between activity in the dorsal ACC (being part of a frontoparietal network usually activated during cognitive tasks) and PCC (being a central node of the default mode network typically activated during rest and suppressed during task engagement) (Fox et al, 2005; Sridharan et al, 2008; Leech and Sharp, 2013; Lin et al, 2015).

The PCC has been implicated in various functions including attention regulation, working memory, episodic memory as well as topographic and topokinetic memory (orientation of the body in the space), although its precise role remains unknown (Raichle et al, 2001; Menon and Uddin, 2010; Leech and Sharp, 2013). Activity in the PCC and precuneus has further been associated with self-referential processing (e.g., rumination, self-reflection) and monitoring of arousal states (Raichle et al, 2001; Greicius et al, 2003; Vogt et al, 2006; Menon and Uddin, 2010).

Retrosplenial cortex (RSC)

Since RSC and PCC are adjacent to each other and heavily interconnected, it has been difficult to disentangle their unique contributions to brain functions. An additional problem is the small size of RSC in relation to the spatial resolution of imaging modalities. In instances where a clear involvement of RSC can be shown in human studies, it has been implicated in working and long term memory and visuospatial functions (Vogt, 2009).

Cingulate regions



Taken from Vogt, *Cingulate Neurobiology and Disease*, 2009

Subgenual and pregenual ACC (sgACC / pgACC):

The two subregions can be identified according to anatomical, functional and neurotransmitter receptor criteria. Area 25 of sgACC is heavily connected with the central nucleus of amygdala and lateral hypothalamus, whereas area 24c of pgACC does not have these projections, as already discussed. Negatively valenced and episodic memories appear to be most frequently stored in sgACC than in pgACC, while happiness and associated memories are most often stored in the rostral part of pgACC mainly in area p32 (Vogt, 2009). This latter area has been reported to have a role in subjective emotional events (Lane et al, 1997).

Subgenual ACC is a common activation site in response to sad stimuli (Phan et al, 2002), however it remains unclear how sadness is evaluated and regulated, and what role the sgACC plays in these processes (Etkin et al, 2011).

In a recent study of probabilistic maps analysis, Palomero-Gallagher et al (2015) showed that functions which have previously been attributed to the complete sgACC should in fact be attributed to cytoarchitectonically distinct areas within this region: area s24 was activated during the processing of sadness and the emotional evaluation of taste, whereas areas s32 and 33 were

associated with fear extinction and pain perception, respectively. Area s32 co-activated with areas of the executive control network and was associated with tasks probing cognition in which stimuli did not have an emotional component, while area 33 co-activated with areas of the sensorimotor network.

Anterior and posterior MCC (aMCC/ pMCC):

The aMCC has been reported to be active during fear while the pMCC appears to have no responsivity during simple emotions (Vogt, 2009); it is interesting that the amygdala projections extend to aMCC and this may contribute to its involvement in fear.

The pMCC is associated with the caudal cingulate premotor area which is easily driven by passive movements and appears to play a lesser role in the reward coding of behavior than the rostral region.

Dorsal and ventral PCC (dPCC/vPCC):

The vPCC has the unique intra-cingulate connections with sgACC (Vogt and Pandya, 1987). The vPCC has a predominant role in sensory evaluation in terms of the self-relevance of objects and places. It appears that vPCC evaluates emotional and non-emotional sensory inputs, it determines their self-relevance via connections with sgACC where long-term memories of valenced events are stored and then such information is directed to MCC for motor system output (Vogt, 2009).

The dPCC has a more profound role in visuospatial functions, receives inputs via the dorsal visual stream, has heavier interconnections with MCC and is activated by familiar over unfamiliar objects and places (Vogt, 2009).

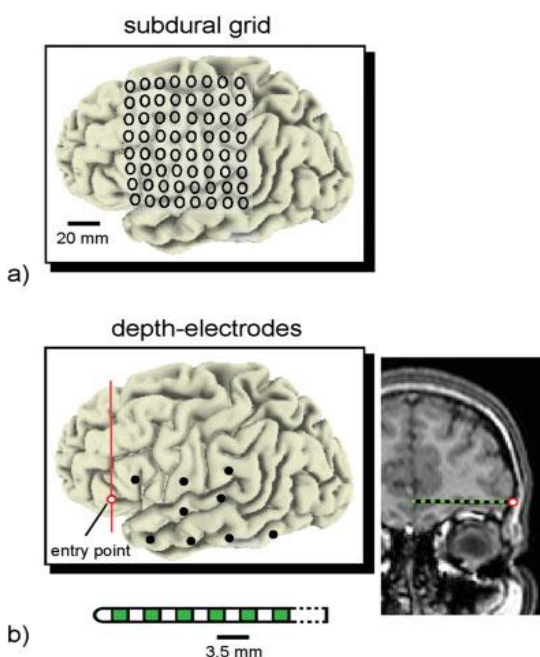
Appendix

Stroop task:

consists of color word stimuli that are presented in font colours that are either congruent (e.g., the word 'red' presented in red) or incongruent (e.g., the word 'red' presented in green) with the semantic meaning of the word. During the task, participants are asked to name the colour of the word, but not to read it. Because incongruent trials involve conflict between the prepotent reading response and the task-appropriate colour-naming response, such trials typically generate longer reaction times and more errors.

STEREO-ELECTROENCEPHALOGRAPHY (SEEG)

In patients with pharmacologically resistant epilepsy, intracranial EEG is used to identify cortical regions critical for seizure onset and identify others that need to be spared at the time of surgery. The intracerebral electrodes sometimes stay in place for more than two weeks in order to localize the origin of fast electrophysiological rhythms that precede seizure onset and that are at the core of the epileptogenic network. Surgical resection of the focus of the seizure has been shown to yield up to 70% success rates for drug-resistant temporal lobe epilepsy. Intracranial EEG is used to test one or several hypothesis regarding the anatomical organization of the epileptogenic network. This sometimes implies that intra-cerebral electrodes are positioned in widely distributed brain regions that might include pathological but also healthy tissue. Therefore, such a clinical context can also provide a unique opportunity to study fundamental questions about neural coding and cognition. Clinical recordings in epilepsy patients are generally performed using macroelectrodes that measure coherent activity of local neuronal populations in the vicinity of the recording site. The most common choice in the clinical routine is to use either stereotactic-electroencephalography (SEEG) or electrocorticography (ECoG) which acquire intracranial data using multilead depth electrodes or subdural grid electrodes respectively (*see following figure*). Subdural grids consist of 2D arrays (or sometimes one-dimensional strips) of electrodes positioned directly on the lateral surface of the brain, with a typical inter-electrode distance of 1 cm (Engel et al, 2005). In contrast, depth electrodes are semi-flexible one-dimensional linear arrays, shaped as narrow needles that penetrate deep into the brain. Such depth electrode implantations are often referred to as Stereotactic EEG because a stereotactic technique developed by Talairach and Bancaud is used to localize the electrodes.

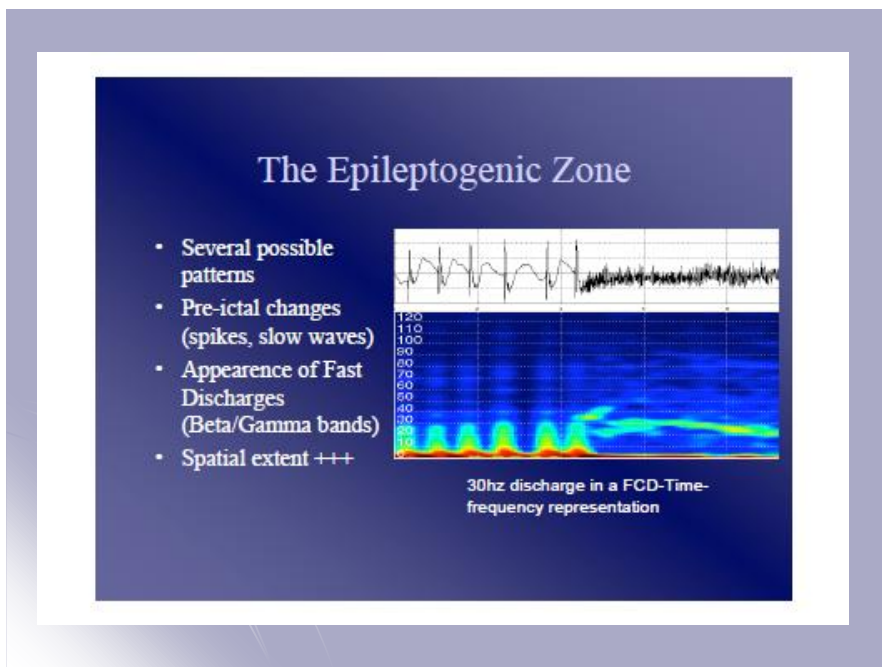


Subdural grids vs. depth electrodes.

(a) Representation of electrocorticographic (ECoG) subdural grid electrodes. Open circles indicate recording sites on a 8-by-8 matrix covering the lateral surface of the somatosensory cortex. (b) Example of implantation with stereotactic encephalography (SEEG) electrodes. Black dots represent the entry points of ten depth electrodes. Each electrode consists of 5–15 contact sites (green squares). In most cases, SEEG electrodes are inserted orthogonal to the interhemispheric plane as shown on coronal MRI slice.

Indeed, SEEG was introduced in 1962 by Bancaud and Talairach in reference to the implantation of intracerebral multi-contact electrodes placed strategically under stereotactic guidance for the purpose of intracranially recording epileptiform activity.

The concept of this approach is the characterization of the epileptic seizure as a dynamic process with a spatial-temporal organization, often multidirectional, and its aim is the study of the ictal electro-encephalographic changes at the very point where they occur (anatomy-electrical relationships) as well as of their initial or secondary reverberations on the clinical picture (electro-clinical relationships) (Talairach and Bancaud, 1973). According to this notion, the site of origin and primary involvement and organization of ictal discharges is defined as the epileptogenic zone, whose surgical removal results in seizure-control.



SEEG electrodes are placed according to a pre-implantation hypothesis of the presumed epileptogenic zone, incorporating the ictal onset zone and regions of early (rapid) spread of epileptic (ictal) activity, with the goal of confirming or rejecting this pre-implantation hypothesis (Kahane et al, 2008). Thus, SEEG represents an anatomy-electro-clinical methodology aiming to verify presurgical, apparently coherent, hypothesis on location and extent of the epileptogenic zone (Bancaud and Talairach, 1965).

The implantation strategy lies on the meticulous analysis of the non-invasively obtained data and requires: (i) an accurate assessment of subjective and objective ictal semeiological chronology, (ii) a careful evaluation of the morphology and location of interictal and ictal discharges on EEG

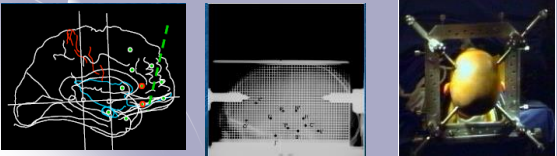
combined with their correlation with the clinical picture. (iii) The evaluation of the concordance of the electro-clinical data with the topography of a possible anatomical abnormality seen on MRI. Any discrepancies in between clinical, anatomical (if any) and neurophysiological data represent an indication for SEEG evaluation, provided that the patient is likely to benefit from surgery. The working-hypothesis, emphasized by Bancaud and Talairach, is the notion of seizure pattern (Bancaud and Talairach, 1965); ictal clinical semeiology must be viewed as a whole, whereas taking individually the signal-symptoms could lead to erroneous interpretation.

Advantages of SEEG include the possibility to record from deep cortical structures, to sample the intrinsic electrical activity of a presumed epileptogenic lesion, to perform bi-hemispheric explorations in the context of possible multifocal seizure onsets, to realize a neurophysiological mapping of cortical but also subcortical structures and to identify pathological interconnected networks sustaining the organization and propagation of ictal discharges and consequently the manifestation of semeiological features.

As a consequence, no standard implantation scheme is utilized, each exploration is individually-tailored to the requirements and the particular characteristics of the single patient and the scheme of electrodes placement is never identical from one patient to another one.

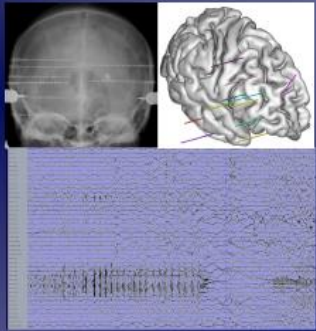
Planning of SEEG exploration
 → Multidisciplinary discussion

- Rigorous definition of the cerebral areas to explore
- Individualized exploration (based on anatomic-electro-clinical data)
- Accurate and precise attainment of the cerebral areas by stereotactic method
- Almost every cerebral area is accessible



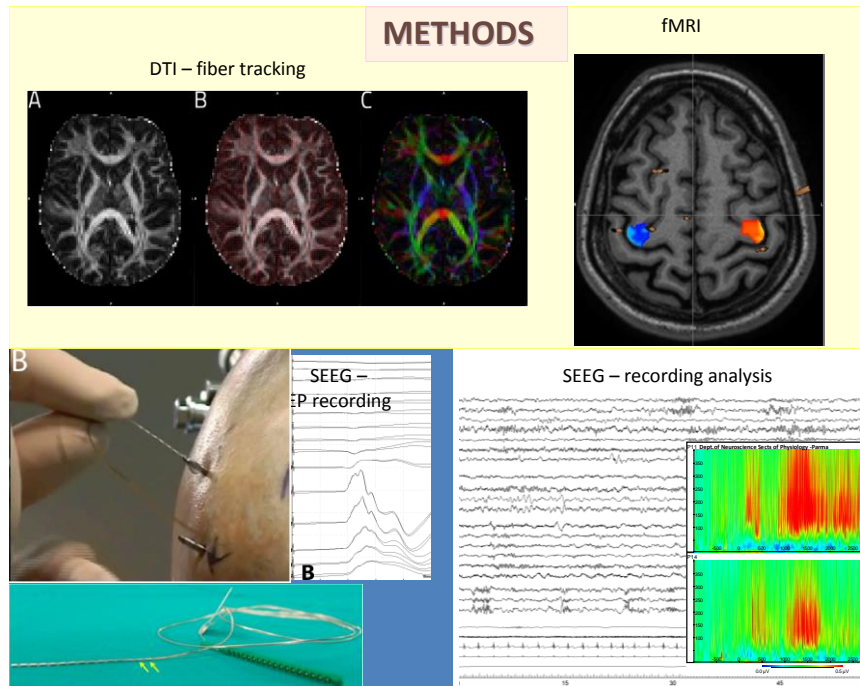
SEEG: A 3D vision of the Epileptic Process

- Records the Intracerebral EEG activity without opening the skull
- Using Macroelectrodes with contiguous contacts (0.8 mm diameter, spaces 1.5mm)
- 10-15 contacts for each electrode
- Video-SEEG (1-3 weeks):electro-anatomical-clinical correlations
- Electrical stimulations
- Possibility to record both superficial and deep brain structures



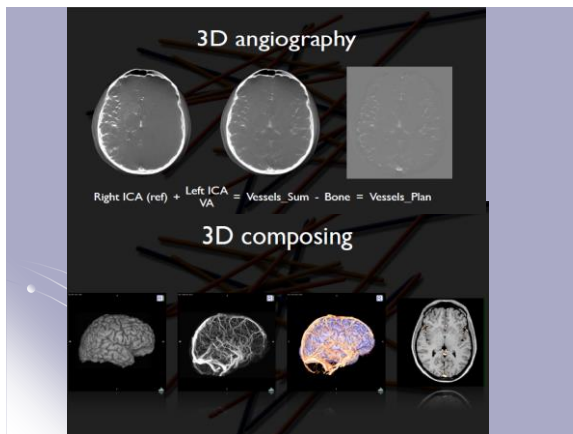
SEEG workflow

Nowadays the original Talairach methodology is integrated with new hardware and software tools (Cardinale et al, 2013). The actual SEEG workflow is adopted in the Niguarda centre since 2009, with more than two hundreds patients undergoing such a procedure.

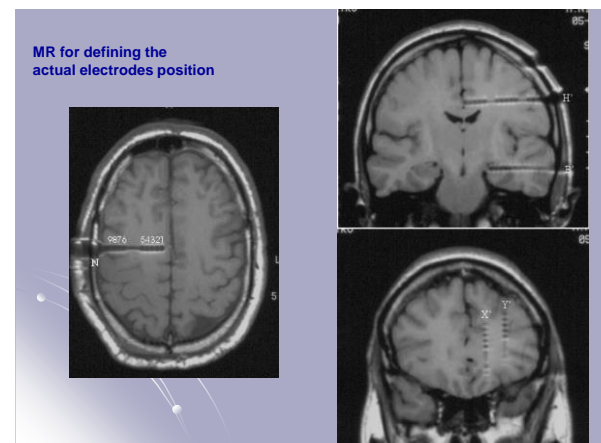
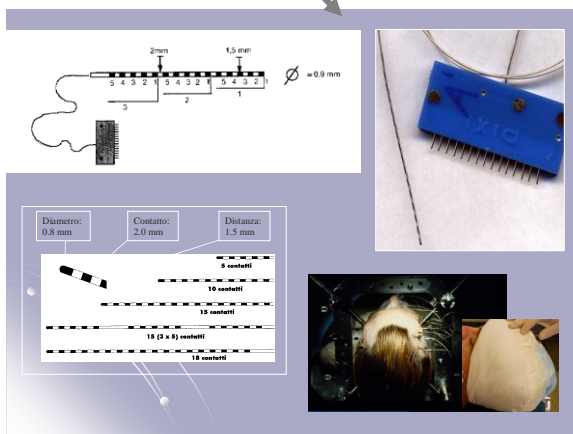


The imaging needed for planning is acquired weeks or months before surgery, so that all the time needed for post-processing and planning can be freely taken. A 3D T1-FFE MRI sequence is obtained, and registered to the cone-beam computed tomography 3D digital subtraction angiography (CBCT 3D DSA, *see following figures*). The latter dataset is acquired with the O-armTM 1000 System (Medtronic, Minneapolis, Minnesota), a mobile robotic radiographic device for intra-operative imaging. This 3D DSA dataset is the reference space for multimodal image-guided planning. Other structural and functional MRI scans are optionally acquired. Entry points and target points are defined in the stereotactic planning software, Voxim (IVS, Chemnitz, Germany). For every trajectory, multi-planar reconstructions, brain and vascular surface rendering, are used for planning. The day of surgery the Talairach frame is fixed under general anaesthesia, and the patient is registered. Therefore, the pre-planned trajectories can be transferred from the scanner space to the surgical one. The robotic assistant (Neuromate®- Renishawmayfield, Nyon, Switzerland) aligns the tool holder with the vectors of the pre-planned trajectories, the skull is percutaneously twist-drilled and the anchor bolts are fixed. Finally, a track is done with a rigid stylet and intracerebral electrodes are immediately advanced into the brain. These multi-lead electrodes (Microdeep Intracerebral Electrodes D08®, Dixi Medical - or Depth Electrodes Range 2069®, Alcis) are semi-rigid, with 0.8 mm external diameter and have no stylet inside; every

contact is 2 mm long, with 1.5 mm inter-leads gap. They are available with 5, 8, 10, 12, 15, and 18 contacts. EEG signal provided by all implanted electrodes is checked in the operating room enabling replacement of malfunctioning electrodes, which is however an uncommon occurrence. A post-implantation 3D CBCT is then obtained with the O-arm for checking the correct positioning of the electrodes.



scheme of SEEG electrode

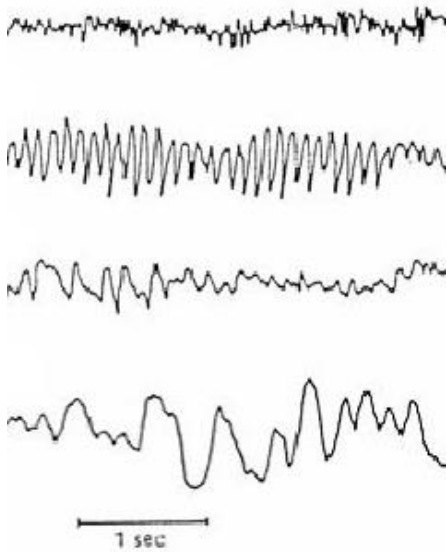


The patient is then awaked and moved to the recovery room for monitoring. Once at least one of the habitual seizures has been recorded, electrical bipolar cortical stimulations of two adjacent contacts are carried out at both low (LF, 1 Hz, pulse-width 2 ms, during 30 s) and high frequency (HF, 50 Hz, pulse-width 1 ms, during 5s) in order to define eloquent cortex of motor, language and visual functions and to reproduce patient's ictal symptoms and signs.

Additionally, in well-selected cases, when a very small epileptogenic area is demonstrated (for instance, periventricular nodules) the same electrodes can be used for radio-frequency lesioning (therapeutic SEEG option).

Appendix:

EEG frequency bands:



14-30 c/s (Hz) beta

8-13 c/s (Hz) alpha

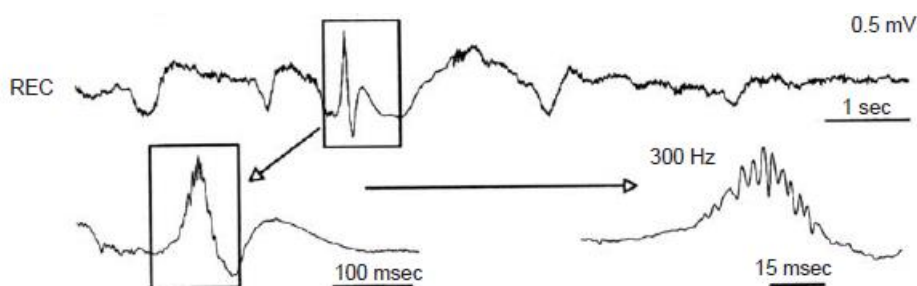
4-8 c/s (Hz) theta

< 4 c/s (Hz) delta

gamma band (>30 Hz) normally is not visible on scalp EEG

High frequency activity (HFA): visible on intracranial EEG

- gamma band: >30 Hz (index of cortical processing in any region that is involved by a task, usually in the range 30-150 Hz: *HFA[30-150]*)
- high frequency oscillations: 80-500 Hz
- ripples: 80-200 Hz (recorded in the normal hippocampus; are believed to promote synchronization and information transfer across long distances)
- fast ripples: 200-500Hz (identified in structures capable of generating spontaneous seizures)



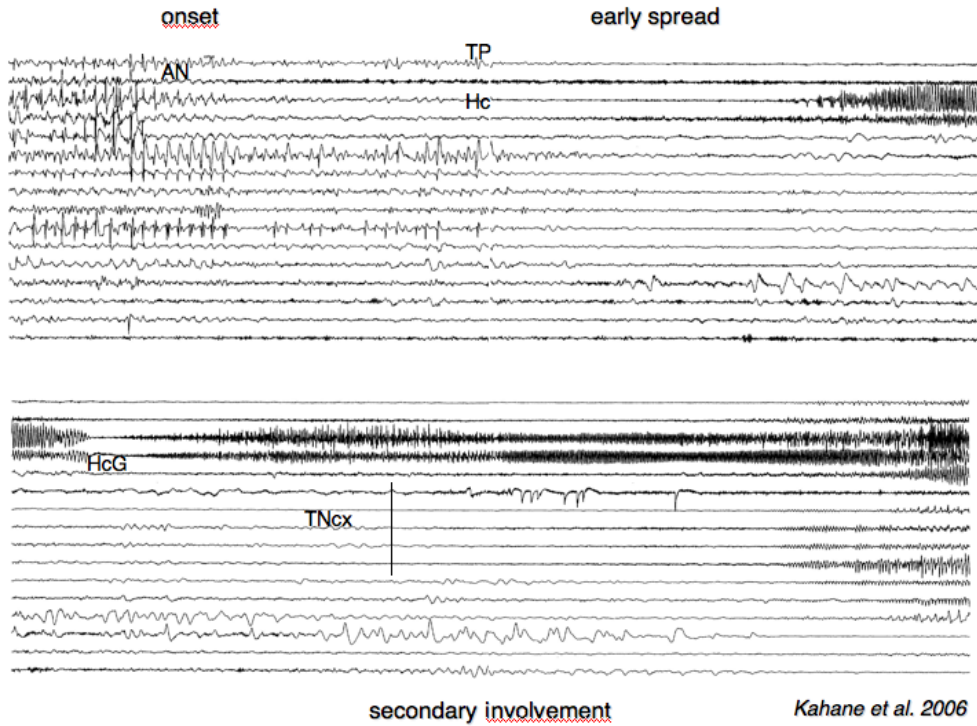
Interictal spike with superimposed fast ripples in the entorhinal cortex of a patient with mesial temporal lobe epilepsy.

Arrows indicate extension of electrical activity in the box. Abbreviations: REC - right entorhinal cortex.

Taken from Luders H, Textbook of Epilepsy Surgery, 2009.

Epileptogenic Zone:

The definition :
The site of the beginning and of the primary organization

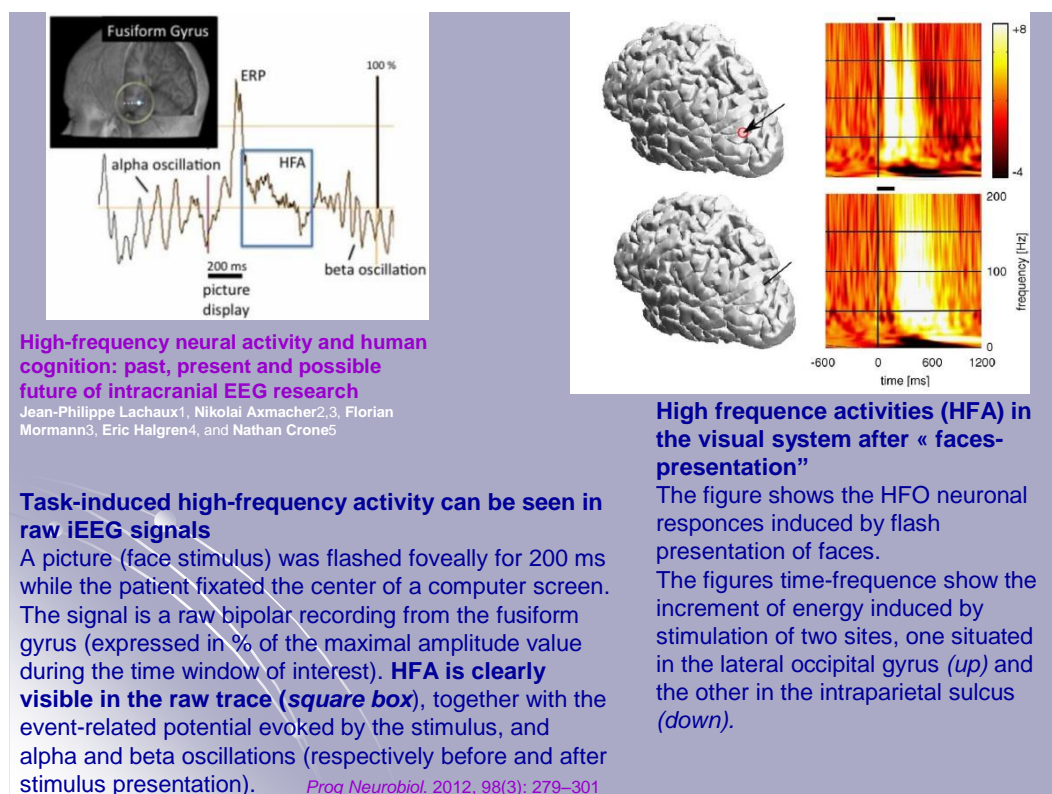


INTRACRANIAL EEG AND HUMAN COGNITION

In the last few years, an increasing number of research groups have turned to intracranial EEG recordings to study the neural bases of human cognition (Lachaux et al, 2012). Because of its invasive nature, its use in humans has mainly been restricted to the clinical circumstances of patients undergoing resective surgery for medically refractory epilepsy, in whom it has been used most often to map the cortical networks responsible for seizures.

However, intracranial EEG also provides a unique window into the spatiotemporal dynamics of the human brain at work, with sub-millimetre and millisecond precision, sometimes at the individual neuron level (Engel et al, 2005).

While early intracranial EEG research was primarily focused on event-related potentials or peri-stimulus time histograms (Lachaux et al, 2003 for review), the emerging trend in ‘cognitive’ intracranial EEG research has been characterized by its strong emphasis on high-frequency neural activity (HFA: 30 Hz and above), which can sometimes be seen in raw intracranial EEG signals (*see following figure*).



A few early intracranial EEG studies had reported that motor tasks and sensory stimulation could modulate HFA (Halgren et al, 1977), but the field really took off with the ‘gamma buzz’: the marked interest of the neuroscience community in gamma-band synchronization and its role in neural representation and communication was fuelled by recent experimental and technological

advances, such as the use of spectral analysis to reveal task-related modulations in multiple frequency components (Jerbi et al, 2009, Lachaux et al, 2012).

Indeed, increasing evidence suggests that gamma-band activity (>30 Hz) might be a particularly efficient index for functional mapping; HFA is well suited to visualizing the onset, magnitude, and duration of changes in neuronal activity during cognitive tasks or in relation to endogenous cognitive processes (Lachaux et al, 2012).

The current understanding of gamma-band responses is that they correspond to a local synchronization mechanism that facilitates neural communication: increased gamma-band activity would thus mean that neurons around the electrode get recruited by the task-at-hand (Dalal et al, 2012). By analogy, gamma-band suppressions, that is transient decrease in gamma-band energy, would correspond to an interruption of local communication and a withdrawing from the task. For this reason, gamma-band responses have been proposed as precise markers of the cortical networks underlying cognition, a suggestion that has meanwhile received further support by studies of multiple cognitive processes (Dalal et al, 2012).

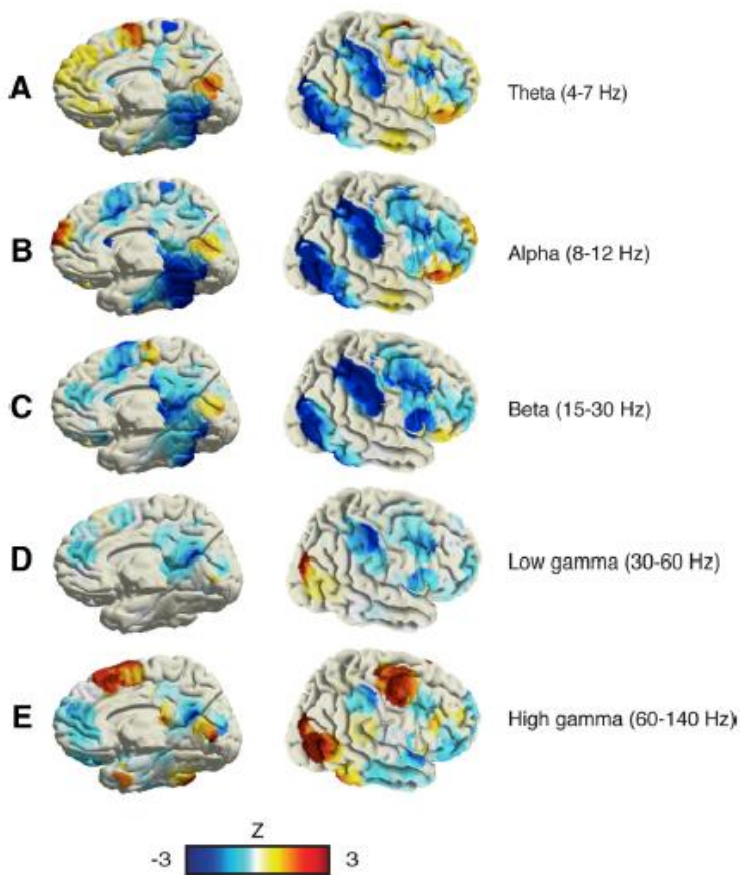
Using intracerebral registrations in humans, Cantero et al studied the topographic distribution of gamma oscillations, both locally and in long distance in the neocortex and in the hippocampus, during different stages of vigilance (Cantero et al, 2004). The authors showed that there was a great variability within the gamma band between different cortical areas during wakefulness and sleep. Moreover, the local coherence in the gamma band either locally (within a cortical region) or in long distance (between different cortical regions) was significantly higher during wakefulness compared to sleep. These data suggest the presence of a functional link between different stages of vigilance and the level of interaction in the gamma band in humans.

Numerous studies have established a tight relationship between increases in the blood-oxygenation level-dependent (BOLD) signal and task-related increases in broadband gamma (~30–150 Hz) in humans (Mukamel et al, 2005; Lachaux et al, 2007) and in animals (Logothetis et al, 2001). More recently, the coupling between negative BOLD responses and suppression of gamma power has also been suggested by direct electrophysiological recordings in the default-mode network known to display BOLD deactivations during attention-demanding tasks. Several studies showed that execution of externally oriented attention-demanding tasks leads to suppressions of broad-band gamma power in specific default-mode network structures (Knyazev, 2013).

Slow-gamma (30–50 Hz) power showed positive correlations with DMN BOLD-signal at rest and decreases during the transition from resting state to an attention task which is interpreted as a correlate of DMN deactivation (Lachaux et al, 2008; Hayden et al, 2009; Jerbi et al, 2010). It appears that alpha (and possibly slow-beta) correlates positively with DMN and negatively with

attentional networks whereas gamma shows positive correlations with most cognitive processes including attention (Fan et al, 2010; Ossandón et al, 2012).

In particular, Ossandon and colleagues, by using extensive brain-wide, intracerebral depth recordings in surgical epilepsy patients performing a visual search task, found that DMN neural populations display task-related high-frequency power suppressions in the high-gamma range (60 -140 Hz), also revealing that the fine-scale temporal dynamics of such broadband gamma power suppression in DMN regions are tightly correlated with task demands and subject performance on a trial-by-trial basis (see following figure, taken from Ossandon et al, 2011).



Spatial distribution of task-related power decreases (blue) and increases (red) during visual search in multiple frequency bands. *A*, Theta (4 -7 Hz). *B*, Alpha band (8 -12 Hz). *C*, Beta band (13-30 Hz). *D*, Low gamma band (30 - 60 Hz). *E*, High gamma band (60 -140 Hz). The distribution of task-related gamma power suppressions is the one that most closely matches typical DMN deactivation patterns. Power patterns in theta and alpha bands did not show comparable suppressions in DMN areas. Beta power suppressions were observed in some DMN areas but also in visual and dorsal attention network areas. Unlike gamma suppressions, beta suppressions in the DMN clusters were not significantly correlated with behaviour.

These findings further suggest that efficient goal-directed behaviour is mediated by an intricate interplay between anti-correlated networks of distributed broadband gamma power increases and decreases (Ossandón et al., 2012).

Indeed, there is growing evidence that rhythmic neural oscillations and their synchronization provide indices of dynamic and flexible communication between and within the cerebral networks underlying a specific behaviour (Fries 2005, Betti et al, 2009). In particular, studies support the role of gamma-frequency band synchronization as a mechanism underlying the dynamic construction of the large-scale neuronal networks involved in object representation (Tallon-Baudry and Bertrand, 1999), binding of visual features (Singer and Gray, 1995; Engel and Singer, 2001), selective attention and memory (Womelsdorf and Fries, 2006; Jensen et al, 2007; Doesburg et al, 2008), sensorimotor integration (Szurhaj et al, 2006), and even very complex processes such as the “aha!” component of cognitive insight (Jung-Beeman et al, 2004; Sheth et al, 2009).

For instance, several intracranial EEG studies have indicated that neural activity associated with HFA plays a role in memory processes.

Several studies have shown sustained increases of gamma band activity during working memory maintenance, which correlates with working memory load in various neocortical regions (Mainy et al, 2007) as well as in the rhinal cortex (Axmacher et al, 2008) and in hippocampus (Van Vugt et al, 2010). These studies have provided insights beyond those of previous fMRI studies, because they have allowed distinctions between transient and sustained responses with a higher temporal resolution than would be possible through analyzing the BOLD response alone.

The HFA modulations observed during working memory tasks may be related to repeated reactivations of neural assemblies, which are each synchronized in the gamma frequency range (Lachaux et al, 2012).

According to an influential computational model, maintenance of multiple items depends on such reactivations during several consecutive cycles of lower-frequency (e.g. theta, between 4 and 7 Hz) oscillations (Lisman and Idiart, 1995; Jensen, 2007), which are independently generated in various brain regions (Raghavachari et al, 2006).

Recent studies have provided experimental evidence for this model by showing increased coupling of the amplitudes of high frequency activity to the phase of theta frequency oscillations during a continuous word recognition memory task (amplitude-modulated activity at various frequencies between 12 and 46 Hz depending on task condition; Mormann et al, 2005) and, more importantly, during working memory maintenance, as compared to inter-trial intervals (amplitude-modulated activity at around 28 Hz; Axmacher et al, 2010) (*see following figure, taken from Lachaux et al, 2012*).

Beta and gamma oscillations may also be phase-locked between widespread frontal, parietal and occipital areas during the rapid storage, modification and retrieval of multiple memoranda in more complicated working memory tasks (Halgren et al, 2002).

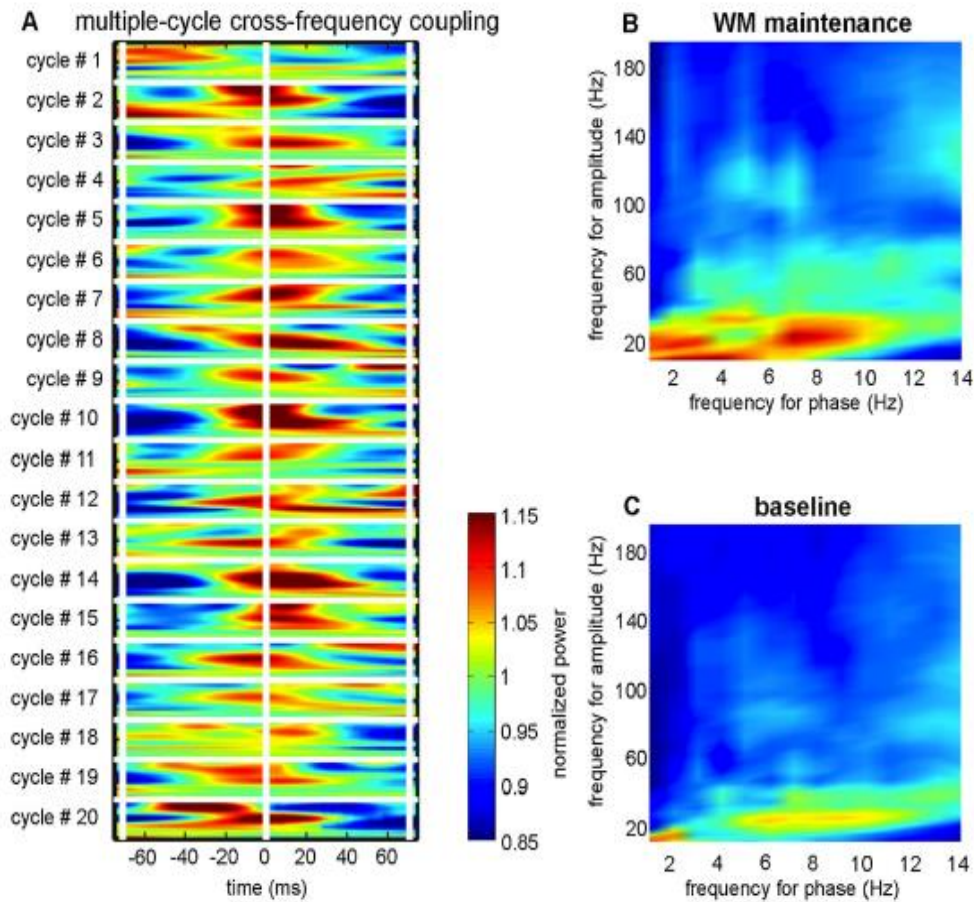


Fig. 3. Cross-frequency coupling during multi-item working memory. (A) During maintenance of multiple items (trial-unique novel faces), hippocampal oscillations in the beta/gamma frequency range occur predominantly during a specific phase range of lower-frequency oscillations in the theta range. These data support a computer model of working memory according to which multiple items can be simultaneously maintained by a multiplexing of cycles of high-frequency activity during specific phases of low-frequency oscillations. This effect is more pronounced during the delay period of the working memory task (B) as compared to an inter-trial baseline (C) as well as compared to surrogate data (not shown).

Figure modified from Axmacher et al. (2010a).

Several studies have also demonstrated an increase in high frequency activity during long term memory formation. In a series of studies, Sederberg and colleagues investigated the role of hippocampal and neocortical high frequency activity recorded with intracranial and subdural EEG electrodes for subsequent memory to words. In their first study (Sederberg et al, 2003), they found that HFA between 28 and 64 Hz at widespread neocortical sites predicted subsequent memory. Similar results were later found in the hippocampus for activity between 44 and 64 Hz (Sederberg et al, 2007a). Furthermore, similar patterns of both hippocampal and neocortical high frequency activity enhancements (between 44 and 100 Hz) were found during successful encoding and retrieval (Sederberg et al, 2007b).

A group of so-called two-step theories of memory formation have suggested that the initial encoding stage, which leads to the formation of labile memory representations, is followed by a

second stage called memory consolidation, which renders memory traces stable against interfering inputs (Marr, 1971; Buzsaki, 1989; McClelland et al, 1995; Squire and Alvarez, 1995) and appears to be linked to very fast (in animals, around 200 Hz) bursts of “ripple” oscillations (Buzsaki et al, 2002). Evidence for human ripples has been found both with micro-electrode (Bragin et al, 1999; Staba et al, 2002; Worrell et al, 2008) and with macro-electrode (Urrestarazu et al, 2007; Axmacher et al, 2008; Worrell et al, 2008) recordings, as well as with semi-invasive foramen ovale electrodes (Clemens et al, 2007). These oscillations, which in humans have a lower frequency at around 100 Hz, should not be confounded with so-called “fast ripples” at 500 Hz, which occur predominantly in the vicinity of the epileptic focus and appear to be related to pathological processes (Bragin et al, 1999; Staba et al, 2002; Foffani et al, 2007) (*see appendix, p. 32*).

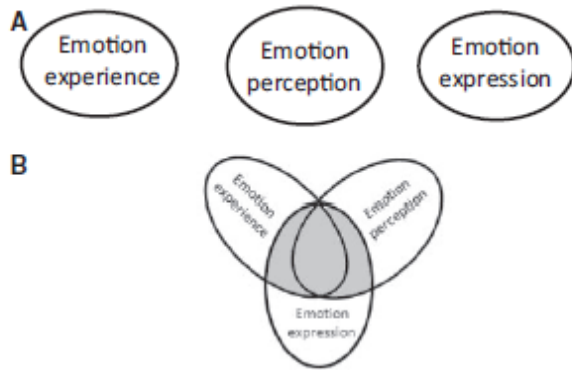
The mechanisms by which sharp wave ripples might promote memory consolidation are starting to be understood. It has been shown that these events are temporally coupled to the occurrence of neocortical sleep spindles (Siapas and Wilson, 1998; Sirota et al, 2003; Clemens et al, 2007), which, in turn, increase after learning and may promote neocortical plasticity via an accumulation of intracellular calcium (Sejnowski and Destexhe, 2000). Therefore, sharp wave ripples may be related to the induction of neocortical plasticity processes by the hippocampus.

In addition, applications of time–frequency analysis to intracranial EEG signals have shown that the recognition of visually presented words is concomitant with a cascade of HFA between 40 and 150 Hz (Crone et al, 2001; Tanji et al, 2005; Mainy et al, 2008) and that HFA in the reading network is strongly modulated by attention (Jung et al, 2008).

Furthermore, various studies have identified serial progressions of activation consistent with distinct stages of perception, semantic analysis and speech production (Brown et al, 2008; Chang et al, 2010; Edwards et al, 2010).

Besides the studies of memory and language, intracranial EEG has been used to investigate emotions. In a recent review (Guillory and Bujarski, 2014) on the contribution of human intracranial electrophysiology to our understanding of the neural representations of emotions, 64 studies which investigated emotional processing using human intracranial electrophysiology (HIE) were identified - the year of publication ranging from 1954 to 2012 - of two main types. The first type included studies which aimed to measure brain activation during viewing of emotionally provoking stimuli; the types of stimuli included presentation of faces with emotional facial expressions (e.g. Ekman faces), presentation of emotionally provoking pictures (e.g. IAPS pictures) and audio presentations of emotionally provoking stories. Second type of studies involved

electrical brain stimulation of specific brain regions and measuring of either self-reports of descriptions of evoked emotional states or measuring the ability of the patient to detect emotional states in others. The authors reported that evidence from HIE methods supports the existence of distinct yet partially overlapping neural systems for emotion perception, emotion experience, and formation of emotional motor acts (*see following figure*).



Graphic conceptual depictions of two distinct models of the neural representation of emotion processing.

(A) Emotion experience, perception and expression are distinctly represented in the brain. (B) Emotion experience, perception and expression share partial overlapping representation. HIE studies support this model.

They also concluded that HIE methods have been largely underutilized in the study of emotional phenomena in humans.

AIM OF THE STUDY

Depending on their content, negative or positive, emotions can promote or slow down the cognitive functions. The inhibiting influence of negative affects on the cognitive control and the positive influence of cognitive tasks on the affects have been attributed to the reciprocal inhibition of the neuronal systems implicated in emotion and cognitive functions, but the mechanisms and the temporal process are not well established.

The present project consisted on performing an analysis of the cerebral activity during a protocol of alternating tasks which necessitated the taking of simple decisions, either within an emotionally neutral or within an emotionally negative context, with the aim

- (iv) to compare the performance in an emotionally-negative condition with the performance in an emotionally-neutral condition,
- (v) to search the electrophysiological responses of the cerebral areas implanted, implicated in the cognitive and in the emotional control in the different conditions,
- (vi) to compare the responses of the different regions of the cingulate cortex implanted in the different conditions.

PATIENTS

Six adult subjects (female/male: 3/3, aged 24-45 years, mean age 34 years) participated in this study. They all suffered from drug-resistant focal epilepsy and were candidates for epilepsy surgery in the “Claudio Munari” Epilepsy Surgery Centre, Niguarda Hospital.

Because the location of the epileptic focus could not be identified using non-invasive methods, the patients underwent intracerebral EEG recordings by means of stereotactically implanted multilead depth electrodes (SEEG). The selection of the sites to implant was made entirely for clinical purposes with no reference to the present experimental protocol.

Patients who took part in this study were selected, because their implantation included various regions of the frontal, parietal, temporal lobe or insular cortex. Exclusion criteria were: psychiatric comorbidity, cognitive deficit, visual field deficit, previous cortical resections.

All patients had normal neurological examination, normal or corrected-to normal vision and were not colour-blind.

The patients performed the task 5 days after the implantation of the electrodes. In agreement with the regulations relative to invasive investigations with a direct individual benefit, patients were fully informed about electrode implantation, stereotactic EEG (SEEG), evoked potential recordings, and cortical stimulation procedures used to localize the epileptogenic and eloquent cortical areas, and the patients gave their informed consent. Furthermore, all patients were informed that the present experiment would not influence the epileptologic diagnostic-therapeutic approach and they gave written consent prior to the experiment.

The anatomo-electro-clinical features of each patient are summarized in the following table:

(Abbreviations: Pt: patient, yrs: years, EZ: epileptogenic zone, R: right, L: left, F2: middle frontal gyrus)

| | Pt 1 | Pt 2 | Pt 3 | Pt 4 | Pt 5 | Pt 6 |
|---------------------------|---|---|---------------------------------|--------------------------|--|---------------------|
| | Female, 45 yrs | Male, 29 yrs | Male, 24 yrs | Male, 33 yrs | Female, 44 yrs | Female, 31 yrs |
| Age epilepsy onset | 43 yrs | 24 yrs | 5 yrs | 9 yrs | 19 yrs | 24 yrs |
| Seizures frequency | weekly | monthly | weekly /monthly | weekly | weekly /daily | daily |
| Seizures type | hypertonic with impairment of consciousness evolving to bilateral, convulsive | dyscognitive /dialeptic with elementary motor signs | hypermotor | hypertonic /dystonic | automotor | dystonic, automotor |
| EEG interictal | in sleep, rare rapid R fronto-centro-parietal abnormalities | in sleep, rare temporal sharp waves, bilateral | in sleep, L frontal sharp waves | frontal bilateral spikes | in sleep, fronto-central spikes, bilateral | R frontal spikes |

| | | | | | | |
|---------------------|--|----------------------|--------------------------|--|--|--|
| EEG ictal | ambiguous, probably R frontal | R posterior temporal | L fronto-temporal | fronto-central bilateral | probably R centroparietal | R fronto-central |
| MRI | unclear; previous exeresis of meningioma in R posterior frontal region | normal | normal | normal | normal | R frontal cortical dysplasia, more evident in F2 |
| Suspected EZ | R precentral /central, with rapid involvement of mesial temporal bilaterally | R temporal | L fronto-temporo-insular | Orbito-frontal, no clear side-predominance | R fronto-centro-parietal, with rapid involvement of L mesial fronto-parietal | R precentral |

The position of the electrodes in each patient is listed in the following table:

(The numbers indicate the contacts of each electrode, progressively increasing from the most internal to the most lateral contacts. The letters indicate the electrodes, they are arbitrary and vary among the various epilepsy centre.

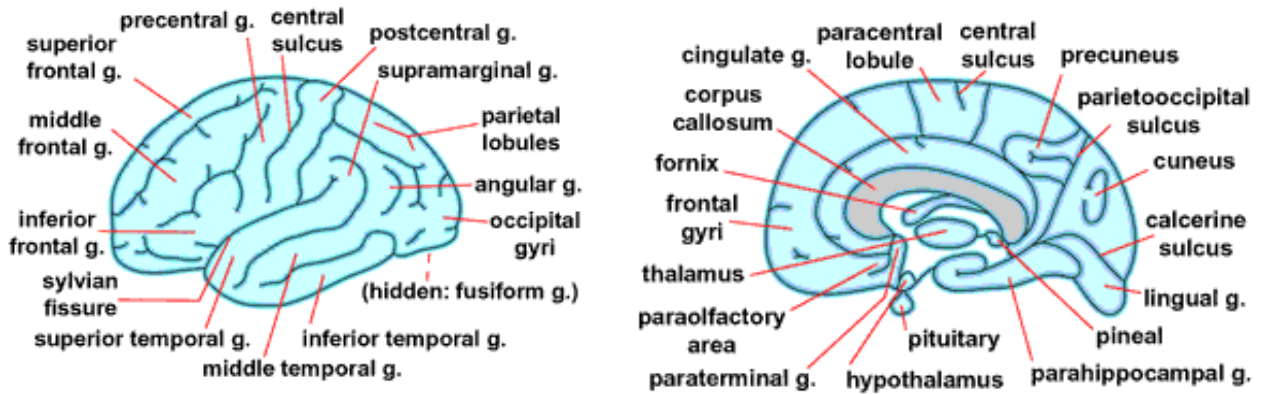
Abbreviations: F1: superior frontal gyrus, F2: middle frontal gyrus, F3: inferior frontal gyrus, Hip: hippocampus, ACC: anterior cingulate cortex (pgACC: pregenual ACC), MCC: mid cingulate cortex (aMCC: anterior MCC, pMCC: posterior MCC), PCC: posterior cingulate cortex, RSC: retrosplenial cingulate cortex, TTG: transverse temporal gyrus, SMA: sensorimotor area, T1: superior temporal gyrus, T2: middle temporal gyrus, T3: inferior temporal gyrus, sup: superior)

| | Pt 1 bilateral | Pt 2 right | Pt 3 left | Pt 4 bilateral | Pt 5 bilateral | Pt 6 right |
|--|---------------------------|-----------------------|----------------------|-----------------------------|---------------------------|-----------------------|
| pgACC | | | H'1-3; G'1-2 | G1-3; X1-2; G'1-3; X'1-2 | G1-2; H1-2; H'1-2 | G1-2; H1-2 |
| aMCC | H1-2 | | F'1-3 | H1-3; H'1-4; J1-2; J'1-2 | F1-3; E1-3 | N1-2; F1-2 |
| pMCC | | H1-3 | | N1-2; P1-3; N'1-2; P'1-3 | N1-3; Y1-2 | |
| PCC | | P1-2 | | | P1-3; P'1-3 | |
| RSC | | Q1-4 | | | W1-3 | |
| Insula long gyri | S'1-4; S1-3 | S1-3; U2-4 | R'1-3; S'1-3 | | | |
| Insula short gyri | U'1-3; U1-3 | R2-3; T4-5; X1-3 | T'1-2; Q'1-3 | | R1-2 | R1-3; X2-3 |
| Hip anterior | B'1-5; B1-4 | B1-5 | B'1-5 | | | |
| Hip posterior, para-Hip gyrus | | C3-5, C1-2 | | | | |
| T1 anterior | | T6-9 | | | | |
| T1 middle | U'6-8; U6-10 | U5-9 | T'4-10 | | | |
| T1 posterior | | W8-11 | | | | |
| T2 anterior | | B9-13 | I'9-11 | | | |

| | | | | | | |
|--|-----------------------------|------------|---------------------------|---------------------------------|---------------|-----------------------|
| T2 middle | B'10-15; B7-14 | C12-14 | B'12-14 | | | |
| T2 posterior | | F11-15 | | | | |
| T3 middle | | D7-9 | | | | |
| TTG | | W3-4 | | | | |
| temporal pole | I'1-10 | I1-9 | I'1-5 | | | |
| frontal pole | | | O'1-2 | | | |
| gyrus orbitalis | | | O'5-10; Y'1-2 | | | |
| gyrus rectus | | | X'1-2 | | | |
| F1 anterior | K'5-7; K3-7 | | X'10-14; Y'13-14 | X7-9; X'5-9 | X1-17 | J5-7; Y1-2; E1-2 |
| F1 middle | | | | J6-8; J'5-7 | Y5-10 | Y6-7 |
| F1 posterior | | | | K5-7; K'5-9 | M6-8 | J1-3; K4-7 |
| F2 anterior | | | | | F5-8 | E7-10 |
| F2 middle | | | G'12-15; F'8-10 | G'11-14 | H7-13; H'8-14 | H7-11 |
| F2 posterior | H7-11 | | H'10-15; E'6-10 | H12-14; H'9-14 | E6-10 | F6-10 |
| F3 middle | | | | | G9-13 | |
| F3 posterior | | | | G11-15 | | G9-13; X8-9 |
| F3 inferior: frontal operculum central operculum parietal operculum | | R7-9; X4-8 | O'11-13; Q'7-10 R'8-10 | | R5-9 | R6-8 |
| precentral gyrus | S'5-10; S4-10 | S7-10 | S'6-10 | | | |
| precentral gyrus | Z'4-12; Z6-9 | H13-15 | M'5-10 | N11-16; Z5-9; N'11-14; Z'5-9 | N6-12 | M6-10; Z8-9; N9-12 |
| postcentral gyrus | P'8-12; P8-14 | P13-17 | | P10-14; P'9-16 | P7-13; P'9-15 | |
| SMA | K'1-2; K1-2; Z'2-3; Z1-4 | | M'1-2 | Z1-4; Z'1-4 | M1-4 | M1-3 |
| pre-SMA | | | E'1-3 | K1-2; K'1-3 | | K1-3 |
| angular gyrus | | Q14-18 | | | W11-15 | |
| supramarginal gyrus | | | | P15-17 | Z6-9 | |
| sup. parietal lobule | | | | | Q4-9 | |
| precuneus | | | | | Q1-2; Z1-3 | |
| paracentral lobule | P'2-5; P1-5 | | | | | Z1-3 |
| fusiform gyrus | | D1-3 | | | | |
| lingual gyrus | | F1-5 | | | | |

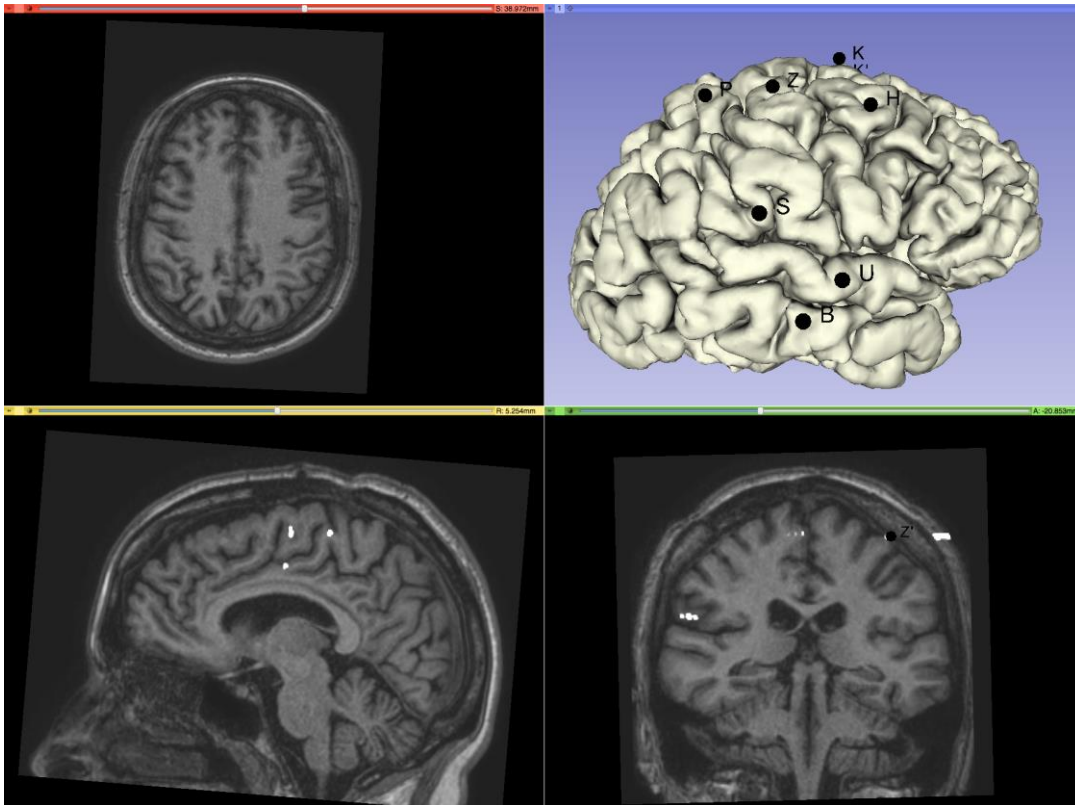
In summary, all patients had electrodes implanted in the cingulate cortex, in the anterior, mid or posterior part; all subjects had electrodes implanted in the frontal lobe, all but one were implanted in the insular cortex and in the parietal lobe while three patients were implanted in the temporal

lobe. Two patients (1 and 4) received a bilateral, quasi symmetrical, exploration while the patient 5 received a right hemisphere exploration with some sentinel electrodes to the left. Patients 2 and 3 underwent a right and left hemisphere exploration, respectively.

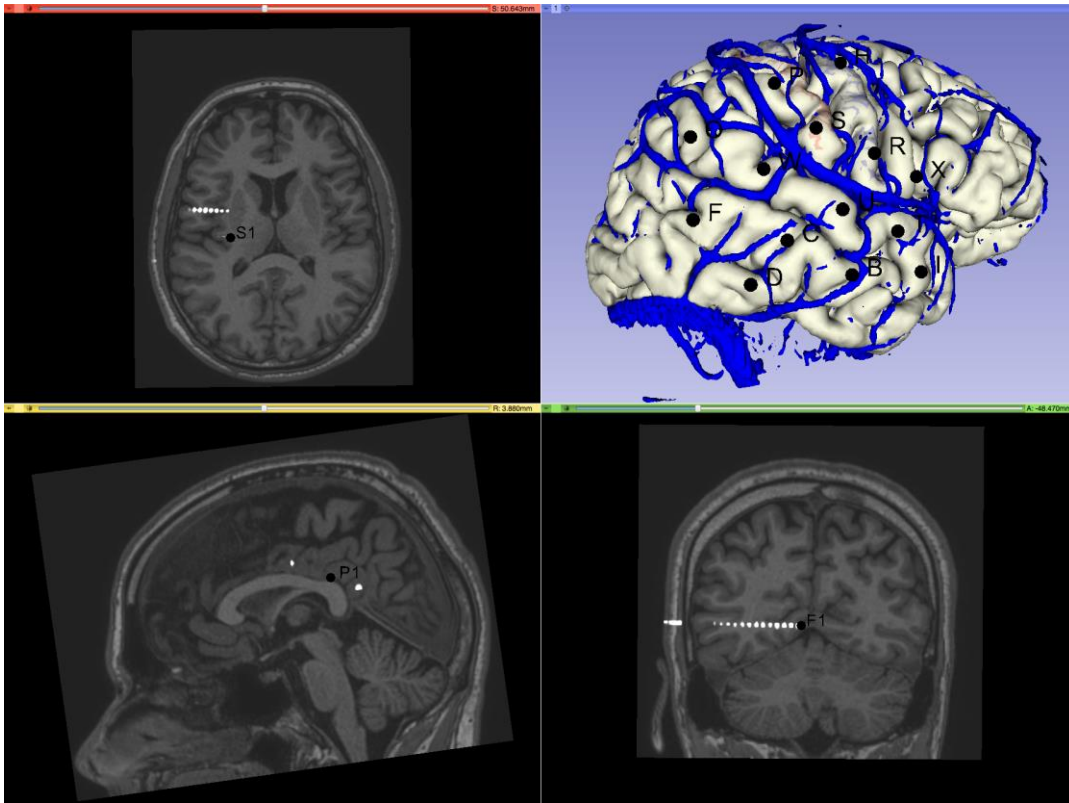


The implantation schemes of the six participants are shown in the following figures.

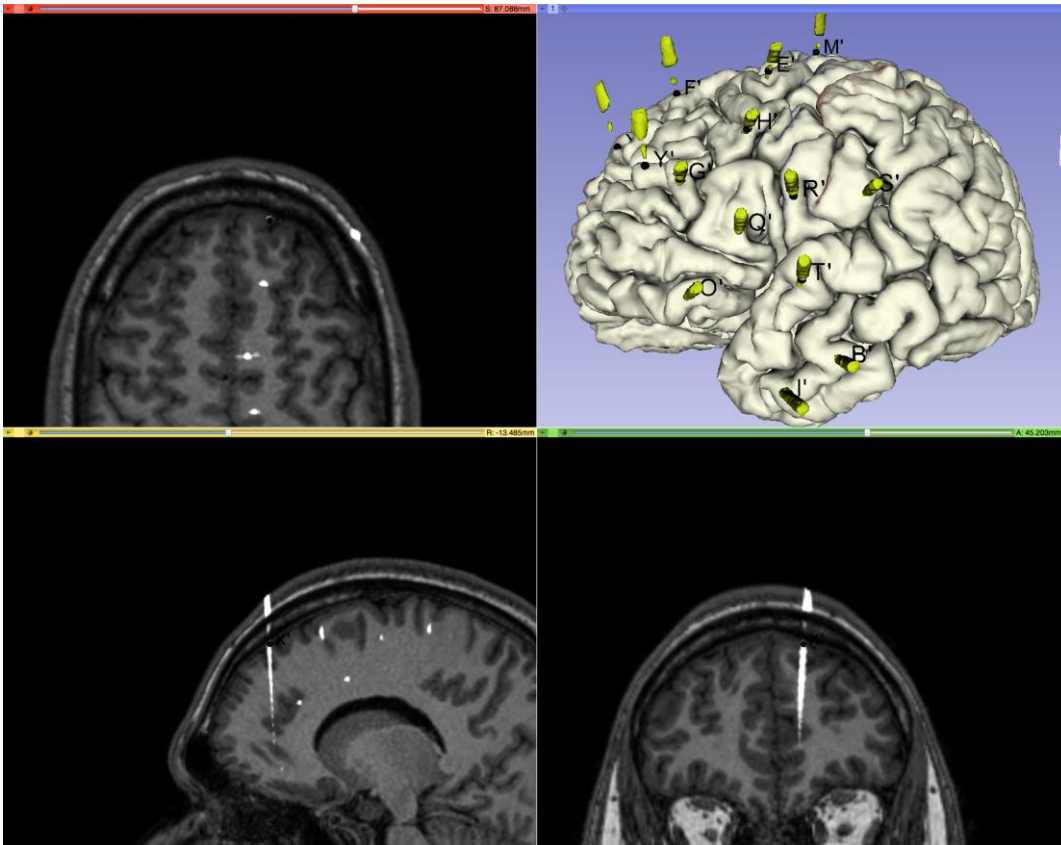
Patient 1



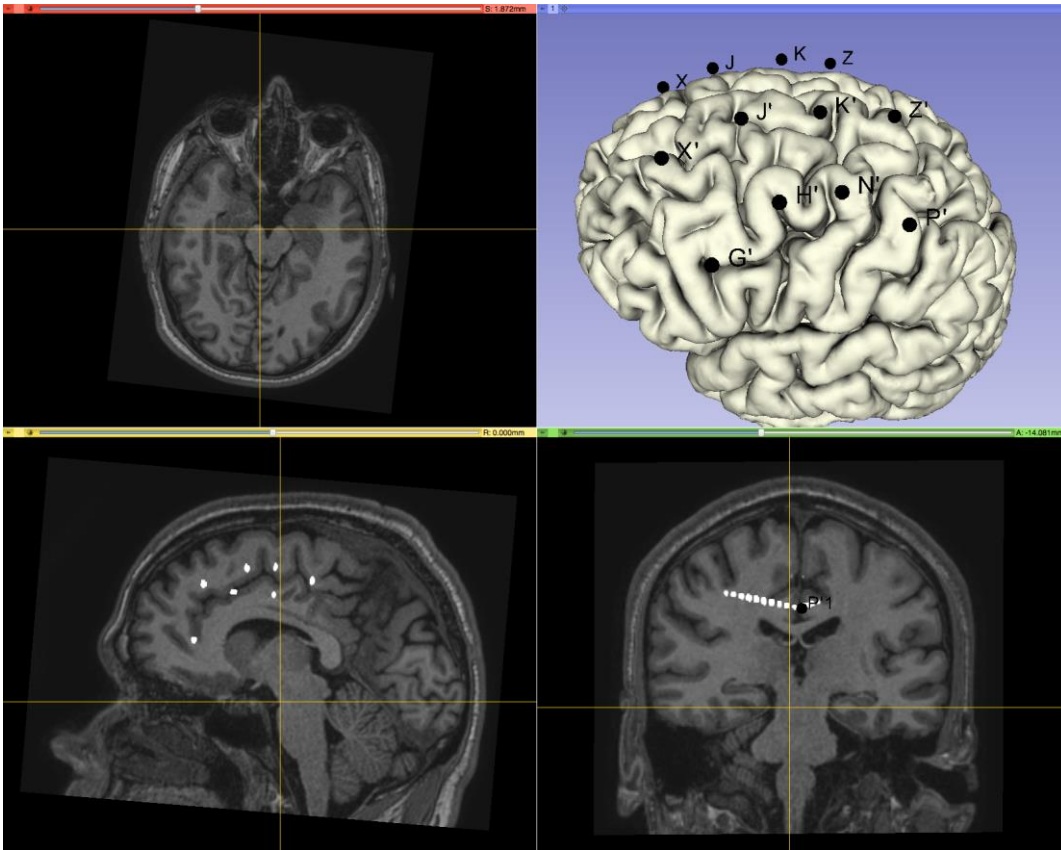
Patient 2



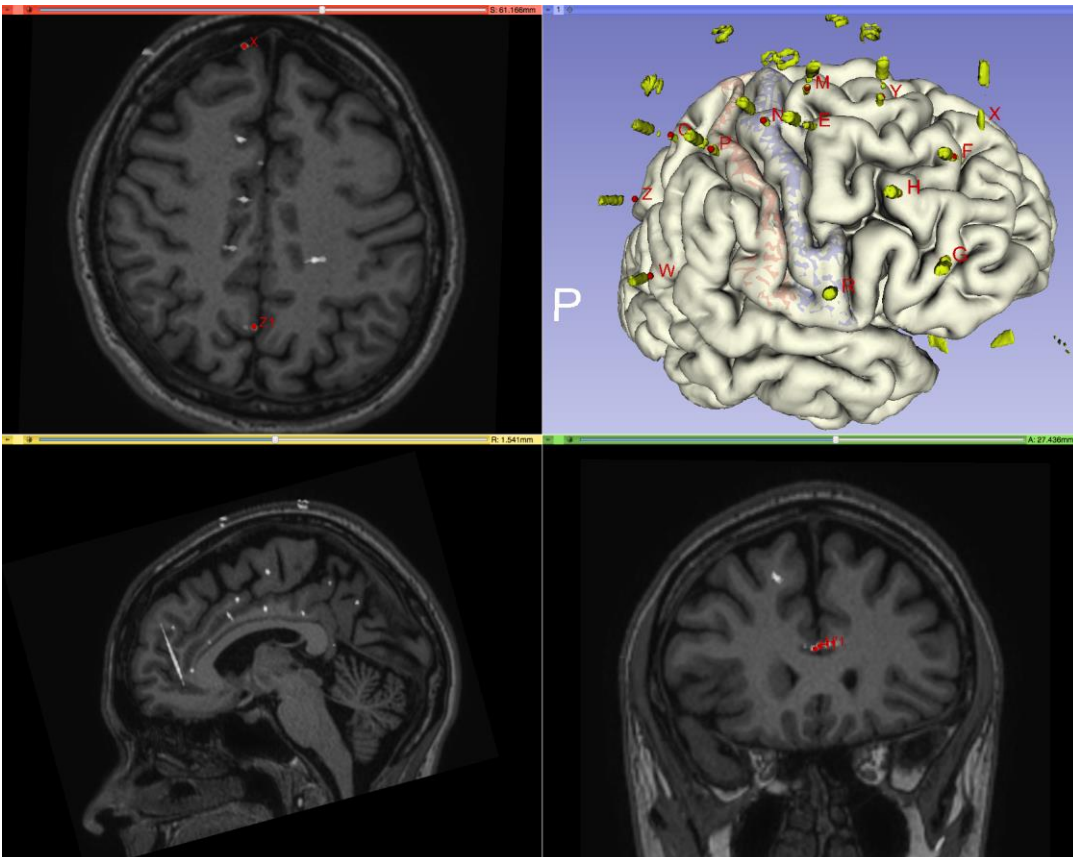
Patient 3



Patient 4



Patient 5



Patient 6

(it was not possible to obtain a master scene of the implantation cause to technical problems)

METHODS

Experiment

The experiment consisted on a protocol of alternating tasks which necessitated the taking of simple decisions, either within an emotionally neutral or within an emotionally negative context.

An emotionally negative context was induced by negative pictures shown for 3 sec to the subjects before their decision making; the pictures were taken from IAPS: International Affective Picture System.

The IAPS has been developed to provide a set of normative emotional stimuli for experimental investigations of emotion and attention. The two primary dimensions are one of affective valence (ranging from pleasant to unpleasant) and one of arousal (ranging from calm to excite). The stimulus-materials evoke reactions across the entire range of each dimension: mean pleasure ratings for these pictures range from very unpleasant to very pleasant. Similarly, a wide range of arousal levels is elicited by these stimulus-materials. The degree of arousal is uncorrelated with the pleasantness of the picture. Pictures depicting unpleasant events, however, show a tendency to indicate high arousal. For items rated as neutral in valence (i.e., those occurring at and near the midline of the valence dimension), arousal ratings do not attain the high levels associated with either pleasant or unpleasant materials. (Lang et al, 2005, [International affective picture system \(IAPS\): Instruction manual and affective ratings](#)).

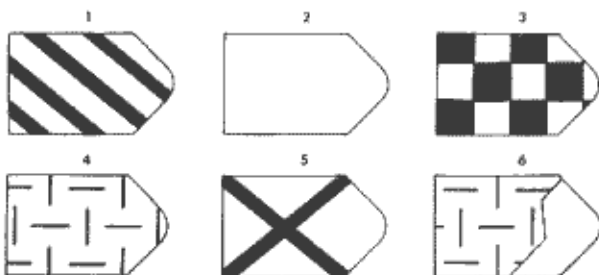
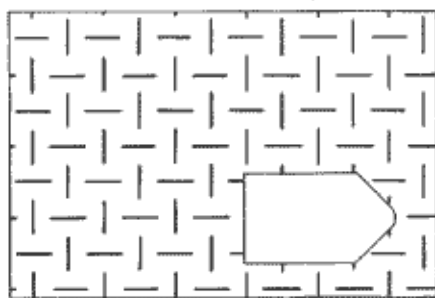
Similarly, neutral images were extrapolated from IAPS.

Both the negative and the neutral pictures shown to the participants were chosen among those with low-moderate arousal (*see for instance the following table and the following pictures which are part of the pictures shown to the participants*).

| Slide N° | Description | Valence mean (SD) | Arousal mean (SD) |
|----------|-------------|-------------------|-------------------|
| 3350 | Infant | 1.88 (1.67) | 5.72 (2.23) |
| 6021 | Assault | 2.21 (1.51) | 6.06 (2.38) |
| 7002 | Towel | 4.97 (0.97) | 3.16 (2.00) |
| 5390 | Boat | 5.59 (1.54) | 2.88 (1.97) |



The Raven's Standard Progressive Matrices (RSPM) were used for the cognitive task. Raven's Matrices is a non-verbal assessment that tests observation skills and the ability to think clearly. In each test item, the subject is asked to identify the missing element that completes a pattern.

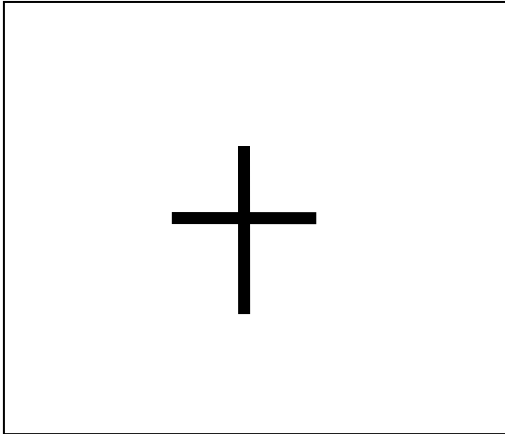


The Raven matrices used in the present trial were simplified in 2 choices.

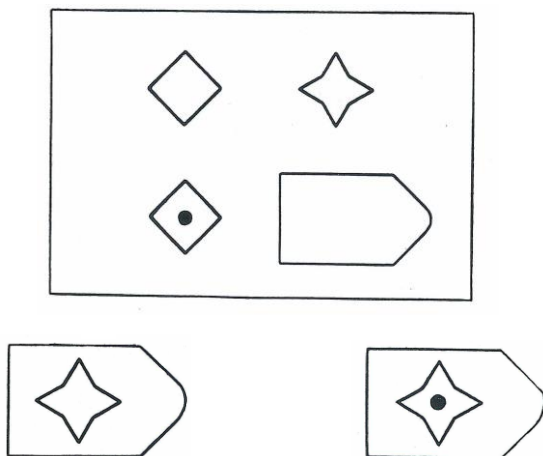
Pictures were shown to the subjects by means of the software E-Prime 2.00 (Psychology Software Tools).

In detail, each subject performed the trial in three experimental conditions:

(i) a “base-condition”, consisting in the vision of slides containing a fixation cross, shown for a duration of 3 sec; during this time the participant was instructed to simply look at the cross.



After 3 sec the fixation cross slide was replaced by a slide with the Raven matrices simplified in 2 choices (see for instance the following figure), projected for a non-fixed (“indefinite”) duration:

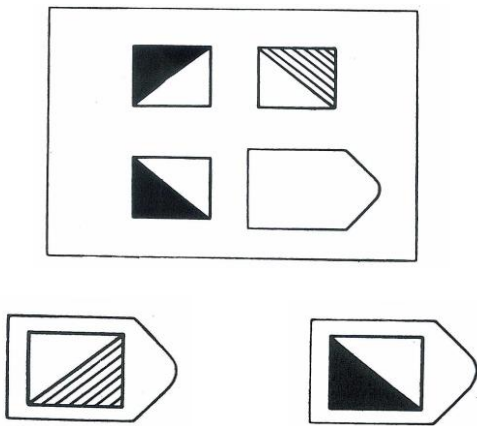
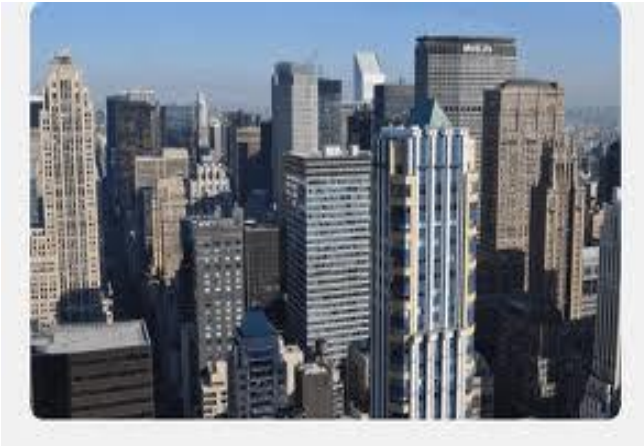


The patient was required to indicate the image that completes the principal one by pressing, as fast as possible, one of the two response buttons: the button M if the solution was located to the right or the button Z when the correct answer was located to the left.

Only once the participant had performed a choice, the Raven slide was replaced by the fixation cross.

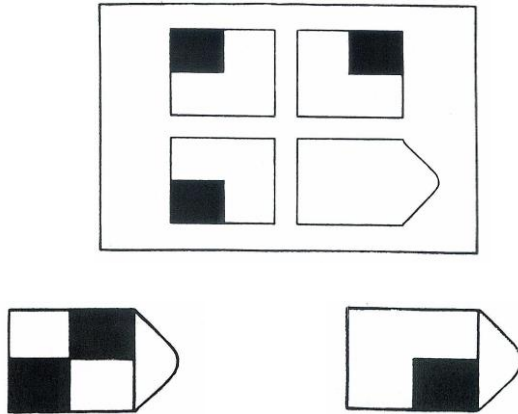
Totally, 80 slides were projected: 40 fixation cross for 3 sec each, alternated with 40 Raven shown for an “indefinite” duration each.

(ii) a “neutral-condition”, in which the fixation cross was replaced by neutral images (see for instance the following pictures):



(iii) a “negative-condition”, in which the fixation cross was replaced by negative valence pictures (see, for instance, the following pictures):





In the three conditions, the Raven slides were projected randomly, yet with similar level of difficulty.

No time limits for responses were imposed so that participants could not use a simple strategy where they made no responses to avoid seeing negative pictures.

The estimated time of the whole experiment was approximately 15-20 minutes.

For the first 4 patients, the succession of the conditions was: neutral, negative, base (neu-neg-base) whereas the last 2 subjects performed the experiment in the following order: base condition followed by negative and neutral one (base-neg-neu).

At the end of the whole test, a questionnaire was offered to the participant aimed to evaluate the intensity of the sensation and the unpleasantness felt during the exposure to the negative pictures (*see for instance the questionnaire offered to the patient 1*).

Che sentimenti ho avuto dopo la visione della prima serie di diapositive

- Indifferenza
- Gioia
- Tristezza
- Non so

Che sentimenti ho avuto dopo la visione della seconda serie di diapositive

- Indifferenza
- Gioia
- Tristezza
- Non so

Quale sentimento riflette meglio quello che provato dopo la visione della seconda serie di diapositive

- Indifferenza
- Tristezza
- Disgusto
- Avversione
- Malinconia
- Ansia
- Non so
- Altro... specificare:

Quanto intenso era il sentimento che ho provato dopo la visione della seconda serie di diapositive

- 2/10
- 6/10
- 8/10
- 10/10

Altri commenti:

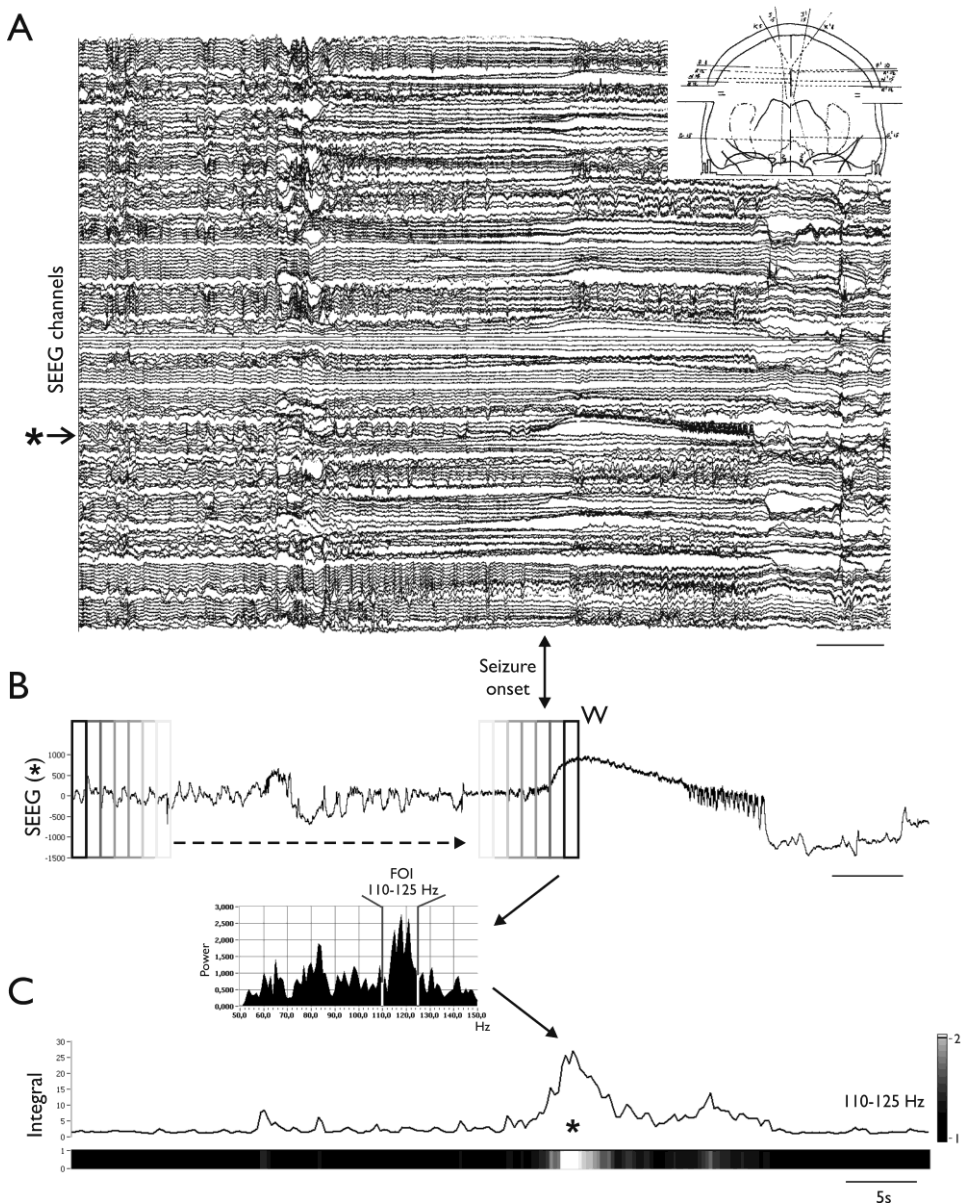
Data

Nome, Cognome (in stampatello)

Firma

Data acquisition and analysis

Stereo EEG signals sampled at 1 kHz were recorded on a Neurofax EEG-1100 system (Nihon Kodan, Japan) with 5 to 18 contacts per intracranial electrode and a maximum number of 170 recording channels. Data were digitized to hard disk with 16-bit resolution. Monopolar SEEG data were exported in ASCII format and converted to the format of the software Elpho-SEEG developed in LabView, in the Besta Institute (Gnatkovsky et al, 2011) (see following figure, A). For all recording sites, data were saved as a full frequency range of fast Fourier transform (FFT) power spectra (0.016-300 Hz) for each epoch (2 sec each) by sliding windows of 500msec with overlap of 100msec (see following figure, B).



A: Complete profile of pre-surgical SEEG recordings (170 channels) from a patient with drug resistant epilepsy. The scheme of the bilateral intracranial electrodes implanted with Talairach's reference frame is shown in the right inset. Onset of a partial seizure is marked by the arrow on the bottom. The trace marked by the asterisk is amplified in B.

B: Method to assess the distribution and power of the Frequency Of Interest (FOI). The power spectrum of the SEEG signal calculated by sliding a 500msec window (W) across all recordings is illustrated in the insert (a FOI of 110-125 Hz is selected as example).

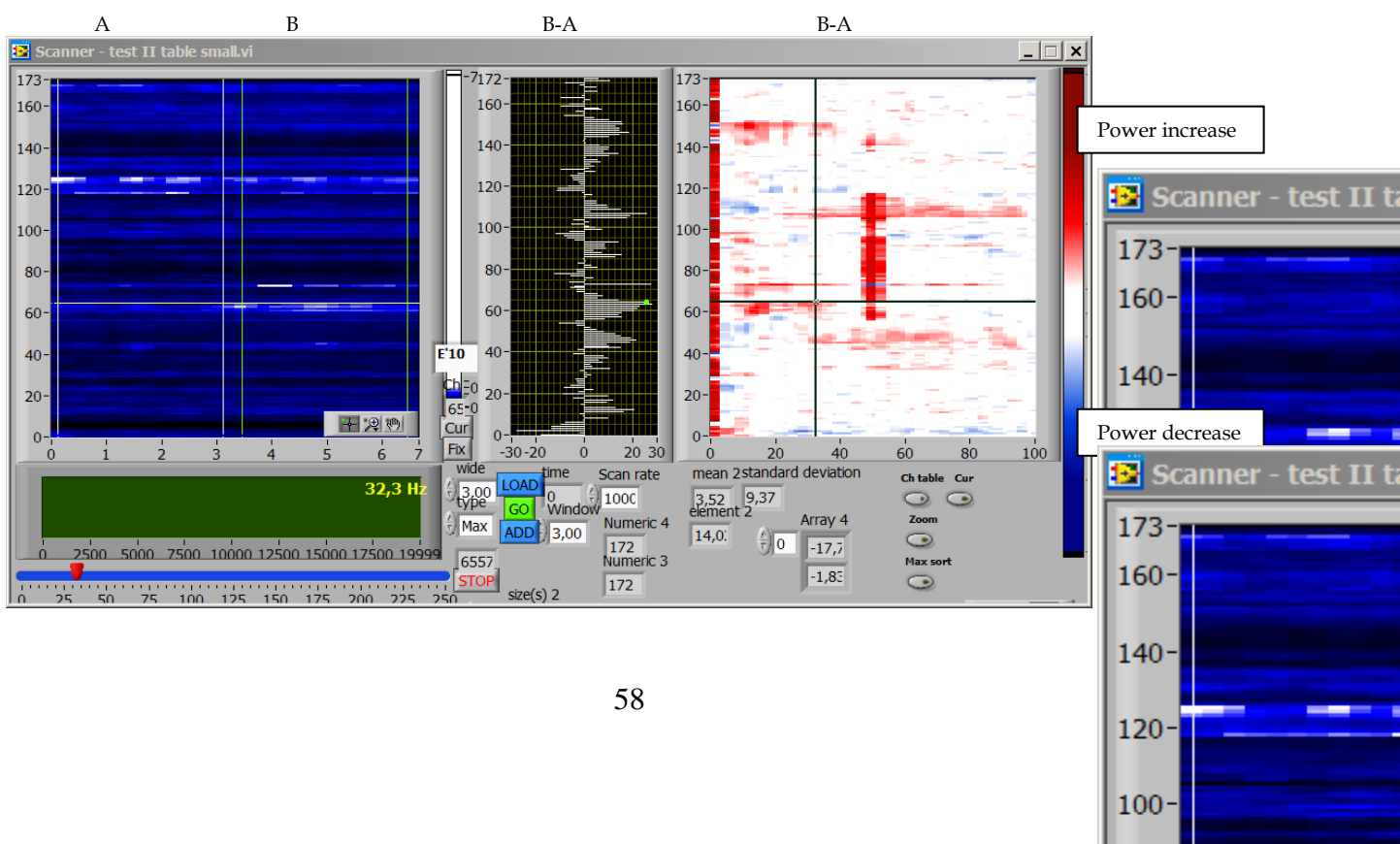
C: changes with time of the FOI power integral of the trace shown in B represented as a continuous

line (upper trace) or as intensity map (lower line). The peak and the corresponding high signal (white, marked by the asterisk) show maximum FOI integral power during the seizure. Time calibration is the same in A, B and C.

For each patient 120 epochs (40 during exposure to negative images, 40 to neutral ones and 40 during exposure to the fixation cross) were averaged and analysed. Similarly, 120 epochs were averaged and analysed during the Raven trial in the three conditions. The integral of the power spectrum was calculated for all frequency ranges included between 1 and 250 Hz and changes with time were represented as a continuous line and as a colour intensity map.

The difference between Frequency Of Interest (FOI) powers at a condition A and at a condition B was calculated (see following figure). Only changes in power larger than threshold significance of 20% were considered and were further utilized for the following analysis.

For each selected frequency range, compared results (B-A powers) were represented as gradient of either red or blue, in case of increase or decrease of power, respectively, during the different conditions. The difference between the two power profiles that reflects the changes in power observed during the condition B compared to the condition A is illustrated in the middle column of the following figure. Negative and positive values show decreases and increases, respectively of the FOI power. As final result a colour-coded map was generated (see last column). Blue and red respectively indicate a decrease and an increase in the power content during the condition B. This comparison was performed for all available frequencies in the range between 1 and 250 Hz. (For instance, in the following picture, at a frequency of 32.3 Hz, the power of the electrical activity measured by the contact 10 of the electrode E' has increased of about 25%, as shown by the green circle in the middle column).



For the present study, the following parameters were examined:

- frequency modifications during the exposure to the neutral images, the negative images and the fixation cross;
- frequency changes during the accomplishment of the Raven trial in the three conditions;
- reaction time (R-T): time between the presentation of each Raven slide and the moment the subject pressed the response button;
- errors committed by each participant during each Raven trial.

Frequency changes between the range 1-140 Hz were included in the study; this frequency range was chosen in order to avoid frequencies faster than 150 Hz that, most probably, indicate abnormal activity related to the epileptogenic process.

Finally, frequency modifications in the gamma band between 30-140 Hz were particularly taken into account.

A total of 1365 contacts were analysed.

Contacts exploring lesional areas and those showing ictal paroxystic abnormalities were excluded.

RESULTS

Behavioural results

For patient 3, reaction time (R-T) was not associated with the emotional content of the pictures but rather with the complexity of the Raven matrices; furthermore the mean reaction time, as well as the total number of erroneous responses, progressively decreased from the first to the last task, indicating learning mechanisms/adaptability, independently of the emotional valence of the associated pictures. This finding could be due either to the low arousal per se of the negative images and to the fact that it is difficult to induce highly disturbing emotions in a "non-ecological" condition in the lab.

Patients 1 and 2 exhibited either slower R-T or more errors in during the accomplishment of the Raven task of the condition (base-condition) that followed the negative one.

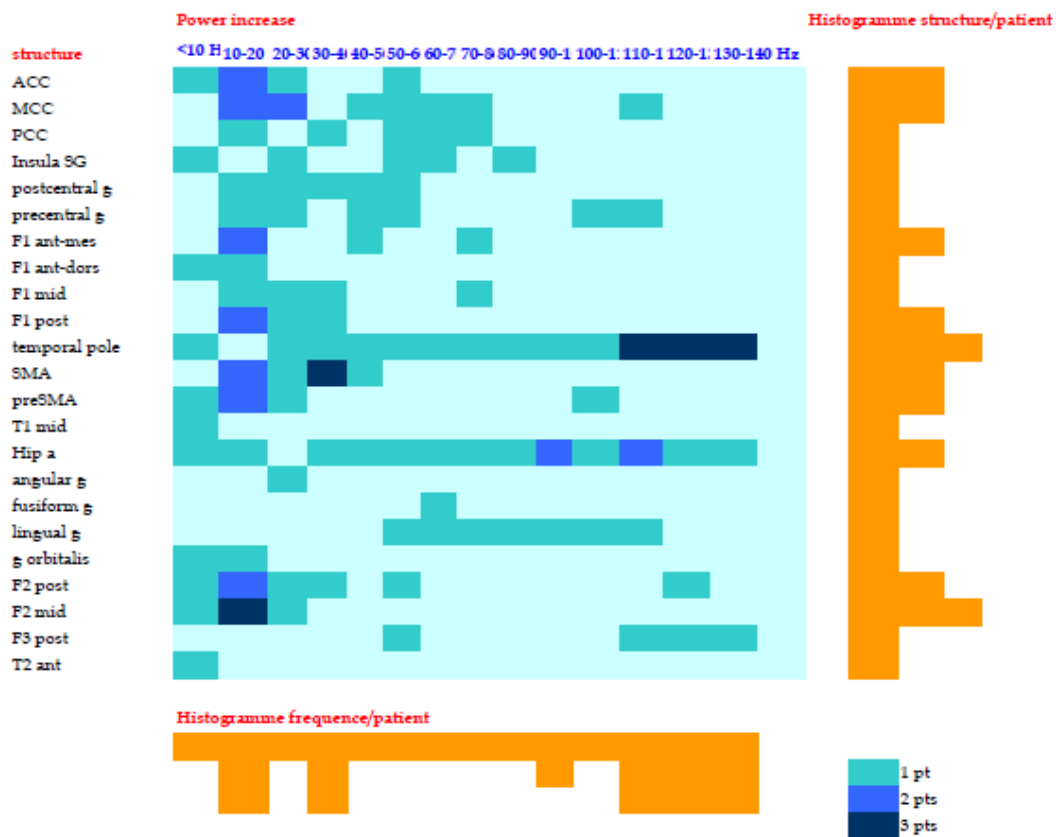
Finally, 3 patients did more errors and showed a faster (patient 4) or slower (patients 5, 6) reaction time in the Raven task of the negative condition compared to the other two ones. Interestingly, patient 4 spontaneously reported that his bad performance was strictly related to the negative-pictures distracters, while patient 5 reported that the negative pictures had very high (negative) valence and arousal, with some pictures provoking to her nausea/vomit and extreme sadness, so a huge effort was required in order to stay on to the task.

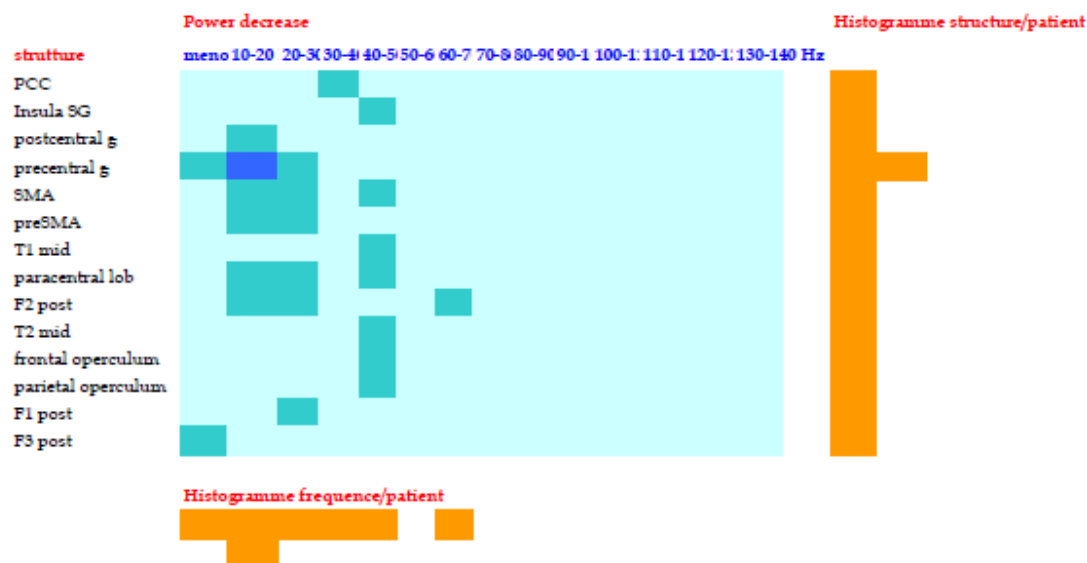
In the questionnaire offered at the end of the test, emotional arousal of the negative images was rated 2/10 by patient 3; 6/10 by patient 6; 8/10 by patient 4; 10/10 by patients 1, 2, 5.

| | Neutral condition | Neutral condition | Negative condition | Negative condition | Base condition | Base condition | notes |
|------|-------------------|-------------------|--------------------|--------------------|----------------|----------------|--------------|
| | Mean R-T | errors | Mean R-T | errors | Mean R-T | errors | |
| Pt 1 | 3241,375 msec | 4 | 3234,15 msec | 2 | 5512,75 msec | 2 | neu-neg-base |
| Pt 2 | 3238,45 msec | 12 | 2375,3 msec | 10 | 2912,87msec | 13 | neu-neg-base |
| Pt 3 | 5692,6 msec | 10 | 4149,8 msec | 8 | 3918,675 msec | 6 | neu-neg-base |
| Pt 4 | 7020,025 msec | 3 | 4445 msec | 9 | 5497,7 msec | 7 | neu-neg-base |
| Pt 5 | 2867,8 msec | 7 | 7814,775 msec | 11 | 7558,725 msec | 4 | base-neg-neu |
| Pt 6 | 3167,475 msec | 7 | 4228,7 msec | 10 | 3155,45 msec | 6 | base-neg-neu |

Frequency modulations

(i) Analysis of frequency activations and suppressions of the explored structures during the exposure to negative images compared with neutral ones, showed that there were 2 peaks of activations, namely between 10-60 Hz - prevalently in the range 10-20 Hz and 30-40 Hz - and between 100-140 Hz and concerned the mid-cingulate cortex (MCC), the SMA-proper (supplementary motor area) in 4 patients, and the short gyri of insula, the temporal pole, the frontal antero-mesial cortex, the pre-SMA, the precentral gyrus and the intermediate part of the middle frontal gyrus in 3 patients.

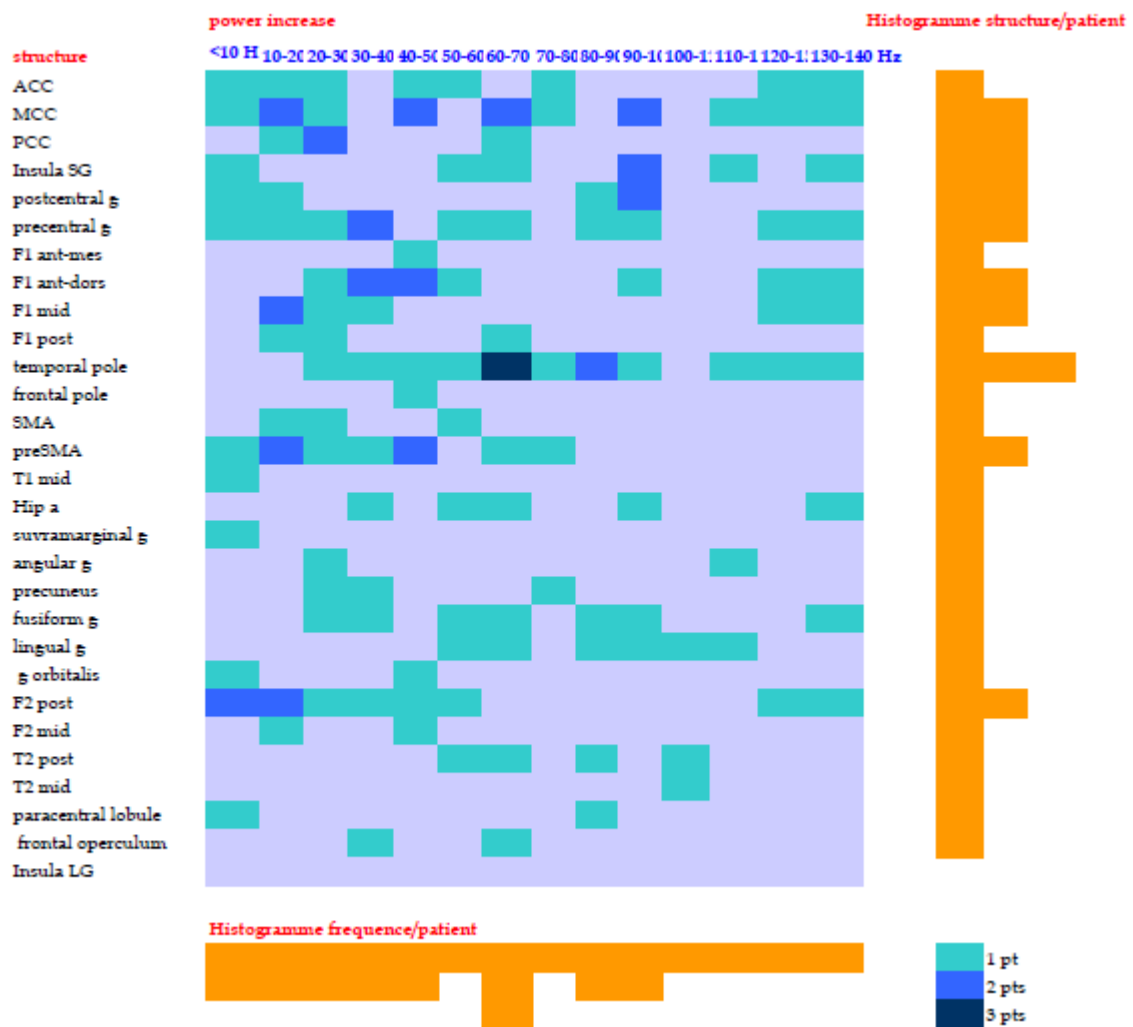


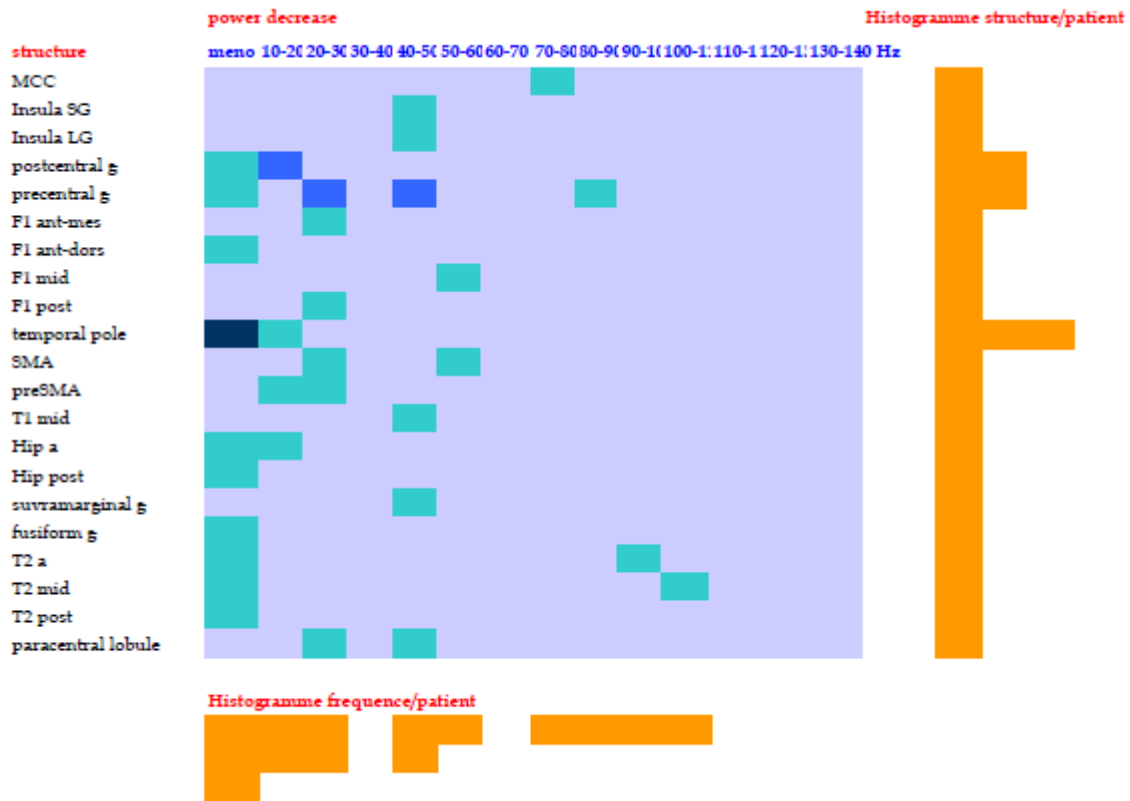


Interestingly, only the short gyri of insula (anterior insular cortex), but not the long gyri, were activated during the exposure to the negative pictures.

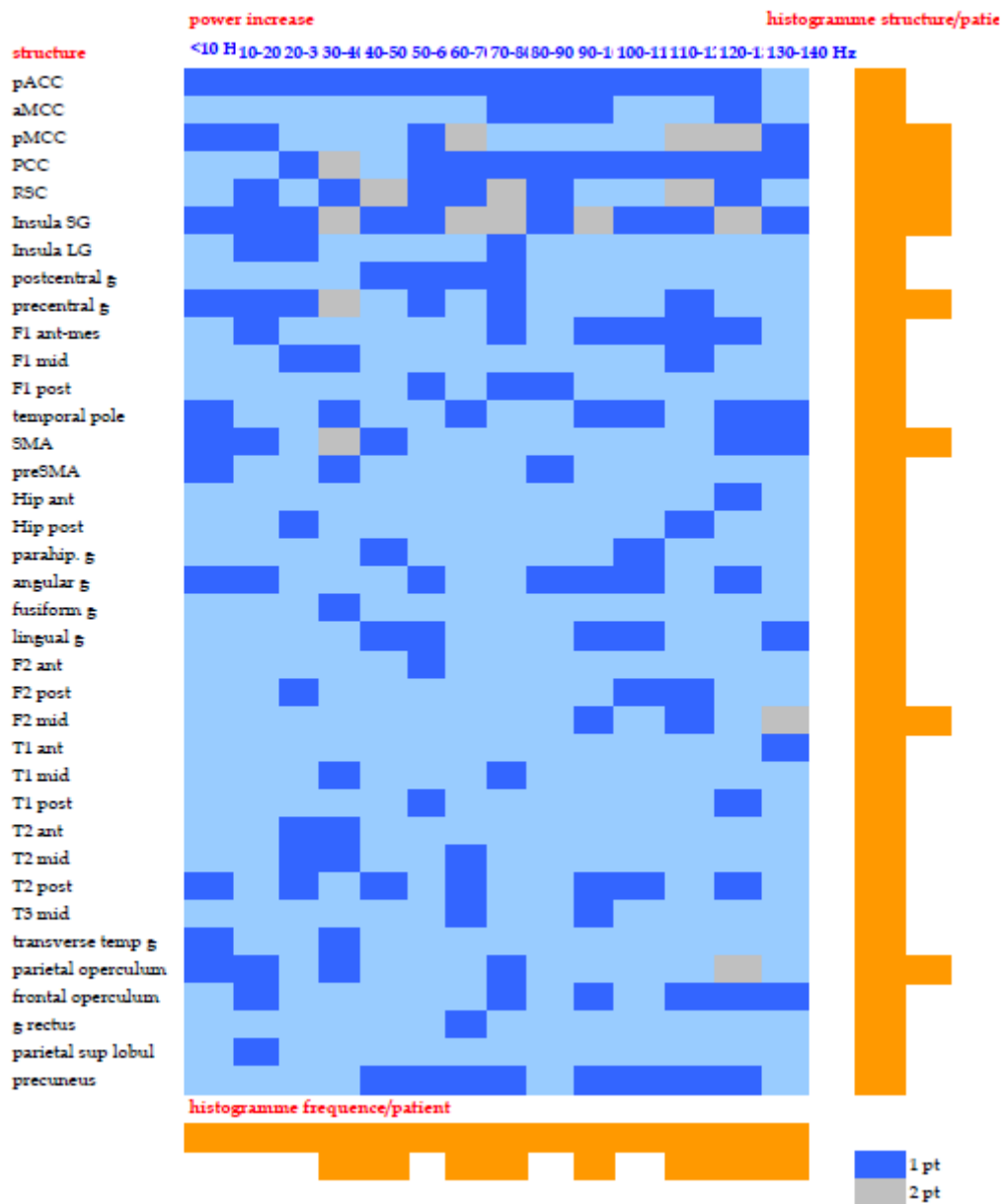
Furthermore, in bilateral implantations, the homologous cortical regions of both cerebral hemispheres were activated and deactivated strictly within the same frequency range.

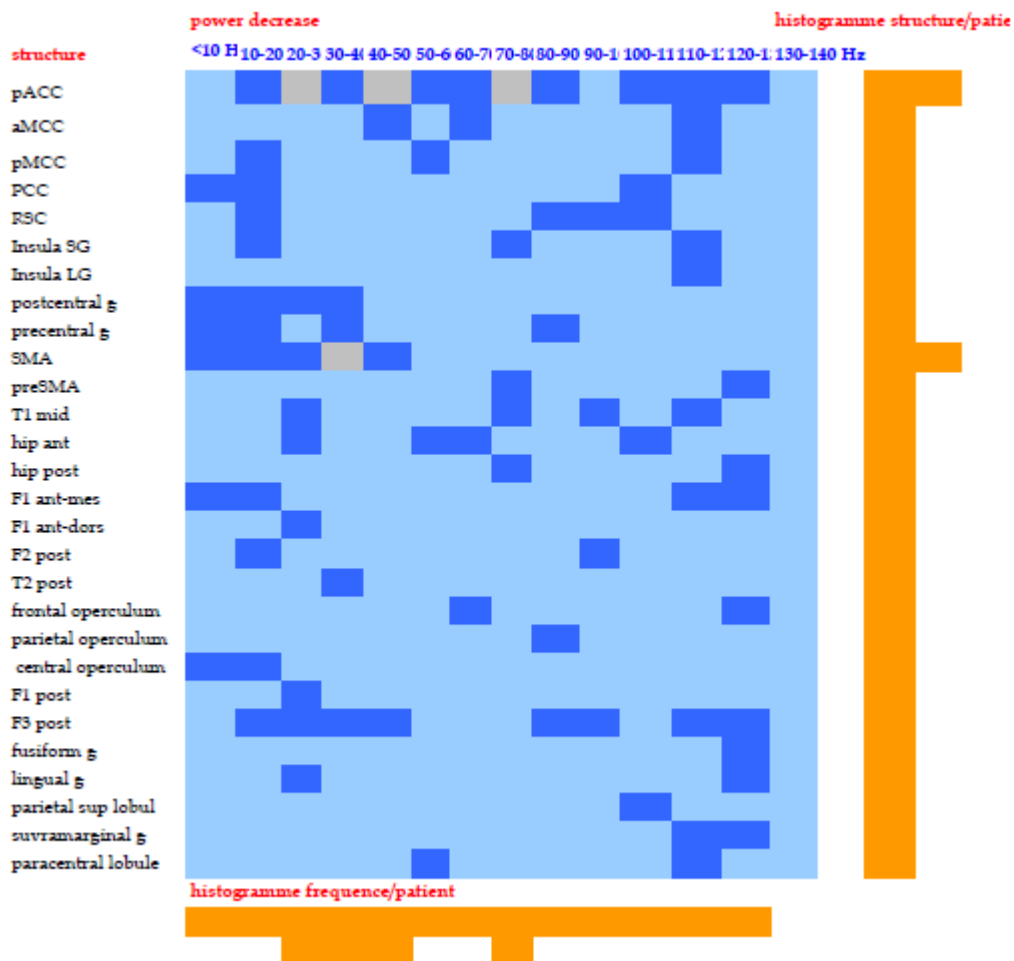
(ii) Comparing the frequency changes during the exposure to negative images with the condition without images (fixation cross), we found a main peak of activations between 40-70 Hz and the structures mostly concerned were the MCC in 5 patients, and the anterior cingulate cortex (ACC), the short gyri of insula, the superior frontal gyrus in its antero-dorsal and posterior parts, the posterior part of the middle frontal gyrus, the pre-SMA and the temporal pole in 3 patients. Additionally, results regarding specifically the insular cortex as well as the bilateral implantations were similar to the previous analysis.



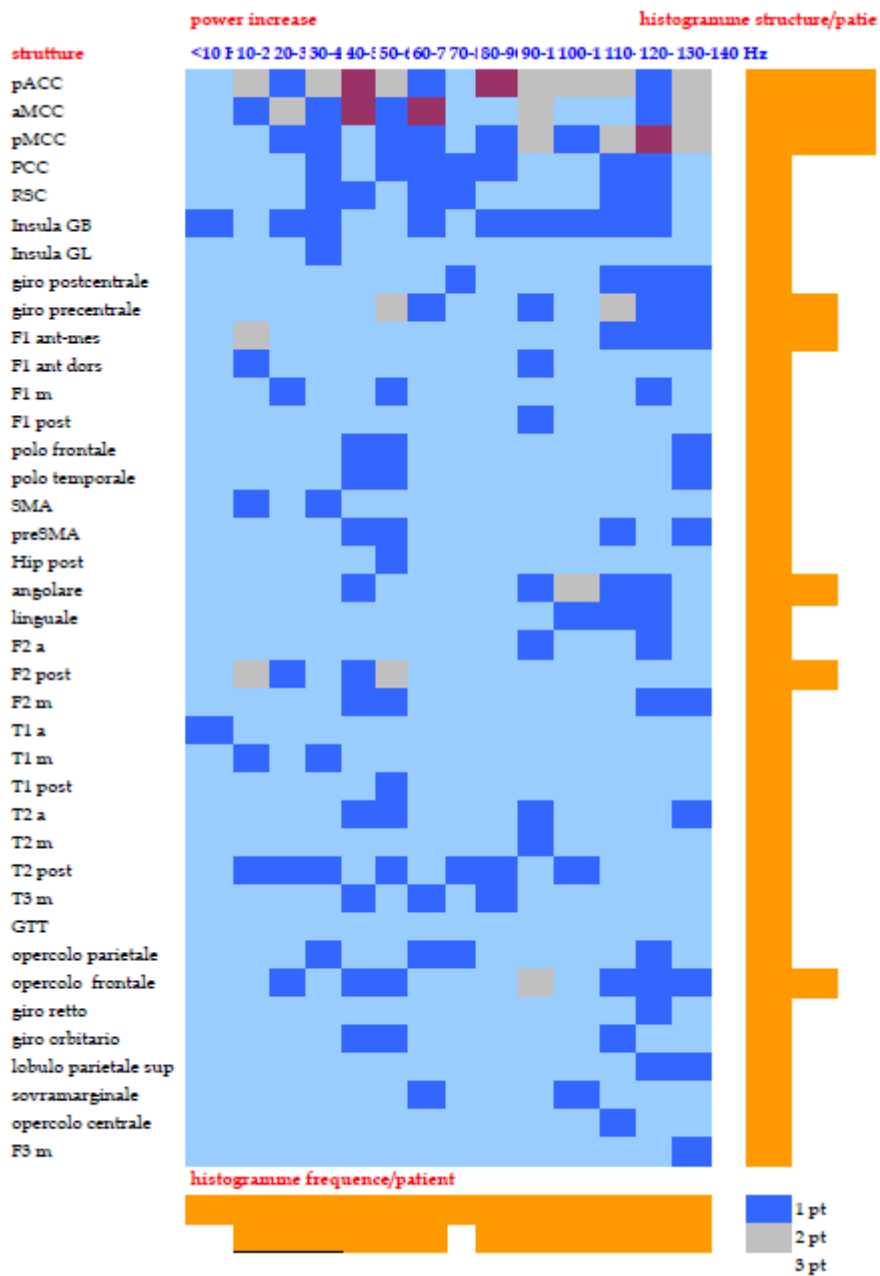


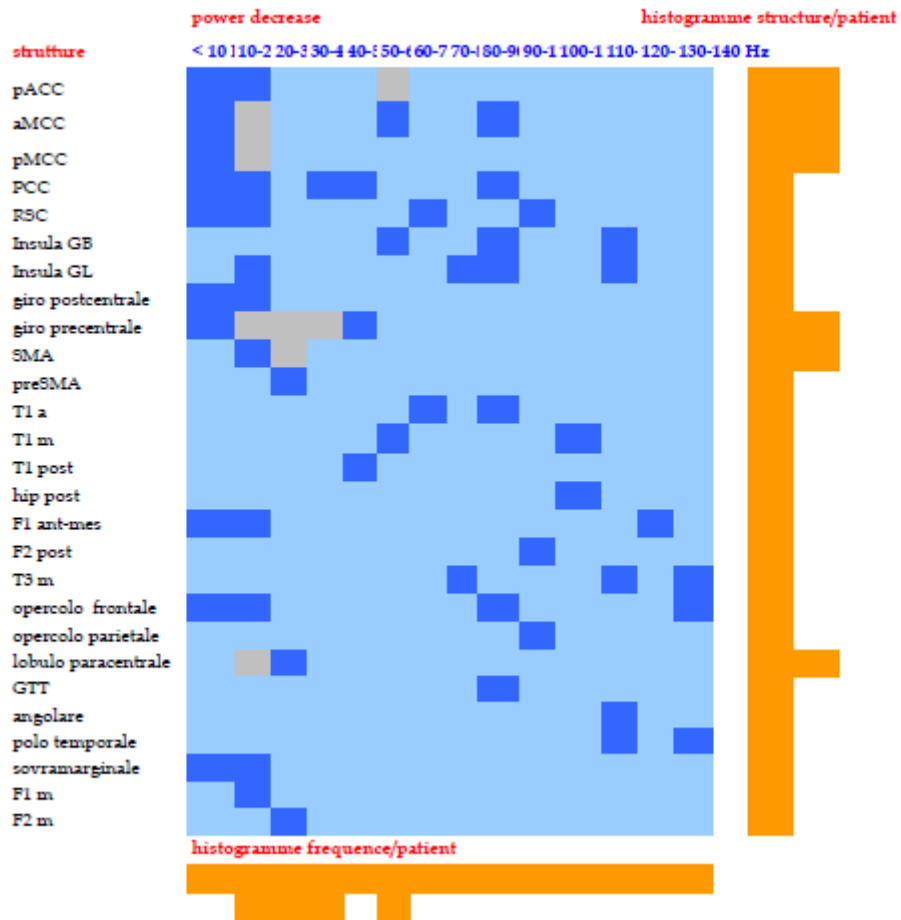
(iii) Frequency modifications during the accomplishment of the Raven trial in the negative condition compared with its accomplishment in the neutral one, resulted in power increase in the gamma band (>30Hz) for 2 participants in the short gyri of insula, posterior cingulate cortex, precentral gyrus, SMA, middle frontal gyrus and parietal operculum as well as in power decrease, mainly in low-gamma band, in SMA and anterior cingulate cortex for 2 subjects.





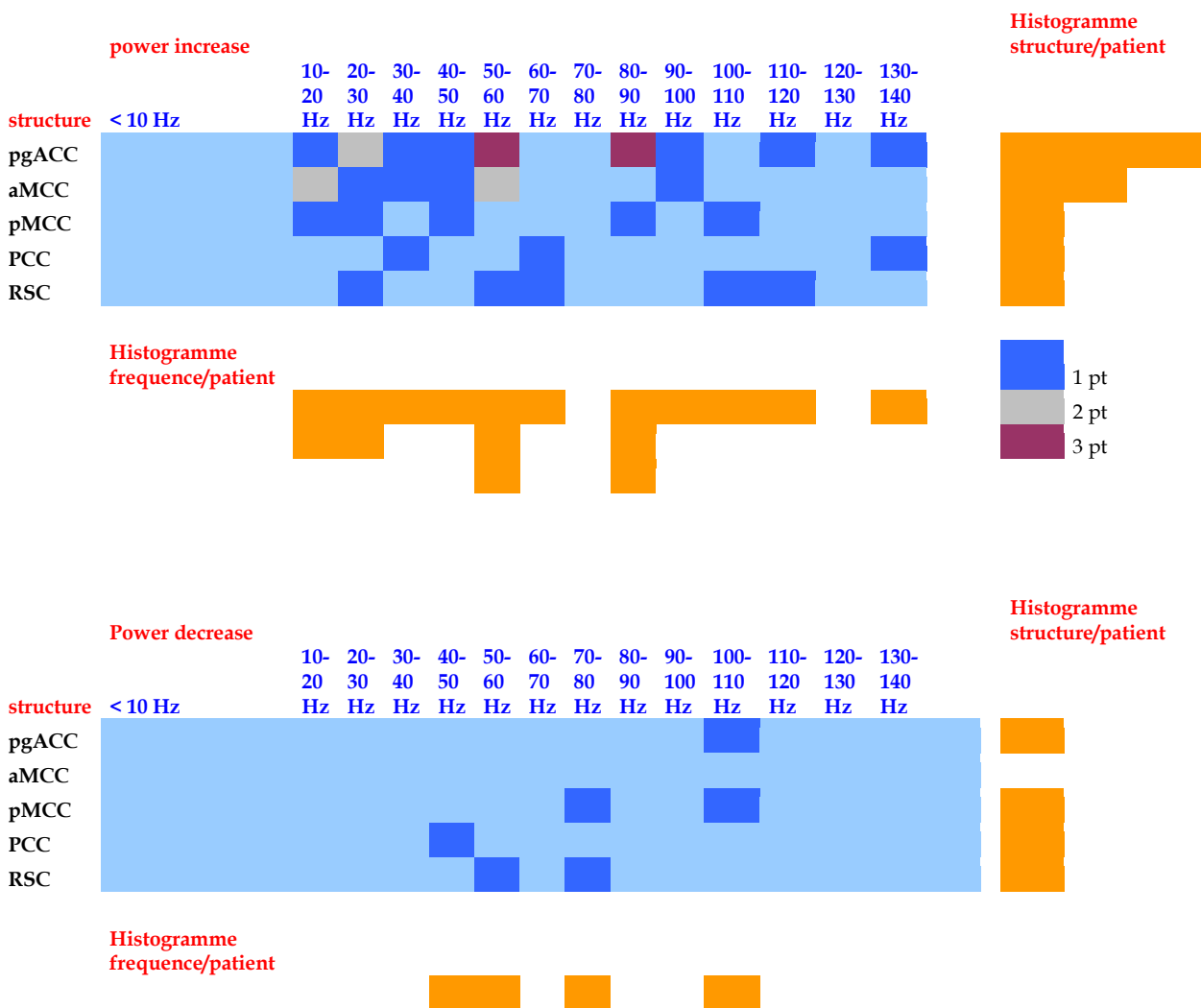
(iv) Frequency modifications during the accomplishment of the Raven trial in the negative condition compared with its accomplishment in the base condition resulted in power increase of the anterior and mi cingulated gyrus in 3 patients mainly in the high gamma band.



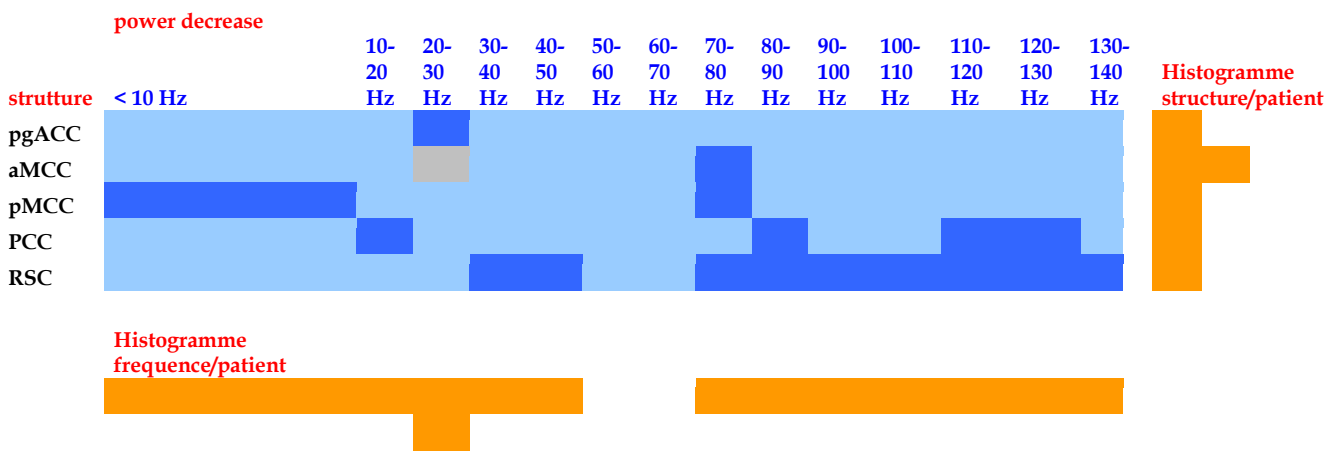
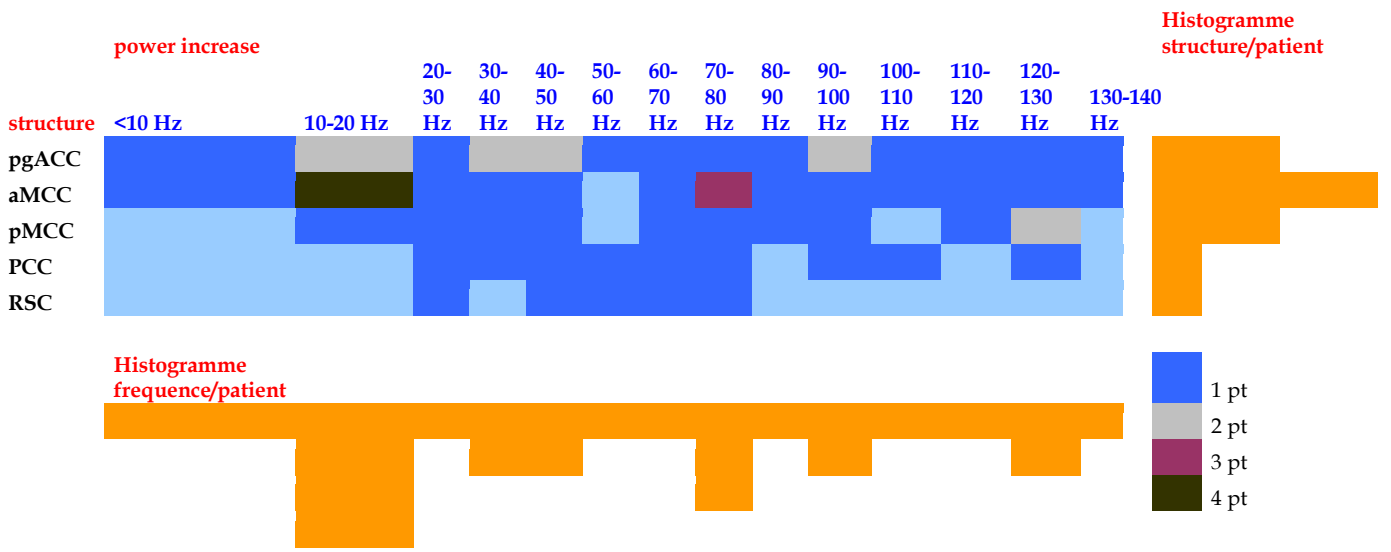


(v) With regard to the cingulate subdivisions, the analysis of frequency activations and suppressions in the different conditions showed the following results:

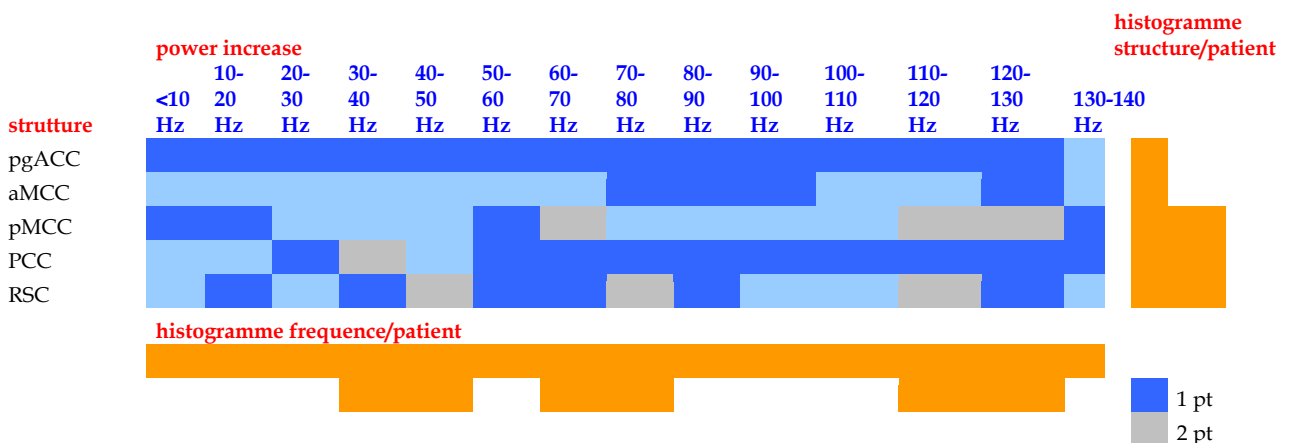
(1) The exposure to negative images compared with the exposure to fixation cross resulted in an activation of the pregenual region of ACC in the high-gamma band (50-60 Hz and 80-90 Hz) in 3 out of 4 subjects (75%) with electrodes implanted in this subregion, while anterior MCC increased its power in 2 out of 5 patients (40%), both in alfa-beta and in gamma range.

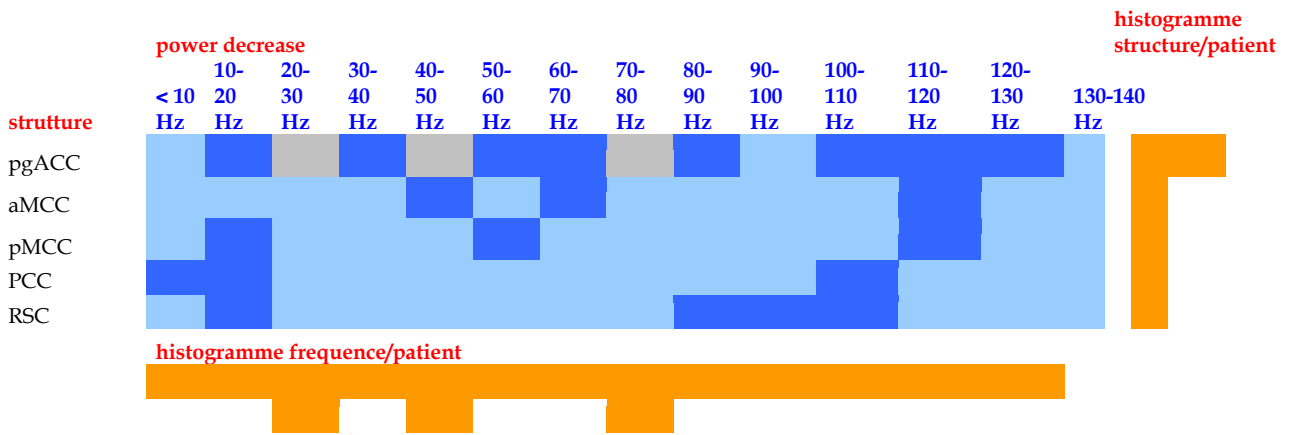


(2) During the exposure to negative images compared with that to the neutral ones, aMCC was activated in the alfa-beta range of frequency in 4 out of 5 subjects, and in the high gamma frequency in 3 (80% and 60% of subjects with electrodes implanted in this subregion, respectively).

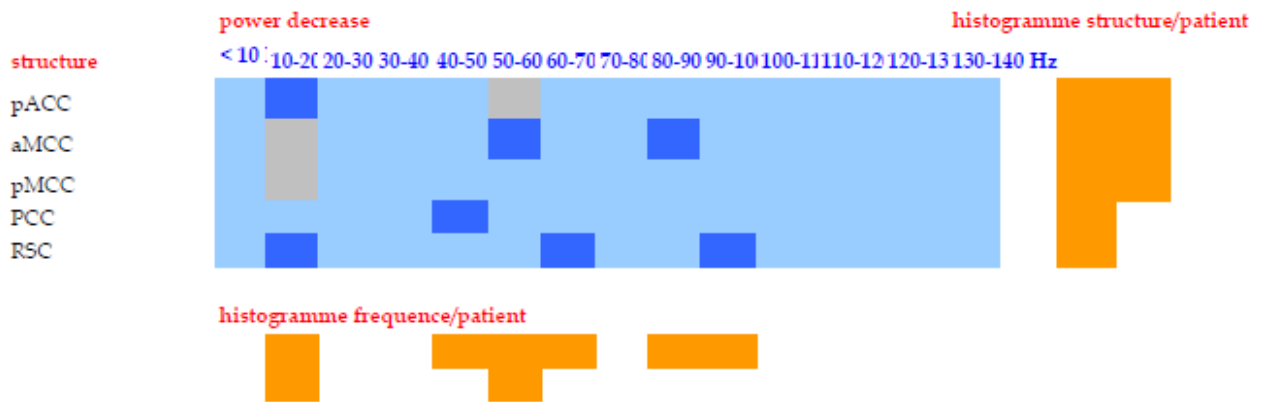
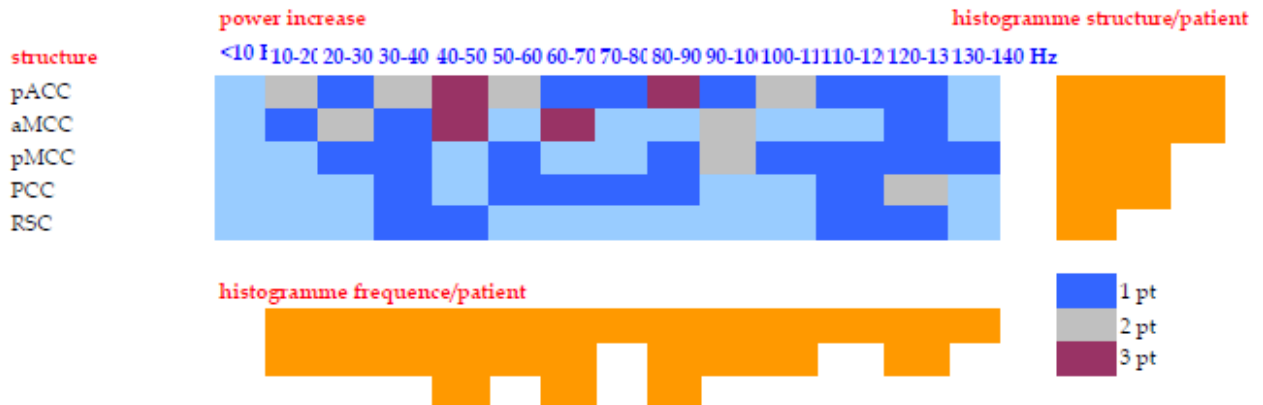


(3) During the accomplishment of the Raven trial in the negative condition compared with its accomplishment in the neutral one, two patients exhibited an activation of the posterior part of the cingulate cortex (pMCC, PCC, RSC) in the gamma band (>30Hz).





(4) During the accomplishment of the Raven trial in the negative condition compared with its accomplishment in the base condition, 3 subjects exhibited activation of the pACC and aMCC in the range 40-90 Hz, while activations in lower and higher frequency ranges concerned the same cingulate subregions but also the pMCC and the PCC in 2 subjects.



(vi) When focusing exclusively on the 3 subjects who exhibited a worst performance - more errors committed along with longer or faster Reaction-Time - during the cognitive test in the negative condition, we found the following results (graphics are not shown):

(1) during the exposure to negative pictures compared with the exposure to neutral ones, there was an activation of aMCC and pgACC both in beta and gamma band, as well as activation of the posterior aspect of superior frontal gyrus and the middle part of mid frontal gyrus in the range 10-20 Hz and activation of SMA in the range 30-40 Hz;

(2) during the exposure to negative pictures compared with the exposure to fixation cross, there was an activation of the superior frontal gyrus, the preSMA and the postcentral gyrus, mainly in high-gamma band, along with a deactivation of the precentral gyrus in a range 20-50 Hz, while both aMCC and pgACC increased their power in the beta and the gamma-band range, respectively;

(3) the accomplishment of the Raven trial in the negative condition compared with its accomplishment in the neutral one resulted in activation of the pMCC, short gyri of insula and mid frontal gyrus in high-gamma frequencies (110-140 Hz) as well as of the precentral gyrus in the range 30-40 Hz;

(4) the accomplishment of the Raven trial in the negative condition compared with its accomplishment in the base condition resulted in deactivation of aMCC and pMCC in the beta-band and in activation of pACC and aMCC in the gamma band, between 30-90 Hz but also in the range 120-130 Hz.

SUMMARY OF THE RESULTS OF FREQUENCY ANALYSIS

A. The frequency modifications, in common, during the exposure to the negative pictures compared with the exposure to both the neutral images (neu) and the fixation cross (base) are illustrated in the following table:

| Structure | Number of participants (%) | |
|----------------------|----------------------------|-----------------------|
| | <i>"Activation"</i> | <i>"Deactivation"</i> |
| | neu-base/total | neu-base/total |
| MCC | 4-5/6 (67-83%) | |
| ACC | 3-3/4 (75%) | |
| SMA | 3-4/5 (60-80%) | |
| Precentral gyrus | 3-3/6 (50%) | 3-4/6 (50-67%) |
| Short gyri of Insula | 3-3/5 (60%) | |
| F1 antero-mesial | 3-3/5 (60%) | |
| F2 middle | 3-3/5 (60%) | |
| Pre-SMA | 3-3/3 (100%) | |
| Temporal pole | 3-3/3 (100%) | |

Power increased both in low-gamma (30-40 Hz) and in high-gamma band (40-70 Hz and 100-140 Hz) mainly in the ACC, the MCC and the SMA-proper, but also in the short gyri of insula, the frontal antero-mesial cortex, the intermediate part of the middle frontal gyrus, as well as in the pre-SMA and the temporal pole.

Interestingly, only the short gyri of insula (anterior insular cortex), but not the long gyri, were activated during the exposure to the negative pictures.

Furthermore, in bilateral implantations, the homologous cortical regions of both cerebral hemispheres were activated and deactivated strictly within the same frequency range.

With regard to the cingulate subdivisions, exposure to negative pictures compared with exposure to both neutral images and fixation cross induced an activation of the aMCC, mainly around 70 Hz.

B. The accomplishment of the Raven trial in the negative condition compared with its accomplishment in both the neutral and the base condition did not result in significant frequency modifications among the involved structures.

With regard to the cingulate region, frequency increases concerned the anterior and mid cingulate cortex without significant differences among the various subdivisions.

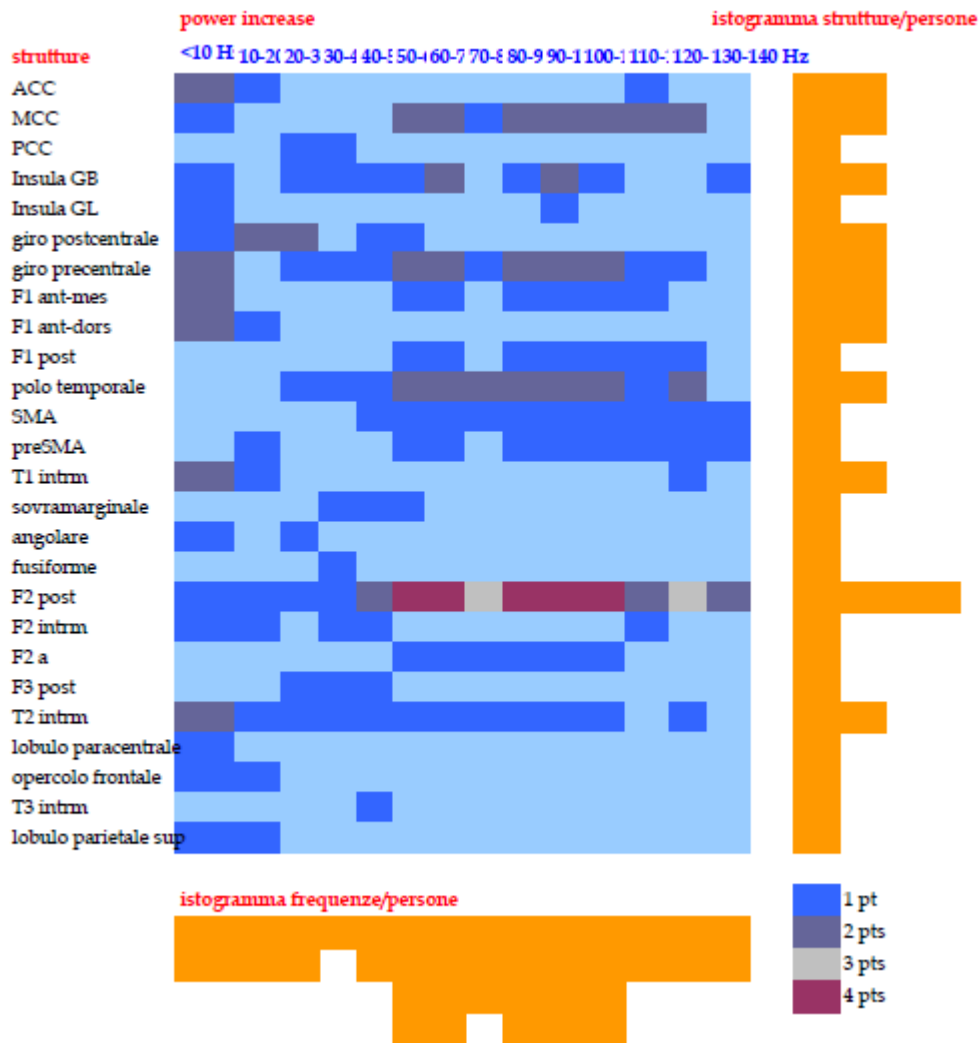
C. When focusing exclusively on the 3 subjects who exhibited a worst performance - more errors committed along with longer or faster Reaction-Time - during the Raven trial in the negative condition, we found that

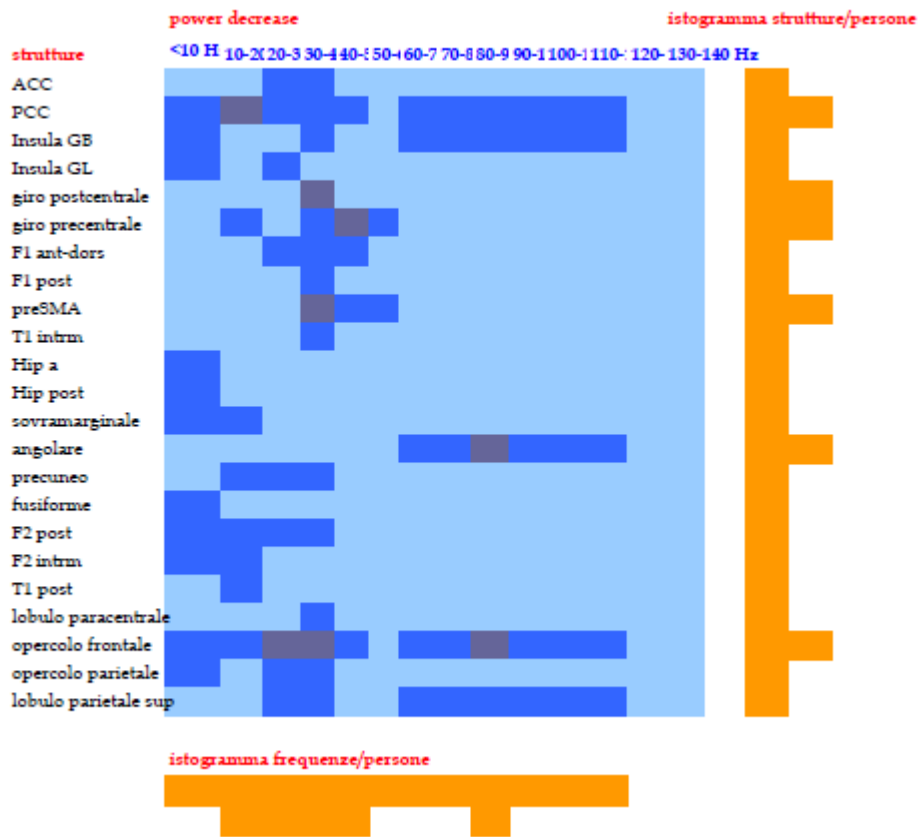
(a) there was an activation of pgACC and aMCC during the exposure to the negative images comparing with the exposure to both the neutral pictures and the fixation cross;

(b) there was an activation of pMCC and a deactivation of aMCC during the accomplishment of the Raven trial in the negative condition compared with its accomplishment respectively in the neutral and in the base condition.

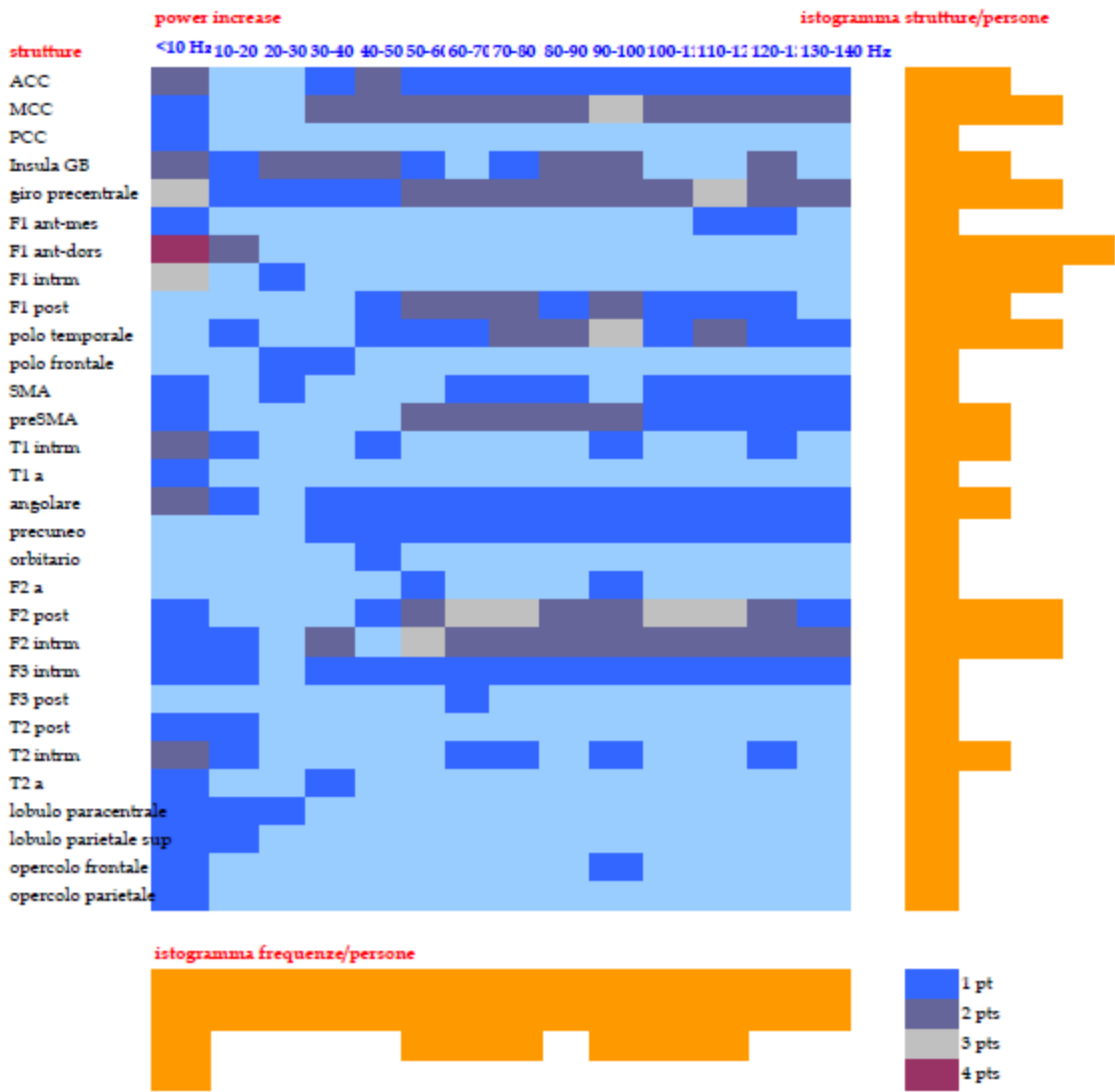
FURTHER RESULTS

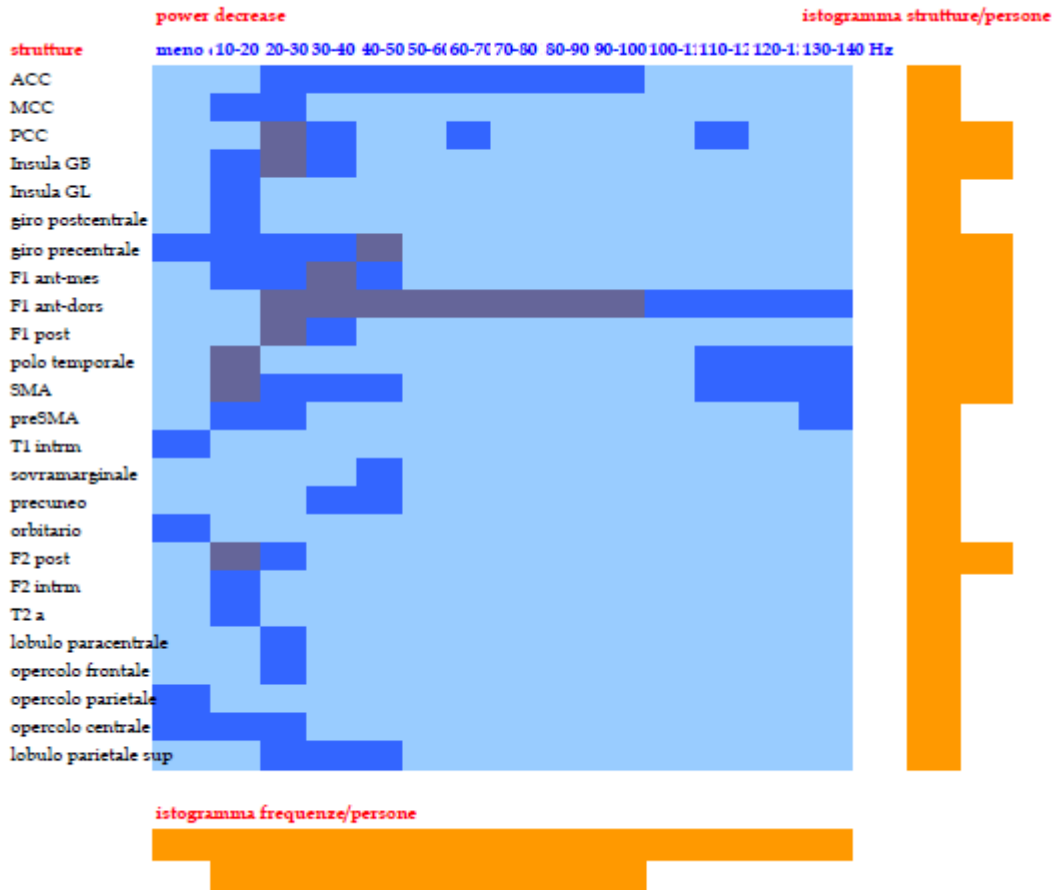
(i) Frequency activations during the cognitive task compared with exposure to the neutral images that immediately preceded it occurred within the range 20-110 Hz for 5 patients, with a peak in 40-50 Hz for 6 patients, and concerned the precentral gyrus and the posterior part of middle frontal gyrus in 4 subjects and the ACC in 3 subjects.





(ii) Accomplishment of the cognitive test in respect to the exposure to the negative images that preceded it resulted in activations between 50-120 Hz for 5 patients, with two peaks in 90-100 Hz and in 1-10 Hz for 6 patients, and concerned ACC, short insula gyri, precentral gyrus, intermediate and posterior parts of middle frontal gyrus and antero-dorsal part of superior frontal gyrus, whereas frequency suppressions were found between 20-50 Hz and involved the precentral gyrus in 4 patients, the SMA, posterior part of middle frontal gyrus and short gyri of insula in 3 patients.





In summary, during the accomplishment of the Raven trial compared with the exposure to the images, both negative and neutral, the most “significant” power increases concerned the ACC in 75-100% of the subjects with electrodes implanted in this structure and the precentral gyrus in 67%. Interestingly, only during the negative condition we found an involvement of the short gyri of insula, which were activated but also deactivated (in different frequencies) in 80% and 60% of subjects respectively.

DISCUSSION

Evolutionary, developmental, social, and neuroscience perspectives stress the importance for survival of investing positively in interpersonal relationships and understanding one's own as well as others' emotions, desires, and intentions (Jackson et al, 2005).

The ability to detect the immediate affective state of another person is considered a precursor to empathy. This corresponds to a state of emotional arousal that stems from the apprehension or comprehension of another's affective state; this state may be similar to, or congruent with, what the other person is feeling (Jackson et al, 2005).

Developmental studies have shown that newborns can imitate various body movements performed by adults, for example, mouth opening, tongue protrusion, lip pursing, finger movements, and also emotional expressions (Field et al, 1982). This initial connection between self and other maybe the foundation for developmentally more sophisticated accomplishments, such as the perception of dispositions and intentions in other individuals (Jackson et al, 2005).

The long history of mammalian evolution has shaped our brains to be sensitive to signs of suffering and distress in one's own offspring. Pain warns of physical threat and danger, on the one hand, and also signals an opportunity to care for and heal the person in pain, on the other. A growing number of fMRI studies have demonstrated that the same neural circuit that is involved in the experience of physical pain is also involved in the perception or even the imagination of another individual in pain (Jackson et al, 2006). Indeed, an impressive body of work with both children and adults has reliably demonstrated that when individuals are exposed to facial expressions of pain, sadness, or emotional distress, brain regions involved in the first-hand experience of physical pain are activated (Singer et al, 2009; Bernhardt and Singer, 2012; Decety, 2015). These regions include the anterior cingulate cortex (ACC), mid cingulate cortex (MCC), anterior insula, supplementary motor area (SMA), somatosensory cortex, amygdala and periaqueductal gray area (Lamm et al, 2007; Decety, 2010). This neural network, underpins a physiological mechanism that mobilizes the organism to react, with heightened arousal and attention, to threatening situations. Given that regions involved in the first-hand experience of physical pain are also active when viewing or thinking about others in distress, activity in these regions has often being interpreted as 'empathy- related', or as direct evidence that one can 'share' the pain of others.

Indeed, according to the influential "shared-networks" hypothesis which guides empathy research, empathic experiences are subserved by activation of the same neural networks which are activated

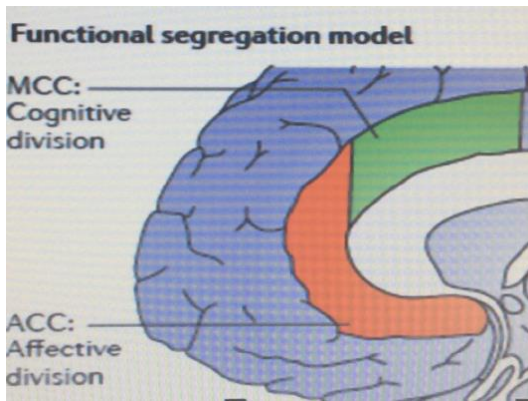
in the first-person experience of an affective state (Preston and De Waal, 2002; Gallese and Goldman, 1998).

Therefore, the results of the present study showing activation of the ACC, MCC and anterior insula during the perception and assessment of someone else's pain and negative affective state, as well as consistent activations of the SMA, the temporal pole and the anterior part of the superior frontal gyrus in the emotional perception, are in line with the existing human imaging studies focusing on empathy for other's pain that have highlighted the role of these regions involved in pain experience (Singer et al., 2004; Botvinick et al, 2005; Jackson et al, 2005).

Indeed, a great amount of studies showed that ACC and anterior insula were activated in response to pain in others (e.g., Botvinick et al, 2005; Budell 2010; Jackson et al, 2005; Lamm et al, 2007; Singer et al, 2004). Moreover, the magnitude of the brain response was related to the amount of pain perceived, both in the ACC and the insula, as well as in premotor, motor, and parietal areas. Studies looking, in particular, at the perception of facial expressions of pain (Botvinick et al, 2005; Saarela et al, 2007; Budell et al, 2010) found that the explicit evaluation of pain versus neutral expressions was associated with increased activation bilaterally in the supracallosal ACC and anterior insula. These areas have also been implicated in the observation and recognition of other emotional expressions, such as disgust (Jabbi et al, 2008, 2007), fear (Morris et al, 1998), anger and sadness and pleasure/happiness (Jabbi et al, 2008, 2007).

With respect to the cingulate subdivisions, despite the progress in functional neuroimaging, key questions about their functional organization and significance of activity remain unresolved. Perhaps the most basic question is whether emotion, pain and cognitive control are segregated into distinct subdivisions of the anterior cingulate cortex or are instead integrated in a common region (Shackman et al, 2011).

In a pair of landmark reviews, Devinsky et al. (1995) and Bush et al. (2000) marshaled a broad range of functional imaging, electrophysiological and anatomical data in support of functional segregation, arguing that the anterior cingulate cortex (ACC; also known as the 'rostral' ACC) is specialized for affective processes, whereas the midcingulate cortex (MCC; also known as the 'dorsal' ACC) is specialized for cognitive processes (*see following figure, taken from Shackman et al, 2011*).

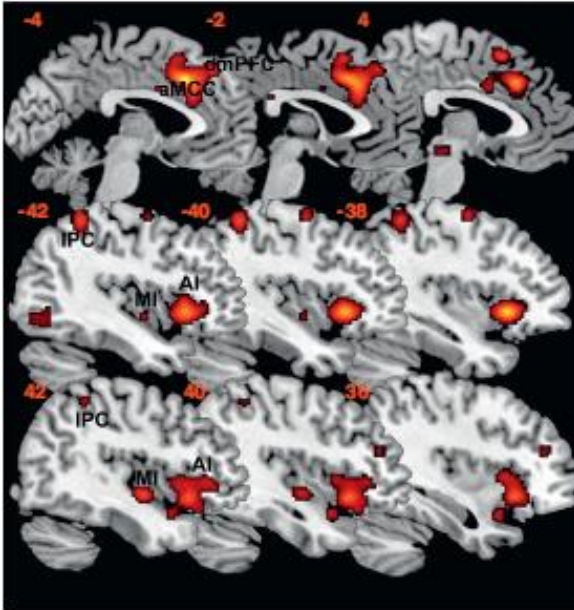


Although the segregationist model remains highly influential, recent imaging data suggests that it is no longer tenable. Indeed, new data implicate MCC in the regulation of autonomic activity (Medford and Critchley, 2010; Luu and Posner, 2003) and the perception and production of emotion (Etkin et al, 2011). Similarly, neuronal recordings demonstrate that MCC is responsive to emotionally charged words in humans (Davis et al, 2005).

The salient finding of the present study highlighting the role of the pregenual ACC (pgACC), anterior MCC (aMCC) and anterior insula during the perception and assessment of someone else's pain and distress is consistent with previous imaging studies of pain processing which have demonstrated their role in the affective aspect of pain processing (Engen and Singer, 2013), thus providing further support for the "shared-networks" hypothesis of empathy.

Although a direct comparison cannot be made here as there was no self-pain condition in our protocol, previous studies described that the ACC peak locations were somewhat more anterior to those typically seen for self-pain (Jackson et al, 2006; Morrison and Downing, 2007), a distinction suggesting that ACC regions for self-experienced versus observed pain may be closely adjacent, but not necessarily overlapping completely (Jackson et al, 2006).

Two recent meta-analyses (Lamm et al, 2011; Fan et al, 2011) summarizing mainly the published neuroimaging work on empathy for pain, highlighted the involvement of the anterior insula and the boundary area pgACC/aMCC (BA 24b,b') in empathy (*see following figure*).



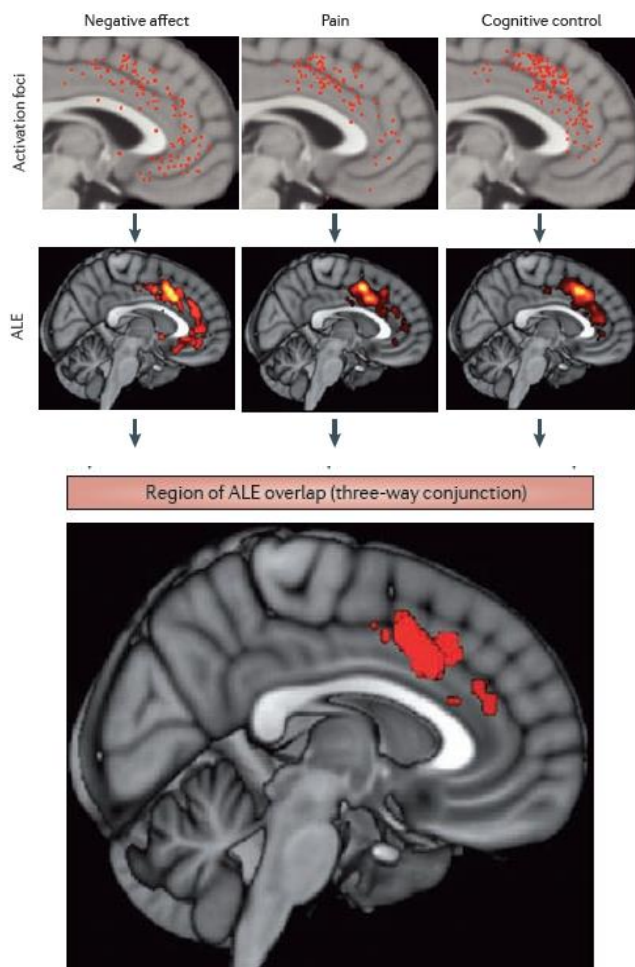
Results from meta-analysis of MRI experiments investigating empathy for pain. **The core network of empathy for pain** consists in dorsomedial prefrontal cortex (dmPFC), aMCC, anterior insula (AI), middle anterior insula (MI) and inferior parietal cortex (IPC). Inset x/z values indicate a stereotactic coordinate of the shown slice in the MNI space.

(taken from Engen and Singer, Empathy circuits, Current Opinion in Neurobiology, 2013, 23:275-282)

These regions have been implicated in a range of different affect related functions: anterior insula has been shown to be reliably involved in the evaluation and experience of emotion (Lindquist et al, 2012) and interoceptive awareness (Craig, 2009); on the basis of both single cell neuron recordings (Hutchison et al, 1999) and fMRI studies (Morrison et al, 2004), the pgACC/aMCC region has been reported to contain neurons responsive to both felt and observed pain. Pregenual ACC/aMCC is strongly connected to the anterior insula (Allman et al, 2010) and has been suggested to play a pivotal role in the integration of pain, negative affect, and cognitive control (Shackman et al, 2011). Anterior insula and pgACC/aMCC also have hub-like position in multiple functional networks (Craig, 2009; Shackman et al, 2011) making them ideally suited to integrate core affective information with contextual input into global feeling states and allowing for the adaptive modulation of behavior by empathic states (Singer and Lamm, 2009). For instance, co-activations of anterior cingulate and anterior insular cortex bilaterally have commonly been described as a “salience network” believed to be involved in the attribution of salience to both internal events and extrapersonal stimuli, thereby guiding behavior (Schilbach et al, 2012; Menon et al, 2010; Kurth et al, 2010; Wiech et al, 2010).

Especially robust links have been forged between activity in the aMCC and the experience of more intense states of negative affect, as with the anticipation and delivery of pain and other kinds of aversive stimuli (Rainville et al, 1997; Vogt, 2005). Furthermore, imaging studies demonstrate that negative affect, pain and cognitive control activate an overlapping region of the aMCC, while anatomical studies reveal that the aMCC constitutes a hub where information about reinforcers can be linked to motor centres responsible for expressing affect as well as executing goal-directed behaviour (Shackman et al, 2011, Albert et al, 2012). Computational modelling and other kinds of

evidence suggest that this intimacy reflects control processes that are common to all three domains (see following figure).



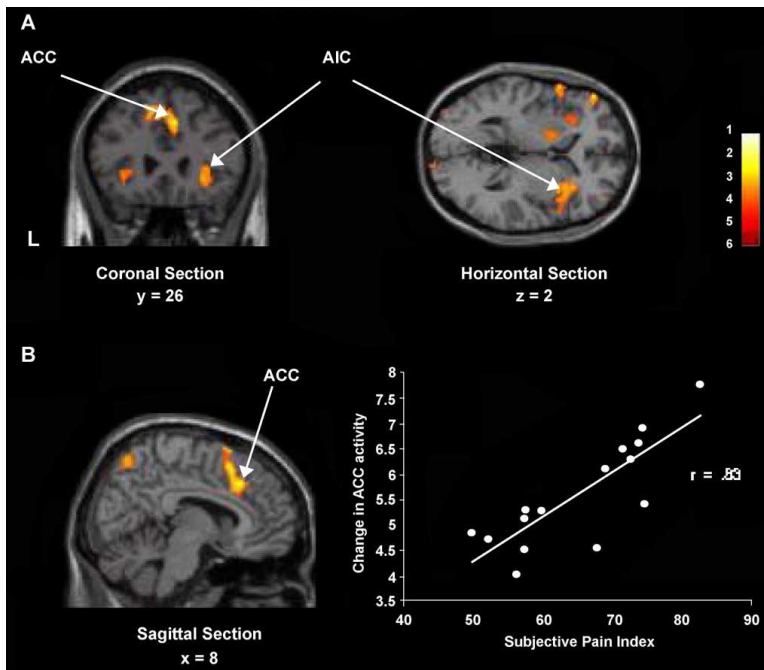
Negative affect, pain and cognitive control activate a common region within the aMCC. The map depicts the results of a coordinate-based meta-analysis (CBMA) of 380 activation foci derived from 192 experiments and involving more than 3,000 participants.

The uppermost panel shows the spatially normalized foci for each domain. The next panel shows thresholded activation likelihood estimate (ALE) maps for each domain considered in isolation. The lowest panel depicts the region of overlap across the three domains. The red cluster indicates the location of a three-way minimum significance conjunction of the three domains. The cluster lies in the anterior midcingulate cortex (aMCC) in the vicinity of areas 32' and a24b'/c' (Talairach coordinates: $x = 0$, $y = 12$, $z = 42$; volume is 11680 mm³). No other cluster reached significance.

(taken from Shackman et al, 2011)

Furthermore, post-scanning interviews and questionnaires indicate that the subjects imagined the level of pain the situation would produce to the other person, which, in fact, draws on both affective and cognitive/evaluative processes (Bush et al, 2000).

Moreover, in the study of Jackson et al, (2005, see following figure) a strong correlation between the ratings and the level of activity within the posterior part of the anterior cingulate (corresponding to the aMCC) was found, supporting the pivotal role of this region in interrelating attentional and evaluative functions associated with pain-evoking situations (Price, 2000). This finding suggests that such a mechanism is also involved in the evaluation of pain in others, and supports the discovery by Hutchison et al (1999) who identified neurons in the anterior cingulate of neurological patients that responded both to painful stimulation and to the anticipation or the observation of the same stimulation applied to another person.



(A) Anterior insular cortex AIC, thalamus and posterior part of the anterior cingulate ACC activation during the observation and assessment of someone else in painful situations contrasted with neutral (No-Pain) situations. Results are superimposed on the MNI MRI template.
 (B) ACC cluster superimposed onto a sagittal section and scatter plot showing the positive correlation between the indexed ratings and the level of activity in this region $x = 14, y = 20, z = 44$.
 (taken from Jackson et al, 2005)

Williams (2003) has emphasized the role of pain expressions in eliciting helping responses from others. According to Botvinick et al (2005), in this connection it may be relevant that one of the areas engaged by pain expressions, the aMCC, has been implicated not only in the processing of pain, but also in studies of motivation (Paus, 2001). On the other hand, the aMCC also appears to play a central role in aversive learning. Based on this, it might be speculated that the aMCC response to witnessed pain might relate, in part, to observational avoidance learning, allowing one to learn to avoid painful outcomes without having to experience them (Botvinick et al, 2005). Moreover, aMCC was associated with fear and anxiety, critical for avoidance behavior (Vogt et al, 2003).

An alternate interpretation would be that the perception and assessment of pain in others leads to an unspecific state of arousal such as personal distress and anxiety (Critchley, 2004). Levels of personal distress have been shown to positively correlate with the level of neural activity in the anterior cingulate, anterior insula and sensorimotor cortices (Yang et al, 2009) during empathy for pain (Banissy et al, 2012).

Regarding structural connectivity, Paus (2001) emphasized the aMCC's strategic anatomical position, as well as its functional role in motor control, cognition and "arousal/drive states" of the organism, as ideal prerequisites to translate intentions to actions. This consideration is supported on the functional level by the separately calculated MACMs (meta-analytic connectivity modeling) over experiments with aMCC activation involving neural systems for "cognition" and "action," respectively (Hoffstaedter et al, 2014). Both analyses revealed the premotor cortex, area 44,

supplementary and pre-supplementary motor area (that represent the decision when to act, [Cunnington et al, 2002, 2003](#)), anterior insula, dorsal striatum, thalamus and the cerebellum, all bilaterally featuring task-base functional connectivity with the aMCC. Together with the dorsolateral prefrontal cortex (that represents the decision if an ongoing action should be stopped or not), these areas in terms of a “core network” represent a neural correlate of intentional motor control ([Demanet et al, 2013](#); [Hoffstaedter et al, 2014](#)).

The aMCC, whose role in cognitive motor control was underlined by the study of [Hoffstaedter et al \(2014\)](#), virtually represents the identical region found by [Shackman et al \(2011, see previous figures\)](#) in their quantitative meta-analyses which featured overlapping activity for the three domains: cognitive control, pain, and negative affect. In their review, the authors concluded that computational models of cognitive control and reinforcement learning may account for this region’s contribution to negative affect and pain. Indeed, both pain and negative affect normally induce the strong intention to control the effective context in order to change the physically or emotionally painful situation ([Hoffstaedter et al, 2014](#)). Thus, pain and negative affect result in activation of the cognitive control system and the “readiness for action”, which crucially includes the aMCC.

[Preston and de Waal \(2002\)](#) formalized a theory of emotional- motor resonance in the Perception-Action Model, which holds that perception of a behavior performed by another automatically activates one’s own representations for the behavior; output from this shared representation automatically proceeds to motor areas of the brain where responses are prepared and executed ([Molnar-Szakacs and Uddin, 2014](#)). Emotional-motor resonance may also be called emotional empathy or embodied simulation – processes related to the same bottom-up, automatic, and evolutionarily early mechanism. Embodied simulation implies transforming perceived actions and emotions into our own inner representations of those actions and emotions. This process, supported by interactions between the mirror neuronal system (MNS) and the limbic system, is fast, automatic, and pre-cognitive, and is thought to support our ability to empathize emotionally (“I feel what you feel”) ([Preston and de Waal, 2002](#)). Current evolutionary evidence suggests that embodied simulation is a phylogenetically early system for empathy, while there is also a more advanced cognitive perspective-taking (or theory of mind, ToM/mentalizing) system mediating empathic responses in humans ([de Waal, 2008](#)). Higher-level cognitive empathy requires that we actively think about, or reflect, on others’ actions and emotional states, including perspective taking or ToM/mentalizing ([de Waal, 2008](#)). Mentalizing refers to the process of understanding another person’s perspective, and appears to depend upon higher cognitive functions such as

cognitive flexibility (Decety and Jackson, 2004). Singer (2006) has proposed that mentalizing allows us to understand mental states such as intentions, goals and beliefs, while embodied simulation allows us to share the feelings of others (Molnar-Szakacs and Uddin, 2014). Low-level embodied processes and higher-level mentalizing processes integrate their signals such that stimuli are “mapped” onto internal representations and combined with information from memory to plan future behavior, select a response and act (Molnar-Szakacs and Uddin, 2014). Mentalizing processes appear to be centered on the mPFC node of the DMN, while embodied simulation processes are implemented by the MNS–limbic system network (Preston and de Waal, 2002; Gallese, 2005; Molnar-Szakacs and Uddin, 2014).

Converging evidence suggests that the aMCC is a core region contributing to cognitive control. The aMCC is specifically responsible for providing a continuously updated account of predicted demand on cognitive resources (Sheth et al, 2012). In situations in which cognitive demands remain constant, this signal facilitates efficiency by accelerating responses; in situations involving rapidly changing demands, it promotes accuracy by retarding responses. Thus, the aMCC is thought to be important in regulating cognitive control over goal-directed behaviour (Sheth et al, 2012).

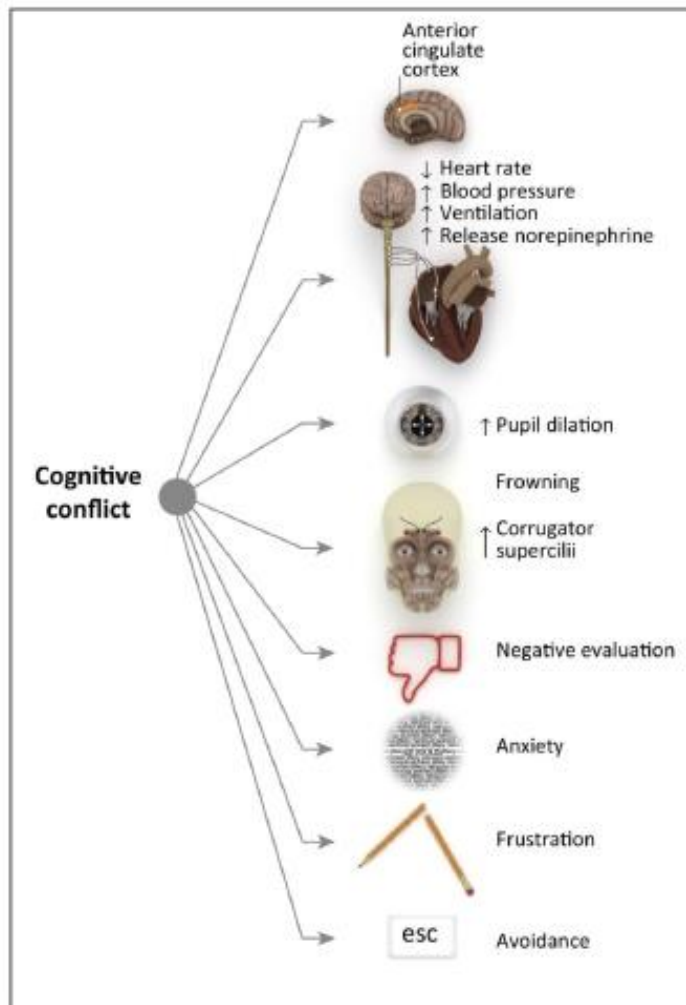
Control control is instigated by cognitive conflict (Inzlicht et al, 2015). The aMCC is activated when cognitive control is needed to deal with interfering signals and plays a major role in conflict monitoring (Botvinick et al, 2004). Conflict monitoring theory focuses on how the monitoring system plays an important role in scrutinizing the moment-to-moment representations of action tendencies for potential conflicts so that inhibitory mechanisms may be engaged to override the unwanted tendency and promote effective goal pursuit (Botvinick et al, 2001). For example, because reading is an overlearned response for literate adults, the word ‘red’ presented in green font will activate both the urge to read the word (i.e., say ‘red’) and the Stroop goal of naming the colour (i.e., say ‘green’), which conflict with one another. When conflict is detected by these systems, a second regulatory system is engaged, biasing behaviour toward the goal-relevant response while suppressing incompatible responses (Inzlicht et al, 2015). These functions are thought to be implemented by the aMCC and the dorsolateral prefrontal cortex, respectively (Kerns et al, 2004). An augmented activation of the aMCC with incongruent compared to congruent trials is a well-established finding in Stroop tasks (Botvinick, 2007).

Conflict is thus at the heart of control (Inzlicht et al, 2015). Conflict, however, is not affectively neutral, it has an emotional cost, it produces negative affect (Botvinick, 2007; Inzlicht et al, 2015).

Many studies point to the aMCC as playing a prominent role on human cognitive conflict (Botvinick et al, 2001; Holroyd and Coles, 2002; Kerns et al, 2004; Gehring et al, 2011). Much of this work focus on errors and the discovery of an evoked brain potential that accompanies errors, called error-related negativity (ERN, Gehring et al, 2011). That the ERN is generated by the aMCC is not surprising given the aversive nature of errors and the long-held view that the aMCC plays a key role in the evaluation of pain and distress (Rainville et al, 1997; Mobbs et al, 2010). The involvement of the aMCC in both conflict and negative affect (Shackman et al, 2011; Koban and Pourtois, 2014) further suggests functional overlap between the two domains.

Thus, an incongruent Stroop trial will register as an aversive signal (Dreisbach and Fischer, 2012) which not only helps make response conflict salient but also helps in preparing corrective actions to manage the conflict. More aversive errors elicit larger aMCC activation and instigate greater post-error adjustments in control (Inzlicht et al, 2015).

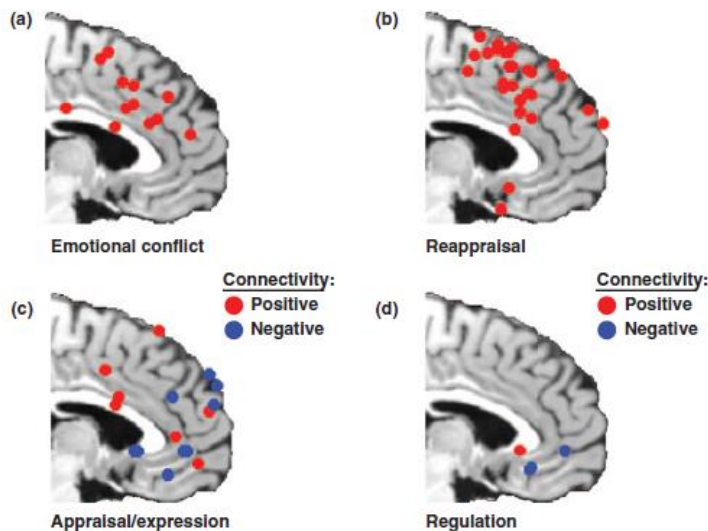
The reactivity of the aMCC to errors is thus likely to represent more than just the cold registration of conflict but may also register as an aversive signal (Aarts et al, 2013), representing a distress- or threat-related response to potential or actual goal failure (Bartholow et al, 2005). In support of this, errors in a cognitive task are associated with a host of physiological changes consistent with the mobilization of defensive motives, such as increased skin conductance, greater cardiac reactivity, corrugator muscle contraction, and increased startle reflexes (*see following figure, taken from Inzlicht et al, 2015*). These same types of tasks also produce feelings of anxiety and frustration (Inzlicht and Al-Khindi, 2012; Spunt et al, 2012).



Cognitive conflict is aversive. Cognitive conflict is associated with a number of emotional primitives. Performing a laboratory control task, such as the Stroop task, increases activity in the sympathetic nervous system, including heart rate deceleration, as well as increases in blood pressure, ventilation (defined as the product of breathing rate and tidal volume), and plasma norepinephrine. Exposure to high-conflict stimulus (such as the word 'red' printed in green) activates the dorsal anterior cingulate cortex (dACC), evokes pupil dilation, leads to contraction of the corrugator supercilii muscle of the face, primes negative evaluation of subsequent stimuli, and produces conscious self-reports of anxiety and frustration. The aversive nature of conflict is also evident because it fosters a behavioral tendency to avoid conflict-laden tasks.

With respect to the pgACC, in the study of [Etkin et al \(2011\)](#), one of the few studies in the cognitive control literature that specifically examined the relationship of prefrontal cortical regions to amygdala activity (using psychophysiological interaction analysis), greater activity in the pgACC was inversely correlated with amygdala activity. Based on the pattern of amygdala responses, the authors argued that amygdala activity is correlated with the degree of conflict on a given trial, and by suppressing amygdala activity the pgACC provides control over this conflict. While the pgACC

exhibited a conflict regulation-related activation, the aMCC was involved in conflict evaluation, together with amygdala, mPFC and dorsolateral PFC (*see following figure*). In a follow-up study, [Etkin et al. \(2011\)](#) observed that this suppression of amygdala activity appears weaker in patients with generalized anxiety disorder relative to healthy controls, providing a potential neural correlate of the difficulty controlling emotional distraction or conflict in this patient population.



Activation foci associated with fear and its regulation. Predominantly dorsal ACC and mPFC activations are observed during classical (Pavlovian) fear conditioning (a), as well as during instructed fear paradigms, which circumvent fear learning (b). Likewise, sympathetic nervous system activity correlates positively primarily with dorsal ACC and mPFC regions and negatively primarily with ventral ACC and mPFC regions, which supports a role for the dorsal ACC and mPFC in fear expression (c). During within-session extinction, activation is observed in both the dorsal and ventral ACC and mPFC (d), whereas during subsequent delayed recall and expression of the extinction memory, when the imaging data are less confounded by residual expression of fear responses, activation is primarily in the ventral ACC and mPFC (e) (*taken from Etkin et al, 2011*).

When we put together functional neuroimaging studies of the anterior cingulate, we find that many reward-related, positively affective, stimuli are mapped to the pgACC in regions that include areas p24 and p32, whereas many unpleasant stimuli are mapped just posterior to this in the aMCC which includes area 24c' ([Grabenhorst and Rolls, 2011](#); [Vogt, 2014](#)). Most of these representations produced by unpleasant stimuli are in aMCC where pain produces activations ([Rolls et al, 2003](#); [Vogt, 2009, 2014](#)).

A hypothesis considered by Rolls in *Emotion and Decision-Making Explained* ([Rolls, 2014, 2015](#)) is that these reward- and punishment-related representations in these ACC regions are relayed from

the medial and lateral orbitofrontal cortex and are used in the cingulate cortex for action-outcome learning. In this type of learning, associations must be learned between actions that are made, and the rewards (pgACC) and the punishers/the outcomes (aMCC) that are obtained. Importantly for this function, actions and movements, are represented in MCC, in which there are two cingulate motor areas (Vogt, 2009), and not in the orbitofrontal cortex which is primarily concerned with value representations and not with actions (Rolls, 2014), and so the pgACC and aMCC are appropriate regions for action-outcome learning, which could not be performed by the orbitofrontal cortex. In performing this type of learning, pgACC and aMCC need to be able to remember actions just made until the outcome is known, which may be seconds later, and therefore it is proposed that attractor networks in these cingulate regions hold in short-term memory the actions just made, so that an association can be made to the outcome when it becomes known, probably using associative (Hebbian) synaptic modification (Rolls, 2015).

It has been argued recently that these reward, punishment, and action-related functions of the ACC and MCC and their close connections with the orbitofrontal cortex and amygdala are separate from the more memory-related functions of the posterior cingulate cortex (PCC) and its closely related areas (Rolls, 2015). For this reason, it has been proposed that we should no longer adhere to the concept of a limbic system, but that if we are to continue with 'limbic' terminology, we should accept that there are two (or more) limbic systems (Rolls, 2014). The PCC has connections via parahippocampal areas with the hippocampus which is involved in episodic memory (Rolls, 2010), and with parietal regions involved in the representation of space, which is usually a component of an episodic memory. The question then arises of why the hippocampus has some connections to the orbitofrontal cortex and amygdala; and for that matter why there may be some connections between the ACC and the PCC (Vogt, 2009; Rolls, 2014). The answer that is proposed is that emotional or affective states may be part of an episodic memory, and must therefore be connected to the hippocampal system, both for storage of an episodic memory and for retrieval of the emotional component of an episodic memory back to the orbitofrontal and anterior cingulate cortex (Rolls, 2014).

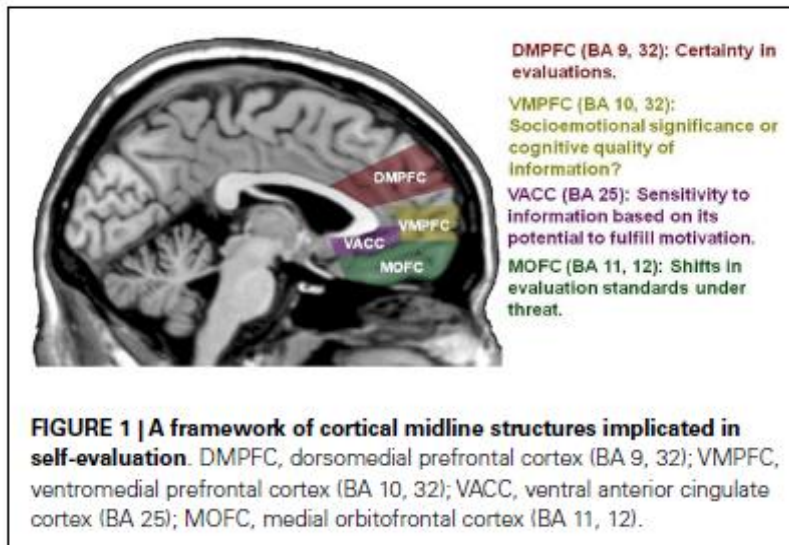
Previous research suggests that healthy individuals commonly show negative correlations between activity in the dorsal anterior cingulate (being part of a frontoparietal network usually activated during cognitive tasks) and posterior cingulate cortex (being a central node of the default mode network (DMN) usually activated during rest) (Fox et al, 2005; Krause-Utz et al, 2014).

Functional connectivity and structural connectivity studies both support that posterior cingulate cortex (PCC) is the DMN core region, which facilitates information integration within the entire DMN and, thus, aids in ongoing behavioural performance (Lin et al, 2015). For instance, within DMN sub-regions or sub-nodes, PCC plays key roles in monitoring one's own internal state and emotions, self-referential processing, problem solving and task-independent thoughts, memory consolidation, social cognition and autobiographical memory (Buckner et al, 2008; Leech and Sharp, 2013). The PCC appears sensitive not only to explicit emotional engagement, for example, during tasks of emotional word processing and face-perception, but also implicit emotional engagement during self-directed attention or evaluation, as well as autobiographical memory (Leech et al, 2011, 2012; Pearson et al, 2011; Leech and Sharp, 2013, Li et al, 2014).

Vogt et al (2006) thus proposed that the PCC may respond to the general emotional content of events, particularly when the nature of processing is self-relevant.

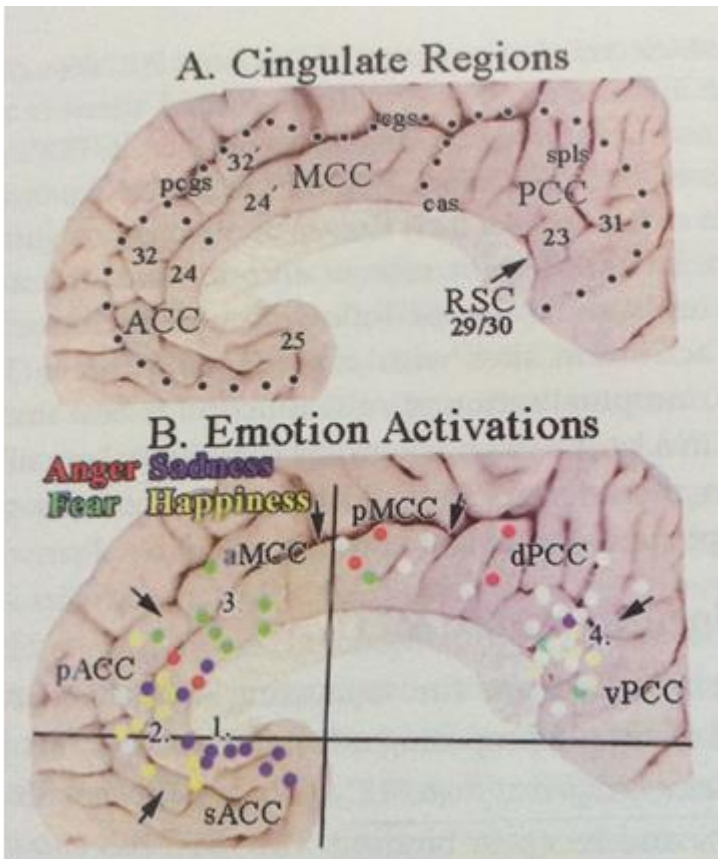
There is evidence that PCC as well as precuneus (PrC) and dmPFC are similarly involved in several shared functions and are jointly important for successful simulation of future events (Buckner and Carroll, 2007), based on the idea of shared networks between episodic remembering and envisioning the future (Amft et al, 2015). This is supported by Andrews-Hanna et al (2010) who point out an increased activity in default mode areas during passive epochs, supposing that people spent a majority of their time thinking about their past and future (Schilbach et al, 2008). Therefore, Amft et al (2015) assumed that PCC/PrC and dmPFC are associated with self-projection, which combines autobiographical memory, imagining the future and perspective taking (Buckner and Carroll, 2007; Spreng et al, 2009) and might be regions within the e-SAD relevant for successful social future behavior.

The integration of function between the DMN and the mirror neuron system (MNS) have been the focus of several recent proposals on the neural bases of self-related cognition (Keysers and Gazzola, 2007; Uddin et al, 2007; Molnar-Szakacs and Arzy, 2009; Molnar-Szakacs and Uddin, 2012; Sandrone, 2013). The results of Qin and Northoff (2011) also lend support to the notion that the self emerges from the interaction of these two neural networks. Their meta-analysis showed recruitment of DMN regions, including the mPFC and PCC, as well as MNS regions, including the inferior frontal gyrus and anterior insula during self-relevant processing (Molnar-Szakacs and Uddin, 2014, *see following figure*)



In the study of [Molnar-Szakacs and Uddin, 2014](#), conjunction analysis evidenced the specific combination of activation in regions within the DMN and regions within the salience network during thought and emotion. This finding is consistent with another study that demonstrated connectivity between regions of the default network (right temporo-parietal junction, vmPFC and PCC/precuneus), aspects of the salience network (anterior insula, SMA, aMCC) and the primary sensorimotor cortex during mentalizing tasks ([Lombardo et al, 2009](#)). Interestingly, this connectivity pattern occurred both when participants were mentalizing about the self, and when they were mentalizing about others, suggesting an overlap between two processes that have been separated in the literature.

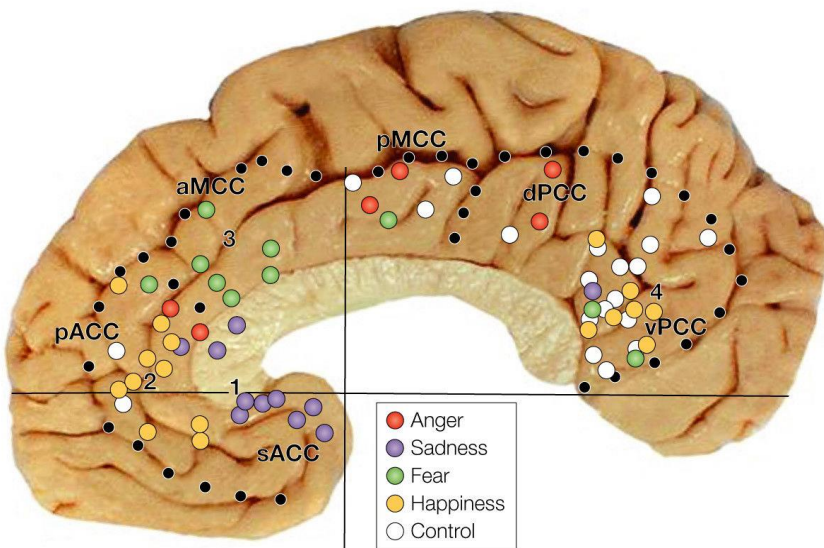
In summary, limbic functions in cingulate cortex must be graded in terms of emotional storage and processing ([Vogt, 2014](#)). Thus, each cingulate region has a different level of emotional processing and access to autonomic input according to following hierarchy: sgACC/pgACC > aMCC > vPCC > dPCC > pMCC ([Vogt, 2005, 2009, 2014](#), see, for example, following figures).



Location of each subregion, including some of the key areas and a summary of overall functions for each.

In figure B, an analysis of the peak voxels associated with activations during simple emotion-generating tasks was plotted; the white dots are for control tasks that do not evolve emotion but use similar stimuli.

(taken from Vogt, 2009)



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Cingulate Emotion Processing

Peak activation sites from 23 studies during simple emotions in the context of the regionalized Cingulated. Four groups of active sites are numbered and control conditions with non-emotional scripts and faces are coded with white dots. Each numbered aggregate of sites is located in a different subregion and this suggests a different role in processing of emotional information; i.e., a different relevance to autonomic integration, skeletomotor output, and personal orientation as predicted by the four-region, neurobiological model (taken from Vogt 2005)

An interesting finding of the present study is the activation of the short, but not of the long, gyri of insula during both exposure to negative pictures and the accomplishment of the Raven trial in the negative condition. Our results support the suggestion that "second-hand" experience of pain follows only an anterior activation pattern of the insular cortex (Corradi-Dell'Acqua et al, 2011; Lamm and Singer, 2011). Indeed, Corradi-Dell'Acqua et al (2011) found that only in the anterior insula (bilaterally) the distribution of cortical activity evoked by seeing another person's hand in pain was spatially similar to that of pain felt on one's own hand. Electrophysiological studies on epileptic patients demonstrated that painful/thermal sensations are elicited by stimulation of mid insula but not anterior insula (Afif et al, 2010). On the other hand, neuroimaging data suggest that, whereas mid insula may code physical properties of painful stimuli, anterior insula primarily reflects its perceived unpleasantness (Rainville et al, 1997; Craig et al, 2000). In this perspective, Corradi-Dell'Acqua et al (2011) suggested that the current theoretical accounts of empathy might be extended by defining both anatomically and functionally two sets of regions in the pain matrix that exhibit different shared properties: one (mid insula and MCC) sharing information specific to the presence of pain, and the other (anterior insula) sharing information about its associated emotional effects. Thus, whereas mid insula and MCC data converge with embodied accounts of processing others' pain (de Vignemont and Singer, 2006; Goldman and de Vignemont, 2009), the functional properties of anterior insula go beyond the mirroring of somatic experiences and involve processes that are also common to the perception of other affective stimuli.

Interestingly, it seems that even more abstract circumstances, such as sensation of injustice or moral disgust, can equally activate anterior insula.

Moreover, the finding that the feeling of pain is not restricted to its physical sensation, but occurs within the individual as a result of observing another's emotional state fits well with recent findings that there is a neural realization of the idea that social relationships can sometimes be painful. This latter aspect was demonstrated in an fMRI study showing that the neural circuit involved in pain processing, including the anterior insula and the ACC, was activated when the participants were socially excluded from an on-line computer game (Eisenberger et al, 2003).

Interestingly, the ACC was more active during exclusion and its activity correlated positively with self-reported distress. The authors argued that social pain is analogous in its neurocognitive function to physical pain.

Intracranial electrophysiology techniques, largely underutilized in the study of emotional phenomena in humans, offer important evidence, which should be incorporated into our current models of emotion representation in the human brain (Guillory et al, 2014). For the human brain,

in contrast to the experimental possibilities with animals, anatomical connectivity cannot be directly assessed, although probabilistic fiber tracking based on diffusion weighted MRI provides decent estimates of axonal connections between brain areas. This fact illustrates the importance of invasive methods able to elucidate the dynamics of neural activation.

The high temporal resolution of human intracranial electrophysiology (HIE) methods offers a unique window into the mechanics of human cognition (Guillory et al, 2014). An example comes from recording of local field potentials during processing of facial expressions as reported by multiple investigators. In these studies, intracranial macroelectrodes are placed over occipital, lateral temporal, amygdalar and orbitofrontal regions. Following the presentation of a photograph depicting a face with emotional expression, initial activation occurs in the primary visual cortex 100 ms following stimulus presentation. Next, activation in the fusiform face area (FFA) occurs at 120–200 ms following presentation of facial stimuli but not of non-facial stimuli (e.g. Pourtois et al, 2010). Next, the FFA and the superior temporal gyrus (STG) activate to emotional faces between 200 and 500 ms (Tsuchiya et al, 2008). Activation of the amygdala to fearful expressions occurs within 200 ms following stimulus presentation and precedes activation in the FFA, STG and orbitofrontal cortex (Krolak-Salmon et al, 2004). This suggests that the amygdala may modulate the activity of the FFA in a retrograde fashion (Guillory et al, 2014). Last, activation of the orbitofrontal cortex occurs 500–1000 ms following presentation of fearful stimuli (Jung et al, 2011). HIE methods suggest that the processing function of brain regions may change with respect to the temporal latency from the stimulus onset (Guillory et al, 2014). The FFA shows early activation to faces independent of facial emotion at 200 ms and distinct late activation based on facial emotion and eye direction at 500 ms (Pourtois et al, 2010). This finding provides evidence to suggest that the role of a certain brain region in cognitive processing may change depending on the latency from stimulus presentation, i.e. the FFA processes all faces early and only later processes facial emotion.

It should be stressed, however, that the term “gamma band” as currently used represents a very broad range of frequencies that likely encompasses a few different neural mechanisms (Nunez and Srinivasan, 2010) therefore caution is needed to rely on it as a “catch-all category.” The literature describing epilepsy-related high frequency oscillations has recognized some differences across this range, using the term ripples to describe activity between about 80–200 Hz but distinguishing them from “fast ripples” that appear to represent a distinct phenomenon between 250–500 Hz (Bragin et al, 1999). In the cognitive domain, more differentiation needs to be made between, for example, 40 Hz narrow-band oscillations and broader 70–120 Hz power enhancements (Wyart and Tallon-Baudry 2008; Crone et al, 2010; Dalal et al, 2012), or even higher frequency phenomena of

about 130–250 Hz (often also referred to as ripples) in the hippocampus and entorhinal cortex (Axmacher et al. 2008; Le Van Quyen et al, 2010) and 600 Hz somatosensory evoked potentials (Curio et al, 1994).

A more nuanced view of these high frequencies should be considered, particularly in light of a recent study demonstrating the specificity of different sub-bands “the neural correlates of cognition are not confined to a specific frequency band and that the big picture can only be achieved by putting the pieces of the puzzle back together, i.e., not only including all frequencies of the spectrum but also various measures of brain responses across multiple spatial scales” (Dalal et al, 2012; Knyazev, 2013).

CONCLUSION

We provide evidence that dorsal cingulate cortex codes emotional processing. Furthermore, our results support the suggestion that "second-hand" experience of pain follows only an anterior activation pattern of the insular cortex.

Our results are in line with the existing human imaging studies focusing on empathy for other's aversive events that have highlighted the role of these regions involved in the direct pain experience.

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