Tesis Doctoral

Procesamiento cortical rápido de estímulos emocionales y toma de decisiones en humanos

Petroni, Agustín

2012-03-30

Universidad de Buenos Aires

Facultad de Ciencias Exactas y Naturales

Departamento de Fisiología, Biología Molecular y Celular

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Tesis presentada para optar por el título de Doctor de la Universidad de Buenos Aires en el área de Ciencias Biológicas

Lic. Agustin Petroni

Director de Tesis: Dr. Mariano Sigman
Tutor: Dra. Lidia Szczupak

Buenos Aires, 2012

Procesamiento cortical rápido de estímulos emocionales y toma de decisiones en humanos.

La percepción de rostros depende de mecanismos complejos que involucran procesamiento paralelo y masivo, a un costo computacional alto. Existe un área cerebral principalmente implicada en el procesamiento esctructural de rostros, el área fusiforme, localizada en la región ventral de los lóbulos occipitales. El área fusiforme está funcionalmente conectada con la amígdala, lo que sugiere la existencia de un circuito involucrado en la extracción rápida de rasgos emocionales. Bajo el postulado teórico de que este circuito estaría embebido en una red extensa, sustrato de cognición compleja necesaria para la interacción social, incluyendo teoría de la mente, testeamos la hipótesis que establece que potenciales corticales modulados por contenido emocional de caras predicen habilidades sociales de los individuos. Nuestros resultados sugieren una asociación directa entre potenciales cerebrales modulados por emociones faciales y cognición social, medida con tres tareas. Testeamos el mismo paradigma experimental en dos grupos de pacientes psiquiátricos que presentan déficits emocionales y ejecutivos: Trastorno por déficit de atención con hiperactividad – y síndrome bipolar. Ambos desórdenes mostraron una ausencia de modulación cortical emocional, y los pacientes bipolares mostraron que la variabilidad en la modulación de componentes en respuesta a emociones faciales es explicada por el estado emocional del paciente (para índices de manía y depresión). Finalmente, mostramos que estos pacientes presentan deficiencias en el procesamiento cortical de recompensas monetarias en una tarea de toma de decisión. La modulación de los componentes electroencefalográficos en respuesta a recompensas mostró una asociación con tareas de cognición compleja

Palabras clave: ERP, cognición social, toma de decisiones, ADHD, desorden bipolar

Rapid cortical processing of emotional stimuli and decision making in humans.

Face perception relies on a complex mechanism that involves massive parallel processing with high computational cost. The brain region implicated in the structural processing of faces in humans is the fusiform face area, located in the ventral part of the occipital lobes. The fusiform face area is functionally connected with the amygdala, which suggests a circuit involved in the rapid extraction of emotional features. Under the theoretical postulate that this circuit is embedded in a more extensive network that supports complex cognition necessary for social interaction including theory of mind, we tested the hypothesis that early cortical potentials modulated by emotional facial stimuli will predict individual social skills. Our results suggest a direct association between brain potentials modulated by facial emotions and social cognition, measured by three different tasks. We tested the same paradigm in two psychiatric disorders that present emotional and executive deficits: bipolar disorder and Attention-Deficit Hyperactivity Disorder (ADHD). Both disorders showed an absence of cortical emotional modulation, and bipolars showed that the variability in the emotional modulation is explained by the emotional state of the patient (for both maniac and depression scores). Finally, we showed that these patients have deficiencies in the processing of monetary reward under a decision making task. Importantly, the feedback modulation is associated to complex cognition.

Keywords: ERP, social cognition, decision making, ADHD, bipolar disorder

Agradezco a las siguientes instituciones por permitir la realización de esta tesis:

Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, CONICET, INECO, FINECO, ANPCyT, Human Frontiers Science program

Agradezco a las siguientes personas por su colaboración en los trabajos que abarcaron la tesis.

Mariano Sigman, Agustín Ibáñez, Facundo Manes, Hugo Urquina, Esteban Hurtado, Raphael Guex, Sandra Báez, Micaela do Nascimento, Alejandro Blenkmann, Nicolás von Ellenrieder, Leandro Beltrachini, Alicia Lischinsky, Teresa Torralba, Fernando Torrente, Marcelo Cetkovich, Juan Kamienkowski, Sergio Strejilevich y Julia Teitelbaum

Un subconjunto de los resultados que integran esta tesis, que se encuentran en el capítulo 2, forman parte de la tesis de maestría en preparación del licenciado Hugo Urquina, Facultad de Psicología, UBA.

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
ARD	Automatic relevance determination algorithm
ASD	Autism spectrum disorders
BD	Bipolar disorder
BDS	Backwards digit span
BIS	Barrat impulsivity scale
COWAT	Controlled oral word association test
dSPM	Dinamic statistical parametric maps
DTI	Diffusion tensor imaging
DVT	Dual valence task
DSM-IV	Diagnostic and statistical manual of mental disorders
EEG	Electroencephalography
EOG	Electrooculogram
ERN	Error related negativity
ERP	Event related potentials
FDS	Forward digit span
fERN	Feedback error related negativity
FG	Fusiform gyrus
FPT	Faux pas test
FTD	Frontotemporal dementia
IFS	INECO frontal screening
IGT	Iowa gambling task
INECO	Instituto de neurologia cognitiva
MADRS	Montgomery-Asberg depression rating scale
MCC	Medial cingulate cortex
MRI	Magnetic resonance imaging
PCC	Posterior cingulate cortex
PFC	Prefrontal cortex
RDGT	Rapid decision gambling task
RDMUR	Rapid decision making under risk
RMET	Reading the mind in the eyes
ROI	Region of interest
RT	Response time
RVLT	Rey verbal list test
SLB	Solution of bayesian learning
STAI	Stait-Trait anxiety inventory
TMT	Trail making test
ToM	Theory of mind
WAIS	Weschler adult intelligence scale
YMRS	Young mania rating scale

General Introduction

Personal background

Before starting this thesis project I worked for more than two years with Dr. Della Maggiore at the School of Medicine, Universidad de Buenos Aires. During those years my research focused on the physiology of the human mirror neuron system.

The mirror neuron system is a frontoparietal network that activates motor brain areas when an individual observes an action passively, that is, without measurable muscular activity. Furthermore, the primary motor cortex of the observer activates in topographical regions congruent to the observed action (e.g. the observation of an arm movement activates arm-muscle neurons in the motor cortex). This process, also called motor resonance, occurs automatically and without awareness of the observer. The mirror neuron mechanism enables the embodiment of motor acts and complex actions of conspecifics. It is proposed as a neural mechanism for empathy, imitation, and action understanding. Several lines of evidence show that human mirror system is only activated by a fraction of the observed actions. In particular, motor resonance occurs with already learned actions, those that belong to our "motor repertoire"(Calvo-Merino, Glaser et al. 2005).

My research project explored how humans acquire new representations in motor resonance. Is the observation of a new action sufficient to retrieve the corresponding motor representation? Or, alternatively, it is necessary the sensorimotor contingency between the observed action and the executed action that drive motor resonance?

We tested the hypothesis that motor resonance arises from sensorimotor contingencies by measuring corticospinal excitability in response to abstract cues previously associated with an action. Corticospinal excitability was higher during the observation of a colored cue that preceded a movement involving the recorded muscle than during the observation of a different colored cue that preceded a movement involving a different muscle. Crucially this facilitation was only observed when the cue was associated with an executed movement but not when it was associated with an observed movement (Petroni, Baguear et al. 2010).

My results provided crucial evidence in support of the sensorimotor hypothesis stating that mirror properties develop from hebbian associations between observed and executed actions (Keysers and Perrett 2004).

Starting a new project

This Ph.D. thesis started at the Integrative Neuroscience Laboratory, Universidad de Buenos Aires,

under the supervision of Professor Sigman. We initiated a collaboration project in social neuroscience with Dr. Facundo Manes and Dr. Agustin Ibañez, director and researcher at the Instituto de Neurología Cognitiva (INECO), respectively. They were interested in the physiological basis of emotion processing of Bipolar and Attention-Deficit Hyperactivity Disorder (ADHD) patients. Dr. Ibañez and Dr. Manes contributed with access to patients, clinical assessment and my training on neuropsychology. Our contribution consisted on physiological testing with our EEG equipment, neuropsychological testing and data analysis. In this way, we started a new interdisciplinary exciting project about emotion perception and social cognition.

Aims and background

The general aim of this thesis is to understand the associations between low level brain signals and complex individual social cognition skills.

The particular aims are:

A0) to design and test an experimental paradigm in which a brain electrophysiological signal evoked by emotional stimuli (faces and words) can be correctly estimated.

A1) to assess individual social cognition skills in healthy subjects and examine its relation to brain signals evoked by emotional stimuli measured in A0.

A2) to investigate this putative association in two psychiatric disorders that present shared emotional and executive deficits.

A3) to estimate the brain components evoked by monetary feedback processing in a decision making task.

A4) to assess clinical and social cognition individual measures in two psychiatric disorders and healthy subjects to examine its association to the brain components estimated in A3.

Humans, as other primates, live immerse in complex social networks. An effective and dynamic interaction between conspecifics requires a precise information exchange about their internal state, mental content and intentions. The body-part that conveys most of this information is the face, one of the most important visual stimuli for humans (Leopold and Rhodes 2010). Efficient processing of emotional facial expressions allows humans and other animals to infer the internal states of their conspecifics (Parr, Waller et al. 2008) [see reviews (Leopold and Rhodes 2010) and (Tate, Fischer et

al. 2006)]. The perception of facial emotion plays a major role for social communication and the regulation of social behavior. Our brain can extract a huge amount of emotional information from very subtle facial cues, such as the curvature of the mouth. Given a massive parallel processing that occurs at high visual areas, the perception of a facial emotion results effortless and almost instantaneously, even in infants. While computers can solve an immense amount of arithmetic calculations in a fraction of a second (note that a simple arithmetic calculation as 357 x 491 seems very difficult to a human), they generally fail in facial affection recognition.
Although little is known about the detailed architecture of the face-processing circuit, some recent studies of advanced magnetic resonance imaging (MRI) techniques combined with lesion studies are starting to shed some light on the main areas and connections involved in this process.

Facial stimuli are processed in special areas of the cortex: Fusiform face area and occipital face area.

Face processing relies on a distributed network of cortical regions in the temporal and frontal lobes together with other cortical regions that are not primarily visual (such as somatosensory cortex), and subcortical structures such as the amygdala (Atkinson and Adolphs 2011). Lesion studies combined with functional magnetic imaging (fMRI) shows that there are at least two specialized areas in the visual cortex that encode the structure of faces, known as the fusiform face area, located in the fusiform gyrus and the occipital face area, located in the lateral occipital lobe. Structural encoding is the integration among parts of a face and their spatial relation into a particular salient object, which naturally emerges as a face in a crowded scene and is perceived as a "pop-up".
Patients who have bilateral focal lesions in the fusiform face area present serious deficits in face recognition. This impairment is called prosopagnosia. Prosopagnosic patients cannot perceive faces. For instance, they usually do not recognize close relatives by their face, and must rely on other cues to identify them. However, in facial perception the fusiform gyrus may play a nodal role within a much complex network.

Facial areas are directly linked to the amygdala

A study that employed tractography techniques (Diffusion Tensor Imaging, DTI) revealed that the mid fusiform gyrus is directly connected to the amygdala and the hippocampus (Smith, Lori et al. 2009). Figure 1 shows the density and thickness of these pathways.

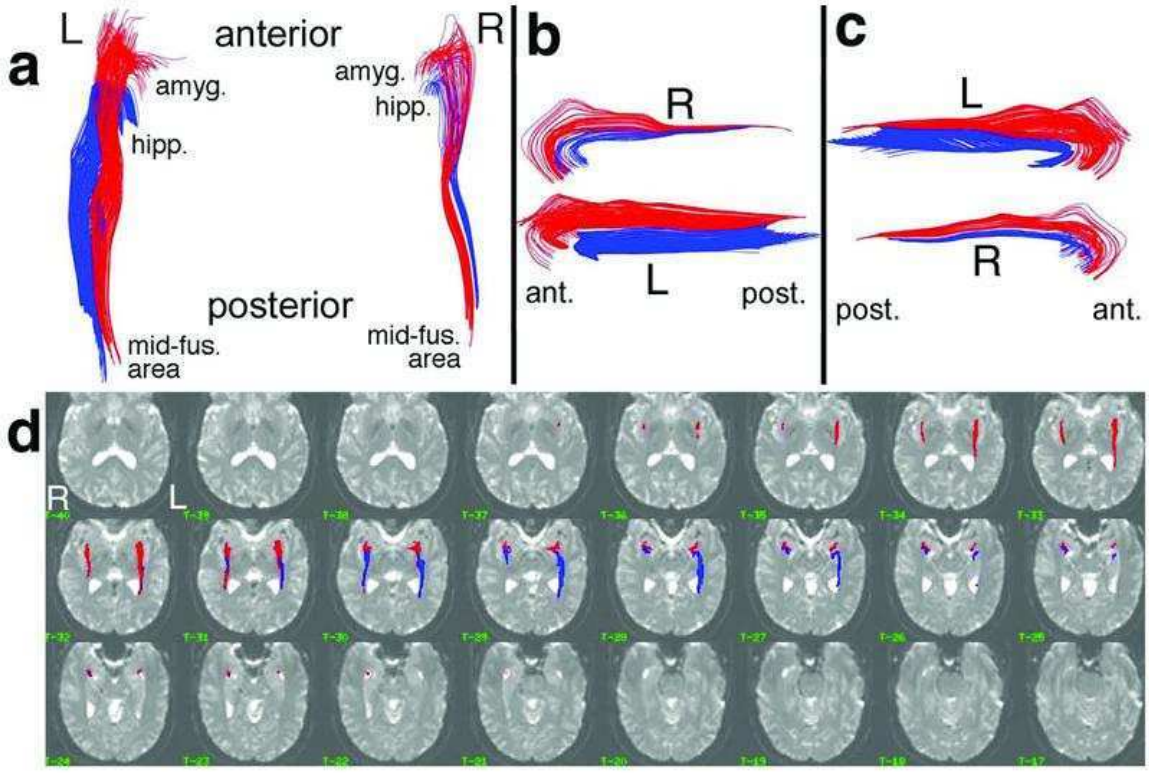

Figure 1. A representative subject showing **typical pathways from fusiform gyrus to amygdala and hippocampus** (and vice versa). In (**a–c**), the amygdalo-fusiform (red) and hippocampo-fusiform (blue) pathways are shown in 3D projection display, viewed from above (**a**), from the left side (**b**), and from the right side (**c**). The views in (**b**,**c**) are slightly obliqued (viewing superior-to-inferior by 20°) to better demonstrate the separation at the medial temporal lobe (see anterior parts of **b**,**c**). A 2D anatomical overlay of the pathways onto contiguous transverse 1.25-mm I0 images (**d**) documents the precise anatomical location. Taken from (Smith, Lori et al. 2009).

The hippocampo-fusiform pathway may be important for memory formation and recognition of faces whereas the amygdalo-fusiform pathway may play a role in emotional processing or emotional modulation of visual areas.

In the same vein, a recent study (Gschwind, Pourtois et al. 2011) used a combination of fMRI and DTI to study the pattern of structural connectivity among the cortical areas involved in face processing. The results show that the fusiform face area and the occipital face area have strong reciprocal connections in the right hemisphere. They found a strong connection between the amygdala and more early visual areas, whereas connections from/to classical face areas to/from the amygdala show to be weaker. The authors suggest that this shortcut to the amygdala is a bottom-up signal that decodes the presence of an emotionally relevant stimulus with a very short latency. In this way, the detection of emotionally relevant face information may take place in the amygdala independently of the degree of processing in facial areas.

The early amygdala activation could allow feedback influences on ongoing cortical processing, driven by the weaker connections from the amygdala to the face areas. A recent study with intracranial recordings implanted in the amygdala of patients shows that the amygdala is activated 120 milliseconds after the facial stimuli onset and 50 milliseconds before the facial areas, a result congruent with the previous model (Pourtois, Spinelli et al. 2010).

Strong evidence supporting an amygdala nodal role for emotion processing of faces comes from lesion studies. For example, bilateral lesions in the human amygdala impair the recognition of emotions from facial expressions (Adolphs, Tranel et al. 1994).

Figure 2 shows a diagram that summarize these results (Gschwind, Pourtois et al. 2011).

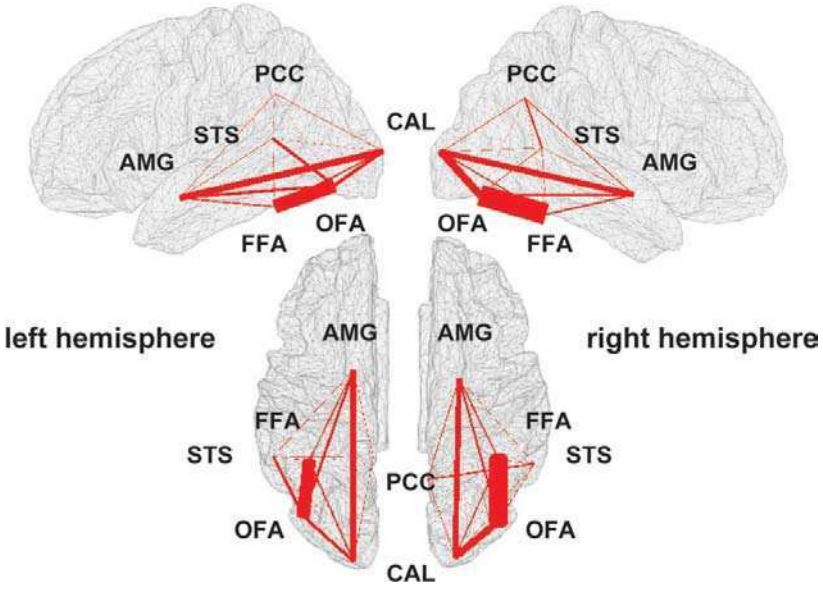

Figure 2. A diagram of the pattern of structural connectivity between cortical areas involved in face processing. AMG: amygdala, OFA: occipital face area, FFA: fusiform face area, STS: superior temporal sulcus, PCC: posterior cingulate cortex, CAL: early visual cortex. Taken from (Gschwind, Pourtois et al. 2011)

Although there were discrepancies among the results from different studies in the relative weight of the direct connections between the amygdala and facial areas, they all highlighted the importance of these connections. A direct connection between facial related areas in the fusiform gyrus and the amygdala strongly suggests that this circuit may play an important role in the rapid access to facial emotion encoding, bypassing other higher order processes such as the semantic content of the stimulus.

The amygdala: a central player in emotional regulation

The amygdala is a subcortical area central to emotion regulation (see figure 3). It has a broad range of connections with other brain regions, allowing it to participate in a wide variety of behavioral functions and playing a fundamental role in complex social behaviors. Some subcortical targets are the hypothalamus for activation of the sympathetic nervous system, the thalamic reticular nucleus for increased reflexes, the nuclei of the trigeminal nerve and the facial nerve, and the ventral tegmental area, locus coeruleus, and laterodorsal tegmental nucleus for activation
of dopamine, norepinephrine and epinephrine.
Figure 4 shows some of the major input and output connections of the amygdala (Phelps and LeDoux 2005) while figure 5 illustrates the high interconnectivity with other brain regions (Pessoa 2008). Some very well studied aspects in which the amygdala is involved are emotional learning (e.g. fear conditioning), memory modulation, arousal, hypoemotionality, loss of fear, hypersexuality, and social behavior.

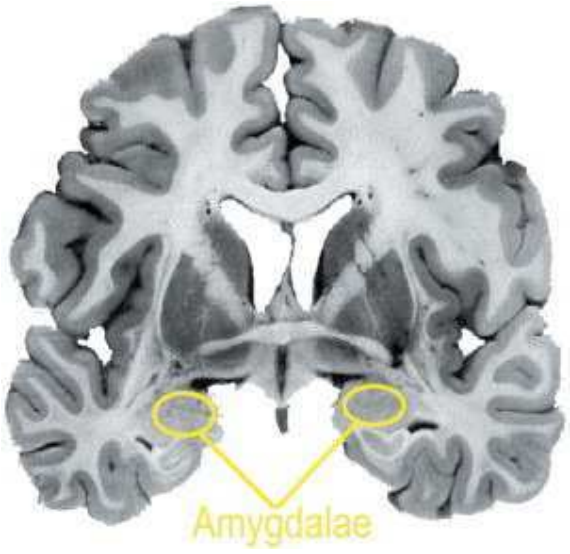

Figure 3. Coronal view of the amygdala. (Davidson and Irwin 1999)

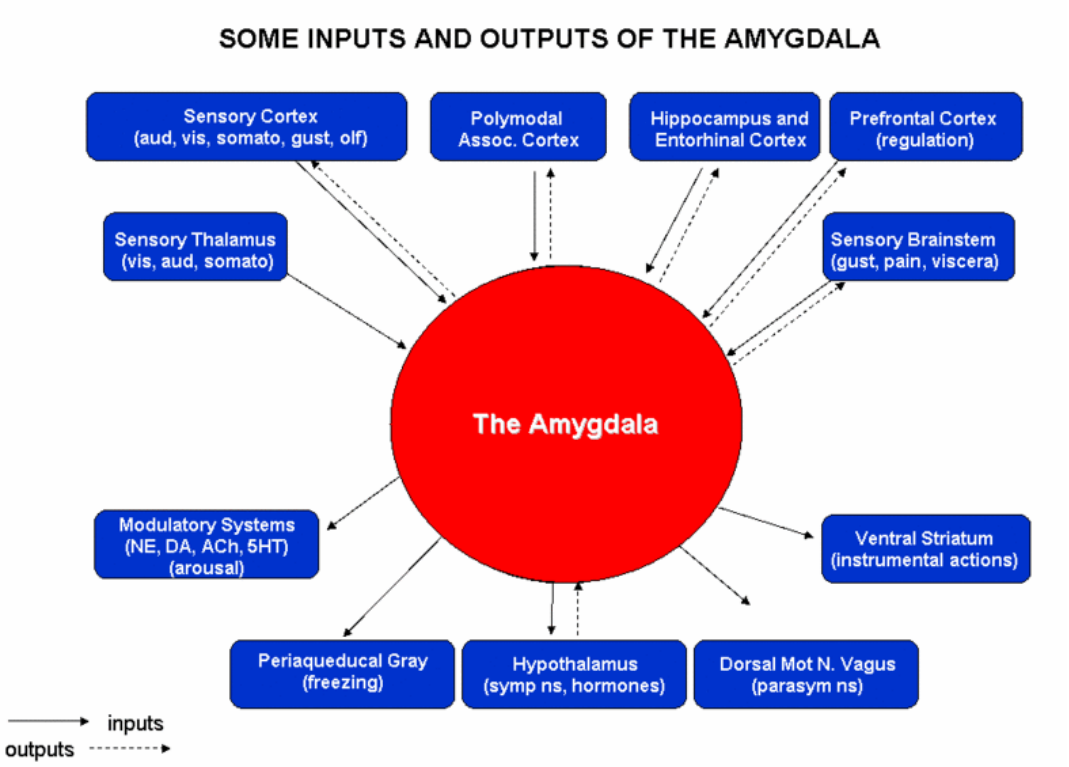

Figure 4: Some of the major input and output connections of the amygdala. Sensory abbreviations: aud, auditory; vis, visual; somato, somatosensory; gust, gustatory (taste); olf, olfactory. Modulatory arousal systems abbreviations: NE, norepinephrine, DA, dopamine, ACh, acetylcholine; 5HT, serotonin). (Phelps and LeDoux 2005)

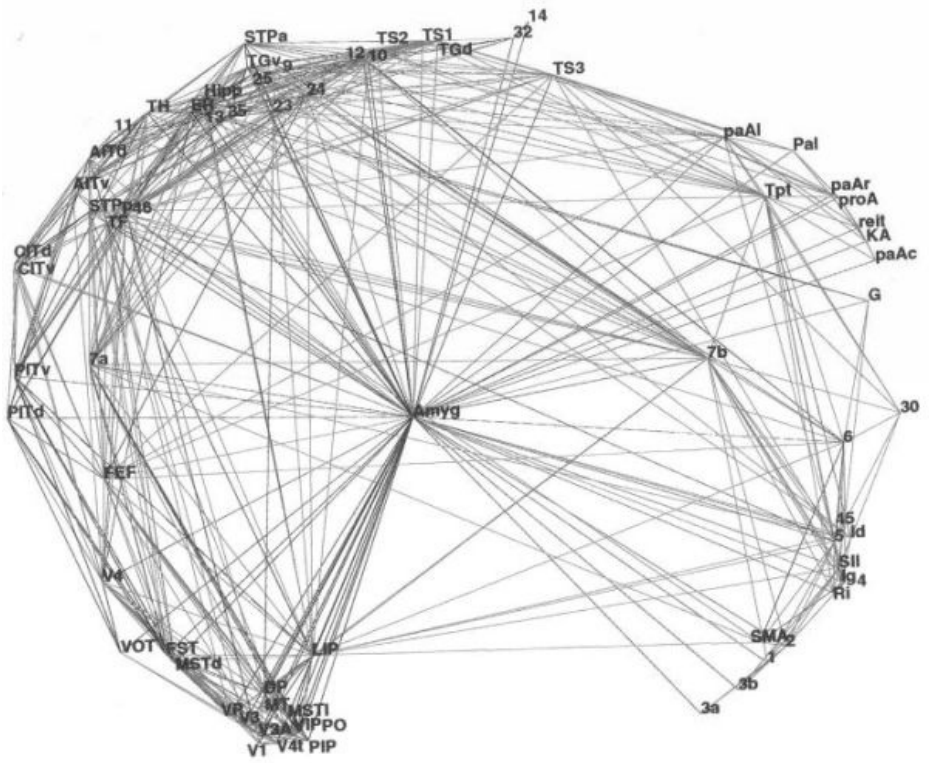

Figure 5. Connectivity diagram of the human amygdala (center of the figure). Note the large amount of connections with other brain areas. Taken from (Pessoa 2008)

An amazing example of the social importance of the amygdala is a recent discovery which shows that the amygdala volume predicts the social group size and complexity in human individuals (Bickart, Wright et al. 2010). Curiously, this result has been replicated for internet social networking of adults, though it may not be surprising, given that real social networks and internet social networks are correlated (Kanai, Bahrami et al. 2011). Regarding complex social cognition, the first approach came from lesion studies. The first lesion studies of social behavior in monkeys took place around the 1930's. The first technique was the surgical removal of the amygdala (Kluver and Bucy 1937; Kluver and Bucy 1939).

In the 1950s techniques became more precise, such as pharmacological lesions, and reversible lesions like mucsimol injection has increased in the last decades. The social behavior alterations induced by these treatments in monkeys included a propensity to shift rapidly in exploring different objects, to approach, ingest, and mount many stimuli indiscriminately, and to show a profound lack of behavioral regulation on the emotional and social meaning of stimuli (Adolphs 2010). Experiments performed in monkeys living in social groups resulted in severe impairments in social behavior. Amygdalectomized monkeys lost their social status and were ostracized by the group (Rosvold, Mirsky et al. 1954).

Lesion studies in humans are extremely scarce, given the low occurrence of focalized bilateral lesions.

Nevertheless, there are a few interesting case studies. A famous case is the patient SM. A series of studies in this patient has documented a remarkably specific impairment in recognizing fear from facial expressions, together with impairments in a variety of social judgments from faces. Regarding social behavior, SM was notably dis-inhibited and showed a propensity to approach and engage with others that occasionally resulted in social difficulties in real life (Buchanan, Tranel et al. 2009)

The amygdala is also implicated in some aspects of decision making and reward processing, as in risk based or emotional decision making (Gospic, Mohlin et al. 2011; St Onge, Stopper et al. 2012). It interacts with prefrontal cortex and frontostriatal loops. A current view denies the strict distinction of cognitive and emotional areas in two separate categories, proposing an integrative view that establishes that a certain area can be cognitive or emotional depending on the global state of the network (Pessoa 2008)

Prefrontal cortex. Emotional perception is regulated by executive control.

Another major player in face perception is the prefrontal cortex (PFC). The PFC is a cortical area central in executive function, decision making and inhibition and also in emotion processing. Its activity determines the state of other areas, including those involved in face emotion perception, allowing the control of behavior by a strong interaction between executive control and emotional responses. A recent study revealed that prefrontal cortex is necessary to control automatic responses triggered by social emotional stimuli, overriding those responses and guiding action (Volman, Roelofs et al. 2011). Prefrontal cortex and amygdala also interact actively when humans make decisions under risky conditions (e.g. gambling). A recent study in rodents provide a more detailed circuitry of this interaction (St Onge, Stopper et al. 2012).

A subregion of the prefrontal cortex, the ventromedial prefrontal cortex, ventral and medial regions of the prefrontal cortex, encompass several interconnected regions that process reward and punishment, regulate emotion, and maintain homeostasis (Ongur and Price 2000). The ventromedial prefrontal cortex has been linked to social behavior since the historical case of Phineas Gage, a nineteenth-century railroad worker who had an iron rod blasted through the front of his head in an accident. Gage survive with preserved intellectual abilities, but his personality changed from shrewd, persistent, and respectable to profane, capricious, and unreliable after the accident (Damasio, Grabowski et al. 1994). Studies involving gambling games show that ventromedial prefrontal cortex patients experience diminished emotional arousal before making risky choices (Bechara, Damasio et al. 1994), as well as diminished regret when considering alternate outcomes after making risky choices. In such games, patients persistently make disadvantageous choices. These results support an influential theory about

the role of emotion in decision-making (including social decision-making), the so-called somatic marker hypothesis (Damasio 1996). The hypothesis states that emotional signals, mediated in part by regions in the ventromedial prefrontal cortex, can be elicited by the anticipation or consideration of the future outcomes of one's actions, and that this signal guides the decision that is made.

Another frontal area involved in emotional regulation is the anterior cingulate cortex (ACC). The ACC is believed to be involved in the executive control of actions, such as in monitoring conflicting response demands, detecting errors, and evaluating the emotional significance of events. The dorsal part of the ACC seems to play a key role in reward-based decision-making and learning. The rostral part of the ACC, on the other hand, is believed to be more involved with affective responses to errors.

Summarizing, face emotional perception relies on areas extracting structural visual information, areas providing memory, areas processing the emotional meaning of a certain face, and areas that control the circuit necessary to organize in space and time a line of action.

Cortical facial processing can be measured with electroencephalography. The N170 potential.

A classical approach to study facial processing with high temporal resolution is electroencephalography (EEG). When a human observes a face, a potential called N170 can be measured at the scalp. The N170 is a cortical marker specifically linked to facial processing, with neural generators in the fusiform gyrus and superior temporal sulcus. The N170 changes its amplitude in response to different facial emotions (see a detailed description in materials and methods section).

Limbic and frontal activity is abnormal in bipolar disorder and ADHD

The interaction between executive functions and emotion regulation is altered in some psychiatric disorders, such as bipolar disorder, and ADHD. The close interaction between limbic and frontal areas may explain the co-occurrence of emotional and executive deficits in these patients.

The bipolar disorder (BD) is a neuropsychiatric disease characterized by unpredictable manic, hypomanic and depressive episodes, related to several neuroanatomical and neuropsychological deficits (Green, Cahill et al. 2007; Delaloye, de Bilbao et al. 2009). Mania is a state of abnormally elevated or irritable mood, arousal, and/ or energy levels. In a way, it is the opposite of depression. Mania varies in intensity, from mild mania (hypomania) to full-blown mania with psychotic features,

including hallucinations, delusion of grandeur, suspiciousness, catatonic behavior, aggression, and a preoccupation with thoughts and schemes that may lead to self neglect. Signs and symptoms of the depressive phase of bipolar disorder includes persistent feelings
of sadness, anxiety, guilt, anger, isolation, or hopelessness, disturbances in sleep and appetite, fatigue and loss of interest in usually enjoyable activities, problems concentrating; loneliness, self-loathing, apathy or indifference, loss of interest in sexual activity, shyness or social anxiety, irritability, lack of motivation, and morbid suicidal ideation (Semple 2005).

Euthymia is a middle or equilibrium state between mania and depression.

Studies of structural MRI show that BD patients have a significant reduction in amygdala volume (Rosso, Killgore et al. 2007). Functional and structural connectivity studies, reveal a functional connectivity decrease between amygdala and ACC in BD, and a significant positive association between ACC-amygdala functional coupling and ventrofrontal white matter thickness (Wang, Kalmar et al. 2009).

Recent reports of BD show cognitive and social cognition deficits including attention, memory, executive functions and social cognition (Inoue, Tonooka et al. 2004; Robinson and Ferrier 2006; Lahera, Montes et al. 2008; Jamrozinski, Gruber et al. 2009; Martinez-Aran, Scott et al. 2009; Martino, Strejilevich et al. 2010).

Probably, several social cognition domains affected in BD are related to more basic (facial and emotional) process. For instance, emotional processing information in BD seems to be impaired (Malhi, Ivanovski et al. 2007; Hassel, Almeida et al. 2008; M'Bailara, Demotes-Mainard et al. 2009; Rosen and Rich 2010). Abnormalities in face processing and emotion recognition have been reported in BD patients (Getz, Shear et al. 2003; Malhi, Ivanovski et al. 2007; Wessa and Linke 2009). Furthermore, those deficits in facial emotional expressions have been associated to psychosocial impairments and mania risk in children and adolescents (Brotman, Guyer et al. 2008; Rich, Fromm et al. 2008). Indeed, brain networks involved in facial encoding and emotional processing overlap with fronto-striatal circuit affected in BD (Pavuluri, O'Connor et al. 2007; Kalmar, Wang et al. 2009). In a similar vein, impaired face emotion processing and social cognition would be related to a deficient connectivity between the amygdala and temporally associated cortical regions (Leppanen 2006; Rich, Grimley et al. 2008). Therefore, deficits in emotional processing in BD are observed at a behavioral as well as a neural level (Guyer, McClure et al. 2007). Basic emotional and social impairments would trigger a vulnerable cognitive profile toward mood regulation and interpersonal behavior deficits (Scott and Pope 2003).

ADHD is a neuropsychiatric condition with onset in childhood that extends over adolescent and adult life with a considerable symptomatic burden and functional impairment. Its medical profile includes problems of self-regulation and self-motivation, distractibility, procrastination, and prioritization. A

recent meta-analysis suggested that the prevalence of adult ADHD, even using higher figures (2.5%), is underestimated (Simon et al., 2009).

ADHD in childhood is more related to hyperactivity and impulsiveness, whereas in adulthood it presents a different profile, with fewer externalizing symptoms and a higher rate of psychiatric comorbidity (Klassen et al., 2010). Nevertheless, deficits in executive functioning have been consistently demonstrated in adults with ADHD (Adler, 2010), as well as impairments on executive function tasks with high working memory demands (Torralva et al., 2010).

Adults with ADHD exhibit a diminished gray matter volume in the ACC and prefrontal cortex, measured by voxel based morphometry MRI (Amico, Stauber et al. 2011). They also present a diminished white matter volume in the ACC measured by DTI (Makris, Buka et al. 2008) as well as cortical thinning in the ACC (Makris, Biederman et al. 2007). Two high resolution MRI studies showed a diminished volume of the amygdala in ADHD patients (Frodl, Stauber et al. 2010; Posner, Nagel et al. 2011)

Although deficits in social cognition are an evident clinical phenomena in ADHD, very little research has been developed in this area (Uekermann et al., 2010). A few reports suggest various deficits in domains such as facial affect recognition (Marsh & Blair, 2008; Pelc et al., 2006; Sinzig et al., 2008), prosody perception (Shapiro et al., 1993), theory of mind (**ToM**; Buitelaar et al., 1999; Sodian et al., 2003; but see Charman et al., 2001 for different results), social skills (King et al., 2009; Matthys et al., 1999) and empathy (Braaten & Rosen, 2000; Dyck et al., 2001). Facial emotion processing seems to be the social cognition process that is most affected in ADHD (Marsh & Williams, 2006). In general terms, these social cognition impairments are consistent with fronto-striatal dysfunction in ADHD (Uekermann et al., 2010a), showing the central nature of social dysfunction in this disorder (Hoza et al., 2000; Maedgen & Carlson, 2000; Wheeler and Carlson, 1994).

Hypothesis

H1) A cortical electrophysiological marker of the processing of facial emotion (N170) is associated with individual differences in complex social cognition skills.

I propose that individual social cognition complex skills that are mediated in part by an extense network including the amygdala will be associated to the modulation of rapid electrophysiological markers of facial emotion, given the strong interaction of visual and facial areas with the amygdala and other social cognition areas.

The theoretical framework of Hypothesis 1 is an intense current debate in social neuroscience about the modularity of some social cognition process. An idea dear to evolutionary psychologists argues that humans suffered selection pressures to evolve social abilities or "modules" of cognition (e.g. the cognitive niche) (Pinker 2010). These structures are specialized for processing social information. The inspiring example of such view is, precisely, facial processing. But these concepts are continuously under debate thanks to the discovery of a disperse and patchy network that activates during face perception (Haxby, Hoffman et al. 2000). Hypothesis 1 is oriented to test the extent to which a rapid cortical signal that indexes face processing is dependent or embedded in a sparse network that support high level social cognition (e.g. ToM).

Three lines of evidence support an association between facial processing and higher-order social cognition skills: studies of (1) healthy participants (Herzmann, Kunina et al. 2010; Hileman, Henderson et al. 2011); (2) participants with autism spectrum disorders (ASD) (Barton, Hefter et al. 2007; Clark, Winkielman et al. 2008; Dziobek, Bahnemann et al. 2010; Kleinhans, Richards et al. 2011; Suzuki, Sugihara et al. 2011); and (3) participants with frontotemporal dementia (FTD) (Fernandez-Duque and Black 2005). All these studies suggest that facial processing is required and related to different high level social cognition skills. However, a possible association between cortical markers of facial processing and neuropsychological social cognition has not been proposed yet.

It is therefore expected that N170 would be associated with neuropsychological performance in social cognition tests. First, N170 would be associated with social cognition, as measured by a test such as the ToM, with any emotional modulation of N170 being directly related to the reading the mind in the eyes test [RMET] (i.e., a theory of mind abilities' evaluation by making emotional inferences from faces (Stone, Baron-Cohen et al. 1998; Barton, Hefter et al. 2007; Parr, Waller et al. 2008; Ahmed and Stephen Miller 2010)) because mental inference is determined by facial emotional content. Second,

the Faux pas test [FPT], another ToM task, would be mediated by executive functions. This is expected because the Faux pas test involves dealing with a high number of cognitive and affective components, including inferences about others' mental states and contextual cues (Riveros, Manes et al. 2010). Consequently, FPT should be related to more complex N170 processing. Third and finally, decision making assessments, using the Iowa Gambling Task [IGT] (especially the first of five blocks), would be associated with cortical emotional processing. Because the first block of the IGT can be consistently associated with ambiguity and influenced by emotion heuristics (Dunn, Dalgleish et al. 2006), it is expected the existence of an association between the N170 emotional discrimination level and the emotion heuristics during first stages IGT performance.

The association between facial emotional valence discrimination and social cognition skills can be explored by testing for correlations between these measures (i.e., emotional modulation index and stimulus type discrimination). Our prediction is that higher performance on the tasks of social cognition would be related to greater discrimination of facial emotional valence and stimulus type as shown by the amplitude of the N170 component. Additionally, we examined the associations between the processing of facial emotion and other neuropsychological abilities, such as general neuropsychological functioning (i.e., classical measures of IQ, memory and attention) and executive functioning. Our second prediction was that higher performance on tasks of executive function would be associated with greater discrimination of emotional valence as shown by the amplitude of the N170 in response to simultaneous (face/word) stimuli.

H2a) BD patients present cortical deficits in processing emotional facial information.
H2b) These deficiencies are associated with *clinical* measures (indices of mania and depression).

As I have already mentioned, BD patients present abnormal volume and connectivity of the amygdala. Given that the amygdala is strongly connected to facial and early visual areas, it is expected that the cortical processing of facial emotions measured by the N170 will be impaired (Hypothesis 2a). Because the severity of BD symptoms may be associated with amygdala abnormal volume and thickness, and given that facial emotional processing relies on this area, it is proposed that individual facial processing measured by the N170 potential modulation will be associated with clinical measures of mania and depression.

N170 studies of structural and emotional processing in BD are scarce. An ERP design of emotional face processing in depressed BD type I has been reported (Degabriele, Lagopoulos et al. 2011). In this study a paradigm of emotional inhibition on presentation of faces, modifying the classic test

emotional go/no-go, is used. Results showed abnormal P100 emotional processing and reduced N170 in BD patients. Nevertheless, no previous studies of structural and emotional face/word processing and their relation to neurocognitive profile in euthymic BD has been reported yet.

H3a) ADHD patients present cortical deficits in processing emotional facial information.
H3b) These deficiencies are associated with executive functioning scores

It has been previously shown that ADHD patients present deficiencies in frontal functioning and in some social cognition tasks. Furthermore, ADHD deficit is accompanied by prefrontal and ACC neuroanatomical deficiencies. As it was mentioned, prefrontal cortex and ACC play a regulatory role in emotional perception. Thus, these network and function deficiencies may be reflected at the cortical level in rapid processing of faces. Additionally, neuropsychological testing of executive functions, an estimate of frontal functioning, may correlate with the degree of deficiency in cortical processing estimated at the N170 potential.
It has been shown that adults with ADHD have impaired social cognition. However, no studies have focused on the brain correlates of the adult ADHD deficits in emotion processing.

An approach which combines measures from neuropsychological and neurophysiologic markers represents a valuable tool to understand abnormal cognitive processing in neuropsychiatry and individual differences. This section seeks to identify behavioral, neuropsychological and electrophysiological possible markers of abnormal emotion processing for faces in adult ADHD compared with controls matched by age, gender, educational level and handedness.

Only a single study has previously assessed facial processing in ADHD indexed by the N170, but included only adolescents. Williams et al (Williams, Hermens et al. 2008) reported an abnormal emotion-related N170, suggesting that the structural facial processing stage is affected in adolescents with ADHD. However, these results must be taken with caution because participants with ADHD also had comorbid depression and anxiety. For adults with ADHD, even though evidence of deficits in the processing of emotion have been reported (Herrmann et al., 2009), no N170 valence effects elicited by facial processing have been previously assessed.

H4a) BD and ADHD patients have cortical deficits in the processing of monetary reward.
H4b) The altered modulation of monetary reward processing in both patients correlate with executive functions performance.

Decision-making is essential in our daily lives. We make many different decisions; some are based on risk and predictability, whereas others are based on uncertainty or emotional heuristics. Current neuroscience research examining decision-making has assessed multiple processes engaged in this complex cognitive ability. Evidence from animals, healthy human volunteers and neuropsychiatric patients highlight the role of the frontostriatal and limbic loops in this process (Glimcher and Rustichini 2004; Bechara and Van Der Linden 2005; Brand, Labudda et al. 2006; Rangel 2008; Rangel, Camerer et al. 2008; Rushworth and Behrens 2008; Kable and Glimcher 2009; Gleichgerrcht, Ibanez et al. 2010). Despite some discrepancies among different decision-making models, three systems are thought to be involved in the frontostriatal and limbic loop: stimulus encoding (i.e., the orbitofrontal cortex), reward-based action selection and monitoring (i.e., the cingulate cortex) and expected reward (i.e., the basal ganglia and amygdala). Thus, impaired decision-making may be the result of different deficits in these (or other) brain areas and may be affected differentially by disparate scenarios. Consequently, the nature of these decision-making deficits is dependent on context and disease.

In this thesis we explore the role of the decision making network in rapid cortical responses to monetary reward. First, we postulate that two psychiatric disorders that present an altered frontal network will show an impaired modulation of early components in response to monetary reward. Second, we predict that this impairment will correlate with their executive functions, measured by neuropsychological tests.

Bipolar disorder (BD) and attention-deficit/hyperactivity disorder (ADHD) usually manifest shared clinical symptoms, present high rates of comorbidity and are challenging to differentiate from each other (Wingo and Ghaemi 2007; Chang 2010; Klassen, Katzman et al. 2010). These disorders affect people by presenting problems in common decision scenarios that have social and vocational effects. Decision-making impairments have been reported in patients with ADHD (Ernst, Kimes et al. 2003; Luman, Sergeant et al. 2010; Schepman, Weyandt et al. 2010) and those with BD (Christodoulou, Lewis et al. 2006; Jollant, Guillaume et al. 2007). Nevertheless, previous decision-making studies using neuropsychology methods have shown inconsistent results for both disorders. In addition, no previous report has assessed a decision-making task that includes the examination of the neural correlates of reward and gambling in adults with ADHD and those with BD. Finally, no study has compared these disorders regarding decision-making domains yet.

General Methods

A main challenge of the present project is the use of techniques coming from clearly different historical scientific traditions. A broad classification of these methodologies may be reduced to three sets: psychophysics, electroencephalography and neuropsychology. In the next paragraphs, the reader will find a brief introduction to each method.

Psychophysics

What and when: Response type and response time.

Psychophysics is one of the most ancient techniques of experimental psychology. A classical definition state that psychophysics is the analysis of perceptual processes by studying the effect on a subject's experience or behavior of systematically varying the properties of a stimulus along one or more physical dimensions (Bruce, Green et al. 1996)

It is, in fact, a discipline in which the observable is behavior, that is, the measurements are limited to what an animal or a person does in response to a presented stimulus (in some settings, however, the responses might not be necessarily linked to an external stimuli).

The stimuli are part of a certain task that takes place in a specially designed experimental setting. The stimuli are manipulated by the researcher, who expects to find variations in the responses as a function of stimulus changes. Responses are voluntary motor acts, such as a button press or a vocal sound. Variations in responses given to continuous or discrete stimulus manipulation are described by mathematical functions known as psychometric functions or psychometric curves. Two variables are of interest to psychophysics: Response type and response time. Both give interesting information about stimulus processing. An example will help to describe the methodology and the type of information obtained. Fiorentini and Viviani (Fiorentini and Viviani 2011) showed subjects pictures of an actor, and asked them to respond with a button press if the emotion of the actor was anger or fear (two alternative forced choice). An interesting manipulation was that they created morphing images that represented intermediate states between anger and fear. Figure 6 shows a typical psychometric sigmoid response curve, where a dimension of the stimulus (morphing degree, 1=anger, 50 = fear) is manipulated in a continuous way.

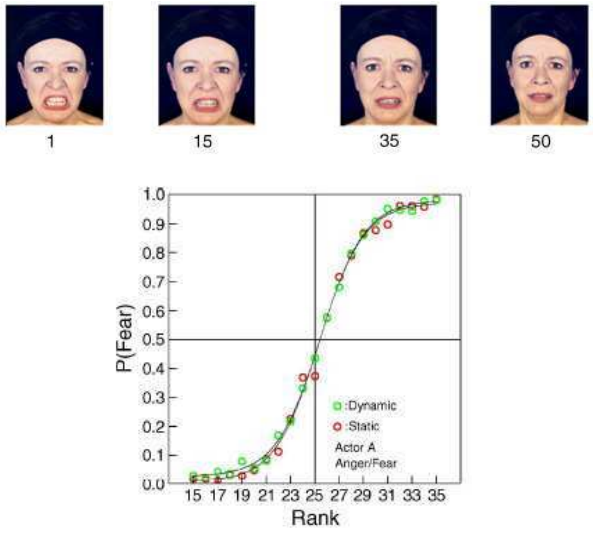

Figure 6. An example of a psychometric curve in response to morphed images between two emotional states. The probability of responding fear as a function of degree of morphing between the 2 images (Anger and Fear) is plotted. Note that only morphed images from 15 to 35 are used, given that more extreme morphs saturated the response (P = 0 or P = 1). (Fiorentini and Viviani 2011).

The obvious limitation of psychophysics is that it does not allow a direct access to the system (e.g. muscle, brain or neuron) and no hypothesis can be directly tested about the mechanisms that are taking place in the substrate. Nevertheless it is of great value to make a first approach or to combine it with physiological methods.

Dual valence task. Our experimental paradigm to estimate the N170 potential in response to faces.

The dual valence task (DVT) was designed to measure behavioral and electroencephalographical responses to facial emotions. It included blocks with emotional faces, blocks with emotional words, and blocks with a simultaneous presentation of emotional faces and words.

Participants were instructed to categorize single (words or faces) or simultaneous (face/word) stimuli that were displayed for 100 ms on a computer screen according to the stimuli's valence, responding as to whether the stimuli were 'positive' or 'negative' as quickly as possible. Incorrect responses were indicated with an 'X' in the center of the screen immediately after the response had been given (see figure 7).

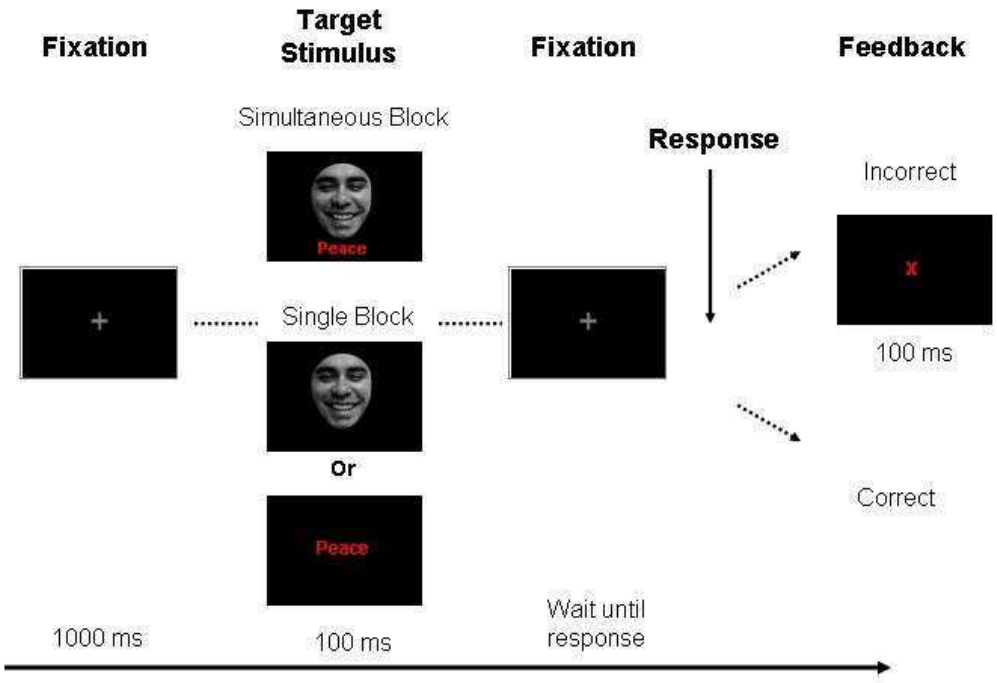

Figure 7. Stimulus design. The trial starts with a fixation cross, followed by a target stimulus: single stimulus face or word, (Single Stimulus Block) or simultaneously presented face and word (Simultaneous Stimuli Block). Feedback was provided only in error trials.

Trial structure. The trial sequence started with a fixation cross that was displayed for 1000 ms, followed by a 100 ms presentation of the stimulus, and finally the presentation of a fixation cross that remained until participants responded (see figure 7). In error-trials, a red cross was presented for 100 ms as feedback. No feedback was provided in trials with correct responses. We used negative feedback to increase the attentional demands of the task and to provide an implicit incentive to give accurate responses (Olson and Fazio 2004; Cody and Teachman 2010; Ibanez, Hurtado et al. 2011). Time between trial completion and onset of the subsequent trial was 1000 ms. The complete task comprised two blocks, each one made up of 320 trials: Single Stimulus Block and Simultaneous Stimuli Block

Single Stimulus Block. Participants were exposed to either a face or a word (with strict alternation between words and faces) displayed in the centre of the screen and they responded accordingly: For faces, they categorized stimuli as either 'angry' or 'happy' and for words they categorized stimuli as either 'pleasant' or 'unpleasant'. See below stimuli construction and validation. The main purpose of including words as single stimulus is compare the response to face stimuli, to examine the degree of discrimination between different stimulus types. Words also provide a stimulus capable of evoke two

emotional states, for design purposes (factorial design). Words also prove to evoke the N170, but no emotional modulation is expected at so early times.

Simultaneous Stimuli Block. Participants were exposed to a face displayed in the centre of the screen with a word displayed 4 degrees beneath it in the lower hemifield. These stimuli were presented simultaneously for 100 ms. Participants were asked to indicate the emotion shown by the face and to ignore the word. In compatible trials the face and a word shared the same valence (e.g. an angry face with the word 'angry'), whereas in incompatible trials they represented opposite valences (e.g. an angry face with a pleasant word). The aim of including words in facial images is to test the interferences of context (in these case words) on stimuli (faces in the center of the screen).

The presentation order of blocks (Single and Simultaneous Stimuli) was counterbalanced across participants. Each block was separated into two sub-blocks of 160 trials. Throughout the experiment, the same two keys were used to indicate responses, but the assignation of key to response type was inverted between sub-blocks. Each sub-block included a brief explanation at the start of which category was assigned to which response key, followed by six practice trials. This procedure follows the designs used in previously published dual-choice association tasks (Hurtado, Haye et al. 2009; Ibanez, Hurtado et al. 2011).

Stimulus construction and validation.

20 pictures of actors' faces were selected from a dataset used in previous studies (Hurtado, Haye et al. 2009). A set of 10 happy and 10 angry pictures, controlled for intensity, brightness, color and contrast, was included. Each actor appeared in two pictures, one of each valence. Pleasant and unpleasant words, controlled for arousal, content, length and frequency, were selected from another previous study (Ibanez, Lopez et al. 2006). 33 pleasant and 32 unpleasant words were randomly selected from the original sets. A greater number of word stimuli were selected relative to the number of faces to reduce the repetition effect of words (Bentin and Peled 1990), a robust modulator of ERPs (Rugg, Mark et al. 1997; Doyle and Rugg 1998). On the contrary, facial ERP modulation can be found with a small number of faces (Maurer, Rossion et al. 2008; Astikainen and Hietanen 2009).

To validate word content, a questionnaire was used to assess pleasantness or unpleasantness of a set of 150 words with a moderate use frequency (Lifcach frequency software). 50 university students, 33 female, mean age 19.62$\pm$ 3.33), participated in the validation (Ibanez, Lopez et al. 2006). Participants rated the set of words using a Likert scale where 1 represented a very positive valence and 7 represented a very negative valence. Repeated measures Analysis of Variance (ANOVA) was used to contrast categorizations for the list of

pleasant and unpleasant words. Significant differences were obtained for the categorization of both lists [$F(1, 73) = 25161$, $p < 0.0001$]. Pleasant words that were ranked between 1 and 3 where selected (72 out of 75 positive words were included). Unpleasant words rated between 5 and 7 were selected (71 from 75 negative words were included).

Decision-making tasks combined with ERPs

Rapid Decision Gambling Task (RDGT).

The RDGT allows us to evaluate the motivational impact of events and the choices that guide behavior (Gehring and Willoughby 2002). Participants viewed two squares, each one containing either the numeral 5 or 25 (possible alternatives). Participants chose one of the squares by pressing a corresponding button on a keyboard. One second after their response, each square turned red (loss) or green (win; see figure 8). If the square turned green, then the amount showed on the square was added to their total amount. If the square turned red, then the amount showed was subtracted from the total. The square not chosen also turned red or green at the same time; thus, participants not only discovered their gain/loss but also discovered what they would have gained/lost. These positive and negative feedback were triggered to obtain ERP waveforms during the EEG recordings. Each experimental session was divided into 24 blocks of 32 trials, and cumulative monetary awards were provided at the end of each block.

We obtained ERPs when these positive and negative feedbacks were triggered; specifically, the feedback error related negativity (fERN) that is modulated by valence (i.e., wins or losses) and the P3 that is modulated by the reward magnitude (i.e., large or small; (Gehring and Willoughby 2002; Yeung and Sanfey 2004).

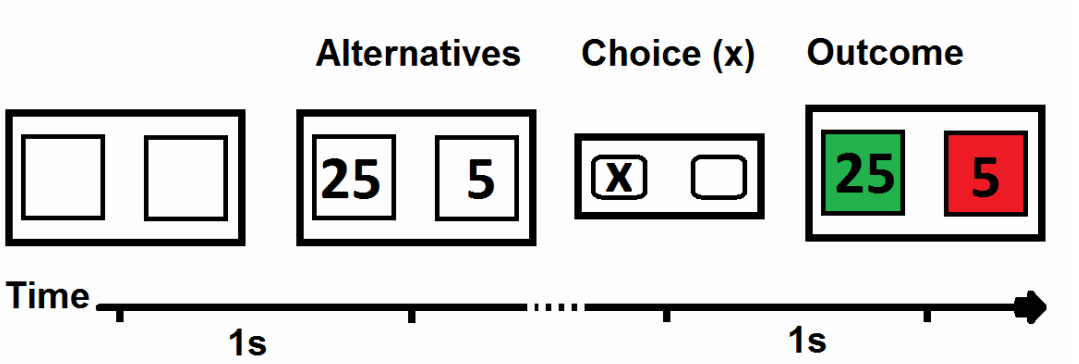

Figure 8. The Rapid-Decision Gambling Task. Participants viewed two squares, containing either a numeral 5 or 25 (Alternatives). After selection one alternative, if the chosen square turned green, then the amount indicated by the chosen numeral (in U.S. cents) was indicated a win added to the total amount. If the chosen stimulus turned red, then the amount indicated was subtracted from the total. As a result, each subject not only discovered if they win or loss, but also what they would have gained or lost had they chosen the other square. In the example, the chosen square turns green, indicating a gain of 25¢. The other square turns red, indicating that the participant would have lost 5¢ if he or she had chosen that square.

EEG

Electroencephalography (EEG) is the recording of electrical activity along the scalp, generated by neuronal activity (see figure 9). It is a technique developed at the end of the nineteenth century, and first applied to humans in the beginning of the twentieth century. Because its relative low cost, EEG is used widespread in everyday clinical diagnosis. It became also a powerful research technique that diversified in the last decades given the rapidly increasing computational power accessible at low cost.

The advantages over other techniques are its low cost, its high temporal resolution (under the millisecond) and its non invasive nature. The main disadvantage of the technique is the relative low spatial resolution. Nevertheless, this limitation has been partially overcome with high density EEGs, and source localization algorithms.

There are two types of analysis of the electroencephalographic signal. The first is continuous or stationary EEG, in which a continuous signal is analyzed. In this case the interest is commonly on the frequency domain (i.e. the change in the power of a typical frequency, say alpha, is used as the experimental variable) and not in the temporal resolution of the signal.

On the other hand, event related potential (ERP) technique, only takes a fraction of the signal time-locked to a stimulus. Now the focus is on the amplitude changes (expressed in microvolts) of the scalp

signal time-related to a stimulus. ERPs technique was developed in the past century, and for years only practiced in a few laboratories. The pioneers of this technique found that certain psychological tasks bring up a well defined signal. ERPs emerged after averaging several trials of the same type (i.e. the same stimulus or the same stimulus category), presenting a singular waveform. They were first identified by its sign and the time of the maximum peak. P300 means a positive potential at 300 milliseconds, N400 a negative potential at 400 milliseconds, and so on. An alternative nomenclature name components according to the relative order of appearance (P1 is the positive signal that first appeared in certain experiments, in this case coincides with P100). A big family of components was described since the early times of ERP technique and replicated in hundreds of laboratories around the world.

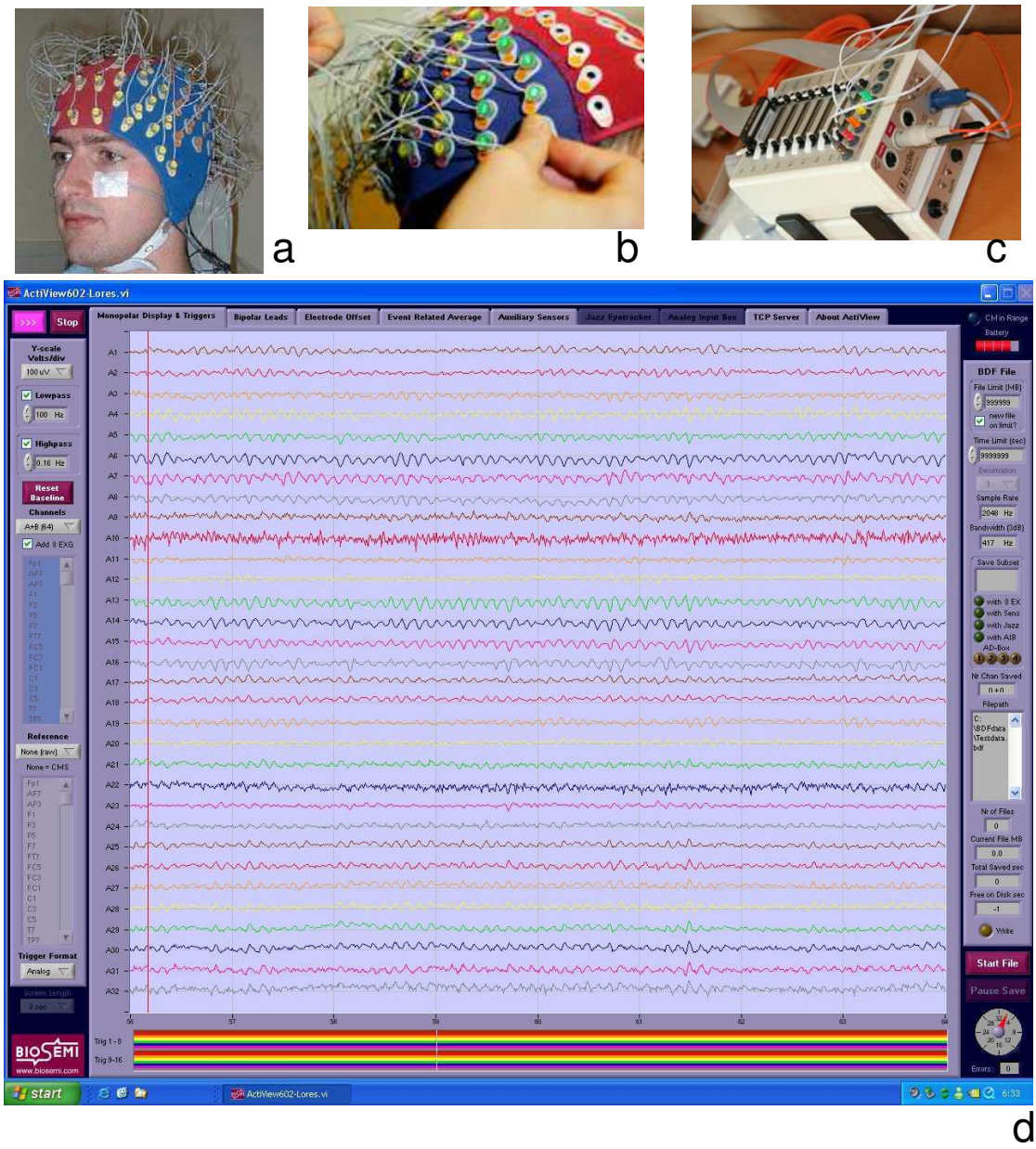

Figure 9. Electroencephalogram. Here are shown some pictures of the Biosemi equipment used in the laboratory. a) Headcap with electrodes. b) Detail of the headcap c) Acquisition box where the electrodes are connected. d) A screen capture of the AcviView software created by Biosemi. Each trace corresponds to one electrode. Each vertical line demarcates a second. Horizontal traces are in 0.1 mV scale.

Measuring brain facial processing in humans: Event related potentials

In this thesis we recorded EEG signals in response to faces with different emotions and, in another experiment, evoked by monetary feedback in a gambling task.

To study facial emotion processing we estimated a classical brain signal referred to as the N170, which shows a negative peak at approximately 140-200 ms post-stimulus, and has been shown to be involved in the processing of faces (Rossion and Jacques 2008). It is also present, although with a lesser amplitude, when humans are exposed to familiar objects, such as houses, trees and cars.

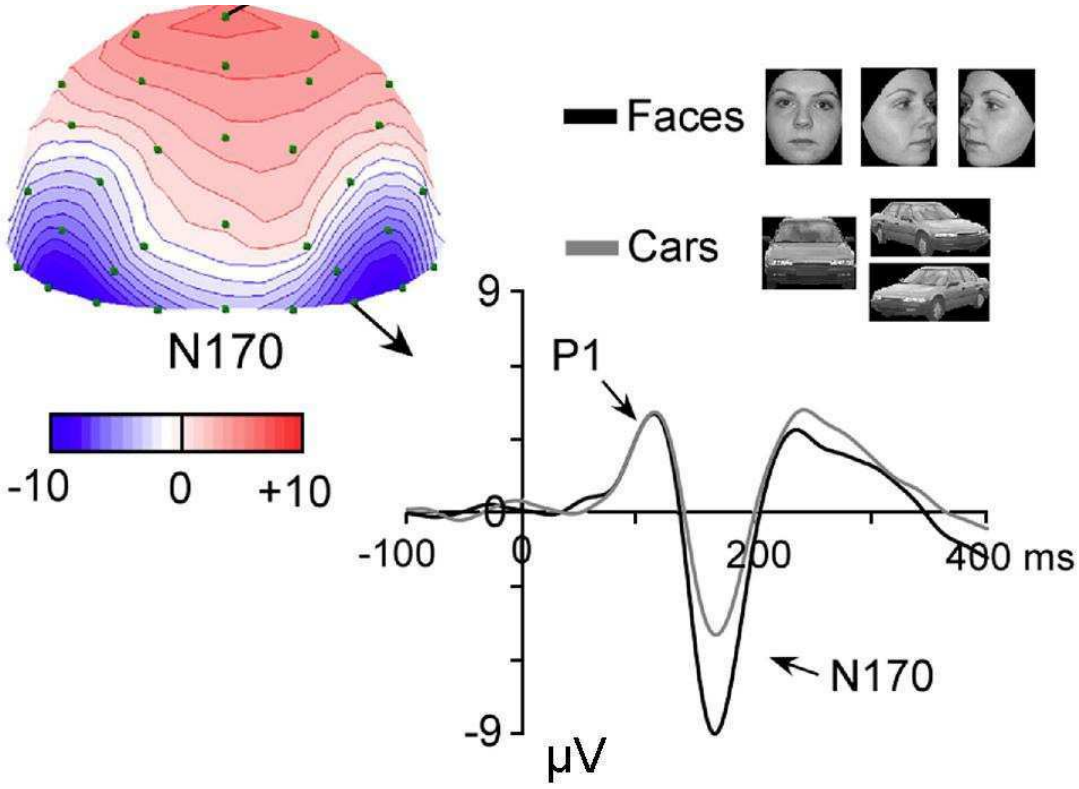

Figure 10. The N170 is a negative component recorded from posterior lateral electrode sites following the presentation of faces and object categories (here pictures of cars). It peaks at about 160–170 ms following stimulus onset and is recorded between 130 ms and 200 ms. It is most prominent at the lowest occipito-temporal electrode sites. The component is larger in response to faces than objects in both hemispheres, with usually a larger response in the right hemisphere. Taken from (Rossion and Jacques 2008).

The N170 component is sensitive to stimulus type (facial or other, see figure 10) (Rossion, Gauthier et al. 2002; Goffaux, Gauthier et al. 2003; Itier and Taylor 2004; Rousselet, Mace et al. 2004; Thierry, Pegna et al. 2006; Churches, Baron-Cohen et al. 2009; Ibanez, Gleichgerrcht et al. 2010). The N170 is affected by emotional valence (Eimer and Holmes 2002; Pizzagalli, Lehmann et al. 2002; Batty and Taylor 2003; Ashley, Vuilleumier et al. 2004; Galli, Feurra et al. 2006; Sprengelmeyer and Jentzsch 2006; Blau, Maurer et al. 2007; Hendriks, van Boxtel et al. 2007; Vuilleumier and Pourtois 2007; Montalan, Caharel et al. 2008; Chammat, Foucher et al. 2010). Moreover, the N170 amplitude can be modulated by interference (e.g., two opposite valence stimuli classifications). In particular, it is

sensitive to the compatibility between the stimulus and background, indicating that it may reflect an interaction between executive functioning and emotional processing (Galli, Feurra et al. 2006; Righart and de Gelder 2006; Righart and de Gelder 2008; Fruhholz, Fehr et al. 2009; Gonzalez-Garrido, Ramos-Loyo et al. 2009). Studies of brain topography have localized the cortical source of the N170 in the fusiform gyrus (FG) (Itier and Taylor 2004; Sadeh, Podlipsky et al. 2010). In summary, the N170 component can be considered as a neural marker of early face-selective processing that is modulated by affective valence and contextual cues.

We used an ERP design of a dual valence task (DVT) to study the ERP stimulus and emotional discrimination in healthy participants and psychiatric patients. In the DVT, faces, words or simultaneous face-word stimuli are presented. Participants are asked to classify the stimuli according to their emotional valence. The modulation of the N170 by three factors (stimulus type, valence and interference) was quantified.

Measuring brain feedback processing in humans: Event related potentials

To study monetary reward processing in a gambling task a potential called feedback error related negativity (fERN) was estimated. A robust error related negativity (ERN) component is observed after errors are committed during various choice tasks, even when the participant is not explicitly aware of it. An event-related potential is also observed following the presentation of negative feedback stimuli in a cognitive task indicating the outcome of a response, often called the fERN. fERN is a product of prediction error signals carried by the dopamine system arriving to the anterior cingulate cortex indicating that events have gone worse than expected (Holroyd and Coles 2002)

We recorded event-related potentials (ERPs) from human participants as they performed the RDGT. Participant choices were followed by feedback that indicated the monetary gains or losses that resulted. The RDGT elicits a feedback error-related negativity (fERN) modulated by reward valence and a P3 sensitive to reward magnitude (Gehring and Willoughby 2002; Yeung and Sanfey 2004).

ERP recordings.

In all the experiments presented in this thesis, EEG signals were sampled at 500 Hz from a Biosemi 128-channel system. Data outside the frequency band, which ranged from 0.1 Hz to 100 Hz, were filtered out during recording. A band-pass digital filter (below 0.3 Hz and over 30 Hz) was applied off-line to remove unwanted frequency components. During recording, the reference was set by default using linked mastoids but it was then re-referenced off-line to average electrodes. Two bipolar derivations were designed to monitor vertical and horizontal ocular movements (EOG). Continuous EEG data were segmented from 200 ms prior to the stimulus to 800 ms after stimulus onset. All segments with eye movement contamination were removed from further analysis using an automatic procedure (Gratton, Coles et al. 1983) and a visual procedure. Artifact-free segments were averaged to obtain ERPs.

N170 Source Localization.

Dipole source models of the N170 component for each condition were estimated using an Automatic Relevance Determination (ARD) algorithm. Source estimation from EEG data can be problematic but the use of ARD resolves this by regularizing the solution space using a parameterized data-dependent prior distribution. A special type of ARD was used, known as Bayesian Learning (SBL) (Wipf and Nagarajan 2009). An Average Lead Field was used as the head model, built from a sample of 305 MRIs of typical participants. Possible solutions were constrained for location to the cortical surface but were not constrained for orientation. This head model is useful for source localization when individual MRI data are not available (Valdes-Hernandez, von Ellenrieder et al. 2009). Given that temporal differences occur between participants and stimulus types, the local minimum within the N170 window was considered for each of them. First, the average signal for the N170 representative electrodes A9, A10, A11, A12 (left) and B6, B7, B8, B9 (right) was obtained, from within a 167-229 ms time window for faces and simultaneous stimuli, and from within a 182-284 ms time window for word stimuli. Next, data from a time window of 55 ms (7 samples at 128Hz) centered on the local minimum of this average was extracted for each participant and for all electrodes (128 channels). Extracted data from all participants was stored in a separate matrix for each stimulus type. A diagonal matrix of 0.25 μV^2 was used as a prior estimate of the matrix of noise covariance. Finally, sources were localized using the noise matrix, the data matrix and the lead field matrix with the ARD algorithm. In this manner, dipoles for faces, simultaneous stimuli, and words were obtained separately. To visually represent the dipoles, the cortex was coregistered with the average image provided by the Montreal Neurological Institute, ICBM-152. For simplicity, only the dipole magnitude during the time window is shown.

N170 Data analysis.

Matlab software and EEGLab toolbox were used for off-line processing and analysis of EEG data. Regions of interest (ROIs) were used to analyze the scalp topography of the ERP components (Oken and Chiappa 1986), which is recommended for dense arrays since it improves statistical power. Following the analysis used in previous studies, each N170 ROI (left and right) consisted of four electrodes around T8 and T7 and lateral posterior sites (Rossion and Jacques 2008): the N170 ROIs were A9, A10, A11 and A12 for the left and B6, B7, B8 and B9 for the right hemisphere. Consistently, those electrodes showed maximal activity, as shown by inspection of the topographical maps. For ERP analysis, the 160-220 ms time window for N170 was visually selected for mean amplitude analysis. Although signal plots show the overall averages of ERPs for each data cell, statistical tests were performed separately on data for each participant using R software (http://www.r-project.org).

Accuracy, reaction times (RTs) and ERPs waveforms were separately averaged for faces, words and simultaneous stimuli and analyzed using a repeated measures ANOVA with the following within-subject factors: 'stimulus type' (two levels: 'faces', 'words') and 'valence' (two levels: 'positive' or 'negative'). In addition, for the simultaneous stimuli, the valence factor was analyzed and 'compatibility' was considered as an additional factor, at two levels: 'compatible' (positive face plus positive word or negative face plus negative word) and 'incompatible' (negative face plus positive word or positive face plus negative word). Finally, for ERPs data, the factor 'hemisphere' was considered (two levels: 'left' and 'right'). For all post hoc comparisons, Tuckey's HSD test was performed.

To obtain correlations between ERPs and neuropsychological performance, N170 global scores of valence, interference and stimulus-type discrimination were calculated for accuracy, RTs and ERPs results. Global scores were tested for correlations with all of the neuropsychological tests (general neuropsychology, social cognition and executive functioning) using Spearman's rank, corrected for multiple comparisons using Tuckey's HSD test. A significance level of $p < 0.05$ was used for all reported results.

Global Scores of accuracy, RT and ERPs.

In order to obtain correlations between ERPs and neuropsychological performance, global scores were calculated for accuracy, RT and ERP results, as follows.

1) Stimulus discrimination: For the discrimination, face and word stimuli responses were used. The

difference between the two was calculated by subtracting the scores for word stimuli from those for face stimuli (face-word). To estimate the interference of words on faces, the difference between face and simultaneous stimuli was calculated by subtracting the scores for simultaneous scores from those for face stimuli (face-simultaneous).
2) Valence discrimination: these indices were calculated by subtracting the results for positive stimuli from those for negative stimuli (negative-positive).
3) Compatibility: For the simultaneous stimuli data, the difference was calculated between results from the compatible condition (e.g. positive face with positive word) and the incompatible condition (e.g. negative face with positive word) by subtracting one from the other (compatible-incompatible).
4) In addition, overall accuracy and overall RT were included as global scores.

fERN and P3 recordings. Source estimation.

Source modeling. Rather than using a single dipole model (e.g., ACC), we estimated the cortical current density mapping of fERN/P3 using a distributed model of 10000 current dipoles. Finally, we reported the activation of the cingulate cortex (anterior, medial and posterior sections) the valence (wins minus losses) at fERN, and the magnitude (large minus small) at P3.

Orientation and dipole locations were fit to the Montreal Neurological Institute's standard brain model. Next, they were adapted to the standard geometry of the EEG sensor net (BrainSuite software). All subsequent processing (i.e., source analysis and visualization) was obtained using BrainStorm software (http://neuroimage.usc.edu/brainstorm/). An extension of the overlapping-spheres analytical model computed EEG forward modeling. EEG data using dynamic statistical parametric maps (dSPM) estimated cortical current maps based on the weighted minimum-norm current estimate (wMNE). We computed an activation threshold from signal baseline.
We separately analyzed ROIs at the anterior, medial and posterior cingulate cortex (aCC, mCC and pCC, respectively) in both hemispheres using a Tzourio-Mazoyer partition (Tzourio-Mazoyer, Landeau et al. 2002). Evoked responses in each ROI were indexed as the absolute power of all current sources for each ROI. Next, we reported the mean values of the three ROIs for valence (wins minus losses) at the fERN latency and magnitude (large minus small) at the P3 latency (see Figure 24B; grey shadows).

Neuropsychology

Neuropsychology is a discipline that uses structured tests and questionnaires (neuropsychological tests) that measure human cognitive functions, usually designed to understand its relation with a specific brain function in healthy subjects. It was developed after the First World War, and some of its tests are nowadays standards, routinely used in the laboratory. They usually involve the systematic administration of clearly defined procedures, typically administered to a single person working with an examiner in a quiet formal environment, free from distractions. Some famous neuropsychological tests are: the Wechsler Adult Memory Scale (WMS), the Wechsler Adult Intelligence Scale (WAIS), and the Wechsler Intelligence Scale for Children (WISC).
Clinical neuropsychology is the application of neuropsychological techniques to the assessment, management, and rehabilitation of people who have suffered illness or injury (particularly to the brain), which has caused cognitive impairments. Clinical neuropsychology is an important complementary tool to diagnose mental deficit or illness. Some of them have been specially designed to diagnose a specific disorder as is the case for autism or ADHD. Most of these tests are standardized, meaning that they have been administered to a large group of healthy individuals before being used in clinical cases.

Neuropsychological tests. *General Neuropsychology*

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Memory. Rey Verbal List Test (RVLT) (Rey 1958).

The standard RVLT starts with a list of 15 words, which an examiner reads aloud at the rate of one per second. The patient is asked to repeat all the words he or she can remember, in any order (Immediate Recall). This procedure is carried out a total of five times. Then the examiner presents a second list of 15 words, allowing the patient only one attempt at recall. Immediately following this, the patient is asked to remember as many words as possible from the first list (Delayed Recall). After an interval of 20 minutes, the examiner reads a list of 50 words, and the patient is asked to tell which of the words was in the firs list (Recognition).

Arithmetic Test (Wechsler 1997).

The arithmetic test is a subtest of the WAIS III. It consists of 20 questions asked in the form of arithmetic problems. Subjects have a time limit to answer. The test ends when two consecutives

incorrect responses are given. The level of difficulty is increased from question to question. The arithmetic test requires attentional resources and working memory. It assesses the level of concentration and arithmetic reasoning.

Neuropsychological tests. Executive Functioning.

To assess participants' executive functioning, a set of several tests were performed. The 'INECO Frontal Screening' test (IFS) (Torralva, Roca et al. 2009) assesses frontal lobe functioning. The IFS yields a global score that is based on several subtasks: 'motor programming', 'conflicting instructions', 'verbal inhibitory control', 'proverb interpretation', 'backwards digit span' and 'spatial working memory'. 'Backward Digit Span' (Wechsler 1997) and the 'Trail Making Test B' (TMT B) (Partington 1949) were used to assess attentional flexibility, sequencing and planning skills. The 'Forward Digit Span' test (Wechsler 1997) was used to assess Working Memory.

The IFS is a brief screening tool based on the extensive clinical experience of INECO staff in their work with patients with executive dysfunction. The IFS incorporates classical subtests designated to assess executive functioning. It presents very good internal consistency and correlates significantly with classical tests of executive function. Its administration takes less than 10 minutes to complete, providing a clear profile of executive functioning.

Digit Span (Wechsler 1997).

It consists of two tasks administered independently. In Forward Digit Span, the subject repeats numbers in the same order as read aloud by the examiner. For Backward Digit Span, the subject repeats numbers in reverse order of that presented aloud by the examiner. The length of the list increases one digit per trial. It is a useful measure to estimate concentration, attention, immediate recall and working memory.

Trail Making Test (TMT) (Partington 1949).

This test requires participants to connect a series of circles with a pen (figure 11). In Part A, the circles are numbered from 1 to 25, and participants must connect them in order. Part B contains circles numbered from 1 to 13 and circles lettered from A to L, and participants must connect the circles in order by alternating from numbers to letters (i.e., 1-A-2-B-3-C, etc.). The scores for both

Part A and B are the total amounts of time required to complete the sequence. Part B has been found to be sensitive to frontal lobe damage (Stuss, Bisschop et al. 2001).

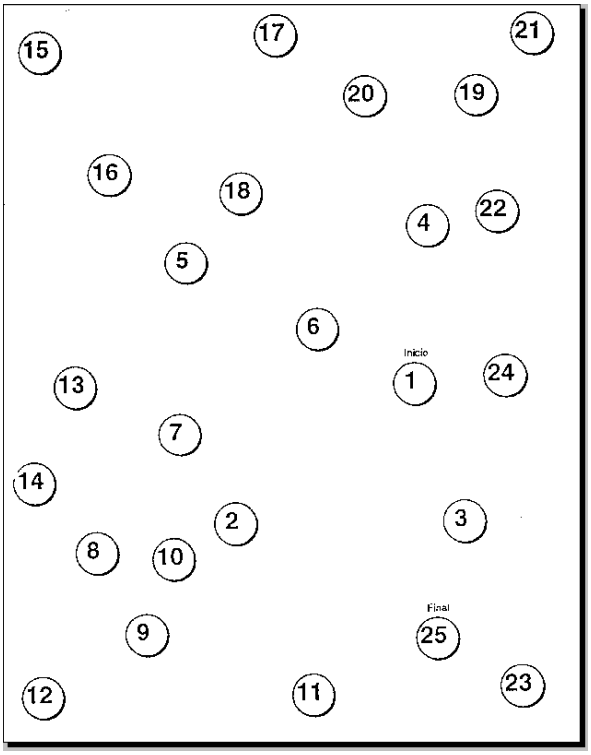

Figure 11. Trial Making Test. part A. Participants connect the numbered circles drawing with a pen. In part B circles have to be connected alternating numbers and letters (1, A, 2, B, etc).

Neuropsychological tests. Social cognition.

Three tests of social cognition were used. First, the computerized version of the 'Iowa Gambling Task' (IGT) (Bechara, Damasio et al. 1997) was included. This task involves the selection of four cards under the condition of uncertainty. It simulates real-life decision making. Second, the 'Reading the Mind in the Eyes' test (Baron-Cohen, Wheelwright et al. 2001; Baron-Cohen and Wheelwright 2004) was included. This task consists of 36 photographs of the eye-region of the face, each of a different person. Participants are required to choose which one of four words best describes what the person in the photograph is thinking or feeling. Third, the 'Faux Pas' test (Stone, Baron-Cohen et al. 1998; Baron-Cohen, O'Riordan et al. 1999; Richell, Mitchell et al. 2003) was included. In this task, participants are asked to discern whether a *faux pas* is present in each of 20 stories. After each story, participants are asked whether something inappropriate was said. If they respond that it was, they are asked to explain why it was inappropriate. It is a test high level theory of mind skills.

Reading the Mind in the Eyes (Baron-Cohen, Wheelwright et al. 2001; Baron-Cohen and Wheelwright 2004)

In this standardized multiple-choice test participants are shown 36 black-and-white photos of the eye region of different persons. Subjects are asked to choose which of four words best describes what the person in the photograph is thinking or feeling (e.g., “terrified,” “upset,” “arrogant,” and “annoyed”; see figure 12) . The individual in each photo displays a particular emotional or cognitive state. This task depends in part of Theory of Mind, the ability to attribute mental states
beliefs, intents, desires, pretending, knowledge to oneself and others and to understand that others have beliefs, desires and intentions that are different from one's own.

Figure 12. Reading the mind in the eyes test. In each trial, one face is shown with four words in the corners. Subjects have to choose the word that best describe what the person in the photograph is thinking or feeling.

Faux Pas Test (Stone, Baron-Cohen et al. 1998; Baron-Cohen, O'Riordan et al. 1999; Richell, Mitchell et al. 2003)

In this test the subject is read a story where one of the characters says something that may or may not contain something that it would be better not to say; that is, a social faux pas. Subjects are exposed to ten stories with a faux pas and ten stories without a faux pas. After each story, the subject is asked whether something inappropriate was said. An additional control question is included to evaluate if

the participant understand the story. The number of faux pas correctly identified or rejected were recorded. A composite score was calculated which included the sum of the correctly identified (hits) and correctly rejected faux pas (rejects). This test is sensitive to medial frontal lesions, because involves some executive components (Stone, Baron-Cohen et al. 1998). This test also depends on ToM.

An interesting paragraph taken from Rebecca Saxe will help to define ToM:

"Young children and apes selectively attend to faces, bodies and actions, and understand basic mental states such as goals and perceptions. However, they do not distinguish between the object of a mental state (what a person's mental state is about, the state of affairs to which the belief or perception refers) and the content (how that state of the affairs is represented, what the person believes or perceives to be true of it). Command of this distinction enables older children to understand how people's mental representations of the world might differ from the way the world really is. As a result, this later developing, uniquely human component of social cognition is called a 'representational Theory of Mind'."

Rebecca Saxe. Uniquely human social cognition (2006).

Iowa Gambling Task (IGT)

The computerized version of the IGT involves continuous card selections from four separate decks (A, B, C and D) and is complete after 100 selections. Each card choice is awarded a certain number of points, but some choices yield penalties (see figure 13). Card choices from Decks A and B ("high risk") generate large wins (e. G. $100) but also heavy losses that may lead to an overall debt. Decks C and D ("low risk") generate smaller wins (e. G. $50 per choice) but also smaller penalties. Persistent selections from these decks yield a profit. The dependent variable of this task is the net score, which is calculated by subtracting the number of choices from the high-risk decks (A+B) from the choices from the low-risk decks (C + D). To quantify the change in decision-making across the course of the task, it is divided in 5 blocks, each with 20 consecutive card choices (Bechara, Damasio et al. 1994). In addition,

we compared participants' net score on the first (1+2) and last (4+5) blocks. IGT is sensitive to ventromedial prefrontal cortex lesions (Bechara, Damasio et al. 1994).

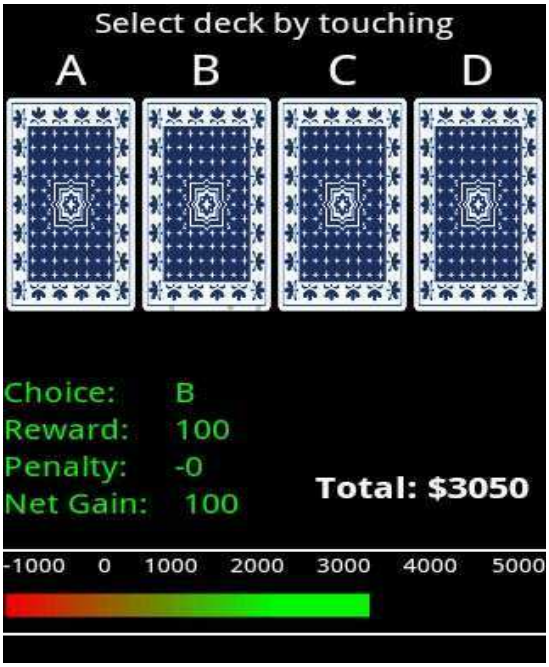

Figure 13. Iowa gambling Task. Participants have to choose cards from any deck. Each time the subject choose a deck, the program showed how much money they gain (or loose) for that card and the total amount of money they have. The rule that subjects have lo learn is that two decks give big gains but also big loses, and in average are less convenient that the other two decks (small gains and small loses, but in average more net gain).

The Rapid Decision Making Under Risk (RDMUR) Task.

We designed a simplified computer gambling task based on a modified version of blackjack (Slovic 1966; Fernandez-Duque 2007). At the beginning of the task, participants read the following instructions on screen: "*In this deck, there are 10 cards. Nine cards are "good," and one is "bad". You will win one dollar for each good card you draw; however, if you draw the bad card, then you will lose everything, and the game will end. You will keep whatever money you win, so try to play as well as possible. Choose one card at a time by clicking on it.*" Participants are told that the Joker is the bad card and that it is randomly placed within the set of ten cards. Finally, participants are asked to play only once but could stop at any time to collect their prize. The task ended when participants stopped or drew the bad card. Using a mouse, participants could either select a face down card or stop the game by clicking the "check-out" box. Participants are unaware that any of the first 8 choices led to wins; in other words, the bad card was always the ninth card (Fernandez-Duque 2007). Because the

expected value in this task is the highest after turning five cards (Slovic 1966), rational decision makers should stop after turning the fifth card.

For those tests for which they were available, standardized norms were used. Otherwise, scores were compared with published data from healthy participants. Scores on the 'Digit Repetition', 'Digit Span' and 'Arithmetic' tests were compared with the standardized scores for the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler 1997). RVLT scores were compared with Schmidt's data (Schmidt 1996). TMT scores were compared with data from Torralva (Torralva, Gleichgerrcht et al. 2010). Scores on the IFS, 'Faux Pas' and 'Reading the Mind in the Eyes' tests were compared with data published by Torralva (Torralva, Roca et al. 2009). Scores on the IGT were compared with Bechara's results (Bechara, Damasio et al. 1997) .

Rapid face perception interacts with a complex system of emotional processing and social behavior

The results are structured in three sections, each corresponding to an independent experiment. Each section in turn is organized as follows: 1) The hypothesis which justifies and motivates the experiment, 2) Specific Methods for the particular experiment and 3) Description of the results and brief summary of the main observations.

Chapter I

The cortical potential N170 is consistently associated with emotion, social cognition and executive functions.

Section I

H1) A cortical electrophysiological marker of the processing of facial emotion (N170) is associated with individual differences in complex social cognition skills.

This section has been done in collaboration with the following colleagues: Andrés Canales-Johnson, Hugo Urquina, Raphael Guex, Esteban Hurtado, Alejandro Blenkmann, Nicolás von Ellenrieder, Facundo Manes and Agustin Ibañez, under the supervision of Professor Mariano Sigman.

SPECIFIC MATERIALS AND METHODS FOR THIS EXPERIMENT

A major part of the results on the first section are, in a way, control experiments. This means a validation of the paradigm, to measure a clear neural signal, that this signal is modulated by the experimental factors in the expected trend, and that the neural sources are in correspondence with that measured by other experimenters.
In this section, healthy subjects completed the DVT while EEG recorded its scalp activity. Psychophysical (performance and RT) and ERP (N170 modulation by facial emotion) results of the DVT were correlated with three types of neuropsychological tests: general neuropsychology, executive functions and social cognition.

Participants

Twenty healthy participants, six females (30.9$\pm$2.3 years old, with 16.6$\pm$0.6 years of formal

education) completed the DVT. In a subsequent session the participants had voluntarily completed a neuropsychological battery that comprised tests of general neuropsychological functioning, executive functioning and social cognition. A questionnaire was administered to all participants to rule out hearing, visual, psychiatric or neurological deficits. The N170 component has been reported in neuropsychiatric studies with both right- and left-handed participants [e.g.(Turetsky, Kohler et al. 2007; Gunji, Inagaki et al. 2009)]. As the current paradigm is used in subsequent experiments of this thesis with neuropsychiatric populations, a small number of left-handed participants were included to reflect the individual variability found in individuals with psychiatric diagnoses. All participants completed the tasks voluntarily and signed an informed consent form in agreement with the Helsinki declaration.

Neuropsychological Assessment.

A subset of 16 participants (four females, mean age 32.5$\pm$2.7, mean years in education 17.3$\pm$0.7) received a battery of neuropsychological tests comprising tests of general neuropsychology (i.e., the Word Accentuation Test, the Rey Verbal Learning Test [RVLT] and the Wechsler Adult Intelligence Scale [WAIS]), executive functioning (i.e., the INECO Frontal Screening test [IFS], the Go/No Go test, the Backward Digit Span test [BDS], the Trail Making Test B [TMT-B], the Forward Digit Span test [FDS]), and social cognition (i.e., The Faux pas test, the reading the mind in the eyes test and the Iowa gambling task).

General Neuropsychology.

Participants were assessed using a neuropsychological battery designed to cover various basic cognitive functions. General neuropsychology was included in order to test general cognitive processes. Memory was assessed by the Rey Verbal Learning Test (RVLT) (Rey 1958), which includes measures of verbal learning, retention and immediate recall. Phonological and semantic fluency were assessed using the Controlled Oral Word Association test [COWAT (Benton, Hamsher et al. 1994)]. An arithmetic test from the Wechsler Adult Intelligence Scale (WAIS) (Wechsler 1997) was also included.

Executive functions

To assess participants' executive functioning, a set of several tests was compiled. The 'INECO Frontal Screening' test (IFS) (Torralva, Roca et al. 2009) was used to assess frontal lobe functioning. 'Backward Digit Span' (Wechsler 1997) and the 'Trail Making Test B' (TMT B) (Partington 1949) were used to assess attentional flexibility, sequencing and planning skills. The 'Forward Digit Span' test (Wechsler 1997) was used to assess Working Memory.

Social cognition.

Three tests of social cognition were used. First, the computerized version of the 'Iowa Gambling Task' (IGT) (Bechara, Damasio et al. 1997) was included. This task involves the selection of four cards under the condition of uncertainty. It was designed to simulate real-life decision making. Second, the Reading the Mind in the Eyes (RMET) test (Baron-Cohen, Wheelwright et al. 2001; Baron-Cohen and Wheelwright 2004) was included. This task consists of 36 photographs of the eye-region of the face, each of a different person. Participants are required to choose which one of four words best describes what the person in the photograph is thinking or feeling. Third, the 'Faux Pas' test (Stone, Baron-Cohen et al. 1998; Baron-Cohen, O'Riordan et al. 1999; Richell, Mitchell et al. 2003) was included. In this task, participants are asked to discern whether a *faux pas* is present in each of 20 stories. After each story, participants are asked whether something inappropriate was said. If they respond that it was, they are asked to explain why it was inappropriate. It is a test of the capacity to identify something that would be (unintentionally) hurtful or insulting to another person..

RESULTS

Behavioral measures of the Dual Valence Task

RTs were shorter to face stimuli than word stimuli, to positive stimuli than to negative stimuli, and to compatible simultaneous stimuli than to incompatible simultaneous stimuli when face valence was positive (see figure 14). All participants performed with greater than 80% accuracy on all of the subtasks of the dual valence task (see table 1).

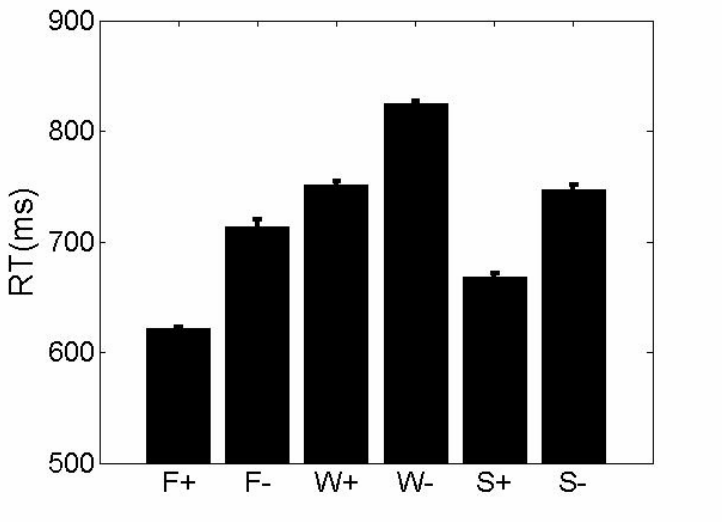

Figure 14. Reaction times on the Dual Valence Task, Mean ± SE. F: face, W: words, S: simultaneous. The signs (+) and (-) corresponds to positive and negative valences, respectively.

Reaction times. There was a strongly significant main effect of stimulus type: $F(2, 38)=2901.0$; $p<0.001$. RT was shorter in response to faces than to simultaneous stimuli and longer in response to words than to simultaneous stimuli. Mean reaction times were: 667.5 ± 2.3 ms for faces, 707.9 ± 3.2 ms for simultaneous stimuli and 787.9 ± 2.3 ms for words. Tukey post hoc comparisons ($MS=51.8$; $df = 38$) revealed significant differences between: faces and words; faces and simultaneous stimuli; words and simultaneous stimuli ($p < 0.01$ in all cases). There was a significant main effect of 'valence' ($F[1, 19]=1419.4$, $p<0.001$) ($M=668.4+2.6$ ms for positive stimuli and $M=747.5\pm4.0$ ms for negative stimuli). Participants responded faster to stimuli of positive valence, for every stimulus type. A significant interaction was found between 'stimulus type' and 'valence' ($F[2, 38]=15.98$ $p<0.001$), which probably reflects the reduction of the 'valence' effect for word stimuli compared to the other stimuli types. Tukey post hoc comparisons ($MS=60.9$; $df = 38$) revealed a significant difference between positive and negative valence for each stimulus type ($p<0.001$ in all cases). For simultaneous stimuli, no significant effects of 'valence' were observed. The factor 'compatibility' had a trend on RT ($p=0.09$). The interaction between valence and compatibility was significant ($F[1, 19]=16.54$, $p<0.001$). Tukey post hoc comparisons ($MS=63.1$; $df=19$) revealed that this effect reflected that RT was shorter for 'compatible' than 'incompatible' stimuli when face valence was positive ($p<0.01$) but not when face valence was negative ($p=0.40$).

Accuracy. All participants performed at above 80% accuracy on all of the subtasks of the DVT. The overall performance on the task yielded a mean accuracy of 0.93 ($SE = 0.011$). A two-way, within-participants ANOVA was carried out on the performance data with 'stimulus type' and 'valence' as

independent factors. No significant main effects were found: $F(2, 38)=0.30$; $p=0.73$ for 'stimulus type' and ($F(1, 19)=3.03$, $p=0.09$ for 'valence'. There was no significant effects of 'compatibility': $F(1, 19)=0.08$, $p=0.76$ and no significant interaction effects For simultaneous stimuli, performance was better for positive than for negative faces ($M=0.94+0.01$ and $M=0.92+0.01$, respectively): $F(1, 19)=5.96$, $p<0.05$.

I. Performance on neuropsychological tests			
	Mean	**SD**	**Normal Range ****
General Neuropsychology			
Premorbid IQ (WAT-BA)	41.1	0.8	37 – 44
RVLT Acquisition	52.4	1.7	48 – 75
RVLT Interference	12.3	0.5	9 – 15
RVLT Recall	7.3	0.5	5 – 12
RVLT Recognition	14.9	0.1	12 – 15
Arithmetic (WAIS)	15.6	0.9	13-15
Forward Digit Span	7.1	0.2	6 – 8
Semantic fluency	24.9	1.4	18 – 28
Verbal fluency (COWAT),	22.7	1.6	15 – 25
Executive functions			
IFS	28.4	0.4	25 – 30
Backward Digit Span	5.7	0.6	4 – 7
TMT-B	61.6	4.1	55 – 120
Go/No Go	100%	0	94 – 100
Social Cognition			
Reading the Mind in the Eyes	26.7	0.9	14 – 36
Faux Pas	19.44	0.2	17 – 20
IGT 1	-1.8	2	-2
IGT 2	3.5	1	8
IGT 3	2.8	1.7	10
IGT 4	5.4	1.5	8
IGT 5	5.7	1.4	8

II. Dual Valence Task Performance				
	Mean	**Measures**		***P<***
		df	***F***	
Accuracy				
Positive faces versus negative faces	PF: 0.94 (0.01) ; NF: 0.92 (0.01)	(1,19)	3.03	n.s
Faces versus words	F: 667.5 (2.3) ; W: 707.9 (3.2)	(2, 38)	0.30	n.s
Reaction Time				
Positive faces versus negative faces	PF: 668.4 (2.6) ; NF: 747.5 (4.0)	(1,19)	1419.40	0.001
Faces versus words	F: 667.5 (2.3) ; W: 707.9 (3.2)	(2, 38)	2901.0	0.001

Event Related Potentials (ERPs)				
	Mean amplitude in µV (*SD*)	**Measures**		***P<***
		df	***F***	
N170				
Faces versus words	RHF: -3.34 (1.11) ; LHW: -1.81 (0.77)	(1,19)	6.06	0.05
Face valence	RHP: -3.97 (1.12) ; RHN: -2.70 (1.10)	(1,19)	66.10	0.001
Simultaneous stimuli valence	PF: -0.91 (0.92) ; NF: -0.45 (0.92)	(1,19)	8.82	0.01
Simultaneous stimuli effect on faces	FW: -2.86 (-1.00) ; FA: -0.67 (-0.92)	(1,19)	44.61	0.001
	RHF: -3.34 (1.17) ; LHF: -2.39 (0.94)	(1,19)	6.25	0.05

III. Correlations ++		
	Correlations with behavioral results	
General Neuropsychology tests		***R***
Premorbid IQ (WAT-BA) versus overall RT		-0.52
RVLT versus accuracy		0.51
RVLT versus RT global score for stimulus discrimination		0.39
RVLT versus RT global score for stimulus interference		0.49
RVLT versus RT global score for valence discrimination		0.60
FDT versus RT global score for stimulus discrimination		0.54
FDT versus global score for valence discrimination		0.48
	Correlations with ERPs	
Executive Functions		
TMT-B versus N170 global scores for valence discrimination in simultaneous stimuli		0.52
Social Cognition		
'Reading the Mind in The Eyes' with N170 global scores for valence discrimination		0.57
Faux Pas versus N170 global scores for compatibility discrimination		0.56
IGT 1 versus N170 global scores for valence discrimination simultaneous stimuli		0.53

++ All correlations presented in the table are significant at p< 0.05, HSD Tukey correction. WAT-BA= Word accentuation Test-Buenos Aires; RVLT= Rey Verbal Learning Test; IFS= INECO Frontal Screening Test; Trial Making Test B; IGT= Iowa Gambling Task; RT= Reaction time; RHF= Right hemisphere faces; LHW= Left hemispheres words; RHP= Right hemisphere positive valence; RHN= Right hemisphere negative valence; F= Faces; W= Words PF= Positive face valence; NF= Negative face valence; FW= Faces with words simultaneously; FA= Faces alone; LHF= Left hemisphere faces

Table 1. Main results for neuropsychological assessments, behavioral measures, ERPs and correlations.

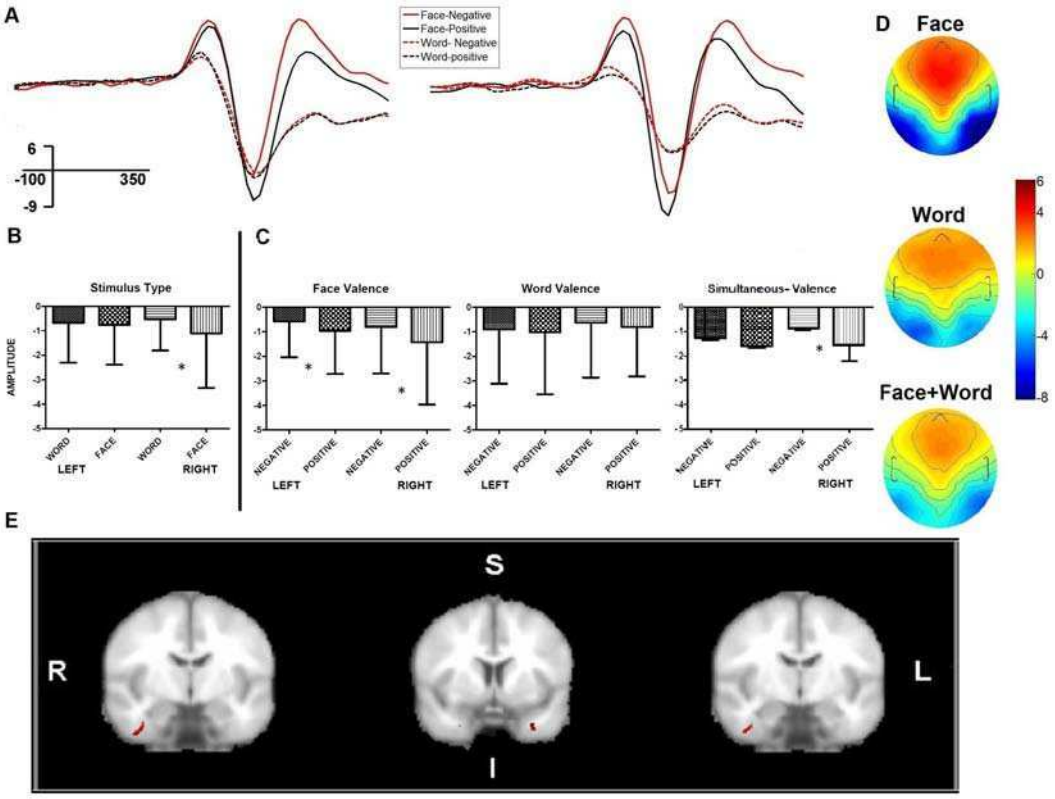

Figure 15. ERPs data and source localization. A) Left and right hemisphere ERPs for face and word stimuli. B) Mean N170 amplitudes for face versus word stimuli in both hemispheres. C) Mean N170 amplitudes for valence effects of face, word and both stimuli in both hemispheres (bars indicate SD). D) Scalp ERPs for face, word and simultaneous stimuli. In each graph, asterisks (*) indicate significant differences. E. Coronal sections of the estimated sources of the N170 component in response to face stimuli (left), word stimuli (middle) and simultaneous stimuli (right). R: Right; L: Left; S: Superior; I: Inferior.

Neuropsychological Assessment

All neuropsychological scores were within the expected normal ranges previously published in other reports (see Table 1)

IGT scores are obtained from 100 choices that participants are asked to make, which are grouped into five blocks of 20 consecutive cards (each one with a net score calculated as [C+D] – [A+ B] decks). The ascending pattern is an index of learning effects: participants automatically learn to choose the more advantageous cards (C and D). The ascending pattern is in agreement with data published by Bechara, (Bechara, Damasio et al. 1997) and other studies (Dunn, Dalgleish et al. 2006).

N170 Source Localization.

The cortical source of the N170 component was estimated for each stimulus type: 1) Faces, 2) Words, and 3) Simultaneous Stimuli (see figure 15D). For face stimuli, the source was located at the FG anterior division, with a peak in the right hemisphere (at coordinates 41,-8,-36). Compared with words and simultaneous stimuli, the face stimuli elicited a higher intensity (145.97 nA.m).
For word stimuli, the mean source was located at the border between the temporal pole and temporal fusiform cortex, anterior division, in the left hemisphere (coordinate -30,4,-37), with an intensity of 62.11 nA.m. A second source of lower amplitude was found in the temporal fusiform cortex, anterior division, in the right hemisphere (coordinate 41,-7,-37, intensity=25.04 nA.m).
Finally, for simultaneous stimuli, two principal sources were identified, located bilaterally. The higher source was located in the temporal fusiform cortex, anterior division, in the right hemisphere (coordinates 41,-7,-37; intensity=48.3 nA.m). The other source was observed in the fusiform cortex, posterior division in the left hemisphere (coordinates -31,-12,-36; intensity= 22.93 nA.m).

N170

The findings from the ERP data followed expected trends for the main experimental factors: words and faces showed left-right asymmetries; the N170 discriminated face valence in both hemispheres (with greater sensitivity in the right hemisphere); the N170 did not discriminate word valence; and N170 amplitude decreased when faces were accompanied by words. In brief, the N170 showed an emotional valence effect for faces but not for words, similarly to those findings from other paradigms that test processing of facial and semantic emotional stimuli (Schacht and Sommer 2009).

N170. Stimulus type effects (Faces versus words).

The comparison of ERPs for faces and words (i.e., stimulus type) revealed no significant main effects when collapsed across both hemispheres (see Figure 15.A, 15.B). In accordance with previous studies that found opposite lateralization of faces and words (Bentin, Mouchetant-Rostaing et al. 1999; Rossion, Joyce et al. 2003), we found a significant interaction between stimulus type and hemisphere ($F[1, 20] = 6.06$, $p<0.05$). Post hoc comparisons (MS = 1.82, df = 20) revealed that the N170 discriminated stimulus type only within the right hemisphere (right hemisphere: -3.34 ± 1.11 μV for faces and -1.81 ± 0.77 μV for words, $p < 0.05$; left hemisphere: -2.39 ± 0.90 μV for faces and -2.31 ± 0.72 μV for words, $p = 0.99$) (Table 1)

N170. Face valence effects.

A significant effect of valence was found ($F[1, 20] = 66,10$, $p<0.01$), which reflects an increased N170 amplitude in response to positive faces as compared to negative faces (-3.35$\pm$0.96 µV and -2.38$\pm$0.95 µV, respectively). There was no significant main effect of hemisphere ($F[1, 20] = 2.056$, $p=0.167$) and no significant interaction between face valence and hemisphere ($F[1, 20] = 11.01$, $p<0.01$). Post hoc comparisons ($MS = 0.16$, $df = 20$) revealed that face valence was better discriminated by the N170 in the right hemisphere (positive: -3.97+1.12; negative: -2.70+1.10, $p<0.001$) than in the left hemisphere (positive:-2.7+0.81 µV; negative: -2.04+0.89, $p<0.05$). See Table 1 and figure 15.A

N170. Word valence effects

Word valence was not discriminated by N170 ($F(1,20) = 0.55$, $p = 0.47$). The interaction between word valence and hemisphere was not significant ($F[1, 20] = 2.84$, $p = 0.11$).

N170. Simultaneous stimuli valence effects

The N170 discriminated the face valence of simultaneous stimuli ($F[1, 19] = 8.82$, $p<0.01$) having a mean of -0.91 ($\pm$0.92 µV SD) and -0.457 ($\pm$0.920 µV SD) for positive and negative faces, respectively (positive >negative, as was the case for face stimuli).
There were no significant main effect differences between the hemispheres for simultaneous stimuli ($F[1, 19] = 0.08$, $p = 0.78$), but there was a significant interaction between valence and hemisphere ($F(1, 19) = 4.88$, $p<0.05$). Post hoc comparisons ($MS = 0.27$, $df = 19$) revealed that face valence was discriminated within the right hemisphere when presented simultaneously with words ($p<0.01$ for right hemisphere and $p = 0.65$ for left hemisphere).

Simultaneous stimuli compatibility

The N170 was not subject to any significant effects of compatibility ($F[1, 18]=0.03$, $p=0.87$) and nor was there any significant interaction effect between compatibility and hemisphere ($F[1, 19]=0.06$, $p=0.81$). The interaction between valence and compatibility was not significant ($F[1, 18]=0.07$, $p=0.79$) either and nor was the three-way interaction between hemisphere, valence and compatibility ($F[1, 18]=2.48$, $p=0.13$).

Simultaneous stimuli effect on faces

A robust effect was found when comparing the N170 ERP evoked by faces and by simultaneous stimuli ($F[1, 19]=44.61$, $p<0.001$). The mean data show that the amplitude of the N170 was lower when faces were presented simultaneously with words compared to when they presented alone ($M=-2.86\pm-1.00$ and $M=-0.67\pm-0.92$, respectively). The same comparison revealed a significant interaction between stimulus type and hemisphere ($F[1, 19]=6.25$, $p<0.05$). Tukey post hoc comparisons ($MS = 0.50$, $df = 19$) revealed that, as reported elsewhere (Brandeis, Lehmann et al. 1995; Eimer and Holmes 2002), N170 amplitude is higher in the right hemisphere than in the left in response to faces ($M=-2.39\pm0.94$ μV for left hemisphere and $M=-3.34\pm1.17$ μV for right hemisphere; $p<0.01$) but there was no significant difference between the hemispheres in response to simultaneous stimuli ($p=0.89$).

In brief, N170 results, in conjunction with source localization, confirm that the N170 component was correctly estimated (Eimer and Holmes 2002; Batty and Taylor 2003; Ashley, Vuilleumier et al. 2004; Blau, Maurer et al. 2007; Sadeh, Podlipsky et al. 2010). Main N170 results are summarized in Table 1.

Correlations

General neuropsychology

Behavioral measures. Correlations were found between general memory (as measured by the Rey Verbal Learning Test) and overall accuracy ($r=0.51$); RTs global score for stimulus discrimination (RTs face-RTs word) ($r=0.39$); RTs global score for stimulus interference (RTs face-RTs simultaneous) ($r=0.49$); and RTs global score for valence discrimination (RTs positive-RTs negative) ($r=0.60$). Working memory (as measured by the Forward Digit Span Test) correlated with the RTs global score for stimulus discrimination (RTs face/RTs word) ($r=0.54$) and the RTs global score for valence discrimination RTs (RTs positive/RTs negative) ($r=0.48$).

Executive Functioning

Behavioral measures. Scores on the INECO Frontal Screening Test correlated with the RTs global scores for stimulus discrimination (RTs face-RTs word) ($r=0.54$) and with the RTs global scores for valence discrimination (RTs positive-RTs negative) ($r=0.54$).

ERPs measures. Scores on the Trial Making Test B correlated positively with the N170 global scores for valence discrimination in simultaneous stimuli ($r=0.52$).

Social cognition

ERPs measures. Scores from the Iowa Gambling Task block 1 correlated significantly with the ERPs global scores for valence discrimination in simultaneous stimuli (r=0.53). Scores on the reading the mind in the eyes test correlated significantly with the N170 global scores for valence discrimination (positive-negative) (r=0.57). Scores on the Faux pas test correlated with the N170 global scores for compatibility discrimination (compatible/incompatible) (r=0.56). Correlation results are summarized in Table 1.

In summary, all the significant correlations have the expected sign, and are, as a group, very consistent.

Memory correlated positively with many basic behavioral skills important for the DVT (RT stimulus and type discrimination)

N170 emotional valence discrimination correlated with a social cognition task (RMET).

N170 stimulus type discrimination correlated with an executive functions task (IFS).

N170 valence discrimination in simultaneous stimuli (word interference over faces) correlated with an executive functions task (TMT-B)

N170 compatibility discrimination in simultaneous stimuli correlated with a social cognition task with an important executive component (Faux Pas).

Section II

The previous experiment showed that complex social cognition and executive functions are associated to N170 facial emotion modulation. The next experiment follows on this path by inquiring the following hypothesis:

H2a) *BD patients present cortical deficits in processing emotional facial information.*
H2b) *these deficiencies are associated with clinical measures.*

This section includes experimental results obtained in collaboration with Agustín Ibáñez, Hugo Urquina, Sandra Báez, Micaela do Nascimento, Raphael Guex, Esteban Hurtado, Alejandro Blenkmann, Leandro Beltrachini , Alicia Lischinsky, Teresa Torralva, Fernando Torrente, Marcelo Cetkovich and Facundo Manes. This work has been done under the supervision of Professor Mariano Sigman.

SPECIFIC MATERIALS AND METHODS FOR THIS SECTION

In this section BD patients and matched controls completed the DVT while EEG recorded its scalp activity. Psychophysical (performance and RT) and ERP (N170 modulation by facial emotion) results of the DVT were correlated with neuropsychological tests and clinical neuropsychology.

Participants

Thirteen adult participants with BD, five females, (M=40.1, SD=2.5 years old), twelve right handed, and 13 healthy controls matched for age (M=39,30, SD=2.51), gender and handedness completed a full clinical, neuropsychological end electrophysiological evaluation. A questionnaire was given to healthy participants to rule out hearing, visual, psychiatric or neurological deficits. All participants gave signed, informed consent in agreement with the Helsinki declaration.

Patient's criteria and recruitment process

All participants with fulfilled DSM-IV criteria for BD. Diagnosis were made by three experts (AL,

FT, and MC). The clinical protocol included questionnaires of informant-based version of Depression Inventory II [BDI-II; (Beck, Steer et al. 1996)] and the Young Mania Rating Scale YMRS (Young, Biggs et al. 1978), to assess depression and mania, respectively. To obtain scores of impulsivity and anxiety, the BIS11 (Barrat Impulsivity Scale BIS11; (Patton, Stanford et al. 1995)], and the STAI trait-state (Spielberger, Gorsuch et al. 1970) were considered. To exclude possible comorbid ADHD we applied the ADHD Rating Scale questionnaire for adults and children (Barkley and Murphy 1998). All patients were euthymic bipolar patients type II without comorbidity. Patients were not receiving antipsychotic medication and didn't have change of medication type or dosage over a period of 4 months.

Neuropsychological Assessment

General Neuropsychology

General neuropsychology evaluated participants' basic cognitive functioning. Memory was evaluated using the Rey Verbal Learning Test (Rey 1958). Attention and concentration were assessed using the Trail Making Test A [TMT-A (Partington 1949)]. Phonological and semantic fluency were assessed using the Controlled Oral Word Association test [COWAT (Benton, Hamsher et al. 1994)]. An arithmetic test, Wechsler Adult Intelligence Scale III [WAIS III; (Wechsler 1997)] was also included.

Executive Functioning

Several tests evaluate executive functioning. The INECO Frontal Screening (Torralva, Roca et al. 2009) was used. Backward Digit Span and TMT-B (Partington 1949) were used to assess attentional flexibility, attentional speed, sequencing and planning skills. Numbers Key and Searching Symbols (Wechsler 1997) were used to evaluate visual perception and organization, visual scanning and the efficient production of multiple motor responses. Ordering Letters and Numbers (Letters & Numbers hereafter) was used to assess mental manipulation and working memory (Wechsler 1997). Finally, a working memory index was derived from performance on the Digit Span, Arithmetic, and Letter–Number Sequencing subtests (Hill, Elliott et al. 2010).

Social Cognition

Two social cognition tasks related to theory of mind were included. First, the Faux Pas test [FPT, (Stone, Baron-Cohen et al. 1998)] which evaluates hurtful or insulting social situations. Second, the Reading the Mind in The Eyes [RMET (Baron-Cohen, Wheelwright et al. 2001)], which assesses individual differences in the ability to infer the affective mental states of other humans.

Data analysis

Off-line processing and analysis of EEG data were performed using Matlab software, EEGLab toolbox and T-BESP software. To analyze scalp topography of the ERP components, regions of interest (ROIs) were used, based on previous DVT ROI selection. ROIs were chosen after visual inspection of each component. Each N170 ROI (left and right) included four adjacent electrodes of the canonical locations around T8 and T7 (Rossion and Jacques 2008): the N170 ROIs were the Biosemi channels A9, A10, A11 and A12 for the left hemisphere and B6, B7, B8 and B9 for the right hemisphere (figure 16).

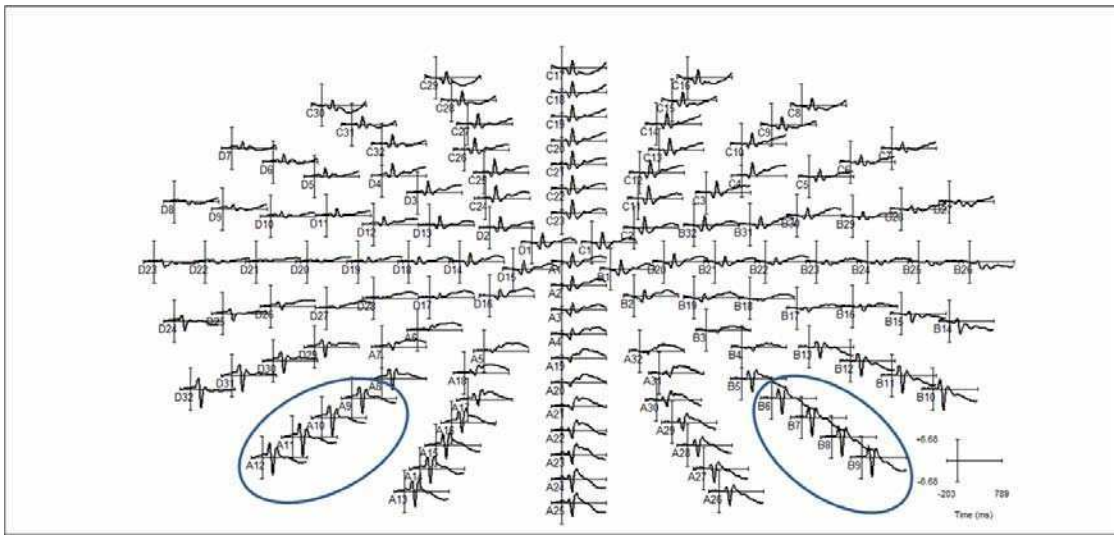

Figure 16. Channel locations and selected electrodes. Figure shows the overall ERP response to faces in the DVT and the ellipses contain selected electrodes for left (A8 to A12) and right N170 (B6 to B9)

To test whether ERP measures of stimulus type and valence were associated with individual cognitive profiles, global scores were correlated with all clinical and neuropsychological tests using Spearman's rank correlations corrected for multiple comparisons (false discovery rate-FDR- correction, which controls the fraction of rejections that are false positives).

RESULTS

Demographic and clinical assessment

Table 2 shows the overall results from the demographic, clinical, and neuropsychological assessments. Regarding demographic data, no differences regarding age ($F(1, 24) = 0.056$, $p=0.81$), gender ($X^2(1)=0.15$, $p=0.69$), educational level ($F(1, 24)=0.26$, $p=0.61$), or handedness ($X^2(1)=0.00$, $p=1$) were observed between groups.

No differences were observed between groups for clinical measures of impulsivity ($F(1, 24)=2.18$, $p=0.15$), depression ($F(1, 24)=0.33$, $p=0.56$), or mania ($F(1, 24)=0.24$, $p=0.62$). However, compared to controls group, the BD patients showed significant differences for the anxiety scale STAI- State ($F(1, 24,)=19.86$, $p<0.001$) and STAI- Trait ($F(1, 24)=16.03$, $p<0.01$).

Neuropsychological assessment

General Neuropsychology

Significant differences were observed in attention and concentration assessed with the TMT-A ($F(1,24)=8.89$, $p=0.006$) and forward digits span ($F(1,24)8.45$, $p<0.01$). No group differences regarding memory were observed for the RAVLT immediate recall ($F(1,24)=0.38$, $p=0.54$), delayed recall ($F(1,24)=0.1$, $p=0.9$) or recognition phase ($F(1,24)=0.25$, $p=0.87$).

The groups did not differ on most tests of executive functioning, including the IFS total score ($F(1,24)=1.85$, $p=0.18$), backwards digit span ($F(1,24)=1.60$, $p=0.21$), arithmetic evaluation -WAIS III ($F(1,24)=0.56$, $p=0.45$), TMT-B ($F(1,24)=0.88$, $p=0.35$) and letters and numbers task ($F(1,24)=0.21$, $p=0.64$). However, compared to controls the phonological fluency task ($F(1,24)=5.39$, $p<0.05$) yielded lower scores in the BD group.

Social Cognition

Performance on FPT was significantly reduced in BD ($F(1, 24)=12.14$, $p< 0.001$) suggesting failures in theory of mind process. For the RMET, no differences between groups were observed ($F(1, 24)=2.68$, $p=0.11$).

Demographic information and neuropsychological test performance				
		BIPOLAR (n = 13)	CONTROLS (n = 13)	P
Demographics	Age (years)	40.15 (9.59)	39.30 (8.5)	N.S
	Gender (M : F)	5:8	5:8	N.S
	Education (years)	16.77 (3.24)	17.38 (2.84)	N.S
	Handedness (R:L)	12:1	12:1	N.S
Clinical Profile	BIS-11	54.23 (22.3)	43.46 (13.7)	N.S
	BDI-II	8.07 (7.06)	6.38 (7.73)	N.S
	YMRS	0.30 (0.85)	0.53 (1.45)	N.S
	STAI – State	23.76 (6.16)	14.15 (4.77)	**0.0001**
	– Trait	27.61 (6.23)	18.61 (5.19)	**0.0005**
General Neuropsychology	TMT-A	42.92 (13.74)	30.23 (6.83)	**0.006**
	Digit repetition	14.46 (3.90)	19.15 (4.31)	**0.007**
	RAVLT			
	Immediate	51.30 (9.44)	53.61 (6.17)	N.S
	DL	7.1 (2.5)	8.2 (2.0)	N.S
	Delayed	11.23 (3.08)	11.23 (2.61)	N.S
	Recognition	14.38 (1.04)	14.46 (1.39)	N.S
	Semantic Fluency	21.00 (6.64)	28.61 (6.13)	N.S
	Phonological fluency	19.07 (1.85)	25.15 (1.85)	**0.029**
Executive Functions	Arithmetic (WAIS III)	14.53 (3.20)	15.62 (4.03)	N.S
	Digits Forward	4.85 (1.07)	5.46 (1.39)	N.S
	TMT-B	82.61 (41.24)	68.92 (32.34)	N.S
	Letters & Numbers	12.30 (2.92)	12.76 (2.08)	N.S
	IFS			
	Total Score	25.23 (2.74)	26.76 (3.03)	N.S
	Motor series	2.46 (1-05)	2.76 (0.44)	N.S
	Conflicting instructions	2.92 (0.28)	3.00 (0.0)	N.S
	Go- no go	2.92 (0.28)	3.00 (0.0)	N.S
	Backward digit span	4.38 (1.12)	4.92 (1.26)	N.S
	Verbal Working memory	1.92 (0.27)	2.00 (0.0)	N.S
	Spatial working memory	3.08 (1.04)	3.23 (0.93)	N.S
	Abstraction capacity	2.85 (1.04)	2.92 (0.28)	N.S
	Verbal inhibitory control	4.69 (1.44)	4.92 (0.95)	N.S
Social Cognition	Faux pas	17.84 (1.99)	19.84 (0.55)	**0.001**
	The Mind in the Eyes	25.30 (4.49)	27.61 (2.36)	N.S

Table 2. All results are shown as Mean (SD) and statistical comparison test results are shown in the right-hand column. BDI-II = Beck Depression Inventory II; YMRS = Young Mania Rating Scale; RVLT = Rey Auditory Verbal Learning Task; DL = Distractor List; TMT= Trail making test; IFS = INECO Frontal Screening. Statistical comparison test result p values are shown when significance was achieved. In all other cases N.S. means a 'non significant' difference.

Dual Valence Paradigm

Behavioral results.

Both groups performed the task with high levels of accuracy (0.92, SD = 0.06 for BD and 0.94, SD=0.04 for control group). A significant valence effect were found, having both groups better accuracy for positive faces, compared to negative ones ($F(1, 24) = 6.01$ $p<0.05$). No valence effects were observed for words ($F(1, 24) = 0.87$, $p=0.35$) or simultaneous stimuli ($F(1, 24) = 1.39$ $p=0.25$). Also, a significant effect of stimulus type was found ($F(1, 24) = 4.20$, $p<0.05$).

Post hoc comparisons evidenced that simultaneous stimuli ($F(2, 48)=3.48$, $p<0.05$) presented low accuracy compared to face and words stimuli. No group's differences were observed. No others effects or interaction were found.

	Face +	**Face -**	**word +**	**Word -**	**Sim + +**	**Sim + -**	**Sim - -**	**Sim - +**
BD (Mean)	0.95	0.93	0.95	0.94	0.94	0.91	0.90	0.89
BD (SD)	0.03	0.09	0.04	0.04	0.05	0.07	0.09	0.09
Controls (Mean)	0.95	0.95	0.94	0.95	0.96	0.94	0.93	0.93
Controls (SD)	0.03	0.04	0.05	0.05	0.03	0.04	0.06	0.05

Table 3. Performance in DVT for patients and controls (fractions). The signs + and – depicts emotional valences. The double signs in the last four columns indicate valence for faces and words, respectively.

Source analysis

Figure 17A shows the distributed activation evoked by the stimulus type conditions (face, word and simultaneous) and 17B the mean source peak as well as the mean fusiform face area (FFA) intensity in controls and BD participants. The source peak of N170 neural activity was observed at different portions of the fusiform gyrus (FG, details of spatial coordinates are provided in table 4): left hemisphere for words, bilateral for faces (controls and patients) and bilateral (right-preponderant) for simultaneous stimuli. Table 4 shows the results of the estimation of the cortical sources for the N170. Standardized current density power was higher for faces and simultaneous stimuli, and lower for words in the case of controls against patients, which is consistent with further observed N170 group differences (see below). When we look at face fusiform area (FFA, see figure 17B), controls presented decreasing FFA activation from face to simultaneous and word stimuli. BD group presented a reduced activation of FFA from faces and simultaneous stimuli compared to controls, in both, left (MNI coordinates of ICBM: -32 -53 -18) and right (MNI coordinates of ICBM: 35 -48 -19) hemispheres.

Opposed to that, word stimuli elicited a strong activation of the left FFA in BD compared to controls.

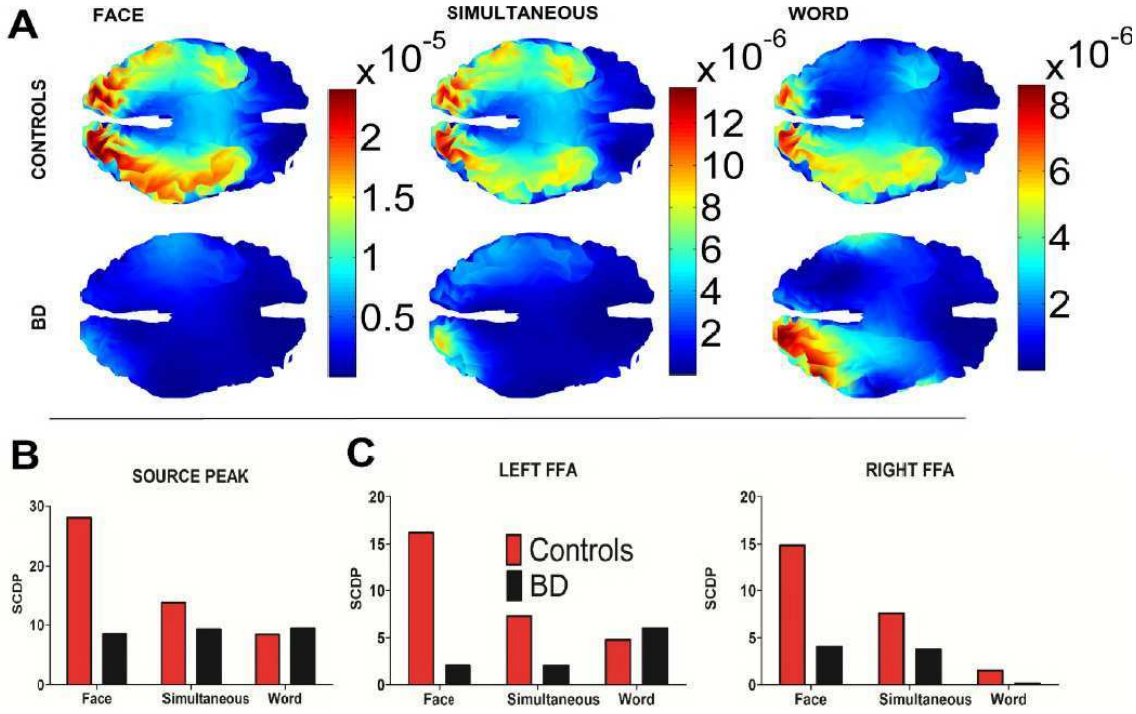

Figure 17. Cortical standardized current density power mapping of N170 (face, word, and simultaneous stimuli). A). N170 source imaging estimation of face, simultaneous and word stimuli for controls (above) and patients (below) with BD. B). Average values of estimated standardized current density power at maximum peaks of activation for each condition at N170 window. C) Average values of N170 estimated standardized current density power at left face fusiform area (FFA) in the temporo-occipital fusiform Gyrus. D) Average values of N170 estimated standardized current density power at right face fusiform area (FFA) in the temporo-occipital fusiform gyrus. SCDP: standardized current density power.

ERP: Stimulus type effects

No main effects of stimulus type (ST; $F(2, 48)=1.74$, $p=0.18$) were observed. Furthermore, no effects of hemisphere ($F(1, 24) = 0.02$, $p=0.87$) or interactions between hemisphere and group ($F(1, 24) = 0.12$, $p=0.73$) were observed. Nevertheless, the ST x hemisphere showed a significant interaction ($F(2, 48)=4.03$, $p=0.02$) evidenced enhanced right lateralized effects of faces. Individual group comparisons of ST suggested a similar pattern, with a preponderance of faces over other stimuli (at

both hemispheres in controls and at right hemisphere in BD. Figure 18A shows the ERPs stimulus type modulation for both groups. In controls, no effects for hemisphere ($F(1, 25) = 0.33$, $p = 0.56$) or interactions between ST and hemisphere ($F(2, 50) = 1.75$, $p = 0.18$) were found. A significant stimulus type effect ($F(2, 50) = 10.41$, $p=0.0001$) was observed. Compared to words, post hoc comparisons over this interaction showed N170 amplitude enhancement in both hemispheres for faces (left $p<0.001$; right $p<0.001$) and simultaneous stimuli (left $p<0.01$; right $p<0.005$) respectively.

BD group not shown significant effects of stimulus type ($F(2.50) = 1.63$ $p= 0.20$). However, the stimulus type x hemisphere showed a significant interaction ($F(2.50) = 3.90$, $p = 0.02$). Post hoc comparisons performed over this interaction (Tukey HSD, df MS = 1.51, df = 50.00) showed enhanced of N170 amplitude in the left hemisphere (faces - simultaneous stimulus; $p = 0.01$) and similar results compared faces and words in the right hemisphere ($p<0.002$).

	Faces					
	Source peak				**Left FFA**	**Right FFA**
	MNI Coordinates			Anatomical Description (HOCSA) Harvard-Oxford Cortical Structural Atlas)	SCDP	SCDP
	X	Y	Z		Mean	Mean	Mean
Control	-18	-78	-17	32% Occipital Fusiform Gyrus; 19% Lingual Gyrus.	28.07	16.20	14.87
BD	-21	-93	-8	28% Left Occipital Pole, 5%; Occipital Fusiform Gyrus, 5 % Lateral Occipital Cortex, inferior division	8.49	2.01	4.02
	Simultaneous					
	Source peak				**Left FFA**	**Right FFA**
	MNI Coordinates			Anatomical Description (Harvard-Oxford Cortical Structural Atlas)	SCDP	SCDP
	X	Y	Z		Mean	Mean	Mean
Control	19	-85	-18	33% Right Occipital Fusiform Gyrus, 8% Lingual Gyrus, 4% Occipital Pole; 3% Lateral Occipital Cortex, inferior division	13.71	7.29	7.56
BD	-24	-86	-20	35% Left Occipital Fusiform Gyrus, 8% Lateral Occipital Cortex, inferior division, 3% Occipital Pole, 3% Lingual Gyrus	9.30	1.99	3.76
	Words					
	Source peak				**Left FFA**	**Right FFA**
	MNI Coordinates			Anatomical Description (Harvard-Oxford Cortical Structural Atlas)	SCDP	SCDP
	X	Y	Z		Mean	Mean	Mean
Control	-11	-85	-18	25% Left Occipital Fusiform Gyrus, 22% Left Lingual Gyrus	8.42	4.78	1.52
BD	-13	-89	-19	33% Left Occipital Fusiform Gyrus, 10% Lingual Gyrus, 5% Occipital Pole 2% Left Lateral Occipital Cortex, inferior division	9.46	5.96	0.17

Table 4. Estimation of the N170 neural generators. FFA: Face fusiform area in the temporo-occipital fusiform gyrus. MNI coordinates for FFA: left (-32 -53 -18) and right (35 -48 -19). SCDP: Standardized Current Density Power. MNI coordinates are provided by ICBM.

ERP: Face valence

A main effect of valence (positive>negative: F (1, 24) = 4.16, p<0.05) and group (controls>BD: F(1, 24) =9.86, p<0.01) were observed. No effects of hemisphere were found (F (1, 24)=0.58, p=0.45). An interaction of group x valence (F (1, 24) =6.77, p<0.05) was found. Tukey post hoc analysis of this interaction (Tukey HSD test, MS = 17.69, df = 24,00) showed that the N170 discriminated face valence in controls (p<0.05). In opposition to controls, BD patients did not show valence discrimination (p=0.29) (see figure 18B). A significant interaction between valence x hemisphere (F (1. 24) = 3.99, p<0.05) evidence the emotional discrimination of facial stimuli in the right hemisphere. Moreover, a face valence x group x hemisphere interaction (F (1, 24) = 7.96, p<0.01), evidenced different lateralized group effects. A post hoc analysis over this interaction (Tukey HSD, MS= 14.797 df= 33.51) evidence that in BD group the N170 failed to discriminate face valence in left (p=0.31) and right hemispheres (p=0.24). Conversely, N170 from controls were modulated in left (p<0.005) and right (p<0.005) hemisphere. In summary, Compared to controls, BD patients showed significant deficit in N170 discrimination for positive face valence in the right hemisphere.

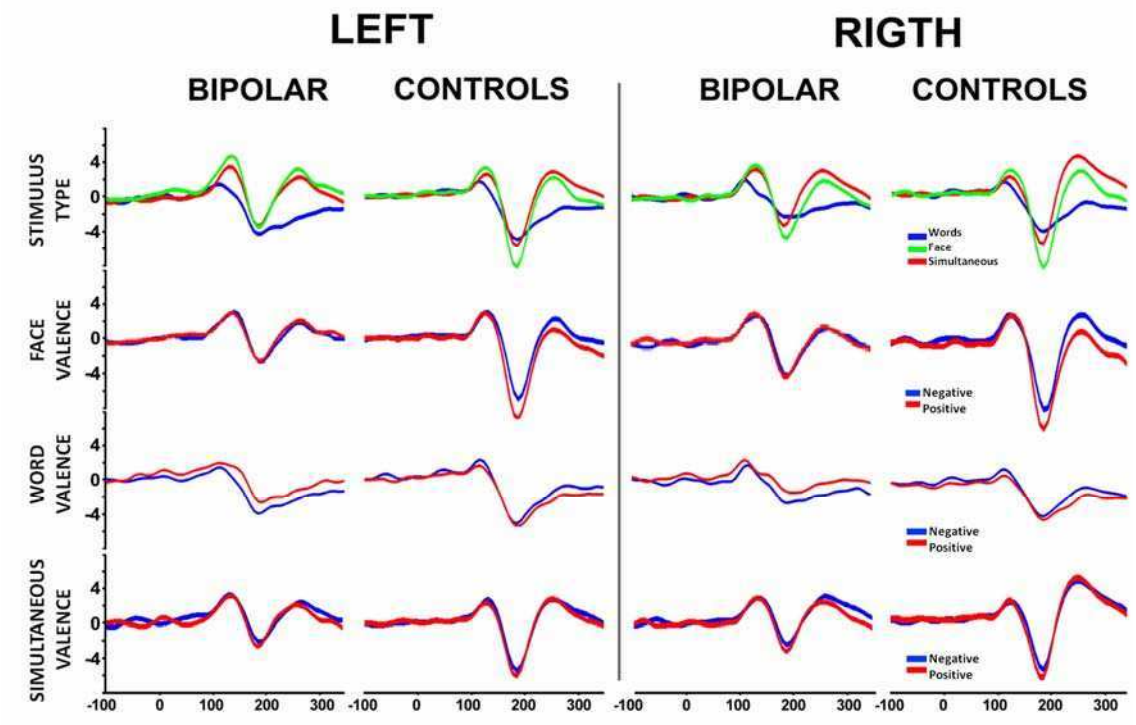

Figure 18. Main N170 results in left and right hemisphere for both groups. First row: stimulus type effects. Second row: Face Valence effects. Third row: word valence effects. Fourth row: simultaneous valence effects.

ERP: Word valence

For word stimuli, no effects of valence ($F(1, 24) = 3.07$, $p=0.09$) group ($F(1.24) = 2.79$, $p=0.10$), or hemisphere ($F(1, 24) = 2.54$, $p=0.12$) were observed. Additionally, no interactions between hemisphere x group ($F(1, 24) =0.21$, $p=0.64$) or valence x hemisphere ($F(1, 24) = 0.26$, $p=0.60$) were found. Nevertheless, a group x valence interaction was observed ($F(1, 24) = 5.62$, $p<0.05$). In BD patients an enhanced N170 amplitude for negative words was observed ($p<0.01$). In addition the amplitude of negative valence words in BD was significant enhanced compared to controls ($p<0.05$). No other effects were observed. Therefore, compared to control group, the N170 amplitude in BD patients presented an early semantic valence modulation (enhancement of N170 to negative words).

ERP: Simultaneous Stimuli

Main effects of group (controls>BD; $F(1, 24) =6.46$, $p<0.05$) and valence (positive >negative; $F(1, 24) =4.33$, $p=0.04$) were observed. No effect of hemisphere ($F(1, 24) = 0.14$, $p= 0.70$) was present. An interaction group x valence $F(1, 24) =5.23$, $p<0.05$ indicated different valence processing of simultaneous stimuli in both groups. A post-hoc comparison over this last interaction (Tukey HSD test, MS=3.56, df=24.00) yielded emotional discrimination of simultaneous stimuli in controls (positive>negative; $p<0.05$), but not in BD ($p=0.42$). No other effects or interactions were significant. Table 5 shows means and SD for these conditions.

In summary, N170 stimulus type discrimination was observed in both groups. BD patients showed N170 deficits in facial and simultaneous stimuli emotional modulation. Furthermore, only BD patients showed an early N170 discrimination for word valence in the left hemisphere (negative>positive).

Correlations with clinical profile

In BD, face valence was inversely correlated with mania ($r = -0.63$ $p< 0.01$) positively with depression scores ($r = 0.59$, $p<0.05$). Word valence was associated with anxiety (STAI Trait; $r = 0.60$, $p<0.05$). In control subjects, only word valence was associated with mania scores ($r = 0.64$, $p<0.05$).

	BD mean (SE)		**Controls** mean (SE)	
	Left	**Right**	**Left**	**Right**
a. Stimulus Type Effects				
Faces	-0.65 (4.98)	-1.71 (4.31)	-5.57 (2.18)	-5.42 (3.15)
Words	-2.15 (4.30)	-1.06 (2.65)	-3.83 (2.80)	-3.23 (2.91)
Simultaneous	-0.88 (3,08)	-1.17 (2,58)	-3.86 (3,13)	-3.97 (3,90)
b. Face Valence Effects				
Positive	-0.31 (4.76)	-1.56 (4,50)	-6.94 (3,49)	-7.09 (3,45)
Negative	-1.00 5.27)	-1.85 (4.38)	-4.20 (2.67)	-3.75 (4.02)
c. Word Valence Effects				
Positive	-1.28 (4.64)	-0.39 (3.62)	-3.90 (2.75)	-3.36 (2.91)
Negative	-3.02 (4.20)	-1.72 (2.58)	-3.75 (3.12)	-3.09 (3.10)
d. Simultaneous Valence Effects				
Positive	-1.2 (4.05)	-1.55 (3.22)	-4.20 (2.57)	-4.46 (3.24)
Negative	-0.55 (3.14)	-0.79 (2.63)	-3.51 (1.93)	-3.49 (3.00)

Table 5. N170 amplitude values in response to stimulus type and valence factors.

General neuropsychology

In BD Patients, word valence showed a positive correlation with attention ($r = 0.59$, $p<0.05$). In controls, word valence correlated significantly with semantic fluency ($r = 0.58$, $p<0.05$).

Executive Functions

In BD Patients, face valence presented a positive correlation with working memory ($r = 0.58$ $p<0.05$). In controls, stimulus type showed a positive correlation with several IFS subtests: IFS total score ($r = 0.67$, $p<0.05$); backward digit span ($r = 0.62$ $p = 0.02$); abstraction capacity ($r = 0.62$, $p<0.05$) and verbal inhibitory control ($r = 0.63$, $p<0.05$).

Theory of Mind

In BD stimulus type showed a positive correlation with FPT ($r = 0.55$, $p<0.05$). Word valence also correlated positively with FPT ($r = 0.61$, $p<0.05$) and RMET ($r = 0.56$, $p<0.05$). In controls, stimulus type showed a correlation with RMET (word valence; $r = 0.63$, $p<0.05$).

In summary, N170 face emotional discrimination correlated with mania and depression (with an opposed sign) in BD patients.

Neuropsychological measures have the expected sign. Theory of mind tasks scores improve with better N170 stimulus type discrimination and word valence in BD. Executive functions tasks scores improve associated with an increase in N170 face valence and stimulus type discrimination in BD.

SECTION III:

In Sections I and II, we showed that face rapid processing indexed by the N170 is associated to neuropsychological measures in healthy subjects and clinical measures in BD. The purpose of this experiment is to explore face processing in ADHD by examining the following hypotheses:

H3a) *ADHD patients present cortical deficits in processing emotional facial information.*
H3b*) These deficiencies are associated with executive functioning scores*

The following colleagues have collaborated in the experiments shown in this section: Agustin Ibáñez, Hugo Urquina, Teresa Torralva, Fernando Torrente, Esteban Hurtado, Raphael Guex, Alicia Lischinsky, and Facundo Manes. This work has been done under the supervision of Professor Mariano Sigman.

SPECIFIC MATERIALS AND METHODS FOR THIS EXPERIMENT

The aim of this experiment is to identify cortical markers of emotion processing in adult ADHD and explore their relation to individual neuropsychological profiles.
Adult participants with ADHD and controls classified stimuli according to its emotional valence (positive or negative).

Participants

Ten adult participants with ADHD, one female, (M=33.1, SD=3.6 years old), three left-handed, completed the dual valence task. Ten healthy controls, matched for gender, age (M=33.0, SD=3.8 years old), handedness, and years of education were recruited (see below and table 6). Participants with ADHD and controls received a thorough neuropsychological battery that comprised measures of general neuropsychology, executive functioning and social cognition. A questionnaire was given to healthy participants to rule out hearing, visual, psychiatric or neurological deficits. All participants gave signed, informed consent in agreement with the Helsinki declaration.

Participant criteria and recruitment process

All participants with ADHD fulfilled DSM-IV criteria for ADHD. Diagnosis was made by three experts (Alicia Lischinsky, Fernando Torrente and Facundo Manes). Participants were recruited from amongst the patients of the Institute of Cognitive Neurology (INECO, Buenos Aires, Argentina), from the Adult ADHD Clinic. From the initial set, 8 patients presented with ADHD combined type (ADHD/C) and 2 patients presented with predominantly inattentive type (ADHD/I). All patients were taking methylphenidate medication which was suspended on the day of ERP recordings. ADHD diagnosis based on the DSM-IV criteria was assessed using the following protocol for adults:

1). ADHD Rating Scale for Adults (Barkley and Murphy 1998) in patient and informant versions. It identifies current and retrospective childhood symptoms corresponding to DSM-IV characterization of ADHD.

2). Depression Inventory II (BDI-II; Beck et al., 1996) and the Young Mania Rating Scale YMRS; (Young et al., 1978), to assess depression and mania, respectively. Scales were administered to patients and controls.

3) Neuropsychological assessment (see methods and next section for details).

Neuropsychological Assessment

Both participants with ADHD and controls received a comprehensive neuropsychological battery that lasted approximately 120 minutes. It included general neuropsychology, executive functioning, and social cognition.

General Neuropsychology

General neuropsychology evaluated participants' basic cognitive functioning (see chapter 1 for details). Memory was evaluated using the Rey Verbal Learning Test [RVLT (Rey 1958)] that comprised verbal learning, immediate and delayed recall and a distractor list. Attention and concentration were assessed using the Trail Making Test A [TMT-A, (Partington 1949)]. Phonological and semantic fluency were assessed using the Controlled Oral Word Association test [COWAT (Benton, Hamsher et al. 1994)]. An arithmetic test, Wechsler Adult Intelligence Scale III [WAIS III (Wechsler 1997)] was also included.

Executive Functioning

Several tests were compiled to evaluate executive functioning. The INECO Frontal Screening (Torralva et al., 2009) was used to assess frontal lobe function indexed by several subtasks: Motor Programming, Conflicting Instructions, Verbal Inhibitory Control, Abstraction, Backwards Digit Span,

Spatial Working Memory, and Go/No Go. Backward Digit Span and TMT-B (Partington 1949) were used to assess attentional flexibility, attentional speed, sequencing and planning skills. Numbers Key and Searching Symbols (Wechsler 1997) were used to evaluate visual perception and organization, visual scanning and the efficient production of multiple motor responses. Ordering Letters and Numbers (Letters & Numbers hereafter) was used to assess mental manipulation and working memory (Wechsler 1997). Finally, a working memory index was derived from performance on the Digit Span, Arithmetic, and Letter–Number Sequencing subtests (Hill, Elliott et al. 2010).

Social cognition

Only one social cognition test was included; the Reading Mind in the Eyes test (RMET) (Baron-Cohen, Wheelwright et al. 2001), which assesses individual differences in the ability to infer the affective mental states of other humans. All neuropsychological performance data is shown in Table 6.

Data analysis

The same data processing and ROI selection were performed as previous sections (see figure 19 for the channel location selection and grand averages). For ERP analysis, the 160-210 ms time window for N170 was visually selected for mean amplitude analysis.

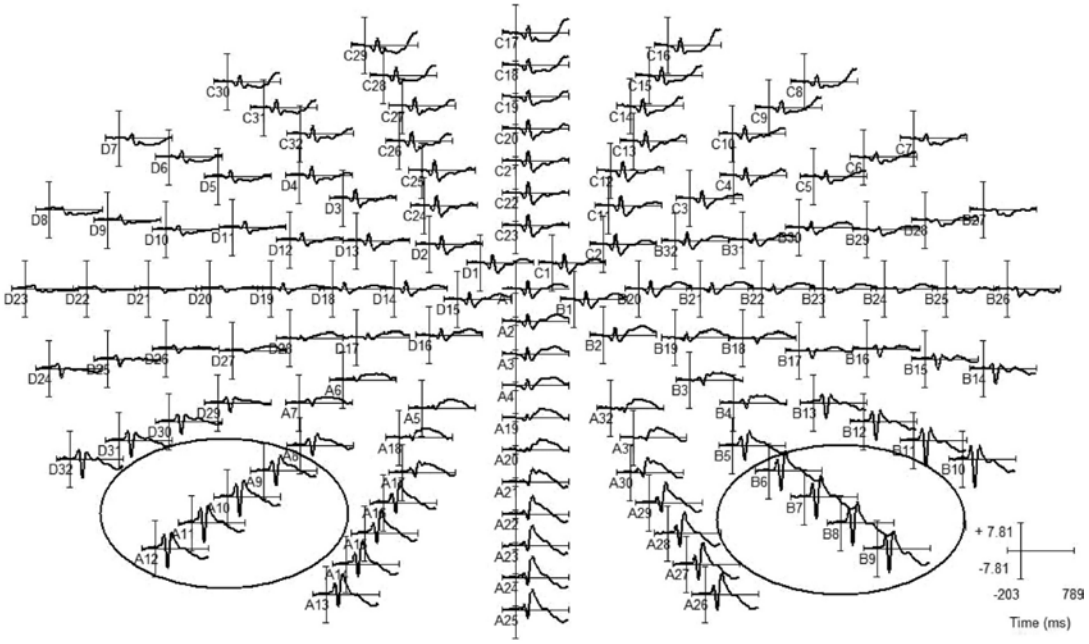

Figure 19. Channel locations and selected electrodes. Figure shows the overall ERP response to DVT and the ellipses contain selected electrodes for left (A8 to A12) and right N170 (B6 to B9)

RESULTS

Demographic and clinical assessment

Table 1 shows the overall results from the demographic, clinical, and neuropsychological assessments.

Demographic data. No differences regarding age ($F(1,18)=0.001$, $p=0.96$), gender ($X2(1)=0.000$, $p=1$), educational level ($F(1, 18)=2.240$, $p=0.15$), or handedness ($X2(1)=0.260$, $p=0.60$) were observed between groups.

Clinical evaluation. ADHD participants showed significantly higher scores on behavioral measures of ADHD symptoms than did control subjects (Barkley ADHD Rating Scale for Adults). There was an expected significant between-group difference between the ADHD-RS-Inattention scale ($F(1, 18)=13.598$, $p<0.005$) and the ADHD-RS- Hyperactivity/impulsivity subscale ($F(1, 18)=5.66$, $p<0.05$) indicating that ADHD participants had significantly higher scores for inattention and impulsivity than did control subjects. A difference between groups for BDI-II scores ($F(1, 18)=6.438$, $p<0.05$) was observed indicating high levels of depression in the ADHD group. No differences between groups were observed for the Young scale ($F(1, 18)=0.545$, $p=0.47$).

Neuropsychological assessment

General Neuropsychology. No group differences regarding memory were observed for the RVLT total score ($F(1, 18)=1.108$, $p=0.30$), and delayed ($F(1, 18)=2.568$, $p=0.13$). However, the RVLT recognition revealed a deficit in the ADHD group ($F(1, 18)=9.184$, $p<0.01$). No differences were observed in attention and concentration assessed with the TMT-A ($F(1, 18)=1.049$, $p=0.32$). No group differences were found on the arithmetic evaluation (WAIS III, $F(1, 18)=0.253$, $p=0.62$). The phonological fluency task ($F(1, 18)=7.862$, $p<0.05$) yielded lower scores in the ADHD group.

Executive Functioning.

The global score on the IFS showed a trend towards lower performance for the ADHD group compared with controls ($F(1, 18)= 3.79$, $p=0.07$). On closer examination, only the IFS subtasks of Abstraction Capacity ($F(1, 18)=4.47$, $p<0.05$) and Spatial Working Memory ($F(1, 18)=6.37$, $p<0.05$) yielded lower scores in the ADHD group. As regards the other measures of executive functioning, attention deficits in the ADHD group were revealed, as measured by digit repetition ($F(1, 18)=34.184$, $p<0.001$). No differences were observed on the Working Memory Index ($F(1, 18)=2.66$, $p=0.11$). No deficits in attentional flexibility, attentional speed or sequencing were observed in the ADHD group as

measured by the TMT-B (F(1, 18)=0.016, p=0.90), Backward Digit Span (F(1, 18)=2.070, p=0.17) and the Letters & Numbers task (F(1, 18)=0.76, p=0.39).

Social Cognition. When comparing percentage accuracy on the RMET, a small deficit was found in the ADHD group, shown by a trend (F(1, 18)=3.48, p=0.08), suggesting that patients had a subtle deficit in the emotional inference process.

		ADHD (n = 10)	CONTROL (n = 10)	P
Demographics	Age (years)	33.1 (3.42)	33.3 (3.64)	n.s
	Gender (M : F)	1:9	1:9	n.s
	Education (years)	15.9 (0.87)	17.8 (0.89)	n.s
Clinical Profile	Handedness (L:R)	3:7	2:8	n.s
	Barkley Inattention	12.30 (2.60)	1.80 (1.14)	0.005
	Hyperactivity	9.20 (2.21)	2.70 (1.60)	0.02
	BDI-II	17.90 (4.29)	5,50 (2,32)	0.02
	YMRS	1.10 (0.64)	0.50 (0.50)	n.s
General Neuropsychology	TMT-A	32.20 (4.41)	38.60 (4.48)	n.s
	Phonological fluency	17.30 (1.41)	22.90 (1.82)	0.05
	RVLT	47.10 (3.80)	52.20 (2.33)	n.s
	DL	7.90 (1.07)	6.60 (0.60)	n.s
	Delayed	10.80 (0.92)	12.90 (0.99)	n.s
	Recognition	12.80 (0.54)	14.80 (0.46)	0.01
	Arithmetic (WAIS III)	14.20 (1.26)	15.10 (0.96)	n.s
Executive Functions	WMI	100.60 (4.38)	110.02 (3.91)	n.s
	Digit repetition	11.80 (1.32)	19.50 (0.93)	0.001
	Digits backwards	4.44 (0.34)	5.10 (0.34)	n.s
	TMT-B	71.00 (6.77)	72.20 (4.23)	n.s
	Letters & Numbers	11.20 (0.80)	12.20 (0.80)	n.s
	IFS Total score	25.30 (0.85)	27.90 (056)	0.045
Social Cognition	RMET	71.32 (3.02)	79.21 (2.43)	0.08

Table 6. Results are shown as Mean (SD) and statistical comparison test results are shown in the right-hand column. BDI-II = Beck Depression Inventory II; YMRS = Young Mania Rating Scale; RVLT = Rey Auditory Verbal Learning Task; DL = Distractor List; TMT= Trail making test; IFS = INECO Frontal Screening; WMI: working memory index. Statistical comparison test result *p* values are shown when significance was achieved. In all other cases *n.s.* is used to indicate a 'non significant' difference.

Dual Valence Paradigm

Behavioral results

Both groups performed the task with an accuracy of 89% or more (see table 7 for mean and SD). The performance on the overall task was very similar for both groups: 0.915%, SD=0.02 for the ADHD group and 0.907%, SD=0.02 for the control group ($F(1, 18)=0.04$, $p=0.89$). For faces, word and simultaneous stimuli, no differences were found for stimulus type ($F(2, 36)=1.8$, $p=0.17$) or group differences ($F(1, 18)=0.08$, $p=0.77$). For faces, no main effects of valence ($F(1, 18)=0.07$, $p=0.79$) or group ((1, 18)=0.95, p=0.34) were found. For words, no main effects for valence ($F(1, 18)=0.26$, $p=0.61$) or group ($F(1, 18)=0.003$, $p=0.95$) were found. Finally, for simultaneous stimuli, an effect of valence was observed (accuracy: positive>negative, $F(2, 18)=4.10$, $p<0.05$) but no group effect ($F(2, 17)=0.55$, $p=0.58$). No congruency effects ($F(2, 18)=0.06$, $p=0.94$) or group differences were observed ($F(2, 18)=0.55$, $p=0.58$) for simultaneous stimuli comparing the congruency of face and word valence. There were no interactions between any of the previously mentioned factors. Table 2 shows the descriptive statistics.

	Face +	**Face -**	**Word +**	**Word -**	**sim ++**	**Sim +-**	**sim--**	**Sim -+**
ADHD mean	0.92	0.93	0.90	0.90	0.93	0.91	0.90	0.90
ADHD SD	0.09	0.05	0.06	0.10	0.07	0.05	0.05	0.05
Controls mean	0.92	0.90	0.91	0.9	0.92	0.89	0.89	0.88
Controls SD	0.07	0.07	0.06	0.07	005	0.08	0.07	0.07

Table 7. Performance of the DVT for patients and controls. The signs + and – depict emotional valences. The double signs in the last four columns indicate valence for faces and words, respectively.

Summarizing the behavioral results, accuracy was high across all conditions for both groups, and despite the small mean differences between conditions, no significant effects were observed for stimulus type in either group. For valence effects, only a small difference was obtained in simultaneous stimuli for both ADHD and control groups (performance was better for positive than for negative valence). No other effects yielded significant differences.

ERPs

Stimulus Type Effects

In a comparison of the N170 amplitudes elicited by faces, words and simultaneous stimuli, a main effect of ST was obtained ($F(2, 36)=4.40$, $p<0.01$), mainly caused by an amplitude enlargement of the N170 for faces. The ST effect was more accentuated over the right hemisphere, as evidenced by ST x Hemisphere Interaction ($F(2, 36)=8.71$, $p<0.001$). We performed a post hoc analysis of this interaction (Tukey HSD test, MS = 1.44, df = 36) and found that faces elicited enhanced N170 amplitudes compared with simultaneous stimuli ($p<0.001$) and words ($p<0.0005$) in the right hemisphere. Although face stimuli presented right>left amplitude differences, this effect was not significant ($p=0.20$). In the left hemisphere, words showed a trend towards enhanced amplitude compared to the right hemisphere ($p=0.057$). No N170 amplitude differences were observed for words compared with faces ($p=0.99$) on the left side. However, a significant N170 amplitude enlargement in response to words was obtained compared with simultaneous stimuli ($p<0.005$) in the left hemisphere. In summary, faces elicited an enhanced amplitude over the right hemisphere (compared with words or simultaneous stimuli), and words elicited an enhanced amplitude over the left hemisphere (compared with simultaneous stimuli). No group differences or other factor interactions were observed for stimulus type discrimination. Both groups discriminated faces to the right and words to the left. Figure 20 shows the ERPs for stimulus type discrimination for both groups and Table 8 details the descriptive statistics.

Valence Effects

Faces. No main effects of valence ($F(1, 18)=1.07$, $p=0.31$), group ($F(1, 18)=0.05$, $p=0.81$) or hemisphere ($F(1, 18)=2.04$, $p=0.17$) were observed. A significant interaction between valence x group ($F(1, 18)=6.49$, $p<0.05$) and a strong interaction between valence x group x hemisphere ($F(1, 18)=18.32$, $p<0.0005$) were found, evidencing different patterns of emotional discrimination between groups in the right hemisphere. Post hoc comparisons performed on this last interaction (Tukey HSD test, MS = 59.05, df = 18.07) showed that controls discriminated facial valence in the right hemisphere, but ADHD participants lacked an N170 valence discrimination. Increased N170 amplitude for positive faces compared with negative ones in the right hemisphere yielded significant effects ($p<0.0005$) in control participants. In contrast to controls, no effects of valence were observed in the left ($p=0.31$) or right hemispheres ($p=0.87$) for ADHD patients. Moreover, when we compared the specific valences between groups in the right hemisphere, no differences were observed between positive and negative stimuli ($p=0.98$). Nevertheless, a strong effect indicated that the ADHD group had a significantly reduced amplitude for positive stimuli, compared with controls ($p<0.01$). No other relevant pairwise comparisons were significant. Figure 20 and table 8 show the N170 effects on valence for controls and patients.

	ADHD mean (SD)		**Controls** mean (SD)	
	Left	**Right**	**Left**	**Right**
a. Stimulus Type Effects				
Faces	-2.49 (1,64)	-2.59 (1.88)	-2.29 (1.64)	-3.95 (1.88)
Words	-1.77 (1.28)	-0.68 (1.15)	-2.91 (1.28)	-1.77 (1.15)
Simultaneous	-0.51 (1.58)	-0.88 (1.95)	-0.94 (1.58)	-2.07 (1.95)
b. Face Valence Effects				
Positive	-2.70 (1.63)	-2.81 (1.88)	-2.51 (1.62)	-4.94 (1.73)
Negative	-2.37 (1.69)	-2.47 (1.92)	-2.06 (1.65)	-2.85 (1.91)
c. Word Valence Effects				
Positive	-1.56 (1.39)	-0.76 (1.15)	-2.96 (1.39)	-1.76 (1.21)
Negative	-1.98 (1.18)	-0.60 (1.21)	-2.86 (1.11)	-1.77 (1.24)
d. Simultaneous Valence Effects				
Positive	-0.74 (1.57)	-1.14 (1.97)	-1.05 (1.12)	-2.48 (1.97)
Negative	-0.28 (1.72)	-0.73 (1.95)	-0.82 (1.62)	-1.57 (1.92)
e. Congruency Effects				
Congruent	-0.37 (1.23)	-0.82 (1.90)	-0.96 (1.56)	-2.01 (1.82)
Incongruent	-0.64 (1.87)	-0.95 (2.02)	-0.91 (1.61)	-2.13 (2.02)

Table 8. N170 amplitude values in response to stimulus type, valence and congruency factors.

Words. For word stimuli, valence was not discriminated by the N170 ($F(1, 18)=0.03$, $p=0.84$). The interaction between word valence x hemisphere was not significant ($F(1, 18)=0.32$, $p=0.57$). No group effects or interactions between group and other factors were observed. Means are shown in table 8. In brief, word valence was not discriminated by N170 in either controls or patients in either hemisphere.

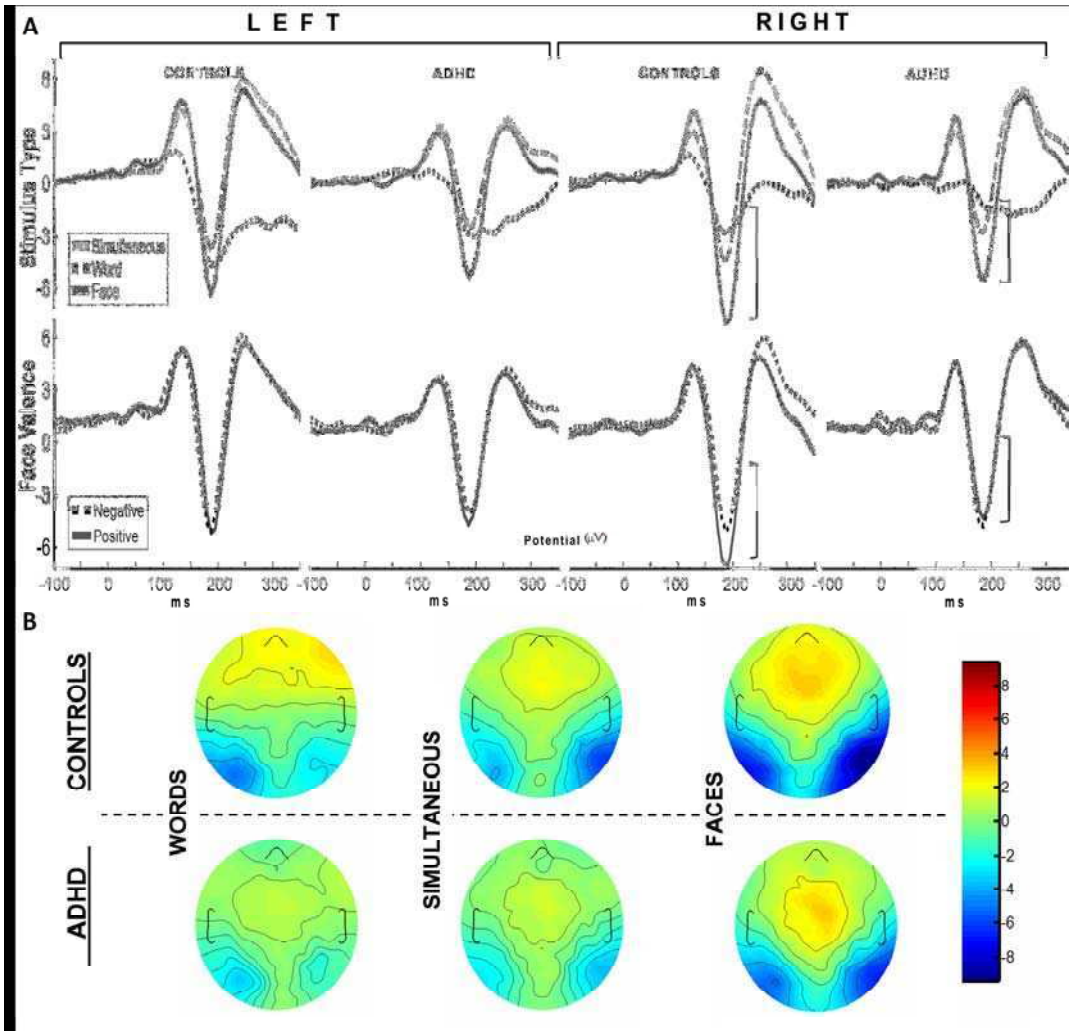

Figure 20. Main ERP results. A). N170 component for both hemispheres and groups. First Row: stimulus type effects. Second Row: Face Valence effects. B). Topographical Maps of N170 window for stimulus type effects (faces, words and simultaneous stimuli) in both ADHD and control groups.

Simultaneous Stimuli. Similar results were observed for simultaneous stimuli as were reported for facial valence discrimination. An interaction between valence x group x hemisphere ($F(1, 18)= 5.63$, $p<0.05$) suggested that controls still discriminated valence effects of simultaneous stimuli in the right hemisphere. Post hoc comparisons performed on this last interaction (Tukey HSD test, MS=30.15, df=18.26) showed that controls discriminated facial valence in the right hemisphere ($p<0.05$), but participants with ADHD lacked an N170 valence discrimination in the right hemisphere ($p=0.89$). No other pairwise comparisons yielded significant effects.

We performed additional analyses to investigate valence effects in relation to congruency between faces and words in the simultaneous stimuli. No effects of valence congruency were observed in the

N170 window, in either hemisphere or group, and nor was there any interaction. Table 8 shows the means and standard deviations for these conditions.

Source Activity

Figure 21A shows the distributed activation evoked by the ST conditions (face, words, and simultaneous) in both, controls and ADHD participants. The source of N170 neural activity was observed at different posterior portions of the fusiform gyrus (FG): left hemisphere for words, peak at –30, –81, and – 20 for controls, and –25, 87, and –21 for patients; right hemispheres for faces, peak at 40, 67, and –12 for controls, and 25, –86, and –18 for patients; and simultaneous stimuli, peak at 26, –76, and –16 for controls and 20, –86, and –20 for patients. Figure 21B and 21C shows the average intensity of the source peak and the FG for N170 window in all conditions and groups.

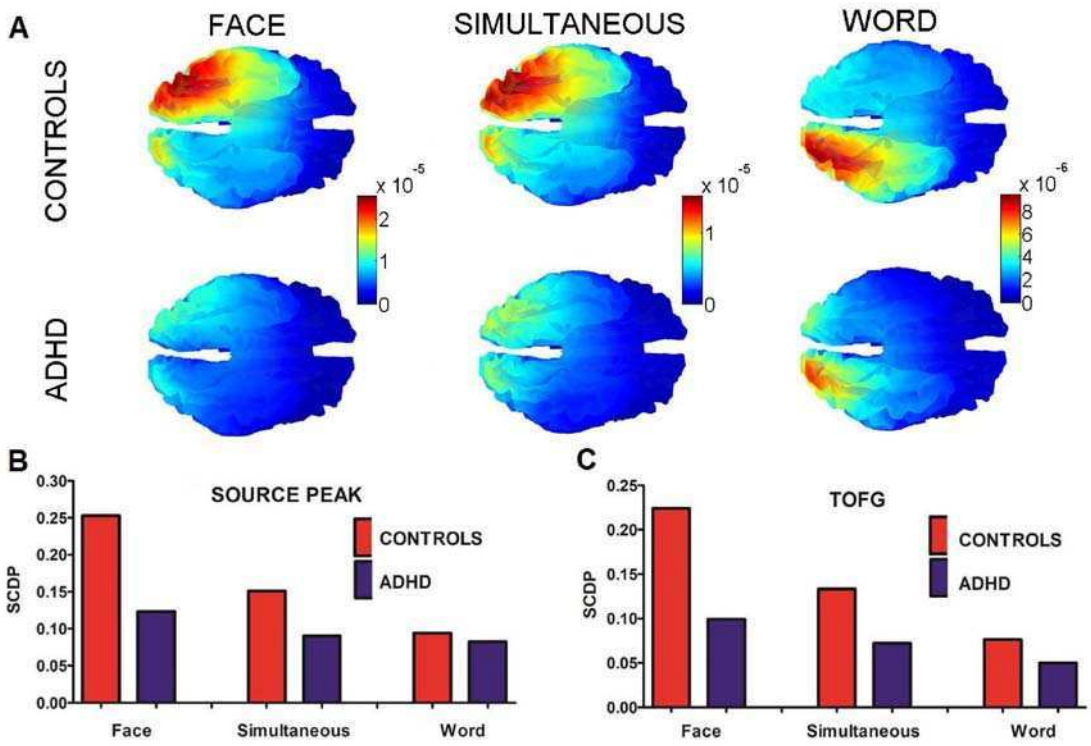

Figure 21. Cortical standardized current density power mapping of N170 (face, word, and simultaneous stimuli). (A) N170 source imaging estimation for controls (above) and patients (below) with ADHD. (B) Average values of estimated standardized current density power at maximum peaks of activation for each condition at N170 window. (C) Average values of N170 estimated standardized current density power at temporo-occipital fusiform gyrus (TOFG).

Multivariate Analysis

Correlations with general neuropsychology.

ADHD Patients. Phonological fluency was correlated with N170 stimulus discrimination (face-word; $r = 0.52$, $p < 0.05$) and face valence (positive-negative, $r = 0.64$, $p < 0.05$).

Controls. The TMT-A was positively correlated with N170 stimulus discrimination (face-word; $r = 0.31$, $p < 0.05$).

Executive Functioning

ADHD Patients. Working memory (Backward Digit Span) correlated with face valence (positive-negative, $r = 0.58$, $p < 0.05$). The N170 of valence discrimination for simultaneous stimuli (positive-negative) correlated with Digit Repetition, ($r = 0.71$, $p < 0.01$), Letters and Numbers (WAIS III) ($r =$

0.68, $p < 0.05$) and the Working Memory Index ($r = 0.54$, $p < 0.02$).

Controls. The TMT-B correlated positively with the N170 valence discrimination for simultaneous stimuli ($r = 0.589$, $p<0.05$) ($r = 0.64$, $p < 0.05$). The N170 valence discrimination for simultaneous stimuli correlated with the Working Memory Index ($r = 0.68$, $p < 0.01$).

Theory of Mind

ADHD Patients. RMET scores correlated significantly with N170 face valence discrimination (happy – angry; $r = 0.51$, $p < 0.05$).

Controls. RMET scores correlated significantly with N170 face valence discrimination (happy – angry; $r = 0.32$, $p < 0.05$).

In summary, all the emergent correlations are meaningful and have the expected sign.

N170 face emotional discrimination correlated in both groups with a social cognition task (RMET)

As occurred in BD, N170 face emotional discrimination also correlated with executive functions in ADHD (2 tasks) and controls (1 task).

And finally, N170 face valence in the presence of interfering words, correlated with two tasks of executive functions.

Chapter II: Error monitoring of monetary reward is affected in bipolar disorder and ADHD

H4a) BD and ADHD patients have cortical deficits in the processing of monetary reward.
H4b) The deficitary modulation of monetary reward processing in both patients correlate with clinical measures and executive functions performance.

This section includes experimental work done in collaboration with Agustin Ibanez, Marcelo Cetkovich, Hugo Urquina, Sandra Baez, Juan Kamienkowski, Teresa Torralva, Fernando Torrente, Sergio Strejilevich, Julia Teitelbaum, Esteban Hurtado, Raphael Guex, Alicia Lischinsky, Facundo Manes, under the supervision of Professor Mariano Sigman.

SPECIFIC MATERIALS AND METHODS FOR THIS EXPERIMENT

This section assesses decision-making using the behavioral and neural correlates of different tasks in adults with ADHD, those with euthymic BD and matched healthy controls. We included affective, risky and rapid-decision gambling paradigms. Specifically, we used the Iowa gambling task [IGT; (Bechara, Damasio et al. 1994)], a simple task of rational decision-making under risk [RDMUR (Fernandez-Duque 2007)] and a rapid-decision gambling task (RDGT) that elicits neurophysiological processes involved in the rapid evaluation of the motivational effect of events (Gehring and Willoughby 2002). We recorded event-related potentials (ERPs) from human participants as they performed the RDGT. Participant choices were followed by feedback that indicated the monetary gains or losses. The RDGT elicits a feedback error-related negativity (fERN) modulated by reward valence and a P3 sensitive to reward magnitude (Gehring and Willoughby 2002; Yeung and Sanfey 2004). We also estimated the neural sources of these components. Finally, to assess the relationship between decision-making tasks and individual differences, a multivariate analysis examined the extensive clinical and neuropsychological participant profiles.

Participants

Fifty participants (BD: n=13; ADHD: n=12; controls: n=25) received a full clinical assessment and neurocognitive profile, and their ERPs were recorded. Patients in the BD and ADHD groups were selected from the outpatient population of the Institute of Cognitive Neurology using the following inclusion criteria: 1) aged between 18 and 55 years old; 2) diagnosed with Type-I /II BD or adult ADHD according to the DSM-IV using the Structured Clinical Interview for DSM-IV (SCID); and 3) euthymia scores less than or equal to 8 points according to the Montgomery-Asberg Depression Rating Scale (MDRS) and less than or equal to 6 according to the Young Mania Rating Scale (YMRS) for at least 8 weeks and with no change in medication type or dosage over 4 months. Patients did not receive antipsychotics. Exclusion criteria were 1) other Axis-I diagnoses, except for generalized anxiety disorder and 2) a history of mental retardation, neurological disease, or any clinical condition that might affect cognitive performance. We assessed all participants using a standard diagnostic process that included neurological, neuropsychiatric and neuropsychological examinations. All patients with ADHD were taking methylphenidate, which was suspended on the day of the ERP recordings because this medication improves task performance (Volkow, Wang et al. 2004).

We recruited 25 healthy controls matched for sex, age, handedness, and years of education from a larger pool of volunteers who did not have a history of drug abuse or a family history of neurodegenerative or psychiatric disorders. All participants provided written informed consent in agreement with the Helsinki declaration.

Clinical, symptomatic and neuropsychological assessment

All participants completed a series of psychiatric and behavioral questionnaires to establish a clinical symptom profile that included depression, mania, impulsivity, anxiety, attention and hyperactivity/impulsivity scores. The Beck Depression Inventory II (Beck 1996) and the Montgomery-Asberg Depression Rating Scale (Montgomery 1979) rated depression. The Young Mania Rating Scale (Young, Biggs et al. 1978) and the Barratt Impulsiveness Scale (Barratt 1959) rated mania and impulsivity, respectively. The State-Trait Anxiety Inventory (Spielberger, Gorsuch et al. 1970) rated anxiety. We obtained an ADHD symptom profile from the inattention and hyperactivity/impulsivity scores of the ADHD Rating Scale for Adults (Barkley and Murphy 1998). A general neuropsychology test evaluated participants' basic attention and memory processes. Several tests, including the INECO Frontal Screening, evaluated executive functioning. Digit and symbol searching and forward digit span tasks evaluated attention, visual scanning and the efficient

production of multiple motor responses. The Rey Auditory Verbal Learning Test, which is composed of verbal learning, immediate and delayed recall and a distractor list, evaluated memory.
Several tests evaluated executive functioning. The INECO Frontal Screening assessed frontal lobe function via several subtasks: motor programming, conflicting instructions, go/no-go, backward digit span, spatial working memory, abstraction capacity and verbal inhibitory control. Trail Making B assessed attentional flexibility and attentional speed. Backward digit span, letter-number sequencing and an arithmetic test assessed mental manipulation and working memory. A go/no-go task that included correct, incorrect and omitted responses as percentages and reaction time assessed inhibitory control. We also included a phonological fluency task.

Data analyses

An ANOVA and Tukey's HSD post-hoc comparisons (when appropriate) compared demographic, neuropsychological and reaction time data across all three groups. The X^2-test examined categorical variables (e.g., sex). For the RDGT, we averaged accuracy and the ERP amplitudes for wins and losses (valence factor) as well as for large and small values (magnitude factor). We included a between-subjects factor for the group (patients with BD, those with ADHD and controls). Offline processing and EEG data analysis were performed using Matlab. After a valence and electrode position analysis of the fERN (Gehring and Willoughby 2002; San Martin, Manes et al. 2010), we selected the FCz site for all analyses based on the higher win-loss amplitude discrimination. A 225-281 ms timeframe for fERN and a 372-464 ms timeframe for P3 were selected for mean amplitude analysis. Although the P3 has more of a central distribution, its effects are reliable at FCz (Nieuwenhuis, Holroyd et al. 2004; Yeung and Sanfey 2004).
To perform multivariate comparisons between the ERPs and the neuropsychology tests, we calculated global scores for (a) valence (fERN: wins minus losses) and (b) magnitude (P3: large minus small). Spearman's rank correlations examined these global scores with regard to all clinical and neuropsychological tests after correcting for multiple comparisons (at $p<0.05$).

RESULTS

Table 9 shows the results from the demographic, clinical, and neuropsychological assessments.

Demographic data

We did not observe between-group differences with regard to age ($F[2, 47]=1.50$, $p=0.23$), sex ($X^2[2]= 0.00$, $p=1.00$) or education level ($F[2, 47]=1.50$, $p=0.23$).

Clinical and neuropsychological evaluation

Clinical evaluation

Patients with ADHD had higher scores of inattention, hyperactivity/impulsivity and depression than controls. In addition, patients with ADHD and those with BD had higher levels of trait anxiety than controls.

There was an expected between-group significant difference for the ADHD-RS-Inattention subscale ($F[2, 47]=12.44$, $p<0.001$) and the ADHD-RS-Hyperactivity/impulsivity subscale ($F[2, 47]=8.90$, $p<0.001$). Post-hoc comparisons (Tukey's HSD test, MS=24.75; df =47.00) showed that participants with ADHD had significantly higher inattention and hyperactivity/impulsivity scores compared to those with BD ($p=0.02$, $p=0.03$, respectively) and controls (both $p<0.001$). We observed a between-group difference for BDI-II scores ($F[2, 47]=5.63$, $p<0.01$). Post-hoc comparisons (Tukey's HSD test, MS=77.28; df =47.00) revealed higher levels of depression for participants with ADHD ($p<0.005$) compared to controls. In addition, we observed a between-group difference for MADRS scores ($F[2, 47]=3.37$, $p=0.42$). Post-hoc comparisons (Tukey's HSD test, MS=16.30; df =47.00) revealed more severe depressive symptoms for patients with ADHD ($p=0.04$) compared to controls.

Table 9. The demographic, clinical, neuropsychological and decision-making results.

		BD (n=13)	ADHD (n=12)	Control (n=25)	BD vs. ADHD	BD vs. CTR	ADHD vs. CTR
Demographics							
	Age (years)	40.2 (9.5)	31.4 (11.0)	35.1(11.2)	N.S	N.S	N.S
	Gender (F:M)	5:8	1:11	9:16	N.S	N.S	N.S
	Education (years)	16.5 (3.2)	15.5 (3.8)	17.2 (2.5)	N.S	N.S	N.S
Clinical Profile	Barkley						
	Inattention	7.6 (7.3)	13.2 (4.8)	2.5 (3.2)	**0.02**	N.S	**0.0001**
	Hyperactivity	7.0 (6.4)	12.8 (4.2)	3.5 (3.3)	**0.03**	N.S	**0.0004**
	BDI- II	8.0 (7.0)	17.4 (13.0)	5.7 (6.8)	N.S	N.S	**0.004**
	MADRS	3.3 (3.7)	4.6 (7.1)	1.0 (1.9)	N.S	N.S	**0.04**
	YMRS	0.3 (0.8)	2.2 (4.3)	0.3 (1.0)	N.S	N.S	**0.04**
	STAI						
	State	23.7 (6.7)	31.3 (10.6)	15.5 (8.7)	N.S	**0.02**	**0.0001**
	Trait	27.6 (6.1)	30.9 (5.5)	19.1 (6.4)	N.S	**0.0007**	**0.0001**
	BIS- 11	54.2 (22.3)	59.1 (24.7)	40.9 (12.8)	N.S	N.S	N.S
Decision Making	IGT net score	1546.5 (493.0)	1571.0 (635.9)	1847.1 (564.1)	N.S	N.S	N.S
	IGT blocks 1 and 2	-1.2 (8.1)	-1.0 (6.3)	0.65 (7.1)	N.S	N.S	N.S
	IGT blocks 4 and 5	1.0 (8.4)	2.7 (8.6)	4.3 (8.2)	N.S	**0.01**	N.S
	RDMUR Task	7.1 (1.0)	6.8 (1.1)	6.7 (1.1)	N.S	N.S	N.S
	RT RDMUR (ms)	133026.4 (29036.5)	135952.1 (67787.4)	159151.5 (77508.5)	N.S	N.S	N.S
Neuropsychological Measures	Digits Forward (WAIS)	6.6 (0.7)	6.6 (1.3)	6.8 (1.1)	N.S	N.S	N.S
	Digits and Symbols (WAIS)	55.6 (17.4)	61.1 (15.5)	60.0 (9.4)	N.S	N.S	N.S
	Symbols Searching (WAIS)	32.8 (6.8)	31.1 (11.1)	35.0 (7.4)	N.S	N.S	N.S
	RALVT						
	Immediate	51.3 (9.4)	49.7 (11.9)	54.4 (6.6)	N.S	N.S	N.S
	Distractor List	7.0 (2.5)	7.6 (3.3)	7.6 (2.1)	N.S	N.S	N.S
	Delayed Recall	11.2 (3.0)	11.2 (4.0)	12.1 (2.2)	N.S	N.S	N.S
	Recognition	14.3(1.0)	13.0 (2.0)	14.6 (1.0)	N.S	N.S	N.S
	IFS						
	Total Score	25.2 (3.2)	25.9 (3.2)	27.3 (2.5)	N.S	**0.05**	N.S
	Motor series	2.4 (1.0)	2.9 (0.2)	2.7 (0.5)	N.S	N.S	N.S
	Conflicting instructions	2.9 (0.2)	3.0 (0.0)	3.0 (0.0)	N.S	N.S	N.S
	Go- no go	2.9 (0.2)	2.9 (0.2)	3.0 (0.0)	N.S	N.S	N.S
	Backward digits span	4.3 (1.1)	4.2 (0.7)	4.8 (1.1)	N.S	N.S	N.S
	Verbal Working memory	1.9 (0.2)	1.7 (0.6)	2.0 (0.0)	N.S	N.S	N.S
	Spatial working memory	3.0 (1.0)	2.8 (0.9)	3.5 (0.1)	N.S	N.S	N.S
	Abstraction capacity	2.8 (0.1)	2.4 (0.1)	2.9 (0.2)	N.S	N.S	**0.008**
	Verbal inhibitory control	4.6 (1.4)	5.0 (1.0)	5.2 (0.8)	N.S	N.S	N.S
	Digits Backward (WAIS)	4.8 (1.1)	4.5 (1.1)	5.3 (1.2)	N.S	N.S	**0.04**
	TMT-B	82.6 (41.2)	70.9 (25.0)	68.6 (15.4)	N.S	N.S	N.S
	Go/no- go Task						
	Correct Responses (%)	90.7 (20.3)	97.7 (5.0)	100 (0)	N.S	**0.03**	N.S
	Commission errors (%)	7.6 (19.8)	4.1 (6.0)	0.37 (2.0)	N.S	N.S	N.S
	Omission errors (%)	9.2 (20.3)	4.5 (7.0)	00 (0.0)	N.S	**0.04**	N.S
	Reaction Time (ms)	392.2 (70.7)	342.0 (131.7)	396.5 (46.9)	N.S	N.S	N.S
	LNST	12.3 (2.9)	11.0 (2.9)	12.4 (2.2)	N.S	N.S	N.S
	Phonologic Fluency	19.0 (6.0)	17.1 (4.7)	22.4 (6.9)	N.S	N.S	**0.02**

Abbreviations. BDI-II: Beck Depression Inventory; MADRS: Montgomery-Asberg Depression Rating Scale; YMRS: Young Mania Rating Scale; BIS- 11: Barratt Impulsiveness Scale; IGT: Iowa Gambling

Table 9. The demographic, clinical, neuropsychological and decision-making results. Abbreviations. BDI-II: Beck Depression Inventory; MADRS: Montgomery-Asberg Depression Rating Scale; YMRS: Young Mania Rating Scale; BIS-11: Barratt Impulsiveness Scale; IGT: Iowa Gambling Task; RDMUR: Rational decision-making under risk; WAIS: Wechsler Adult Intelligence Scale; RALVT: Rey Auditory Verbal Learning Test; IFS: INECO Frontal Screening; TMT-B: Trail Making B; and LNST: Letters and Numbers Task.

The Young Mania Rating Scale scores also showed significant between-group differences ($F[2, 47]=3.46$, $p=0.03$). Post-hoc comparisons (Tukey's HSD test, MS=4.77; df =47.00) revealed higher levels of manic symptoms for patients with ADHD ($p=0.04$) compared to controls. We did not observe between-group differences for the BIS-11 scores ($F[2, 47]=2.52$, $p=0.09$). However,

significant differences between groups for STAI- State subscale ($F(2,47)=13.57$, $p<0.001$) and STAI-Trait subscale ($F(2,47)=16.85$, $p<0.001$) were observed. State subscale posthoc comparisons (Tukey test, HSD, MS=74.28; df =47.00) showed that BD ($p=0.02$) and ADHD ($p<0.001$) participants had significantly higher scores than control subjects. Also, post hoc comparisons (MS=38.27; df =47.00) showed higher scores for Trait subscale in BD ($p<0.001$) and ADHD ($p<0.001$) patients compared with the control group.

Neuropsychological assessment

The global score of the executive-function INECO Frontal Screening showed significant differences between groups ($F[2, 47]= 3.53$, $p < 0.05$). Specifically, patients with BD had lower go/no-go IFS subscale scores compared to controls and lower abstraction capacity IFS subscale scores than with ADHD. Furthermore, we observed impairments in patients with ADHD with regard to executive control and working memory. Posthoc comparisons (Tukey test, HSD, MS=7.54; df =47.00) showed lower performance for the BD group compared with controls ($p < 0.05$). On abstraction capacity IFS subscale, significant differences between groups were observed ($F(2, 47)=4.93$, $p < 0.05$). Posthoc comparisons (Tukey test, HSD, MS=0.24; df =47.00) showed lower performance in the ADHD group ($p<0.01$) compared with controls. On the Go-no go Task, accuracy on go trials ($F(2, 47)=3.31$, $p < 0.05$) and omission responses percentage ($F(2, 47)=3.17$, $p < 0.05$), showed significant differences between groups. Posthoc comparisons on accuracy (MS=111.49; df =47.00) showed lower performance for the BD group compared with controls ($p < 0.05$). Also, post hoc comparisons (Tukey test, HSD, MS=120.69; df =47.00) showed that BD had significantly higher omission responses percentage than did control subjects ($p < 0.05$). No differences were observed on either the commission responses percentage ($F(2, 47)=2.17$, $p=0.12$) or the reaction time ($F(2, 47)=2.63$, $p=0.08$).

Regarding the other measures of executive functioning, the score on verbal Phonologic Fluency Task showed significant differences between groups ($F(2, 47)=3.86$, $p < 0.05$). Posthoc comparisons showed lower performance for the ADHD group compared with controls ($p<0.01$). The score on the Backward Digit Span showed a trend towards lower performance for the ADHD group ($F(2, 47)= 3.14$, $p=0.05$). In contrast, no differences were observed between groups on the TMT-B ($F(2, 47)=1.10$, $p=0.34$), or the Letters and Numbers task ($F(2, 47)=1.36$, $p=0.26$).

The neuropsychological assessment of decision-making (IGT and RDMUR)

The IGT net score did not reveal a between-group difference ($F[2, 47]=1.36$, $p=0.26$). Furthermore,

we did not observe an interaction between block and group. To compare the initial and final blocks, we performed a separate analysis between the average of Blocks 1-2 and 3-4. Although an ANOVA did not find group differences in Blocks 1-2 ($F[4, 90]=1.05$, $p=0.38$), it did for Blocks 4-5 ($F[4, 90]=3.50$, $p < 0.01$). Post-hoc comparisons (MS=57.75, df = 47) revealed that patients with BD had impaired performances compared to controls ($p=0.01$, see Figure 22.A).

When comparing RDMUR tasks (Figures 22.B and 22.C), we did not observe significant between-group differences with regard to total score ($F[2, 47]=0.64$, $p=0.52$) or total reaction time ($F[2, 47]=1.07$, $p=0.34$).

The neurophysiological measures of Decision-Making

Reaction time. We did not observe main effects of valence or magnitude, nor did we observe group effects or interactions. However, patients with ADHD had longer response times in general compared to controls. Regarding overall RTs, a group effect was obtained ($F(2, 47)=3.47$, $p < 0.05$). Post hoc comparison performed over this effect (Tukey HSD test, MSE = 1798, df = 47) evidenced that ADHD patients made longer responses (M=1039ms, SD=122) than to controls (M= 650ms SD=84). No differences were observed between BD (M=825ms, SD=117) and controls. No main effects or interactions of valence and magnitude were observed in reaction times.

RDGT: ERPs

fERN. We did not observe main effects of valence ($F[1, 47]=3.30$, $p=0.07$) or magnitude ($F[1, 47]=0.15$, $p=0.69$); however, as expected, we observed significant valence x group ($F[2, 47]=3.62$, $p < 0.05$) and magnitude x group interactions ($F[2, 47]=5.11$, $p<0.005$). To analyze the simple effects for control participants as well as those with ADHD and those with BD, we examined the fERN component of each group separately (see Table 10 for descriptive statistics).

Controls. We did not observe an effect of magnitude ($F[1, 11]=0.34$, $p=0.85$); however, as expected, a significant effect of valence ($F[1, 11]=10.69$, $p<0.01$) revealed less positive amplitudes on trials with losses than those with wins. In addition, we observed a significant valence x magnitude interaction ($F[1, 11]=11.52$, $p<0.01$). Post-hoc comparisons (MS=2.27; df =47.00) revealed that amplitudes after a large win were more positive than those after large ($p<0.001$) and small losses ($p < 0.05$).

Patients with BD. We did not observe an effect of valence ($F[1, 12]=0.29$, $p=0.59$); however, we did find a significant effect of magnitude ($F[1, 12]=7.50$, $p < 0.05$), revealing that the amplitudes associated with large reward were more positive than those associated with smaller ones. There was not a significant valence x magnitude interaction ($F[1, 12]=0.70$, $p=0.41$).

Patients with ADHD. We did not observe an effect of valence (F[1, 11]=0.02, p=0.87); nevertheless, an effect of magnitude (F[1, 11]=3.54, $p < 0.05$) showed that, similar to patients with BD, the amplitudes associated with large magnitude were more positive than those associated with smaller ones. There was no significant valence x magnitude interaction (F[1, 11]=1.12, p=0.31). Figure 23.A shows the main effects of valence on fERN for all groups.

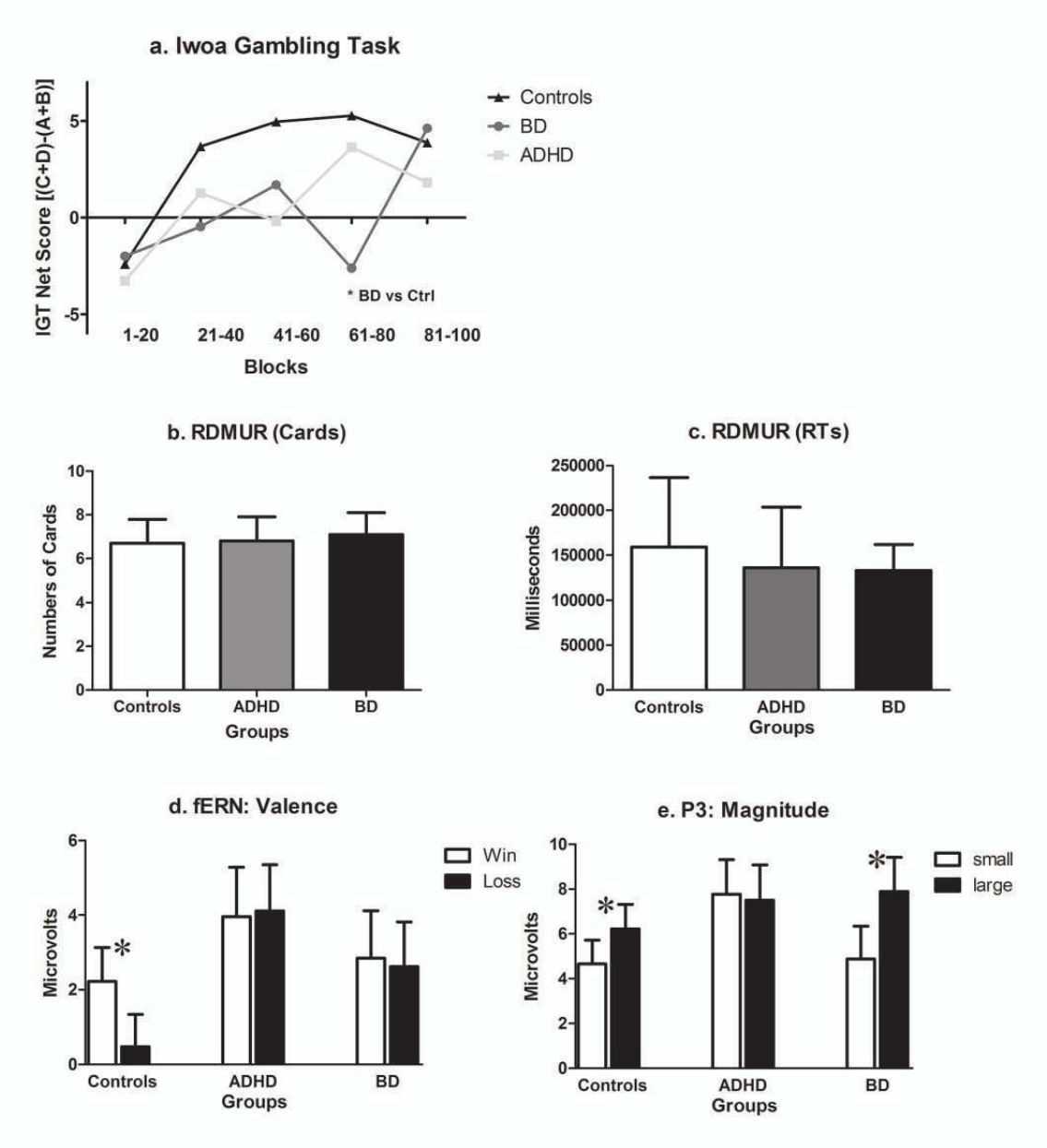

Figure 22. Decision-making task results (IGT, RDMUR and RDGT). A) IGT net score of Blocks 1 to 5; B) The number of cards selected in the RDMUR task; c) Total reaction time in the RDMUR task; D) Valence effects in the RDGT task; ERP mean amplitudes at the fERN timeframe; and E) Magnitude effects in the RDGT task; ERP mean amplitudes at the P3 timeframe. Boxes indicate SDs in b, c, d and e.

	BD mean (SD)	ADHD mean (SD)	Controls mean (SD)
fERN			
Valence			
Win	2.85 (1.27)	3.96 (1.32)	2.22 (0.91)
Loss	2.62 (1.20)	4.11(1.24)	0.48 (0.86)
Magnitude			
5	1.94 (1.26)	3.01 (1.31)	1.21 (0.90)
25	3.53 (1.20)	4.49 (1.25)	1.49 (0.86)
Interaction			
Win 5	1.82 (1.28)	4.75 (1.33)	1.90 (0.92)
Win 25	3.87 (1.36)	3.17 (1.42)	2.53 (0.98)
Loss 5	2.05 (1.30)	4.40 (1.36)	0.92 (0.94)
Loss 25	3.18 (1.19)	3.81 (1.24)	0.04 (0.86)
P3			
Valence			
Win	6.77 (1.44)	7.33 (1.50)	5.52 (1.04)
Loss	6.00 (1.55)	7.94 (1.62)	5.35 (1.12)
Magnitude			
5	4.21 (1.48)	7.77 (1.54)	4.65 (1.07)
25	8.89 (1.52)	7.50 (1.58)	6.22 (1.09)
Interaction			
Win 5	4.92 (1.47)	7.73 (1.53)	4.72 (1.06)
Win 25	8.62 (1.56)	6.94 (1.63)	6.33 (1.13)
Loss 5	4.82 (1.61)	7.82 (1.68)	4.59 (1.16)
Loss 25	7.17 (1.62)	8.06 (1.69)	6.12 (1.17)

Table 10. ERP descriptive statistics. Mean (SE) amplitude values of valence and magnitude for patients with BD, those with ADHD and controls

P3. There was a main effect of magnitude ($F[1, 47]=12.39$, $p<0.001$). In addition, we observed a significant interaction between magnitude and group ($F[2, 47]=4.52$, $p < 0.05$). As before, we analyzed the P3 component of each group separately.

Control Group. A significant effect of magnitude ($F[1, 24]=10.40$, $p<0.005$) revealed that the amplitudes associated with large reward magnitudes were more positive than those associated with small magnitudes. There was not a significant effect of valence ($F[1, 24]=0.20$, $p=0.65$) or a valence x magnitude interaction ($F[1, 24]=0.14$, $p=0.90$).

Patients with BP. A significant effect of magnitude ($F[1, 12]=16.57$, $p<0.001$) revealed that large reward magnitudes were more positive than small magnitudes. This effect was almost two times larger than the effect observed in the control group. There was not a significant effect of valence ($F[1, 12]=1.20$, $p=0.29$) or a magnitude x valence interaction ($F[1, 12]=1.35$, $p=0.26$).

Patients with ADHD. We did not observe significant main effects of magnitude ($F[1, 11]=0.10$,

p=0.75) or valence (F[1, 11]=0.28, p=0.60) or their interaction (F[1, 11]=0.32, p=0.57).

Figure 23 shows the main effects of valence on fERN (23.A) and effects of magnitude (23.B) for all groups. Figures 22.D and 22.E summarize the ERPs results. Reward valence affected fERN in controls, but we did not observe an effect for either patient group. There were magnitude effects at P3 in the controls, which were reduced in patients with ADHD and enhanced in those with BD.

Source activity

Figure 24.A shows the distributed activation evoked by the valence and magnitude of the rewards. Following a t-value comparison between signal and noise, valence presented a maximum over 268 ms (fERN) and magnitude presented a maximum over 432 ms (P3). Consistent with the ERP results, both patient groups presented a reduced activation of reward valence at fERN window compared to controls. The magnitude discrimination at P3 was more reduced in patients ADHD, followed by those with BD and controls. The source of fERN/P3 neural activity was estimated to be at different portions of the cingulate cortex (aCC, mCC and pCC). The cingulate activity at the fERN window (Figures 24.B and C, top) was reduced for patients with ADHD and those with BD compared to controls (valence effect). Medial and posterior cingulate regions of interest (ROIs) showed magnitude effects at P3, decreasing from controls to patients with BD to those with ADHD (Figures 24.B and C, bottom).

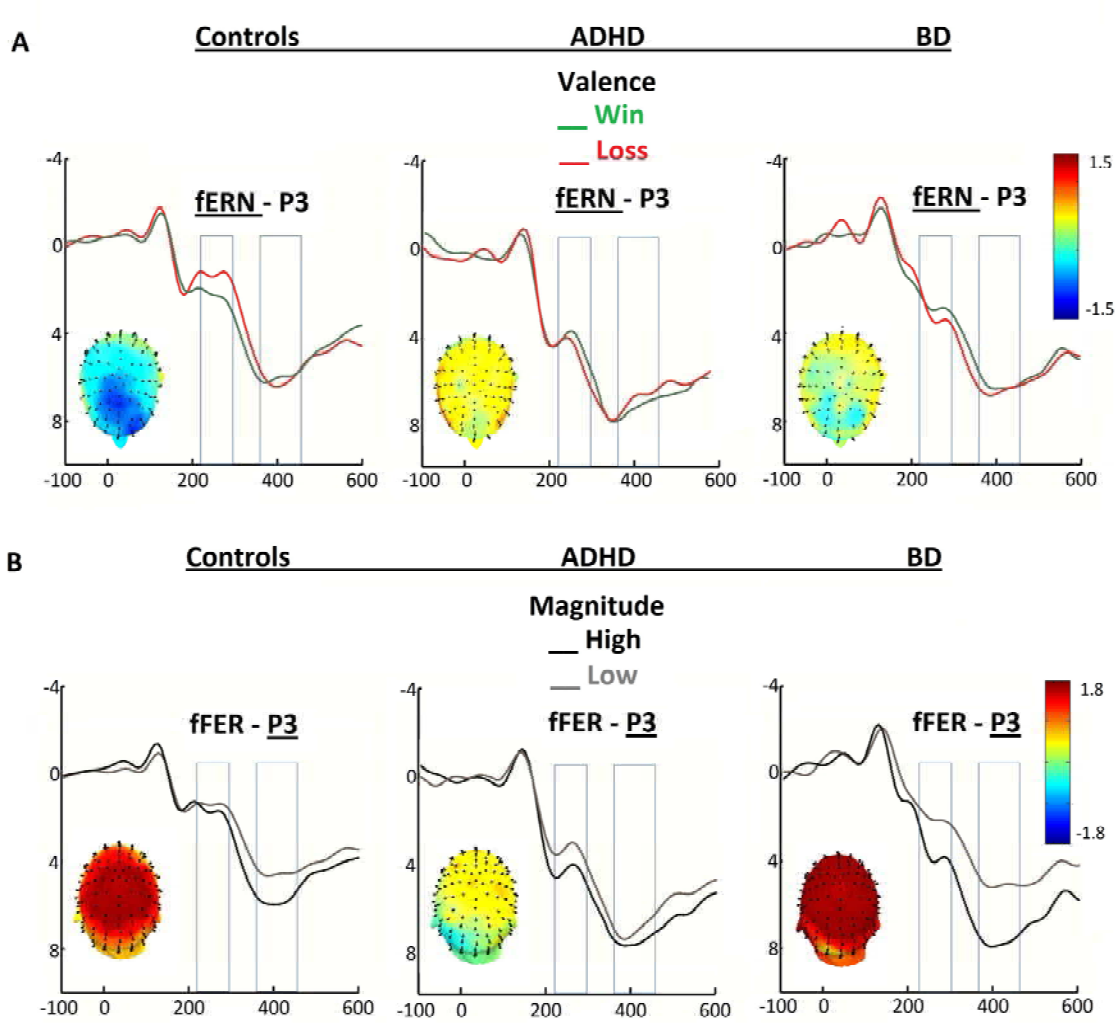

Figure 23. fERN and P3 modulation of valence and reward magnitude. A) FERN Valence modulation (wins vs. losses) in controls, patients with ADHD and those with BD. Voltage maps show the scalp modulations (losses minus wins) at the fERN timeframe. B) Magnitude modulation (large vs. small rewards) in controls, patients with ADHD and those with BD. The P3s of controls discriminated reward magnitudes whereas this effect was absent in patients with ADHD but enhanced in patients with BD. Voltage maps show the scalp modulations (large minus small) at the P3 timeframe.

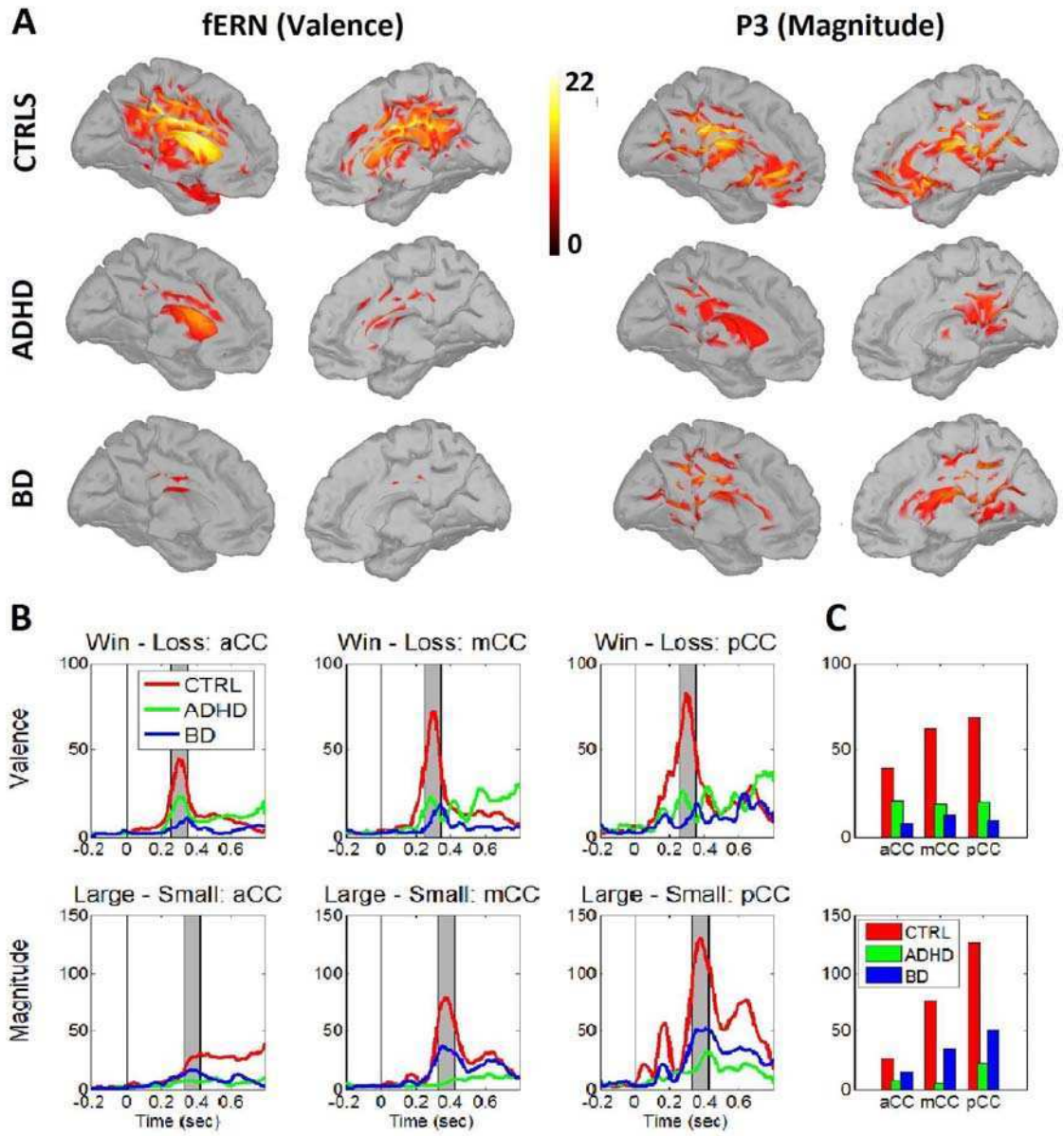

Figure 24. Cortical current density mapping of valence and reward magnitude. A. The source estimation of distributed valence dipoles (fERN, left) and magnitude effects (P3, right) for controls, patients with ADHD and those with BD. Color-map values represent the t-values of comparisons between signal and noise. B. A time-series of the absolute power activation evoked by valence and reward magnitudes at the anterior, medial and posterior cingulate cortex (aCC, mCC, pCC). C. The average values of absolute power at aCC, mCC and PCC for the valence and magnitude effects for all groups. We obtained the ROIs at aCC, mCC and pCC using a Tzourio-Mazoyer partition.

Correlations (Clinical/Neuropsychological Assessments and ERPs)

Control Group. Impulsivity (BIS-11: r=-0.32) and depression (MADRS: r=-0.48) were negatively correlated with fERN win/loss discrimination. ADHD-RS-Inattention subscale scores were positively correlated with P3 amplitudes of magnitude discrimination (r=0.40). Working memory (backward digits span) was negatively correlated with P3 magnitude discrimination (r=-0.40).

Patients with BD. Depression level (MADRS total score, r=-0.47 and Beck-II, r=-0.41) was negatively correlated with win/loss discrimination. Anxiety scores (STAI- Trait) were positively correlated with P3 magnitudes discrimination (r=0.61). Inhibitory control (incorrect responses on a go/no-go task) was positively correlated with fERN win/loss discrimination (r=0.36) and with P3 magnitude discrimination (r=0.43). Go/no-go reaction times were negatively correlated with fERN win/loss discrimination (r=-0.39).

Patients with ADHD. Significantly high ADHD-RS-Inattention (r=-0.55) and ADHD-RS-Hyperactivity-impulsivity subscale scores (r=-0.39) were negatively correlated with fERN win/loss discrimination. With regard to executive functions, the IFS total score was positively correlated with fERN win/loss discrimination (r=0.43). Working memory (numbers and letters, r=0.54; WAIS-working memory index, r=0.41) and attention (WAIS-digit score; r=0.58) were also positively correlated with fERN win/loss discrimination.

In summary, both patients presented an impaired valence modulation of the fERN, but a modulation in magnitude of the monetary reward, in contrast to controls. In relation to P3, Controls and BD, but not ADHD, presented and effect of valence.
fERN presents all meaningful and consistent correlations.
In controls fERN win/loss discrimination correlates negatively with impulsivity and depression scores.
In Bipolar patients fERN win/loss discrimination correlates negatively with depression and slow reaction time in inhibitory control, and positively with inhibitory control performance (both executive functions).
In ADHD patients fERN win/loss discrimination correlate negatively with inattention and hyperactivity scores and positively with performance in four executive functions tasks.
P3 did not present meaningful correlations.

General Discussion

The set of experiments presented here coherently provide support for a view in which rapid facial recognition is not a modular process, independent of cognitive, emotional and social representations. First, we showed that the N170 was affected by social cognition scores. It must be emphasized that the relevance of this finding is that the N170 is a very rapid component (only 170 ms) of face recognition which has been observed even in subliminal presentations. This has led to think that it is a feed-forward, automatic encoding of a face which only later on interacts with other systems that provide social and emotional information. Instead, our data show that even this very early component is affected by such cognitive features. The results of this thesis then establish that the global influence of a broad network that acts very rapidly in the first encoding stages of perception (section I).

In what follows we discuss in detail how these results relate to controversies on face recognition and emotion and social processing, their more general implications for the organization of brain computations and clinical implications.

Taking the results in section I, we can conclude that the broad network that takes part in early face perception is implicated in complex social cognition, including theory of mind, but also in frontal executive functions, reflecting a close interaction between both systems. This result also support the view of a brain network with dynamic transitions between emotional and more cognitive states, a version of which establishes that same brain areas may account for cognitive or emotional responses depending on the context or task demands (Pessoa 2008). In fact, two psychiatric disorders that present shared social cognition and frontal deficits show an impaired N170 in response to facial emotions (sections II and III).

A similar association occurs between low level rapid processing of monetary feedback and executive function tasks (Chapter II). A rapid and short (millisecond scale) brain potential (fERN) evoked by monetary feedback showed a robust and consistent association with frontal functioning clinical measures in ADHD, depression in BD, and both types of measures in controls. In particular, fERN valence modulation correlated negatively with depression scores in BD, negatively with inattention and hyperactivity scores in ADHD and negatively with both depression and impulsivity in controls. This result suggests that rapid feedback processing is embedded in a complex frontal network that takes part in planning, action monitoring, and global control of other networks, severely affected in ADHD. But it also takes part in emotional state regulation in BD. Note that in both patients fERN valence modulation is also associated with executive functions measured by neuropsychology.

The results of this thesis show that early perception may not be modular, but distributed. The currently dominant view among many cognitive psychologists proposes two broad sets of processes: those that are controlled and those that are automatic. The dichotomous scheme is summarized in a recent review (Lieberman 2007), which enumerates the various properties attributed to controlled and automatic processing. Controlled processes have long been assigned a host of other attributes: They are slow, effortful, reflective, arise late in evolution and development, and often involve language-based declarative reasoning and reflective thinking. Automatic processes are thought to be faster, spontaneous, reflexive, shared in common with a wide range of species and dominant early in development, and often involve emotions (Adolphs 2009). This view influenced another view, which argues that emotional processes as facial perception are automatic and central to social evolution, and hence evolved to a dedicated module. Some evidences support this view, mainly the existence of the FFA. However, the FFA also can be activated by nonface objects provided that subjects acquire substantial expertise with them, such as birds, cars, or butterflies in experts for those categories (Gauthier, Skudlarski et al. 2000). Although the disproportionate activation by faces argues for a domain-specific module specialized to process a particular category of stimuli (faces) (Kanwisher 2000), the other data argue for a particular type of processing rather than processing for a particular stimulus category (Tarr & Gauthier 2000). Other imaging data have argued that faces are never represented in a single cortical region, but in a distributed region of cortex considerably more extensive than the FFA (Haxby et al. 2000)

Our findings provide evidence towards a distributed but stable network of social cognition, whose interactions occurred at a short time-scale, with strong feedback connections. It includes low-level components (as the rapid extraction of facial emotion) and high order processors (e.g. those that manipulate other's state of mind and social context).

The amygdala may be a nodal component in the maintenance and regulation of this network, in part because its massive connectivity with other brain areas and also for its nodal position within the network. Studies with bilateral amygdala lesioned patients support this view (Buchanan, Tranel et al. 2009).

In healthy subjects, the N170 response to facial emotional valence, but not to stimulus type, is associated with three social cognition tasks: the reading the mind in the eyes test, Faux pas test and the first block of the Iowa Gambling Task. Better social skills are related to greater N170 valence discrimination. First, scores on a measure of theory of mind related to emotional inference (RMET) correlated significantly with the N170 emotional discrimination. This result suggests that the more basic theory of mind processes (e.g., emotional inference) are supported, at least in part, by early brain activity that is sensitive to facial emotional valence. Second, scores on the Faux pas test (FPT)

correlated with the N170 compatibility discrimination. The compatibility effect may be associated with the cognitive ability to make inferences about others' mental states at a more complex level. Additionally, the FPT involves dealing with a high number of cognitive and affective components, including inferences about others' mental states and contextual cues (Riveros, Manes et al. 2010), as compared to the RMET (Stone, Baron-Cohen et al. 1998; Baron-Cohen, Wheelwright et al. 2001; Ochsner 2008; Ahmed and Stephen Miller 2010). Our pattern of association for the two tests follows the direction of this distinction (the FPT as associated with more complex ToM processes and the RMET with more basic emotional stages). Finally, we found that only the first block of the Iowa Gambling Task, which contains five blocks, correlated significantly with the ERPs emotional discrimination for simultaneous stimuli. This first block consists of an exploration of the cards used in the task. It reflects decision making under total uncertainty (because participants are unaware of the cards' properties) and is related to emotional decision making. This association between emotional processing and the first IGT block is relevant because the subsequent four blocks of the IGT cannot be considered to reflect decision making under conditions of ambiguity, but rather, they reflect decision making under conditions of risk (Dunn, Dalgleish et al. 2006). Research that was conducted using participants with neuropsychiatric diagnoses also supports this distinction (Torralva, Roca et al. 2009). The current findings suggest that basic emotional discrimination is related to an implicit and emotional ability to make decisions in an ambiguous context.

The N170 emotion discrimination in simultaneous stimuli in healthy subjects correlated positively with Trial Making Test B (TMT-B). This result suggests that there is an association between simultaneous task segregation, and the physiological segregation needed to focus on a face and ignore a word. Moreover, TMT-B is a test that is sensitive to frontal lobe damage (Gouveia, Brucki et al. 2007), suggesting that the early ERPs discrimination of face valence in the presence of interfering stimuli, which occurs in many cognitive processes that require executive control, depends on frontal lobe executive functioning.

Consistent with previous reports, the main source of the N170 was estimated in the right FG for faces (Rossion and Gauthier 2002); (Rossion, Joyce et al. 2003) and in the left FG for words (Maillard, Barbeau et al. 2010); (Rossion, Joyce et al. 2003). In addition, simultaneous stimuli (face-word) elicited a bilateral (right predominant) activation of the fusiform cortex. These results highlight the role of the lateralized FG in object recognition of category-specific visual information (Rossion, Joyce et al. 2003).

Two psychiatric disorders that present anatomical and functional connection deficits in some shared areas implicated in social cognition (e.g. amygdala and ACC) showed an affected brain processing of facial emotions and reward processing in a gambling task. These results are in line with our previous findings, suggesting that the social cognition network is heavily disbalanced in these disorders. Our

findings have an important clinical relevance, because they can be used to design and develop electrophysiological techniques to help in the detection of pathologies at early stages, its management and treatment. Facial processing may be altered before the full manifestation of these disorders during development, especially for BD. The same principle can be applied to the fERN, which showed very consistent associations with frontal deficits (e.g. executive functions) and clinical state. The fERN reward discrimination covaries in a consistent way with depression in BD and inattention and hyperactivity scores in ADHD.

BD presented a reduced N170, and a reduced facial emotional modulation (in both, facial and simultaneous stimuli). Furthermore, BD patients presented an early cortical discrimination of negative words valence, suggesting the activation of negative bias in the semantic stimuli processing. N170 source analysis evidenced reduced BD fusiform gyrus activation. An important result is the association of deficiencies in facial emotional modulation and clinical measures, in particular indices of mania and depression (inversely and directly correlated, respectively). Nevertheless, BD presented a normal accuracy in the DVT, may be due its easiness, relying on redundant circuits to solve the task.

Regarding words, BD group showed amplitude enhancement of N170 negative valence in the left hemisphere, suggesting an early attentional bias toward negative information. The reactivity toward negative semantic information is consistent with the increased perception of allocation to negative than to positive emotional cues (Leppanen 2006; Eimer and Holmes 2007). Additionally, enhanced recognition of negative facial expression, such us disgust (Harmer, Grayson et al. 2002), have been reported in euthymic BD (Malhi, Lagopoulos et al. 2007).

In agreement with previous studies (Henry, Van den Bulke et al. 2008), we found that BD patients showed higher levels of anxiety. According with previous reports, the pattern of cognitive functioning revealed that BD patients showed deficits in the attentional domain (Elshahawi, Essawi et al. 2011) and some failures in executive tasks (Torralva, Roca et al. 2009). Also, as previously demonstrated (Martino, Strejilevich et al. 2010), we found lower performance in BD group on FPT, suggesting failures in theory of mind process.

The social perceptual component of theory of mind consists in the capability to perceive mental states of others based on observable information like facial expressions, and include the capacity to distinguish between people and objects (Tager-Flusberg and Joseph 2003). Accordingly, the results exposed in this thesis showed that stimulus type and word valence are associated with theory of mind measures, which may be related with the deficits observed in BD patients in these processes. Thus early abnormal semantic and facial processing would influence object recognition and emotional categorization process, affecting the building blocks of further impaired social cognition skills (de Almeida Rocca, de Macedo-Soares et al. 2008).

Abnormalities in prefrontal cortex (PFC) and amygdala circuitry appear to be critical factors in the

dysregulation of affective disorders (Hariri, Bookheimer et al. 2000; Rich, Fromm et al. 2008).

Although ADHD showed high accuracy on the DVT, the adults with ADHD showed deficits in N170 emotion discrimination for facial stimuli. In particular ADHD presented reduced N170 amplitude for positive stimuli in the right hemisphere.

Notably, in ADHD participants, N170 emotion processing was associated with performance on an emotional inference theory of mind task and N170 for simultaneous stimuli was associated with executive functioning, especially working memory.

Recently, it has been proposed that in ADHD, a possible reduction in amygdala activity [see (Plessen, Bansal et al. 2006)] in response to positive stimuli may lead to reduced activation of the reward system and in turn to impaired processing of positive emotional stimuli (Herrmann, Schreppel et al. 2009). ADHD appears to involve predominantly right hemispheric dysfunction [for a review see (Barr 2001) and (Booth, Burman et al. 2005)]. Impaired emotional facial processing is the most consistently reported form of social cognitive impairment in ADHD (Uekermann, Kraemer et al. 2010).

Participants with ADHD presented deficits in recall performance on the RAVLT, as well as some executive impairment, which is not a new issue (Torralva, Gleichgerrcht et al. 2010). In addition, we found a subtle deficit in theory of mind indexed by the RMRT, and this task correlated with cortical deficits in face valence. At the same time, in the ADHD patients the ERPs for simultaneous stimuli valence discrimination were associated with higher levels of executive functioning and working memory. Both executive and theory of mind deficits in ADHD have been reported elsewhere, and these deficits are often both associated with the disorder (Kalmar, Wang et al. 2009; Uekermann, Kraemer et al. 2010).

The finding of a combined executive and social impairment in ADHD is consistent with current neural models of cognition (Pessoa 2009) and particularly with dysfunction of frontostriatal structures in ADHD [for reviews (Bush, Valera et al. 2005; Marsh and Williams 2006; Uekermann, Kraemer et al. 2010)]. We identified brain markers of impaired facial emotion discrimination in participants with ADHD. Those deficits were related to subtle differences in theory of mind and executive functioning, supporting the frontostriatal dysfunction hypothesis of ADHD.

Decision Making

Patients with ADHD presented a neural pattern indicative of deficient valence (fERN) and reward

magnitude learning (P3). This pattern was associated with clinical evaluations of impulsivity, hyperactivity and inattention as well as impairments in executive function and working memory. These results are consistent with the clinical features of ADHD with regard to decision-making: If the learning of valence and reward magnitude from the environment is impaired, then information concerning which decisions are most important will be reduced. Thus, decisions will be based on impulsivity or will not have a learned strategy.

Patients with BD presented a pattern of cortical modulation based on the saliency of reward magnitudes regardless of learning via feedback. There was no fERN valence modulation; conversely, only the magnitude of the reward affected this variable. This results are consistent with the hypothesis that there is reduced sensitivity to emotional reward or punishment contexts in BD (Chandler, Wakeley et al. 2009). The ERP pattern of the data of chapter II was associated with mood states (i.e., clinical measures of depression and anxiety) and inhibitory control.

We found reduced activity in the cingulate cortex (aCC, mCC and pCC) in both patient groups compared to controls. This activity was especially reduced for patients with BD at the fERN (valence) and those with ADHD at the P3 (magnitude). These results suggest that one of the main circuits associated with decision-making, the so called "action selection-monitoring system", is impaired for both groups but at different stages.

The results are relevant in numerous aspects. First, the behavioral measures of affective and risky gambling tasks are not sensitive enough to assess these disorders' well-known deficits in decision-making. Second, both patient groups show an abnormal neural processing of valence and reward magnitudes to a gambling task but that this pattern was associated with different clinical and neuropsychological profiles. Finally, these results are consistent with the models of cingulate cortex activation to reward, action selection and action monitoring.

Higher levels of inattention, hyperactivity and impulsivity were associated with reduced fERN win/loss discrimination in patients with ADHD, which confirms the association between impulsivity and decision-making these patients (Malloy-Diniz, Fuentes et al. 2007). In addition, executive function was associated to decision-making-related ERPs, which confirms previous reports of an association between inhibitory control, decision making and working memory (Mantyla, Still et al. 2010). The latter result suggests that difficulties in sustaining attention when updating working memory affect the decision-making of patients with ADHD. Likewise, this results are consistent with reports of reduced responses to rewards and reinforcements in children with ADHD (Iaboni, Douglas et al. 1997; Crone, Jennings et al. 2003), which suggests an impaired sensitivity to learning via feedback (Luman, Oosterlaan et al. 2005).

As expected, patients with ADHD had higher inattention and hyperactivity/impulsivity scores than those with BD and controls. Patients with ADHD also had higher levels of depression, which is common in this clinical population and congruent with previous reports (Torralva, Gleichgerrcht et al. 2010).

Chapter II results reveal a clinical association between neural substrates and the common, well-known impairments of decision-making in patients with ADHD and those with BD.
At a theoretical level, chapter II results highlight the role of monitoring systems and their relevance in decision and reward processing. Although the orbitofrontal cortex is one of the most relevant areas in decision-making, a network that includes monitoring systems and reward processing has been revealed (Rushworth, Behrens et al. 2007; Rangel 2008; Rangel, Camerer et al. 2008; Kable and Glimcher 2009; Gleichgerrcht, Ibanez et al. 2010). The role of the cingulate cortex in selection and monitoring, along with that of the amygdala and basal ganglia in reward systems, should be affected in patients with ADHD and those with BD [(Wang, Kalmar et al. 2009); for a review of the latter group, see (Marchand and Yurgelun-Todd 2010)].

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