UNIVERSITÀ DI PISA

PhD Course in Basic and Developmental Neuroscience

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"*A study on cerebral activity by means of combined EEG-fMRI in neuropsychological disorders in childhood*"

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Contents

ABSTRACT

This study is composed by two parts, both focusing on post-calcarine ventral, occipito-temporal visual pathway (“ventral stream”), and on occipito-temporal cortex, structures involved in images and in face processing. In the first part of the study I have analyzed gamma-band ERSP (event-related spectral perturbations) and fMRI BOLD activations in response to recognizable and not recognizable visual stimuli, in typical children and in children affected by "ventral type" Cerebral Visual Impairment, trying to show how the deficits in "ventral" tasks could be investigated using both a neurophysiological and a neuroimaging approach. However I was not able to reproduce preliminary, promising data on gamma-band ERSP because of excessive electrical noise during EEG recordings, most likely because of an equipment radical and unexpected change. Despite these issues, taking advantage of the peculiar features and strength points of the new equipment (a dense-array EEG machine), I continued my work on visual perception and the occipito-temporal visual network using ERPs recordings (part 2), that are substantially less affected from the AC electrical noise usually present in every EEG recording. In particular, I recorded high density ERP responses to neutral and emotional visual face stimuli in typical children and in children affected by Autism Spectrum Disorder, a condition in which face-processing neural networks have been often found dysfunctional in neurophysiological and functional neuroimaging studies. However, evidence regarding face processing in Autism Spectrum Disorders is still contradictory and neurophysiological methods used are heterogeneous. Therefore I designed and applied an experimental paradigm trying to control most of the known or suspected confounding variables in this kind of studies. Using neutral and emotional faces, and trees as non-face stimuli, I was able to modulate both

latency and amplitude of the main face-sensitive ERPs (N170, P1, peak-to-peak N170) as a function of stimulus and group conditions. These findings support the hypothesis of an early (first 200 msec) impairment in both neutral and emotional face processing in children affected by Autism Spectrum Disorders.

RIASSUNTO

Questo studio è composto da due parti, entrambe focalizzate sulla via visiva ventrale post-calcarina (ventral stream) e sulla corteccia occipito-temporale, strutture coinvolte nel processamento delle immagini in generale e dei volti. Nella prima parte dello studio ho analizzato le risposte ERSP (Event Related Spectral Perturbations) e le attivazioni BOLD in risposta stimoli visivi riconoscibili e non riconoscibili, in bambini a sviluppo tipico e in bambini affetti da Cerebral Visual Impairment di tipo "ventrale", provando a dimostrare come i deficit nei compiti "ventrali" possono essere studiati utilizzando metodi neurofisiologici o di neuroimaging. Tuttavia non sono stato in grado di riprodurre i risultati iniziali, probabilmente a causa di un cambiamento sostanziale delle apparecchiature e del setting sperimentale. Nonostante queste difficoltà, sfruttando le caratteristiche peculiari e i punti di forza della nuova apparecchiatura (EEG ad alta densità), ho continuato la mia ricerca sulla percezione visiva e sulle strutture neurali occipito-temporali deputate alla visione tramite registrazione di ERPs (parte 2), che soffrono notevolmente meno del rumore di fondo da corrente alternata che è comunque presente in ogni registrazione EEG. In particolare, ho analizzato gli ERPs in risposta a stimoli costituiti da volti neutri e volti esprimenti emozioni in bambini a sviluppo tipico e in bambini affetti da Disturbi dello Spettro Autistico, una condizione nella quale i network neurali responsabili del processamento dei volti sono spesso stati trovati disfunzionanti sia in studi di neuroimaging che neurofisiologici. Tuttavia le evidenze pubblicate ad oggi a questo riguardo sono ancora contradditorie ed i metodi neurofisiologici utilizzati sono molto eterogenei. Pertanto ho messo a punto ed applicato un paradigma sperimentale con lo scopo di controllare la maggior parte delle variabili confondenti note o sospette in questo tipo di studi. Utilizzando volti

neutrali ed emozionali, ed immagini di alberi come stimoli non-volto, sono riuscito a modulare sia la latenza che l'ampiezza dei principali ERPs volto-sensibili (N170, P1, peak-to-peak N170) in modo differenziale tra i due gruppi in base alla classe di stimoli. Questi risultati supportano l'ipotesi di una compromissione precoce (primi 200 millisecondi) nel processamento di volti neutri ed emozionali in bambini affetti da Disturbi dello Spettro Autistico.

- PART I -

Gamma-band ERSP and BOLD activations to visual stimuli in typical developing children and in children affected by Cerebral Visual Impairment

INTRODUCTION

Oscillatory activities in brain electrical activity

Background

Rhythmic oscillatory patters are known to be a relevant part of brain electrical activity since the first EEG recording obtained by Hans Berger in 1929 (Berger, 1929). The alpha band oscillations are easily recognizable, have an amplitude between 10 and 50 μV, a frequency of 8-12 Hz, and are known to be modulated by diverse brain functions (Basar et al., 1997). The beta rhythm was later identified as an oscillatory pattern with a frequency of 12-30 Hz. Waves slower than the alpha band where initially named delta and later divided into delta (0-4 Hz) and theta (4-8 Hz) bands. It took many years since then to identify oscillations between 30 and 80 Hz, which took the name of gamma activity (Chatrian et al., 1960). EEG oscillations with higher frequency as the omega rhythm (80-120 Hz) have been identified only in recent years, mainly because EEG activities, as a general rule, tend to decrease in amplitude as frequency increases **(fig. 1, 2)**. Despite this, rhythms with frequencies as high as 600 Hz are documented, (Curio et al., 1994). The functional meaning of brain activity in alpha, theta and delta bands begun to be investigated relatively soon because these signals are easily recognizable, even with the

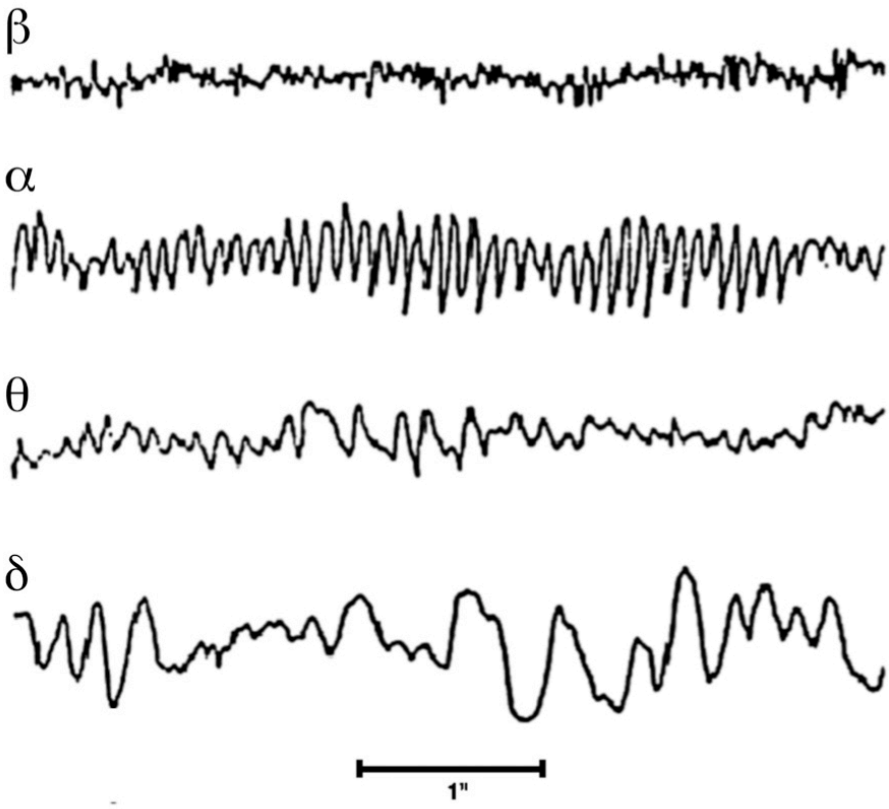


Fig. 1 Main EEG oscillatory activities, easily recognizable in a standard recording with the naked eye

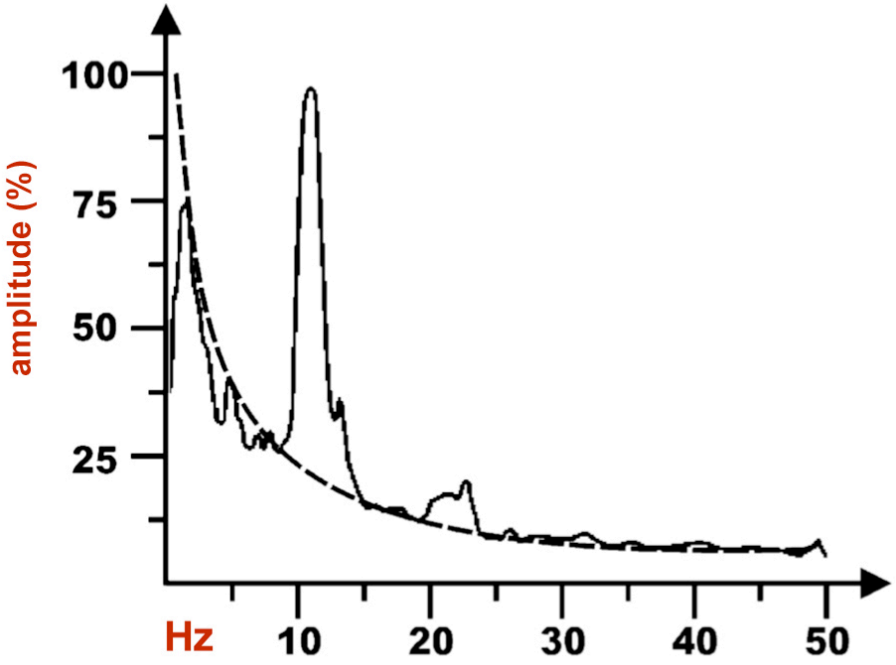


Fig. 2 The relative contribution of different frequencies to the total amplitude of cerebral activity

naked eye, in EEG recordings (Basar et al., 1997; Basar et al., 1980; Demiralp et al., 1992; Steriade et al.,1990). However oscillations in the beta, gamma and omega band can be studied only with the aid of *ad hoc* methods.

Brain electrical oscillations can show various degrees of phase-synchrony, and this can happen in the domain of space (spatially distinct oscillators bursting in phase) or in the domain of time (same oscillator bursting in phase from trial to trial). Phase synchrony and it's effects must be took into account when trying to study the possible functional meanings of brain oscillatory activities. (Steriade et al.,1990). We can identify thee kinds of phase synchrony between recordable brain electrical signals: inter-neuronal, inter-electrodes and inter-trial. *Inter-neuronal phase synchrony* happens between single neurons in a relatively small area, so that their membrane potential oscillate in phase. *Inter-electrodes phase synchrony* occurs on a larger scale, between spatially distinct but functionally related sites. However this kind of synchrony reflects a rather coarse neurophysiological phenomenon, since only the effects of simultaneous activation of a large group of neurons can reach the surface of the scalp, and therefore each electrode will actually record the activity of many neurons and neural circuits (Basar et al., 1980, Steriade et al., 1990). In particular, it has been estimated that a single electrode records the activity generated by a cortical area in the order of 10 cm (Nunez et al., 1995). The third kind of phase synchronization, the *inter-trial phase synchrony*, is particularly relevant for the analysis of event-related spectral perturbations (ERSP).

ERSP can be divided in two different types: evoked and induced (Basar et al., 1980, Herrmann et al., 2005). Evoked ERSP are strictly time-locked to stimulus onset, and therefore can be revealed on averaged EEG epochs. Induced ERSP on the other hand exhibit a jitter in latency from stimulus onset, and thus can be quantified only if data are transformed in the frequency

domain (removing phase information) before averaging epochs **(fig. 3)** (Herrmann et al., 2005). This different time dynamic might reflect different functions, although evoked and induced ERSP could be anyway underpinned by the same neural circuitry.

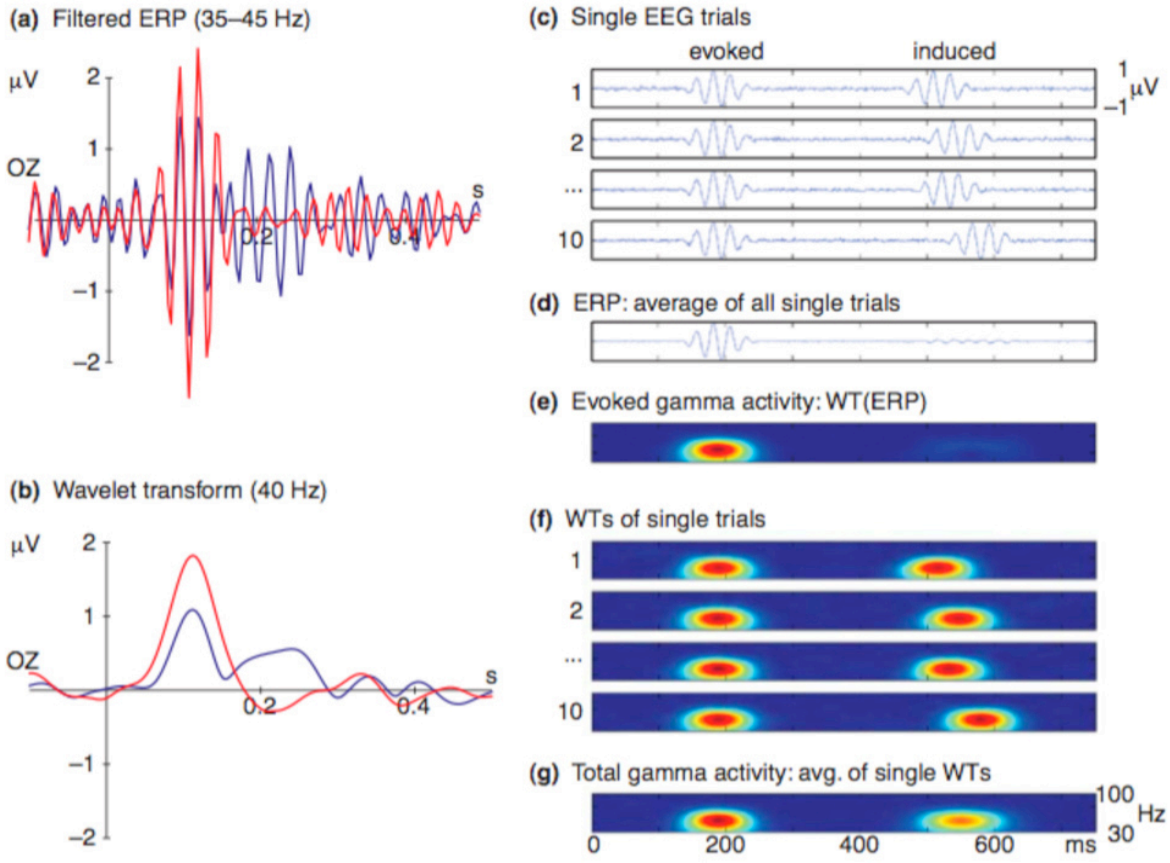


Fig. 3 Analysis of evoked and induced gamma activity (Hermann et al. 2005)

a) traditional procedure: a low-pass filter has been applied to the ERP to show the oscillating properties of signals

b) the wavelet analysis shows the amplitude of the oscillatory event

c) single EEG trials series: the two distinct activation are recognizable in every trial

d-e) trials average: the induced fraction has vanished because of the latency jitter of the induced response

f) epoch by epoch wavelet analysis. It shows the early evoked response, at constant latency, and the induced one, later and at variable latency

g) average of single epochs after wavelet analysis

Spontaneous, induced, evoked and steady-state gamma ERSP

In recent years a particular interest for gamma band ERSP has gradually appeared in neuroscience (Basar-Eroglu et al., 1996). This attention can be explained by the fact that gamma ERSP are closely related to diverse cognitive functions (Engel et al., 2001). Gamma-band ERSP can be dived into four categories: spontaneous, induced, evoked and steady-state (Galambos et al., 1992).

Spontaneous gamma-band ERSP contribute to a fraction of EEG/MEG signals, are thought to be linked to thalamocortical oscillatory activities, and have been related to attention and consciousness (Llinas et al., 1992). *Induced* gamma-band ERSP have been recorded from cerebral cortex of different animal species in response to diverse sensory stimuli (Engel et al., 1992). Induced gamma-band ERSP has been interpreted as reflecting the building process of a non-ambiguous neural engram, obtained by connecting the different features of a perceived object. Gamma-band ERSP can also be linked to the different mental representations of an object as well as to motor activity related to it (Roelfsema et al., 1997). *Evoked* gamma-band ERSP can be recorded in an earlier time window than the induced ERSP, and have been recorded also in sub-cortical structures in animal studies in response to basic sensory stimulation (Basar et al., 1980, Demiralp et al., 1996). *Steady-state* gamma-band ERSP consist in evoked response to repetitive simple stimuli such as clicks or pure tones, and they reach the maximum amplitude response at around 40 Hz stimulus rate repetition (Galambos et al., 1981).

Spontaneous gamma-band ERSP are recorded without any task for the subject. A repetitive stimulus is used in order to record this kind of response, usually presenting it at the same frequency rate of the oscillation of interest (e.g. 40 Hz). Induced and Evoked gamma-band ERSP on the other hand consist in a transient, event-related response to a stimulus that usually also generate

conventional ERPs (Event Related Potentials) in overlapping time windows: different signal analysis procedures can reveal one or both kind of response **(fig. 3, 4)**. Although this different types of gamma-band oscillations behave differently in terms of temporal dynamics and stimulus-related features, there is evidence that they may be generated by the same neural structures (Basar et al., 1980; Pantev et al., 1991; Herrmann et al., 2001). Basar (Basar et al., 1980) measured intracranial field potential to show that brain structures respond to a stimulus with a transient ERSP that happens in the same frequency range those same structures usually fire during spontaneous activity. This phenomenon, named "the response susceptibility" support the hypothesis of a common neural substrate for these different types of gamma-band ERSP (Herrmann et al., 2001). In addition, the generators of auditory steady-state and induced ERSP were both located in the auditory cortex (Gutschalk et al., 1999; Herdman et al., 2002), both in primates and humans (Brosch et al., 2002; Crone et al., 2001). Similarly, steady-state and event-related ERSP have been located into the human visual cortex (Hillyard et al., 1997; Muller et al., 1997), both in primates (Fries et al., 2001, Rols et al., 2001) and in humans (Tallon-Baudry et al., 2005). Lastly, induced and evoked gamma-band ERSP seem to reflect overlapping cognitive processes (Tiitinen et al., 1993; Yordanova et al., 1997; Fries et al., 2001; Engel et al., 2001; Debener et al., 2003; Herrmann et al., 2004a).

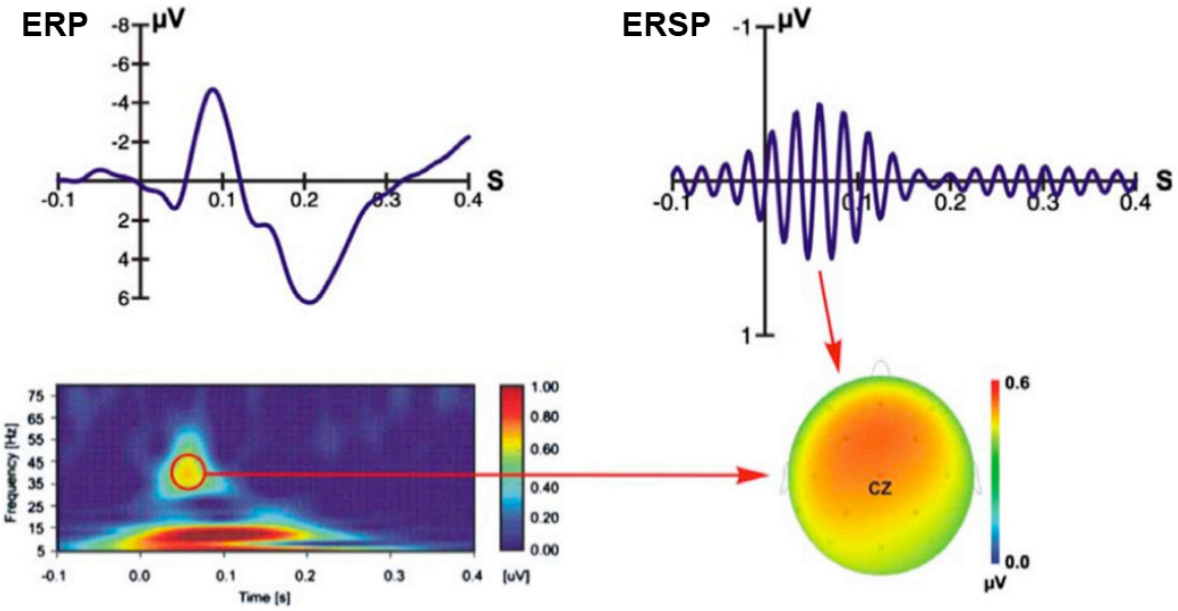


Fig. 4 The ERPs and ERSPs responses are simultaneously generated and can be differentiated using standard filters or frequencies transformations

Gamma-band ERSP in the Visual System

Most of the first evidences about a functional role of gamma-band neural synchrony in brain electrical activity came from recordings obtained from the visual cortex of anesthetized cats (Eckhorn et al., 1988), and non-human awake primates (Kreiter et al., 1996). In humans and experimental animals gamma-band activity increases in cortical occipital regions when the subject observes a coherent moving pattern versus a random one (Lutzenberger et al., 1995). Gamma-band ERSP can be recorded even when the coherent stimulus is actually an illusory stimulus, as the Kanizsa triangle **(fig. 5)**, or a multistable stimulus (Tallon-Baudry et al., 1996; Keil et al., 1999). In particular Tallon-Baudry et al. (1997) used an elegant study design: the stimulus consisted of well-known optical illusion of the Dalmatian dog "hiding" in a mimetic background **(fig. 6)**: subject were naive to the illusion, gamma-band ERSP were recorded before and after the needed training to recognize the

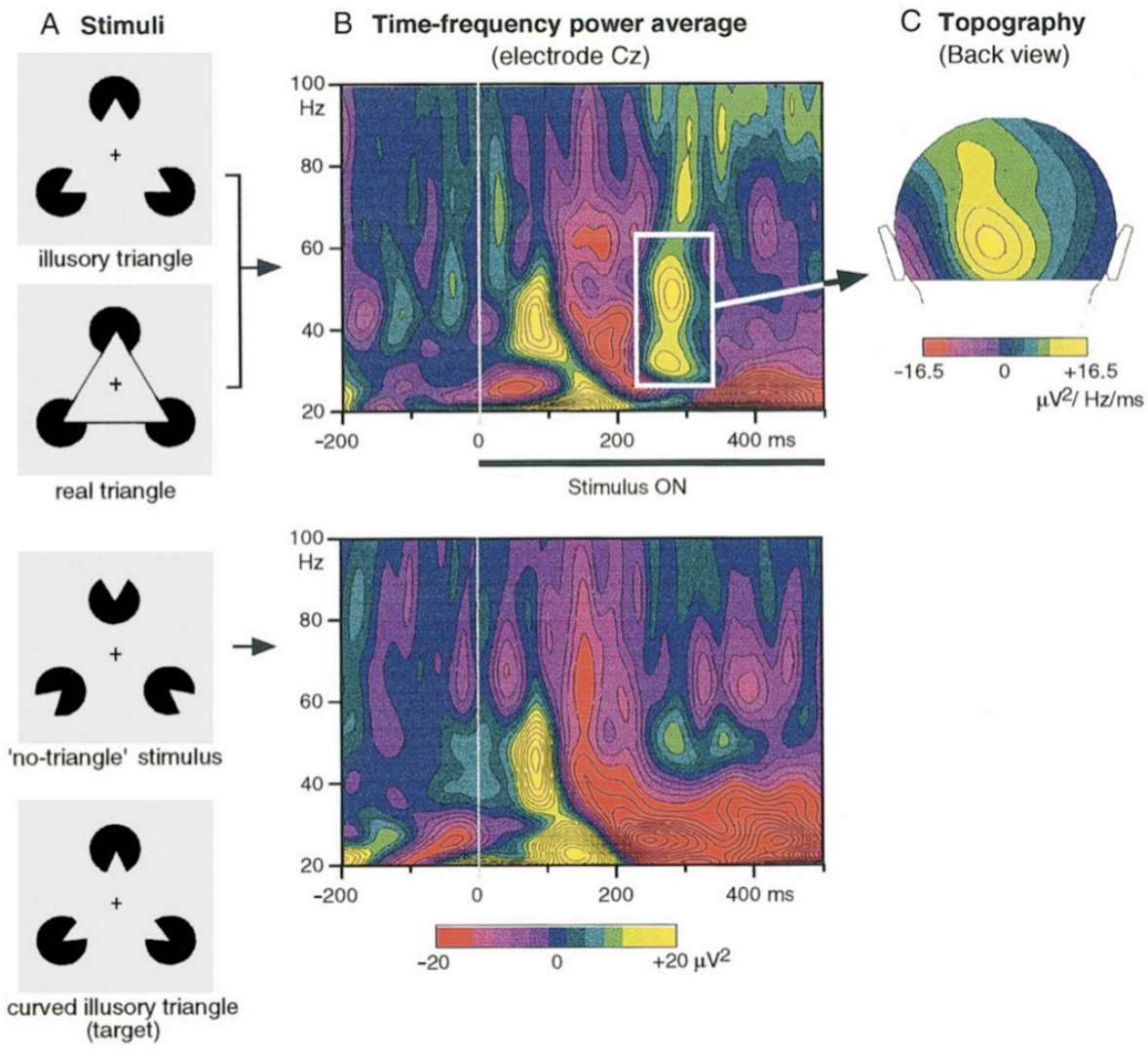


Fig. 5

A) Illusory (Kanisza) and real triangles evoke comparable responses. The non-triangle stimuli was used as control stimulus

B) Time-Frequency power average representation of signal registered at CZ electrode: two subsequent bursts of oscillating activity are recognizable: the first one at 100 ms, at about 40 Hz (the evoked fraction, with no differences for the two types of stimuli) and the following one (the induced fraction) at 280 ms and 30 – 60 Hz

C) Power map of gamma activity ranging from 30 to 60 Hz, in the time window from 250 ms to 350 ms, during the illusory triangle stimulus. The maximal activity is registered on occipital electrodes

(Tallon-Bowalry et al., 1996)

illusion and showed to be of higher amplitude on the posterior regions only when the stimulus was perceived as a dalmatian dog. These studies have found gamma-band ERSP with a frequency of 30-60 Hz, peaking at 200-400 msec from stimulus onset. Some aspects of this kind of response have been interpreted as the activation of bottom-up neural processes involved in

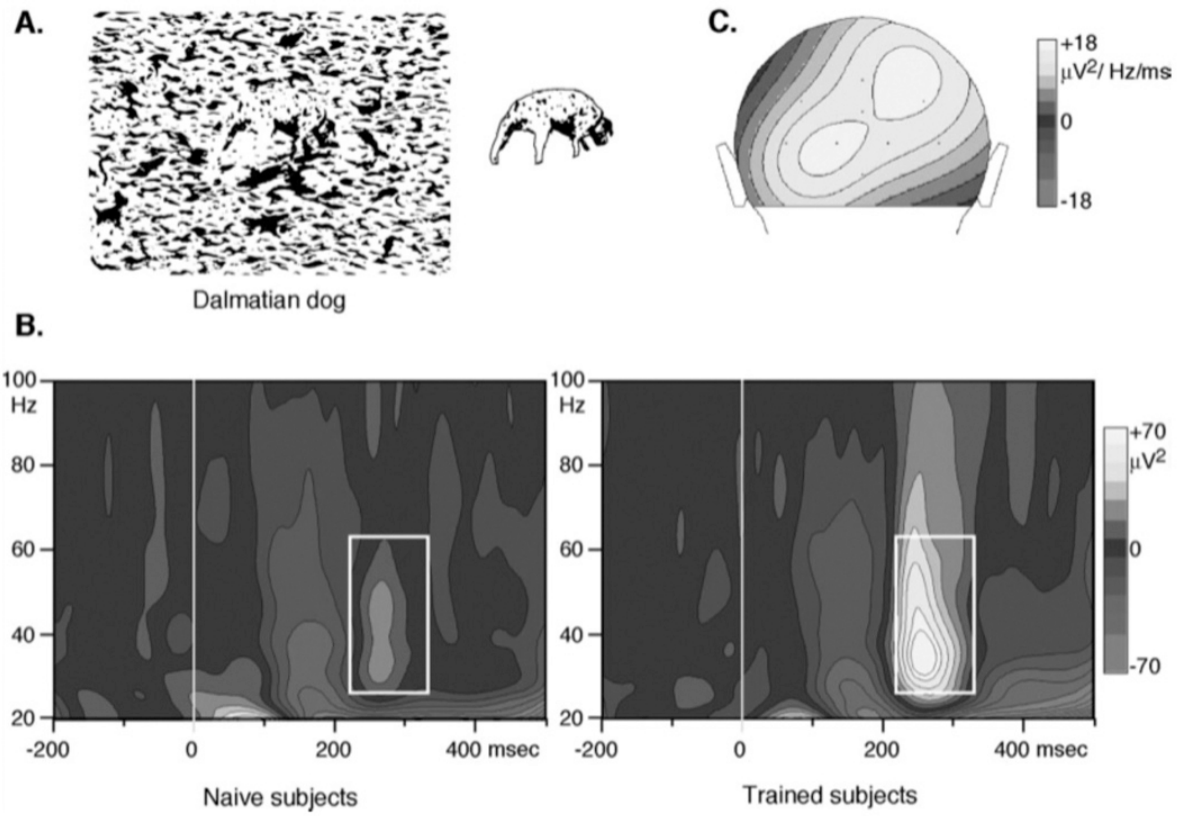


Fig. 6

A) Example of stimuli used in both the experimental conditions (pre and post training for the correct stimulus recognition)

B) Gamma-activity representation in the same group, pre and post training: a pronounced gamma-activation is evident in the second condition

(Tallon-Boudry et al., 1997)

perception, supporting the hypotheses of a link between fast oscillations and consciousness (Engel et al., 2001). Anyway also top-down processes should be taken into account, like the activation of an internal representation that is required in order to start a visual search for any object(Muller et al., 2004). Most of the evidence about gamma-band ERSP and the visual system comes from studies on the induced, non-phase locked type of gamma-band ERSP. Evoked gamma-band ERSP can't be usually modulated by the task, instead are typically influenced by the physical properties of the stimulus, like dimensions, contrast, complexity, eccentricity and spatial frequencies (Busch et al., 2004; Schadow et al., 2007; Frund et al., 2007). Induced gamma-band ERSP can be manipulated altering the semantic content of stimulus, comparing responses

to images of real objects with meaningless control images obtained by pixels scrambling or more sophisticated image processing techniques used in order to keep unaltered the physical properties of stimuli (Busch et al., 2006; Freunberger et al., 2007; Sadr et al., 2007)

Gamma-band ERSP in the Auditory System

Kaiser et al. recorded auditory gamma-band ERSP using a mismatch paradigm, comparing frequent bilateral to rare unilateral sounds, and found a gamma-band ERSP at 50-80 Hz on posterior parietal regions (Kaiser et al., 2000; 2002). Similar ERSP have been recorded using words versus non-words (Palva et al., 2002), and sound with different duration (Kaiser et al., 2007) or intensity (Schadow et al., 2007). Auditory gamma-band ERSP have also been related to arousal level (Griskova et al., 2007). Hannemann et al (2007) studied gamma-band ERSP using transformed words that could be identified only after training, and found induced ERSP to be of higher amplitude in left temporal area only in the after-training condition. These evidences confirm the general opinion of a link between coherent perception and gamma-band ERSP (especially the induced type) also in the auditory system.

Gamma-band ERSP and sensory integration

Growing evidence is supporting the hypothesis that gamma-band ERSP may be particularly relevant to understand surprisingly diverse cognitive processes. Beshel et al. (2007) recorded gamma-band ERSP in the in the olfactory bulb of rats during an odor discrimination task, and found the magnitude of response to be proportional to task difficulty: in particular the gamma-band activation was higher when the task consisted in discriminating odors that were similar rather than different. These authors suggest that this activation may reflect a change in the olfactory system dynamics that takes

place when stimuli are perceived as ambiguous, in order to optimize the resolution of sensory scanning. Gonzales et al. (2006) recorded a lateralized gamma-band ERSP during the preparation of a motor response, and Arnfred et al (2007) showed how a parietal gamma-band ERSP could be obtained with a proprioceptive stimulus by rapidly changing the weight of an object held in hand. Senowski et al (2007) were able to modulate gamma-band ERSP using simple auditory and visual stimuli presented in different spatiotemporal configurations at various synchrony levels: they found a positive correlation between the ERSP amplitude and the level of synchrony in stimuli presentation. Another evidence supporting the hypothesis of an integrative role of gamma-band activities come from a relatively simple experiment. Yuval-Greenberg et al. (2007) recorded gamma-band ERSP to simultaneous presentation of animal images and verses, so that these stimuli were congruently presented (same animal picture and verse), or incongruent (different animal picture and verse): they found induced gamma-band ERSP to be stronger for congruent stimuli couples than for incongruent ones, while as expected the evoked gamma-band ERSP where not affected by this type of semantic experimental manipulations. Lastly, Kanayama et al. (2007), using a "rubber hand illusion" paradigm, found a stronger gamma-band ERSP when the subject experienced a congruent multisensory event (same tactile stimulus seen on the rubber hand and applied to the real hand) rather than an incongruent one (different tactile stimulation seen on the rubber hand and applied on the real hand).

Match and Utilization Model (MUM) and oscillatory activities

Many studies on gamma-band activities have shown that gamma-band oscillations are modulated by a variety of cognitive processes as attention, object recognition, speech perception, and working memory (Tiitinen et al.,

1993; Yordanova et al., 1997 Herrmann et al., 2001; Fries et al., 2001; Debener et al., 2003). Gamma-band oscillations have been recorded in many animal species including insects (Stopfer, 1997) and mammals (Brosch et al., 2002), and therefore can be thought to reflect a quite general neural process.

The processes underlying neuronal plasticity involved in learning and memory may be similar to those processes which contribute to the stabilization of neuronal connections and the activity-dependent synapses plasticity (Cohen-Cory, 2002; Sheng et al., 2002). Both processes involve membrane receptor activation, intracellular signaling cascades and gene transcriptions that modify synapses number and spatial distribution (Johnston et al., 2001; Sweatt, 2001). In other words, the brain seems to use a similar sequence of neuronal modifications needed for shaping and strengthening of emerging circuitry in the immature developing brain, as well as for consolidating the more subtle changes that happen during memory traces formation in adults. However the "plasticity advantage" of the immature brain should always be kept in mind: thanks to the overabundance of connections the immature brain can realize plastic changes through both short and large-scale reshaping, while in the mature brain changes could be limited to activity-dependent rearrangement of dendritic spines (Trachtenberg et al., 2002).

The Match and Utilization Model (MUM) postulates that memory traces are reinforced every time the same neurons fire during the activation of the same neural engram. If a neuron in the occipital cortex that fires in response to an horizontal line is coupled to another neuron in higher areas that fires in response to a face, then both may be considered as a part of the memory trace for that face: this connection was built through the frequent presentation of a horizontal line (e. g. the lips) along with a face. This process produces a feedback effect through bidirectional connections, and a gamma-

band ERSP may appear and be recorded as a signature of the "search for meaning" of a perceived or remembered face or object (Herrmann et al., 2004b). The MUM offers the advantage of explaining many evidences about gamma-band ERSP in different paradigms used in experiments: the higher gamma-band activation in response to stimuli which already have a memory trace can be explained easily using this model (Tallon-Baudry et al., 1998; Gruber et al., 2002; Gruber et al., 2005; Kaiser et al., 2003). Other studies have shown that words induce a stronger gamma-band response versus pseudo-words (Pulvermuller et al., 1995), as well as known faces versus unknown faces (Keil et al., 1999), and recognizable object versus random dot patterns (Revonsuo et al., 1997). In other words, since mental representations pre-exist for words, known faces and objects and do not exist for pseudo-words, unknown faces or random dot patterns, the former will evoke a stronger gamma-band response.

Even if gamma-band oscillations have been related to memory activity, they could reflect mostly low-level processes, happening mainly in the sensory areas. When higher-level processes are involved, like working memory, then also theta and alpha oscillations comes into play (Basar et al., 2000; Klimesch, 1999). For example, during delayed matching memory tasks the alpha-band activity is higher when the number of information to be remembered is bigger (Busch et al., 2003; Herrmann et al., 2004c; Jensen et al., 2002; Schack et al., 2002). The activity in the theta band, known to be linked to the hippocampus (O'Keefe, 1993; O'Keefe et al., 1999; Tesche et al., 2000; Buzsaki, 2002), can be recorded during memory recall tasks (Klimesch et al., 2001) and is of higher amplitude for known objects, target objects, or old objects versus unknown, non-target, or new objects (Burgess et al., 1997; Klimesch et al., 2000; Van Strien et al., 2005). It was also showed as this slower rhythms can exhibit phase-synchrony with gamma-band activity (Schack et al., 2002;

Burgess et al., 2002; Fell et al., 2003), suggesting that both type of oscillations may reflect interactive processes during memory traces formation and consolidation. Lastly, when studying multiple-frequency rhythms interaction must be kept in mind that amplitude, frequency and phase of each rhythm may influence each other in different ways **(fig. 7)**

According to Varela et al. (2001) in the MUM framework the slower rhythms could provide the temporal segmentation required for the subsequent activation of neural populations that fire at faster frequency. For example, while remembering a list of elements, this mechanism implies the high-frequency repetition of every single element and the low-frequency repetition of the entire list. Lisman and Idiart (1995) suggested that these frequency are in fact gamma-band and theta-band oscillations **(fig 8)**, and moreover they think that the memory buffer size is related to number of gamma-cycles in a theta-cycle, while the speed in recalling the single elements is related to the gamma-band oscillation frequency. While many experimental evidences support this model (Vogel et al., 2004; Jensen et al., 2002;Rizzuto et al., 2003; Canolty et al., 2006), it still remains unclear how this process exactly happens.

Neural synchrony and GABAergic interneurons

Studies on lesions and developmental manipulations (Engel et al., 1991, 2001) indicate that neural synchrony in the high frequency band is mediated mainly by corticocortical connection linking neurons in the same or in different cortical areas. These and other studies suggest that high frequency are mainly used by intracortical circuits, while subcortical structures, like thalamus and hippocampus, seem to use mostly slower-frequency oscillations like alpha, theta and delta (Llinas et al., 2006; Steriade, 2005; Steriade, 2006).

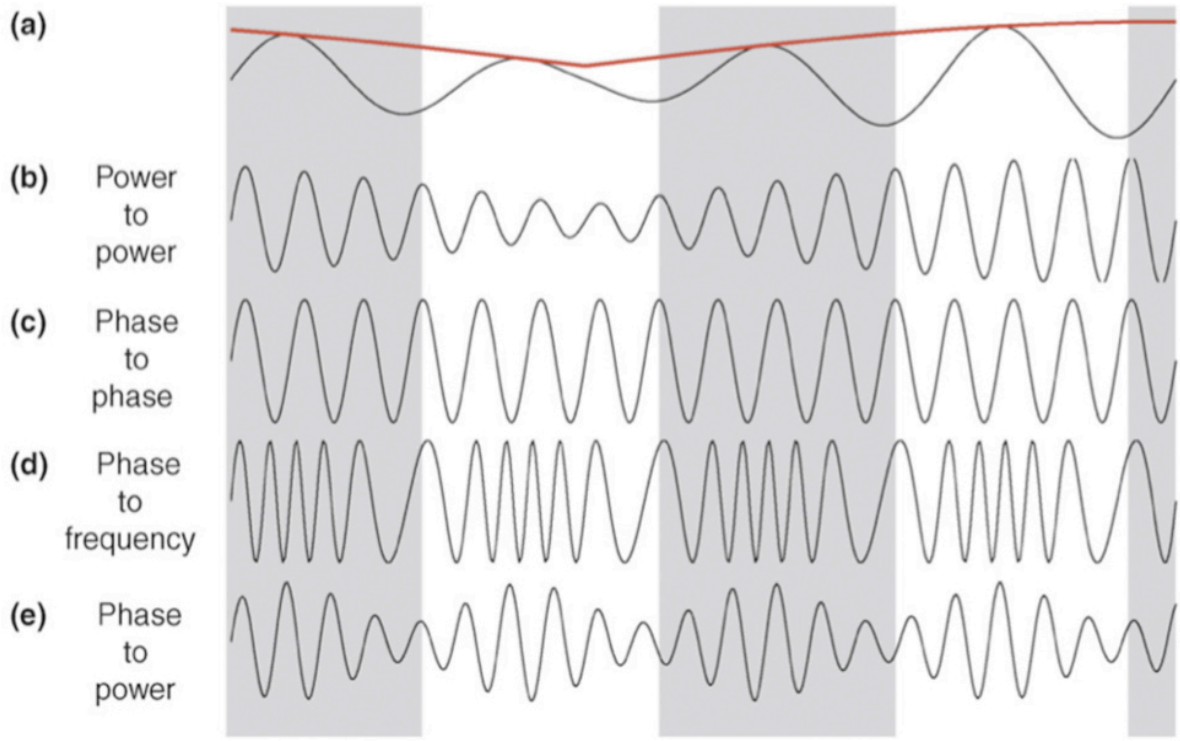


Fig. 7 Different modalities of interaction between frequencies

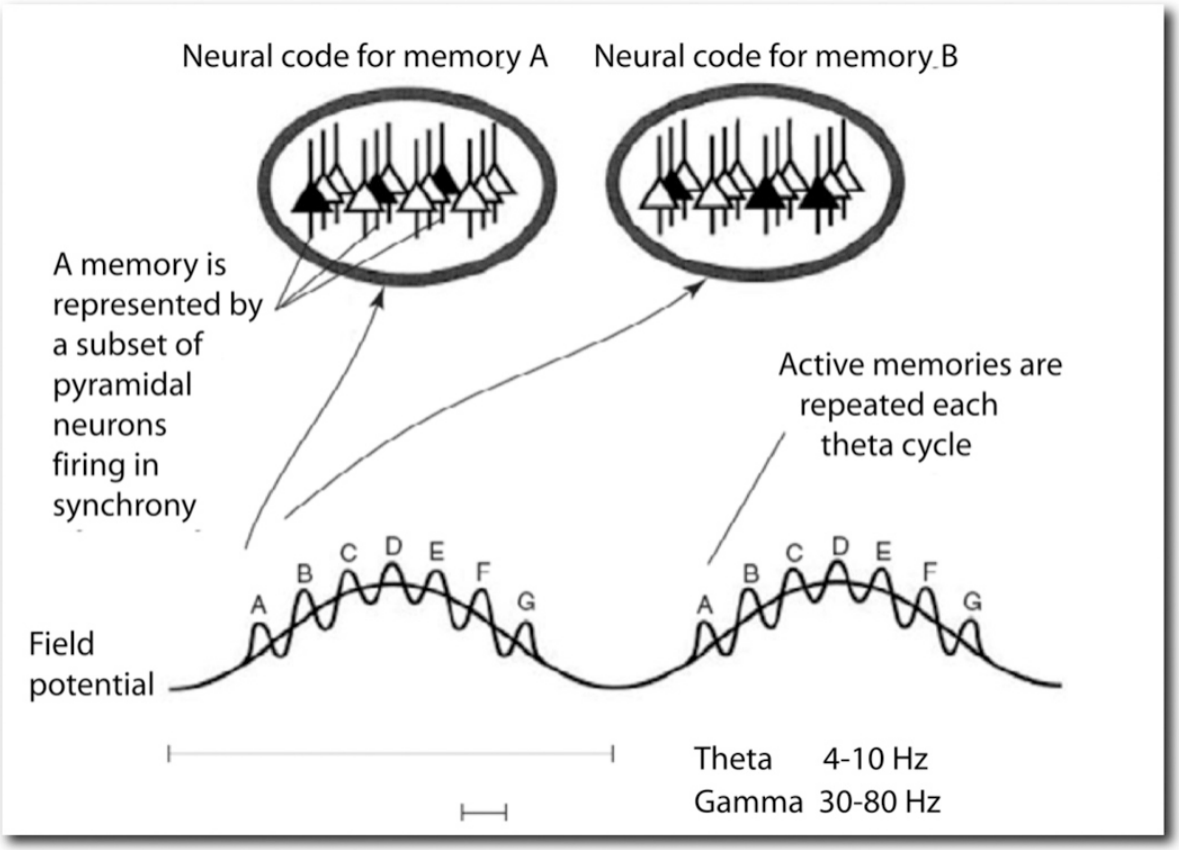


Fig. 8 Temporal segmentation controlled by theta-gamma oscillation (Varela et al., 2001). The memory contents (A-G) are sequentially activated in different gamma-cycles. This pattern is repeated every theta cycle

High-frequency rhythms production and synchrony involves different neurotransmitters systems. GABAergic neurons seem implied in high-frequency oscillation production and their short-range synchrony, while glutamatergic connections appear to control power, duration and long-range synchrony (Traub et al., 2004). Moreover cholinergic transmission seems to modulate the state-dependent facilitation of high-frequency oscillations (Rodriguez et al., 2004; Wespatat et al., 2004). In terms of microanatomy, GABAergic interneurons may be the "neural hardware" needed for the oscillatory processes described. The main difference between cortical interneurons populations is the target of their innervation, such as the dendritic or perisomatic area. The functional consequences of this anatomic difference have been tested by invasive recordings of hippocampal neurons (Buhl, 1994; Bragin et al., 1995; Cobb, 1995; Miles, 1996). It is believed that dendritic inhibition is involved in modulation of excitatory inputs to target neuron, while the perisomatic inhibition is likely involved in output control by synchronizing the action potentials generation (Freund et al., 1996). Hyppocampal perisomatic GABAergic interneurons target the body, the proximal portion of dendrites and of the axon, and are generally configured in an ideal way in order to control and synchronize the neural output pattern (Bragin et al., 1995; Cobb, 1995; Buzsaki et al., 1995; Miles, 1996). The activation of a single perisomatic interneuron can synchronize the action potential of about 1000-2000 innervated neurons. Among the different subtypes of GABAergic interneurons, the most likely candidates for having a crucial role in generation of gamma-band oscillation are the interneurons containing parvalbumine: thanks to reciprocal connection and the presence of gap-junctions this kind of interneurons can act as a functional syncytium, able to modulate its function with a very high temporal accuracy (Gibson, 1999; Tamas et al., 2000; Amitai, 2002).

Gamma-band activity in neuropsychiatric disorders

It soon became apparent that there are significative individual differences in gamma-band activity between single subjects across various conditions (Struber et al., 2000). It was also shown that an excess or defect of such "cognitive" activity is typical of some disorders. This evidence is somehow expected if we consider true the hypothesis that gamma-band neuronal activity plays a relevant role in cognitive processes. There are various evidence about a gamma-activity role in epilepsy, ADHD, schizophrenia, autism, dementia, migraine and even in conditions as stroke or periventricular leukomalacia.

Gamma-band activity and Epilepsy. Seizure triggering has been extensively studied in several animal models. Two mechanisms seem to be of fundamental importance: the decrease of inhibitory activity mediated by the GABAergic system, and excitatory glutamatergic system hyperactivity (Treiman, 2001). For example, kainic acid, a strong glutamatergic agonist, can induce seizures in rats (Pisa et al., 1980), and can increase gamma-band activity (Medvedev, 2002). Spontaneous gamma activity power during interictal EEG recordings has been shown to be up to ten times higher in subjects affected by generalized idiopathic epilepsies than in controls (Willoughby et al., 2003). Intracranial recordings through subdural electrodes showed that, before a seizure, there was an increase in the amplitude in 40-50 and 80-120 Hz frequency bands (Fisher et al., 1992). The fact that these changes in patients with neocortical epilepsy are realized almost exclusively in the proximity of epileptogenic foci appear to confirm the role of gamma band activity in epilepsy (Worrell et al., 2004). Some authors consider the epileptic brain activity as a natural response to an excessive increase in gamma-band activities (Medvedev, 2002).

Gamma-band activity and ADHD. It is easy to imagine that in an attention disorder systems deputed to control attention may be hypoactive, but the presence of hyperactivity suggests that the initial ADHD disfunction may consist in an *excessive* neuronal excitation. In healthy subjects both visual and auditory target stimuli evoke a stronger gamma-band response than non.target stimuli, and can induce a stronger phase synchrony, likely because of attentive top-down processes activation (Yordanova et al., 1997; Herrmann et al., 2001). In a study using lateralized auditory stimuli as a target, Yordanova et al. (2001) found that evoked gamma-band ERSP and its phase synchrony were stronger in children with ADHD, but only when stimuli were presented to the right ear. Knowing that the motor response was given only for target stimuli presented to the right ear, it seems that this kind of gamma-band lateralization in ADHD subject could be explain by an excessive high-frequency coupling between sensory and motor areas.

Gamma-band activity and Schizophrenia. Schizophrenia is usually characterized by delusions, hallucinations, disorganized speech and by negative symptoms as affective flattening, alogia, avolition (DSM-IV). The defective integration of sensory inputs and memory traces is considered as a core deficit in this disorder (Gray, 1998). While this phenomenon is clear during hallucinations, a similar mechanism may underlie the diffuse disorganization of thoughts that is also typic of this disorder. Several studies has shown that in subject with schizophrenia steady-state gamma-band ERSP is weaker than control subjects (Wada et al., 1995; Clementz et al., 2004; Kwon et al., 1999). This evidence has been interpreted as a reflex of degenerative changes in sensory brain structures. Kissler et al. (2000) have shown that in healthy subjects arithmetic tasks induce a gamma-band activity increase in the left hemisphere, while subjects affected by schizophrenia lack this response. As already mentioned, gamma activity has been related to a

"feature coupling" mechanism during objects perception. Regarding this function, Spencer et al. found that illusory Kanizsa triangle provokes a weaker gamma-band activation in schizophrenic patients. (Spencer et al., 2003; 2004). Taken together, these studies generally show a gamma-band activity reduction in schizophrenia, however other evidences have showed how gamma activity could be even higher than controls when positive symptoms are present (Lee et al., 2003).

Gamma activity and Autism Spectrum Disorders. Is currently thought that some of the core deficits in Autism Spectrum Disorders (ASD) may be the consequence of reduced neural synchronization (Belmonte et al., 2004; Brock et al., 2002). Grice et al. (2001), using a face-perception paradigm, found gamma activity to differentiate faces from non-faces in control group but not in ASD individuals. As in schizophrenia, auditory steady-state gamma-band response appears to be weaker in ASD patients (Wilson et al., 2006). On the other hand Orekhova et al. (2007) found an increase in high frequency band during a sustained attention task. Evidence on ASD is however controversial similarly to schizophrenia data, as in both disorders it suggests a mixed hypo-hyperfunction model.

Gamma activity and Periventricular Leukomalacia. To our knowledge, only one study has specifically examined the influence of periventricular leukomalacia (PVL) lesions on gamma-band activity: using a biological motion perception paradigm in a MEG experiment, Pavlova et al. (2007) found that while in normal subjects gamma-activity burst peaked at 170 ms on the right parieto-temporal region, in PVL subjects this burst is delayed (290 msec) and shows an opposite lateralization pattern.

The "gamma axis" of neuropsychiatric disorders. All of these experimental evidences point towards a relevant role of gamma-band activity in neurological and psychiatric conditions. The hypothesis that there may be a

"gamma axis" **(fig. 9)** for these groups of disorders is supported by additional evidence. Gamma activity in rat hippocampus is is significantly enhanced by phencyclidine, which inhibits dopamine re-uptake (Ma et al., 2002). Haloperidol, a D2 antagonist, can suppress gamma activity (Ahveninen et al., 2000). There is therefore a positive correlation between dopaminergic activity

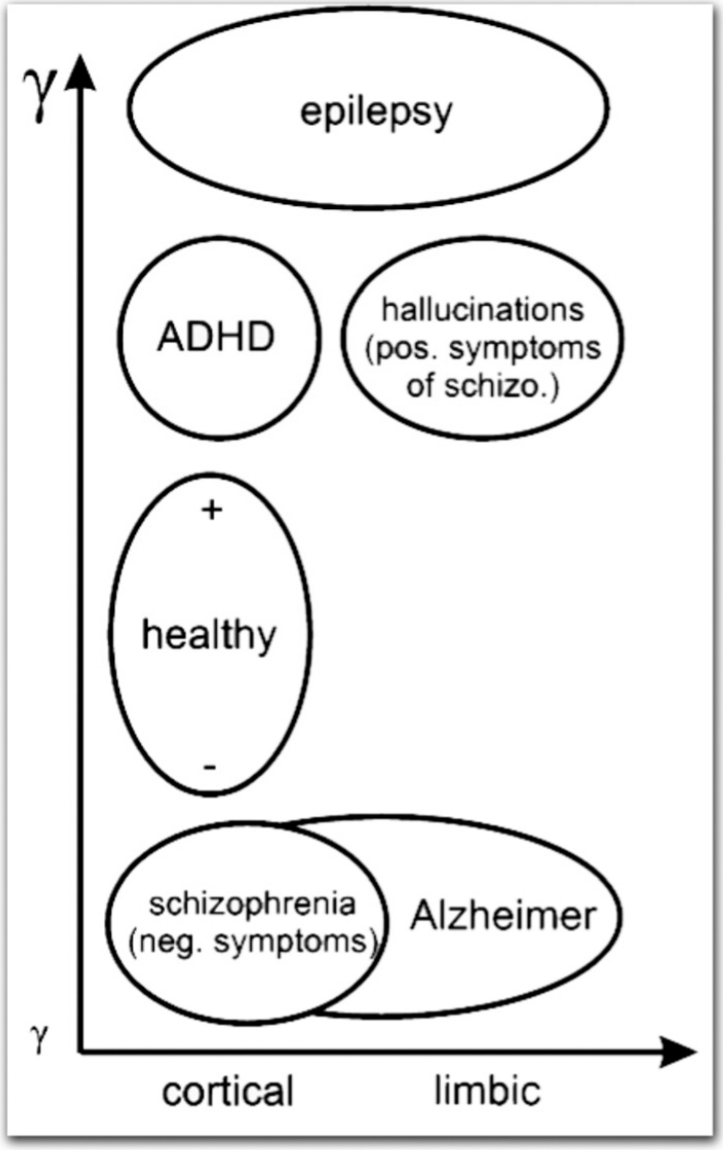


Fig. 9 Hypothetical relation among gamma-activity, cerebral regions and neuropsychiatric disorders. In ADHD patients, the gamma-activity is more intense than in normal subjects. Concerning schizophrenic patients, it is shown the relationship between positive-negative symptoms and excess-defect gamma activity. Alzheimer Disease is related to a reduction in gamma-synchronization. An extremely high level in gamma activation could trigger epileptic seizures due to a cortical hypersynchronization

and gamma oscillations, and this could be related to the influence of dopamine on both GABAergic and glutamatergic transmission (Wang et al., 2002; Price et al., 2001). Dopamine plays a central role in schizophrenia: neuroleptics are basically D2 antagonists, and substances such as amphetamines, cocaine, methylphenidate, as well as L-DOPA are capable of triggering symptoms similar to the typical positive symptoms of schizophrenia. Therefore an increase in dopaminergic activity seems to facilitate gamma-band activation as well as positive symptoms generation. Also the glutamatergic hyperexcitability, typical of epilepsy, may be modulated by dopaminergic systems (Starr, 1996).

The relationship between some symptoms of these disorders and the level of gamma activity can be explained through an integrative model proposed by Herrmann (2004b,c). **Figure 10** shows a simplified integrative model between sensory inputs and memory traces. During the perception of an object, if it lacks a preexisting mental representation, only "weak" synaptic connections are activated between primary and secondary sensory areas, resulting in a weak gamma-band activation **(fig. 10a)**. If instead a mental representation is present **(fig. 10b)** then the connections resonate more, as suggested by several evidences. This model could also explain the déjà vu phenomenon often observed in epileptic patients and hallucinations observed in schizophrenic patients. Usually a higher gamma-band synchronization reflects the recognition of a perceived scene (Herrmann et al., 2004b,c). If the pathological increase of gamma-band activity reaches levels normally present during the perception of known stimuli, then the scene will generate the feeling of unknown familiarity, or déjà vu **(fig. 10c)**. The déjà vu experience is frequent in patients with epilepsy (Spatt, 2002), but it is also reported in healthy subjects, more often when taking drugs that increase dopamine levels as amantadine (Taiminen et al., 2001). Hallucinations can be explained in a

similar way, considering them responsible for the pathological increase of gamma-band activity in the absence of sensory input, which would therefore result in a illusionary perception **(fig. 10d)**.

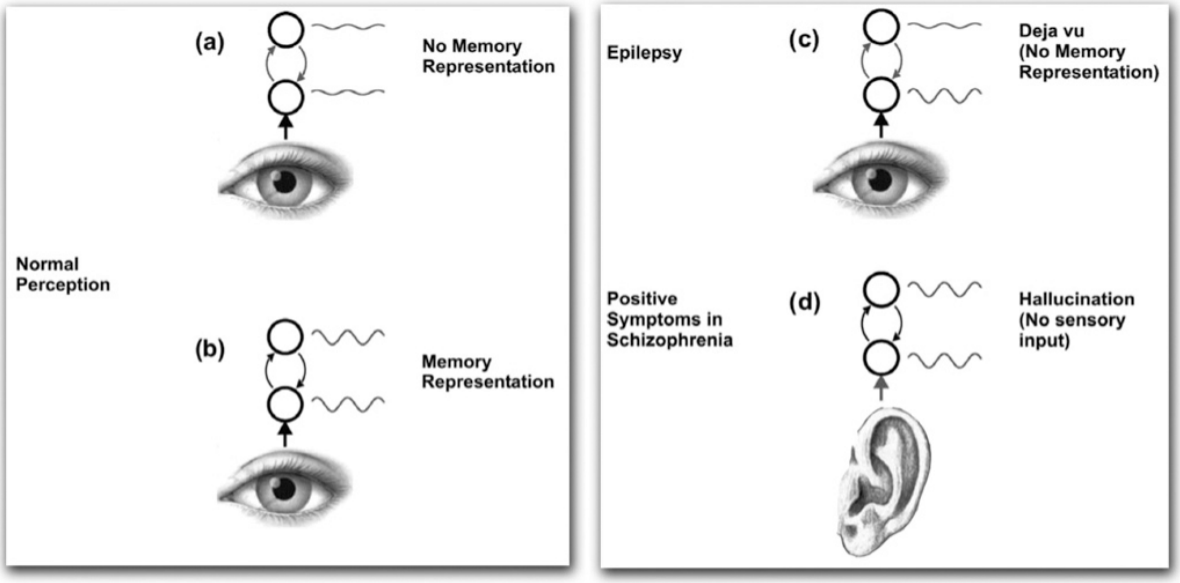


Fig. 10 Model proposed for explaining the connection between some pathological conditions and gamma activity

a) When there is no mnesic representation of a perception there is low synchronization

b)In presence of mnesic representation, the high synchronization is detected as gamma-activation

c) If there is a pathologic gamma burst in primary sensory areas, this leads to a familiar sensation triggered by an unknown stimulus

d) Allucinations are experienced when there is a gamma-activity though no stimulus is perceived

"what" and "where" in the visual brain

The interest for vision and for the "visual brain" has received a great drive in recent years thanks to the availability of new fMRI techniques - however visual systems has been the subject of great interest in the past too. Since the seventeenth century, in fact, several scientist have directed their interest to vision, initially focusing attention on anatomical and then on functional organization: Newton, Descartes, Panizza, von Graefe, Ferrier, Munk, are some of the “greats” who helped uncover anatomic and functional basis vision. Bartolomeo Panizza (1785-1867) first localized vision in the occipital cerebral cortex using animal models and autoptic investigations. In the second half of the nineteenth century experimental studies of David Ferrier and Hermann Munk confirmed that occipital cortex plays a key role in vision (Ferrier et al., 1897). Over time the focus has gradually shifted from basic components of visual perception to the neural processes underlying object recognition and subsequent object-directed neural processes. In the ‘70s, after first evidences from primates studies, vision researchers begun to think of two distinct visual systems, one deputed to space exploration and a second to object perception and recognition (Denny-Brown et al., 1976). This hypothesis was extended in the next decade: Ungerleider and Mishkin in 1982 suggested that there is a dorsal occipito-parietal route that analyzes the spatial location of objects, and ventral occipitotemporal route which plays a critical role in object identification and recognition (Mishkin et al., 1982). Referring to this distinction between spatial and object vision, the terms "*what*" and "*where*" were used to summarize the functions performed respectively by the dorsal and ventral system. First evidences of this distinction came from clinical observations of patients presenting with dissociate disorders related to the spatial vision or object recognition. Patients with bilateral posterior parietal damage easily recognize an object, but they do not know how to describe the

spatial position and relations. In contrast, patients with bilateral occipitotemporal lesions are able to identify the spatial characteristics, while they don't even recognize simple line drawings of familiar objects (Farah, 2000; De Renzi, 2000). Similar observations derived from experimental studies in monkeys confirm the general distinction between the *what* and *where* processes relative to objects perception. The distinction between a *what* and *where* route is not universally accepted (De Renzi, 2000; Zeki, 1983; Desimone et al., 1985; Sereno et al., 1998), however Milner and Goodale (Milner et al., 1993) underline that both systems, both dorsal ventral, carry information about objects structure and their spatial location, and that both are under modulatory influence of attention. Each route uses the *same* informations in different *ways*. Processes carried out by the dorsal stream analyze, moment by moment, spatial informations needed for object localization and motor responses, while on the other hand the ventral stream transform informations into a perceptual whole: this allow us to identify objects, give them the appropriate meaning and establish causal relationships. Therefore both ways cooperate to produce a pivotal model of adaptive behavior: object identification and processing of the set of possible actions modulated by its particular affordances.

OBJECTIVES

Only few studies have explored ventral stream functions in children affected by Cerebral Visual Impairment (CVI). This study aims to investigate gamma-band ERSP in healthy subjects and patients suffering from CVI with a clear "ventral" pattern of deficits in response to a visual stimulus in a classical paradigm: images of real objects versus pictures of unrecognizable objects. I also developed an fMRI paradigm using the same stimuli and a similar paradigm. Both experiments were devised to explore ventral stream function. The decision to combine the two techniques depended not only on the possibility of combine high spatial resolution of fMRI with high temporal resolution typical of EEG, but also by the fact that the gamma-band frequencies appear to positively correlate with the BOLD effect (Foucher et al., 2003; Mukamel et al., 2005; Lachaux et al., 2007; Axmacher et al., 2007). Since gamma-band ERSP can be modulated by a great variety of experimental conditions it seems crucial to carefully plan the experimental setting in order to rule out potential confounding variables. This has been done by accurate elaboration and selection of stimuli as well as by simplifying at the most the task required.

MATERIALS AND METHODS

Subjects

Four healthy subjects (age 25-28 y) underwent the neurophysiology test, one subject was analyzed with the fMRI protocol. Two children (CN, 7 years and GG, 15 years) affected by CVI where enrolled in the study. Both children were chosen because they showed a clear "ventral" deficit in behavioral testing and underwent both the neurophysiology and the fMRI experiment, however the fMRI recording of the younger one showed too many artifacts and was excluded from further analysis.

Stimuli preprocessing

As shown in **figure 11**, a series of images can be thought of as points lying in a multidimensional space, where each dimension corresponds to one of the ways in which an image can vary: for example a 100x100 pixels grayscale image can be represented as a point lying in a 10.000 dimensions space, where each dimension corresponds to the brightness of each pixel (Sadr et al. 2007). Therefore, when using any set of images, is like using a series of discrete stimuli, which are in fact “far” from each other in terms of physical characteristics (brightness, contrast, spatial frequencies). The RISE (Random Image Structure Evolution) paradigm (Sadr et al., 2007) provides the generation of a series of visual stimuli progressively modified in order to “fill” the ideal trajectory from one image to the other, in a measurable *continuum*. The RISE procedure can be considered as a particular type of morphing procedure (Benson et al., 1993) or image degradation (James et al., 2006). A simplified version of this technique consists in inverting random pairs of pixels in any given image. With the summation of inversions, the image gradually

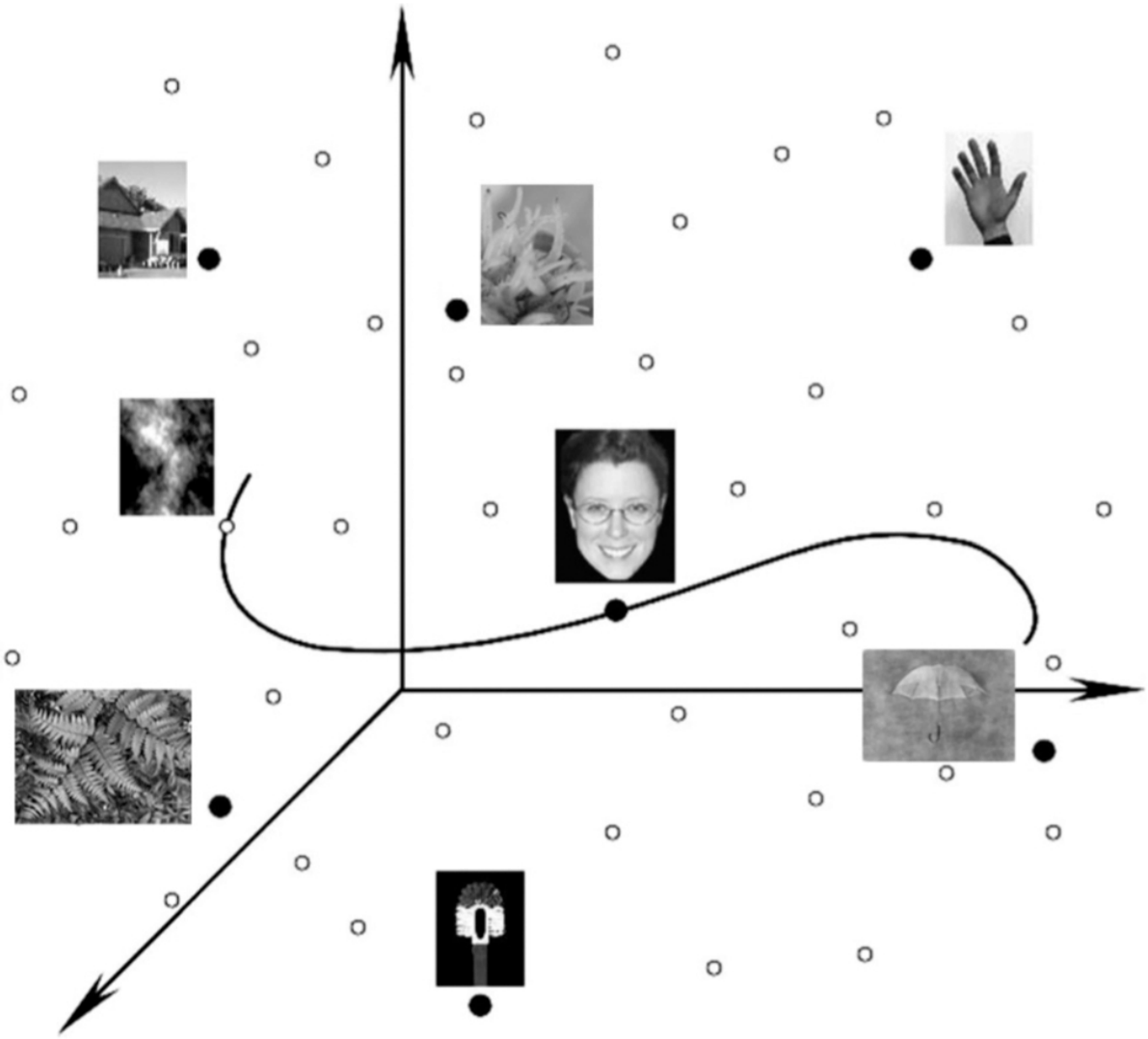


Fig. 11 Any given image can be thought as a point lying in an n-dimensional space, where the specific images used in a paradigm are represented by other points which anyway belong to a relatively small subset of all theorically possible variations. RISE paradigm can generate a measurable continuum (black line) which connects every possible variation

dissolves into a random noise **(fig. 12)**. This procedure keeps constant some features the image (brightness, relative proportion of colors) but still has the important limitation of not preserving the spatial frequencies of the original image, in a similar way as other image processing techniques in which images are partially occluded or modified by the addition or multiplication of random. Therefore an alternative but more challenging approach consists in extracting the frequency spectrum from an image in order to manipulate its

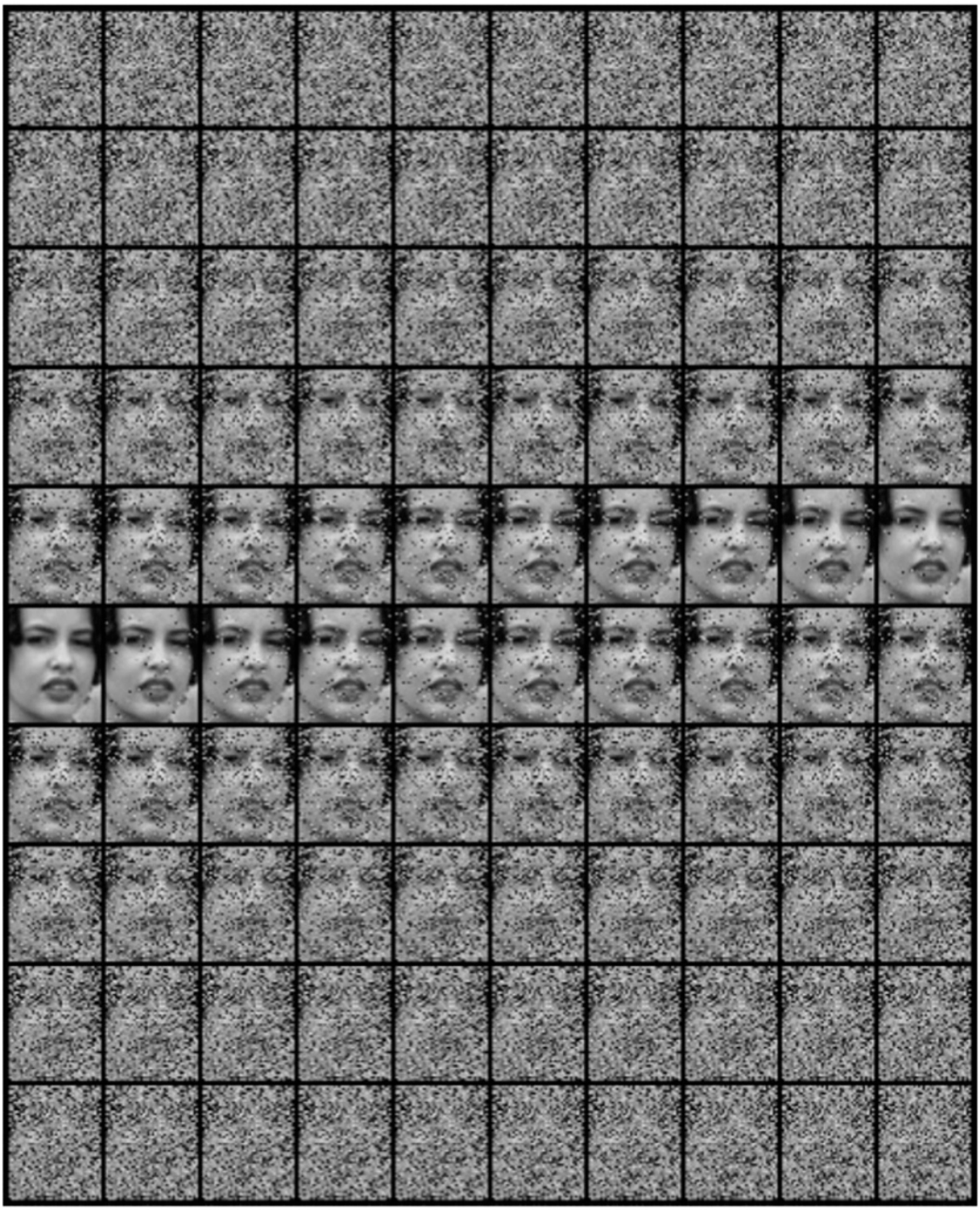


Fig. 12 RISE sequence generated by the progressive scrambling of image portions (in this case single pixels). The original image is in the first column, at the beginning of the sixth line

spatial structure (phase) without affecting the original power (amplitude) spectrum. It has been shown that most information in natural images is relative to the global phase spectrum, so that the randomization of phase results in the degradation of spatial structure of the image. Then, in the simplest case, the phase spectrum the original image is gradually transformed into a random spectrum, producing a series of images progressively less comprehensible. Moreover, considering also a number of separate images, it is possible in this way to "fill" the gaps between every image. RISE technique was therefore chosen to work around two fundamental issues for the analysis of γ oscillations: the influence of the physical characteristics of the stimulus and the need for a large number of stimuli from a homogeneous class in order to prevent the progressive decrease in response following γ the repeated presentation of that stimulus (Gruber et al., 2002; 2004), and finally the need to have two classes of stimuli (familiar and not-familiar) which were the similar at the most in terms of non-semantic features.

Stimuli used in this study were 120 pictures of real objects of everyday use. They have been processed using the RISE paradigm in order to obtain the "familiar" and "not familiar" stimuli classes, as well as a series of intermediate images progressively emerging from random noise **(fig. 13, 14)**. In a preliminary stage I tried to determine the effective stimuli comprehensibility by administering them to a sample of school-age children (28 subjects, age 7-11 years, average 9.2 years) **(fig. 15)**.

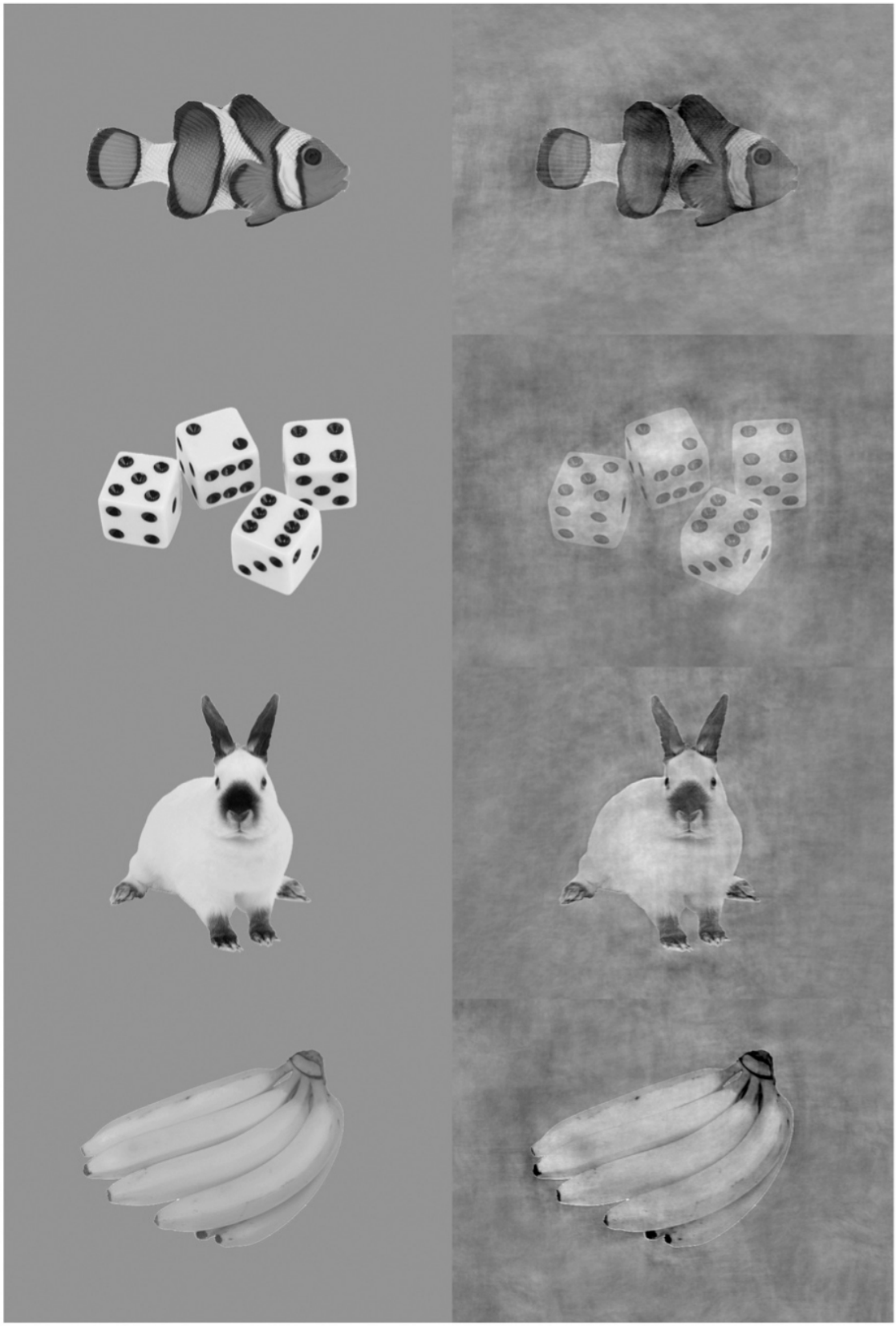


Fig. 13 Stimuli preprocessing: original images, on the left, and, on the right, processed images

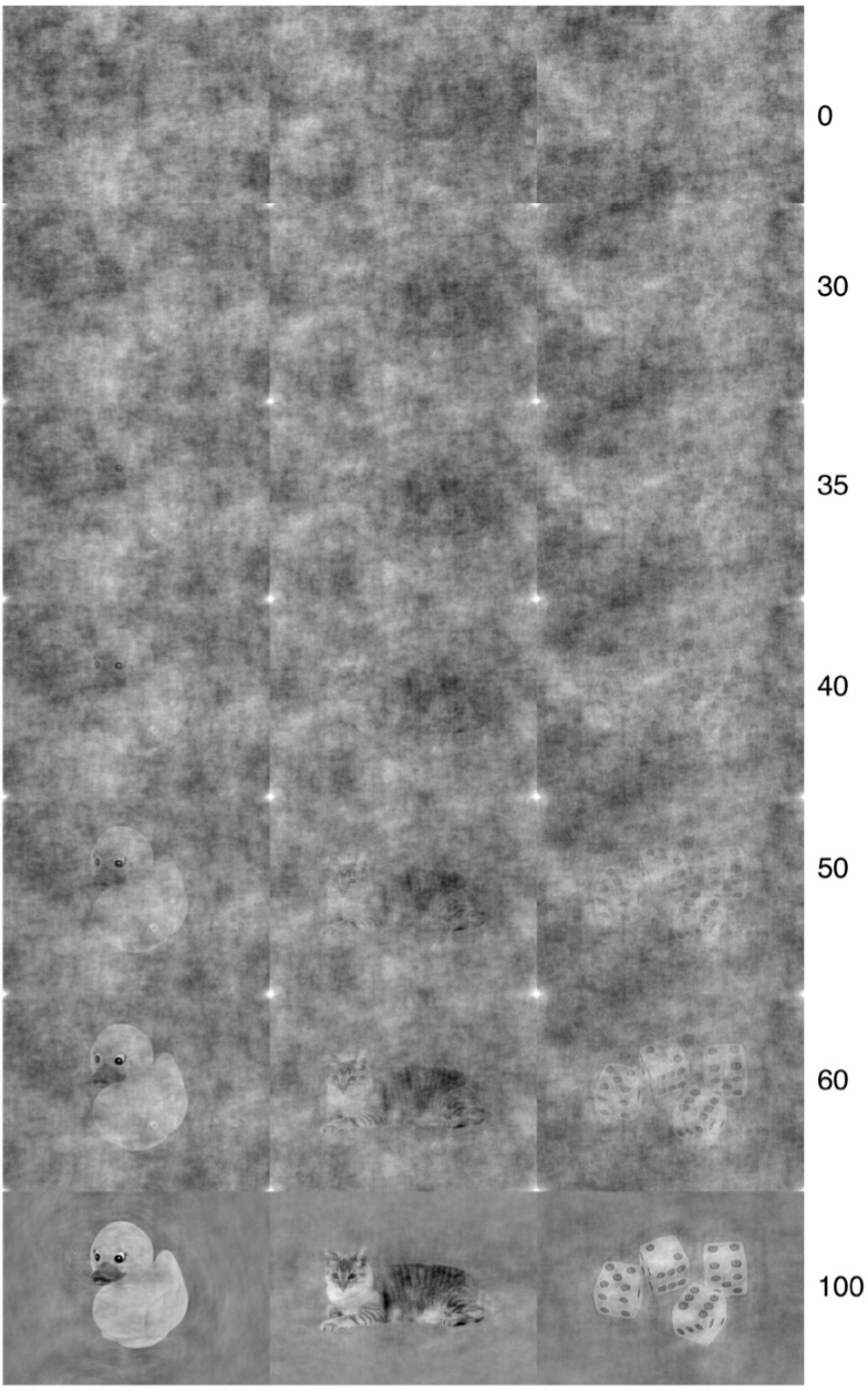


Fig. 14 Examples of the different degradation levels obtained through the progressive randomization of phase spectrum

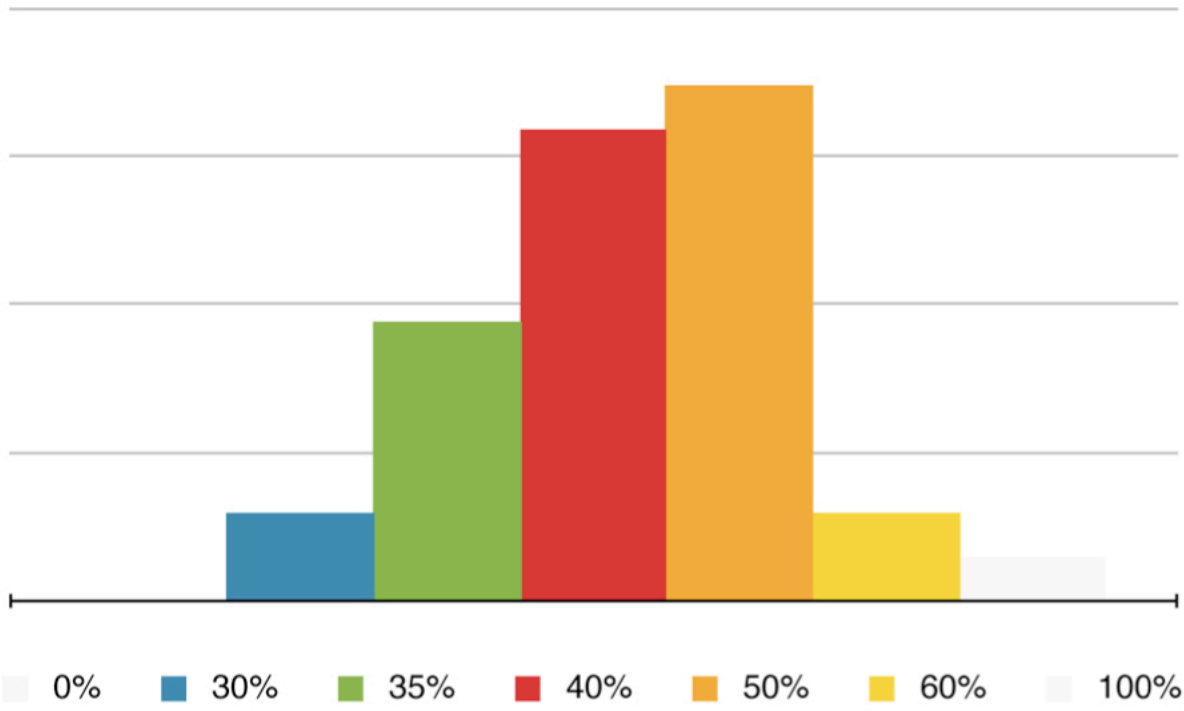


Fig.15 Characterization of stimulus comprehensibility. Images were shown to a group of healthy children, starting from the hardest level (0% of the original phase information) to the lowest (100% of the original phase information). The majority of images were recognized within the 5° degradation level, corresponding to the 50% of original phase information preserved

Procedures - Neurophysiology

100 familiar stimuli (75% of the original phase information) and 100 unfamiliar stimuli (0% phase preserved) were used, presenting them in a randomized order. Each trial consisted in the presentation of a fixation cross for a randomized time between 500-700 msec, followed by the presentation of the stimulus for 800 msec, and again from a fixation cross for 800 msec. In order to minimize the influence of motor activities, subjects were asked to respond only at the end of each epoch, when a question mark was presented to indicate the answer request about the recognition or non-recognition of the image **(fig. 16)**. The EEG was recorded with a Neuroscan system with 22 electrodes placed according to the 10-20 system, sampled at 512 Hz and filtered online between 1-100 Hz. Impedances were kept below 10 kOhm. The

EEG was segmented into epochs including 500 ms prior and 1500 msec following stimulus presentation. Epochs were processed with the Morlet wavelet procedure, using the Octave open-source environment.

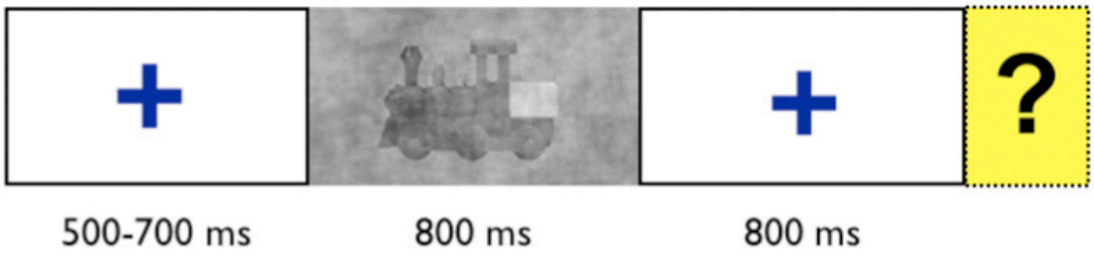


Fig.16 Trial used for gamma-frequencies analysis

Procedures - fMRI

We chose to employ 4 levels of image degradation (L0, L1, L2, L3 - corresponding to 50%, 40%, 30% and 0% of the original phase information). **Figure 17** schematically illustrates the paradigm. Each stimulus was presented for 3000 ms, the interval between images was 12 s. The duration of each epoch is 6'12", the total duration of the experiment was about 21 min. The images were projected using a pair of fMRI-compatible goggles. Subject were asked to look at the stimuli trying to recognize the objects depicted. BOLD images were acquired using a 1.5 Tesla GE device, using a Gradient-Echo EPI sequence (TR = 3000 msec, TE = 50 msec; fa = 90°). In each session 124 acquisitions of anatomical volume were obtained, composed by 21 slices of 5 mm thickness. Additional T1-weighted anatomical images were acquired with the same localization of functional images in order to allow proper alignment. The data were analyzed with software Brainvoyager QX.

In order to identify regions involved in visual processing of object, we analyzed the difference between averaged activations to the Rest condition

and the Stimuli (L0, L1, L2, L3) in all three epochs, using a General Linear Model analysis and a not-corrected *p* level of <.001. In order to identify regions involved in visual recognition (LOC) we evaluated the difference between averaged activations to L3 and L0+L1, while to underline the differences between control subjects and the child with CVI we evaluated the difference between the averaged activations of L2 and L3 using the same procedure.

An analysis of variance (ANOVA) was performed in order to evaluate variations in hemodynamic timing response in the 4 conditions stimulation represented by L0, L1, L2, L3. Lastly we performed a ROI analysis on the fusiform gyrus.

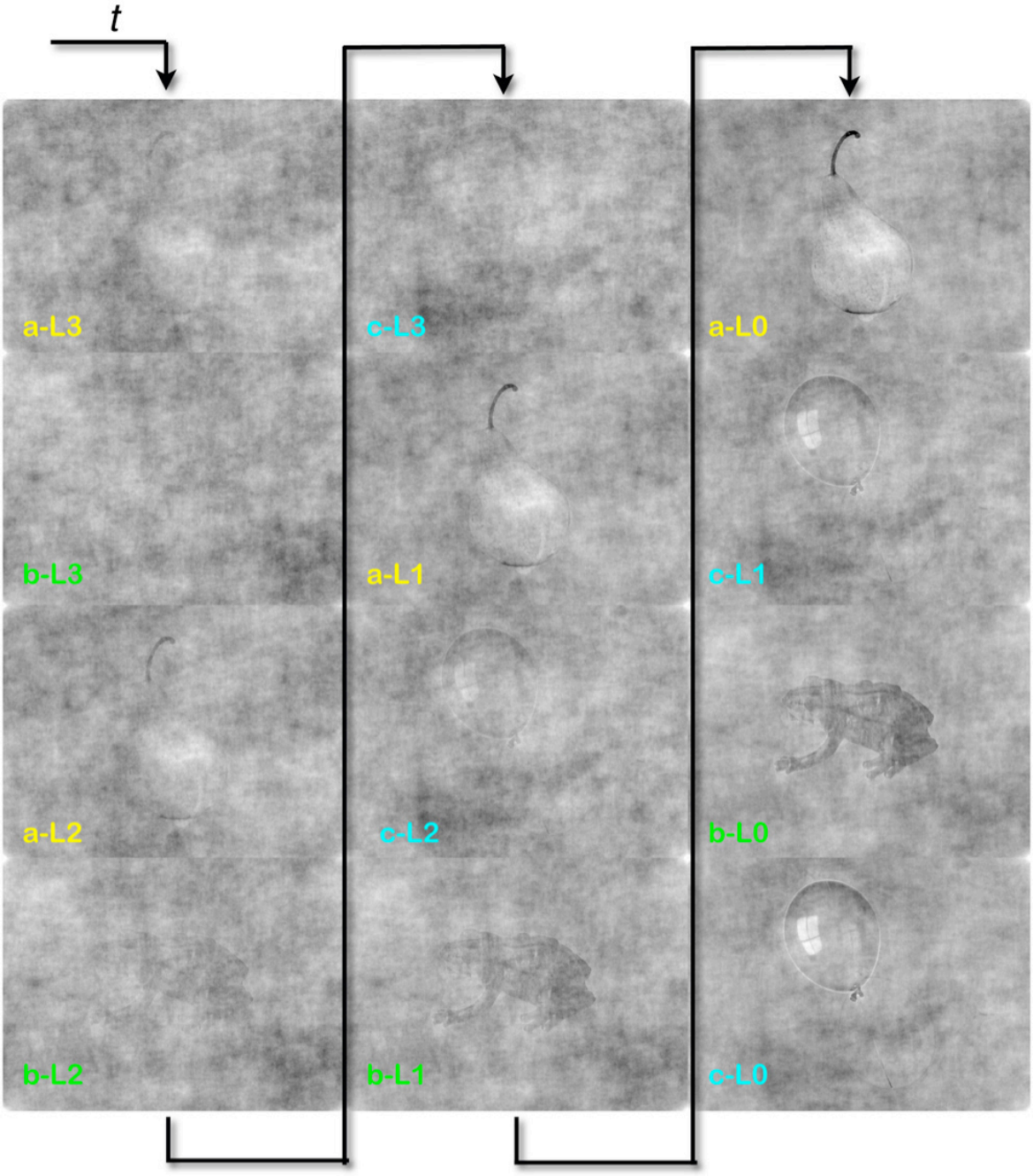


Fig. 17 fMRI paradigm: a, b, c represent the different items. Images are shown in a pseudo random modality: the more difficult version of an image is never presented before the easier version of the same images. After every image there is a plain grey picture as a rest condition

RESULTS

Results - Neurophysiology

Stimulus presentation elicited gamma-band activations both in the evoked and the induced fraction. Both activations seem to be quite restricted in space and time (**fig. 18*a-e***). In healthy subjects, the power of evoked gamma-band ERSP was not affected by stimulus class (familiar/not-familiar), as shown in **figure 18c**. The amplitude of the induced gamma-band ERSP however, was modulated by stimulus class, being significantly higher ($p<.05$) for familiar stimuli than not-familiar (**fig. 18f**). Regarding the comparison between the two groups of subjects, the latency of the induced gamma-band ERSP was significantly delayed in children with CVI for the class of familiar stimuli ($p<.05$), while the latency for the class of unfamiliar stimuli showed no significant differences. The difference in amplitude of the induced ERSP in the two groups was not analyzed, as it's highly variable between subjects.

Results - fMRI

First condition: stimuli (L0 + L1 + L2 + L3) versus Rest. In the control subject areas of activation are observed ($p<.05$), including in particular the primary visual cortex (V1 and V2), the lateral occipital complex (LOC) and the fusiform gyrus (**fig. 20a**). No dorsal stream activation were observed (MT, ICP). Also in the CVI subject we observed areas of activation ($p<.05$) including in particular the primary visual cortex (V1 and V2), the lateral occipital complex (LOC) and fusiform gyrus (**fig. 20b**). No dorsal stream activation were observed (MT, ICP). Compared to the control subject, the CVI subject shows a weaker and more fragmented activation.

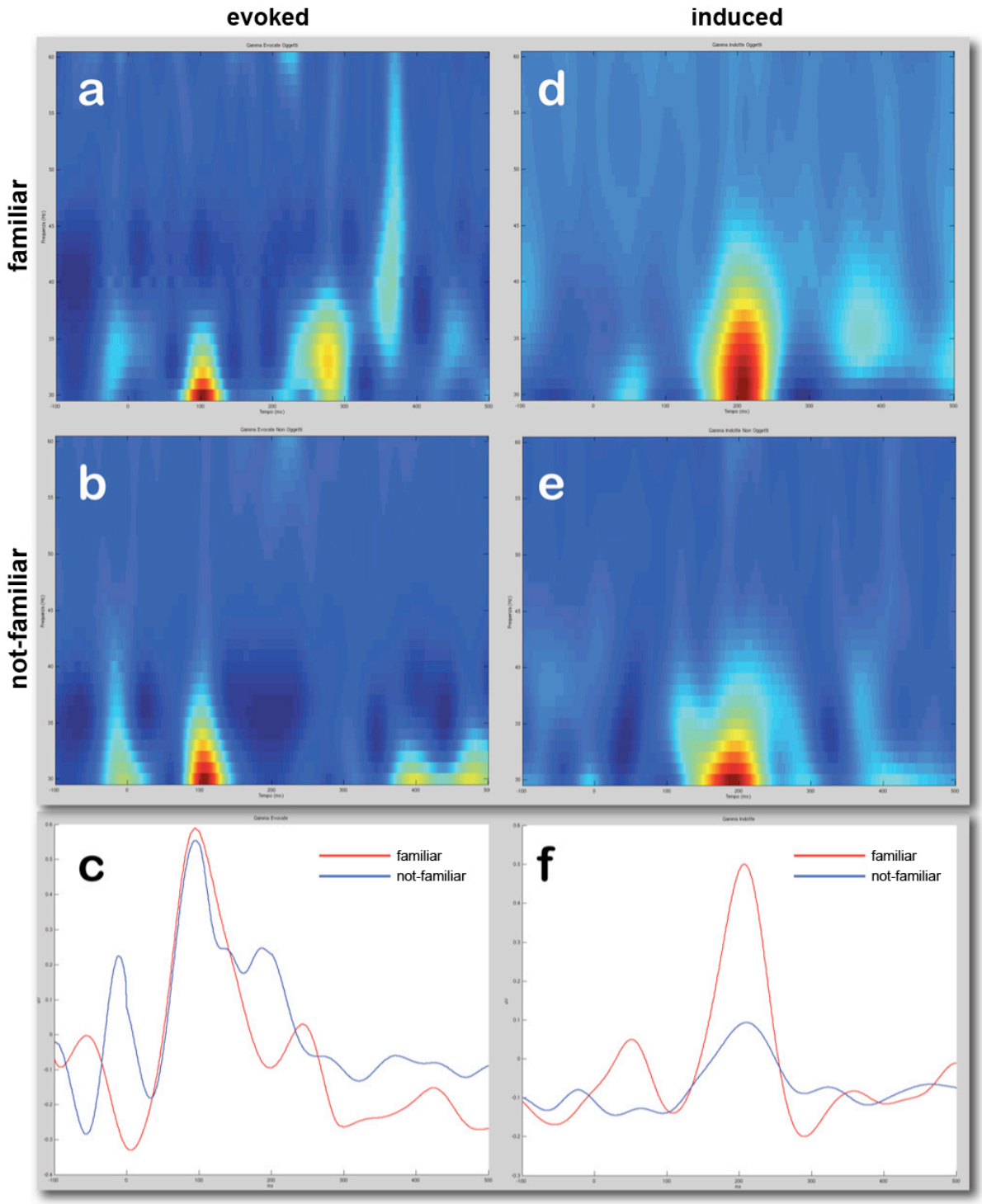
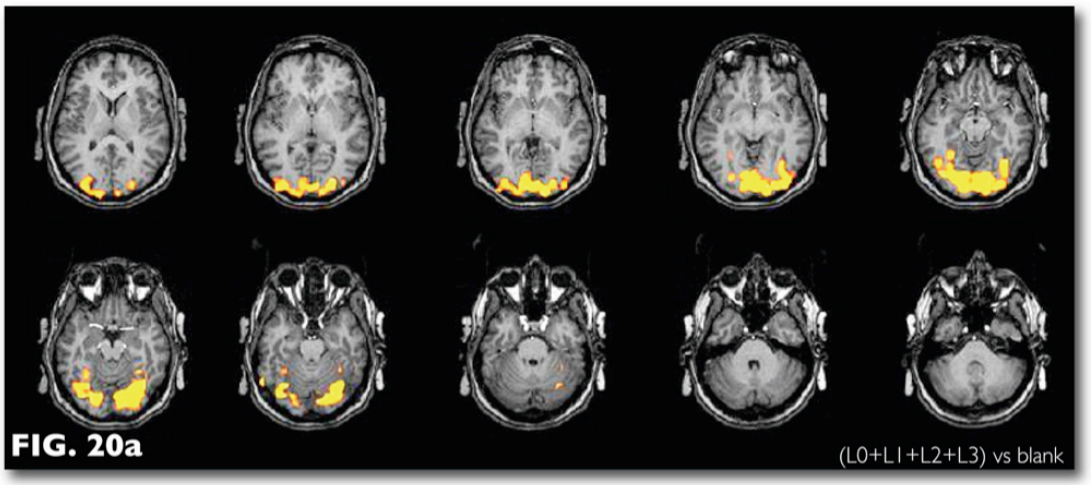
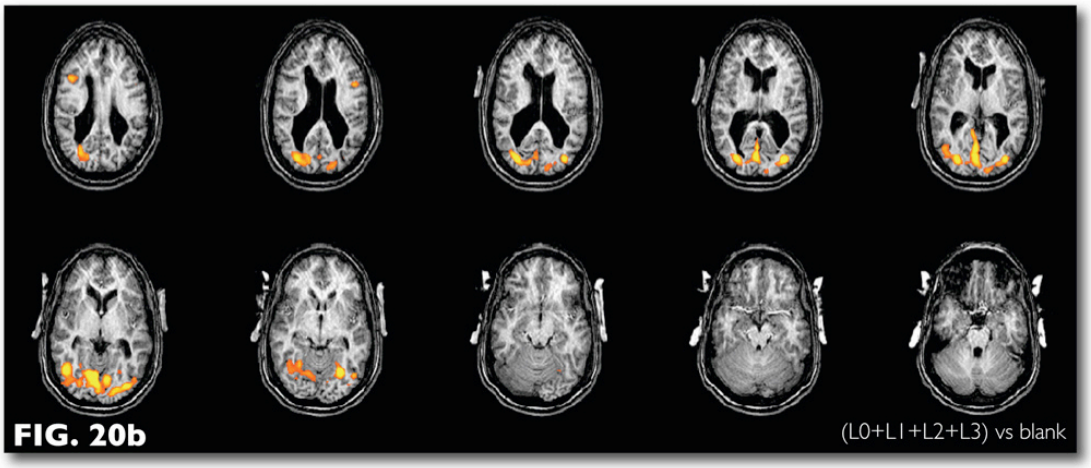


Fig. 18 Evoked and Induced gamma-oscillation in healthy subjects

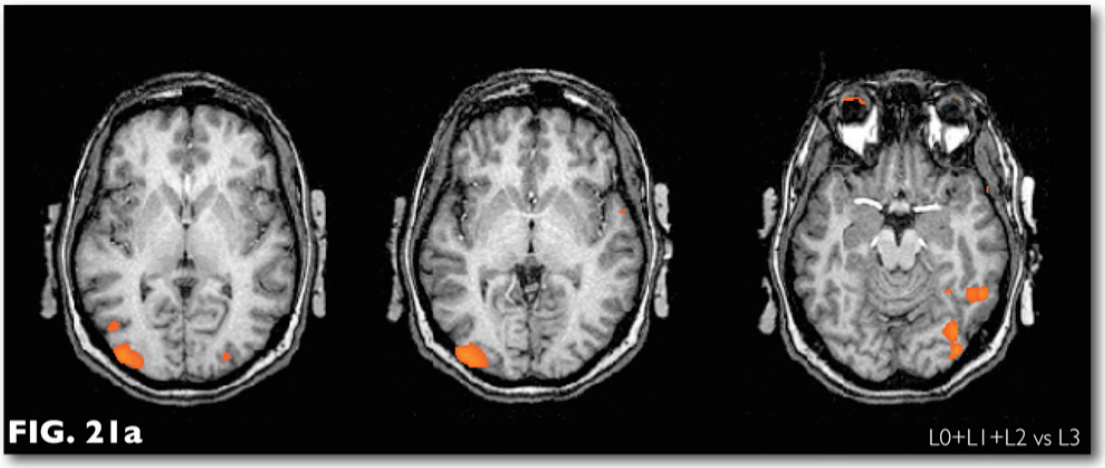


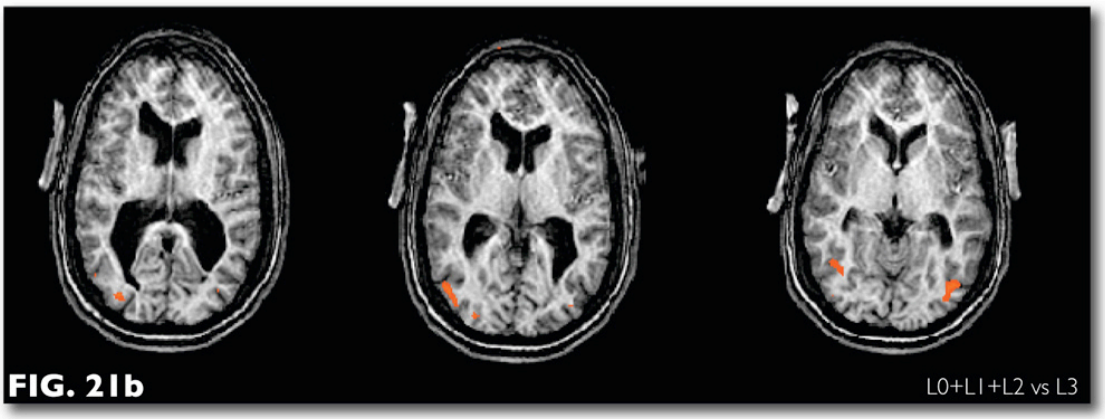


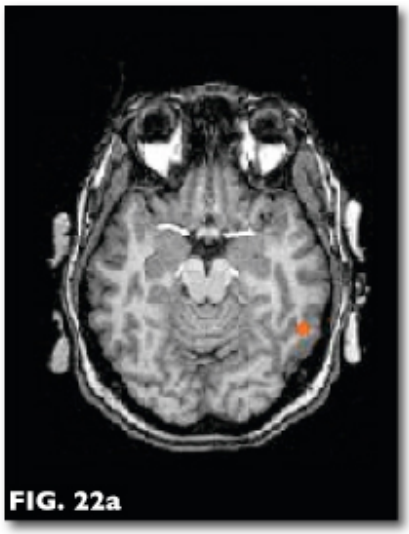
Second condition: recognizable objects (L0 + L1 + L2) versus control stimulus (L3). In healthy individuals areas of activation (p<.005) are observed in right Lateral Occipital Complex (X = 35, y = -79, Z = 4) and in the fusiform gyrus bilaterally (mFus, TX = - 47, Y = - 48, Z = 15) (**fig. 21a**). In the CVI subject we observed areas of activation (p<.005) in right Lateral Occipital Complex, and in the fusiform gyrus bilaterally **(fig. 21b)**. The contrast used eliminates in both subjects activations in the primary visual area, confirming the well-controlled physical features of stimuli employed

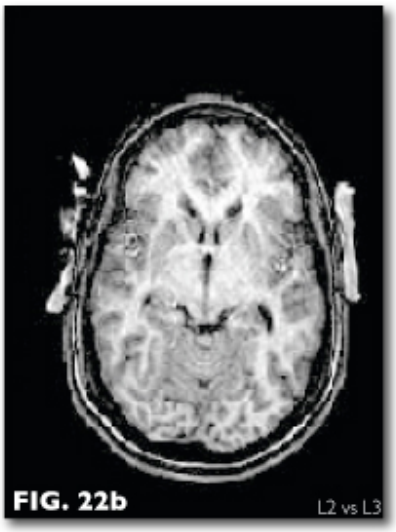
Third condition: L2 vs L3. In order to highlight areas of activation related to object recognition at high level of image degradation we used the L2 vs L3 condition.

In healthy individuals a small but highly significant (p<.0005) activation area was observed around the anterior portion of the left fusiform gyrus **(fig. 22a)**. In the CVI subject L2 vs. L3 contrast shows no significant activation **(fig. 22b)**.









DISCUSSION

Results obtained from gamma-band ERSP analysis are consistent with the literature evidence. Induced gamma band ERSP were significantly stronger to familiar stimuli, confirming the hypothesis of gamma-band ERSP as the reflex of the construction of the cortical representation of the perceived object. Evoked gamma band ERSP was not influenced by stimuli class, confirming that the stimuli were correctly preprocessed. Evoked gamma band ERSP may sometimes be modulated by stimulus class, but only when top-down influences are not ruled out by the experimental paradigm like in the present study. Regarding the CVI subject, latency shift of induced gamma band ERSP seems to correlate well with the "ventral" deficits he shows on behavioral tests.

The fMRI confirmed the similarity in the physical features of stimuli used: in the second condition (L0 + L1 + L2 vs. L3) there is a clear disappearance of the activation on primary visual areas, indicating that they were equally activated by the two main (familiar and not familiar) stimulus class, while is still present an activation in the extrastriate cortex (LOC mFus), induced by familiar stimuli (L0-2) but not by not familiar stimuli (L3). The third condition of the fMRI study (L2 vs. L3) showed small but highly significant differences ($p < 0.001$) in activation in healthy subjects, and no significant difference in the child with CVI, suggesting that in the latter the hardest level of intelligibility (L2) is not in fact recognized, showing a comparable pattern of activation compared with not-familiar stimuli, (L3).

This study was carried out with the intent to develop an experimental paradigm combining EEG and fMRI techniques, in order to verify both the correct preprocessing of stimuli and, in perspective, the potential simultaneous recording using a comparable experimental design. Both

techniques are characterized by strengths and weaknesses, but generally speaking neurophysiological procedures are less invasive, more flexible, more suitable for routine use, and are especially useful even in very young children, but however they suffer from a well-know low spatial resolution. In this study I've tried to show how a rigorous procedure in stimuli preprocessing can be used to generate well-controlled stimuli classes with respect to their lower-lever physical properties that are however still effective in differentially modulate both EEG and BOLD activations depending on their semantic content.

- PART II -

High Density ERPs to neutral and emotional faces in typical developing children and children with Autism Spectrum Disorders

INTRODUCTION

Face processing and face recognition have been deeply studied and discussed during the last decades in disparate scientific branches. Within psychology, several areas have underlined the importance of face processing abilities and have supported research on it: in particular, cognitive psychology has considered the presence in humans of face processing specific and complex abilities as the evidence of a *qualitatively* different perception of faces compared to other objects and, therefore, of the belonging of faces to a 'special' class of stimuli. Neurosciences, showing the involvement of specific brain areas and neural circuits involved in face processing, consider this process as a high specialized brain function. Because faces represent the first and fundamental communication channel between the infant and his caregiver, face processing has been also considered as a major object of interest by developmental psychology. Lastly, experimental evidences about complex face processing abilities in other animal species corroborate the opinions about the highly adaptive function of this competence that, therefore, has been widely investigated also by an evolutionary point of view.

Face processing: behavioral evidence and developmental theories

The ability to recognize somebody from the face features represent an especially effective and most of all a crucial skill for social interactions. Therefore is it not unexpected that the interest for this ability (and specifically its evolutive path) is lasting from many decades. As an example one of the basic question, "when a child reaches adult-like performance in face processing" is yet to be clearly answered. Studies in childhood showed very powerful discrimination abilities since early age. Newborns can recognize their own mother (Bushnell, 2001; Pascalis et al., 1995), discriminate the identity of novel faces with (Pascalis & de Schonen, 1994) or without hair (Turati et al., 2006), and recognize the identity of novel faces presented from different points of view (Turati et al., 2008; also see Pascalis et al., 1998, in 3-month-olds). Moreover 6-9 moths old children can identify faces belonging to different races and even different species (Kelly et al., 2007; Pascalis,et al., 2002). Notwithstanding this evidence for a very early, sophisticated and plastic ability, laboratory studies consistently show a continuous, long lasting development pathway that is not completed until late adolescence. As a basic example, memory for faces greatly improves from 5 years to adulthood (e.g., Carey et al., 1980; Mondloch et al., 2004, 2002). One of the pivotal questions about this unusually long evolutive path is why this happens, more than how.

In the huge bulk of literature we can identify two main general theories about face processing that trace back face processing impressive development to a specific face-oriented neural system, or to a diffuse brain maturation, the latter imputing the apparent face perception maturation mainly to the enhancing of general developmental improvements in concentration, visual

attention, explicit memory, etc. Historically the former theory was the first and most popular, but the latter is anyway gaining supporters, leaving the question still open.

Face-specific perceptual development theory

While acknowledging the early face-processing abilities in young children, this theory asserts that face processing keeps on developing until late childhood, and this phenomenon is greatly influenced by the typically human social life experience with faces. Changes in face-processing system directly influence enhancing in perceptive tasks and likely support improvements in memory, allowing a more effective coding of novel faces and/or a more accurate comparison with distractors when recalling informations from memory. We can identify three specific proposals to explain the exact nature of developmental changes in face perception. The first proposal postulates that changes happen in the holistic/configural face processing. The exact nature of holistic/configural perception is not yet known, but there's general agreement in considering these key-factors: a) a strong perceptual integration of information carried by the whole face, b) processing of "second order" features, in which the distance between facial features deviates from the "first order" pattern shared by all faces. The second proposal postulates that the perceptual integration and the coding of informations about the second order features are independent subcomponents (Maurer, Le Grand, & Mondloch, 2002). The third and last proposal hypothesizes the existence of a single and integrated system for all spatial informations, including the shapes of local features as well as the relative distance between them, in other words both first and second order features. In adults holistic processing is usually studied with some standard paradigms. Faces produce a disproportionate inversion effect on recognition memory: all objects are remembered worse if

presented upside-down, but this effect is significantly bigger for faces than for a wide range of objects (Diamond & Carey, 1986; Robbins & McKone, 2007; Scapinello & Yarmey, 1970; Yin, 1969). The general opinion is that this happens because holistic processing only works on upright presented faces. In the composite effect, aligning the top half of a well-known face (e.g. Silvio Berlusconi) with the bottom half of another one (e.g. Pier Luigi Bersani) produces the perceptive experience of a new face, and moreover discrimination is harder if the two halves are aligned than misaligned. In the part-whole effect (Tanaka & Farah, 1993), memory for a face part (e.g. Mary's nose) is worse if presented alone (Mary's nose versus Jane's nose) than in the context of a whole face (Mary's nose in Mary's face versus Mary's nose in Jane's face). In the part-in-spacing-changed-whole variant (Tanaka & Sengco, 1997) memory for a face's part (Mary's nose) is worse in a spacing-changed version of the whole face (Mary's nose in Mary's face with eyes moved closer) than in the unaltered face (e.g., McKone, Aitkin, & Edwards, 2005; Rhodes, Brake, & Atkinson, 1993). These holistic effects appear to be clearly visible for upright faces, but absent or substantially reduces for inverted faces, faces with scrambled parts, and several classes of objects like dogs, cars, houses and "greebles" (McKone, Kanwisher, & Duchaine, 2007; Robbins & McKone, 2007).

Turning back to childhood, an early developmental theory argued that holistic processing emerges at about 10 years old (Carey et al., 1980). Recently has been proposed that some aspects of holistic processing are already mature in younger children, but other aspects continue to develop until adolescence due to extended experience with faces. Another version of the face-specific perceptual development theory postulates that face processing developmental changes could happen in the "face-space" (Ellis, 1992; Humphreys & Johnson, 2007; Johnston & Ellis, 1995; Nishimura et al., 2008; Valentine, 1991), namely a multidimensional space in which dimensions code

physical properties that differentiate single faces, every subject is a point, and in the multidimensional center lies the "average" face. Face-space theory has been used to explain different properties of face recognitions in adults, including typical versus distinctive face effects (Valentine & Bruce, 1986), caricature effects (Rhodes, et al., 1987), preference for attractive faces (attractive faces are usually more "average" - Rhodes, et al 1999), and adaptation aftereffects (Leopold, O'Toole, Vetter, & Blanz, 2001). Lastly the other-race effect (worse discrimination for other-race than own-race individuals) is often attributed to face-space dimensions being tuned to suit the most frequently observed faces (own-race), leading to confusion errors for other-race faces (Valentine, 1991). Regarding development, the key-hypothesis of many face-space theories argues that dimensions of face-space are determined through experience and continuous tuning throughout life. Children may use less dimensions than adults, or the same number of dimensions differently weighted, or code less accurately the discriminative criteria along each dimension, or lastly the whole system could be heavily influenced by the presence of familiar faces (Humphreys & Johnson, 2007; Johnston & Ellis, 1995; Nishimura et al., 2008). Given that face-space dimension are thought to respond quickly to the most common kind of faces to which they are exposed (Rhodes et al., 2005), another possible age-related (even if not *strictu sensu* developmental) change is that the face-space of children could be better tuned for children's faces, while adult's face-space could be better tuned for adult faces - presuming that there are differences in rate of exposure between different ages (Cooper et al., 2006). Lastly, another version of development in face-specific processes focus attention on the actual ability of children to perceptually encode a novel face: Carey (1992) proposed that children do not efficiently form representation of novel faces as adults do - therefore even if face-space coding and holistic perception are

early-mature, the construction of a stable, viewpoint independent representation of a novel face is not (Mondloch, Geldart, Maurer, & Le Grand, 2003).

To summarize, the face-specific perceptual developmental theory argues that the improvement easily seen in face tasks between 5 years and adulthood is mainly underpinned by changes in the perceptive system itself. Reshaping in holistic processing, in face-space, and in encoding of novel faces are all processes that may be involved in the developmental path of face-processing.

General cognitive development theory

This theory (e.g. Carey, 1981; Pellicano, et al., 2006) argues that developmental improvements in face tasks are entirely due to general cognitive development. Depending on the task considered, key-factors would include: memory ability; ability to use deliberate task strategies; resilience to distractors; ability to narrow or widen the attention focus; fine discrimination in line alignment (Vernier acuity), and diffuse enhancing of conduction speed in visual, motor and other systems. All this factors are well-known to improve throughout childhood and several till adolescence. Must be underlined that the general cognitive development theory argues that perceptual coding of faces is actually fully mature early - so all the subsequent development on experimental task performance can be explained by development of other factors.

Face processing in Autism Spectrum Disorders

Behavioral, eye tracking and fMRI studies

Autism Spectrum Disorders (ASD) are a group of conditions characterized by specific difficulties in social and emotional information processing. Along with the well-know major diagnostic hallmarks of ASD (impairment in social communication and interaction, restricted and stereotyped interests and behavior), children with an ASD diagnosis often show early and severe impairments in processing social and emotional information that could be strictly connected to face processing abilities disruption. Several authors argue that difficulties in the use and comprehension of informations conveyed by human faces could represent a core deficit of autism (e. g. Baron-Cohen, 1993; Dawson, et al. 2002). Indeed, even Kanner (1943) described autism as a "disorder of affective contact", moreover the current DSM-IV-TR diagnostic criteria for ASD include items explicitly related to deficits in identifying and processing emotion: “marked impairments in the use of multiple nonverbal behaviors, such as ...facial expression...” and “lack of social or emotional reciprocity” (APA 2000). In the last years many authors have published studies on face processing in typical subjects and in adults and children affected by ASD. However, despite the volume of published evidences, findings about face processing and in particular emotional face processing in ASD are still inconsistent: some studies have found intact face processing abilities in ASD (eg. Loveland et al., 1997; Castelli 2005), while others found profound deficits (e.g. Macdonald et al., 1989; Riby et al. 2008). Many eye-tracking studies showed that subjects affected by ASD may have a quite different gaze behavior than controls especially in emotional faces tasks, e.g. looking less at eye regions (e. g. Corden 2008) or looking too much or too little in specific

face areas useful for emotional decoding, like upper, lower or external face regions (Baron-Cohen et al. 1997). Even if there are eye-tracking reports of normal gaze behavior in ASD (Bal 2010), the general evidence points towards the presence of abnormalities, even if the nature of differences reported varies.

In neurotypical individuals, the core brain regions implicated in all types of face processing include the inferior occipital gyri, lateral portion of the fusiform gyrus (especially a region named the fusiform face area, or FFA), and posterior superior temporal sulcus (pSTS) (Haxby et al. 2000). Brain structures dedicated to face processing can be also usefully divided as belonging to cortical and subcortical routes. The first evidences of this distinction came from neuropsychological studies on adult individuals with hemispatial neglect and prosopagnosia (e.g. Johnson, 2005). In prosopagnosia, a cortical disorder where the ability to recognize familiar faces is impaired, there is usually a deficit in face identification that is often more severe than the impairment in recognizing facial expressions. This finding suggested that face identification and emotional evaluation of facial expressions could be underpinned by at least partially distinct structures. In fact, in the last years, the neural system deputed to human face recognition has been divided into two parts: a core system which is responsible for the visual analysis of faces and includes the inferior occipital gyrus, the posterior superior temporal sulcus (pSTS) and the FFA, and a 'wider' system in which distinct brain areas, such as amygdala, limbic system, insula, and anterior temporal cortex, process the information in a more sophisticated way (Haxby et al. 2000; Nichelli & Benuzzi, 2005). However intracortical recordings have shown that even frontal structures can take part in the face perception process (Barbeau et al., 2008) **(fig. 23)**.

fMRI studies investigating general and emotional face processing in ASD, like behavioral and eye tracking studies have led to mixed results. Although

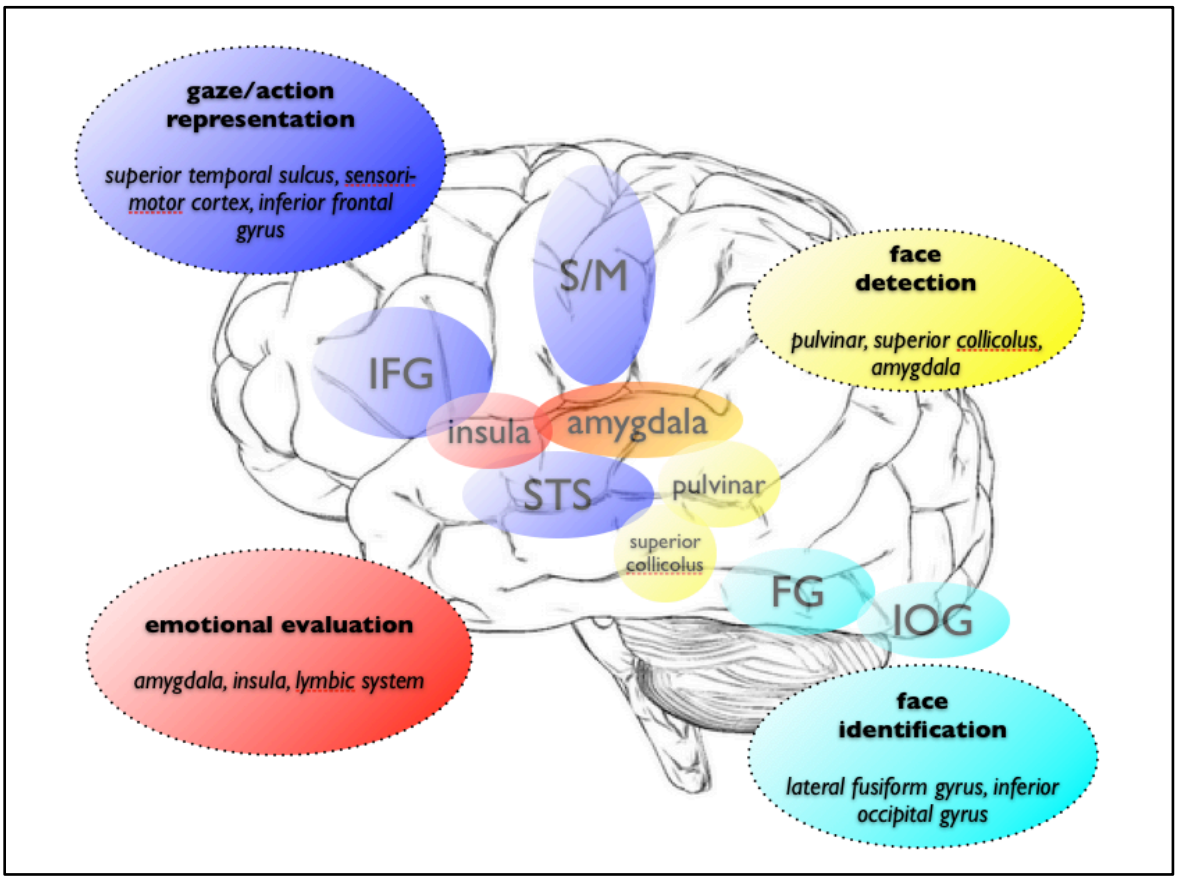


Fig.23 Main cortical and subcortical structures involved in face processing: function illustrated by colors

many studies about face emotion processing report decreased FG activation in ASD (e. g. Bolte et al. 2006; Piggot et al. 2004; Wang et al. 2004) relative to control groups, this finding might not relate to emotion processing specifically; it is possible that the FG activation found in controls is associated with identity-level rather than emotion processing. Intriguingly, studies that have combined eye-tracking with fMRI or manipulated gaze to faces during fMRI (Hadjikhani et al. 2004) have shown that individuals with ASD do activate the FG when they look at the eyes. Taken together, these findings suggest that ASD subjects may use alternative means to recognize emotions, and this might be because brain regions involved in preconscious aspects of face emotional processing, like the amygdala, fail to activate in ASD. Nearly

all neuroimaging studies that used an implicit FER task report decreased amygdala activity in the ASD group (Ashwin et al. 2007; Dapretto et al. 2006), suggesting that the amygdala does not function normally during face perception in ASD, at least when participants are not required to attend to the displayed emotion.

ERP studies

Although the literature on face processing in autism has gained momentum in the past few years, the first ERP study to use face stimuli in ASD was actually performed in 1971, using only two scalp electrodes. In this study, children with ASD were compared to age matched, typical controls. Typical children differentiated stranger and mother's face based on more negative amplitude response to stranger, while the children with autism showed no difference in cortical response to the two stimuli (Small et al. 1971). Using high density ERPs, impairments in face processing have now been well characterized by Dawson et al. In their first study (2002c), low functioning children with autism, ages 3–4, were compared to both IQ and age matched controls. Children were shown pictures of mother's face versus stranger's face, and in a comparison paradigm were shown familiar versus unfamiliar objects. As evidenced by their P400 and Nc, children with autism did not differentiate between mother and stranger, but did show differential response to unfamiliar objects as compared to familiar objects. In a reanalysis of this study, they found that there was an absence of the expected right hemispheric lateralization to faces in the children with developmental delay or autism, and that there were more negative responses to faces and faster responses to objects in the autism group. Similar abnormalities have been demonstrated in high functioning adults as well. O'Connor et al. (2007) performed a face recognition paradigm in which faces and facial parts (eyes

and mouth), as well as objects, were shown to adults with Asperger's syndrome and typical controls. The Asperger's adults exhibited slower N170 latencies to both faces and facial parts compared to controls, but did not show such a difference to objects. More recently Webb et al. (2009) reported comparable results in a group of adults affected by ASD.

Dawson's group (2004) then investigated neural responses to emotion in autism. The N300, an analogue of the mature N170, is an early component that is larger to fearful or angry faces and reflects increased allocation of attention to negative emotions. Using the same group of low functioning preschoolers with autism, compared to typical controls, children were shown pictures of a female face with either a neutral or fearful expression. Additionally, various behavioral observations were made using tasks centered on social orienting, joint attention, and response to distress. In this study, typical children showed the expected larger amplitude N300 response to fear faces compared to neutral, whereas the children with autism showed no differential response. Additionally, faster latency of the N300 in the autism group correlated with better joint attention, social orienting, and attention to social distress. O'Connor et al. (2005), in a study of both children and adults with Asperger's syndrome, found delayed face-processing components during emotion identification compared to age-matched controls in adults only, along with poorer performance in adults, but not children. Wong and colleagues (2008), in contrast to the other studies, report normal surface ERP in children with high-functioning autism, but in dipole source analysis, found weaker and slower responses originating in frontal, fusiform, and visual cortices, along with slower and larger responses in parietal somatosensory cortices. The latter finding may again relate to more effortful processing of facial emotions in autism (Wong et al. 2008).

To summarize, evidences from ERPs studies in face processing in ASD, in a similar way as those from behavioral, eye-tracking and fMRI studies, are still unclear or even contradictory, suggesting the need for more standardized, comparable and realistic paradigms in order to uncover subtle differences in face processing abilities, and to be able to rule out the effects of compensatory strategies that may develop along time.

OBJECTIVES

Despite the huge bulk of experiments done until the present time, evidence from behavioral, neurophysiological and functional imaging studies on face processing in Autism Spectrum Disorders is still incomplete and contradictory. At least some part of this confusion is most likely ascribable to the great heterogeneity in paradigms and methods used and in subjects enrolled.

In order to overcome this and other common issues, I have designed the methods of this study with the purpose of controlling most of confounding variables at different levels (e.g. stimulus, task, attention, basic gaze control), and to be able to process data in different ways (e.g. automatic and manual tools, different references, different ROIs) to observe the effect on data of these manipulations.

My objective was to record and measure face-sensitive ERPs to neutral and emotional (happy and fearful) faces and to a third control stimulus (trees), as a measure of early (first 200 msec) impairment in face-specific networks in children with Autism Spectrum Disorders. Along with the analysis of absolute latency and amplitude values of N170, I performed a parallel analysis using latency and amplitude values from the positive preceding peak (P1) in order to obtain peak-to-peak N170 (ppN170) values, a procedure that may help to rule out the influence of individual and developmental factors of variability on ERPs measures (Kuefner et al. 2010).

METHODS AND MATERIALS

Subjects

Subjects were 10 children aged 6-13 years (mean 10.2 years), with an ASD diagnosis following DSM-IV criteria. Other inclusion criteria were: a total IQ ≥ 80, VIQ and PIQ ≥70, absence of neurological disorders, epilepsy or known genetic conditions. All subjects underwent a clinical assessment of the ASD (Autism Diagnostic Observational Schedule-G, Autism Diagnostic Interview-R, Social Communication Questionnaire, Repetitive Behavior Scale, Early Development Questionnaire), broader phenotype evaluation (Broader Phenotype Autism Spectrum Scale), adaptive functions evaluations (Vineland II), psychopathologic evaluation (Child Behavior Check List, Parent Stress Index, Krueger Asperger Disorder Interview, Kiddie-SADS-PL).

As a control group we recruited 7 children aged 6-13 years (mean 9.7 years), with normal or corrected to normal visual acuity, and no history of neurological or psychiatric conditions. Written informed consent was given by parents in all cases.

Stimuli

We employed 3 kinds of stimuli: faces, trees and cartoons.

Faces stimuli were acquired from a widely used database (Tottenham et al. 2009) of standardized face expressions. We selected 30 faces belonging to 10 subjects (5 males and 5 females) displaying happiness, fear, and a neutral expression. 10 tree stimuli were chosen from a set of royalty-free realistic paintings of different kinds of trees.

Trees were used as non-face stimuli: we chose to employ this kind of stimulus because they share with faces first order relations and natural multidimensional, genetically and environmentally driven similar variability.

Colorful cartoons stimuli were only used to help the subject to focus attention on the monitor, and sometimes they were exchanged with images of the subject's favorite cartoon if a strong preference for a cartoon character was mentioned. Faces and trees stimuli (the real stimuli) were cropped in order to make them similar in pixel size and to delete external facial features (hair, ears, neck) to avoid focusing attention on these parts of the stimulus; they were converted to greyscale and standardized in contrast and luminance (**fig. 24**).

ERP procedure

Subjects entered the lab at least 15 minutes before the actual experiment started in order to familiarize with the lab environment and to habituate vision to the setting ambient light. In this time interval child's head was measured and the vertex was marked. An appropriate size 128 channels HydroCel Geodesic Sensor Net (HCGSN 128; Electrical Geodesics Inc; Tucker, 1993) was dipped into a solution of lab-grade (18MOhm/cm^2) distilled water, KCl, and baby shampoo for 5 minutes and fitted on the child's head. Impedances were measured and kept below 50kOhm. Data was continuously acquired at 250 samples per second. The whole experiment consisted of 4 blocks of about 5 minutes with 3 pauses in between to allow the subject to rest or move if needed (on the second pause a second impedance check was done). Every block was composed by 100 stimuli (10 happy faces, 10 fearful faces, 10 neutral faces, 10 trees, 10 cartoons - every stimulus repeated twice) presented in a randomized order. Subjects were asked to press a button with

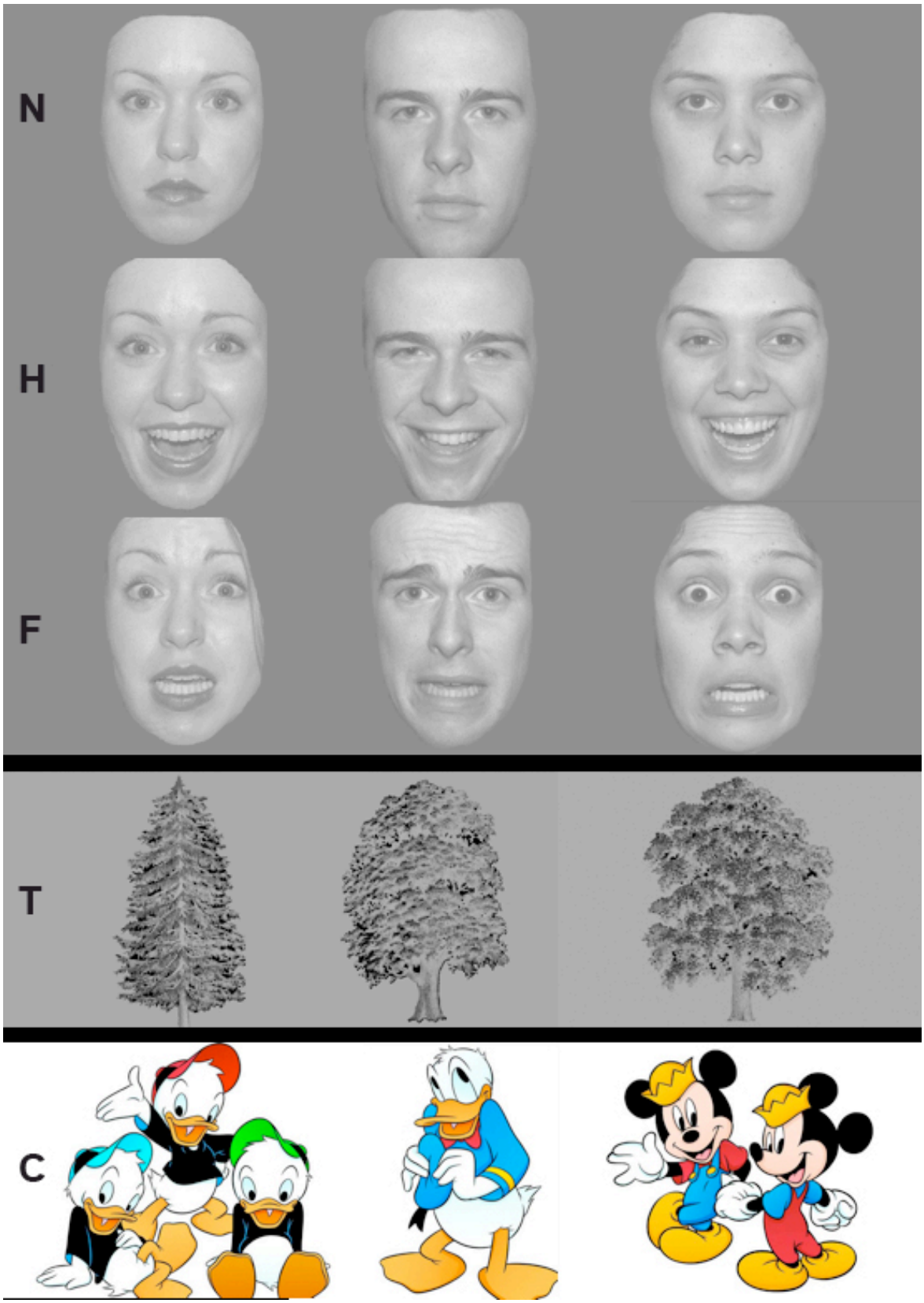


Fig.24 Stimuli used in the present study: neutral faces (N), happy faces (H), fearful faces (F), trees (T), cartoons (C)

their preferred hand when a cartoon stimulus was shown. The task was devised in order to rule out motor artifacts, cerebral motor-related activity, attention, anticipatory responses, and any other task-related effect, configuring a purely implicit, covert face-perception task.

Stimuli were presented for 850 msec and interleaved with a fixation cross with a randomized duration of 500-1500 msec to avoid expectation effects. Reaction times of button press were collected. The experiment was run on E-Prime on a PC running Windows XP and presented on a 17" flat-panel. Vertical syncing between stimulus presentation and the 100 Hz display refresh was assured. Before and after every recording a timing test was performed using a photocell connected to the amplifier to ensure constant offset delays between actual stimulus presentation and events sent to the DAC (data acquisition computer). In the pilot phase of the study (run on adult subjects) this offset was about 10 msec (an already excellent offset), but with subsequent adjustments and enhancements to the experiment code, hardware and setting set up we were able to lower it and keep it at 6 msec with an SD of less than a msec.

Since we didn't employ a dedicated eye-tracker, in order to be sure that subjects were really looking at the display during stimulus presentation, a firewire digital camera was positioned right above the presenting display and a digital recording was acquired during the whole experiment. Moreover before the actual experiment presentation we asked the subject to look at a fixation cross that was presented in the center and in each corner of the display (while already video-recording) as a mean to have a reliable idea of gaze target when reviewing data.

Data processing and analysis

All data processing was run offline on the DAC, a PowerMac G5 machine, running Net Station 4.3.1 . First of all video and EEG raw data were visually inspected to check for artifacts, bad channels, and to check for subjects paying attention to stimuli presentation. EEG and video data were segmented in 1000 msec epochs, made up of the whole 850 msec stimulus presentation and 150 msec before, used afterward for baseline correction. Each EEG+video epoch was again inspected and epochs in which subject wasn't looking (or looking at display borders) and/or with excessive artifactual activity were marked as bad and not used in further analyses. Epochs were labeled according to stimulus kind: neutral face: "neutral", happy face: "happy", fearful face: "fear", tree:"tree", cartoon "cartoon". "Cartoon" epochs were excluded from further analysis. A semi-automated artifact detection algorithm was run on epochs in order to mark bad channels, eye blinks, eye movements. Bad channels were defined in the tool spec as channels with a ≥200 μV drift in a moving average of 80 msec in a single epoch, and a channel was marked bad for the entire recording time if it resulted bad for ≥ 20% of the epochs. Eye blinks were defined as a ≥140 μV drift in a moving average of 80 msec. Eye movements were defined as a ≥ 55 μV drift with the same other parameters. Notably, Net Station eye blinks and movement detection algorithm uses 2 couples of dedicated electrodes (namely n°125, 126, 127, 128, see **fig. 25** for electrode location) to enhance its detection rate. Bad channels were interpolated, and ocular artifact removal procedure was applied. Data were visually inspected to check for unexpected effects in between every artifact correction and detection step, and manual correction was applied when necessary. Epochs were averaged for every subject and for

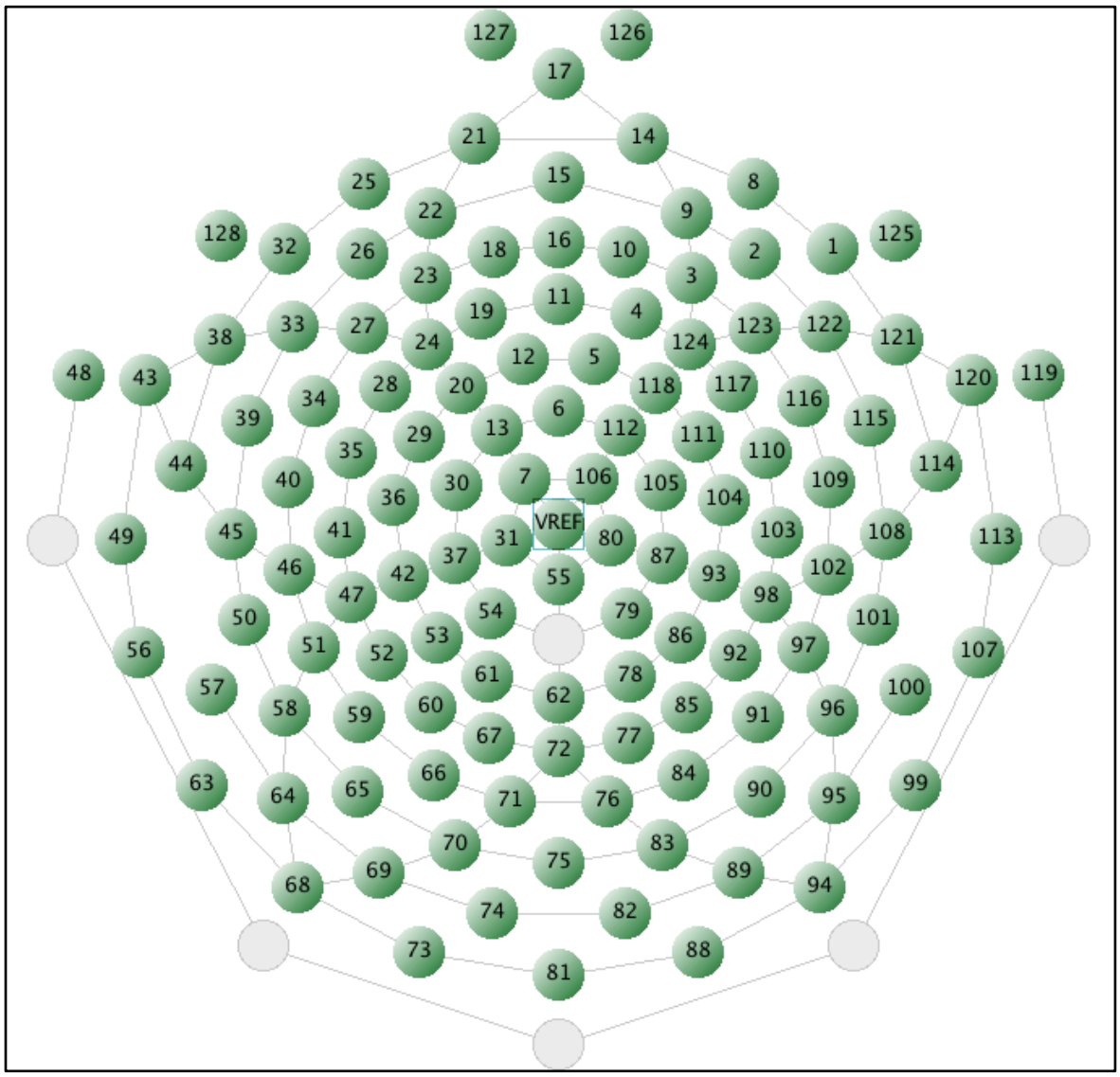


Fig. 25 HGSN sensor layout, nose up

every class of stimuli, re-referenced to the average reference, and baseline corrected using 100 milliseconds before stimulus onset.

Scalp ROIs and time windows were defined on the base of the literature, grand average and single subjects waveforms inspection, and topographical maps inspection. Right ROI (R-ROI hereafter) was defined as electrodes n°96 (P8/T6), 95(P10), 90(PO8) and 89, and left ROI (L-ROI hereafter) as electrodes n °58(T5), 64 (P9), 65 (PO7) and 69 **(fig. 26)**.

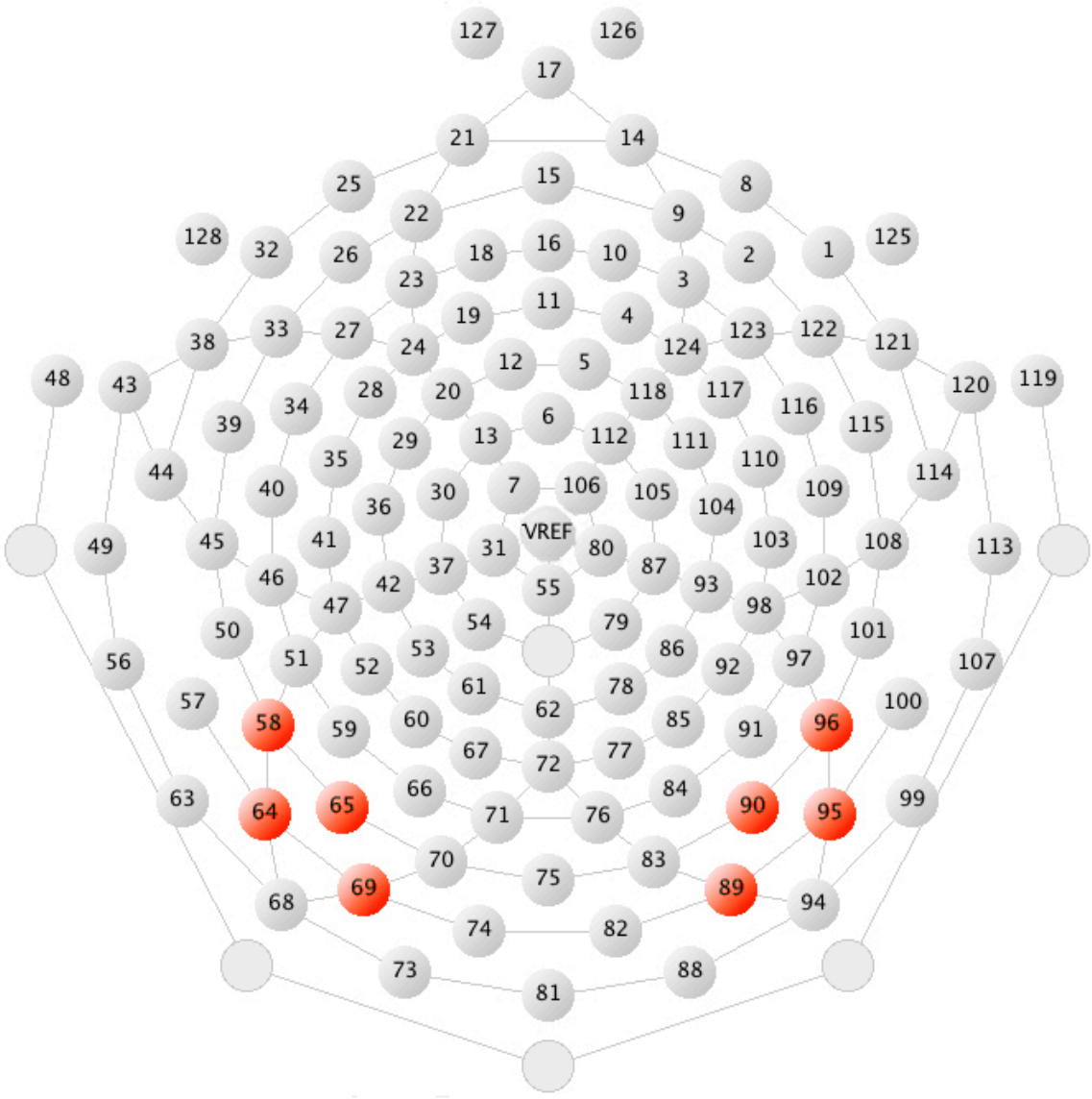


fig.26 Left and Right ROIs used in the present study. Right ROI = electrodes n°96(P8/T6), 95 (P10), 90(PO8) and 89. Left ROI = electrodes n°58(T5), 64 (P9), 65 (PO7) and 69

N170 was identified as the most negative or negative-ongoing peak between 130 and 200 msec, and P1 was defined as the most positive preceding peak. Individual time windows where manually set for every peak in every subject and condition and a statistic extraction tool was run to obtain numerical data on peaks latency and amplitude. Every measure was manually checked by inspecting every peak in each single waveform, in order to avoid errors in results extraction. Latency and amplitudes were averaged across

ROI's electrodes, obtaining a mean local value for every peak considered. As a final step before statistical analysis, absolute N170 latency and amplitude were corrected subtracting P1 values from each waveform, obtaining this way "peak to peak" N170 latency and amplitude values (ppN170 hereafter). It seems important to emphasize that P1 peak in this study was measured with the main purpose of obtaining ppN170 measures, in fact all the analysis were performed using measures obtained from the same ROIs, and not to study P1 *per se*.

For each component of interest, a Group (ASD versus TYP) by Stimulus (neutral faces versus tree), by Hemisphere repeated measures analysis of variance (ANOVA) was conducted as a first step, in order to highlight if ASD group showed a disruption in general face processing ability.

Emotional modulation of face processing was investigated through a Group (ASD versus TYP) by Face emotional expression (neutral vs happy vs fear; Face Emotional Effect: FEE hereafter) by Hemisphere repeated measures ANOVA. Lastly, in order to highlight the direction of significant differences between Stimulus independent variables, *post-hoc* t-tests were performed.

RESULTS

Recorded ERPs latencies and amplitudes for each condition in both groups are reported in **table 1**.

Group*Stimulus*Hemisphere repeated measures ANOVA

P1 latencies showed significantly different values with respect to Stimulus ($p<.05$) and Stimulus*Group ($p<.05$). In a similar fashion P1 latencies are influenced by Hemisphere ($p<.05$) differently in the two groups (Hemisphere*Group, $p<.05$). P1 amplitudes resulted influenced only by the Stimulus condition ($p<.05$), in a similar way in the two groups.

N170 and ppN170 latencies don't show any Hemisphere effect, but a significant Stimulus ($p<.05$) and Stimulus*Group effect ($p<.05$).

N170 and ppN170 amplitudes are modulated in a significantly different way by Hemisphere ($p<.05$), Stimulus ($p<.05$), and Hemisphere*Stimulus ($p<.05$). No group effects were found. Full-scalp topographical maps obtained from data used in this analysis are shown in **figure 27**; L-ROI and R-ROI waveforms are shown in **figure 28**. See **table 2** for ANOVA results details.

Group*FEE*Hemisphere repeated measures ANOVA

P1 latencies are significantly influenced ($p<.05$) by Face Emotional Expression (FEE), but Group differences relatively to emotion modulation only show a trend to a significant effect ($p=.08$). P1 latencies show moreover a lateralization (Hemisphere $p<.05$). *Post-hoc* t-test show that the significant effect is dependent by neutral face stimulus. Also P1 amplitudes show different lateralization induced by stimulus class (Hemisphere*FEE $p<.05$). No Group effects were found.

N170 latencies don't show an Hemisphere effect. Differences between the two groups are dependent by FEE ($p<.05$). T-test shows a stronger effect with

happy faces in the left Hemisphere. Fear faces produce differences with only a trend to significance (p=.07). No effects on N170 amplitude were observed.

ppN170 latencies show a partially different modulation pattern. There is an Hemisphere effect (p<0.5) and a significantly different lateralization in the two groups (Hemisphere*Group p<.05). FEE *per se* doesn't produce any effect, but FEE*Group does (p<.05). ppN170 amplitude show effects induced by lateralization and by FEE, but not by Group. Grand mean waveforms obtained from data used in this analysis are shown in **figure 28, 29, 30.** See **table 3** for ANOVA results details and **table 4** for t-tests values.

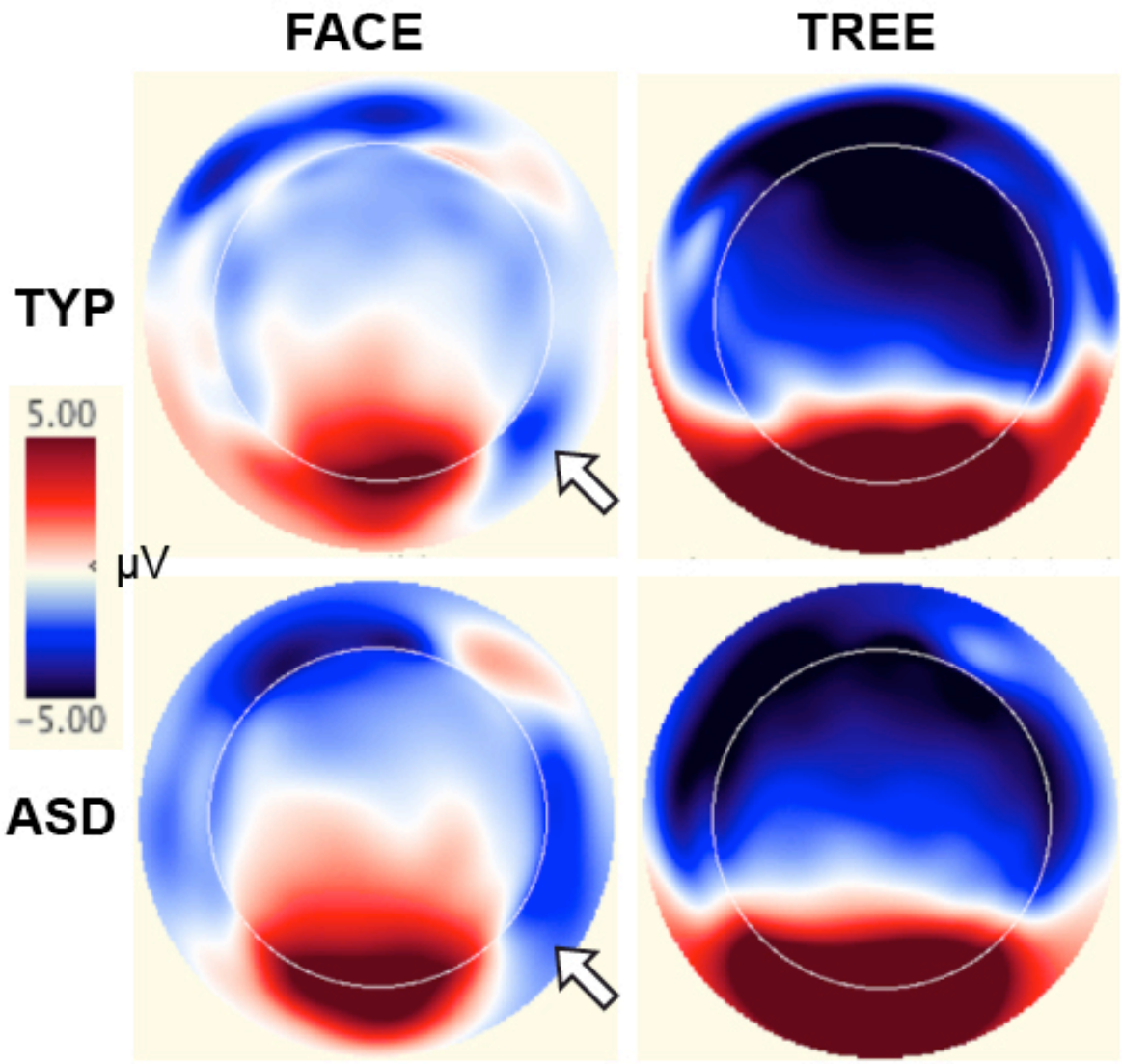


fig. 27 Full scalp averaged topographical maps for typical group (top), ASD group (bottom), neutral faces stimuli (left), tree stimuli (right). Time window from 162-166 msecs from stimulus onset. Arrow on R-ROI. Canthomeatal line marked in white.

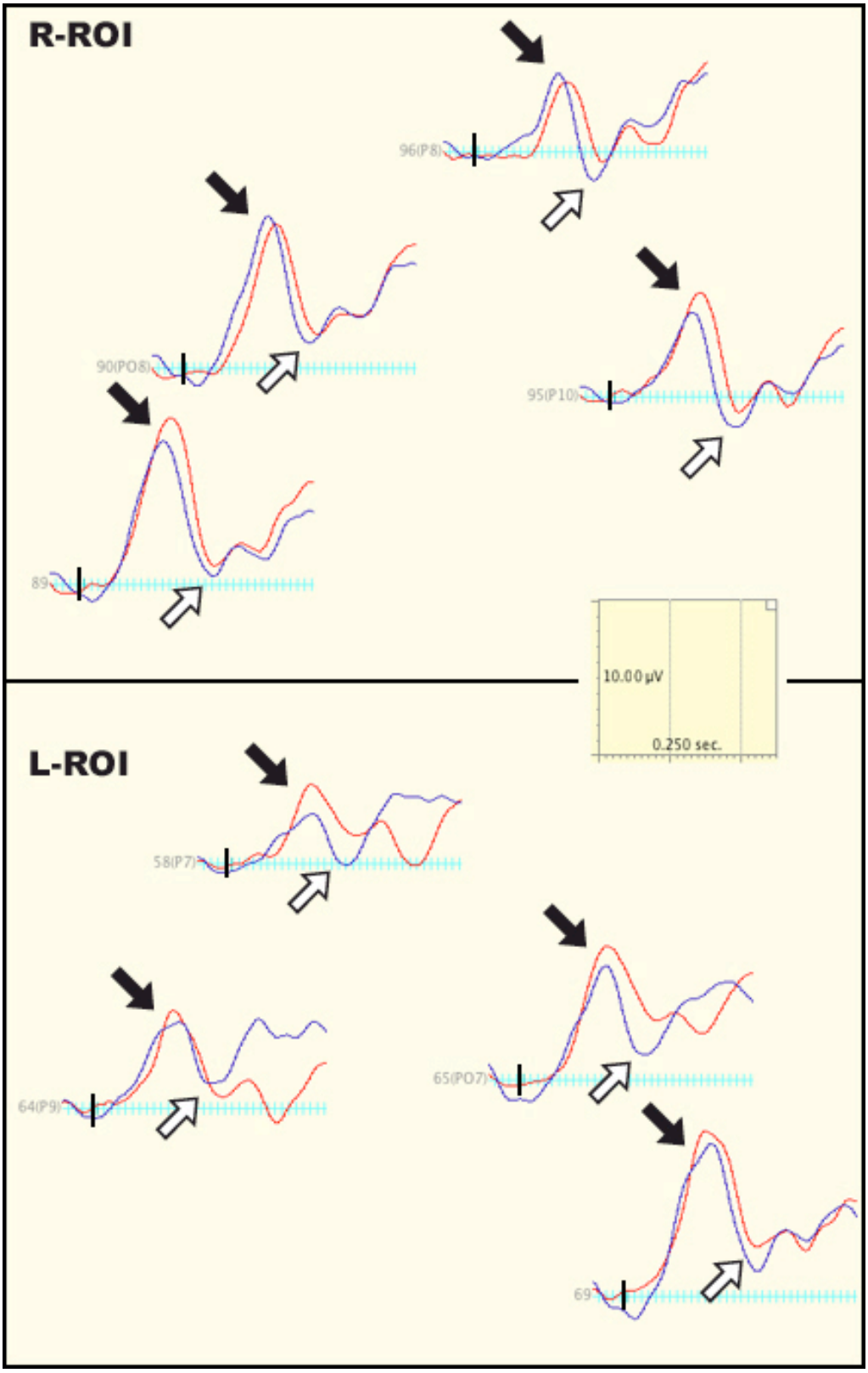


fig. 28 Left and Right ROI Grand Mean waveforms for both groups to neutral faces stimuli (blue= TYP group; red=ASD group). Black arrow = P1. White arrow = N170.

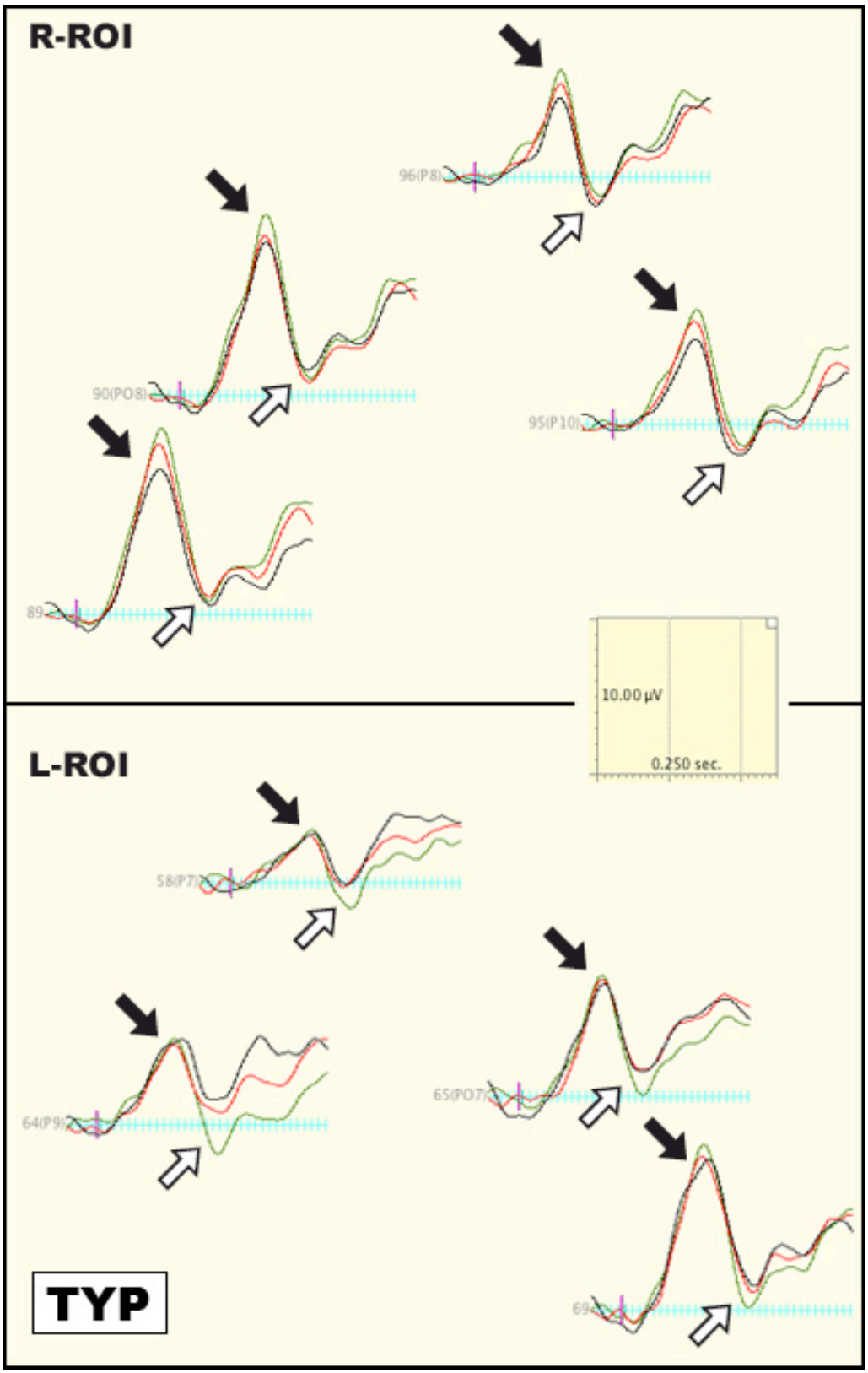


fig. 29 Left and Right ROI Grand Mean waveforms for TYP group to neutral and emotional faces stimuli (black = neutral faces; red = fearful faces; green = happy faces). Black arrow = P1. White arrow = N170.

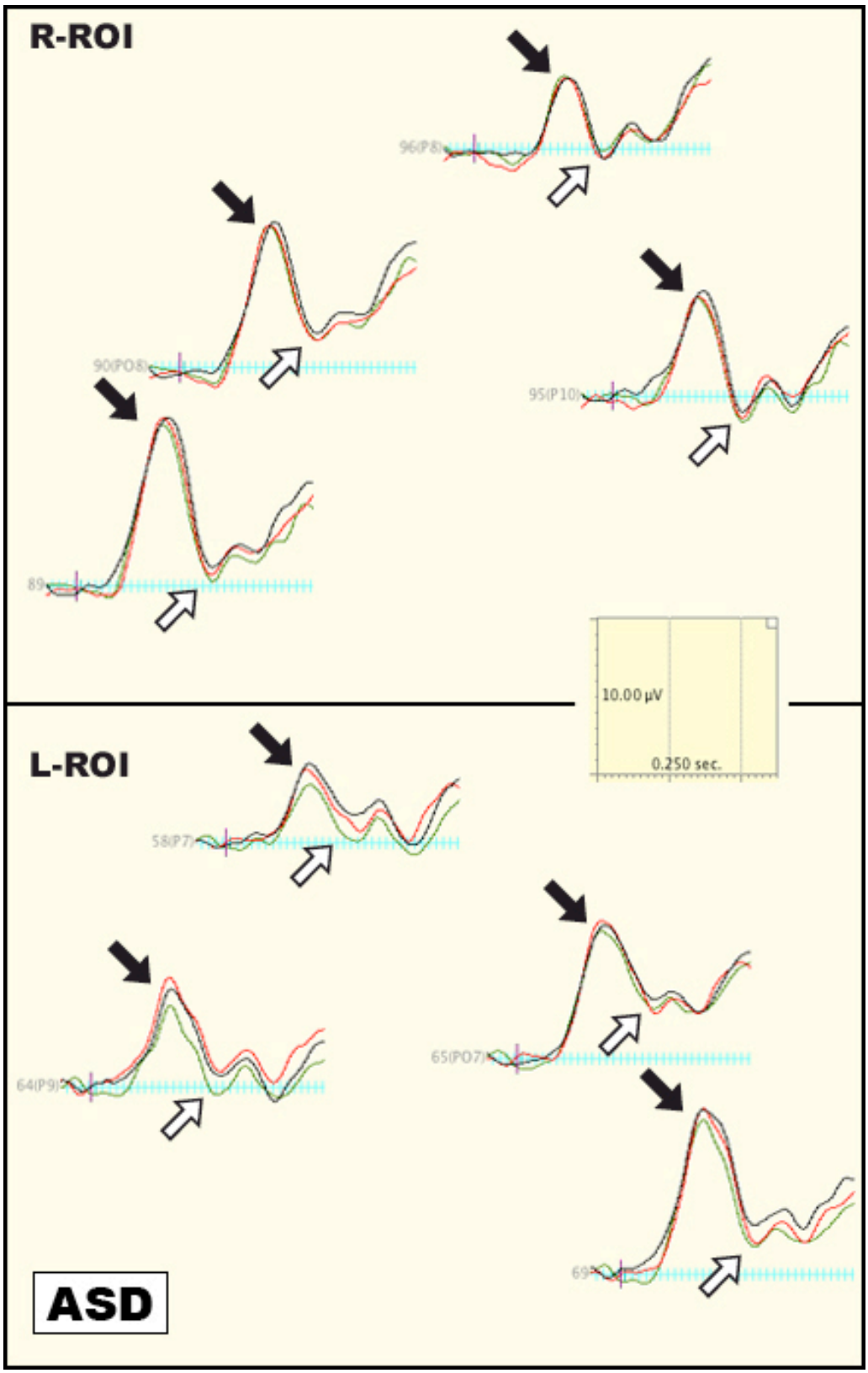


fig. 30 Left and Right ROI Grand Mean waveforms for ASD group to neutral and emotional faces stimuli (black = neutral faces; red = fearful faces; green = happy faces). Black arrow = P1. White arrow = N170.

Component	Measure	Hemisph.	Stimulus	TYP		ASD	
				Mean	St. Dev.	Mean	St. Dev.
P1	Latency	Right	Neutral	113,4	5,8	126,9	7,9
		Left	Neutral	117,4	5,9	115,9	4,1
		Right	Happy	115,9	4,3	119,7	8
		Left	Happy	112,3	6,8	109,9	13,7
		Right	Fear	114,4	7,6	121,9	9,4
		Left	Fear	107,4	5,8	116	11,2
		Right	Tree	126,7	5,3	119,7	8,5
		Left	Tree	126,3	5,3	126,3	8,5
N170	Latency	Right	Neutral	172,6	9,5	186,5	17,9
		Left	Neutral	171	10,9	184,7	19,9
		Right	Happy	173,1	12	188,9	21,4
		Left	Happy	170	9,2	185,1	17,1
		Right	Fear	174,3	13,3	182,7	17,9
		Left	Fear	172,6	11,5	183	10,5
		Right	Tree	175,4	10,1	162,1	14,1
		Left	Tree	172,6	14	159,2	10,9
ppN170	Latency	Right	Neutral	59,1	9,9	59,6	17,8
		Left	Neutral	53,6	10,8	68,8	20,2
		Right	Happy	57,3	10,5	69,2	23,3
		Left	Happy	57,7	6,6	75,2	24,9
		Right	Fear	59,8	12,8	60,8	19
		Left	Fear	65,1	11,4	67	10,4
		Right	Tree	48,7	9,7	42,4	17,8
		Left	Tree	46,3	14,1	32,9	13,9
P1	Amplitude	Right	Neutral	9,1	4,6	9	3,8
		Left	Neutral	7,6	1,5	9,4	4,8
		Right	Happy	11,6	2,8	8,1	5
		Left	Happy	6,2	5	6,9	5,2
		Right	Fear	11,4	4,3	8,1	4
		Left	Fear	8,5	3,6	8,6	5
		Right	Tree	14,7	4,9	12,2	4,7
		Left	Tree	11,4	4,6	11,1	6,3
N170	Amplitude	Right	Neutral	-2,5	2,2	-1,2	5
		Left	Neutral	-0,9	3,3	-0,1	3,6
		Right	Happy	-3,6	4,9	-3,3	5,5
		Left	Happy	-4,8	8	-2,1	4,7
		Right	Fear	-1,5	4,6	-2,8	5,1
		Left	Fear	-1	6,2	-0,2	3,9
		Right	Tree	7,8	4,5	4,9	4,4
		Left	Tree	4,6	4,6	6,7	6,2
ppN170	Amplitude	Right	Neutral	-11,6	3,8	-10,2	5,9
		Left	Neutral	-8,6	3,1	-9,3	5,2
		Right	Happy	-15,2	4,8	-11,3	6,4
		Left	Happy	-11	5,2	-9	4,2
		Right	Fear	-13	2,5	-10,9	6,4
		Left	Fear	-9,5	5,1	-8,9	5
		Right	Tree	-6,9	3,3	-7,3	4,3
		Left	Tree	-6,8	4,9	-4,4	1,8

Table 1 ERPs latencies and amplitudes for each condition in both groups

Component	Measure	Source	F	Sig.
P1	Latency	Hemisphere	,067	,799
		Hemisphere*Group	6,189	,025
		Stimulus	22,305	,000
		Stimulus*Group	12,462	,003
		Hemisphere*Stimulus	23,806	,000
		Hem*Stim*Group	66,587	,000
N170	Latency	Hemisphere	1,526	,236
		Hemisphere*Group	,001	,971
		Stimulus	11,603	,004
		Stimulus*Group	16,563	,001
		Hemisphere*Stimulus	,147	,707
		Hem*Stim*Group	,001	,977
ppN170	Latency	Hemisphere	1,076	,316
		Hemisphere*Group	,926	,351
		Stimulus	38,256	,000
		Stimulus*Group	9,552	,007
		Hemisphere*Stimulus	5,869	,029
		Hem*Stim*Group	11,570	,004
P1	Amplitude	Hemisphere	1,181	,294
		Hemisphere*Group	,692	,419
		Stimulus	17,166	,001
		Stimulus*Group	1,696	,212
		Hemisphere*Stimulus	2,771	,117
		Hem*Stim*Group	,025	,875
N170	Amplitude	Hemisphere	,186	,672
		Hemisphere*Group	1,746	,206
		Stimulus	44,774	,000
		Stimulus*Group	,557	,467
		Hemisphere*Stimulus	3,908	,067
		Hem*Stim*Group	6,065	,026
ppN170	Amplitude	Hemisphere	4,486	,051
		Hemisphere*Group	,035	,854
		Stimulus	13,892	,002
		Stimulus*Group	,125	,728
		Hemisphere*Stimulus	,225	,642
		Hem*Stim*Group	70611	,015

Table 2 Repeated Measures ANOVA: Hemisphere (right/left) x Stimulus (Neutral Faces/ Trees) x Group (ASD/TYP)

Component	Measure	Source	F	Sig.
P1	Latency	Hemisphere	28,491	,000
		Hemisphere*Group	10,428	,006
		Stimulus	3,494	,043
		Stimulus*Group	2,633	,088
		Hemisphere*Stimulus	1,135	,335
		Hem*Stim*Group	5,849	,007
N170	Latency	Hemisphere	,966	,341
		Hemisphere*Group	,009	,926
		Stimulus	,424	,658
		Stimulus*Group	3,119	,059
		Hemisphere*Stimulus	,566	,574
		Hem*Stim*Group	,148	,863
ppN170	Latency	Hemisphere	4,316	,055
		Hemisphere*Group	4,202	,058
		Stimulus	1,943	,161
		Stimulus*Group	4,009	,029
		Hemisphere*Stimulus	,542	,587
		Hem*Stim*Group	1,699	,200
P1	Amplitude	Hemisphere	3,477	,082
		Hemisphere*Group	3,179	,095
		Stimulus	,452	,641
		Stimulus*Group	,888	,422
		Hemisphere*Stimulus	4,357	,022
		Hem*Stim*Group	,696	,507
N170	Amplitude	Hemisphere	1,353	,263
		Hemisphere*Group	,641	,436
		Stimulus	2,417	,106
		Stimulus*Group	,327	,724
		Hemisphere*Stimulus	2,067	,144
		Hem*Stim*Group	1,322	,282
ppN170	Amplitude	Hemisphere	5,764	,030
		Hemisphere*Group	,663	,428
		Stimulus	4,274	,023
		Stimulus*Group	2,386	,109
		Hemisphere*Stimulus	1,400	,262
		Hem*Stim*Group	,096	,909

Table 3 Repeated Measures ANOVA: Hemisphere (right/left) x Stimulus (Neutral/Happy/Fear faces = FEE) x Group (ASD/TYP)

Component/Measure		Hemisphere	Stimulus	Levene Test		T-test			
				F	Sig.	t	Df	Sig.	Means diff
P1	Latency	Right	Neutral	1,285	,275	-3,84	15	,002	-13,47
		Left	Neutral	,615	,445	,629	15	,539	1,52
		Right	Happy	1,700	,212	-1,14	15	,269	-3,84
		Left	Happy	2,798	,115	,424	15	,678	2,38
		Right	Fear	,152	,702	-1,73	15	,104	-7,47
		Left	Fear	3,217	,093	-1,83	15	,086	-8,57
		Right	Tree	3,769	,071	1,919	15	,074	7,01
		Left	Tree	1,878	,191	-,004	15	,997	-,01
N170	Latency	Right	Neutral	3,064	,100	-1,87	15	,081	-13,92
		Left	Neutral	1,107	,309	-1,65	15	,119	-13,70
		Right	Happy	2,118	,166	-1,75	15	,100	-15,75
		Left	Happy	1,932	,185	-2,12	15	,051	-15,10
		Right	Fear	,500	,490	-1,04	15	,311	-8,41
		Left	Fear	,001	,973	-1,94	15	,071	-10,42
		Right	Tree	,350	,563	2,13	15	,050	13,32
		Left	Tree	,340	,569	2,221	15	,042	13,37
ppN170	Latency	Right	Neutral	2,333	,147	-,061	15	,952	-,45
		Left	Neutral	2,028	,175	-1,81	15	,090	-15,22
		Right	Happy	2,726	,119	-1,25	15	,228	-11,91
		Left	Happy	4,191	,059	-1,80	15	,092	-17,48
		Right	Fear	1,323	,268	-,114	15	,911	-,94
		Left	Fear	,105	,751	-,349	15	,732	-1,85
		Right	Tree	1,993	,178	,848	15	,410	6,31
		Left	Tree	,040	,844	1,943	15	,071	13,38
P1	Amplitude	Right	Neutral	,257	,620	,040	15	,969	,082
		Left	Neutral	8,689	,010	-,974	15	,346	-1,83
		Right	Happy	1,328	,267	1,679	15	,114	3,50
		Left	Happy	,117	,737	-,256	15	,802	-,64
		Right	Fear	,111	,744	1,625	15	,125	3,31
		Left	Fear	,688	,420	-,050	15	,960	-,11
		Right	Tree	,153	,701	1,056	15	,308	2,49
		Left	Tree	,574	,460	,092	15	,928	,26
N170	Amplitude	Right	Neutral	3,821	,070	-,636	15	,534	-1,29
		Left	Neutral	,044	,837	-,642	15	,530	-1,09
		Right	Happy	1,450	,247	-,131	15	,897	-,33
		Left	Happy	1,736	,207	-,868	15	,399	-2,65
		Right	Fear	,626	,441	,512	15	,616	1,24
		Left	Fear	1,154	,300	-,303	15	,766	-,74
		Right	Tree	,008	,931	1,305	15	,212	2,87
		Left	Tree	,618	,444	-,754	15	,462	-2,09
ppN170	Amplitude	Right	Neutral	1,248	,281	-,540	15	,597	-1,38
		Left	Neutral	10,312	,006	,333	15	,744	,73
		Right	Happy	,241	,631	-1,33	15	,202	-3,84
		Left	Happy	,207	,655	-,882	15	,391	-2,01
		Right	Fear	4,751	,046	-,811	15	,430	-2,06
		Left	Fear	,082	,779	-,253	15	,804	-,62
		Right	Tree	,660	,429	,197	15	,847	,37
		Left	Tree	7,806	,014	-1,40	15	,180	-2,35

Table 4. Post-hoc T-Test with Group (TYP vs. ASD) as independent variable

DISCUSSION AND CONCLUSIONS

In TYP, P1 latency is faster for face stimuli than for tree stimuli, and is especially faster on right hemisphere. In ASD P1 latency after face stimuli presentation exhibits an inverse behavior than in TYP. In fact in ASD P1 latency in response to face stimuli peaks earlier in left rather than in right hemisphere, and right hemisphere peak latencies to tree stimuli are faster than right hemisphere latencies to face stimuli. Stimuli effect are also present in P1 amplitude (smaller for faces) but no difference between the two groups reaches the significant value. P1 latency shows moreover a different modulation with respect to emotion showed by face, with a stronger effect in the right hemisphere. Hemisphere doesn't produce significant differences between the two groups, while emotion does, even if this effect is restricted to neutral faces in right hemisphere. In fact in ASD group P1 to neutral faces in the right hemisphere peaks significantly later than in TYP group. P1 amplitude is influenced by emotion in a similar way in the two groups. These results indicate that face perception influence on P1 latency and lateralization is significantly different between the two groups. This effect is only marginally mediated by emotions. Therefore it's possible to infer that general face processing ability disruption in ASD is reflected in P1 latencies and lateralization, but not in its amplitude, independently by the emotion showed by the face. In this study P1 was measured using exactly the same ROIs chosen for N170 analysis, therefore these results on its modulation by face and facial emotions can't be easily generalized. If however we consider P1 values obtained in this way as reflecting early face-sensitive ongoing neural processes, than these results are in agreement with those reporting significant

differences in ASD compared to controls subjects in ERPs latency, amplitude or hemispheric distribution (e.g. Dawson 2002c, 2004, 2005a; O'Connor 2007).

N170 and ppN170 latencies and amplitudes show the same specificity for face with respect to tree stimuli. In particular, in a similar way as P1, N170 and ppN170 latencies are faster for faces in TYP group but not in ASD group. In fact in ASD group N170 and ppN170 latencies for faces are delayed with respect to both TYP latencies to faces and ASD latencies to trees. Face specificity of N170 and ppN170 amplitude is instead reflected also by lateralization, but no differences is observed between groups. These result on N170 and ppN170 are comparable with those obtained by O'Connor et al. (2007) and Dawson et al. (2005), adding evidence to the hypothesis of a general face processing abilities disruption in ASD, that can be revealed at least during development.

Concerning influence of emotions on N170 and ppN170, we can observe different but congruent phenomena. According to analyses performed with neutral face versus. FEE as contrast, N170 shows group effects only in its latencies, in particular relatively to group differences in processing emotions. ASD group process faces slower in comparison with TYP group and the difference reaches a significant value for happy face condition and a trend to significant value for fear face condition, both in left hemisphere. ppN170 latency shows differences also with respect to lateralization. In fact, besides a slower response to faces and a differential effect produced by emotions in ASD, ppN170 latencies are differently lateralized in the two group for neutral and happy faces condition. Differently from N170, ppN170 shows a face specific effect also in its amplitude (Hemisphere and FEE effects) even if differences don't concern the two groups. Results coming from analysis of N170 and ppN170 components suggest that their latencies along with their amplitudes show a specificity for faces with a clear lateralization only in the

latter measure. While ppN170 shows a modulation by emotions in its latency and amplitude, N170 shows it only in its latency. Looking at group differences in general face processing ability, we note that face specific N170 waveform is delayed in ASD group. These results are similar for both N170 and ppN170, however ppN170 becomes more sensitive in seizing group differences in emotion modulation. In fact, ppN170 analysis finds differences relatively to FEE and Hemisphere effects in the two group, likely because of a summation of P1 and N170 absolute peak values. These results about the modulation of N170, and its peak-to peak corrected analogue ppN170, can be overall considered in line with those obtained by Dawson's group (2002c, 2004, 2005a,b). An important exception, reporting comparable surface ERPs in both ASD and TYP, is represented by Wong's et al. study (2008): however must be underlined that even if they used an implicit emotion processing task (as in the present study), participants attention was anyway directed to face stimuli, differently from the present study in which a dedicated stimulus class (cartoons) was used for the specific and only purpose of directing attention away from face stimuli. This methodological choice has been recently supported by evidences suggesting that attention can modulate N170 differently in ASD and control subjects (Churches et al. 2010). Moreover other studies have recently showed that in neurotypical individuals attention can differentially modulate N170 depending on perceptual load and low/high face stimuli discriminability (e. g. Mohamed et al., 2009).

Taken together, these findings support the opinion about an early (first 200 msec) impairment in general face processing abilities and in particular in emotional faces processing in children with ASD. N170 was influenced by both face stimuli *per se* in the groups, as well as emotional content, and this differences became even more significant with the applied correction reflected in the ppN170. To our knowledge, this peak-to-peak analysis has

never been used to investigate face sensitive ERPs in ASD studies, but notably it has been used by Kuefner et al. (2010) to demonstrate that this "correction" can rule out developmental effects on N170 from about 5 years of age until adulthood.

Concerning the effects observed on the P1, it seems important to underline that they can't be easily compared with other literature evidences because in this study its latency and amplitude values (obtained from the same ROIs used for N170 analysis, and not from proper P1 ROIs) were used with the specific purpose of correcting N170 values in order to eliminate developmental and maybe even individual factors that may result confounding when a standard, absolute way of measuring ERP data are used.

The flexibility of the equipment used in this study (an EGI's GES300) suggests two logical future steps: neural sources modeling (GeoSource 2.0 recently received an US FDA 510k pre-market clearance letter for child head models - www.egi.com) and fMRI co-registration, ideally in combination with eye-tracking techniques to better monitor gaze behavior.

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