Individual differences in emotion processing

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Abstract

During the last decades neuroscientists have put significant efforts towards a definition of a unique and comprehensive emotion brain circuit. However, internal and external variables influencing emotion behavior are much more prominent than expected. The present doctoral thesis aims to add some crucial knowledge on individual differences of emotions, as well as their biological underpinnings, by merging evidence obtained with psychological, genetic and brain imaging assessments. In particular, I adopted a protocol of affective state induction, by which I investigated the effect of temporary variations of mood on the emotion processing in healthy subjects at both the behavioral and neuronal level. Then, I have also investigated the interaction between affective states and affective traits on the emotional behavior as well as the interaction between affective states and genetic traits. Moreover, this thesis has characterized in healthy subjects the neural correlates of the emotion intelligence ability, an additional important aspect in the emotional *panorama*. Finally, I studied emotion brain connectivity in a schizophrenia population and in a population of healthy subjects at familial or genetic risk for schizophrenia.

Findings of the thesis demonstrated that temporary affective states are capable of modulating emotions even at an early, automatic stage of processing, at both behavioral and neuronal level. Moreover, this modulation is affected by personality and genetic traits of the individual. Furthermore, this thesis revealed that social and emotional abilities also represent a source of variability in the way brain processes the emotional information, positing the neural basis of conceivable interventions in this direction. Finally, the present work discovered that emotional anomalies in schizophrenia subtend a specific breakdown of the brain connectivity. Particularly, this breakdown is also found in healthy individuals at familial risk for schizophrenia or simply carrying a dopamine variant conferring risk for the disorder.

Tiivistelmä

Viime vuosikymmeninä neurotieteijlijät ovat nähneet valtavasti vaivaa määritelläkseen erillisen tunne-aivoneuroverkon. Tämän hetkisen tutkimuksen valossa kuitenkin vaikuttaa siltä, että sisäiset ja ulkoiset tekijät vaikuttavat ihmisten tunne-käyttäytymiseen odotettua enemmän. Tässä esitetty väitöskirjatukimus tähtää ymmärtämään tunteisiin vaikuttavia yksilökohtaisia, sekä biologisia tekijöitä yhdistämällä tutkimustietoa genetiiksta, psykologiasta sekä aivokuvantamisesta. Sovelsin työssäni tunnetiloja aiheuttavaa protokollaa (eng. Affective state induction-protocol), jolla tutkin mielialojen hetkellisten muutosten vaikutusta tunteiden prosessointiin käyttäytymyksellisellä, sekä neuronaalisella tasolla. Lisäksi tutkin tunnetilojen ja yksilöllisten tunnetekijöiden vaikutusta toisiinsa ja käyttäytymiseen, sekä geenien ja yksilöllisten tunnetekijöiden interaktiota. Ennenkaikkea työni kartoittaa terveiden yksilöiden tunneäly-kyvyn neuronaalisia korrelaatteja, jotka ovat niin sanotun emotionaalisen panoraman osatekijä. Lisäksi perehdyin kliinisen skitsofrenia populaation, ja geeniperimänsä tai perhtaustansa takia riskiryhmässä olevan terveen populaation tunteiden aivo-konnektiivisyyden tutkimukseen.

Väitöskirjatutkimukseni tulokset näyttivät, että väliaikaiset tunnetilat moduloivat tunteita jo hyvin varhaisessa, automaatiisessa prosessoinnin vaiheessa, sekä käyttäytymyksellisesti, että neuronaalisesti. Havaitsin myös, että kyseiseen tunteiden modulointiin vaikuttaa yksilön persoonallisuuspiirteet, sekä geeneettiset tekijät. Lisäksi tutkimuksessani kävi ilmi, että sosiaaliset sekä emotionaaliset kyvyt saattavat osaksi selittää sitä vaihtelevuutta mikä havaittiin aivojen tunteiden prosessoinnissa, täten osoittaen neuronaalisten interventioiden olevan vakuuttava suunta jatkotutkimuksile. Lisäksi vaitöskrjatutkimuksessani selvisi, että skitsofreniassa havaitut tunneperäiset poikkeamat johtunevat erityisestä aivokonnektiivisesta katkosesta. Kyseinen katkos on myös havaittu terveidein yksilöiden aivoissa, jotka ovat perhetaustansa takia riskialttiita sktisofrenialle, tai joilla on skitsofrenialle altistava dopamiini variantti.

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Bari, May 2018

Tiziana Quarto

List of original publications

This thesis is based on the following articles, which are referred to by their numerical order in the text:

1. **T. Quarto**, G. Blasi, K.J. Pallesen, A. Bertolino, E. Brattico. **"Implicit processing of visual emotions is affected by sound-induced affective states and individual affective traits."** *PLoS One. 2014 Jul 29;9(7):e103278. doi: 10.1371/journal.pone.0103278.*

2. **T. Quarto**, M.C. Fasano, P. Taurisano, L. Fazio, L.A. Antonucci, B. Gelao, R. Romano, M. Mancini, A. Porcelli, R. Masellis, K.J. Pallesen, A. Bertolino, G. Blasi, E. Brattico. **"Interaction between DRD2 variation and sound environment on mood and emotion-related brain activity."** *Neuroscience 2017 Jan 26; 341:9-17. doi: 10.1016/j.neuroscience.2016.11.010.*

3. **T. Quarto**, G. Blasi, C. Maddalena, G. Viscanti, T. Lanciano, E. Soleti, I. Mangiulli, P. Taurisano, L. Fazio, A. Bertolino, A. Curci. **"Association between Ability Emotional Intelligence and Left Insula during Social Judgment of Facial Emotions".** *PLoS One. 2016 Feb 9;11(2):e0148621. doi: 10.1371/journal.pone.0148621. eCollection 2016.*

4. **T. Quarto**, I. Paparella, D. De Tullio, G. Viscanti, L. Fazio, P. Taurisano, R. Romano, A. Rampino, R. Masellis, T. Popolizio, G. Pergola, A. Bertolino, G. Blasi **"Familial risk and a genome-wide supported DRD2 variant for schizophrenia predict lateral prefrontal-amygdala effective connectivity during emotion processing".** *Schizophrenia Bulletin. 2017 Sept 16 doi: /10.1093/schbul/sbx128. Epub ahead of printing.*

Abbreviations

BFQ: Big Five Questionnaire
BMS: Bayesian Model Selection
BOLD: blood-oxigenation-level-dependent
CC: cytosine/cytosine
CT: cytosine/thymine
D2L: D2 long
D2S: D2 short
DCM: Dynamic Causal Modeling
DSM: Diagnostic and Statistical Manual of Mental Disorders
EC: emotion control
EI: Emotional Intelligence
EP: exceedance probabilities
fMRI: functional Magnetic Resonance Imaging
GG: guanine/guanine
GLM: general linear model
GT:guanine/thymine
HC: healthy controls
HRF: hemodynamic response function
IFG: Inferior Frontal Gyrus
IQ: Intelligence Quotient
lPFC: lateral prefrontal cortex
MSCEIT: Mayer–Salovey–Caruso Emotional Intelligence Test
PANSS: Positive and Negative Syndrome Scale
PET: positron emission tomography
POMS: Profile of Mood States
ROI: region of interest
RT: reaction times
SCZ: patients with schizophrenia
SIB: healthy siblings of patients with schizophrenia
SMC: somatic marker circuitry
SNP: single nucleotide polymorphism

SPM: Statistical Parametric Mapping

STAI X2: State Trait Anxiety Index

TT: thymine/thyimne

V1: primary visual cortex

vmPFC: ventromedial prefrontal cortex

1 INTRODUCTION

1.1 What is an emotion?

"Everyone knows what an emotion is, until asked to give a definition" (Fehr 1984). Notwithstanding the large number of studies on this field, researchers have not yet found an agreement on the definition of this fundamental human process. Indeed, the paradox of emotions is that, on the one hand, they seem self-evident and obvious when examined introspectively; on the other hand, they have been extremely difficult to define in objective scientific terms (Anderson and Adolphs 2014). Despite this paradox, most researchers would probably agree that emotions include (but are not limited to) certain expressive behaviors (e.g., facial expressions) that are associated with internal brain states that we, as humans, subjectively experience as "feelings" (Dolan 2002).

But how can we study the biological and chemical aspects of these expressive behaviors? To answer this question, neuroscientists have borrowed from the evolutionary theories of emotions the emphasis on the role that evolution has played in shaping the unique and the common features of emotions, as well as their current function. In this perspective, emotions evolved for their adaptive value in dealing with fundamental life tasks (Ekman 1999). Each emotion thus prompts us in a direction which in the course of evolution has done better than other solutions in recurring circumstances that are relevant to goals (Jonson-Laird and Oatley 1992). Importantly, the evolutionary perspective posits that the basic emotions are innate and universally recognized (Darwin 1872; Ekman 1972). Basing on these principles, the study of emotions from a biological perspective and across species and cultures became affordable, thus laying the foundations for the identification of an emotion neural circuit. However, while neuroscientists have put great efforts towards this objective and whether the development of brain imaging tools have contributed in this sense, the task has not been successfully completed. Indeed, internal and external variables influencing this human unique phenomenon are, for better or worse, much more prominent than expected. As a matter of fact, a unique and comprehensive emotion neural circuit is still far from being identified, as far is the classification of all the variables influencing or perturbing this process.

The present doctoral thesis is focused on the individual differences in the emotional processing. Through this work, I wish to add some crucial knowledge by merging evidence obtained with psychological, genetic and brain imaging assessments, in order to complete our understanding of the biological aspects of emotions. This thesis consists of four studies which will be introduced next, after illuminating their backgrounds.

1.2 Expressive behaviors of emotions: Facial expressions

With its fine musculature and its (mostly) hairless nature, the human face has evolved as a major signalling and communication channel for emotions, through facial expressions. This evolution took place in parallel with the acquisition of bipedalism, which place the face in a fully exposed-to-the-view position and favoured the development of vision as a prominent sensory modality to gather information on the environment – including conspecifics (George 2013).

In his research on the expression of emotion, Charles Darwin (Darwin, 1872) examined the facial expression of animals, and particularly the primates, in order to discover the origins of expressive movements in man. Darwin's main observation was that some expressions made by non-human primates are similar to those of man both in terms of physical features, and in terms of the general utility of expressions. Indeed, Darwin considered the expression of emotions essential to the welfare of group-living species: through facial expressions and vocalizations, animals communicate how they feel and this communication serves to regulate social interactions and reproduction as well as to protect conspecifics from threats. Many of the facial expressions in primates appear to have evolved, as Darwin suggested, from intention movements, the incomplete or preparatory phases of actions. These actions include attack, locomotion toward and away, protective responses and movements associated with respiration and vision (Darwin 1872; Huber 1933; Andrew 1965; Hinde 1966). For example, the threat postures of chimpanzee contain the intention to attack (mouth open and ready for biting) and move toward (body musculature tense and ready to advance), while the submissive postures contain elements derived from protective responses (retraction of lips or ears) and the intention to move away from the sender. Importantly, the regularity with which many expressions and postures occur within a species indicates that these behaviors have developed phylogenetically through evolution. A further corroboration to this evolutionary perspective derived from the Darwin's observation of newborn and blind subjects. They are able to product and detect emotional facial expressions that are not acquired, but innate. This finding suggested strongly that the acquisition of most expressive human emotion behavior was less dependent upon learning than it was on the actualization of innate tendencies. According to Darwin, this was especially true for the expression of the basic emotions such as fear, anger, happiness, sorrow, disgust and surprise. On the other hand, Darwin believed that the expression of the so-called secondary emotions (more elaborate emotions) was subject to social and cultural variations, thus probably acquired by imitation and reward.

All the observations made by Darwin lead to the conclusion that facial expressions of basic emotions are a product of the human evolution, are mostly dependent on primary brain structures present already in newborns and are independent of learning or cultures; production and recognition

of facial expressions of emotions are, then, innate and universal abilities. These pioneering observations were, years later, confirmed by Ekman and his group with several experiments. For example, they demonstrated that prototypical Western facial expressions are well recognized in non-Western countries (Izard 1971; Ekman 1972; Matsumoto 1989). Moreover, they provided evidence that people in very different cultures produce very similar facial expressions in response to certain situations or when portraying their reactions to a standard imagined situation (Eibl-Eibesfeldt 1972; Ekman 1972).

Once the facial expressions have been identified as the most reliable expressive behaviors of emotions, highly significant for humans, and universally produced and recognized across species and cultures, they fast became the preferred stimuli in the experiments of affective neuroscience. Indeed, the physiological reaction to facial expressions represents a measurable and objective phenotype that can break free from the undefined concept of subjective feelings (such as joy or sadness) and fly towards a more scientifically sustainable biological circuit (LeDoux 2012). In particular, using functional Magnetic Resonance Imaging (fMRI), the processing of emotional faces has been associated with increased activation in a number of visual areas (fusiform gyrus, inferior and middle occipital gyri, lingual gyrus), limbic areas (amygdala and parahippocampal gyrus, posterior cingulate cortex), temporoparietal areas (inferior and superior parietal lobule, middle temporal gyrus, insula), prefrontal areas (medial frontal gyrus), subcortical areas (putamen) and the cerebellum (Fusar-Poli, Placentino et al. 2009). Importantly, the large number of fMRI studies (more than 8500) published in this topic has corroborated the concept that the facial emotion brain circuit is a complex structure. Indeed, despite the innate and mostly universal nature of production and recognition of emotional faces, the associated brain processing is highly variable across individuals. Source of variations may be genetic or psychological aspects, or the interaction between these and the external context. Moreover, facial emotion processing is multi-faceted and multi-component. Thus, the brain processing of facial emotions is highly dependent on the task administered to participants and on which component, facet this specific task triggers. This latter aspect is deeper treated in the next section.

Considering the prominent use of faces as emotional stimuli in the affective neuroscience and taking into account the above-described theoretical aspects linking the facial emotion to the emotion *per se*, this thesis will refer to "emotion processing" or "facial emotion processing" alike.

1.3 Implicit and explicit emotional processing

The physiology of emotion processing includes different components, which may elicit different and complex brain patterns (Critchley, Daly et al. 2000; Blasi, Lo Bianco et al. 2009; Fusar-Poli,

Placentino et al. 2009). For instance, in some social contexts, the emotional stimuli might require effortful explicit interpretation of its meaning in order to guide correct choices of action or behavioral responses. However, in familiar situations, emotional signals are automatically processed and the behavior is adapted without full cognitive awareness (Critchley, Daly et al. 2000). Several studies in the field of facial emotions have dissociated this double processing administering to subjects two different tasks: the explicit task consisting in emotional labeling or social judgment of faces, and the implicit task consisting in sex or age discrimination. Results of these studies have proven the existence of distinct neural substrates of these two types of emotional processing (Fusar-Poli, Placentino et al. 2009). For example, a more automatic and intuitive (implicit) processing of emotional stimuli appears to be mainly mediated by the amygdala, while explicit emotional evaluation prominently engages the prefrontal cortex, including its lateral portion (Gusnard, Akbudak et al. 2001; Phillips, Drevets et al. 2003; Ochsner, Knierim et al. 2004; Ochsner, Ray et al. 2004). Importantly, these brain regions are functionally connected, as indicated previously (Ochsner, Bunge et al. 2002; Stein, Wiedholz et al. 2007; Delgado, Nearing et al. 2008; Erk, Mikschl et al. 2010). In this regard, animal and human studies suggest that different patterns of brain functional connectivity as a function of specific subcomponents of emotional processing are likely (Sotres-Bayon, Cain et al. 2006; Phillips, Ladouceur et al. 2008). Previous work proposes that limbic regions modulate cortical areas during automatic processing of emotional stimuli, whereas the direction of the modulation is inverted during explicit emotional evaluation or regulation (Davis, Gross et al. 2011). Overall, this earlier body of work suggests that it is crucial to investigate the reciprocal functional influence of limbic and cortical regions and how it relates to different components of emotion processing.

Importantly, the existence of multiple components in the emotion processing makes essential the correct choice of a neuropsychological task related to the specific aim of the study, as it has been done in the present thesis.

1.4 Individual differences in Emotion Processing

1.4.1 Affective states and affective traits

Affective states: Mood and emotion are two words that are used by psychologists and laypeople alike to refer to different aspects of affect (Ekman 1999). Emotions are defined as episodic and synchronized changes in the organism reflecting the quick identification of salient stimuli in the environment and the production of adaptive behavioral and physiological responses (Fossati, 2012). Most of the scientists would agree that emotions (at least the ones called “basic”) tend to be relatively brief, lasting for seconds, and that they represent immediate adaptational reaction in an encounter

with the environment (Lazarus, 1994). Moods or affective states, on the other hand, are described by most theorists as general affective background, with no specific direction, that would usually be less intense and last much longer than emotions (Davidson and Eckman, 1994; Beedie, Terry and Lane; 2005). Some authors state that the daily life of an individual is experienced as a continuous stream of affect, where moods and emotions constantly interact to each other resulting in complex combinations of them (Watson and Clarke, 1994). In this regard, the ability to recognize and label emotions contained in facial expressions is modulated by current mood (Demenescu, Kortekaas et al. 2010). Bouhuys and colleagues (Bouhuys, Bloem et al., 1995) induced temporary variations in subjects' mood with sad or happy music, which led to a modification of the labeling of emotionally ambiguous faces. In particular, participants labeled faces as happier when they were in an elated mood and as sadder when a negative mood was induced. Similarly, induced recollection of emotional autobiographical memories significantly affected the number of emotional faces detected by subjects, increasing the detection of frowning faces after sad mood induction and of happy faces after positive mood induction (Fitzgerald, Arnold et al. 2011). Together with other similar findings (Fox, Russo et al. 2001; Koster, De Raedt et al. 2005; Fitzgerald, Arnold et al. 2011), these studies suggest that individuals in a negative affective state recognize more negative stimuli compared to positive or neutral stimuli, whereas individuals in a positive affective state tend to be more accurate in recognizing positive targets.

Affective traits: Stable individual emotional dispositions, referred as affective traits (such as self-assessed trait anxiety), also play a fundamental role in the recognition of emotional stimuli. For example, individuals with higher trait anxiety tend to misclassify neutral expressions as angry and are more sensitive to threatening faces (Kessler, Roth et al. 2007; Friedman and Forster 2010). The relationship between affective traits and affective states is not entirely understood. It has been argued that some affective traits may represent long-term *sequelae* of affective states (Akiskal, Hirschfeld et al. 1983; Chien and Dunner 1996). On the other hand, some affective states are more likely to be achieved by people with specific affective traits (Mathews and MacLeod 1985; Larsen and Ketelaar 1991). For example, there is evidence that extroverts and neurotics may be differentially sensitive to stimuli that generate positive and negative affect, respectively (Gray and Spencer 1981). Neurotics present heightened emotional reactivity to negative mood induction, whereas extroverts compared with introverts are more emotionally reactive to positive mood induction (Larsen and Ketelaar 1991). Similarly, individuals with higher trait anxiety seem more likely to adopt a threatening interpretation of ambiguous information, when surrounded by a negative environment (MacLeod and Mathews 1991). These studies allow us to hypothesize that affective traits may be associated not just with

different emotional recognition but also with different emotional reactivity to affective state induction techniques. It is possible that affective states and affective traits interact and integrate to produce complex behavioral patterns in a predictable way. Affective states or mood can be successfully regulated with drugs that operate directly on different neurotransmitters in the brain as well as via stimuli (e.g., music) in the environment that impact our senses and, although in a less direct manner, induce plastic changes in the brains' circuits.

1.4.1.1 Music: a tool for the affective state induction

Music represents an affective state induction technique (Vastfjall, Larsson et al. 2002), which is non-intrusive and easily applied. Indeed, music is used by most people for self-regulation of emotions in everyday life (Thayer, Newman et al. 1994; Saarikallio S. 2007), and its power to reduce tension, modulate mood, and raise energy has been widely documented (Thayer, Newman et al. 1994; Lesiuk 2010; Chanda and Levitin 2013). Music is used to modulate affective states in a large number of neurological and psychiatric disorders (Maratos, Gold et al. 2008), and brain traumas (Sarkamo, Tervaniemi et al. 2008; Guetin, Soua et al. 2009; Erkkila, Punkanen et al. 2011).

The profound effects of music on transient affective states are documented in relation to explicit emotional processing of facial stimuli, which was biased towards the emotional valence of the musical stimuli. Specifically, activity in cortical brain regions involved in auditory and emotional processing increased during recognition of a positively valenced face when positively valenced music had been presented either simultaneously or as prime (de Gelder, Pourtois et al. 2000; Spreckelmeyer, Kutas et al. 2006; Logeswaran and Bhattacharya 2009). However, these studies focus only on the conscious labeling of facial expressions. Moreover, the previous studies utilize only music having sad or happy/pleasant connotations, not allowing for generalization to other sound environments that might be relevant for pathological conditions within the anxiety disorder spectrum (such as noise or relaxing natural sounds). Hence, very little is known about how relaxing or irritating sound-induced mood might influence the implicit emotional processing of faces in healthy subjects, i.e., occurring when faces are presented to the subjects without any explicit emotional recognition or labeling task (Critchley, Daly et al. 2000; Haxby, Hoffman et al. 2000; Hariri, Tessitore et al. 2002; Calder and Young 2005; Blasi, Lo Bianco et al. 2009; Fusar-Poli, Placentino et al. 2009). Even less is known about whether the affective properties of relaxing or irritating sound environments impact all individuals similarly or whether some individuals with defined personality and affective traits are more affected than others by one kind of environment over another. In other words, do sound-induced

affective states interact with individual affective traits? In this doctoral thesis, these questions have been addressed in Study 1 via the SoundFace task, a new-built task created *ad hoc* for these purposes (see details on the Methods section).

1.4.2 Mapping neurogenetic mechanisms of individual differences in emotion

Identifying the biological mechanisms that give rise to individual differences affords a unique opportunity to develop a deeper understanding of complex human behaviours, disease liability and treatment (Hariri 2013). One step towards the uncovering of biological mechanisms consists in illustrating the predictive relationship between regional brain activation and such individual differences, thus uncovering the neural system supporting that specific behavior. Thus, while in Study 1 I have focused on the behavioral characterization of sound-induced mood effects on the implicit emotion processing, in Study 2, I have focused on the neural correlates of this behavior.

Moreover, an important next step is to systematically identify the underlying mechanisms driving variability in the neural system functions. In this regard, recent neuroimaging studies employing pharmacological challenge paradigms have revealed that even subtle alterations in monoamine neurotransmission can have a profound impact on the functional response of brain circuitries supporting human behavior (Hariri 2013). Similarly, multimodal imaging studies (fMRI combined with positron emission tomography [PET]) are revealing how variability in brain activation emerges as a function of the underlying variability in key brain signaling pathways (e.g., increased dopamine signaling predicts increased amygdala reactivity). The next logical step is to identify the sources of interindividual variability in key neurochemical signaling mechanisms. In the modern era of human molecular genetics, this step is firmly planted in the direction of identifying common variations in the genes that influence the function or availability of components in these neurochemical pathways. Because DNA sequence mutations across individuals represent the ultimate wellspring of in emergent molecular, neurobiological, and related behavioral processes, understanding the relationship among genes, brain, and behavior is important for establishing a mechanistic foundation for individual difference in behaviour and related psychiatric diseases (Hariri 2013). In this regard, the imaging genetics approach tags a possible way towards this aim.

Applying the imaging genetics approach to this doctoral thesis, I explored the neural, biological and genetic correlates of the sound-induced effects on the emotion behavior. I started from the idea that a possible mechanism by which sounds, and particularly music, modulate mood states

and emotion processing relies on dopamine signaling. First, music appears to impact brain physiology via dopamine signaling, as previously indicated by animal and human studies with animal models (Panksepp and Bernatzky 2002; Sutoo and Akiyama 2004; Akiyama and Sutoo 2006; Salimpoor, Benovoy et al. 2011). Second, human and animal studies indicated that dopamine neurotransmission is crucially involved in emotion processing and behavior (Gendreau, Petitto et al. 1998; Hariri, Tessitore et al. 2002; Salgado-Pineda, Delaveau et al. 2005). Third, convergent evidence in humans suggests that dopamine is involved in the regulation of mood (Diehl and Gershon 1992; Willner 1995; Yatham, Liddle et al. 2005; Cousins, Butts et al. 2009). Altogether, these findings suggest that the increase in dopamine signaling associated with musical sounds may represent the biological mechanism behind their well-known effects on emotion processing and mood.

However, the above-described effects of sounds on emotions and mood are highly variable across individuals (Stansfeld 1992; Brattico and Pearce 2013; Martinez-Molina, Mas-Herrero et al. 2016). A series of findings suggest that some variability in music or noise perception is heritable (Drayna, Manichaikul et al. ; Peretz and Hyde 2003; Heinonen-Guzejev, Vuorinen et al. 2005; Kanduri, Ukkola-Vuoti et al. 2013; Oikkonen, Onkamo et al. 2016). In this regard, previous studies indicate that a specific genetic variation related to a crucial determinant of dopamine signaling, i.e., the D2 receptor, modulates D2 expression and signaling. In particular, D2 receptors exist in two alternatively spliced isoforms, the D2 long (D2L) isoform located primarily post-synaptically and the D2 short (D2S) isoform, functioning as pre-synaptic autoreceptor (Usiello, Baik et al. 2000). Earlier studies suggest an association between an intronic single nucleotide polymorphism (SNP) within the DRD2 gene (11q23) (rs1076560, guanine/thymine [G/T]) and the relative expression of these two isoforms. In particular, the T allele shifts splicing from D2S to D2L, decreasing the D2S/D2L ratio relative to the G allele (Zhang, Bertolino et al. 2007). Thus, a greater amount of D2S associated with the GG relative to GT genotype may correspond to lower synaptic levels of dopamine. Furthermore, this SNP predicted steady-state dopamine signaling in the striatum and its correlation with prefrontal cortical activity during performance of a working memory task (Bertolino, Taurisano et al. 2010). Finally, rs1076560 GG homozygous human healthy individuals also, compared with GT subjects, have lower emotion control scores as well as greater amygdala and Inferior Frontal Gyrus (IFG) activity during emotional face processing (Blasi, Lo Bianco et al. 2009).

In Study 1 and 2, I map the road back from the behavior to genes, passing by the neural correlates of sound-induced mood. In particular, I investigated the relationship between *DRD2 rs1076560* and sound environments, and their interaction on mood state as well as brain activity during implicit emotional faces processing, particularly in key regions whose activity is modulated

by dopamine and which sustain emotion and music processing, i.e., the nucleus accumbens, the amygdala and the IFG (Fusar-Poli, Placentino et al. 2009; Koelsch 2014).

1.4.3 Ability Emotional Intelligence

As described above in this doctoral thesis, the emotional brain processing appears affected by a large number of variables (e.g., affective states, personality traits and genes) which may also interact between each other resulting in a complex and ever-changing phenomenon. Another important aspect of this complex picture is represented by the so-called Emotional Intelligence. The framework of Emotional Intelligence (EI) (Mayer JD 1997) integrates aspects of emotional information processing, emotion regulation and behavioral responses to emotional stimuli (Austin 2005). In particular, the ability to process one's own and others' emotions is an essential feature of EI.

Theoretical and empirical research has led to the development of several models of EI, thus providing diverse ways of conceptualizing and measuring it. These models can be grouped into two main theoretical approaches, described as mixed/trait models or ability models. The first incorporates both abilities and qualities such as personality and motivational traits, optimism, empathy, and character (Bar-On 1997), and it has been assessed by self-report measures (Dawda and Hart 2000). The second conceptualizes EI as a form of intelligence emphasizing the effective processing of emotional information (Mayer JD 1997). Ability EI has typically been assessed by maximal-performance measures, similar to the assessment of intelligence quotient. That is, some individuals have a greater ability than others to carry out sophisticated information processing about emotions and emotion-relevant stimuli and use this information as a guide to thinking and behavior (Mayer J. D., P. et al. 2002). This study focuses on the Ability EI model. Intrinsic to this choice is the idea that EI abilities cannot exist outside the social context in which they operate. In order to use these abilities, one must be aware of what is considered to be a suitable performance by the social context with which one interacts. Furthermore, Ability EI has a great deal to offer to the challenge of understanding human health behavior and how to best promote it. Conceptualizing EI as a form of intelligence/ability – and not as a personality trait – has the advantage of implementing the training programs on the emotional correlates of mental health, aiming at improving individuals' well-being (Lopes, Grewal et al. 2006; Ruiz-Aranda, Castillo et al. 2012; Castillo, Salguero et al. 2013).
Consistently, previous studies have suggested that Ability EI predicts job performance and academic achievements (Lanciano, Curci et al. 2012; Lanciano 2014a; Lanciano and Curci 2014b), as well as positive social interaction (Lopes, Salovey et al. 2005), mental health (Davis and Humphrey) and

well-being (Martins, Ramalho et al. 2010), while impaired or deficient Ability EI has been linked to substance abuse (Hertel, Schutz et al. 2009), anxiety and depression (Lizeretti and Extremera 2011).

While research on the associations between EI and life-outcome has been quite prolific, less is known about the brain correlates of EI. Previous models (Bar-On, Tranel et al. 2003) suggest that the physiology of EI overlaps with those of an emotional decision-making circuitry known as the Somatic Marker Circuitry (SMC) (Damasio 1996; Bar-On, Tranel et al. 2003; Bechara and Damasio 2005). This circuit consists of three primary brain structures - the amygdala, which triggers initial signals of emotional salience in response to a relevant stimulus; - the insula, which contributes to the "feeling" of emotion by neutrally mapping these somatosensory and visceral sensations, which can later be "simulated" within the brain when a comparable emotion-evoking stimulus is encountered in the future; - the ventromedial prefrontal cortex (vmPFC), which integrates emotional signals with cognitive representations.

The idea of the SMC developed as a response to a number of intriguing observations made in neurological patients with focal damage in the vmPFC who presented severe impairments in personal and social decision making, in spite of otherwise largely preserved intellectual abilities, as measured by conventional IQ tests(Damasio 1979; Damasio 1994). Specifically, these patients had difficulty planning their work day, their future over immediate, medium and long ranges, and difficulty choosing suitable friends, partners and activities (Damasio 1996). Moreover, lesions of the amygdala and insular regions, also compromise somatic state activation and decision making (Bechara 1999; Maddock 1999; Damasio, Grabowski et al, 2000). Interestingly, in a more recent research, Bar-On and colleagues ((Bar-On, Tranel et al. 2003) have also reported that patients with lesions of the vmPFC, amygdala or insular cortex presented significantly lower levels of EI compared with patients presenting lesions in other brain regions.

Neuroimaging results on healthy individuals also support the association between SMC and EI (Killgore and Yurgelun-Todd 2007; Reis, Brackett et al. 2007; Kreifelts, Ethofer et al. 2010; Koven, Roth et al. 2011; Killgore, Weber et al. 2012; Killgore, Schwab et al. 2013; Takeuchi, Taki et al. 2013). For example, structural studies have found that measures of EI are positively related to gray matter volume of the vmPFC (Koven, Roth et al. 2011; Killgore, Weber et al. 2012) and to white matter integrity in the right anterior insula (Takeuchi, Taki et al. 2013). Moreover, functional magnetic resonance imaging (fMRI) studies indicated that activation of regions within the SMC during a social reasoning task and passive vision of fearful faces was negatively correlated with measures of EI (Reis, Brackett et al. 2007). Other fMRI studies using emotional stimuli reported positive correlations between EI and activity of some cortical emotional processing regions (superior temporal sulcus and vmPFC), while failing to find activation in more primitive regions such as the

amygdala or insula (Kreifelts, Ethofer et al. 2010; Killgore, Schwab et al. 2013). However, only a small number of these studies investigates EI as Ability. In particular, no study has so far investigated the brain correlates of Ability EI during a social task eliciting both social decision making and evaluation of facial expressions, two crucial components of emotional processing and social interactions (Damasio 1996; Mayer J. D., P. et al. 2002).

The aim of Study 3 was to investigate the relationship between Ability EI scores, and brain activity during social behavior involving emotional facial evaluation and decision making. Specifically, I hypothesized that Ability EI scores would predict activity in SMC regions during social judgment of facial expressions.

1.4.4 At the borders of the individual differences in the emotion behavior: Psychopathology

The psychiatric community actually posits the individuals in a continuum from normal to pathological behavior. Individual differences in the emotion behaviour will, then, discriminate the individuals within the "normal" segment of this continuum. However, there is a point where high anxiety, low emotion control, low or elated mood, poor social skills, become pathology. In the "pathological" segment, the individual differences in the emotion behavior can still discriminate individuals, but in this case the variability should be considered in the spectrum of the specific pathology by which the individual is affected.

Which psychopathology is interested by abnormal emotional behaviour? Every human behavior is emotionally coloured. In each single moment, whether we think or act, whether we are looking into our loved one's eyes or involved in an extremely difficult mathematical reasoning, regardless of our consciousness, we are always inside an emotion (Arciero 2009). Thus, we can always extrapolate from each situation its proper emotional connotation for ourselves (Arciero 2009). In this sense, each pathological alteration of the human behaviour should necessarily involve alterations in the emotion functions. In this view, particularly suitable is the case of schizophrenia that, with delusions and hallucinations, is considered the most perceptive-cognitive pathology across the major psychiatric diseases, but that is also profoundly affected by abnormal emotional behaviour.

Schizophrenia is a highly heritable disorder (Tandon, Nasrallah et al. 2009), and the study of emotional anomalies connected with this disorder would be crucial for the understanding of the genetic and biological underpinnings of human emotion behavior. However, notwithstanding the well-established link between emotional anomalies and schizophrenia (Tandon, Nasrallah et al. 2009), the brain functional mechanisms translating genetic risk for this brain disorder into these

clinical symptoms have not been fully characterized yet (Aleman and Kahn 2005; Li, Chan et al. 2010; Anticevic, Van Snellenberg et al. 2012). For example, a number of studies investigating regional brain activity in patients revealed reduced recruitment of the amygdala in response to emotional stimuli (Phillips, Williams et al. 1999; Gur, McGrath et al. 2002; Paradiso, Andreasen et al. 2003), while others indicated intact or even greater recruitment of this brain region (Crespo-Facorro, Paradiso et al. 2001; Kosaka, Omori et al. 2002; Holt, Kunkel et al. 2006). Furthermore, reduced (Takahashi, Koeda et al. 2004; Williams, Das et al. 2007) or greater (Taylor, Liberzon et al. 2002) prefrontal cortex activation in patients with schizophrenia (SCZ) compared with healthy controls (HC) have been reported during different emotional tasks. Thus, the brain regional activation does not appear to be a reliable brain phenotype for the study of emotional anomalies of schizophrenia. On the other hand, clinical neuroscientists increasingly postulate that schizophrenia is a disorder of brain network organization (Rubinov and Bullmore 2013). Consistent with this perspective, well credited models have suggested that anomalies in the influence of dopamine receptors on NMDAR-mediated changes in synaptic efficacy (Stephan, Friston et al. 2009; Friston, Brown et al. 2016) may subtend altered brain functional integration, or "disconnection", in schizophrenia (Weinberger 1993; Andreasen, Paradiso et al. 1998; Friston 1998; Friston 2005; Stephan, Baldeweg et al. 2006; Pettersson-Yeo, Allen et al. 2011; Friston, Brown et al. 2016). Accordingly, previous studies in SCZ reported altered functional connectivity between the amygdala and prefrontal regions during emotion processing (Das, Kemp et al. 2007; Leitman, Loughead et al. 2008; Anticevic, Van Snellenberg et al. 2012; Vai, Sferrazza Papa et al. 2015; Cao, Bertolino et al. 2016; Potvin, Lungu et al. 2017).

An important factor to take in consideration when focusing on the identification of reliable and key brain correlates of emotional processing in schizophrenia is that brain activity in patients may be confounded by state variables, including pharmacological treatment and levels of symptoms (Blasi, Popolizio et al. 2009; Rasetti, Mattay et al. 2009). A strategy to overcome this issue is the study of healthy siblings of patients with schizophrenia (SIB), who share on average fifty percent of genetic variation with probands, and their brain activity is not affected by state variables. Thus, investigation of these individuals is a first step in disambiguating if and how anomalous processing of emotions is linked with risk for schizophrenia. However, only few studies have been performed to date using this approach and they have reported inconsistent results (Habel, Klein et al. 2004; Rasetti, Mattay et al. 2009; van Buuren, Vink et al. 2011; Lo Bianco, Blasi et al. 2013). In particular, previous findings in SIB suggest that the functional coupling between the amygdala and the cingulate cortex during implicit processing of emotional faces is not a trait phenotype of schizophrenia (Rasetti, Mattay et al. 2009). On the other hand, other results obtained with effective connectivity approaches

in unaffected first-degree schizophrenia relatives provide opposite evidence. For example, a study in adolescent offspring of SCZ indicated reduced effective connectivity between the amygdala and the prefrontal cortex as measured with Dynamic Causal Modeling (DCM) (Diwadkar, Wadehra et al. 2012). Similarly, a more recent study (Cao, Bertolino et al. 2016) revealed reduced graph-based connectivity during emotional face processing in a subnetwork including the limbic and visual cortex as well as the pallidum and the thalamus in relatives of SCZ compared with controls. Thus, different functional connectivity approaches may lead to inconsistent findings across studies. Overall, the paucity and the inconsistency of the results in this field call for further investigation.

Another important point is that the investigation of anomalies in emotion processing in SIB is only a first step in order to identify emotion-related brain endophenotypes for the disorder. To further support the utility of such phenotypes for genetic investigations, another step is the study of their relationship with genetic variants increasing risk for schizophrenia. In this regard, it is well known that dopamine and the dopaminergic D2 receptor are crucial for emotion processing (LeDoux 1998; Pezze and Feldon 2004), modulate physiology of the amygdala and the prefrontal cortex (Levey, Hersch et al. 1993; Rosenkranz and Grace 2001; Seamans and Yang 2004), and have been strongly implicated in schizophrenia (Howes and Kapur 2009). Furthermore, variation within the D2 gene (*DRD2)* has been associated with emotional phenotypes (Blasi, Lo Bianco et al. 2009). Moreover, the largest genome-wide association study to date indicated that the C allele of a SNP in close proximity to the D2 coding gene *DRD2* (rs2514218 cytosine/thymine [C/T]) is associated with diagnosis of schizophrenia (Consortium. 2014), and with schizophrenia-related phenotypes (Zhang, Robinson et al. 2015; Vink, de Leeuw et al. 2016).

In Study 4 I aimed to investigate the association of familial risk and of a genome-wide supported variant increasing risk for schizophrenia with patterns of brain functional effective connectivity during emotional processing. Unlike other recent studies (Cao, Bertolino et al. 2016), I focused on effective connectivity between the amygdala and the lateral prefrontal cortex (lPFC), which are brain regions functionally coupled (Ochsner, Bunge et al. 2002; Stein, Wiedholz et al. 2007; Delgado, Nearing et al. 2008; Erk, Mikschl et al. 2010), modulated by dopamine (Levey, Hersch et al. 1993; Rosenkranz and Grace 2001; Seamans and Yang 2004), previously associated with schizophrenia (Phillips, Williams et al. 1999; Gur, McGrath et al. 2002; Kosaka, Omori et al. 2002; Taylor, Liberzon et al. 2002; Paradiso, Andreasen et al. 2003; Takahashi, Koeda et al. 2004; Holt, Kunkel et al. 2006; Williams, Das et al. 2007), and strongly involved in emotion processing (Hariri, Bookheimer et al. 2000; Ochsner, Ray et al. 2004; Ochsner and Gross 2005). With this aim, I used DCM, which is an effective connectivity approach describing how the present state of one

neuronal population causes dynamics in another neuronal population and how this interaction changes under the influence of external perturbations (e.g., experimental manipulations) or brain activity (Stephan, Penny et al. 2010). Thus, this approach is not affected by the limitations of other methodologies addressing brain functional connectivity which do not account for directionality, influence, or causality between interacting regions (Birnbaum and Weinberger 2013). Therefore, it is well suited for unveiling directionality of cortico-limbic connectivity during implicit and explicit emotional processes.

Here, I first investigated patterns of lPFC-amygdala effective connectivity during emotion processing in a sample of HC to establish the physiology of these networks. Then, I studied the putative modifying effect of familial risk for schizophrenia on effective connectivity patterns. Finally, to further support the utility of these phenotypes for genetic studies, I investigated whether *DRD2* rs2514218 affects dynamics of effective connectivity. I hypothesized that effective connectivity between the amygdala and the lPFC during emotion processing may be modulated by risk for schizophrenia. In particular, I hypothesized that SCZ and SIB may exhibit a similar alteration of physiological models of amygdala-lPFC effective connectivity and that *DRD2* variation might be associated with such anomaly.

2 AIMS

This doctoral thesis is primarily aimed to deeply investigate all possible sources of individual variability in the emotion behavior, going from genes to affective traits and states and to emotion abilities. Moreover, my aim was to investigate the neural and biological correlates of emotion anomalies presented in schizophrenia patients and whether these are related with genetic and familial risk for this disorder.

In general, this thesis reviews how the integration of psychology, neuroimaging, molecular genetics can work toward the ultimate goal of understanding the detailed mechanisms mediating individual differences in human emotional behaviour and, in turn, the establishment of predictive markers of the disease vulnerability.

Specific aims:

Does a permanently sound-induced affective state influence emotional processing at an implicit, automatic level? Can affective traits modulate this process? What are the brain correlates of sound-induced affective states? Does individual genetics matter?

I have designed an *ad hoc* neuropsychological task called SoundFace, in which sound environments are used to induce mood changes during implicit emotional faces processing. In Study 1 I have investigated the behavioral correlates of sound-induced mood on the implicit emotion behavior. Moreover, I have verified the existence of a modulation of these behavioral correlates by individual affective traits, with the aim to uncover putative interactions between affective traits and states. In Study 2, using an imaging genetics approach, I have examined the neural and genetic correlates of sound-induced changes on mood and emotional behavior.

Does the Emotional Intelligence Ability represent another source of variability in emotional brain processing?

Affective traits and states are not the only sources of individual differences in emotion behavior. In the last two decades, researchers have started to investigate a new construct that can distinguish the individuals in their emotional actions: Emotional Intelligence (EI) Ability. This construct conceptualizes EI as a form of intelligence dealing with emotions and the processing of emotional information, and it has typically been assessed by maximal-performance measures, similar to

assessment of the intelligence quotient. In Study 3 I have investigated the effect of the EI scores on the brain activity during an explicit emotional task.

How schizophrenia alters the emotional brain processing? Is this alteration a specific trait rather than a clinical state of the disorder, thus linked with its genetic and familial risk?

Emotion behavior is very different across individuals. There is a point in which these differences become pathology. The pathological emotion behavior is a feature of many psychiatric disorders, whether these are categorized in the sphere of affective disorders or not. Moreover, this aspect seems to be a precursor rather than a consequence of the disorder. Thus, understanding the neural and biological underpinnings of the emotion anomalies is a primary interest in psychiatry. However, many studies have failed in finding a consistent emotion-related neural anomaly that can be used as a biomarker of disease. Recent hypotheses suggest that pathological phenotypes in psychiatric diseases may have the basis in brain connectivity rather than regional dysfunctions. Taken this into account, in Study 4, I have investigated the alteration of brain connectivity during implicit and explicit emotional faces tasks in patients with schizophrenia, their unaffected siblings and healthy controls carrying a dopamine genetic variant conferring risk for this disorder.

3 METHODS

3.1 Participants

The participants in Study 1, 2 and 3 were healthy subjects from the region of Puglia, Italy. Inclusion criteria were absence of any psychiatric disorder, as evaluated with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV), of any significant neurological or medical condition revealed by clinical and magnetic resonance imaging evaluation, of history of head trauma with loss of consciousness, and of pharmacological treatment or drug abuse in the past year. The Wechsler Adult Intelligence Scale–Revised was used to evaluate the Intelligence Quotient (IQ) (Wechsler 1981), the Edinburgh Inventory (Oldfield 1971). to measure handedness and the Hollingshead Four Factor Index (Hollingshead and Redlich 1958) to measure socio-economic status (Table 1-4). In addition, for Study 1 and 2, in which the experimental procedure required music listening, subjects were also screened for their musical expertise and hearing loss. Subjects with musical training lasting more than 10 years were excluded from the study, because they were considered as musicians and musical expertise might represent a confounding factor in the analysis. This threshold was based on previous published articles investigating behavioral and neural differences in perception and emotional brain systems between musicians and non-musicians (Brattico, Pallesen et al. 2009; Pallesen, Brattico et al. 2010; Brattico, Bogert et al. 2015; Reybrouck and Brattico 2015).

For Study 4, SCZ, SIB and HC were recruited (Table 4). The DSM IV was used to confirm diagnosis of schizophrenia for patients and to exclude any psychiatric disorder for SIB and HC. All SCZ had been on stable pharmacological treatment with first- or second-generation antipsychotics for at least 8 weeks before entering the study. Symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein et al. 1987). Furthermore, pre-morbid IQ was measured with the Italian version of the Wide Reading Achievement Test, revised (Sartori 1997). Exclusion criteria were identical to the other studies.

The research protocol of the four studies was approved by the local ethics committee "Comitato Etico Indipendente Locale of the Azienda Ospedaliera Ospedale Policlinico Consorziale" of Bari, Italy. Informed written consent was obtained from all participants before participation after the procedures had been fully explained to them. In study 1 and 2, subjects were compensated with cinema tickets.

Table 1: Demographic data of sample in Study 1

	All (n=32)	High STAI X2 (n=16)	Low STAI X2 (n=16)	High EC (n=16)	Low EC (n=16)
Age, years	26.8 (3.7)	26.5 (3.4)	27.1 (4)	27.5 (4)	26.1 (3.3)
Gender, *n*					
➢ **Male**	11	5	6	7	4
➢ **Female**	21	11	10	9	12
Handedness	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)
Hollingshead index	31.9 (13.2)	33.9 (13.9)	29.9 (12.2)	31.3 (11.7)	32.5 (14.6)

Table 2: Demographic and genetic data of sample in Study 2

	GG (n=26)	GT (n=12)	Yates-corrected X^2	F	P
Age, years	28.1 (5.7)	26.4 (5.3)		0.7	0.4
Gender, *n*					
➢ **Male**	8	7	1.6		0.2
➢ **Female**	18	5			
Handedness	0.9 (0.2)	0.6 (0.2)		2.7	0.11
Hollingshead index	40.6 (19.1)	44.1 (19.1)		0.2	0.63
IQ	116 (9)	109 (9)		1.2	0.29

Table 3: Demographic data of sample in Study 3

	Age (years)	Females	Hollingshead	Handedness	IQ
Subjects (*n*=63)	29.4 (6.3)	34	41.8 (16.7)	0.8 (0.4)	112 (12.3)

Table 4. Demographic and genetic data of samples in Study 4

Characterization of lPFC-amygdala effective connectivity in HC					
	HC (n=217)				
Age, years	26.1 (6.6)				
Gender, *n*					
➢ Male	105				
➢ Female	112				
Handedness	0.7 (0.5)				
Hollingshead index	37 (17.3)				
IQ	107.7 (16.1)				
Effect of familial risk for schizophrenia on lPFC-amygdala effective connectivity					
	HC (n=56)	SIB (n=36)	SCZ (n=40)	Yates-corrected X^2	P
Age, years	31.4 (10.4)	35.4 (10.1)	33.2 (8.5)		N.S.
Gender, *n*					
➢ Male	30	13	24	3.42	N.S.
➢ Female	26	23	16		
Handedness	0.8 (0.4)	0.8 (0.5)	0.8 (0.5)		N.S.
Hollingshead index	29.6 (12.9)	28.6 (15.3)	28.2 (14.4)		N.S.
Premorbid IQ	111 (5.3)	108.8 (8.9)	108.1 (7.8)		N.S.
Chlorpromazine equivalents			536 (249)		
PANSS total score			72.7 (15.5)		

Association of *DRD2* rs2514218 with lPFC-amygdala effective connectivity

	CC (n=39)	TC (n=39)	TT (n=39)	Yates-corrected X^2	P
Age, years	27.23 (5.87)	27.18 (8.27)	27.44 (7.84)		N.S.
Gender, *n*					
➢ Male	20	17	18	<0.001	N.S.
➢ Female	19	22	21		
Handedness	0.87 (0.41)	0.77 (0.58)	0.87 (0.41)		N.S.
Hollingshead index	39.88 (15.28)	42.63 (16.15)	40.59 (17.61)		N.S.
IQ	108.51 (11.21)	109.95 (10.75)	108.2 (8.24)		N.S.

3.2 Genotyping

Participants of Study 2 and 4 also underwent venipuncture for subsequent DNA extraction from peripheral blood mononuclear cells. Approximately 200 ng of DNA were used for genotyping analysis. In Study 2 subjects were genotyped for *DRD2* rs1076560. This SNP was analyzed with allele-specific PCR primers as described previously (Zhang, Bertolino et al. 2007; Bertolino, Fazio et al. 2009; Bertolino, Fazio et al. 2009). In Study 4, Illumina HumanHap550K/610-Quad Bead Chips (San Diego, California) has been used to genotype the whole genome of the sample. Briefly, each individual blood sample was whole-genome amplified, fragmented, precipitated and resuspended in appropriate concentrations of hybridization buffer. Denatured samples were hybridized on prepared Illumina Human550K/610-Quad Bead Chips. After hybridization, the Bead Chip oligonucleotides were extended by a single labeled base, which was detected by fluorescence imaging with an Illumina Bead Array Reader. Normalized bead intensity data obtained for each sample were loaded into the Illumina Genome Studio (Illumina, v.2010.1) with cluster position files provided by Illumina, and fluorescence intensities were converted into SNP genotypes. For the purpose of the Study 4 the extraction focused on *DRD2* rs2514218. In Study 2, all subjects were genotyped and included in the analyses, while, in Study 4, DNA samples were available only for a partial group of HC. Moreover, to meet specific methodological demands related to the Bayesian nature of the analysis conducted in Study 4, the genotype groups carrying the major allele of rs2514218 were downsized to match the

minor allele group. Sample size and demographical details of each genotype group are reported in Table 2 and 4.

Collection of blood samples and genotyping has been conducted in the psychiatric hospital in Bari (Italy). For genotyping of Study 4, the sxtracted DNA samples have been sent to the research institute of CBM in Trento (Italy), where has been conducted the genotyping.

3.3 Faces task

The Faces task (Blasi, Lo Bianco et al. 2009; Lo Bianco, Blasi et al. 2013; Taurisano, Blasi et al. 2013) consisted of two runs, each presenting angry, fearful, happy and neutral facial expressions from a validated set of facial pictures (NimStim, http://www.macbrain.org/resources.htm) (Tottenham, Tanaka et al. 2009). During one run (emotional perceptual processing - implicit processing), subjects identified the gender of each face. In the other run (explicit emotional evaluation – explicit processing), they had to decide if they would like to "approach" or "avoid" the face. The order of stimuli was randomly distributed. However, the same stimuli were presented in both runs with the same order. During one run (emotional perceptual processing - implicit processing), subjects identified the gender of each face. In the other run (explicit emotional evaluation – explicit processing), they had to decide if they would like to "approach" or "avoid" the face following their own personal criteria, bearing in mind that there were no right or wrong responses. Moreover, all subjects were instructed to respond with the thumb of the right hand. From stimulus appearance, two seconds were allowed for behavioral responses. The presentation of the two runs was counterbalanced across participants. Each stimulus was presented for 500 ms, with the interstimulus interval randomly jittered between 2 and 7 seconds. The total number of stimuli was 144: 30 angry, 39 fearful, 37 happy, and 38 neutral faces. Duration of each run was 6 minutes 8 seconds. A fixation crosshair was presented during the interstimulus interval (Figure 1 – Faces task).

In the four studies here reported I have used a version of the Faces task differently adapted to meet the different aims of the studies. Indeed, in Study 1 and 2 I have only focused on the implicit processing, while in Study 3 I have focused on the explicit processing and in Study 4 I have investigated both the implicit and explicit processing. Moreover, in Study 1 and 2, music and noise sequences were also played in background for mood manipulation, and fearful faces were not presented. Thus, the Music and Noise conditions, each lasting 5 min 8 sec, were both presented to the subjects in a counterbalanced order. In Study 1, for task validation purposes, a Silence condition was also added to the experiment (Figure 2 – SoundFace task).

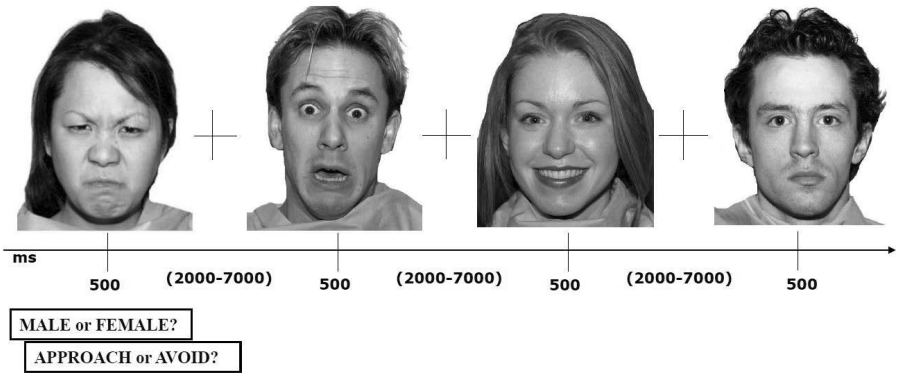

Figure 1: Faces task. During one run of this task (emotional perceptual processing - implicit processing), subjects had to identify the gender of each face. In the other run (explicit emotional evaluation – explicit processing), subjects had to decide if they would like to "approach" or "avoid" the angry, happy, neutral and fearful facial expressions. Note: The images were taken from NimStim Face Stimulus Set (http://www.macbrain.org/resources.htm) with the permission of the authors.

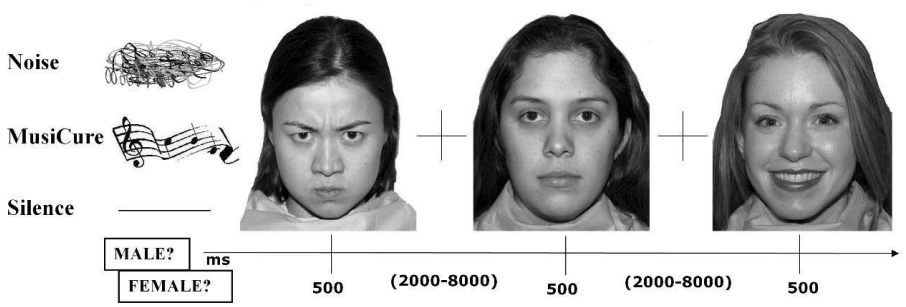

Figure 2: Soundface task. Figure showing the implicit emotion-processing task. In this task, subjects were asked to identify the gender of angry, happy or neutral facial expressions while listening to a relaxing soundtrack (MusiCure) or while listening to amplitude-modulated noise or during silent background. Note: The images were taken from NimStim Face Stimulus Set (http://www.macbrain.org/resources.htm) with the permission of the authors.

3.4 Sound stimuli for mood manipulation (Study 1 and 2)

The music background consisted of a 5-minute representative cross-section of a contemporary, specially designed sound environment, named "MusiCure" (Nilsson 2009), which has been tested in surgery rooms, post anesthesia care units, neonatal and psychiatric wards with documented effects on patients' wellbeing (Thorgaard, Ertmann et al. 2005; Fredriksson, Hellstrom et al. 2009). The Noise background consisted in noise sequence that retained the main acoustic

characteristics of MusiCure. In particular, I used the MIRToolbox (freely available toolbox of Matlab implemented at the University of Jyväskylä, Finland (Lartillot and Toiviainen, 2007)), to extract the amplitude spectrum of MusiCure, which was applied to a white noise signal that was then amplified in the average frequency range of MusiCure. The goal was to create a noise stimulus sequence optimally balanced to MusiCure in the main acoustic features such as loudness, amplitude modulation, overall frequency range and temporal structure.

3.5 Behavioral measures

3.5.1 Personality trait, mood state assessment and sound affective ratings

In Study 1, prior to the experiment, all subjects completed the Big Five Questionnaire (BFQ) (Caprara, Barbaranelli et al. 2003) and the State Trait Anxiety Index (STAI X2) (Spielberger, Schmid et al. 1989). The BFQ measures personality traits according to the Big Five Factors Model (McCrae and Costa 1987) and includes five dimensions (energy, friendliness, conscientiousness, emotional stability, and openness), which are organized into two facets each (energy: dynamism and dominance; friendliness: cooperativeness and politeness; conscientiousness: scrupulousness and perseverance; emotional stability: emotion control and impulse control; openness: openness to culture and openness to experience). The dimension "emotional stability" refers to aspects of "negative affectivity" (Caprara, Barbaranelli et al. 2003). Within this dimension, the facet "emotion control" is defined as the capacity to cope adequately with one's own anxiety and emotionality. The STAI X2 measures the Anxiety Index as a personality trait.

In Studies 1 and 2, in order to measure mood state changes associated with the sound background, the Profile of Mood States (POMS) questionnaire (Farnè 1989; McNair 2005) was presented on a screen before starting the task and after each run. For Study 1 the questionnaire was projected on computer screen in a room were all the experiment toke place, for Study 2 it was projected on mirror inside the scanner, were the SoundFace task was administered. Responses to the POMS questionnaire and affective ratings were obtained by pressing on a button box the 4 buttons associated to the 4 possible answers in the POMS questionnaire (from "this adjective is totally false for me" to "this adjective is totally true for me"). After each run and before the POMS questionnaire, six different affective ratings were also acquired. In particular, subjects were asked to rate on a 4-point scale how happy, sad, arousing, pleasant and disgusting the Music or Noise sounded. In Study 2, during these behavioral measures, subjects lied down in the scanner, but fMRI images were not acquired.

3.5.2 Emotional Intelligence Test

To measure Ability EI, in Study 3, each participant completed, at the psychiatric hospital in Bari few days before the fMRI session, the validated Italian version (D'Amico 2011) of the Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT) (Mayer J. D., P. et al. 2002), which includes 141 self-administered items to assess individual skills at perceiving, using, understanding and managing emotions. The MSCEIT yields an EI Total score and two sub-scores, Experiential EI and Strategic EI. High scores on Experiential EI indicate proneness to perceive emotions and effectiveness in using emotional information to facilitate thought and performance. This area includes two subscales measuring abilities described as Perceiving and Using emotions. The second area is Strategic EI. High scores on this area implicate excellent capacity in understanding emotional information and in managing emotions of themselves and of others. Strategic EI comprises two subscales measuring abilities described as Understanding and Managing of emotions. MSCEIT scoring was based on the consensus scoring methods outlined in the manual (Mayer J. D., P. et al. 2002).

3.6 Demographic and behavioral data analysis

ANOVAs and χ^2 were used to assess potential differences between groups (divided by trait, genotype, or diagnosis) for all demographic variables, affective ratings of sound stimuli and behavioral data (mood state and/or task performance). Fisher's LSD tests were used for post-hoc analysis on behavioral data within each group. In Study 3, the EI score was treated as a continuous variable, thus Pearson's correlations and regression analyses were conducted to investigate its relationship with continuous demographic and behavioral data. ANOVA was used to investigate the effect of gender on EI score.

3.7 fMRI Data Acquisition

FMRI was performed at the hospital in San Giovanni Rotondo, a city located 200 Km away from Bari (Italy), on a GE Signa 3T scanner with a gradient echo-planar imaging sequence (repetition time, 2000 ms; echo time, 28 ms; 26 interleaved slices, thickness of 4 mm, gap of 1 mm; voxel size, 3.75 X 3.75 X 5; scan repetitions, 180; flip angle, 90°; field of view, 24 cm; matrix, 64x64). The first four scans were discarded to allow for signal saturation. The visual stimuli were presented via a back-projection system while sound stimuli were presented binaurally through MRI-compatible headphones with standard comfortable volume of about 70 dB. All stimuli were presented using the stimulation software Presentation (Version 9.00, Neurobehavioral Systems, Albany, CA, USA).

3.8 fMRI Data Analysis (Study 2, 3, 4)

Analysis of the fMRI data was completed using Statistical Parametric Mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm). Images, for each subject, were realigned to the first volume in the time series and movement parameters were extracted to exclude subjects with excessive head motion (> 2 mm of translation, > 2° rotation). Images were then re-sampled to a 3 mm isotropic voxel size, spatially normalized into a standard stereotactic space (Montreal Institute on Neurology, MNI, template) and smoothed using a 8 mm full-width half-maximum isotropic Gaussian kernel to minimize noise and to account for residual inter-subject differences. A box car model convolved with the hemodynamic response function (HRF) at each voxel was modeled. For each run, vectors were created for angry, happy, fearful (when applicable) and neutral faces. Six subject-specific movement parameters obtained after the realignment procedure were included in the model as covariates of no interest in order to control for potential effects of motion. Predetermined condition effects at each voxel were created using a t statistic, producing a statistical image for BOLD responses to brain processing of stimuli representative of each condition, i.e., angry, happy, and neutral faces versus fixation crosshairs during both runs. ANOVAs or regressions were then used at the second-level to investigate the effect of categorical (e.g., Sound Conditions, Facial Expressions, Diagnosis, Genotype) or continuous predictors (EI score). These analyses were constrained by a mask obtained by combining group activation maps associated with processing of each facial expression during each task, in order to focus our analyses on voxels activated during the task compared to the baseline. For group statistics, I used a statistical threshold of $p<0.05$, minimum cluster size [k]=10, family-wise error corrected using as regions of interest (ROIs) the IFG, nucleus accumbens and amygdala for Study 2, the vmPFC, amygdala, and bilateral insula for Study 3, the visual cortex, amygdala and lPFC for Study 4. These ROIs were identified with the Wake Forest University Pickatlas (http://fmri.wfubmc.edu/software/PickAtlas). These regions were chosen a priori based on earlier neuroimaging studies investigating the effect of the specific variables under examination in Studies 2, 3 and 4 [e.g., Study 2: (Blasi, Lo Bianco et al. 2009; Salimpoor, van den Bosch et al. 2013; Fusar-Poli, Placentino et al. 2009); Study 3: (Killgore, Schwab et al. 2013; Damasio 1994; Damasio 1996); Study 4: (Levey, Hersch et al. 1993; Phillips, Williams et al. 1999; Gur, McGrath et al. 2002; Ochsner, Ray et al. 2004; Pezze and Feldon 2004; Erk, Mikschl et al. 2010;). Outside these ROIs, no activation cluster survived the alpha threshold for the contrasts of interest. Finally, blood-oxigenation-level-dependent (BOLD) responses were extracted from significant clusters using MarsBar (http://marsbar.sourceforge.net/).

3.9 Effective connectivity (Study 4)

In Study 4, DCM (version 10) as implemented in SPM8 was used to investigate lPFC-amygdala effective connectivity (Friston, Harrison et al. 2003). In DCM, regional time series derived from a general linear model (GLM) analysis are used to analyze connectivity and its modulation by experimental conditions. DCM models hidden neuronal dynamics and the influence that one neuronal system exerts over another (Friston, Harrison et al. 2003). It allows modeling of the endogenous coupling between two regions, which is context independent ("intrinsic connections"). The impact of experimental stimuli can be modeled directly on specific regions ("driving input") or on the strength of coupling between two regions ("modulatory input").

Time series extraction. Three brain regions crucially involved in processing of emotional faces were included in the model: the primary visual cortex (V1) (as the region of access of visual stimuli), the amygdala, and the lPFC. Regional time series were extracted at the single-subject level using a combination of functional and anatomical criteria. In particular, the clusters resulting from the ANOVAs investigating the main effect of emotion in the GLM analysis were masked with anatomical ROIs (Brodmann Area 17, amygdala, lateral superior, middle and inferior frontal gyrus) as defined with the Wake Forest University PickAtlas (http://fmri.wfubmc.edu/cms/software#PickAtlas). Then, the peak of activity within these ROIs was used as the center of an 8-mm radius sphere from which the first eigenvariate was extracted. Given that all peaks were located in the right hemisphere, I focused the analysis in this hemisphere only.

Model space and selection. The Bayesian Model Selection (BMS) analysis focused on the modulation of lPFC-amygdala effective connectivity by contextual stimuli (e.g., facial expressions presented during implicit vs. explicit emotional faces task). Two models were built assuming bilateral intrinsic connections between V1, the amygdala and the lPFC, as well as V1 as the driving input region. These two models differed from each other for the influence of the modulatory effects of facial expressions during implicit or explicit processing on the connections between the amygdala and the lPFC. In our first model ("Bottom-up"), the modulatory input (all faces vs. crosshair) impacted the connection from the amygdala to the lPFC. In the second model ("Top-down"), the modulatory input impacted the connection from the lPFC to the amygdala (Figure 3).

After model set up, random-effects BMS analyses were performed in order to calculate exceedance probabilities (EP) (i.e., the probability that one model is more likely than another model) in each comparison of interest, that is, implicit vs. explicit processing of facial expressions in: 1. the total sample of HC; 2. the matched samples of HC, SCZ, SIB; 3. DRD2 rs2514218 TT, CT and CC of HC. All the BMS analyses were performed for the explicit and implicit run separately.

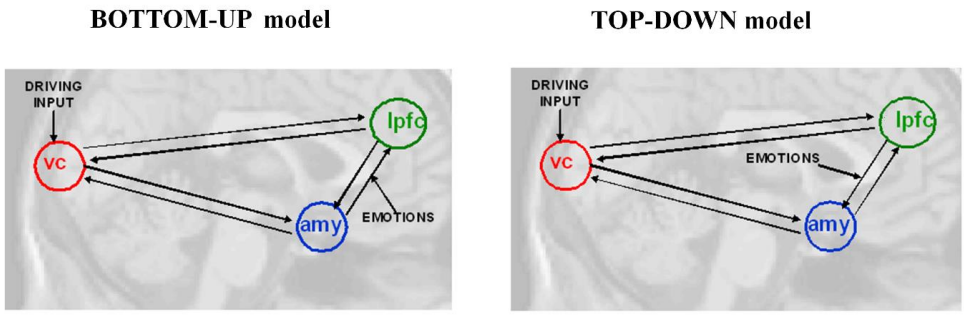

Figure 3: Models of effective connectivity tested in the study. In the Bottom-Up model the emotions modulates the connection from the amygdala (amy) to the lpfc (lateral prefrontal cortex), while in the Top-Down model the emotions modulates the connection from the lpfc to the amy.

4 RESULTS

4.1 Sound-induced affective states and individual affective traits can alter the behavioral responses to emotional faces at an implicit level (Study 1);

In Study 1 I found an interaction between the sound-induced affective state and implicit processing of facial expressions. Subjects had faster reaction times during processing of happy faces in the MusiCure condition (associated with more positive affective states) as compared with processing of angry faces during the Noise condition (associated with more negative affective states) (Figure 4). Thus, while a positive-oriented affective state elicited by MusiCure seems to facilitate the implicit emotional processing of positive, happy facial expressions, a negatively oriented affective state elicited by Noise acts in the opposite way during the implicit processing of angry faces. Importantly this happens already at an automatic, early stage of processing of emotional faces.

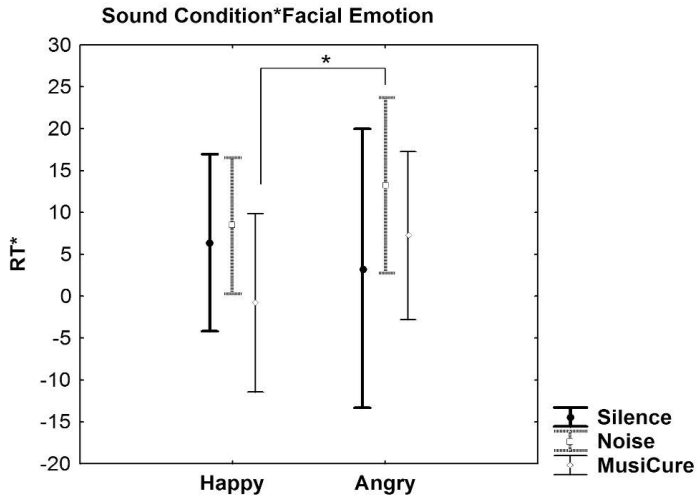

Figure 4: Sound condition by facial emotion. Graph (mean ±0.95 confidence interval) showing Sound Condition by Facial Emotion interaction on the derived index of RT during implicit processing of faces stimuli. Post hoc analyses revealed that this interaction results from faster responses to happy faces during the MusiCure condition compared with angry faces during the Noise condition. Asterisk shows statistical significance at $p<0.05$. See text for statistics.

Furthermore, in Study 1 I found that individuals with greater trait anxiety (as assessed by the STAI X2) were faster in implicitly processing facial emotions during MusiCure than during Silence. In contrast, subjects with lower trait anxiety were slower in processing emotions during Noise than during Silence. These results suggest that high anxiety subjects are more sensitive to the emotion regulating impact of a relaxing soundtrack than those with lower anxiety rates. In contrast, subjects

with lower anxiety rates are more affected by the Noise-induced negative effects on reaction times (RT) during the implicit processing of facial emotions, compared with high anxiety subjects (Figure 5). Similar results were present in the analysis of emotion control scores. Even if only at the trend level, subjects with a lower control of their emotions (as assessed by the emotion control [EC] subscale of the BFQ) had lower mean RTs while implicitly processing facial emotions during MusiCure than during Silence, whereas subjects with higher emotion control had higher mean RTs while implicitly processing emotions during Noise (Figure 6).

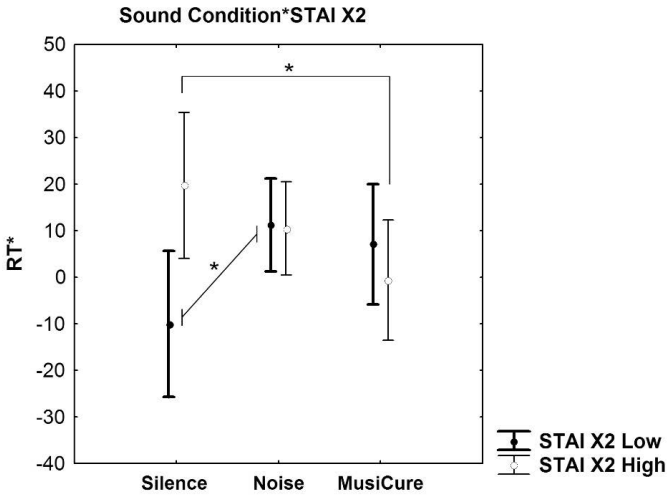

Figure 5: Sound condition by trait anxiety. Graph (mean ±0.95 confidence interval) showing Sound Condition by Trait Anxiety interaction on the derived index of the RT during implicit processing of faces stimuli. During Music, only individuals with greater Trait Anxiety had significant increases in their RTs when responding to faces in comparison to the Silence condition. During Noise only subjects with low trait anxiety had a significant reduction in RT compared with the Silence condition. Asterisks show statistical significance at $p<0.05$. See text for statistics.

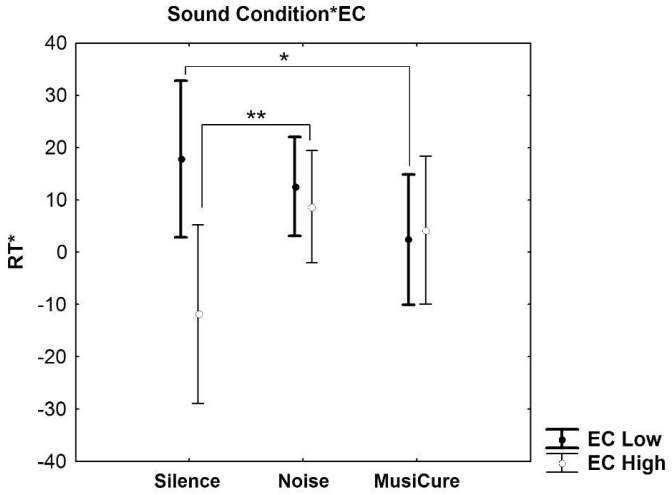

Figure 6: Sound condition by emotional control. Graph (mean ±0.95 confidence interval) showing Sound Condition by Emotional Control interaction on the derived index of RT during implicit processing of faces stimuli. During Music, only subjects with low EC had significant increases in RT when responding to faces in comparison to the Silence condition. During Noise, only individuals with high EC had greater RTs in comparison to the Silence condition (*$p<0.05$; **$p<0.1$). See text for statistics.

4.2 *DRD2* genotype predicts the impact of sound environments on affective states and emotion-related brain activity (Study 2);

Study 2 extends results of Study 1 suggesting that the effect of sounds on affective states during implicit processing of emotional faces has also a brain functional correlate. Indeed, in this study I found lower activity of right inferior frontal gyrus, left nucleus accumbens and left amygdala during Music as compared to Noise (Figure 7).

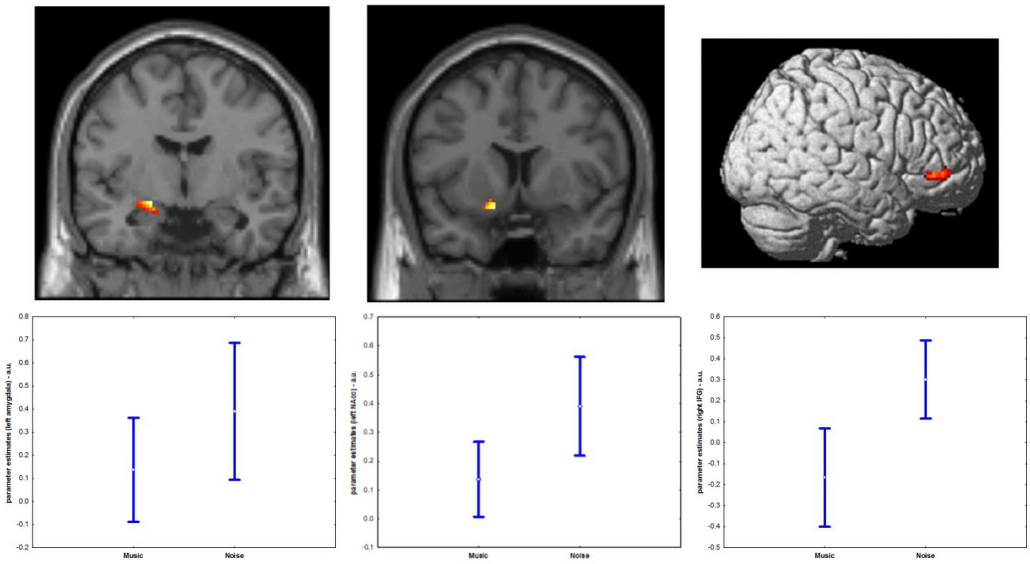

Figure 7: Main effect of Sound Condition. Coronal section and render image showing brain regions in which a main effect of Sound

Condition was present. Images were thresholded at $p<0.05$ FWE corrected. Plots (mean±0.95 confidence interval) showing a main effect of Sound Condition on BOLD signal change in left amygdala, left nucleus accumbens and right Inferior Frontal Gyrus (IFG).

Moreover, in Study 2 I found that both affective states and brain activity during emotion processing are modulated by DRD2 genetic variation, hence adding new insights on possible biological mechanisms sustaining individual differences in regulatory properties of sound environments. More specifically, we found that *DRD2* rs1076560 is associated with the effect of music and noise environments on behavioral measures of mood states as well as on brain physiology associated with the implicit processing of emotional faces. At the behavioral level, DRD2 GG subjects had better mood scores after Music exposure, while GT subjects had worse mood scores after Noise exposure, with respect to the baseline (Figure 8). At the imaging level, GT subjects exhibited lower nucleus accumbens activity while implicitly processing emotional faces during Music compared to Noise, whereas no difference between sound environments was observed in GG subjects (Figure 9). Notably, I also found a three-way interaction between DRD2 genotype, sound environment and facial expression, such that GG subjects had lower IFG activity while implicitly processing threatening angry faces during Music compared to Noise, while no difference between sound environments was present in GT subjects (Figure 10).

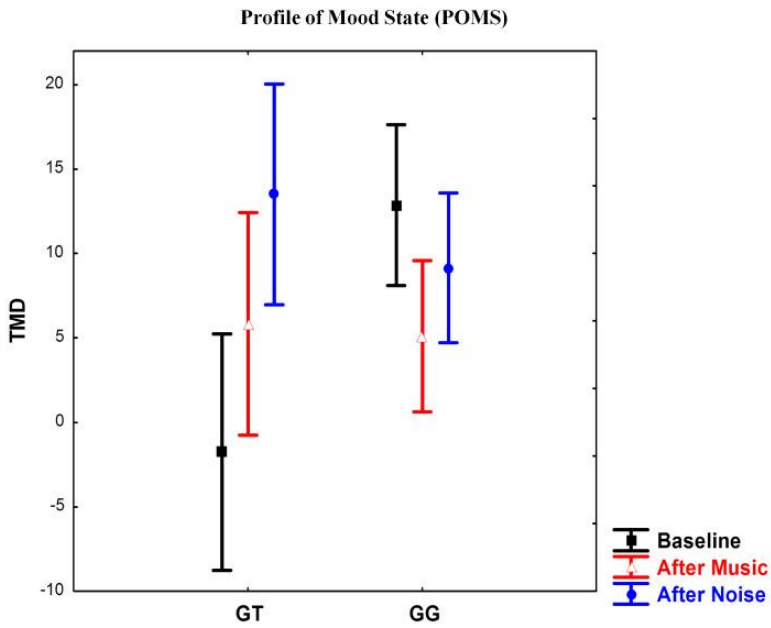

Figure 8: Profile of Mood State (POMS). Plot (mean±standard error) showing a significant interaction between DRD2 Genotype and Sound Condition on the total mood disturbance (TMD) scores of POMS questionnaire. See text for statistics.

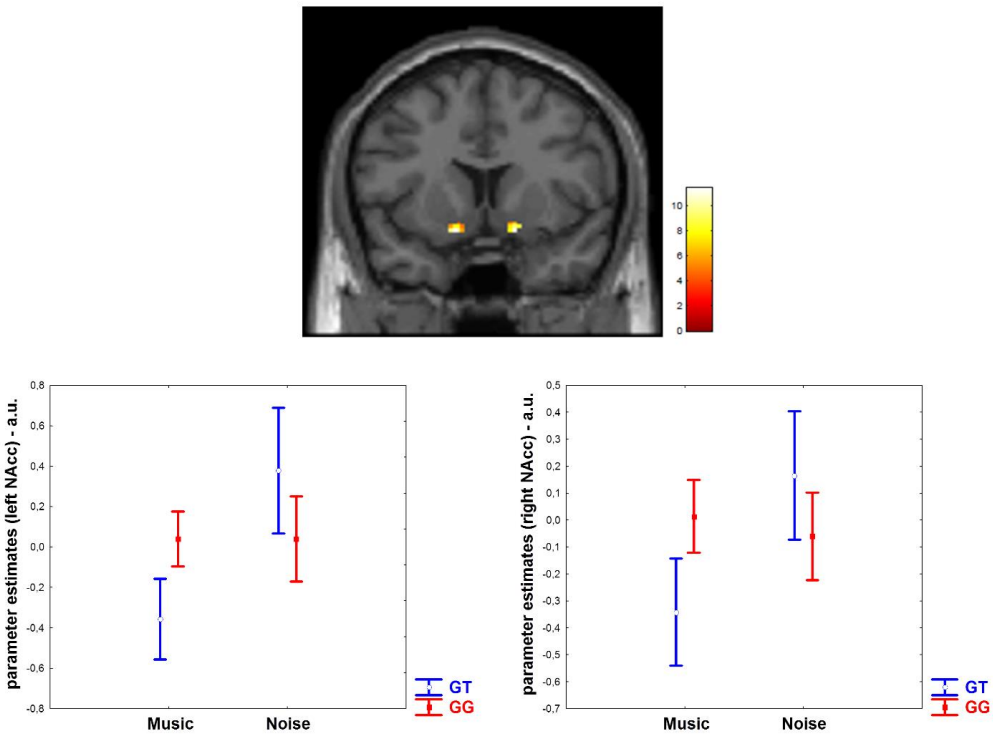

Figure 9: Interaction between DRD2 Genotype and Sound Condition. Coronal section showing brain regions in which an interaction between Sound Condition and DRD2 Genotype was present. Images were thresholded at $p<0.05$ FWE corrected. Plots (mean±0.95 confidence interval) showing an interaction between DRD2 and Sound Condition on BOLD signal change in bilateral nucleus accumbens.

Interaction between Sound Condition, *DRD2* Genotype and Facial Expression

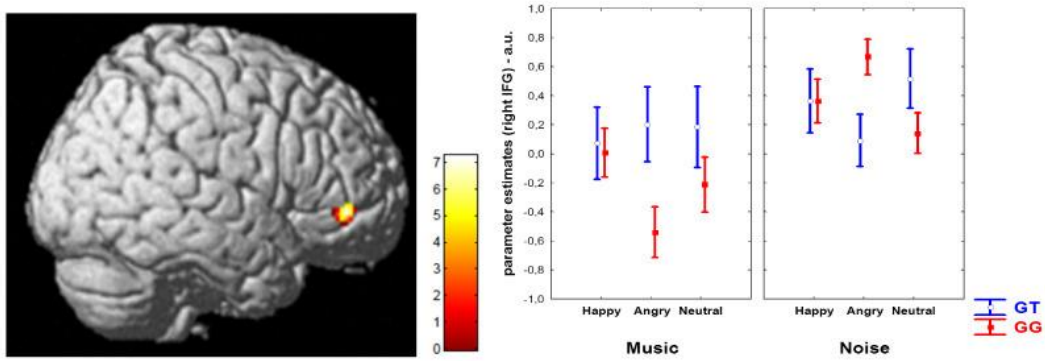

Figure10: Interaction between Sound Condition, DRD2 Genotype, Facial Expression. Rendered images showing brain region in which an interaction between Sound Condition, Facial Expression and DRD2

Genotype was present. Images were thresholded at p<0.05 FWE corrected. Plots (mean ± standard error) showing an interaction between Sound Condition, Facial Expression and DRD2 Genotype on BOLD signal change in right Inferior Frontal Gyrus (IFG).

4.3 Association between Emotional Intelligence and brain activity during social judgment of emotional faces (Study 3);

Study 3 aimed to expand the knowledge on the possible individual variables affecting brain correlates of emotional faces processing. The results of this investigation suggested that brain activity during explicit processing of emotional faces is associated with the scores of the Ability EI test. Specifically, greater EI total score predicted greater left insula activity during social judgment of fearful faces but lower activity of this region during social judgment of angry faces (Figure 11). Thus, EI (e.g., the ability to identify and regulate emotions) is linked with the ability to integrate different emotional signals mediated by the insular cortex activity.

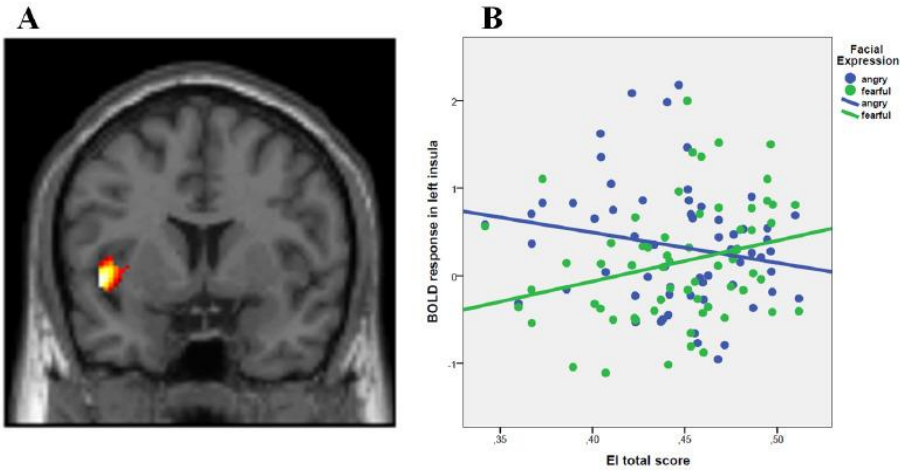

Figure 11: A. Coronal section showing the interaction between EI total score and Facial Expression in left insula. **B.** Scatterplot depicting the relationship between EI and activity in left insula during social judgment of fearful faces and angry faces. See text for statistics.

4.4 Familial risk and a genome-wide supported DRD2 variant for schizophrenia predict lateral prefrontal-amygdala effective connectivity during emotion processing (Study 4)

In Study 4 I have characterized the role of psychopathology and its genetic risk on brain dynamics during both implicit and explicit facial emotion processing. In particular, I have focused on schizophrenia, a psychiatric disease strongly associated with social and emotional dysfunctions. This

choice is also in line with a special interest of this doctoral thesis in the emotional functions or dysfunctions related with the dopamine receptor signalling, which is involved in schizophrenia-related phenotypes.

Results of Study 4 indicate that effective connectivity is dysfunctional in both SCZ and SIB (the latter carrying 50% of genetic risk for the disease). In greater detail, in both these groups of individuals the "Top-Down" model is more likely than the "Bottom-Up" model during both implicit and explicit emotion processing. Given that HC had the "Bottom-Up" as the winning model during implicit processing and the "Top-Down" as the winning model during explicit processing, these results indicate that the probability for a physiological model of effective connectivity in SCZ and SIB during implicit processing of emotional stimuli is not preserved (Figure 12A).

Intriguingly, I also found in HC a similar between-group modulation of lPFC-amygdala effective connectivity by DRD2 rs2514218, which has been associated with diagnosis of schizophrenia in the largest genome wide association study to date (Consortium. 2014). Here, the alteration of patterns of effective connectivity in HC homozygous for the schizophrenia risk C allele was similar to the pattern present in SIB and in SCZ. As in SCZ and SIB, I found that the physiological pattern of amygdala/lPFC effective connectivity in CC HC is altered during implicit emotion processing, such that there was no winning model in this genotype group. On the other hand, the T allele predicted the physiological model of effective connectivity between these brain regions (Figure 12B). Thus, these results are consistent with the likely involvement of D2 signaling in schizophrenia and with its relevance for emotion processing. More in general, they support the use of effective connectivity during emotion processing for genetic investigations aimed at identifying true endophenotypes for the disease.

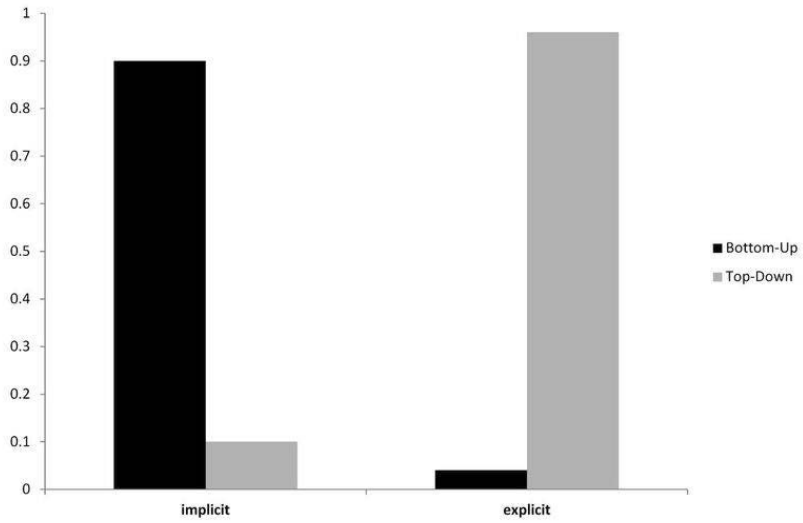

Figure 12: Graph showing Exceedance probability (EP) of the "Bottom-Up" and "Top-Down" models of effective connectivity between the amygdala and the lPFC in healthy controls (HC) during implicit emotion processing and explicit emotional evaluation.

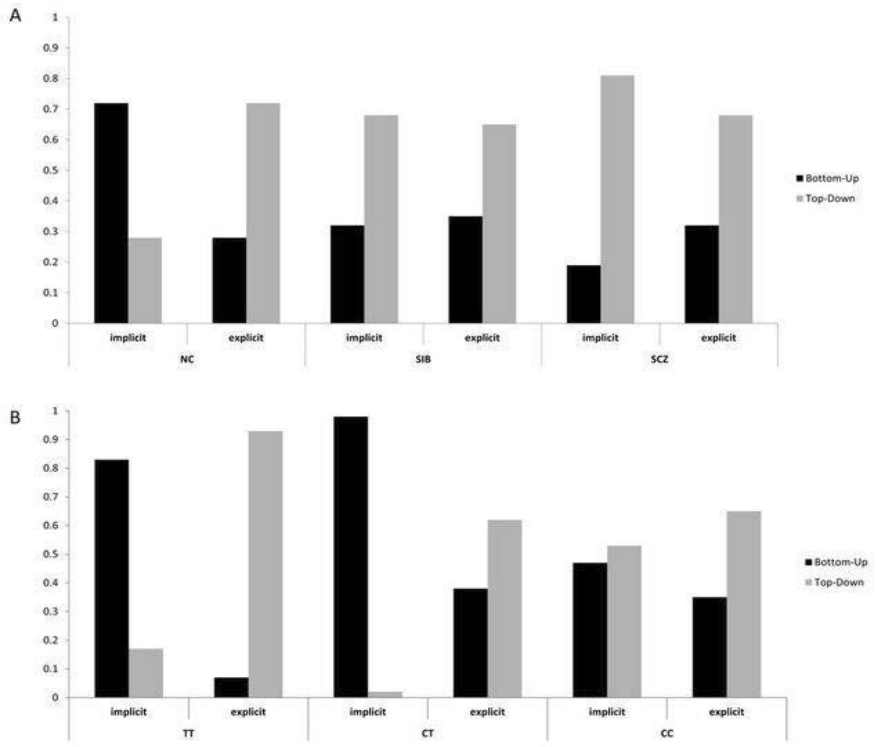

Figure 13: Exceedance probability (EP) of the "Bottom-Up" and "Top-Down" models of effective connectivity between the amygdala and the lPFC in matched samples of HC, SCZ and SIB. B. Exceedance probability (EP) of the "Bottom-Up" and "Top-Down" models of effective connectivity between the amygdala and the lPFC as a function of DRD2 rs2514218 in HC.

5 DISCUSSION

The studies included in this doctoral thesis investigated the individual variability in the normal and abnormal emotion behavior, with a particular interest on its neural and biological underpinnings and on its translation in pathological phenotypes. Specifically, this thesis intended to integrate psychology, neuroimaging and molecular genetics with the ultimate goal of establishing predictive markers of disease vulnerability.

5.1 Affective states, affective traits, and genes.

With the aim of investigating individual sources of emotional variability, Study 1 characterized the behavioral effects of temporary affective states on the implicit emotion processing. Specifically, I have designed an *ad hoc* neuropsychological task (SoundFace task) in which I have used sound environments (Music, Noise, Silence) to induce mood changes while subjects were involved in the implicit processing of faces with different facial expressions. Results revealed that subjects had faster reaction times during processing of happy faces in the relaxing condition as compared with processing of angry faces during the irritating condition. Previous studies (Bouhuys, Bloem et al. 1995; Fox, Russo et al. 2001; Koster, De Raedt et al. 2005; Fitzgerald, Arnold et al. 2011) revealed that a temporary variation in affective state can modify the explicit, conscious labelling of emotional faces. Extending this evidence, results of Study 1 indicated that changes in affective states, induced by the sound environment could affect emotional responses also during an implicit, automatic processing of facial emotions. Thus, while a positive-oriented affective state seems to facilitate the implicit emotional processing of positive, happy facial expressions, a negatively oriented affective state acts in the opposite way during the implicit processing of angry faces. Considerable evidence from previous studies on implicit emotion processing suggests that negative stimuli, in light of their relevance in the surrounding world, may attract more attention ('preferential engagement') and hold attention longer ('delayed disengagement') than neutral or positive stimuli (Hansen and Hansen 1988; Fox, Russo et al. 2001; Huang and Luo 2007; Estes, Verges et al. 2008; Holmes, Bradley et al. 2009; Feldmann-Wustefeld, Schmidt-Daffy et al. 2011). Thus, it is plausible that the negative mood induction in Study 1 modulated the implicit processing of angry emotions possibly through re-directing and holding attentional resources to the threatening emotional information, which is more relevant in a negative mood context (Cavanagh and Davey 2001). On the other hand, positive emotional faces *per se* do not need greater emotional load to be processed (Hodsoll, Viding et al. 2011). Hence, these results suggest that when happy faces occur in a sound-induced positive mood context they engage even less emotional resources compared with the other mood contexts.

In Study 1 I also aimed to uncover putative interactions between affective states and individual affective traits on the implicit emotion processing. In particular, I investigated how trait anxiety and EC are associated with behavioral responses at an implicit emotional task performed during experimental induction of affective states. Previous studies indicated that some affective states are more likely to be achieved by people with specific affective traits (Larsen and Ketelaar 1991; MacLeod and Mathews 1991). In particular, Gray (Gray and Spencer 1981) suggested that extroverts and neurotics are differentially sensitive to stimuli that generate positive and negative affects, respectively. Accordingly, I found that individuals with greater trait anxiety were faster in implicitly processing of facial emotions during the relaxing music condition than during Silence. In contrast, subjects with lower trait anxiety were slower in processing emotions during the irritating Noise condition than during Silence. These results suggest that high anxiety subjects are more sensitive to the emotion regulating effects of a relaxing soundtrack than those with lower anxiety rates. In contrast, subjects with lower anxiety rates are more affected by the NoiseNoise-induced negative effects on RT during the implicit processing of facial emotions, compared with high anxiety subjects. Even if only at the trend level, subjects with a lower control of their emotions show behavioral patterns similar to the high anxiety subjects. This finding demonstrates that individual affective traits interact with affective states on the emotion behavior, even at an early, automatic stage of processing.

In Study 2, using an imaging genetics approach, I have examined the neural and genetic correlates of the sound-induced effects previously characterized in Study 1. In particular, I have investigated the effects of sound-induced affective states on the emotion-related brain activity. Moreover, I have focused on the modulation of these effects by a dopamine receptor genetic variant (*DRD2 rs1076560*). As expected, sound-induced affective states are associated with differential brain activity of key emotional areas. In particular, the relaxing music sequence is associated with lower activity of right inferior frontal gyrus, left nucleus accumbens and left amygdala during Music as compared to Noise. Moreover, these sound-induced effects have a genetic modulation. These findings suggest that genetic variability of dopamine receptors affects sound environment modulations of mood and emotion processing. Results revealed that DRD2 GG subjects had better mood scores after music exposure, while GT subjects had worse mood scores after Noise exposure. Also, GT subjects exhibited lower nucleus accumbens activity while implicitly processing emotional faces during music compared to Noise, whereas GG subjects had lower IFG activity while implicitly processing threatening angry faces during music compared to Noise.

Earlier studies revealed that the DRD2 rs1076560 polymorphism is associated with the relative expression of D2S/L, such that GG subjects have relatively greater post-mortem brain

expression of D2S compared with GT individuals (Zhang, Bertolino et al. 2007). Importantly, pre-synaptic D2S autoreceptors control the level of dopamine release via inhibitory feedback (Starke, Gothert et al. 1989; Rosenkranz and Grace 2001; Schmitz, Benoit-Marand et al. 2003). Thus, a greater amount of D2S associated with the GG relative to GT genotype may correspond to lower synaptic levels of dopamine. Thus, it is possible that the interaction between DRD2 variation and sound environment that we observed in Study 2 lies on the genetic modulation of D2 signaling in the brain. Likewise, previous evidence suggests that D2 receptor signaling plays an important role in the modulation of mood (Diehl and Gershon 1992; Willner 1995; Yatham, Liddle et al. 2005). For example, D2 receptor blockade has been associated with depressive-like symptoms, while the administration of D2 agonists leads to manic-like behavior in both healthy and clinical populations (DG 2011).

On this basis, a possible interpretation of Study 2 results may be based on the effects of both genetic variation and sound environments on dopamine signaling during emotional face processing. In particular, I propose that the relaxing music sequence in this study might have increased striatal dopamine release in the whole sample of subjects during face processing (as suggested by human and animal evidence: Sutoo and Akiyama, 2006; Menon et al., 2006; Salimpoor et al., 2011). However, in GT subjects with lower expression of D2 autoreceptors (thus greater dopamine release at baseline), the increase of dopamine induced by music did not elicit significant mood changes but still led to lower emotion-related accumbens activity to faces with respect to the Noise condition. Alternatively, in GG subjects with greater expression of D2 autoreceptors (thus lower dopamine release at baseline), the increase of dopamine induced by music led to improved mood compared to baseline and to a decrease of the IFG activity during angry face processing with respect to the Noise condition. The IFG is crucially involved in higher-order emotional functions, such as the regulation of emotional behavior and correct interpretation of social signals (Blasi, Lo Bianco et al. 2009; Fusar-Poli, Allen et al. 2010). Thus, it is possible that the three-way interaction that I found in the IFG relies on the importance of this brain region for discriminating the social relevance of emotional expressions.

In general, results of Studies 1 and 2 indicate that sound-induced affective states can modulate emotion processing at both behavioral and neural level. Remarkably, individual affective traits and individual genetic background modulate the impact of the affective state experimentally induced. In particular, results of Study 2 reveal for the first time a direct link between a dopamine genetic trait and mood effects of music and noise in humans. Indeed, this study represents the first use of the imaging genetics approach in the field of music and sounds in general. This approach allows the observation of the link between genes and phenotypes via a true biological path that goes

from functional genetic variations (for which the effects on molecular function is known) to brain physiology subtending behavior.

5.2 Emotional Intelligence

Affective states, personality traits and genes are not the only sources of individual differences in emotion behavior. Recently, researchers have started to investigate a new construct that can distinguish the individuals in their emotional actions: Emotional Intelligence (EI) Ability. This construct conceptualizes EI as a form of intelligence dealing with emotions and assessed by maximal-performance measures, similar to assessment of the intelligence quotient. The framework of EI (Mayer JD 1997) integrates aspects of emotional information processing, emotion regulation and behavioral responses to emotional stimuli (Austin 2005). Study 3 investigated the effect of EI on the activity of brain regions within the SMC during social judgment of facial expressions of emotions. Results revealed that greater EI total score predicted greater left insula activity during social judgment of fearful faces but lower activity of this region during social judgment of angry faces. These results suggest that the left insula of subjects with higher EI scores may be more sensitive to the variation of emotional valence of faces during a social judgment task, than the left insula of subjects with lower EI scores.

Insular cortex is one of the key regions within the SMC (Damasio 1996), crucial for the bodily feeling of emotion (Damasio 1994). Accordingly, this area has been defined a key area for ‘‘interoceptive awareness”, i.e. the ability to correctly perceive all bodily signals and efficiently integrate them in a single emotional framework, through connections with other neural sources (Craig 2010). Based on this literature, results of Study 3 may be interpreted in a conceptual framework in which EI (e.g., the ability to identify and regulate emotions) may be linked with the ability to integrate different emotional signals mediated by the insular cortex. In fact, according to previous models (Fridlund 1994), angry and fearful faces represent qualitatively different forms of threat. Fearful faces are thought to signal the presence of a significant, yet undetermined source of danger within the environment, referred to as ‘ambiguous threat’. On the other hand, angry faces represent a more direct form of threat, often used in face-to-face encounters to exert dominance. Consistently, previous reports have also highlighted that anger and fear produce qualitatively different bodily reactions (Kragel and Labar 2013). In this line of reasoning, our findings suggest that EI may modulate the relationship between left insula activity and processing of different emotional information and bodily reactions conveyed by angry vs. fearful faces.

Findings of Study 3 are in line with previous studies finding a significant association between Ability EI and brain activity. In these previous studies, brain activity was investigated during a social reasoning task (Reis, Brackett et al. 2007) or during a passive viewing of faces (Killgore, Schwab et al. 2013). However, the EI construct indicates social decision making and evaluation of facial expressions as two key components of emotional processing and social interactions (Damasio 1996; Mayer 2002). Study 3 is novel because is the first study investigating the brain correlates of Ability EI during a social task eliciting both these components.

In conclusion, findings of Study 3 suggest that EI ability represents an additional source of variability in the emotion processing, particularly related with the brain physiology of social decision making, a higher level of emotional functioning.

5.3 Emotion dysconnectivity in schizophrenia

To complete the picture of the emotional individual differences, Study 4 explored the role of psychopathology and its genetic risk on brain dynamics during both implicit and explicit facial emotion processing. In particular, we have focused on schizophrenia, a psychiatric disease highly heritable and strongly associated with emotional dysfunction (Tandon, Nasrallah et al. 2009). A peculiarity of this study is also the use of Dynamic Causal Modelling for investigation of the effective connectivity, which allows to infer causality and directionality of the functional connections between regions during tasks (Friston, Brown et al. 2016). With this method, I have first investigated the physiological amygdala-lPFC connectivity in a large sample of healthy controls (HC) during implicit and explicit emotion processing. Subsequently, I have compared DCM patterns in a sub-sample of HC, in patients with schizophrenia (SCZ) and in healthy siblings of patients (SIB), matched for demographics. Finally, I have investigated in HC association of lPFC-amygdala effective connectivity with a genome-wide supported variant increasing genetic risk for schizophrenia and possibly relevant to emotion processing *(DRD2* rs2514218). In HC, I have found that a "Bottom-up" amygdala-to-lPFC pattern during implicit processing and a "Top-down" lPFC-to-amygdala pattern during explicit processing were the most likely directional models of effective connectivity. Differently, implicit emotion processing in SIB, SCZ, and HC homozygous for the schizophrenia risk rs2514218 C allele was associated with decreased probability for the "Bottom-up" as well as with increased probability for the "Top-down" model.

A possible interpretation of our findings in HC may be based on the known primary role of the amygdala in perceptual processing of emotional stimuli (Hariri, Bookheimer et al. 2000) and of

the lPFC in the explicit evaluation of emotional stimuli and emotional regulation (Ochsner, Knierim et al. 2004; Ochsner and Gross). Also, several findings suggest that emotional stimuli imply a faster amygdala response compared to those of associative cortices, such as the lPFC (Quirk, Armony et al. 1997). Thus, it is possible that the amygdala acts as a first functional node in the processing of emotional information conveyed by our task involving implicit, perceptual processing. Then, the amygdala may send relevant inputs to the lPFC that exerts a role in integrating emotional information in a more general context of information processing, as previously suggested (Pessoa 2008). Differently, the explicit emotional part of the Faces task needs integration of emotional regulation, social and cognitive functions, which are more supported by the lPFC according to previous literature (Phillips, Drevets et al. 2003; Ochsner, Ray et al. 2004; Ochsner and Gross 2005; Pessoa 2008). Thus, a task-mediated flow of information from the lPFC to the amygdala may contribute to modulate more automatic responses sustained by the latter brain region when regulatory processes based on social and/or cognitive evaluation of emotional stimuli are required.

Results of Study 4 indicate that the probability for a physiological model of effective connectivity in SCZ and SIB during implicit processing of emotional stimuli is not preserved. In greater detail, in both these groups of individuals the "Top-Down" model is more likely than the "Bottom-Up" model during both implicit and explicit emotion processing. These findings suggest a task-specific breakdown of the physiological flow of information between the amygdala and the lPFC in SCZ. Importantly, they also suggest that the abnormal pattern of effective connectivity during implicit emotion processing is a crucial phenotype of schizophrenia and that it is associated with familial risk for the disorder, rather than with specific state variables, including pharmacological treatment and levels of symptoms. In this regard, these results are in line with models proposing altered brain functional integration as a key pathophysiological mechanism for schizophrenia (Andreasen, Paradiso et al. 1998; Friston 1998; Friston ; Stephan, Baldeweg et al. 2006; Pettersson-Yeo, Allen et al. 2011; Friston, Brown et al. 2016), and consistent with studies reporting anomalous functional coupling between the amygdala and prefrontal regions in SCZ and in subjects at greater risk for this disorder (Das, Kemp et al. 2007; Leitman, Loughead et al. 2008; Anticevic, Van Snellenberg et al. 2012; Diwadkar, Wadehra et al. 2012; Modinos, Pettersson-Yeo et al. 2012; Pulkkinen, Nikkinen et al. 2015; Vai, Sferrazza Papa et al. 2015; Cao, Bertolino et al. 2016).

Particularly, I have also found in HC a similar between-group modulation of lPFC-amygdala effective connectivity by DRD2 rs2514218, which has been associated with diagnosis of schizophrenia in the largest genome wide association study to date (Consortium. 2014). Here, the alteration of patterns of effective connectivity in HC homozygous for the schizophrenia risk C allele

was similar to those present in SIB and in SCZ. Indeed, we found that the physiological pattern of amygdala/lPFC effective connectivity in CC HC is altered during implicit emotion processing, such that there was no winning model in this genotype group. These results are consistent with the likely involvement of D2 signaling in schizophrenia and with its relevance for emotion processing (Blasi, Lo Bianco et al. 2009). More in general, they support the use of effective connectivity during emotion processing for genetic investigations aimed at identifying true endophenotypes for the disease.

5.4 Limitations

The main limitation of this thesis is represented by the intrinsic nature of the topic under investigation. The emotions, in fact, include multiple components not all measurable by objective instruments. One of these components is the appraisal, which represents the significance that one emotional event or stimulus assumes for the individual. In other words, the appraisal indexes the way one individual feels, or better to say the way one individual is aware to feel. This aspect is only measurable via the so called "self-reports", such as subjective psychological measures. In this thesis we use self-reports of the affective states and traits. Even when carefully administered, self-reports are susceptible to a number of confounds, including social desirability effects, response bias, distortion due to social stereotypes, or personal defense and avoidance (Eriksen, 1960, Holender, 1986). Notwithstanding these confounds, these subjective measures still represent the best approximation of one's feeling and emotional appraisal and are fundamental for interpreting and completing other kinds of objective measures (e.g. brain imaging).

Another important limitation is represented by the fact that the experimental settings of the four studies included in this thesis, are far to be environmental. Fear, happiness and anger, are basic emotions experienced in contexts that are important for the individual's survival. However, the use of the functional magnetic resonance, significantly limits any attempt to make the setting more real. On the other way, it represents an objective and very informative measure of the emotion "on line" and we believe that what we see in this setting is the same emotion that one individual would feel in a real context, just at a lower intensity.

The present thesis also investigates the biological aspects of the individual differences, looking at some genetic traits. Importantly, the imaging genetic approach allowed to fully characterize the pathway from the genes to behavior, passing by brain physiology. This richness of variables investigated (genes, brain, behavior, psychological phenotypes), exposes to difficulties of

recruitment. The sample size of the Study 3 suffered these difficulties. However, we made the intentional choice to have a smaller sample in favor of a richer phenotype characterization.

5.5 Conclusions

Emotions are one of the most complex and unique human phenomenon. The complexity and uniqueness are mainly ascribable to the fact that emotions, while universally recognized and produced, still possess a large variability across individuals in the way they are acted, experienced and processed by the brain. For this reason, modern neuroscience has not yet fully characterized the neural and biological underpinnings of this human behavior.

This thesis, with its focus on psychological, genetic and pathological sources of emotional variability, represents a scientific attempt towards a more complete understanding of human emotion behavior. With this aim, this work adopted an imaging genetics approach, a novel methodological approach characterized by the integration of the most up-to-date neuroimaging and genetics techniques. Moreover, by using healthy, unhealthy and at-risk populations, this doctoral thesis intended to explore, in its possibilities, the largest window of human emotion behavior.

Findings of this thesis demonstrated that temporary affective states are capable of modulating emotions even at an early, automatic stage of processing, at both behavioral and neuronal level. Moreover, this modulation is affected by personality and genetic traits of the individual. An additional value of this latter finding is that, by demonstrating the effect of a dopamine genetic variant with a known molecular function, it unveils a possible biological mechanism at the base of the emotion-related effects of temporary affective states.

Furthermore, this thesis revealed that social and emotional abilities also represent a source of variability in the way brain processes the emotional information. Importantly, abilities rather than traits, are strongly modulated by the environment, and can possibly be achieved by learning. Thus, this finding posits the neural basis of conceivable interventions in this direction.

Finally, the present work discovered that emotional anomalies in schizophrenia subtend a specific breakdown of the connection going from the amygdala to the lPFC during automatic, early processing of emotions. Particularly, this breakdown is also found in healthy individuals at familial risk for schizophrenia or simply carrying a dopamine variant conferring risk for the disorder. This finding allows to consider the emotion brain dysconnectivity as a good biomarker for early diagnosis and intervention in schizophrenia and validate the involvement of dopamine neurotransmission in emotion functions and dysfunctions.

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Appendix