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THE ROLE OF ADULT ATTACHMENT IN THE RISK PATHWAYS FOR PSYCHOSIS: MODULATION ON PERSONALITY TRAITS, EMOTIONAL AVAILABILITY AND NEUROBIOLOGY OF EMOTION PROCESSING

Coordinatore:
Chiar.mo Prof. Giuseppe Mininni
Docente guida:
Chiar.ma Prof.ssa Rosalinda Cassibba

Dottorando:
Dott.ssa Linda Antonella Antonucci

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Introduction

According to attachment theory, children can rely since the moment of birth on a behavioral adjustment system that ensures them the proximity to the primary attachment figure. In an evolutionary perspective, this system is highly adaptive, since it provides the child with the necessary protection from several environmental dangerous stimuli during an extremely vulnerable stage of development (Bowlby, 1969; 1973). Furthermore, Bowlby (1973) argued that the guidance of the caregiver within the attachment relationship may facilitate in the child the acquisition of the abilities necessary for survival. Therefore, it could be argued that attachment relationships shape the basis of the individual personality and action tendencies, becoming a significant factor influencing the subsequent emotional experiences, even during adulthood (Sroufe and Waters, 1977). Consistently, negative experiences within the attachment relationships may lead to emotional maladjustments which may interfere with the structuring of a stable mental foundation (Mikulincer and Shaver, 2007). While the link between attachment and psychopathology is still unclear, it has been shown that psychological problems can increase attachment insecurity (Davila, Burge et al. 1997, Cozzarelli, Karafa et al. 2003, Solomon, Dekel et al. 2008), which in turn is associated with psychopathology.

Of all mental disorders, psychotic spectrum diseases (i.e., schizophrenia and bipolar disorder) are certainly the most severe and disabling mental illnesses because of several reasons. First, because they are characterized by a chronic course with frequent relapses (Geller, Tillman et al. 2004). Moreover, the rehabilitation of patients suffering from these disorders is difficult because of a non-sufficient response to pharmacological treatment, which concurs to the decline in social and personal functioning of the patients (Tohen, Zarate et al. 2003). However, several studies have highlighted that encouraging results in terms of recovery have been achieved when patients suffering from psychosis were treated during their first episode (Robinson, Woerner et al. 1999, Robinson, Woerner et al. 1999).

It is also well known that being affected by psychosis often represents a condition of social exclusion for patients, which concurs to the hard social, functional, working and personal recovery of this population, together with the demanding burden requested to families and mental health services in terms of management and care planning (Hegarty, Baldessarini et al. 1994). For these reasons, a better understanding of the relationship between attachment insecurity and psychosis will increase the likelihood of early identification and care of subjects in which the disease may not have fully manifested yet. For example, schizotypy is associated with an increased risk to develop a psychotic disorder (Kwapil, Gross et al. 2013, Poulton, Caspi et al. 2000, Barrantes-Vidal, Gross et al. 2013). Based on this association, the study of schizotypy can be useful to address the environmental determinants of risk for schizophrenia and to understand how to plan early intervention strategies for people at risk for these disorders, facilitating the understanding of developmental individual trajectories (including risk and protective factors).

Furthermore, literature agrees on the fact that infants of mothers experiencing mental health diseases are susceptible for the later development of psychopathology and for poor functioning affecting several developmental areas (Goodman and Gotlib 1999, Wan and Green 2009), therefore it is of pivotal importance to identify factors influencing the relationship between maternal psychopathology and child subsequent potential mental health problems in order to plan effective early intervention strategies.

Given that psychotic disorders have a polygenic architecture that, interacting with environmental factors, makes the pathophysiology of these disorders very complex and heterogeneous (Gottesman et al., 1987), neurobiological measures might be more effective than behavioral ones in explaining the risk for these disorders [literature here]. These measures can be obtained through the use of imaging techniques, such as functional magnetic resonance imaging (fMRI).

Overall, based on these assumptions, in a prevention-based framework, this project aims to understand whether and how early childhood experiences, also interacting with genetic factors potentially involved in the risk for psychosis, may shape behavioral and brain phenotypes linked to the risk mechanisms of the disease. This is of crucial interest for the

planning of early identification and intervention strategies directed to at risk for psychosis people which may involve also the investigation and the analysis of the individual Internal Working Models.

Therefore, based on the theoretical background here discussed, this project aims to elucidate how attachment dynamics are involved in the risk pathways for psychosis along three studies, each corresponding to a specific aim.

- Study 1 aims to investigate the potential association between adult attachment style, perceived maternal bonding and schizotypal traits in a large cohort of normal controls.
- Study 2 aims to assess, in a cohort of mother-infant dyads, the relationship between schizotypal traits and adult attachment state of mind in predicting dyadic emotional availability and to test the potential relationship between maternal schizotypal traits and temperamental dimensions of the child;
- Study 3 aims to investigate the gene-environment interaction between a variation of the oxytocin receptor (OXTR rs2268493), essential in social processes and in the early experiences of the mother-child relationship, and resulted associated with a level of social cognition deficits in patients with schizophrenia (Davis et al., 2014), and early experience of maternal care in determining functional changes in brain activity, measured *via* fMRI, during emotional processing.

Study 1 - association between adult attachment style and perceived maternal bonding with schizotypal traits: a new potential risk factor for psychosis

1.1. Background

1.1.1. Implications of the individual attachment style for mental health along the lifespan

1.1.1.1. The caregiver-infant attachment bonding

Attachment theory and its potential applications and implications for mental health have strongly interested clinicians and psychologists. Attachment theory emerges from the work of John Bowlby and Mary Ainsworth, who combined pivotal concepts and assumptions of psycho-analysis, cognitive and developmental psychology. Their aim was to precisely define and describe the attachment behavioral system (Bowlby 1969, Bowlby 1980), which has been experimentally tested and further detailed in the last 30 years.

A behavioral system is represented by a species-unspecific program organizing behavior in functional ways, for example increasing the chances of reproduction in specific environmental conditions (Bowlby, 1980, Mikulincer and Shaver, 2003) in an evolutionary framework, thus determining choices and behaviors of the individual. It therefore has a strong biological function. The attachment behavioral system, based on the emotional bonding between caregiver and child, emerges in order to manage the biological need of protection from dangers. This so-called "proximity seeking" drive therefore directs individual behaviors with the assumption that, if the child maintains proximity to the attachment figure providing support and care (i.e., the caregiver), she would be protected by dangerous environmental conditions (Mikulincer and Shaver, 2003), thus increasing the chances of survival and the potential reproduction. According to attachment theory (Bowlby, 1969, Ainsworth, 1978), the attachment system is active when adverse environmental conditions require the disengagement of the exploratory behavioral system

(Zeanah, Berlin et al. 2011) in order to receive support by the attachment figure. Therefore, when the child will *feel* secure (Torquati and Vazsonyi 1999) if close to the caregiver, its motivation to exploration and discover of the environment will gradually increase, thus determining the deactivation of the attachment behavioral system and the re-activation of the exploratory system.

Attachment is shaped during the first years of life, in line with the behavioral and physical abilities of the infant. Bowlby (Bowlby 1988) assumed that the attachment-exploratory behavioral systems alternation remains active along the entire lifespan. Following this view, proximity seeking is for the adult individual the way to adaptively respond to environmental pressure during stressful periods, traumatic experiences or adverse events (Mikulincer and Shaver, 2003), when being close to someone offering comfort increases the possibility of social adjustment.

It could be argued, therefore, that the eligibility of a caregiver to the role of attachment figure relies on the degree of protection perceived by the child when the proximity seeking instinct emerges (Hazan and Shaver 1987). Furthermore, the attachment figure should facilitate the coping with stress and negative emotion, thus representing a "secure base" (Bowlby, 1969, 1980, Mikulincer and Shaver, 2003) and being the starting point of a safe environmental exploration for the child, giving him the confidence that care and support will be guaranteed in case of need.

Previous literature by Ainsworth et al. (Ainsworth 1978) used the Strange Situation Procedure (SSP) to reveal different and distinct patterns of activation of the caregiver-child attachment system, which may range between a high degree of attachment security and different patterns of insecurity, mainly represented by avoidance and anxiety. Attachment avoidance implies a de-activation of the attachment system to different and individual extents in favor of the exploratory behavioral system, due to the perception of the non-availability of the caregiver in case of need. Attachment avoidance is motivated by the fact that the caregiver is thought to be non-responsive and not emotionally involved with the individual, who attempts in different ways (such as suppression of emotion expressions

and/or negative features of self) to constantly keep the attachment behavioral system on a low range of activation. Conversely, attachment anxiety is characterized by a tendency to hyper-activate the attachment system: in most cases, the attachment figure is not considered a secure base due to chaotic, unpredictable and conflicting behaviors directed to the individual. For these reasons, subjects report that they do not feel comfortable in experiencing the environment and will therefore increase the proximity seeking–oriented behaviors, since the caregiver is not experienced as a secure base.

1.1.1.2. Features of the attachment system in adulthood

The repeated interactions with the attachment figures and the consequent perceived response to the proximity seeking attempts of the child shape the attachment emotional bonding and determine the quality of the caregiver-child attachment relationship (i.e., the attachment style – Ainsworth et al. 1978). These experiences tend to be organized in cognitive schemes giving the child a representation of the self and the other, determining how to behave and what to expect in terms of fulfilling of needs within the relationship with others. These Internal Working Models (IWMs) systematically influence attachment relationships (Feeney 1999, Simpson, Rholes et al. 2003) and have been defined as a "guidance system" (Belsky 2002) crucial for individuals in order to direct actions, choices and behaviors and to give *"a mental simulation and prediction of likely outcomes of various attachment behaviors"* (Mikulincer and Shaver 2007). Even if IWMs tend to be generated during childhood because of the experiences within the caregiver-child interaction, they seem to remain stable in adulthood, when they represent the mental frame orienting individuals about behavior and expectations within social interactions and especially in close relationships. Given therefore that IWMs can be considered the core element of one's attachment style (Vrticka and Vuilleumier 2012) and therefore determine the attachment individual differences, it could be argued that IWMs characterize the adult attachment style, which in turn may have strong implications in adult social processes, shaping the quality and the features of interactions with known and unknown individuals and, above

all, romantic relationships (Fisher, Aron et al. 2006, Fraley, Niedenthal et al. 2006, Niedenthal, Brauer et al. 2002, Vrticka et al. 2012).

In this context, studies have elucidated that attachment relationships are crucial along the entire lifespan for emotion processing and regulation (Adam and Gunnar 2001, Adam, Gunnar et al. 2004, Kobak, 1999). Nowadays the emotional system is in fact considered the primary system modulated by attachment behaviors and representations (Bowlby, 1973). Attachment security in fact is thought to facilitate emotion regulation and to enhance behaviors of affiliation between peers. Moreover, it tends to be associated with a high level of self-esteem, self-stability and satisfaction (Canterberry and Gillath 2013), thus further corroborating the hypothesis that adult attachment style could influence social, personal, affective and parental functioning (Fisher et al. 2006). Therefore, the influence of childhood experiences of attachment on adult personality and relationships (especially romantic relationships) style is likely to be mediated by attachment security/insecurity, represented by IWMs. In this context, Mikulincer and Shaver (2007) have elucidated that the main social and interpersonal systems modulated by attachment style during adulthood include (a) romantic and sexual relationships, (b) self-regulation and perceived personal growth, (c) emotion processing and regulation, (d) interpersonal dynamics and (e) parenting behaviors and familial functioning. In this line of reasoning, attachment dysregulations can be crucial in social-affective disturbances.

Therefore, adult attachment style represents a systematic organization orienting needs, emotion regulation strategies and social behaviors (Bowlby, 1969, Shaver and Mikulincer, 2002), whose vehicle is the IWM organization based on the individual history of attachment experiences with parents (Fraley and Shaver, 2000). Based on the three major attachment styles (Secure, Anxious and Avoidant) identified through the SSP administration to caregiver-child dyads (Ainsworth et al. 1978), the insecure adult attachment style is mainly organized along two dimensions, defined as *attachment-related anxiety* and *attachment-related avoidance* (Brennan et al. 1998). In this definition space, the

Secure type is given to individuals in which both attachment anxiety and avoidance are low.

Individuals characterized by attachment-related anxiety (parallel with the anxious/ambivalent/resistant type identified by Ainsworth et al., 1978) intensify their proximity-seeking attempts due to their desire for attention and protection. These individuals are strongly vigilant to social threats, adverse environmental events and rejection experiences. In terms of emotion regulation strategies, these individuals tend to intensify the impact of negative emotions (Bartholomew and Horowitz 1991, Griffin and Bartholomew 1994, Mikulincer and Shaver, 2007, Vrticka et al. 2012).

On the other hand, subjects characterized by attachment-related avoidance (parallel with Ainsworth's avoidant type) perceive proximity seeking as dangerous, disavow the need of being comforted by others and avoid closeness and intimacy. In terms of emotion regulation strategies, they tend to suppress the impact of emotions (Mikulincer and Shaver, 2007, Vrticka et al. 2012) in order to avoid that others can perceive their feelings and internal states, preventing the possibility of rejection.

An additional category defines the so-called "fearful" or "disorganized" subjects (Bartholomew and Horowitz, 1991, Griffin and Bartholomew, 1994, Main, Kaplan et al. 1985), who are characterized both by high attachment-related anxiety and avoidance, reflecting negative IWMs both of self and others.

Based on these assumptions, a central concept of the attachment theory is that individual differences in terms of attachment style can be transmitted along generations (Besser and Priel 2005, van Ijzendoorn 1995). In this line of reasoning, the so-called "intergenerational transmission of attachment" (Sette, Coppola et al. 2015) represents the process favoring continuity of attachment patterns from a generation to another. This process has crucial consequences on parenting behaviors since the caregiver-child relationship is the main context in which the interaction funding the structure of IWMs take place.

1.1.1.3. Assessment of the adult attachment dispositions

Over the past 30 years, the investigation of individual differences in terms of adult attachment style has been organized along two main lines of research, reflecting two different conceptualizations of adult attachment (Scharfe and Bartholomew 1998, Shaver and Mikulincer, 2002).

On one hand, several researchers have proposed that attachment security shapes and influences IWMs (which tend to remain stable for the entire life of individuals) throughout childhood memories, modulating the way the individual sees himself and approaches others in close relationships. This concept is the basis of the so-called *attachment developmental trajectory* (Belsky et al. 2002). In this context, researchers have successfully used Adult Attachment Interview (AAI, George et al. 1985) to investigate the adult state of mind with respect to attachment childhood experiences (under the conceptual framework of its developmental roots - Belsky, 2002) and its relationship with emotion regulation strategies, such as repression and suppression of feelings and memory, coping with negative emotions and dissociation mechanisms (Dozier and Kobak 1992).

The AAI is a semi-structured interview developed in order to assess the adult current state of mind regarding attachment experiences in childhood. The classification which is possible to derive from the administration of this interview is based on the evaluation of the speaker of his own memories and implies the recall of both general (semantic) and specific (episodic) event occurred during childhood. Assigning a subject to the Secure category (F) or to the Dismissing (D), Entangled (E) or Unresolved (U) is primarily based on the ability of the subject to coherently organize, retrieve and understand his childhood experiences and on the proficiency in recognizing the effects and the impact of the events recalled during the interview on shaping his adult personality and way to react to emotional situations (Main and Hesse 1990, van Ijzendoorn 1992, van Ijzendoorn 1995).

On the other hand, other authors (Hazan and Shaver 1987, Feeney 1999) argued that attachment security and insecurity are modulated by actual relationships, therefore IWMs

are a "work in progress" system (Belsky et al. 2002) originating moment by moment from direct experiences with others also in adulthood, which interact with childhood experiences in shaping IWM and their guidance function, rather than being determined only by childhood experiences in the context of the interaction with the attachment figure. Following this *attachment social trajectory*, adult attachment style has been assessed using several self-report instruments, such as the Experiences in Close Relationships – ECR (Brennan et al. 1998), the Attachment Style Questionnaire – ASQ (Feeney et al. 1994) and the Relationship Questionnaire – RQ (Bartholomew 1990, Bartholomew and Horowitz 1991). This type of instruments can capture conscious attachment-related mental processes, unlike AAI whose developmental substrate seems to elicit unconscious psychological mechanisms through narrative processing.

Despite the theoretical (developmental vs. social approach) and methodological (narrative vs. self-report approach) differences between the two research trajectories on attachment behaviors, studies have indicated that self-report measures are associated with AAI continuous and categorical coding (Shaver and Fraley 2000, Shaver and Mikulincer 2002). Thus, even if AAI is considered a direct tool to examine IWMs, while self-report measures can provide researchers with indicators of differences in several cognitive and emotional processes which are modulated by attachment style, these two theoretical perspectives might be integrated, using AAI coding together with the conscious indicators derived from self-report attachment measures in order to uncover unconscious processes through more direct measures (Shaver and Mikulincer, 2002).

1.1.2. Implications of attachment insecurity on psychopathology

As stated before, if the attachment figure is perceived by the infant as uncaring and unsupportive, the proximity seeking instinct will not be satisfied, likely determining low perceived security, negative models of the self and others and potential emotional maladjustments, therefore, interfering with the foundation of a secure attachment style and, as recently stated by Mikulincer and Shaver (2012), of a stable mental foundation. Even if the link between attachment and psychopathology seems to be moderated by a

large array of biological and environmental factors (Mikulincer and Shaver 2012), several studies in clinical and non-clinical samples have coherently demonstrated that attachment insecurity seems to characterize people affected by several mental disorders, ranging from depression (Catanzaro et al. 2010), anxiety (Bosmans, Braet et al. 2010), obsessive compulsive disorder (Doron, Moulding et al. 2009), borderline personality disorder (Barone et al., 2011), post-traumatic stress disorders (Ein-Dor, Doron et al. 2010), eating disorders (Gormley et al. 2010) and psychosis (Berry, Band et al. 2007, Berry, Barrowclough et al. 2007, Berry, Wearden et al. 2007). Even if the link between attachment and psychopathology is still unclear, several studies have demonstrated that psychological problems can increase attachment insecurity (Davila, Burge et al. 1997, Cozzarelli, Karafa et al. 2003, Solomon, Dekel et al. 2008) and that attachment insecurity is significantly associated with psychopathology, even if in a non-specific direction so far.

Understanding more clearly how attachment and psychopathology are related to each other is crucial especially for psychosis disorder and schizophrenia, which represent the most severe and disabling mental disorders because of several reasons. First, because they are characterized by a chronic course with frequent relapses (Geller, Tillman et al. 2004). Moreover, the rehabilitation of patients suffering from these disorders is difficult because of a non-sufficient response to pharmacological treatment, which concurs to the decline in social and personal functioning of the patients (Tohen, Zarate et al. 2003), but several studies have highlighted that encouraging results in terms of recovery have been achieved when patients suffering from psychosis were treated during their first episode (Robinson, Woerner et al. 1999, Robinson, Woerner et al. 1999).

It is also well known that being affected by psychosis and schizophrenia often represents a condition of social exclusion for patients, which concurs to the hard social, functional, working and personal recovery of this population, together with the demanding burden requested to families and mental health services in terms of management and care planning (Hegarty, Baldessarini et al. 1994). For these reasons, better understanding the relationship between attachment insecurity and psychosis will increase the likelihood of

early identification and care of subjects in which the disease may not have fully manifested yet.

1.1.2.1. Attachment insecurity, psychosis and schizophrenia

Psychosis disorders, among which the most severe is schizophrenia, involve the presence of symptoms spanning from unconsciousness, delusions, sensitive hallucinations, flattened and/or altered affect (APA 2013). Some authors have suggested that the perceptual dissociative symptoms of psychosis may be exacerbated in patients by frightening, rejecting and unloving parental behaviors, causing disorganized model of self and others (Hesse 1999, Liotti 1992). Caregivers with a low level of care in their parenting style may in fact induce in children the development of multiple incompatible IWMs that cannot be integrated with each other in a coherent manner, therefore leading to reality perception disturbances in adulthood (Mikulincer and Shaver 2007). According to this view, several studies have indicated the existence of a significant association between diagnosis of schizophrenia and insecure states of mind following AAI classification (Dozier 1990, Dozier et al. 1991). Specifically, the avoidant/dismissing strategy occurred more frequently in patients diagnosed with schizophrenia, relative to those diagnosed with an affective disorder category (Dozier, Cue et al. 1994, Tyrrell and Dozier 1997). Other studies revealed that individuals diagnosed with schizophrenia and classified as dismissing through the AAI had a higher level of positive symptoms (i.e., delusions and/or hallucinations). These results, in the context of studies assessing the adult attachment state of mind with the AAI, are coherent with the results of other studies in which the adult attachment style was assessed using self-report measures. In detail, literature shows that high ratings of attachment anxiety and avoidance were associated with psychotic symptoms severity (Mickelson, Kessler et al. 1997) and with less efficient coping ability during recovery (Drayton, Birchwood et al. 1998, Tait, Birchwood et al. 2004).

Significant results are reported also with respect to the perceived maternal care received by subjects during infancy and reported through self-report questionnaires during adulthood and its association with psychosis and schizophrenia diagnoses. This is in line with the attachment theory, positing that IWMs are built based on the quality of the interaction experienced during childhood and orient a complex system of social and emotional behaviors. In detail, through the use of the self-administered questionnaire Parental Bonding Instrument (PBI, Parker 1990), studies have revealed that low parental care (Parker, Fairley et al. 1982, Helgeland and Torgersen 1997, Willinger, Heiden et al. 2002) and high parental overprotectiveness (Onstad, Skre et al. 1994, Parker, Fairley et al. 1982, Helgeland and Torgersen 1997, Willinger, Heiden et al. 2002), which are collapsed in the "affectionless control" parental style category (Parker 1990), were associated with schizophrenia diagnosis, with an earlier age of initial hospitalization (Parker et al. 1982). and with a higher rate of re-hospitalization after 9 months (Parker et al. 1982). Furthermore, patients who experienced an "affectionless control" parental style tended to experience a higher number of relapses and a more severe course of the illness (Warner and Atkinson, 1988). However, these findings are not consistent with evidence failing in reporting a significant association between PBI and relapse (Baker, Helmes et al. 1984, Lebell, Marder et al. 1993). Other studies have revealed consistent results linking the occurrence of traumatic experiences, leading to disorganized attachment strategies, to psychosis diagnoses. Traumatic events such as physical, sexual or emotional abuse seem to be correlated with negative outcomes in psychosis (Doering, Muller et al. 1998, Fowler 2000, Mueser, Goodman et al. 1998). Furthermore, lower levels of parental care seem to be associated with the onset of psychosis (Janssen, Krabbendam et al. 2005).

1.1.2.2. Attachment insecurity and schizotypy

The term schizotypy was introduced more than 60 years ago to describe *"a broad phenotype of schizophrenic–like psychopathology and impairment*" (Kwapil and Barrantes-Vidal 2015). According to several authors, schizotypy would represent a vulnerability to schizophrenia spectrum disorders expressed at a personality level (Barrantes-Vidal, Grant et al. 2015,

Meehl 1962, Rado 1953). This vulnerability, interacting with the genetic and environmental factors conferring risk for schizophrenia (Caspi, Sugden et al. 2003, Gottesman, McGuffin et al. 1987), would shape the risk for schizophrenia along a wide range of phenotypic variance. In other words, schizotypy can be described as the latent personality organization that conveys liability for schizophrenia (Lenzenweger 2010, Figure 1.1) that can be identified through familial/biological, clinical, and psychometric-laboratory index approaches (Lenzenweger 2006). In this line of reasoning, studies have demonstrated that schizotypy is associated with increase in the risk for developing a psychotic disorder (Kwapil, Gross et al. 2013, Poulton, Caspi et al. 2000, Barrantes-Vidal, Gross et al. 2013), and therefore it represents a useful framework to study the determinants of risk for schizophrenia and, on these basis, to understand how to plan useful identification and early intervention strategies for people at risk for these disorders, facilitating the understanding of developmental individual trajectories (including risk and protective factors).

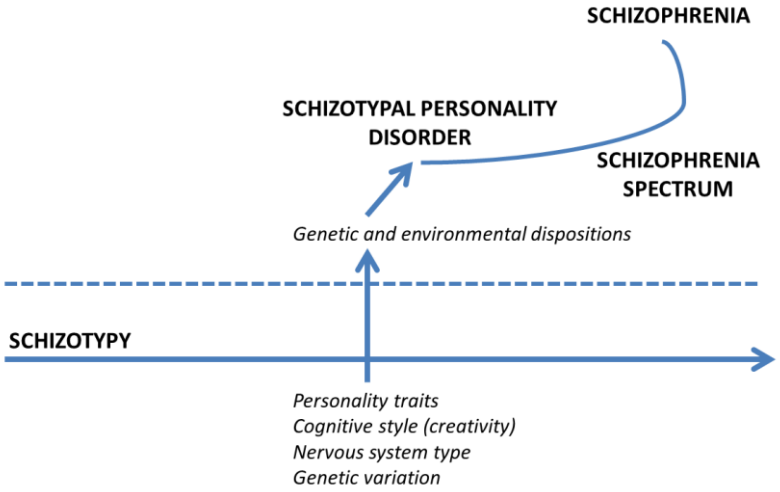

Figure 1.1: diagram showing the potential continuum between schizotypal disposition and schizophrenia (adapted by Claridge and Beech, 1995).

However, the wide phenotypic variance characterizing the schizotypy-schizophrenia continuum is represented at the level of symptoms severity (clearly more debilitating in full blown schizophrenia, rather than in presence of the sole schizotypal personality trait

or disorder) and domain, with people experiencing symptoms and impairments ranging from mild disruptions (odd beliefs, mild withdrawal) to marked deficits (hallucinations, formal thought disorder). Furthermore, this heterogeneity is evident at the etiological, developmental, and treatment response levels, and the heterogeneity of schizotypy and schizophrenia appears to be characterized by a common multidimensional structure, based on positive and negative subthreshold symptoms (Kwapil and Barrantes-Vidal 2015). In fact, as schizophrenia is organized along positive (i.e., delusions and hallucinations), negative (i.e., flattened and/or altered affect) and disorganized (i.e., thought and speech alterations) symptomatologic dimensions (Lenzenweger and Dworkin 1996, Liddle 1987, Kwapil and Barrantes-Vidal 2015), schizotypy seems to mirror this factorial structure in non-clinical samples (Bentall, Claridge et al. 1989, Cicero and Kerns 2010, Lewandowski, Barrantes-Vidal et al. 2006, Raine, Reynolds et al. 1994). Specifically, positive schizotypy seems to be characterized by odd beliefs, unusual perceptual experiences, negative affect and dysregulation in affects. On the other hand, negative schizotypy involves avolition, asociality and flattened affect (Vollema and van den Bosch 1995). The disorganization dimension includes disruptions in the ability to organize thoughts and behaviors.

The investigation of attachment insecurity modulation capacity not only on schizophrenia but only on schizotypy is intriguing in line with the view that schizophrenia and schizotypy may not be considered separate nosologic categories, but part of a continuum. This is crucial in a prevention-oriented view because studies have demonstrated that several micro-environmental risk factors are involved in the psychosis susceptibility pathways. In this context, a recent meta-analysis of 20 studies suggested that parental communication deviance (de Sousa, Varese et al. 2014) and perceptions of parental behavior, particularly lower perceived care (Meins, Jones et al. 2008), are related both to psychosis and schizotypal traits. Furthermore childhood adversities, especially childhood trauma, not only increase the risk of psychosis (Varese, Smeets et al. 2012) but adversities such as bullying, neglect and abuse have been linked to schizotypy (Sheinbaum, Kwapil et al. 2014, Velikonja, Fisher et al. 2015) therefore allowing to hypothesize, as posited by

Barrantes-Vidal et al. (2015), that social interactive experiences involving the "intention to harm element" can be related to psychosis more than non-specific traumas, such as the death of a close person (van Nierop, Lataster et al. 2014).

Consistently, studies have demonstrated in non-clinical samples the existence of an association between insecure attachment and schizotypy (Berry, Wearden et al. 2006, Berry, Wearden et al. 2007, West and Keller 1994), with specific associations between anxiety and positive schizotypal trait of cognitive disorganization, and avoidance and introvertive anhedonia.

Furthermore, other authors (Wilson and Costanzo 1996) indicated the existence of a relationship between anxious attachment and schizotypal personality disorder: secure individuals had lower schizotypal tendencies, while avoidant subjects had higher anhedonia and schizophrenism score, while anxious participants had higher magical ideation and schizophrenism scores, suggesting therefore that attachment-related anxiety may be related to positive schizotypy, while the minimization of the impact of interpersonal relationship (i.e., attachment-related avoidance) seemed to increase schizotypy along both positive and negative dimensions. Interestingly, Sheinbaum et al. (2014) have demonstrated in a non-clinical sample that physical and emotional trauma not only were associated with positive and negative nonclinical psychotic experiences, but that fearful attachment significantly mediated this relationship, thus supporting that disorganized attachment IWMs have a role in risk for psychosis and supporting the hypothesis that these should be re-considered as a factor importantly intervening in psychosis vulnerability pathways.

1.2. Goal of the project

- **AIM:** despite several evidences in literature testifying the association between attachment insecurity and schizotypy, no study has directly tested the causal link between these two variables. It is clear that the attachment-schizotypy relationship may involve bi-directional influences (Wilson and Costanzo 1996), but understanding whether and how schizotypy dimensions are modulated by attachment style (whose structure is based on IWMs built during infancy) would be key in order to better understand the potential environmental modifiers of psychosis risk, thus allowing clinicians and psychologists to better program early intervention strategies in order to prevent full blown schizophrenia. Therefore, the goal of the current study is to investigate the potential association between adult attachment style, perceived maternal bonding and schizotypal traits in a large cohort of normal controls.
- **EXPECTED RESULTS:** we expect that both adult attachment style and perceived maternal bonding will significantly predict schizotypy scores independently on the instrument used for the evaluation of attachment.

1.3. Materials and methods

1.3.1. Sample characteristics

The subjects enrolled in this study included 237 healthy controls, whose demographic and neuropsychological characteristics are reported in Table 1.1. All subjects underwent an extensive clinical interview in order to assess the absence of any psychiatric diagnosis through the Structured Clinical Interview for DSM-IV (First et al. 1996). Additional exclusion criteria were presence of any neurological or psychiatric disorder and of any other medical condition and history of significant drug or alcohol abuse (no active drug use in the past year). All subjects were given a complete description of the study and its procedures. Written informed consent was obtained only after full comprehension of the protocol.

	Whole Group	PBI high MC	PBI low MC	RQ secure	RQ insecure
N	237	127	110	122	115
Gender Ratio (M/F)	114/123	56/71	58/52	53/69	61/54
Age (mean±SD)	27.17±8.45	26.90±8.36	27.48±8.57	27.40±8.91	26.93±7.95
Education (mean±SD)	15.25±2.21	15.62±1.89	14.90±2.45	15.30±1.99	15.20±2.42
Socio-Economic Status (mean±SD)	38.30±15.96	40.94±16.36	35.24±14.97	39.19±15.06	37.38±16.87

***Table 1.1**: demographic information of Study 1 sample*
(PBI: Parental Bonding Instrument, MC: Maternal Care, RQ: Relationship Questionnaire).
N=sample size; SD=Standard Deviation. Age and Education are reported in years.

1.3.1. Instruments

1.3.1.1. Evaluation of adult attachment style in the attachment social trajectory: self-administered questionnaires

1.3.1.1.1. The Relationship Questionnaire (RQ)

The Relationship Questionnaire (RQ, (Bartholomew and Horowitz 1991) is composed by four short paragraphs, each describing a prototypical attachment pattern as it applies in close adult peer relationships. RQ can capture the IWMs guiding adult relationship with significant others and it is possible to derive a score assessing the IWMs related to the self and those related to others. By the combination of the two IWMs continuous scores it is

possible to derive a categorical description of the IWMs: Secure (with positive models of both self and others), Preoccupied (with a negative self-model and a positive other-model), Dismissing (with a positive self-model and a negative other model), and Fearful (with negative models of both self and others). For example, the prototypical description of the Secure attachment pattern reads as follows: *"It is easy for me to become emotionally close to others. I am comfortable depending on them and having them depend on me. I don't worry about being alone or having others not accept me".* Respondents were instructed to rate on 7-point scales the extent to which each description corresponds to their behavior in relationships with others. RQ seems to address global attachment orientation, that is, the general model of self and others in relation to attachment (Griffin and Bartholomew 1994, Bartholomew and Horowitz 1991, Collins and Read 1994).

For analysis purposes, we focused on the four way RQ classification here proposed. Furthermore, all non-secure classifications (preoccupied, dismissing and fearful) were collapsed in the "insecure" category, thus allowing to perform statistical analysis with a RQ two-way classification.

1.3.1.1.2. The Experiences in Close Relationships (ECR)

The Experiences in Close Relationships Scale (ECR, Brennan et al. 1998) is a self-report questionnaire that aims to investigate the feelings and behaviors related to romantic attachment through a list of statements that are grouped along two dimensions: "anxiety about abandonment" and "avoidance of closeness". The subject is therefore required to report, on a 7-point Likert scale (1 = strongly disagree to 7 = strongly agree), his level of agreement to each of the 36 items of the questionnaire.

The "anxiety" factor includes intense concerns for romantic relationships, fear of being abandoned and frequent requests to greater involvement of partners, the second factor, "avoidance", includes difficult and uncomfortable feelings in approaching emotions and in relying on partners. By combining anxiety and avoidance score it is possible to derive a categorical factor describing the quality of the romantic attachment style along 4 categories which are equivalent to the classification of attachment styles proposed by Bartholomew (1990): Secure (low avoidance - low anxiety), Preoccupied (low avoidance - high anxiety),

Dismissing-Avoidant (high avoidance - low anxiety) and Fearful-Avoidant (high avoidance - high anxiety).

In this study, we focused on continuous scores of ECR anxiety and avoidance.

1.3.1.2. Evaluation of perceived maternal bonding

Perceived maternal bonding was measured using the Parental Bonding Instrument (PBI), which is based on the subjects' memories of their parents during the first 16 years of life (Parker et al. 1980). According to the principles of attachment theory, Parker (1980) posits that nurturing and parenting abilities may influence the quality of the mother-child relationship. Specifically, the perception of a loving and emotionally close parent seems to favor the development of a secure attachment in the child. On the other hand, a perceived cold and intrusive parent can lead to a problematic child development and to subsequent psychological disorders (George et al. 1985).

The PBI is a 25-item self-report questionnaire investigating two main dimensions, "care" and "overprotection". The "care" dimension reflects perceived parental warmth, affection, and involvement in contrast to coldness, indifference, and rejection. On the other hand, the "overprotection" dimension reflects perceived parental psychological control and intrusion in contrast to the encouragement of autonomy and independence. Subjects were asked to score their mother's attitudes using a 4-point scale. Maternal bonding evaluated by the PBI can be classified into four parental bonding style according to the possible combinations of maternal care and overprotection and following published cut-off scores (respectively, 27 for maternal care and 13.5 for maternal over-protectiveness Parker, 1980): "Optimal bonding" (high care, low overprotection), "neglectful parenting" (low care, low overprotection), "affectionate constraint" (high care, high overprotection), and "affectionless control" (low care, high overprotection). The PBI has long-term stability (Wilhelm, Niven et al. 2005) and its subscales have a high level of test-retest reliability and internal consistency (Parker et al. 1980).

In this study, we focused on the four-way categorical classification and on continuous scores of maternal care and overprotection for analysis purposes.

1.3.1.3. Evaluation of schizotypal traits

The Schizotypal Personality Questionnaire (SPQ, Raine 1991) is a widely used self-report instrument that evaluates schizotypal personality disorder according to DSM-III-R (American Psychiatric Association 1987).

It is a self-assessment questionnaire consisting of 74 items with dichotomous response format (yes/no), in which participants are required to circle their response, assigning one point for each "yes."

The questionnaire items can be clustered into nine sub-dimensions that investigate the nine correspondent diagnostic criteria for schizotypal disorder: ideas of reference (9 items), odd beliefs/magical thinking (7 items), unusual perceptual experiences (9 items), paranoid ideation/suspiciousness (8 items), social anxiety (8 items), no close friends (9 items), restricted affect (8 items), odd/ eccentric behavior and appearance (7 items) and odd speech (9 items).

These nine sub-dimensions can be further clustered into three domains/factors: cognitive-perceptual, interpersonal and disorganized (Calkins, Curtis et al. 2004, Chen, Hsiao et al. 1997, Claridge, McCreery et al. 1996, Gruzelier 1996, Raine et al. 1994, Reynolds, Raine et al. 2000). The first factor (cognitive-perceptual) identifies deficits that are very close to the positive psychotic symptoms, such as ideas of reference, magical thinking, unusual perceptual experiences and paranoid ideation (i.e., *"Have you ever seen things invisible to other people?"* or *"Do sometimes your thoughts are so strong that you could almost hear them?"*), the second factor (interpersonal) describes deficits that resemble to psychosis negative symptoms, such as social anxiety, lack of close friends, inappropriate or flattened affect and, as for the previous factor, paranoid ideation (i.e., *"I have little interest in learning about other people"*), the third factor (disorganized) refers to the presence of strange behaviors and communication styles that can be considered odd or eccentric (i.e., *"People consider me a little eccentric"* or *"Sometimes I use words in an unusual way"*).

SPQ psychometric properties (internal consistency, test-retest reliability, convergent validity and discriminant validity criteria) have been extensively analyzed and were

found to be satisfying (Compton, Goulding et al. 2009, Fossati, Feeney et al. 2003, Wuthrich and Bates 2006).

The SPQ is largely used for the screening of schizotypal personality in the general population with a good research applicability in studies investigating genetic risk trajectories of schizophrenia and psychosis spectrum disorders. This instrument therefore is used to deeply characterize subject's personality schizotypal traits (Chen, Hsiao et al. 1997, Raine et al. 1994), to relate schizotypal dimensions to schizophrenia diagnosis (Chen et al. 1997) and identify individuals that may be experiencing an "At Risk Mental State" (ARMS, Yung and McGorry 1996) for psychosis.

1.3.2. Data analysis

To verify the existence of an association between adult attachment style and/or perceived maternal care and schizotypal traits, ANOVAs and regression analysis were computed. More in detail:

a. To test the effect of adult attachment state of mind (measured through RQ and ECR) in an attachment social trajectory on schizotypal dimensions (measured through the SPQ), we performed:

- An ANOVA using RQ two-way classification (secure vs. insecure) as categorical factor and the three SPQ factors (cognitive-perceptual factor score, interpersonal factor score and disorganized factor score) as within factor; in the RQ "insecure" category subjects classified as preoccupied, dismissing-avoidant and fearful-avoidant were collapsed;
- Regression analysis having, respectively, ECR anxiety and ECR avoidance as continuous predictors and, respectively, the total SPQ score, the cognitive-perceptual factor score, the interpersonal factor score and the disorganized factor score as dependent variable.

b. To test the effect of perceived maternal bonding on schizotypal traits, we performed:

- An ANOVA using the two way PBI categorical classification of maternal care as independent variable (cutoff score: 27, Parker et al. 1979, 1989) and the three SPQ

factors (cognitive-perceptual factor score, interpersonal factor score and disorganized factor score) as within factor;

- An ANOVA using the two way PBI categorical classification of maternal over-protection as independent variable (cutoff score: 13.5, Parker et al. 1979, 1989) and the three SPQ factors (cognitive-perceptual factor score, interpersonal factor score and disorganized factor score) as within factor.

All analyses were performed through Statistica 10 and thresholded with α=0.05. Results were Bonferroni corrected for the number of test used in the whole analysis set (3: RQ, ECR, PBI).

1.4. Results

1.4.1. Effect of adult attachment style on schizotypal dimensions

1.4.1.1. RQ-SPQ association

The ANOVA conducted using the RQ two-way classification as categorical factor on schizotypal dimensions revealed:

1. A main effect of RQ (F=18,88; Bonferroni corrected p= 0.00006, Figure 1.2/a);
2. A significant interaction between RQ and SPQ factor (F=11,01, Bonferroni corrected p=0.00006, Figure 1.2/b); Fisher post hoc analysis revealed that RQ insecure subjects had higher SPQ scores than RQ secure subjects in the interpersonal factor (p=0.0001) and in the disorganized factor (p=0.0001). This pattern almost reached signifcance in the cognitive-perceptual factor (p=0.053).
3. A main effect of SPQ factor (F= 83.05; Bonferroni corrected p=0.00003);

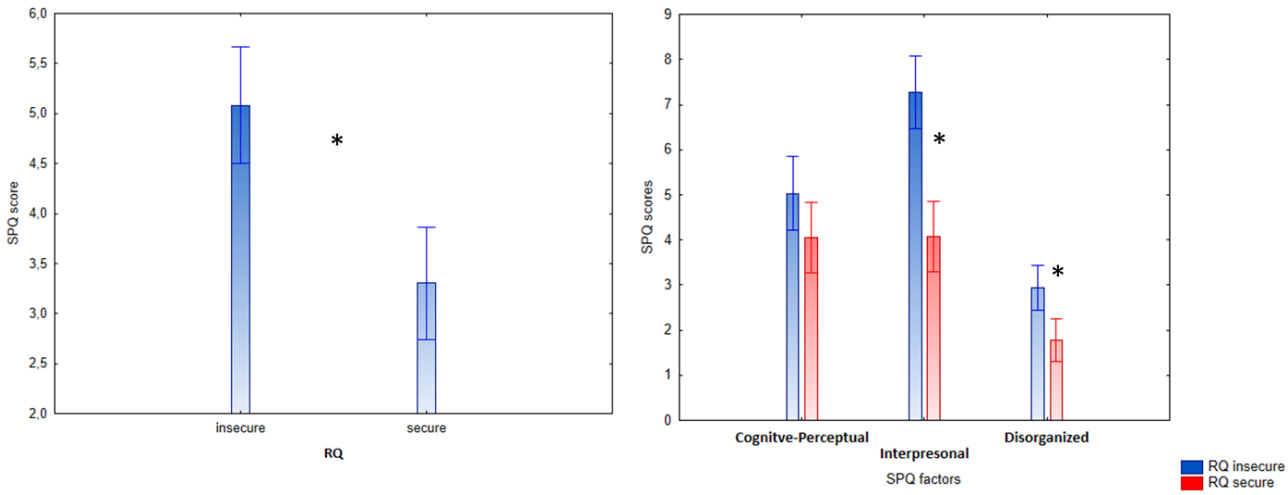

Figure 1.2: *histograms showing (a) the main effect of RQ attachment style on SPQ score; (b) the interaction between RQ attachment style and SPQ factors on SPQ scores.*

1.4.1.2. ECR-SPQ association

Regression analysis between ECR avoidance dimension scores and schizotypal dimensions revealed:

1. ECR avoidance scores and SPQ total score (R=0.179, Bonferroni corrected p=0.018, Figure 1.3/a),

2. ECR avoidance scores and SPQ interpersonal factor score (R=0.239, Bonferroni corrected p=0.0003, Figure 1.3/b),
3. ECR avoidance scores and SPQ disorganized factor score at a trend level (R=0.152, Bonferroni corrected p=0.057, Figure 1.3/c),

On the other hand, no significant association was found between ECR avoidance scores and SPQ cognitive-perceptual factor scores (p>0.9).

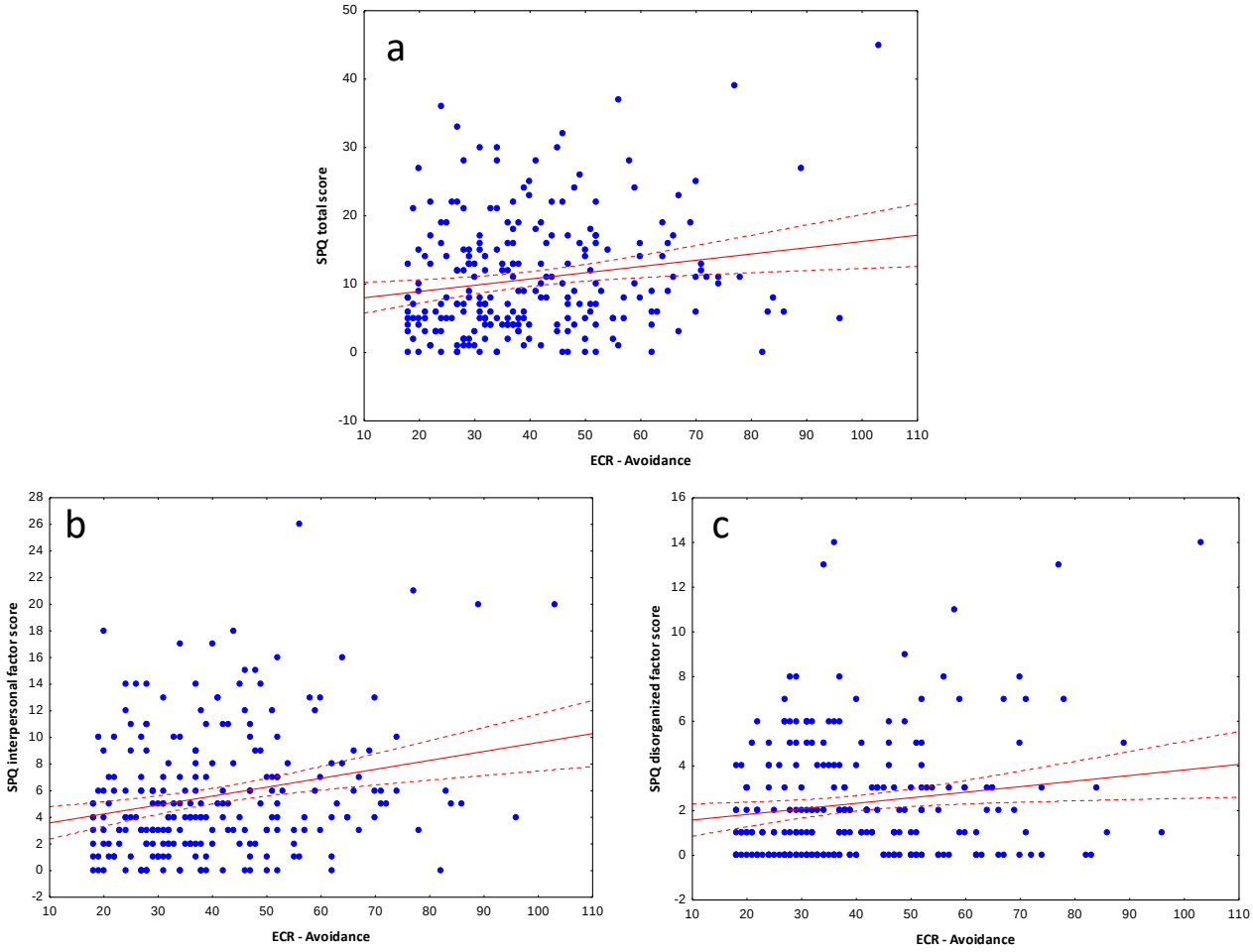

Figure 1.3: *scatterplots of the positive significant associations between ECR avoidance and: (a) SPQ total score, (b) SPQ interpersonal factor score, (c) SPQ disorganized factor score.*

Furthermore, correlation analysis between ECR anxiety dimension scores and schizotypal dimensions revealed the existence of significant positive associations between:

1. ECR anxiety scores and SPQ total score (R=0.362, Bonferroni corrected p=0.0003, Figure 1.4/a),
2. ECR anxiety scores and SPQ cognitive-perceptual factor score (R=0.327, Bonferroni corrected p=0.0003, Figure 1.4/b),

3. ECR anxiety scores and SPQ interpersonal factor score (R=0.3391, Bonferroni corrected p=0.0003, Figure 1.4/c),
4. ECR anxiety scores and SPQ disorganized factor score (R=0.215, Bonferroni corrected p=0.003, Figure 1.4/d).

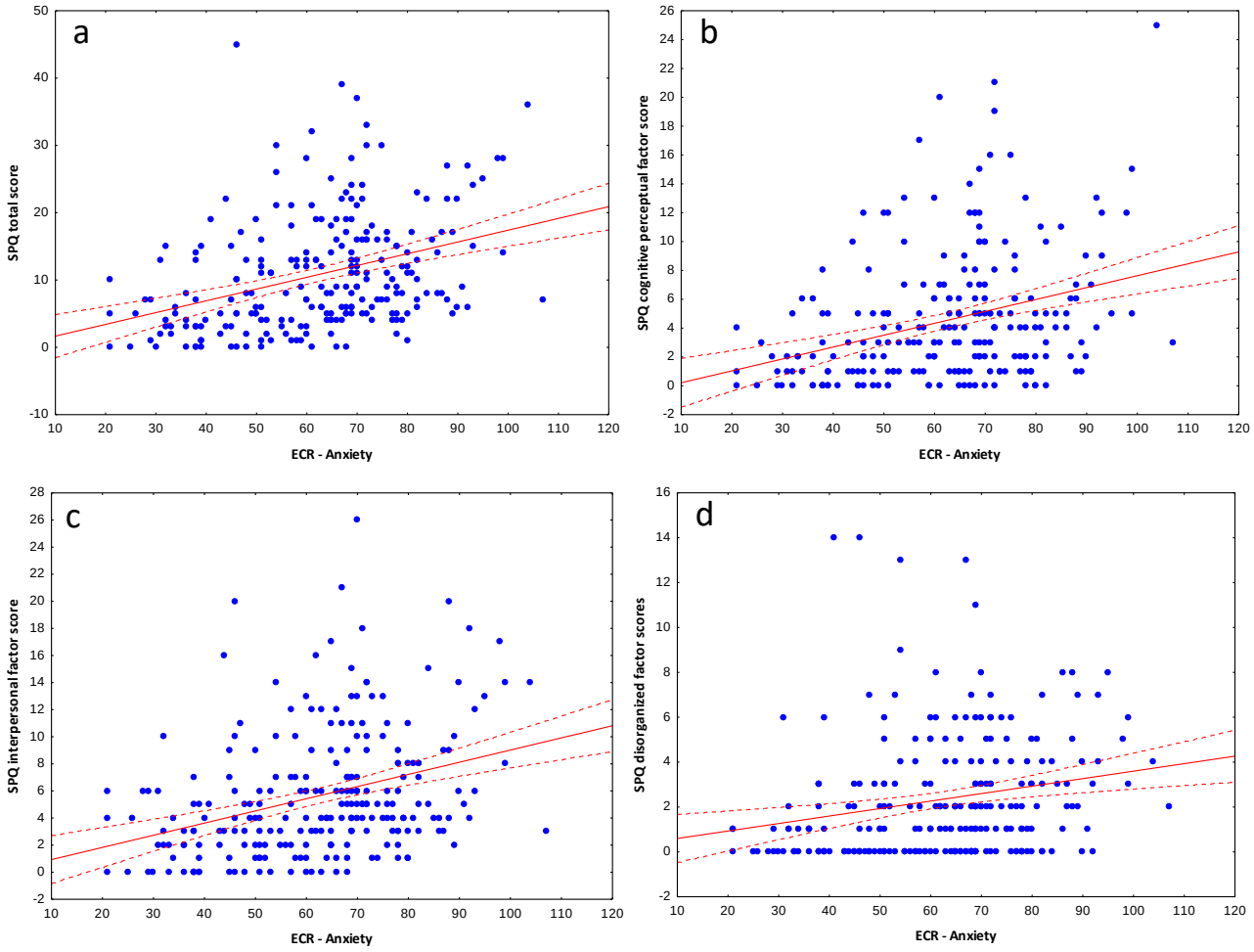

Figure 1.4: *scatterplots of the positive significant associations between ECR anxiety and: (a) SPQ total score, (b) SPQ cognitive perceptual factor score, (c) SPQ interpersonal factor score, (d) SPQ disorganized factor score.*

1.4.2. Effect of perceived maternal bonding on schizotypal dimensions

The ANOVA conducted in order to test the effect of perceived maternal care through the two way PBI maternal care classification (low vs. high) on schizotypal personality traits revealed:

1. a main effect of PBI maternal care (F=15.38; Bonferroni corrected p= 0.0004, Figure 1.5/a);

2. A significant interaction between PBI maternal care and SPQ factor (F=4.41, Bonferroni corrected p=0.038, Figure 1.5/b); Fisher post hoc analysis revealed that PBI low maternal care subjects had higher SPQ scores than PBI high maternal care subjects in the cognitive-perceptual factor (p=0.021), in the interpersonal factor (p=0.000005) and in the disorganized factor (p=0.0269).
3. A main effect of SPQ factor (F= 81.35; Bonferroni corrected p=0.00003);

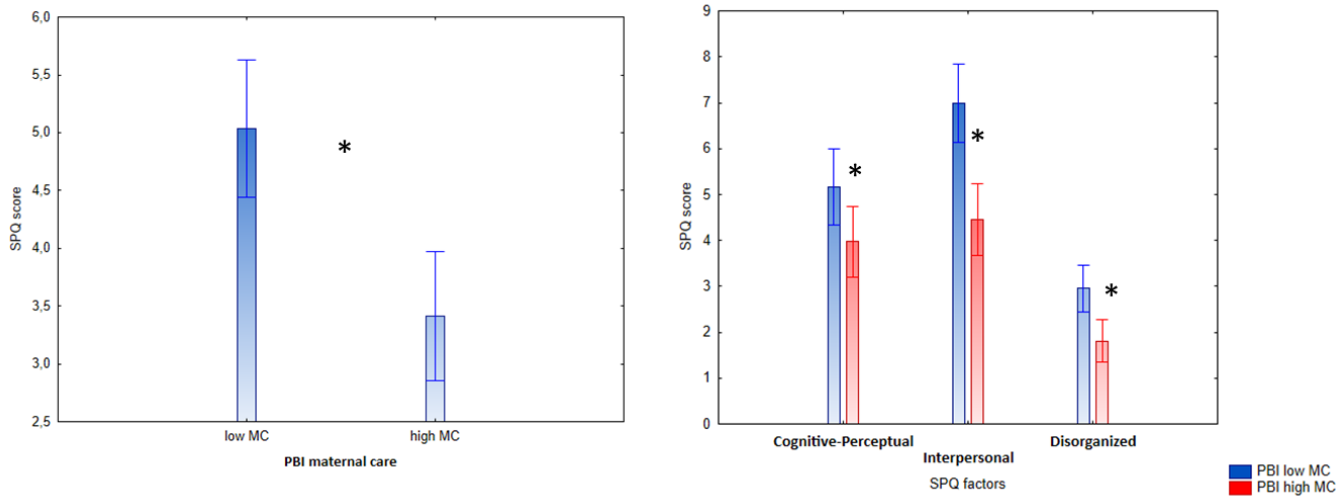

Figure 1.5: *histograms showing (a) the main effect of PBI maternal care on SPQ score; (b) the interaction between PBI maternal care and SPQ factors on SPQ scores. MC=maternal care.*

The ANOVA conducted in order to test the effect of perceived maternal over-protection through the two way PBI maternal over-protection classification (low vs. high) on schizotypal personality traits revealed:

1. a main effect of PBI maternal over-protection (F=7.304; Bonferroni corrected p= 0.022, Figure 1.6);
2. A main effect of SPQ factor (F= 74.54; Bonferroni corrected p=0.00003);
3. No significant interaction between PBI maternal over-protection and SPQ factors (p>0.1).

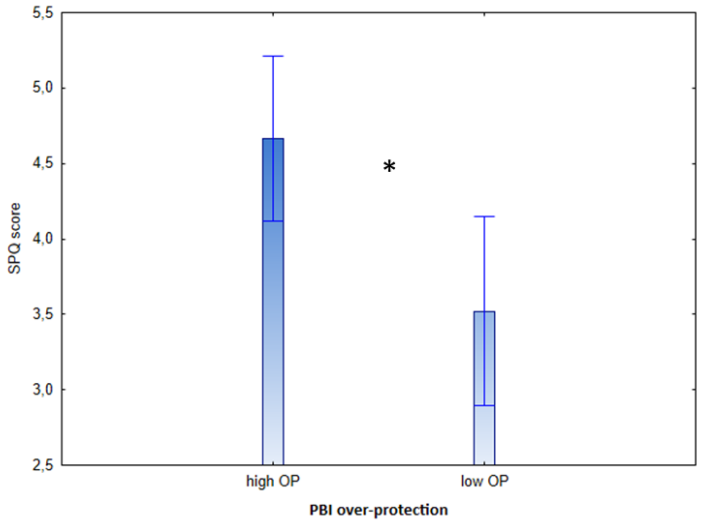

Figure 1.6: *histogram showing the main effect of PBI maternal over protection on SPQ score.*

1.5. Discussion

The current study had the goal of investigating the potential association between adult attachment style, perceived maternal bonding and schizotypal traits in a large cohort of normal controls. Our results revealed that:

- There was a main effect of adult attachment style (measured through the RQ) on SPQ scores and a significant interaction between RQ adult attachment style and SPQ factors. In detail, insecure subjects had generally higher SPQ scores than secure and, the effect was driven by the interpersonal and disorganized factors.
- There was a significant relationship between adult romantic relationships style (measured through the ECR) and SPQ dimensions. This relationship was positively significant both between ECR avoidance and SPQ dimensions (total, interpersonal and disorganized score) and between ECR anxiety and SPQ dimensions (total, cognitive-perceptual, interpersonal and disorganized score).
- There was a main effect of perceived maternal care (measured through the PBI) on SPQ scores and a significant interaction between PBI perceived maternal care and SPQ factors. Analysis revealed that low maternal care subjects had generally higher SPQ scores than high maternal care subjects. Specifically, low maternal care paralleled higher SPQ scores in all SPQ factors (cognitive-perceptual, interpersonal and disorganized score) compared to high maternal care.
- There was a main effect of perceived maternal over-protection (measured through the PBI) on SPQ scores, indicating that high maternal over-protection subjects had higher SPQ scores than low maternal care over-protection subjects. However, no significant interaction between PBI maternal over-protection and SPQ factors was found.

As concerns the attachment dimensions, our data therefore support the hypothesis that IWMs are in a tight relationship with one of the main proxies for the risk for psychosis,

i.e., schizotypal traits. This is in line with previous evidence indicating the association between attachment styles and the development of a personality disorder (Fonagy and Luyten, 2009). Several studies have in fact revealed that an insecure attachment style in adulthood is associated with borderline, histrionic, narcissistic and schizotypal personality disorders (Dakanalis et al. 2015, Fossati, Feeney et al. 2003, Fossati, Gratz et al. 2016, Outcalt, Dimaggio et al. 2016). In this context, with respect of schizotypal personality disorder, Sheinbaum et al. (2013), coherently with our results, demonstrated the existence of a significant association between adult attachment style, measured through the RQ, and schizotypal traits. Furthermore, studies have demonstrated an association between insecure attachment and schizotypy in non-clinical samples (Berry, Wearden et al. 2006, Berry, Wearden et al. 2007, West and Keller, 1994), as well as Wilson and Costanzo (1996), who demonstrated the existence of a relationship between anxious attachment and schizotypal personality disorder.

Therefore, our results corroborate the hypothesis that IWMs is involved in shaping a personality trait associated with psychosis risk (Yung, Yuen et al. 2005). Furthermore, our results indicate that not only IWMs in adulthood, but also the perception of the parenting style experienced during childhood, are in a significant relationship with schizotypy. Specifically, both perceived maternal care and over-protection seemed to modulate schizotypal traits.

Therefore, both low maternal care and high over-protection (which collapsed together represent the "affectionless control" parental style), are associated with higher SPQ scores. Previous literature is fully consistent with our results, demonstrating that the affectionless control style seems to confer a generalized vulnerability to psychopathology (Giakoumaki, Roussos et al. 2013). Indeed, this pattern is associated with anxious (Gallagher and Cartwright-Hatton 2008, Otani, Suzuki et al. 2009, Reti, Samuels et al. 2002, Reti, Samuels et al. 2002) personality traits in nonclinical populations and is associated with borderline personality disorder (Byrne, Velamoor et al. 1990), depression (Duggan, Sham et al. 1998, Handa, Ito et al. 2009, panic disorder (Someya, Kitamura et al. 2000, Wiborg and Dahl

1997) and particularly schizophrenia (Helgeland and Torgersen 1997, Onstad, Skre et al. 1994, Parker, Fairley et al. 1982, Willinger, Heiden et al. 2002). The PBI low care/ overprotection pattern also predicts relapse rates (Parker, Fairley et al. 1982, Parker, Johnston et al. 1988, Parker, Johnston et al. 1988) and recovery (Tait, Birchwood et al. 2003) in schizophrenia patients. Furthermore, Giakoumaki et al. (2013), through a Principal Component Analysis, revealed that the overprotection/low care combination as captured by the PBI seems to increase risk for the emergence of both schizotypal and anxious personality traits in healthy young adult males. This therefore confirms that maternal bonding style can modulate the vulnerability to psychopathology.

In this context, our results are relevant because, using a large sample of healthy controls subjects, they support an association between both IWMs and maternal bonding with the development of clinically overlapping personality traits similar to those seen in schizophrenia (Helgeland and Torgersen 1997, Onstad, Skre et al. 1993, 1994, Parker, Fairley et al. 1982, Ponizovsky, Nechamkin et al. 2007), irrespectively of the instrument used, suggesting a health to disease continuum (Giakoumaki et al. 2013). Thus, problematic parenting, as well as insecure attachment style, seems to be an early ''hub'' in the route to psychiatric morbidity (Favaretto, Torresani et al. 2001) and the schizophrenia spectrum (Brody 1981), given the association with schizotypal personality as suggested by our findings.

Some methodological limitations need to be taken into consideration in the interpretation of the present findings. The use of questionnaires introduces the possibility of reporting biases, including social desirability biases. Furthermore, the cross-sectional design of the study limits the conclusions that can be drawn concerning the causal directions of the relationships between associated variables, even though regression models resulted statistically significant. Finally, influences of third variables such as negative affect cannot be ruled out.

Despite these limitations, the associations between adult attachment, perceived maternal bonding and schizotypy, support the investigation of the concept of adult attachment style

in samples of subjects experiencing prodromal symptoms of psychosis or at the first episode of the disorder.

Study 2 – the role of schizotypy in the relationship between maternal adult attachment style and dyadic emotional availability: a new potential target for preventing child insecure attachment representations?

2.1. Background

2.1.1. Factors influencing attachment security: the role of maternal sensitivity

Internal Working Models (IWMs) are built by the infant basing on the interactions experienced during childhood with her attachment figures and shape a complex mental representations system. Thus, it could be hypothesized that IWMs and, therefore, adult attachment style, are in a tight relationship with the caregiving system and the parenting behavior. More in detail, in line with the notion that attachment style modulates the way emotions are perceived and regulated at the individual level (Adam and Gunnar, 2004, Vrticka et al. 2012) the IWMs of the caregiver are thought to modulate his ability to interpret the emotional signals of the child, thus influencing the sensitivity and the contingency of the caregiving responses to the needs manifested by the infant (Ainsworth, 1982, Main 2000, Sette et al. 2015). In this framework, sensitivity is defined as a caregiver's ability to perceive child signals, to interpret them correctly, and to respond to them appropriately (Ainsworth et al., 1974, DeWolff and van Ijzendoorn 1997, Bakermans-Kranenburg, van Ijzendoorn et al. 2003), Cassibba and van Ijzendoorn 2005, Juffer, Bakermans-Kranenburg et al. 2005, van Ijzendoorn and Bakermans-Kranenburg, 2005). Although sensitive parenting will often imply warmth within interactions (Lohaus, Keller et al. 2004, Oppenheimer, Hankin et al. 2013, Spinrad, Eisenberg et al. 2012), warmth only refers to the affective quality of the interactions, such as smiling, positive voice tone and physical affection, and it is known to also occur without sensitive responsiveness, which in turns requires contingency and time-coordination with child signals (Mesman and Emmen 2013).

Several studies testify the double bind relationship between attachment style and sensitivity. More specifically, Sette et al. (2015) reported that secure caregivers seem to be

protective, caring and helpful, thus succeeding in responding in a sensitive manner to the needs manifested by the infant. By contrast, insecure caregivers tend to be rejective, over-protective, anxious or neglecting. Furthermore, they seem to be uncomfortable with physical closeness to the child and to be less receptive than secure caregivers towards the cues of the infant (Sette et al. 2015). In this framework, maternal sensitivity can be considered the most significant mediator of the intergenerational transmission of attachment (Atkinson, Goldberg et al. 2005, Biringen 2000), thus being a core feature of the positive parenting promoting the security of attachment in children. In fact, a wide body of literature has suggested that children caregived by secure individuals will more likely develop a secure attachment style, and on the other hand the negative parenting experiences determined by the insecure attachment style of the caregivers will significantly raise the possibility that children will subsequently develop an insecure attachment organization (De Wolff and van Ijzendoorn, 1997, McElwain and Booth-LaForce 2006, Raval, Goldberg et al. 2001, Sette et al. 2015). In this context, a famous van Ijzendoorn meta-analysis (1995) confirmed the linear relationship between the caregiver's IWMs, maternal sensitivity and the attachment style of the infant, finding a 75% concordance between parental and infant attachment organizations across 18 studies when secure vs. insecure attachment styles were compared.

This is noteworthy, due to the fact that over 30 years of studies have strongly suggested that attachment security during childhood has crucial consequences in terms of social and emotional development across the lifespan, because the mental representation system that the infant builds on the basis of the interactions with the attachment figure will shape and determine feelings, behaviors and expectations (Matas et al. 1978, Main et al. 1985, Bost, Vaughn et al. 1998, Thompson and Zuroff 1999). Other studies have also suggested that the attachment style can modulate cognitive (Meins 1997) and language abilities (van Ijzendoorn et al. 1995), while an emerging line of research across psychology and psychiatry has also suggested a role of the quality of IWMs in the risk and the onset of psychopathology (Fonagy and Luyten, 2009, Berry, Band et al. 2007, Berry, Barrowclough et al. 2007, Berry, Wearden et al. 2007, Vrticka et al. 2012).

2.1.2. The missing link between attachment style and maternal sensitivity

Based on these assumptions, a central concept of the attachment theory is that individual differences in terms of attachment style can be transmitted along generations (Besser and Priel 2005, van Ijzendoorn 1995). In this line of reasoning, the so-called "intergenerational transmission of attachment" (Sette, Coppola et al. 2015) represents the process favoring continuity of attachment patterns from a generation to another. This process has crucial consequences on parenting behaviors since the caregiver-child relationship is the main context in which the interaction funding the structure of IWMs take place.

As previously reported, the main vehicle of the intergenerational transmission of attachment seems to be constituted by IWMs (Bowlby, 1969, Sette et al. 2015). An important field in which the influence of attachment experiences on the adult functioning is the caregiving system. George and Solomon (2008), through their "assimilation model of caregiving", proposed in fact that the caregiver who can integrate his experiences with the child into his mental representation system constituted by the IWMs organization would be able to reproduce models of care already experienced in his childhood. Therefore, the caregiver's ability to organize her thoughts, feelings and emotions is supposed to affect her ability to integrate, attend and respond to infant cues, therefore modulating the quality of her responses and the subsequent sensitivity capacity (Main 2000). In this framework, several studies (Atkinson, Goldberg et al. 2005, Biringen 2000) support the hypothesis that emotional availability and maternal sensitivity constitute a significant mediator of the intergenerational transition of attachment. The model in which maternal sensitivity has been identified as the most important mediator of the relationship between caregiver and infant attachment security has been known as the "linear model of the intergenerational transmission of attachment" (Sette et al. 2015). On the other hand, other authors have suggested the role of ecological constraints as moderators of the transmission process (Aviezer, Sagi-Schwartz et al. 2003, Sagi, van Ijzendoorn et al. 1997, van Ijzendoorn and Bakermans-Kranenburg 1997). Specifically, while past studies considered sensitivity as the main moderator of the intergenerational transmission of attachment, these authors

hypothesized that psychological attributes of the mother, as well as her dyadic relationship with the partner, the perceived social and emotional support and several other environmental variables may be associated with the quality of mother-infant attachment (Belsky and Fearon 2008). Therefore, it could be argued that these variables may be associated not only with attachment style, but also with maternal sensitivity, thus being indirect modulators of the infant attachment style.

The intergenerational transmission of attachment, therefore, is re-conceptualized as a dynamic process involving parent and child characteristics, as well as ecological factors (van Ijzendoorn and Bakermans-Kranenburg, 1997). Thus, rather simply focusing on the parenting variables impacting the transmission process (i.e., maternal sensitivity and attachment style) the role of other individual variables of both caregivers and children should be further explored (Figure 2.1). This would be of key importance in order to investigate whether and how individual (and contextual) factors are recognized as moderators which can affect each level of the process and might contribute to the discontinuity in attachment transmission in one or more points.

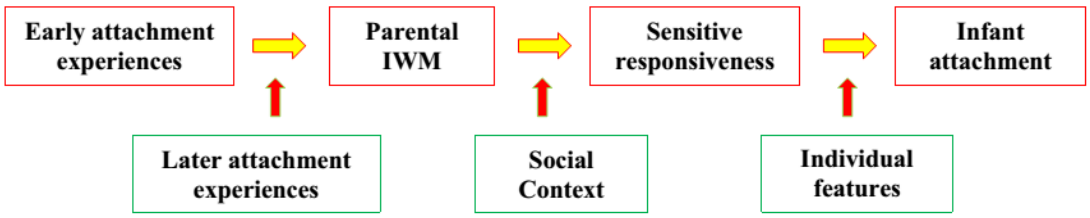

Figure 2.1: the ecological model of the intergenerational transmission of attachment (van Ijzendoorn and Bakermans-Kranenburg, 1997, Sette et al. 2015).

For example, several studies have demonstrated that the concordance of husband and wife attachment representations may contribute to the stability of the past IWMs, thus promoting the intergenerational transmission of attachment (van Ijzendoorn and Bakermans-Kranenburg, 1997). However, later attachment experiences may promote changes in the IWMs, such as romantic disconfirming experiences (for a review, see Sette

et al. 2015). Coherently, the broader social context in which individual and contextual characteristics converge, may modulate the intergenerational transmission of attachment by modulating the caregiver's sensitive behavior. For example, studies have shown that a supportive relationship with a partner correlates with the type of parenting which may promote attachment security (Belsky and Jaffe 2006, Tarabulsy, Bernier et al. 2005). Other studies revealed that marital and social support may influence caregiving behaviors (Smith, Landry et al. 2000), while personal characteristics of both mothers and children have been only poorly investigated. This is particularly relevant because of evidence linking psychopathology to maternal behavior.

2.1.3. The role of maternal psychopathology in the mother-child relationship

Literature agrees on the fact that infants of mothers experiencing mental health diseases are susceptible for the later development of psychopathology and for poor functioning affecting several developmental areas (Goodman and Gotlib 1999, Wan and Green 2009), therefore it is of pivotal importance to identify factors influencing the relationship between maternal psychopathology and child subsequent potential mental health problems in order to plan effective early intervention strategies. At this level, research has mainly focused on maternal depressiveness and anxiety, while psychosis has been only poorly investigated.

Specifically, several studies have indicated a significant association between insecure attachment in infants (which is in a really tight relationship with the development of psychiatric conditions - Fonagy e Luyten, 2009, Berry et al. 2007, Vrticka et al. 2012) and maternal psychopathology, especially when symptoms are chronic or recurrent, investigating the role of the maternal state of mind with respect of childhood attachment experiences and of maternal emotional availability (Wan, Abel et al. 2008). In this framework, this so-called "intergenerational transmission of psychiatric risk" can be explained considering the previously described "ecological model of the intergenerational transmission of attachment" (van Ijzendoorn and Bakermans-Kranenburg, 1997), which

identifies maternal psychopathology as a factor able to influence maternal sensitivity and the quality of dyadic interaction and, eventually, the attachment style of the infant.

Psychiatric disorders are often associated with irresponsible strategies of parenting, characterized by withdrawal and scarce focus on the interaction with the child (Goodman and Brumley 1990), Wan et al. 2008), which resembles to the parenting style often found in parents with a disorganized state of mind with respect to attachment experiences, in turn determined by poor sensitivity (Main and Hesse 1990). Both psychiatric and disorganized individuals in fact are characterized by disorienting and frightening behaviors (Abrams, Rifkin et al. 2006) and appear hostile and scarcely supportive in the context of the dyadic interaction with the child (Goldberg, Benoit et al. 2003).

In this context, maternal depression has been previously associated with lower maternal responsiveness and affection and with greater intrusiveness and punishments (Goodman e Gotlib, 1999), together with a lower feeling of connection and with higher negative feelings towards the child (Cornish, McMahon et al. 2006).

The investigation of the relationship between maternal psychopathology and infant attachment style, however, did not lead to consistent results. Some studies have demonstrated that maternal depression is significantly associated with avoiding or disorganized patterns of attachment in children (Martins and Gaffan 2000). On the other hand, meta-analytic studies have indicated only a weak effect of maternal depression on infant attachment insecurity (Atkinson, Goldberg et al. 2005) or no association between depression and disorganized attachment (van Ijzendoorn and Bakermans-Kranenburg, 1997). This discrepancy can be explained by methodological reasons (i.e., different sample sizes and different statistical pipelines across studies) or by the existence of other factors acting as mediators or moderators the relationship between maternal psychopathology and child attachment style (Wan and Green 2009). In this context, studies have demonstrated that the relationship between maternal depression and child attachment style seems to be moderated by symptom severity. Furthermore, McMahon et al. (McMahon, Barnett et al. 2006) revealed that 75% of children of mothers experiencing depression had an insecure attachment style at 12 months. Specifically, chronicity of the

illness seemed to be predictive of insecurity or disorganization of attachment (Campbell, Brownell et al. 2004). Campbell et al. (Campbell, Matestic et al. 2007) explained this specific relationship between symptoms, infant attachment and chronicity of illness in light of the fact that maternal depressive symptoms may exert a significant effect on child attachment through maternal behavior. Mothers experiencing depression are less sensitive and proactive, show decreased levels of involvement with their children (Carter, Garrity-Rokous et al. 2001, Cohn and Campbell 1992, DeMulder and Radke-Yarrow 1991) and are highly intrusive and impatient (Eamon and Zuehl 2001, Lyons-Ruth, Dutra et al. 2006). Therefore, maternal sensitivity may have a crucial role not only in the intergenerational transmission of attachment, but also in the intergenerational transmission of psychiatric risk, even though this has not been empirically tested yet. More in detail, Campbell et al. (2007) revealed in fact that maternal depression can modulate maternal emotional availability and the dyadic interaction quality with the child. Lower symptoms severity in fact was correlated with higher maternal sensitivity. This relationship seemed to be highly significant when children showed higher responsiveness and involvement in the context of the mother-child interactions.

Furthermore, maternal adult attachment style may influence the relationship between maternal depression and insecure childhood attachment. McMahon et al. (2006) in fact revealed that adult attachment style interacts with depression duration of illness on childhood attachment insecurity: mothers affected by chronic depression and having an insecure adult attachment style were more likely to have a child with an insecure attachment style (65% of probability for mothers with brief depressive symptoms and 76% of probability for mothers with chronic depression).

In the context of psychotic disturbances, several studies have focused on the interaction deficits that psychosis may exert impacting the quality of mother-child interactions (Goodman and Brumley 1990, Persson-Blennow, Naslund et al. 1986, Wan, Abel et al. 2008), but at the moment only few studies have investigated the role of psychotic symptoms on child attachment insecurity. In this framework, infants of mothers suffering from schizophrenia were more likely to develop attachment insecurity, especially

regarding the avoidant pattern of attachment (Dangelo 1986, Naslund, Persson-Blennow et al. 1984), while results on bipolar disorder are controversial because some studies (DeMulder e Radke-Yarrow, 1991) report a highly significant association between maternal psychopathology and child disorganized attachment, while other studies (Hipwell, Goossens et al. 2000) did not confirm this association.

All these studies, therefore, suggest that besides considering the simple association between maternal psychopathology and child attachment insecurity, the modulation of maternal psychopathology on maternal sensitive behavior should be deeply investigated, because studies seem to suggest that mothers experiencing psychiatric symptoms may have infants with insecure attachment patterns because of the mediating role of maternal sensitivity and availability in the context of dyadic interactions. Furthermore, in this context, no studies have directly tested how schizotypy may impact maternal sensitivity and, therefore, the whole intergenerational transmission of attachment process. As stated before, schizotypy represents an element of vulnerability to schizophrenia spectrum disorders expressed at a personality level (Barrantes-Vidal, Grant et al. 2015) and its relationship with attachment security and perceived maternal care is controversial but demonstrated (see Study 1).

2.1.4. The relationship between personal characteristics of mothers and children: implication for maternal sensitivity

In this intergenerational transmission of attachment framework, it is important to understand whether other factors may influence maternal sensitivity and responsiveness, besides maternal adult attachment style and maternal psychopathology, such as personal characteristics of the child. Literature has often considered the child as passive within the dyadic interactions with the caregiver. Modern psychological conceptualizations, instead, posit that psychosocial development of the child depends not only on parenting behaviors, but also on the interaction between personal characteristics of parents and children (Mertesacker, Bade et al. 2004, Osofsky and Connors, 1979, which is supposed to be synchronous, mutual and balanced (Crockenberg 1981, Papousek and vonHofacker 1995).

One of the main child characteristics which seems to be able to influence parenting behavior is child temperament (Bates, Maslin et al. 1985, Bates, Wachs et al. 1995, Papousek and vonHofacker 1995, Rothbart 1986, Thomas and Chess 1977). The terms "temperament" and "personality" have been used to describe heritable (approximately between 20 and 60% for temperament - Saudino, 2005 – and between 40 and 50% for personality – Jang, Livesley et al., 1996) and relatively enduring aspects of the person that help explain individual differences in behavior (Rothbart 1986, Rothbart and Goldsmith 1985, Tellegen, Lykken et al. 1988) ("temperament" is more frequently encountered in work involving infants and children, whereas "personality" is used more in reference to adult traits).

Since the 80s, developmental research has spent many efforts in identifying the biological basis of child temperament. Research evaluating the physiological correlates of behavior identified the main areas of child temperament along three behavioral dimensions, that is, behavioral inhibition to novelty (Roweton 1995), regulation of negative emotion (Kagan, Snidman et al. 1995) and modulation of the attentional level. By contrast, other studies have deeply investigated the psychological characteristics with a biological-constitutional basis which may define the core of child temperament.

Specifically, temperament is identifiable as a "stylistic component of behavior" (Thomas and Chess, 1977), thus not determining the reason why the child acts, but the way he does. Furthermore, temperament is defined as a dynamic factor mediating the environmental influences on the personality structure of the individual. Authors in fact revealed that infant is characterized by innate traits guiding the way he interacts with the attachment figures. By these innate traits, she is able to influence her environment, but she is also influenced by the feedback of her actions coming from the environment. Therefore, temperament is linked with parenting behavior in a double-way influence relationship. In this framework, the quality of the mother-child interactions is modulated by the way caregivers and infants are able to match their personal innate traits in order to guarantee a mutual adaptation to each other (the so-called "goodness of fit", Thomas e Chess, 1977), such that if lack of adaptation is present in the relationship, this can be considered a

potential factor of maladjustment for the subsequent development of the child. Authors identified three main dimension of temperament (emotion, attention and motor activity). By the combination of these dimension, it is possible to define three temperament profiles: "easy" (adjusts easily to new situations, quickly establishes routines, generally cheerful and easy to calm), "difficult" (slow to adjust to new experiences, likely to react negatively and intensely to stimuli and events) and "slow to warm up" (somewhat difficult at first but become easier over time).

It is likely that "easy" children are perceived by their caregivers as having a high level of adaptability and as being easy to calm and with a positive mood, while children showing intense emotionability or that seem frightened or shy and being highly reactive to frustration and changes are perceived by parents as "difficult" (Bates, Wachs et al. 1995, Thomas and Chess, 1977).

In this context, Scarr (Scarr 1996) proposes a mechanism whereby temperament influences children's experiences and outcomes. According to this theory, since early infancy temperament sets a chain of events in which parents and others react to the infant's behavioral style, the infant reacts back, and, thus, through a cycle of mutual reinforcement and influence, over time the infant's preexisting temperamental tendencies are sustained and magnified. The cycle can have implications for the child's attachment security because temperamentally difficult infants are more likely than temperamentally easy infants to evoke parental role dissatisfaction and insensitive caregiving, which in turn, may lead to insecure infant attachment. Findings of inverse relations between infant temperamental difficultness and maternal warmth and responsiveness (Mangelsdorf, Gunnar et al. 1990, Milliones 1978, Vandenboom and Hoeksma 1994) support the theory, as do positive associations between maternal responsiveness and infant attachment (Pederson, Gleason et al. 1998, Seifer, Schiller et al. 1996, Biringen 2005). Furthermore, Susman-Stillman et al. (SusmanStillman, Kalkoske et al. 1996) indicated that the child temperament observed at 6 months predicted maternal sensitivity towards the child, which in turn predicted child attachment security at 12 months. The indirect link between child temperament and child attachment security is further corroborated by a wide variety of studies (Calkins and Fox

1992, Goldsmith and Alansky 1987, Izard, Haynes et al. 1991, Seifer, Schiller et al. 1996, Weber, Levitt et al. 1986), even if other studies did not find a statistically significant association between the two variables. For example, Crockenberg (1981) demonstrated that difficult temperament was able to predict insecure attachment, but only in combination with a condition of scarce social support for mothers. Consistently, Belsky et al. (Belsky, Fish et al. 1991) revealed that negative emotionality of the child at 3 months predicted his attachment in security at 9 months, but only when associated with low maternal responsiveness. Therefore, further research focused on the identification of potential mediators and moderators of this relationship are warranted.

Another relevant moderator of the relationship between child temperament and child attachment style is constituted by personality traits of the mothers. Studies have elucidated that personality characteristics may have a mediation role in this relationship by influencing maternal sensitivity, availability and warmth. More in detail, significant associations were found between mother's sociability and maternal sensitivity and warmth towards the child (Belsky, Rosenberger et al. 1995, Kochanska 1997, Mangelsdorf, Gunnar et al. 1990) and between negative emotionability of the mother and attachment insecurity of the child (Egeland and Farber 1984, Kochanska 1997, Weber, Levitt et al. 1986). Furthermore, Mangelsdorf et al. (1990) examined how maternal personality traits may mediate the relationship between child temperament and child attachment security. In this study, child susceptibility to stress measured at 9 months predicted attachment insecurity but only in combination with high "constraint" (rigidity, traditionalism, and low risk-taking).

Based on these results, it is possible to hypothesize that difficult child temperament (which is mainly determined by the emotionality dimension) is associated with attachment insecurity only in combination with maternal personality traits which may exert a negative impact on parental sensitive behavior, thus compromising the ability of the child to seek warmth and support. Therefore, child temperament would not influence directly parenting behavior, but this relation is in turn mediated by individual psychological traits of the mother (Crockenberg 1986, Seifer et al. 1996).

Therefore, a crucial factor which may moderate the effect of child temperament on attachment insecurity and which would be interesting to evaluate in its impact on maternal behavior and, subsequently, on child attachment insecurity, is constituted by personality traits of the mother. This variable in fact may represent a risk factor for psychopathology. Schizotypal personality trait in fact, for example, which may determine the onset of subthreshold psychotic symptoms, may determine difficulties in the coordination of rhythms and actions in the mother-child relationship, thus determining low level of emotional sensitivity and responsiveness.

2.2. Goal of the project

- **AIM:** following the ecological model of the intergenerational transmission of attachment, and based on the study here examined, it could be hypothesized that maternal psychopathology may represent a risk factor for maternal sensitivity and, therefore, it may have deleterious indirect effect for child attachment in security and for the IWMs structure of the infant. On the other hand, maternal availability and sensitivity (which are directly modulated by adult attachment style, following the linear model of the intergenerational transmission of attachment) may also be modulated by personal characteristics of both caregivers and infants, such as respectively personality traits and child temperament (i.e., emotional availability) that may ultimately interact with harsh conditions (such as maternal psychopathology) in producing child attachment insecurity. Therefore, the aims of this study are:
  - **a.** To assess, in a cohort of mother-infant dyads, the relationship between schizotypal traits and adult attachment state of mind in predicting dyadic emotional availability;
  - **b.** To test the potential relationship between maternal schizotypal traits and temperamental dimensions of the child.
- **EXPECTED RESULTS:** we expect to find a significant modulation of both adult attachment state of mind and schizotypal traits on emotional availability. Furthermore, we expect to find a significant association between maternal schizotypal traits and temperamental dimensions of the child (especially in the emotionability domains).

2.3. Materials and methods

2.3.1. Sample characteristics

For this study, 41 mother-infant dyads were recruited. Mothers were contacted by telephone and briefly informed about the purpose of our study. Those who expressed interest in the research and were willing to participate were informed in detail about the data collection methods and administration tools. Mothers were selected so that the sample would include only healthy mothers with at least a child aged between 5 and 12 years. All subjects had undergone an extensive clinical interview in order to assess the absence of any psychiatric diagnosis through the Structured Clinical Interview for DSM-IV (First et al. 1996). Additional exclusion criteria were presence of any neurological or psychiatric disorder and of any other medical condition and history of significant drug or alcohol abuse (no active drug use in the past year). All subjects were given a complete description of the study and its procedures. Written informed consent was obtained only after full comprehension of the protocol.

This sample is part of the sample recruited for Study 1. Demographic information of mother-infant dyads is reported in Table 2.1.

	Age (mean±SD)	Gender ratio (M/F)	Education (mean±SD)	Socio-Economic Status (mean±SD)
Mothers	39.36±5.14	0/41	14.5±3.5	28.06±11.29
Children	7.32±1.78	18/23	/	/

Table 2.1*: demographic information of Study 2 sample.*
N=sample size; SD=Standard Deviation. Age and Education are reported in years.

2.3.2. Instruments

2.3.2.1. The attachment developmental trajectory: the Adult Attachment Interview (AAI)

The Adult Attachment Interview (AAI) is a semi-structured interview designed by George, Kaplan and Main (1985) for the investigation of adult attachment state of mind. It

assesses the current individual's mental organization regarding subjects' childhood experiences with their attachment figures, through the analysis of formal and communicational aspects of the narrative emerging from the transcript (Main and Goldwyn 1984).

The AAI consists of 18 questions that are asked to the subject in a predetermined order. The interviewer makes all that is necessary to fit the instrument to the construction of the speech chosen by the subject, leaving the necessary time to think about the questions and to expand enough topics. Subject is asked to recall childhood attachment experiences both giving a general evaluation of the experience and referring specific autobiographical episodes. The questions are centered on experiences with the primary attachment figures in childhood (i.e., generally mother and father) and investigate memories of any difficult situations in which the presence of a parent is required, and the presence of traumatic events or significant losses. The interviewee is therefore asked to reflect on his own history and to rethink about past experiences and beliefs considering current experiences as an adult and parent.

AAI questions are designed to activate the attachment system in adults (Dozier and Kobak 1992), trying to make the subject come back with the mind to those attachment experiences which, in childhood, requested the attachment system activation. In this framework, the AAI can be viewed as an assessment of the individual's ability to maintain a balance and to be consistent when reflecting on events related to attachment experiences occurred previously or circumstances that disturbed him emotionally. The technique has in fact been described as an attempt to *"surprise the unconscious"* (George et al. 1985), and a quick glance reveals how the interview several times put the interviewee facing the risk of contradicting or not being able to support the next or previous statements. In this regard, van Ijzendoorn defines this technique as: *"A revolutionary, though simple, shift of attention from the objective description of the childhood experiences, current mental representation of these experiences and the content of autobiographical memories in the form in which the autobiography is presented"*.

The attribution of the categorical adult attachment state of mind is based on the correspondence between the organization of the mental representation world of the subject and some features of the language and discourse. In other words, the narrative transposition of the "shape of the mind" and the structure of thoughts about the content elicited by questions should be as correspondent as possible and, in this line of reasoning, coherent (Main and Goldwyn 1994). The content and form of the text are analyzed through two different type of scales and related sub-scales: the subjective experience scale and the state of mind scales (Main and Goldwyn 1994).

Through the subjective experience scale, the interviewer scores on five nine-point scales (Loving, Rejecting, Involving/Role Reversing, Neglecting, Pressure to achieve) the best estimate of the parent's probable behavior during childhood (i.e., direct and believable accounts of parental affection, evidence for rejection derived from direct or via a compilation of direct and indirect statements).

On the other hand, state of mind scales scores are designed to capture salient attachment-related aspects of the speaker's present state of mind. As stated before, the AAI classification of the transcript is based entirely upon the speaker's apparent current state of mind, rather than their reported attachment history. This means that speakers who appear to have had negative experiences in childhood may well be judged secure, so long as they obtain high scores for overall coherence. The 9-point state of mind scales therefore assess the degree to which the speaker is considered by the coder to be, for example, "angrily preoccupied" with a given parent, or "idealizing". In addition, the use of "passive discourse or of a "disorganized and/or disoriented" state during the discussion of potentially traumatic experiences are scored. State of mind is scored through the following scales:

1. Coherence of transcript and coherence of mind, which quantify the speaker's ability to present and assess the past and its influences in a way which makes it reasonable to the listener and suggests few interpretations contradictory to those offered. High scores in these subscales are necessary for a Free-Autonomous (F) adult state of mind classifications.

2. Metacognitive Monitoring, defined as the ability to monitor and report on the processes of thinking and recall which take place during the interview. High scores in this subscale are likely associated with (F) classifications.
3. Idealization, assessing the discrepancy between the overall picture or presentation of the parent taken from the speaker's speech at the abstract or semantic level, and the reader's inferences regarding the actual behavior of the parent as based upon other aspects of the transcript.
4. Inability to recall childhood, which assesses the speaker's insistence upon the inability to recall childhood, especially when it serves to block further queries or discourse.
5. Derogation, which deals with the cool, contemptuous, derogating dismissal of attachment.
6. Fear of loss, which analyzes any expression of an unfounded current fear regarding the possible death of the child.

High scores in subscales (3), (4), (5) and (6) characterize Dismissing (DS) transcripts.

7. Involving/Preoccupying anger, which scores certain forms of language in which the speaker becomes lengthy, unclear or irrelevant in describing provoking incidents, feelings, or persons.
8. Passivity, which scores a specific type of speech in which subjects seem vague and odd, possibly reflecting momentary internal interferences.

Scales (7) and (8) characterize Entangled-Preoccupied (E) transcripts.

Two additional scales relative to the unresolved state of mind analyze the speech in order to assess whether, in presence of a traumatic experience (i.e., loss or abuse), the speaker seems frightened or unresolved.

Based on these scales, it is possible to give to the transcript a categorical classification (Main and Goldwyn 1994):

a. Secure/Autonomous (F), characterized by a coherent, consistent and collaborative text. Generalized descriptions of relationships with parents are supported by specific memory. Discourse is reasonably fluent and the speaker seems at relative

ease with the topic, appearing to value attachment relationship, regarding them as influential.

b. Dismissing (DS): interview is incoherent, with inconsistent portrayals of experience. The speaker attempts to direct attention away from attachment experiences and often unconvincingly portrays a positive childhood experience, or indicates that negative attachment experiences have not adversely affected personal development.
c. Entangled/Preoccupied (E): these speakers' attention is relatively inflexibly focused upon attachment figures or experiences. Thus, the influence of attachment-related experiences appears to preoccupy the speaker and the text is confusing, as well as containing irrelevant passages that often are markedly vague and may weakly emphasize good experiences. Some include oscillations between good and bad evaluations of past or present.

In the current project, transcripts were coded by me, after having achieved the AAI certificate of reliability. Continuous state of mind scores and AAI categorical classification were used for analysis purposes. AAI transcription files were encrypted with an alphanumeric code and deprived of any sensitive information (i.e., personal names, city names).

2.3.2.2. Evaluation of schizotypal traits

The Schizotypal Personality Questionnaire (SPQ, Raine 1991) is a widely used self-report instrument that evaluates schizotypal personality disorder according to DSM-III-R (American Psychiatric Association 1987).

It is a self-assessment questionnaire consisting of 74 items with dichotomous response format (yes / no), in which participants are required to circle their response, assigning one point for each "yes."

The questionnaire item can be clustered into nine sub-dimensions that investigate the nine correspondent diagnostic criteria for schizotypal disorder: ideas of reference (9 items), odd beliefs/ magical thinking (7 items), unusual perceptual experiences (9 items), paranoid ideation/ suspiciousness (8 items), social anxiety (8 items), no close friends (9 items),

restricted affect (8 items), odd/ eccentric behavior and appearance (7 items) and odd speech (9 items).

These nine sub-dimensions can be further clustered into three domains/factors: cognitive-perceptual, interpersonal and disorganized (Calkins, Curtis et al. 2004, Chen, Hsiao et al. 1997, Claridge, McCreery et al. 1996, Gruzelier 1996, Raine et al. 1994, Reynolds, Raine et al. 2000). The first factor (cognitive-perceptual) identifies deficits that are very close to the positive psychotic symptoms, such as ideas of reference, magical thinking, unusual perceptual experiences and paranoid ideation (i.e., *"Have you ever seen things invisible to other people?"* or *"Do sometimes your thoughts are so strong that you could almost hear them?"*), the second factor (interpersonal) describes deficits that resemble to psychosis negative symptoms, such as social anxiety, lack of close friends, inappropriate or flattened affect and, as for the previous factor, paranoid ideation (i.e., *"I have little interest in learning about other people"*), the third factor (disorganized) refers to the presence of strange behaviors and communication styles that can be considered odd or eccentric (i.e., *"People consider me a little eccentric"* or *"Sometimes I use words in an unusual way"*).

SPQ psychometric properties (internal consistency, test-retest reliability, convergent validity and discriminant validity criteria) have been extensively analyzed and were found to be satisfying (Compton, Goulding et al. 2009, Fossati, Feeney et al. 2003, Wuthrich and Bates 2006).

The SPQ is largely used for the screening of schizotypal personality in the general population with a good research applicability in studies investigating genetic risk trajectories of schizophrenia and psychosis spectrum disorders. This instrument therefore is used to deeply characterize subject's personality schizotypal traits (Chen, Hsiao et al. 1997, Raine et al. 1994), to relate schizotypal dimensions to schizophrenia diagnosis (Chen et al. 1997) and to identify individuals that may be experiencing an "At Risk Mental State" (ARMS, Yung and McGorry 1996) for psychosis.

2.3.2.3. Evaluation of maternal emotional availability

The Emotional Availability Scales (EAS) are a codification method proposed by Biringen (2000) in order to assess the dyadic emotional availability. The author's idea was to

understand the role of emotion processing and regulation in caregiver-infant interactions (Biringen et al. 1998).

Through video-recorded observation of dyadic interactions and the administration of the codification subscales it is possible to assess the quality of the caregiver-child interactions, with specific information about the quality of the dyadic connection. EAS can be used with any type of attachment figure and adults until child is 14 years old.

In this study, the video-recorded observations of mother-child interactions were conducted in a natural setting (i.e., in the living room of the home of every dyad) and scheduled according to the dyad's physiological needs, such as sleep and nutrition.

The video-recording sessions were organized to guarantee the maximum flexibility with respect to the needs of the dyad in order to avoid interferences by other members of the family and/or excessive alterations of the usual rhythms of family life.

The whole video-recording session lasted 30 minutes and involved two game sessions lasting 15 minutes each:

a. Unstructured play: for the first 15 minutes, dyads were invited to play as they usually do in daily activities, ignoring as much as possible the presence of the operator, but with a game set accurately chosen for the research that did not vary along the dyads. This game set included building blocks and puzzles. All elements differed from each other for the level of difficulty (since our research focused on children aged between 5 and 12 years). The decision to provide several different games was strategic, in order to elicit and subsequently investigate the driving and supportive behavior of the mother with the child during the initial phase of choice.
b. Structured play: for the last 15 minutes, we aimed to evaluate the degree of collaboration/cooperation and the dyadic interaction structure when both elements of the dyad were focused on the same task having a common goal. To this aim, we used the game "Jenga" (Figure 2.2), adapting it to the purposes of our observation. Jenga is composed by 54 wooden blocks. To set up the game, dyads had to stack the initial tower, which had eighteen levels of three blocks placed adjacent to one another along their long side and perpendicular to the previous level. During the

game, dyads were asked to remove, taking turns or seeking for an agreement, one block at a time from the tower. Then, they were asked to balance the removed block on the top of the tower, creating a progressively taller but less stable structure. We asked therefore the dyads to collaborate in order to grow the tower upwards avoiding the collapse, then to choose together the bricks to extract and possibly decide who would have taken the "practical role" from time to time.

***Figure* 2.2:** *example of the Jenga wooden blocks tower.*

Video-recorded dyadic observations were then coded by a properly trained observer, who analyzed the whole video-records using the EAS system. The key EAS psychological concept is emotional availability (Biringen 2000), defined as the quantity and quality of emotional exchanges between the members of the dyad. EAS is therefore able to capture the overall quality of the emotional relationship through the analysis of interactional exchanges. Unlike approaches that consider the individuals separately, through EAS subscales the observer can analyze both interactive and mutual signals to infer the quality of parental behavior within the specific interactional environment.

The EAS coding system is composed of 6 subscales, 4 of them focus on the emotional availability of the caregiver (sensitivity, structuring, non intrusiveness and non hostility)

while 2 subscales assess aspects of the child's emotional availability (child responsiveness and child involvement).

Below is a brief description of the 6 subscales (Biringen et al. 1998):

- Sensitivity (score: 1-7): emphasizes affective interactions and negotiation of conflict and dyssynchronous interactions. High scores are assigned when a relaxed climate with respect to interactional conflict and desynchronies, including the successful repair of such situations, is observed. Parents should be able to pick up children's emotional signals but also emit their own.
- Structuring (score: 1-7): refers to the ability of the parent to support learning and exploration without overwhelming the child's autonomy and in a way to which the child is receptive. Involves providing rules, regulations, and a framework of interactions.
- Non Intrusiveness (score: 1-7): refers to the ability to be available to the child without being interfering, overprotective or overwhelming.
- Non Hostility (score: 1-7): covert or overt, refers to ways of talking to or of behaving with the child that are generally patient, pleasant and harmonious.
- Child Responsiveness (score: 1-7): it is manifest in children's affective interactions with parents and in their secure base behavior. Refers to the ability of child to explore on his own and to respond to the parent in an affectively available way and to the balance of emotional connection and autonomy between parent and child (that may be shown through proximity-seeking and distancing, visual contact or topics in conversation and play).
- Child Involvement (score: 1-7): refers to the ability of the child to involve the parent in interactive exchanges. This would entail initiating eye contact, asking questions, narrating a storyline, or showing and demonstrating materials to the parent in a comfortable, non-urgent and positive manner.

The observer is asked to code the video-recorded material following the indicators of every subscale referring to a 1-7 range. For this project, three composite scores were used for analysis purposes:

a. EAS total score, obtained by computing the arithmetic mean of the scores of all 6 EAS subscales;
b. EAS mother score, obtained by computing the arithmetic mean of the scores related to the 4 EAS subscales which focus on maternal emotional availability (i.e., sensitivity, structuring, non intrusiveness and non hostility);
c. EAS child score, obtained by computing the arithmetic mean of the scores related to the 2 EAS subscales which focus on child emotional availability (i.e., child responsiveness and child involvement).

EAS coding was performed by me after having followed a lab training with an EAS certified coder. EAS data files, as for AAI, were encrypted with an alphanumeric code. Therefore, the coder was blind of the AAI classification of the mother at the time of the coding of the EAS data.

2.3.2.4. Evaluation of child temperament

For the assessment of child temperament, we chose the "Questionari Italiani del Temperamento" forms (QUIT -Axia 2002).

QUIT are a self-administered instrument specifically designed for the primary caregiver of the infant (depending on the environmental context in which QUIT administration is required – i.e., home, school) and include different forms, depending on the age of children (Form 1-12 months, Form 13-26 months, Form 3-6 years old, Form 7-11 years old). In the current study, therefore, all mothers were asked to compile the 3-6 years old or the 7-11 years old QUIT, depending on the age of the child at the time of the observation. Mother were explained that QUIT had no right or wrong answers, and that no answers expected by the examiners were present. Therefore, they were encouraged to provide truthful answers, in order to favor as much as possible a portrait of the child temperament which was as close as possible to reality.

General instructions, present at the beginning of each questionnaire, asked the parent to think about the child's behavior in the last week, in order to avoid generalizations, and to provide answers on a frequency scale ranging from "almost never" to " almost always". The presence of items about both positive behaviors and negative behaviors makes the

instrument objective and reduces the impact of disturbing factor such as social desirability and memory problems.

Each item proposed (68 in the 3-6 years form and 61 in the 7-11 form) describes a specific behavior of the child in everyday situations within three general areas: child interacting with others, child playing and child performing a task. The parameters used to evaluate the behavior are constituted by frequency, intensity and/or duration, the rate at which it triggers a behavioral response and how the behavior described is susceptible to external influence.

Items are then clustered along 6 temperament dimensions according to the theoretical model at the basis of the QUIT implementation (Axia 2000):

1. Social Orientation, which describes the alert to others (i.e., 3-6: *"He speaks for a long time with family and friends"*, 7-11: *"Looks immediately at the person who calls him"*),
2. Inhibition to novelty, which describes the child's tendency to inhibit her reaction to new stimuli (i.e., 3-6 and 7-11: *"Faced with a new task, shows signs of concern"*),
3. Motor activity, which describes the motor activation (i.e., 3-6: *"While playing, if forced to move from one place to another, walks placidly"*, 7-11: *"When involved in a game runs for long time"*),
4. Positive Emotionality, which describes the positive emotional expressions of the child (i.e., 3-6: *"While playing, he laughs very much"*, 7-11: *"While playing with other kids, laughs for a long time"*),
5. Negative Emotionality, which describes the negative emotional expressions of the child (i.e., 3-6: *"When upset, remains sulky for a long time"*, 7.11: *"Remains sad or sulky for a long time"*),
6. Attention, which mainly describes the persistence of the attentional orientation (i.e., 3-6: *"While involved in a task, he looks around"*, 7.11: *"He dedicates long time to new tasks"*).

Dimensions (4) and (5) are crucial because, by combining their scores, it is possible to define a so-called "temperament style" (Axia 2002):

a. Emotional temperament, characterized by average scores in positive and negative emotionality,
b. Calm temperament, characterized by low scores both in positive and negative emotionality,
c. Normal temperament, characterized by high positive emotionability and low negative emotionability,
d. Difficult temperament, characterized by high negative emotionability and low positive emotionability.

For the purposes of this study, however, it was decided not to use this classification, focusing on the continuous scores of every QUIT dimension.

QUIT have good psychometric properties in terms of reliability and construct validity. The ease and speed of compilation make such questionnaires particularly suitable for their use in several fields, such as research, clinical, counseling and school.

2.3.3. Data analysis

To test the relationship between schizotypal traits and adult attachment state of mind (assessed, following the attachment developmental trajectory, through the AAI) in predicting dyadic emotional availability (measured through the EAS), we performed separate:

a. ANOVA, Pearson's *r* correlation analysis and linear regression analysis, depending on the possibility to treat the variables of interest as categorical or continuous predictors. More in detail:

- To test the association between adult attachment state of mind and schizotypal traits, we performed an ANOVA with AAI categorical classification (F, DS, E) as categorical factor and, respectively, the total SPQ score, the cognitive-perceptual factor score, the interpersonal factor score and the disorganized factor score as dependent variable. To further corroborate our results, Pearson's correlation analysis was conducted in order to test the association between the SPQ total score and the AAI state of mind scores of two specific subscales (involving/preoccupying

anger regarding mother and passivity), due to our results (see Study 2 results section).

- To test the association between adult attachment state of mind and emotional availability, we performed:
  1. an ANOVA with AAI categorical classification (F, DS, E) as categorical factor and, respectively, the EAS total score, the EAS mother score and the EAS child score as dependent variable,
  2. correlation analysis with, the AAI subscale "coherence of transcript" score and, respectively, the EAS total score, the EAS mother score and the EAS child score as dependent variable.
- To test the association between schizotypal traits and emotional availability, we performed linear regression analysis between, respectively, the total SPQ score, the cognitive-perceptual factor score, the interpersonal factor score and the disorganized factor score and, respectively, the EAS total score, the EAS mother score and the EAS child score as dependent variable.

b. A moderation process analysis in a regression-based path analytic framework through the PROCESS macro for SPSS (http://www.processmacro.org/index.html). We tested whether maternal schizotypal traits may act as moderator variable in the relationship between adult attachment state of mind and dyadic emotional availability. Both main effects and interactions were investigated. Adult attachment state of mind was tested both in a categorical, dichotomous way (secure vs. insecure mothers) and in a continuous way, through the use of the coherence of transcript scale of mind score.

On the other hand, to test the relationship between maternal personality traits and child temperament dimensions, we performed Pearson's correlation analysis between, respectively, the total SPQ score, the cognitive-perceptual factor score, the interpersonal factor score and the disorganized factor score and, respectively, separate scores of every of the six quit dimensions (i.e., social orientation, inhibition to novelty, motor activation,

positive emotionality, negative emotionality and attention). All analyses were thresholded with α=0.05,

2.4. Results

2.4.1. Association between adult attachment state of mind and schizotypal dimensions

The ANOVA performed with AAI categorical classification (Secure, Dismissing, Preoccupied) as categorical factor and, respectively, the total SPQ score, the cognitive-perceptual factor score, the interpersonal factor score and the disorganized factor score as dependent variable revealed a main effect of AAI classification on SPQ total score (F=3.88, p=0.029, Figure 2.3). Fisher post hoc analysis revealed significant differences between Dismissing and Preoccupied subjects (p=0.009) and a statistical trend between Secure and Dismissing subjects (p=0.09).

The main effect of AAI classification on SPQ cognitive-perceptual factor and disorganization scores revealed statistical trends (respectively, F=2.65, p=0.083, F=2.76, p=0.079). No significant main effect was found when testing the main effect of AAI classification on SPQ interpersonal factor scores (p=0.154).

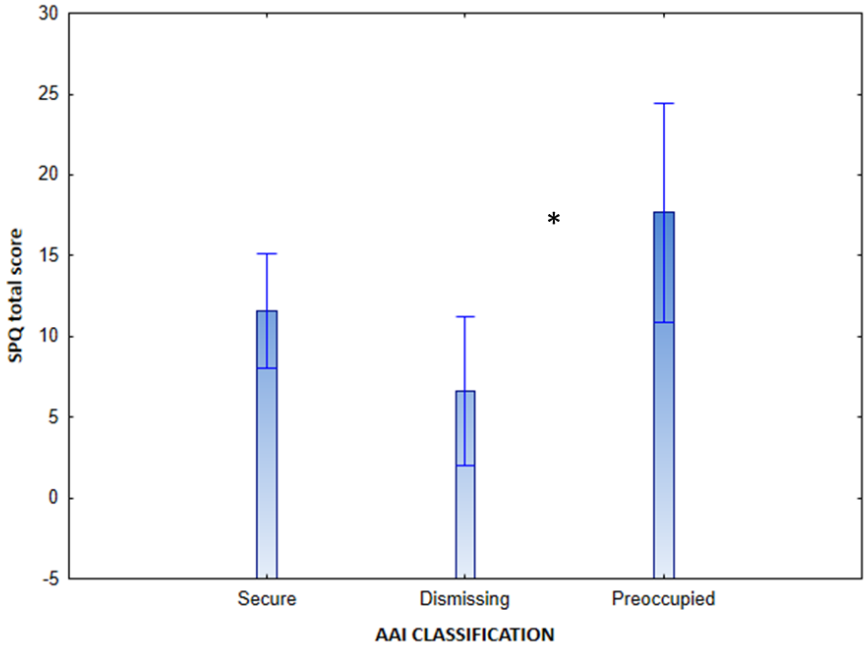

Figure 2.3: *histogram of the ANOVA investigating the main effect of AAI classification on SPQ total score.*

Because the Preoccupied category seems to be the only insecurity category associated with higher schizotypal traits, we performed Pearson correlation analysis between SPQ total score and the scores of the AAI state of mind scales determining Preoccupied classification, that is, involving anger towards mother and passivity. Results revealed the existence of significant positive correlations between SPQ total scores and (a) involving anger towards mother (r=0.36, p=0.021, Figure 2.4/a), and (b) passivity (r=0.41, p=0.008, Figure 2.4/b).

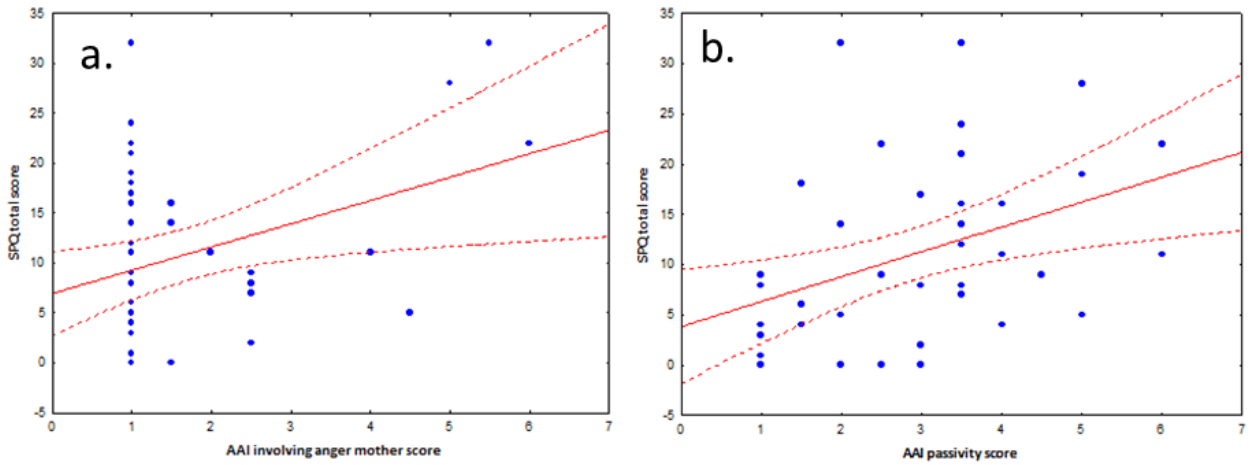

Figure 2.4: *scatterplots of the correlation analysis between SPQ total score and (a) AAI involving anger mother score and (b) AAI passivity score.*

2.4.2. Association between adult attachment state of mind and maternal emotional availability

The ANOVA investigating the main effect of AAI classification on EAS scores revealed a main effect of AAI adult attachment style on:

- EAS total score (F=4,78, p=0.014, Figure 2.5/a). Post hoc analysis revealed significant differences between DS and E subjects (p=0.022).
- EAS child score (F=3.43, p=0.043, Figure 2.5/b).

No significant main effect of AAI classification was found on EAS mother score (p=0.7).

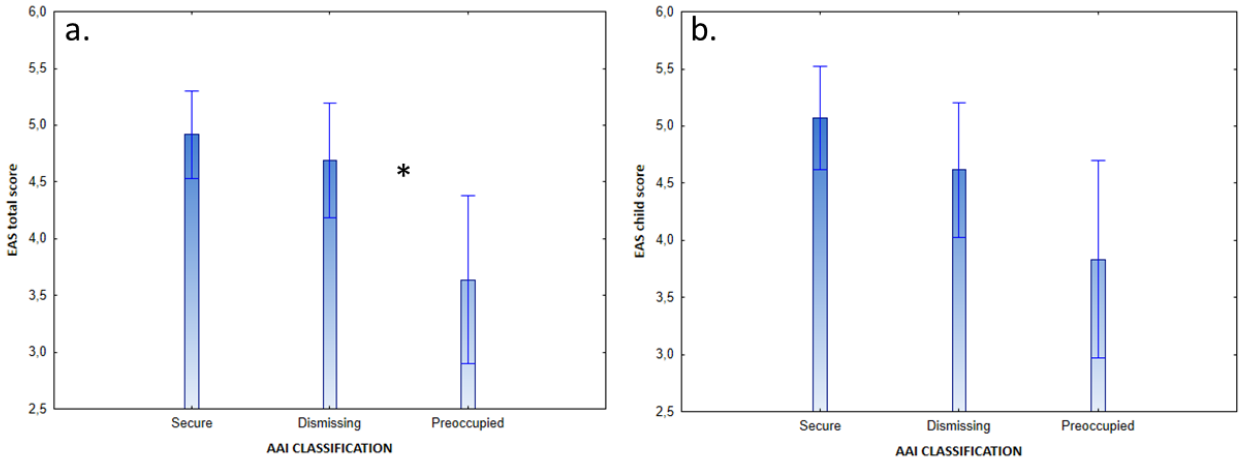

Figure 2.5: *histograms of the main effect of AAI classification on (a) EAS total score, (b) EAS child score.*

Correlation analysis further corroborate our results revealing a significant positive relationship between AAI state of mind "coherence of transcript" scale and (a) EAS total score (r=0.33, p=0.033, Figure (2.6/a) and (b) EAS child score (r=0.35, p=0.024, Figure 2.6/b).

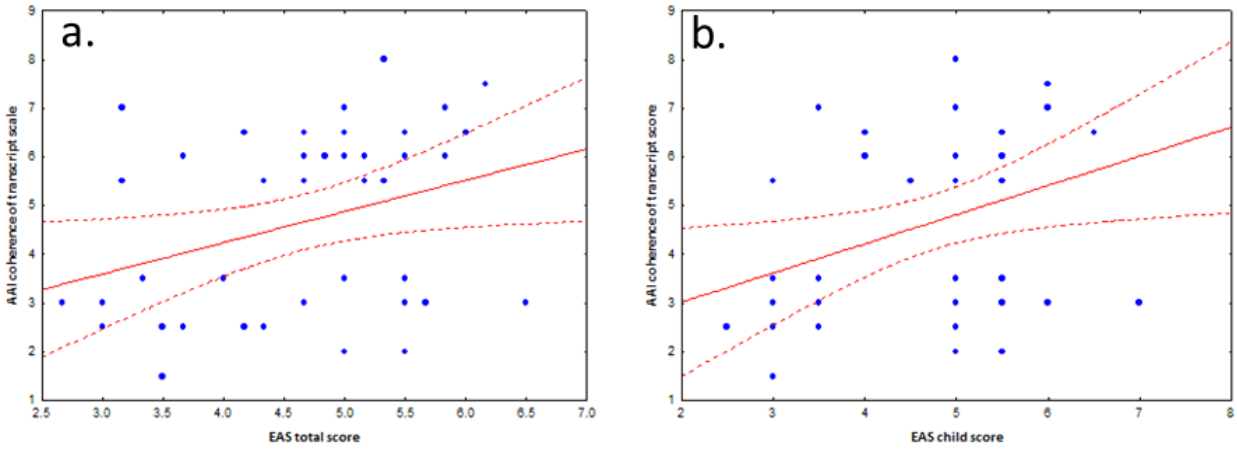

Figure 2.6: *scatterplots of the correlation analysis between AAI coherence of transcript score (a) EAS total score and (b) EAS child score.*

2.4.3. Association between schizotypal dimensions and maternal emotional availability

Regression analysis used inserting SPQ scores one at a time (respectively, total, cognitive-perceptual, interpersonal and disorganized) and EAS scores (respectively, total, mother, child) revealed significant negative associations between:

- SPQ total score and EAS total score (R=-0.31, p=0.045, Figure 2.7/a),

- SPQ cognitive perceptual factor score and EAS total score (R=-0.31, p=0.047, Figure 2.7/b),
- SPQ disorganized score and EAS total score (R=-0.48, p=0.005, Figure 2.7/c).

All other regression analysis gave no significant results (all p>0.1).

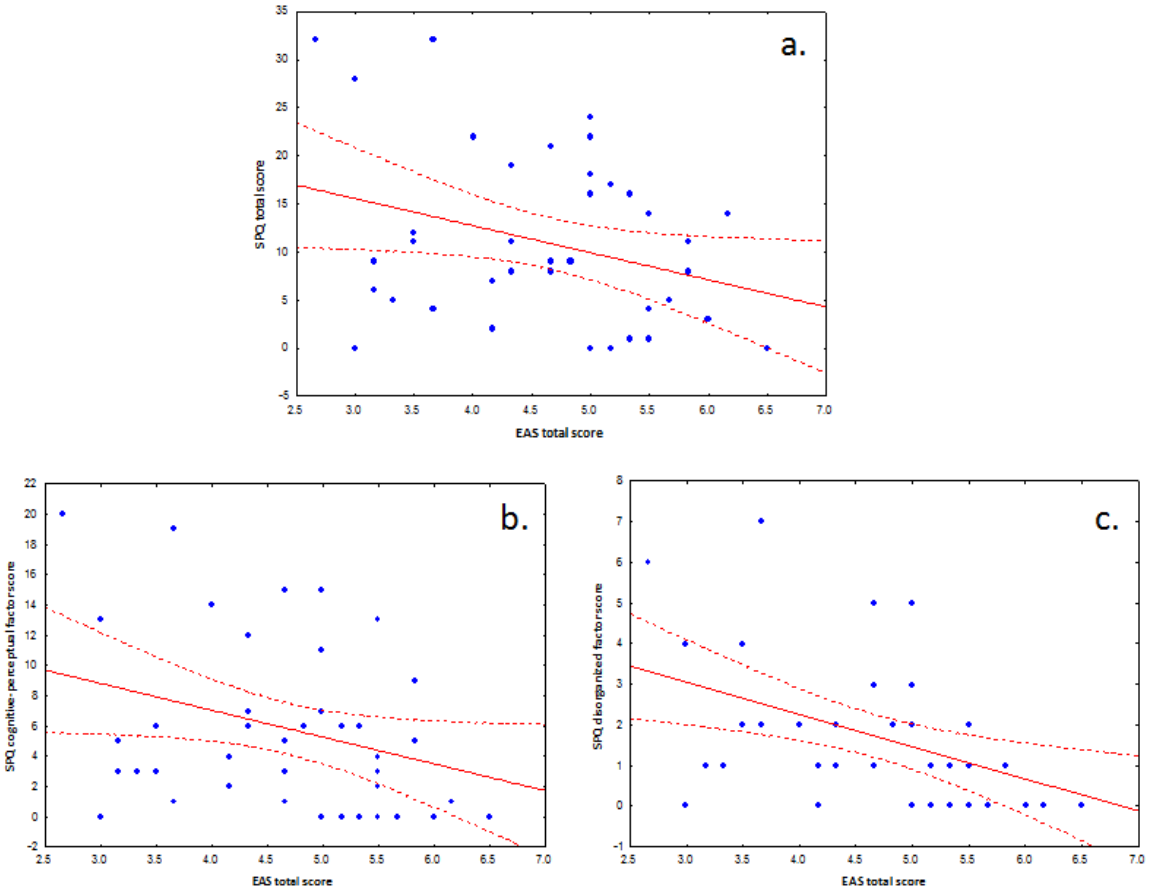

Figure 2.7: *scatterplots of the correlation analysis between EAS total score and (a) SPQ total score, (b) SPQ cognitive-perceptual factor score, (c) SPQ disorganized score.*

2.4.4. Moderation process analysis results

Results of the moderation process analysis performed through the PROCESS macro revealed:

- a main effect of adult attachment state of mind on dyadic emotional availability both in the model where adult attachment was treated as a dichotomous variable (b=0.612, p=0.038) and in the model where adult attachment was treated as a continuous variable (b=0.173, p=0.027);

- a main effect of maternal schizotypal traits on dyadic emotional availability both in the model in which adult attachment was treated as a dichotomous variable (b=-0.036, p=0.035) and in the model in which adult attachment was treated as a continuous variable (b=-0.034, p=0.046);
- no moderation effect of maternal schizotypal traits in the relationship between adult attachment and dyadic emotional availability, neither in the model in which adult attachment was treated as a dichotomous variable (b=0.023, p=0.479), nor in the model in which adult attachment was treated as a continuous variable (b=0.006, p=0.545).

2.4.5. Association between maternal personality traits and child temperament dimensions

Pearson's correlation analysis between, respectively, the total SPQ score, the cognitive-perceptual factor score, the interpersonal factor score and the disorganized factor score and, respectively, separate scores of every of the six QUIT dimensions (i.e., social orientation, inhibition to novelty, motor activation, positive emotionality, negative emotionality and attention) revealed significant association between:

- SPQ total score and positive emotionality (r=-0.32, p=0.043, Figure 2.8/a).
- SPQ total score and inhibition to novelty (statistical trend, r=0.27, p=0.083),
- SPQ interpersonal factor score and positive emotionality (r=-0.34, p=0.031, Figure 2.8/b),
- SPQ interpersonal factor score and inhibition to novelty (r=0.039, p=0.011, Figure 2.8/c),

All other correlation analysis gave no significant results (all p>0.2).

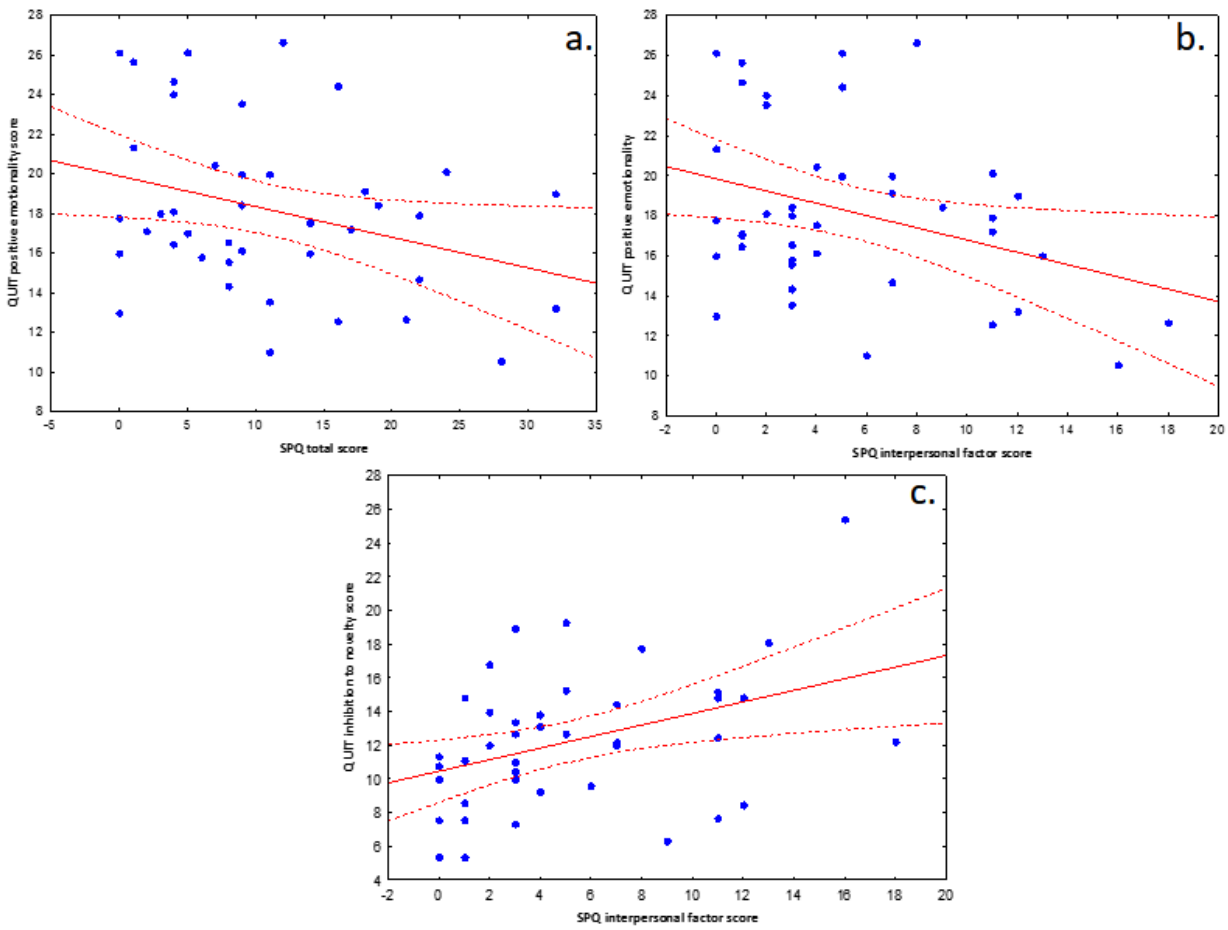

Figure 2.8: *scatterplots of the correlation analysis between (a) SPQ total score and QUIT positive emotionality, (b) SPQ interpersonal factor score and QUIT positive emotionality, (c) SPQ interpersonal factor score and QUIT inhibition to novelty score.*

2.5. Discussion

Study 2 had the aim of investigating, in a cohort of mother-infant dyads, (a) whether schizotypal traits may exert a function of potential mediator in the relationship between adult attachment state of mind and maternal emotional availability, and (b) the potential relationship between maternal schizotypal traits and temperamental dimensions of the child. Results revealed:

- a significant association between adult attachment style, measured by the AAI, and SPQ total score, where preoccupied subjects had higher levels of schizotypy when compared to avoidant and secure subjects.
- in line with the previous findings, statistically significant positive correlations between SPQ total score and AAI state of mind scale scores characterizing the preoccupied adult state of mind (i.e., involving anger towards mother and passivity). Specifically, mothers with high anger and passivity scores had high levels of schizotypy.
- a significant association between adult attachment style, measured by the AAI, and the general maternal emotional availability score obtained through the EAS, where preoccupied mothers had lower emotional availability scores than avoidant and secure mothers. Results remained significant and coherent when considering the EAS score reflecting the child involvement and responsiveness during dyadic interactions with the mother.
- in line with the previous results, statistically significant positive correlations between AAI coherence of transcript and both EAS total and child score, that is, the more the transcript of mothers are coherent, the more the emotional availability referred both to the dyad and to the child increase.
- statistically significant negative correlations between EAS total score and SPQ dimensions (total, cognitive-perceptual and disorganized scores), that is, the more maternal sensitivity increases, the less levels of schizotypy are present in mothers.

- a main effect of both SPQ total score and AAI categorical and continuous score on dyadic emotional availability in a moderation process model, but no moderation effect of SPQ total score in the relationship between adult attachment state of mind and dyadic emotional availability.
- statistically significant negative correlations between maternal SPQ dimensions (total and interpersonal scores) and child positive emotionality temperament trait, that is, the more mothers have high levels of schizotypy, the less children are able to express and regulate positive emotions,
- statistically significant positive correlations between maternal SPQ dimensions (total and interpersonal scores) and child inhibition to novelty temperament trait, that is, the more mothers have high levels of schizotypy, the more children are inhibited towards new stimuli,

As concerns the first two points, the association between attachment style and the schizotypal personality trait suggests that the adult state of mind with respect to attachment experiences depends on the severity of schizotypal trait. This finding is consistent with a large body of literature that shows a direct link between attachment styles and personality disorders (Fonagy and Luyten, 2009). Moreover, this finding supports the results of Study 1. Coherently, the most recent conceptualizations related to personality disorders suggest that disturbed IWMs can exert a significant influence on the onset of these diseases (Fonagy, Steele et al. 1991, Westen 1991).

However, in the present study it was found that not all insecure subjects have high levels of schizotypy, but that preoccupied subjects have statistically significant higher levels of schizotypy when compared to both avoidant and secure subjects. This result seems to be in contrast with several studies that have shown that individuals more likely to develop schizotypal personality disorder are those who have a pattern of dismissing attachment (Mikulincer, Shaver, 2003, Dozier, Cue et al. 1994, Tyrrell and Dozier 1997). This discrepancy may be explained in light of the three symptomatologic dimensions of schizotypy (positive, negative and disorganized). In fact, the literature seems to suggest

that the association between attachment style and schizotypy varies according to the specific symptomatologic dimensions of schizotypy considered.

In this context, Sheinbaum et al. (2013) have reported the presence of conflicting results in the literature concerning the association between a specific category of insecure attachment and positive, negative or disorganized schizotypy: they found a significant association between preoccupied attachment style and positive schizotypy, between dismissing attachment style and negative schizotypy, and between fearful attachment style and disorganized schizotypy.

The fact that in our sample preoccupied subjects have higher levels of schizotypy may point to the fact that these individuals have a greater vulnerability to the positive symptoms. This greater vulnerability is confirmed by the statistical trend reflecting the association between AAI adult attachment style and the SPQ cognitive-perceptual score.

In this context, Fossati et al. (2003) found that the SPQ cognitive-perceptual factor (which includes symptoms as reference ideas, magical thinking, unusual perceptual experiences, paranoid/suspicious thoughts) seems to be associated with the positive symptomatologic dimension of the schizotypy/schizophrenia continuum identified by Arndt (Arndt, Alliger et al. 1991); on the other hand, the SPQ interpersonal factor (which includes social anxiety, close friends, restricted affect) seems to be associated with the negative dimension of the schizotypy/schizophrenia continuum. By contrast, the SPQ disorganization factor (which includes strange behavior or eccentric and extravagant speech) seems to be associated with the degree of disorganization of the schizotypy/schizophrenia continuum.

Therefore, it could be argued that attachment style modulates a personality trait which may be involved in the development of positive symptoms. A possible speculation is that suspiciousness and irrational fears could result from a negative bias in the social information processing. Instead, reference ideas and magical thinking may be a cognitive strategy to protect the individual from irrational fears in the relationship with figures perceived as unpredictable (Tiliopoulos and Goodall, 2008). In this view, even the typical

symptoms of the disorganized schizotypy dimension can be explained in the light of their relationship with previous experience of attachment, in fact speech inconsistency may be associated with representations of attachment (Main et al. 1985). In this regard, Fonagy et al. (Fonagy and Target 1997) found that adults with insecure attachment had lower meta-cognitive abilities and, therefore, were less able to think about themselves and others, to mentalize what other people think and be aware of the effects of their actions. Therefore, disorganized schizotypal traits (odd or eccentric behavior and extravagant speech) could be the consequence of a lack of awareness of the effect that their behavior, speech and appearance exert on others.

Correlation analysis further corroborate this results, given the fact that we found statistically significant positive correlations between the AAI state of mind scales scores associated with the preoccupied style and the total SPQ score, that is, higher scores of involving anger towards mother and of passivity were associated with higher schizotypy levels.

The involving anger towards mother AAI state of mind scale refers to expressions of involving/preoccupied anger which are not limited to discussions of childhood. Speakers become lengthy, unclear, or irrelevant in describing provoking incidents, feelings, seeming to create distortions in language within the interview. On the other hand, the passivity scale reflects momentary or pre-existing defects relying on genuine incapacities for seizing on more exact meanings. This vague speech style may represent an internal interference that causes the loss of untoward thoughts, memories or impulses.

It seems therefore that some crucial features of the schizotypal style of language and thought (that is, the tendency to say inappropriate things, using such vague language or too elaborate and full of metaphors to be incomprehensible, likely leading to persecution feelings) are in line with the main features that characterize AAI preoccupied speakers.

Furthermore, our results confirm that there is a significant association between the AAI state of mind and the EAS dyadic emotional availability. Specifically, dyads with

preoccupied mothers have lower levels of emotional availability when compared to dyads with avoidant and secure mothers. This is in line with several previous studies positing that insecure mothers show lower levels of maternal sensitivity than secure. Accordingly, Biringen et al. (2000) found that both AAI classification and continuous scores can be considered significant predictors of maternal sensitivity and responsiveness of the child. Moreover, Oyen et al. (Oyen, Landy et al. 2000) examined the relationship between adult attachment style, assessed through the AAI, and maternal sensitivity, assessed by the EAS. Results revealed that mothers classified as secure were more sensitive to child signals. On the other hand, preoccupied mothers seemed to be less sensitive and to have suboptimal interactions with the child. Furthermore, Negrao et al. (Negrao, Pereira et al. 2016) investigated the association between maternal representations of attachment and sensitive behaviors, confirming that mothers with a preoccupied state of mind are less sensitive during the interaction with children. On the contrary, secure attachment representations are associated with greater emotional availability.

Our results also highlight a significant difference between preoccupied and dismissing subjects in terms of emotional availability, that is, preoccupied mothers seem to have low emotional availability scores than dismissing. In this regard, Haydon et al. (Haltigan, Roisman et al. 2014) demonstrated that both dismissing and preoccupied subjects are associated with lower emotional availability levels but, while distancing mothers seem to have low levels of maternal sensitivity, preoccupied mothers typically set the relationship with the child based on high levels of intrusiveness, which potentially lead to low levels of emotional availability, thus supporting the hypothesis that not simply insecure state of mind is related to low emotional availability, but that every insecure attachment style has specific characteristics that may lead to poor parenting. Other research confirms that differences in terms of adult attachment state of mind predict how mother perceives child signals and how child responds to mother's cues (Hesse 1999).

In this line, Crowell and Feldman (Crowell and Feldman 1988) tested the association between adult attachment and maternal sensitivity, comparing the interactions of secure,

distancing and preoccupied mothers with their preschool children. Secure mothers supported and provided assistance in a clear way, while distancing mothers were less warm and more focused on the task completion by the child. On the other hand, preoccupied mothers were confusing and asynchronous during the interactions. These mothers were characterized by an unpredictable responsiveness: sometimes warm and kind, sometimes coercive, supporting the hypothesis that adult attachment may be a predictor of sensitivity and of the quality of the mother-child interaction.

Further support to the fact that the preoccupied adult attachment style is more likely than the dismissing one to be associated with low emotional availability is given by studies demonstrating that a preoccupied style is associated with high anger levels within the mother-child interactions, as well as with a higher level of intrusive behavior in dyadic contexts (Adam et al. 2004). These variations in emotionability of the parent may therefore lead to subsequent changes in the parental behaviors, leading ultimately to that sense of unpredictability often experienced in this kind of relationships (Lovejoy, Graczyk et al. 2000).

Therefore, according to Main (Main 1996), it could be argued that the confusion and inconsistency that characterize AAI preoccupied transcripts reflect mothers' inability to provide adequate and effective responses in the mother-child interactions. In detail, the preoccupied state of mind seems in fact to be a purely self-centered model of interaction which does not include the recognition of the signal of needs expressed by the child, resulting in a poorer quality of dyadic interactions and in low emotional availability levels.

The fact that, on the other hand, attachment security may be protective for what concerns the quality of parenting is demonstrated by the presence of a significant positive correlation between EAS scores and the AAI coherence of transcript scale scores. This result is in line with previous literature (Biringen et al. 2000, van Ijzendoorn et al. 1997) positing that AAI mental coherence can explain a large amount of variance of emotional availability. Furthermore, Coppola et al. (Coppola, Vaughn et al. 2006) tested the reliability and validity of the Italian version of the "Attachment Script Representation"

(Treboux, Crowell et al. 2004) and tested the relationship between adult attachment representations and emotional availability levels in mothers. Results confirmed that mother with secure IWMs had high levels of mental coherence during the AAI and higher levels of maternal sensitivity, when compared to insecure mothers.

Our results also highlighted the existence of significant negative correlations between SPQ dimensions (total, cognitive-perceptual and disorganized scores) and EAS emotional availability total score, that is, the more SPQ scores are high in mothers, the low the dyadic emotional availability. This finding is consistent with studies investigating the relationship between schizotypy and insecure attachment (Korver-Nieberg, Berry et al. 2014, Berry, Barrowclough et al. 2007) and with attachment theory, which attributes a crucial role to IWMs in the definition of the sensitive parental behavior. In fact, as stated previously, parents of schizotypal subjects seem to be emotionally distant, confounding and often humiliating, contributing therefore to the shaping of negative representations of self and significant others. Furthermore, several studies have suggested that both the full-blown psychosis and schizotypal characteristics may be associated with deviance in parental communication (de Sousa, Varese et al. 2014) and with poor maternal care (Meins, Jones et al. 2008). Specifically, Giakoumaki et al. (2013) found a significant association between schizotypal personality and anxious and parental overprotective behavior.

In our study, we found a significant correlation between EAS scores and SPQ cognitive-perceptual and disorganized scores, that is, higher SPQ level in these factors are associated with low mother-child emotional availability. As mentioned before, the cognitive-perceptual factor measures the positive symptomatologic dimension of schizotypy, while the disorganization factor detects the amount of disorganized behavior at a trait level, such as strange behavior or eccentric and extravagant speech (Calkins, Curtis et al. 2004, Chen et al. 1997, Claridge, McCreery et al. 1996, Raine et al. 1994, Reynolds, Raine et al. 2000). Our data therefore suggest that these two factors, compared with the interpersonal one, are those which have the greater impact on mother-child emotional availability, and this is likely because they include the evaluation of cognitive and behavioral abilities

which are at the basis of sensitive behavior, i.e., the ability to perceive signals from the environment and to interpret them correctly in order to respond appropriately. In fact, the compromised meta-cognitive ability, which is core in schizotypy (Tiliopoulos and Goodall, 2008), may also lead us to hypothesize that this impairment does not allow the mother to consider the child as a mental agent (Meins, Fernyhough et al. 2001) and to reflect on his individual mental state. A sensitive behavior requires this tuning ability of the caregiver with the mental experience of the child to understand her needs and to make her feel that is able to send signals and that the environment is provided to receive them and is able to respond adequately (Fonagy et al. 1991).

The results of our moderation process analysis allow a deeper understanding of our results. In fact, we found a negative main effect of SPQ total score on dyadic emotional availability (that is, mothers with higher level of schizotypy are part of dyads with a lower level of mother-child emotional availability). Furthermore, a positive effect of, respectively, AAI classification and coherence of transcript score on dyadic emotional availability (that is, secure mothers – or mothers with higher coherence of transcript levels – are part of dyads with a higher level of mother-child emotional availability) was present. These results confirm that both adult attachment style and maternal personality traits which represent a vulnerability condition for psychosis may influence dyadic emotional availability, which according to previous literature is the main vehicle of the intergenerational transmission to attachment (Sette et al., 2015). Therefore, since this early relational experiences may lead to the structuring of negative IWMs, and given that these mental representations tend to remain stable over time, like an action guiding system (Belsky et al. 2002), it could be posited that IWMs will also guide parental behavior, including maternal availability and sensitivity. On the other hand, mothers with high levels of schizotypy which may have likely developed negative mental patterns of self and others, will be less sensitive than secure mothers. This is coherent with our AAI-SPQ results and with the fact that higher levels of schizotypy are associated with an insecure adult attachment state of mind, which is a predictor of the emotional availability capacity.

However, no moderation effect of SPQ total score in the relationship between adult attachment style and dyadic emotional availability was found. These variables seem therefore to act as independent predictors of emotional availability, rather than interacting between each other in determining lower dyadic sensitivity levels. Given the contemporary existence of significant main effects both of schizotypy and adult attachment, this lack of moderation effect may be due to the small sample size of Study 2 (N=41) or to the effect of other intervening variables which were not object of the current study (i.e., marital satisfaction, acute and chronic stress). Further studies therefore are warranted to understand whether these variables may interact in more complex ways, or with other environmental or personal variables.

Furthermore, results revealed significant negative associations between maternal SPQ dimensions (total and interpersonal) and child temperament traits (positive emotionality) and positive associations between SPQ interpersonal factor of mothers and QUIT inhibition to novelty measured in children. Our data therefore suggest that higher levels of schizotypy in mothers are correlated to lower levels of positive reactivity to stimuli in children, and that on the other hand high SPQ scores in the interpersonal domain of mothers are associated with high environmental inhibition in children.

Positive emotionality is one of the six QUIT temperament dimensions and measures the child's tendency to respond to positive emotional expressions. Goldsmith (Goldsmith and Alansky 1987) considers emotionality as a central and constitutive component of temperamental individual differences and that is the reason why in the Italian model of temperament (Axia 1994), compared to the original Thomas and Chess theory (1977), took into account not only a single dimension referring to the general emotional mood, but operationalized this construct along two separate factors (positive and negative emotionality). Despite the fact that research on the genetics of behavior claimed that emotional tuning and emotion processing may have a significant hereditary component (Gabbay 1992, Loehlin 1992, Axia 2000), the fact that in our study we found significant

correlations between maternal personality and child temperament may indicate that emotionality as a trait may also be affected and modulated by the primary environment.

In fact, despite temperamental characteristics can be defined as a set of individual differences with strong biological-constitutional basis that become manifest through expressed behavior, appearing quite early and remaining relatively stable during the development (Bates, 1989), Thomas and Chess (1977) recognized the dynamic nature of this construct. More precisely therefore temperament may be re-defined as child innate characteristics that allow her to interact with attachment figures and that are going to influence and be influenced by environmental feedbacks. In this perspective, negative correlations between QUIT positive emotionality and SPQ dimensions may represent a form of functional adaptation of the child to ensure the balance in her environmental context, in line with the concept of "goodness of fit" (Thomas and Chess, 1977).

This notion is confirmed by the negative correlation between QUIT positive emotionality and SPQ interpersonal factor: taking into account that the SPQ interpersonal factor includes evaluation of social anxiety and absence of close friends and constrained affects, it could be posited that, even if present at a sub-clinical level in mothers, these characteristics may influence the emotional capacities of the child to the extent that manifestation and expression of positive moods are inhibited, thus likely making it difficult for the child to adapt to an environment that does not give her adequate feedbacks about these expressions.

As for positive emotionality, the positive correlation between child novelty inhibition and maternal interpersonal SPQ trait can be explained in the light if the fact that the interpersonal SPQ factor evaluates social deficits and social retreat. Inhibition to novelty is another of the six QUIT temperament dimensions. Buss and Plomin (1984) previously distinguished between the temperament trait describing the degree of inhibition of child in front of novel environmental stimuli and a more general tendency to socialize, respectively correspondent with the “Inhibition to novelty” and “Approach/Retreat” temperament trait of the Axia model (1994) on the basis of which QUIT was build.

In this line of reasoning, our results suggest that mothers who tend to be unsociable and have few social relationships, who have high social anxiety levels and tend not to express their emotions may be discouraged to respond to environmental stimuli and therefore may not support a positive attitude towards novelty in children, likely influencing them in considering environment as potentially dangerous.

It is also important to note that the SPQ interpersonal factor, which has not been found to be significantly correlated neither with emotional availability, nor with adult attachment state of mind, is the only SPQ sub-dimension which is correlated with child temperament traits in a statistically significant way. This is in line with the fact that, while cognitive-perceptual and disorganization SPQ dimensions measure individual personality dimensions, the interpersonal SPQ dimension is more focused on social behaviors and tendencies. In this context, the influence that negative schizotypy, represented by interpersonal factor scores, seems to exert on parental behavior appears to be direct, because it influences child temperament traits that which modulate her environmental interaction tendencies. On the other hand, positive schizotypy, represented especially by cognitive-perceptual SPQ scores, seems to exert a specific influence on mother-child dyadic emotional availability. It may be therefore hypothesized that the influence of maternal positive schizotypy on child behavior may be mediated by maternal sensitivity and emotional availability, while the influence of negative schizotypy on child behavior seems to be more direct and constituted by an unfavorable attitude towards environmental stimuli. Future studies with complex statistical models and larger sample sizes are warranted in order to test this hypothesis.

In summary, schizotypy represents a vulnerability factor for the onset of schizophrenia spectrum disorders expressed in terms of personality (Barrentes-Vidal et al. 2015), and it seems to have a crucial role also in modulating key determinants of child attachment security, which in turn (taking into account also Study 1 results) may be considered an environmental risk factor for the conversion to psychosis in the schizotypy/schizophrenia spectrum. Our results are relevant because further characterize how attachment and

psychopathology are associated, and this may be crucial to increase the likelihood of early detect the risk for psychosis and to take charge of subjects in which these disorders have not yet fully manifested.

Attachment theory therefore may be considered an intriguing theoretical framework to understand the impact that early relationship experiences, along with other genetic and environmental factors, may have on the development of schizophrenia-like psychopathology and, consequently, to be able to program early intervention strategies.

Study 3 – Interaction between perceived maternal care and a genetic variant coding for the oxytocin receptor gene (OXTR rs2268493) on behavior and brain activity during explicit emotion processing: a neuroimaging study

3.1. Background

3.1.1. Attachment style modulates emotion processing and regulation: insights from behavioral studies and neuroimaging

3.1.1.1. Attachment style implications on emotion processing and regulation

Attachment style and IWMs seem to influence choices, tendencies and behaviors, especially at the social-interactive level. Attachment orientations in fact seem to alter, enhance or suppress the generation, the processing and the regulation of emotion, shaping action tendencies (Cassidy and Kobak 1988, Shaver and Mikulincer 2002).

Modern models of the emotion system organization (LeDoux 2012, Phillips, Drevets et al. 2003, Phillips, Drevets et al. 2003) posit that this system include core and rapid processes, in order to respond fast, automatically and often unconsciously to emotions and gain safety and comfort. This "safety vs. danger" (Vrticka and Vuilleumier 2012) type of emotion processing generates therefore automatic behavioral responses in term of approaching or avoiding the environmental stimulus which generated the emotional experience. In line with this view, Porges (Porges 2003) raised the hypothesis that this core "safety vs. danger" automatic processing would be the base of the mechanisms motivating the activation of proximity-seeking behaviors, on one hand, or the elicitation of social aversion strategies, on the other hand. In a recent review (Vrticka et al. 2012), authors stated that both the approach and avoidance action tendencies may be modulated by individual IWMs and attachment style.

In fact, if emotions may be conceptualized as *"a set of thoughts and action tendencies supported by specific psychological processes"* (Cooper, Shaver et al. 1998), it can be posited that their generation will be consequent to the appraisal of events in relation with individual goals and desires (Shaver et al. 1987, Figure 3.1). Therefore, the emerging emotions will be experienced through changes in the accessibility of mental contexts and

individual feelings (Oatley 1996). Furthermore, emotions emerge following an environmental change, often unconsciously, appraised in relation with individual goals and wishes (Oatley 1996). If these changes are perceived as undesirable, negative emotions will be generated, and the specific emotion depends on the specific goal and wish activated (i.e., the "appraisal pattern", Lazarus 1991, Shaver, Schwartz et al. 1987). After the activation of this system of wishes, goals and concerns, the emotion will be manifested both at the physiological (i.e., blood pressure, muscle tension, neurochemical changes) and at the psychological level (i.e., thoughts, feelings, action, non-verbal language).

At this point, the individual can choose to make regulatory efforts that alter not only the manifestation of the emotion, but that seem to be able to influence the whole emotional experience (Shaver et al. 1987).

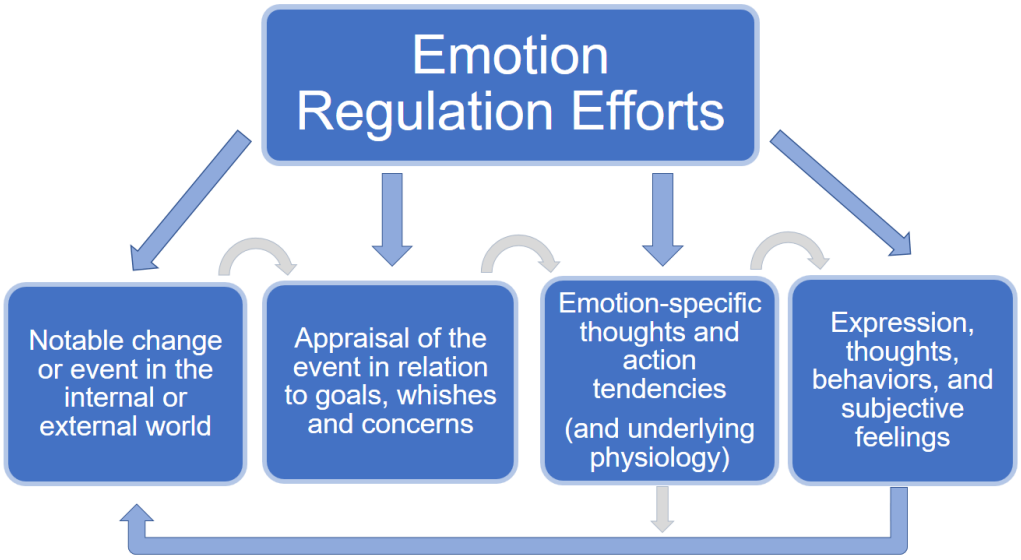

Figure 3.1: model of the whole emotion experience process (Shaver et al. 1987).

According to Shaver and Mikulincer (2002), attachment security seems to facilitate emotion regulated strategies and makes these efforts capable of alleviating distress, giving the individual a perceived sense of comfort and support. If secure individuals experience an unpleasant change in the environment, they seem to be able to generate problem solving strategies (i.e., planning of action to do, capacity of stopping interfering thoughts) and to seek help from other people in order to reach care and comfort. It seems also that

secure individuals, more than insecure, are able to perceive themselves as stable and resilient in experiencing environmental changes, therefore demonstrating also a strong self-reflective capacity that make them able also to read emotional states in others and to integrate the emotional experience in the self (Fonagy, Steele et al. 1991, Shaver and Mikulincer 2002).

On the other hand, literature describes the emotion processing and regulation strategy associated with attachment-related avoidance as deactivating. These individuals seem to be moved by the desire to suppress pain and discomfort caused by cool and rejecting attachment figures (Cassidy and Kobak 1988) and, with this aim, they seem to inhibit painful activation of the attachment system. Avoidant individuals seem to learn through the lifespan how to downplay environmental threatening changes and stop monitoring the availability of the attachment figure (Kobak et al. 1993), emphasizing their self-efficacy while derogating or dismissing need of intimacy and closeness manifested by others (Bowlby 1988). Blocking the emotional experience (especially negative emotional experiences, such as anger, fear, anxiety, shame and guilt), therefore, is functional for the deactivation of the entire attachment system (Mikulincer and Shaver 2003), interfering with the problem-solving capacity. These individuals seem in fact to be incapable of accepting uncertain or confounding information that may imply a need for seeking help (Mikulincer 1998), avoiding to notice and make manifested their own emotional reactions.

Hyperactivation of negative emotions, instead, seem to characterize anxiety-related attachment. The emotional experience of individuals high in attachment anxiety in fact seems to be constantly sustained and exaggerated, because these people seem to be guided by a wish to receive a greater extent of attention from the attachment figure in order to receive a higher level of protection (Cassidy and Kobak 1988, Mikulincer, Gillath et al. 2002). The attachment system is therefore constantly and highly activated and this is manifested by their tendency to exaggerate the perception of threats in the social environment, by the emphasization of their sense of helplessness and vulnerability and by a constant vigilance towards the unavailability of the attachment figure (Cassidy and Berlin 1994). Problem solving is therefore characterized by negative beliefs about self and

others (Collins and Read 1994) and pessimistic ideas about the individual's ability to manage distress. The attention is therefore shifted on internal indicators of distress (Cassidy and Kobak 1988, Shaver and Mikulincer 2002), i.e., focalization on the physiological correlates of the emotional experiences, or the recall of threatening experiences. Furthermore, anxious individuals seem to be able to link negative experiences, representations and feelings with each other, so that the recall of a single thought can trigger all others (Shaver and Mikulincer, 2002).

Because of these individual differences in terms of emotion regulation and processing, the modulation of attachment style in adults on the emotional domain has been investigated through several experimental paradigms. For example, some authors (Fraley and Spieker 2003, Niedenthal, Brauer et al. 2002) investigated emotion processing through a movie morph paradigm composed by facial expressions with different emotional valence (happy, angry, sad). Results revealed that insecurely attached adult individuals detected the onset and the offset of all emotions earlier than secure subjects, thus raising the hypothesis that insecure individuals can have a hyper-activation of the whole emotion processing system. It is important to note that emotional stimuli were depicted on faces on unknown individuals, thus indicating that IWMs and attachment style have deep influences on emotion processing, even with unfamiliar stimuli. Other evidence showed that individuals with high scores in attachment anxiety rated fear and sadness as more arousing, when compared with secure subjects. On the other hand, individuals with high scores in attachment avoidance rated these emotions as less arousing (Rognoni, Galati et al. 2008), consistently with the view posited before stating that attachment anxiety is strictly related to the hyper-activation of the emotional system, while attachment avoidance is associated with a general de-activation of the emotional processing and regulation strategies.

3.1.1.2. Neural correlates of emotion processing and regulation

Considerable research has been conducted in the last 40 years to better identify and understand the neural mechanisms subserving emotion processing. A wide variety of studies has fully explained and described the strong neurobiological background of emotion processing, which had identified a complex network made of cortical and

subcortical areas differentially involved in decoding facial expressions, in approaching and avoiding emotional stimuli basing on their valence (positive or negative) and in emotion regulation processes (LeDoux 1996, Phillips et al. 2003a, 2003b). The first attempt of describing this complex network has been made in 1952 by MacLean (Maclean 1952) who identified the "limbic system", a functional anatomical network composed by structures of the limbic lobe, such as parahippocampus, cingulate gyrus, dentate gyrus, subcallosal gyrus, hippocampus, amygdala, habenula, anterior thalamic nuclei, mammillary body. All these loci are thought to subserve emotion processing (Kotter and Meyer 1992, LeDoux 2000).

Several studies have tried to test MacLean's hypothesis and tried to better understand the neurobiological basis of emotion processing and regulation. In this context, evidence has revealed several interactions between the limbic system originally described by MacLean and neocortical structures tightly involved in cognitive processes (such as prefrontal cortex and orbital cortical regions), probably due to the strong existing connections between amygdala and neocortex (Damasio 1994, LeDoux 1996, 2000), thus raising the hypothesis that the theoretical application of the "limbic" paradigm could result in too simple and reductionist conclusions and that the investigation of the pathways involved in emotion processing would benefit of an integrated approach considering the interactions between emotion and cognition systems.

According to Phillips (2003), emotion processing relies on three related processes (Figure 3.2):

1. the identification of emotionally salient information in the environment,
2. the generation of emotional experiences and behavior in response to (1),
3. the regulation of emotional experiences and behavior.

The last may involve an inhibition of (1) and (2) so that the affective state and behavior generated in response to environmental stimuli are contextually appropriate.

The identification of salient information (process 1) relies primarily on ventral regions of the anterior cingulate cortex, on ventromedial prefrontal cortex and thalamic dorsomedial nucleus (Alexander, Naeser et al. 1990), as well as on subcortical regions such as insula

and amygdala (Calder, Lawrence et al. 2001). Specifically, the insula is located at the basis of the lateral fissure and has a role in the autonomic response to aversive stimuli, fear reactivity and anticipatory anxiety, and in the identification of displays of disgust in others (Calder et al. 2001, Phillips, Young et al. 1997). On the other hand, the amygdala is a small, almond-shaped region within the anterior part of the temporal lobe. Calder et al. (2001) have emphasized the importance of the amygdala for the identification of emotional expressions displayed by others, in particular threat-related emotions such as fear, but also sadness and happiness. In addition, the amygdala is involved in the response to non-facial displays of emotion, including unpleasant auditory, olfactory and gustatory stimuli, and in memory for emotional information (Calder et al. 2001).

Process 2 (generation of emotional experiences and behavior), which involves the generation of emotional experiences and behavior in response to environmental changes, primarily relies on amygdala, especially in response to fearful stimuli, and on insula, especially in response to disgust-related stimuli (Calder et al. 2001). Other regions implicated in process 2 include the ventral anterior cingulate gyrus (including subgenual and pregenual or rostral regions), which is important for autonomic function and emotional behavior (Drevets 2000), the ventromedial prefrontal cortex (especially its orbitofrontal portion), which has direct connections with the amygdala and is a key region for the perception of pleasant and unpleasant odours, flavours and tactile stimuli, as well as for the representation of the reward value of a stimulus and the way in which this representation guides goal-directed and normal social behavior (Damasio, 1994), and the ventrolateral prefrontal cortex, implicated in the induction of sad mood and the recall of personal emotional memories (Drevets 2000).

On the other hand, emotion regulation (process 3) relies on a "dorsal nervous system" (Phillips et al. 2003), including dorsal regions of the anterior cingulate gyrus and dorsomedial and dorsolateral prefrontal cortices, structures which have a pivotal role in selective attention, planning, motor responses to emotional stimuli and the integration of these processes with emotional inputs (Drevets 2000).

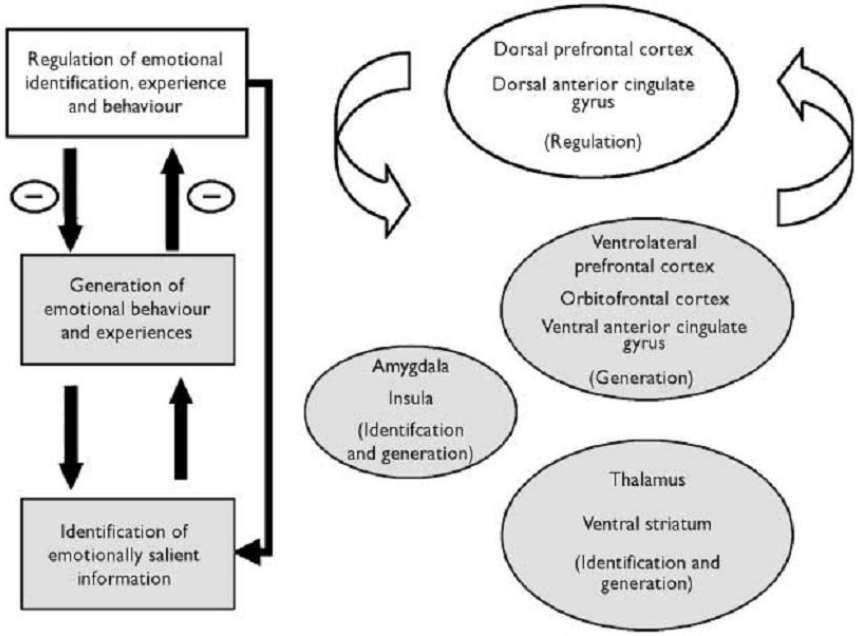

Figure 3.2: graph depicting the three main processes of the emotional system and the brain areas involved in every sub-process (Phillips et al. 2003).

Several authors have indicated that abnormalities in terms of activation and functional connectivity strength of these brain areas during emotional tasks seem to characterize several psychiatric disorders, such as bipolar disorder, major depression disorder, and schizophrenia. More in detail, neuroimaging studies on patients with schizophrenia have demonstrated volume reductions in the amygdala, insula, thalamus and hippocampus (Wright, Rabe-Hesketh et al. 2000), as well as a failure to activate limbic regions in response to emotional stimuli (Crespo-Facorro, Paradiso et al. 2001).

3.1.1.3 Modulation of attachment style on the neurobiology of emotions

Despite the crucial and key role of attachment style on the emotional system and its strong implications for both developmental psychology (Mikulincer and Shaver 2007) and mental health (Fonagy and Luyten 2009), the neural correlates of adult attachment style have not been fully investigated. Only some studies have attempted to investigate the modulation of attachment-related variables on the neurobiological features of emotions, focusing through several instruments on the neurobiological correlates of the two main dimensions of attachment insecurity, anxiety and avoidance, which could differently affect emotion regulation abilities.

In this context, Donges et al. (Donges, Kugel et al. 2012) used a set of faces with positive, negative and neutral emotional valence in a functional Magnetic Resonance Imaging (fMRI) session to evaluate the potential effect of attachment anxiety (measured through the RQ questionnaire) on cortical and subcortical activity during emotion processing. The authors found that individuals who had high scores on attachment anxiety showed increased activity in left prefrontal areas, such as BA10 and BA47, which are strongly implicated in judgment and social closeness (Cunningham, Johnson et al. 2003), globus pallidus and claustrum, which on turn seem to be important for the tendency of mimicking (Arkadir, Morris et al. 2004), and right cerebellum, which is implicated in social interactions and in the processing of happy faces (Critchley, Daly et al. 2000) than those who had low levels of attachment anxiety, but only when the faces were masked with happy expressions. These data suggest that people who exhibit high levels of attachment anxiety could be more motivated to recognize positive (i.e., happy) signals on people's faces in order to reach a higher level of intimacy. These results seem to be consistent with those found by Gillath et al. (Gillath, Bunge et al. 2005). In this paper, the authors had the aim to investigate anxiety and avoidance (assessed with the ECR questionnaire) as two main dimensions of the attachment style which could modulate the individual capacity of emotion regulation. With the hypothesis that anxious individuals could exhibit anomalies in terms of emotion regulation if exposed to social exclusion or experience of loss in the context of significant relationships, the authors found that, when they thought about scenarios with negative emotional valence, individuals who were high in attachment anxiety had increased activation in the anterior temporal pole cortex but decreased activation related to the orbito-frontal cortex than people high in attachment avoidance. This decreasing in activation in a key-area for the emotion regulation (Levesque, Eugene et al. 2003, Roberts, Beer et al. 2004) could be the result of a specific strategy of coping with negative emotions. On the other hand, avoidant people seem to fail in deactivating the orbito-frontal cortex, suggesting that they are less efficient in managing the strategies of coping with thoughts having a negative emotional valence (Mikulincer, Dolev et al. 2004). Moreover, the authors found that less avoidant people showed a decrease in activity

located also in left prefrontal cortex than the more avoidant ones. This result, linked to the fact that the authors found that individuals who had higher level of anxiety had a more direct access to negative memories than avoidant people, as revealed by an increase in activity located in memory-related areas such as hippocampus (Eichenbaum 2004), suggests that adult attachment could be able to modulate not only the emotion-related neural activity: based on these studies, it could be argued that attachment style could potentially and differentially modulate the activity related to cognitive functions, especially memory and attention. Due to the relationship between adult attachment, cognitive functions and neurobiological activity related to cognitive functions, a study by Warren et al. (Warren, Bost et al. 2010) had the primary aim of investigating how adult attachment and adult (current) state of mind about childhood experiences could possibly modulate the relationship between emotion and cognition. It is well-known that all the attachment experiences and their related memories generate and are reflected in distinct and individual patterns of emotional behavior and regulation, as well as individual differences in attachment could be reflected in differences in cognitive evaluation (Main, Kaplan et al. 1985). These emotion and cognition patterns in which attachment experiences could have a special role seem to be self-confirming over time and seem to influence cognitive functions such as memory and attention related to childhood experiences in the context of the mother-infant relationship (Bowlby, 1988). Considering also the tight relationship between emotion and attention (Compton 2003), there could exist an attention bias toward certain types of emotional information and memories (i.e., negative experiences). Moreover, an adult state of mind in respect to infant experiences of attachment classified as insecure has been previously associated with increased suppression of negative feelings and dysregulated emotional response (Cassidy and Kobak 1988), as suggested by previous studies in which insecure adults showed higher electrodermal activity while thy underwent the AAI interview than the secure subjects. This could be interpreted as a mechanism of suppression of the negative valence of feelings that could emerge in the context of the interview (Roisman, Tsai et al. 2004). In this study, the authors used the Attachment Script Assessment (ASA, Waters and

Rodrigues-Doolabs 2004) to assess attachment and subjects performed an emotion-word Stroop task while they underwent fMRI. Consistent with the hypothesis that there could exist an emotional bias due to emotions with negative valence, the emotion-word Stroop task showed in subjects classified as insecure an effect of interference due to unpleasant words which affected performance. Moreover, lateral and medial orbito-frontal cortex were more active during the processing of unpleasant words in insecure subjects, suggesting that this increase of activation could be interpreted as a strong attempt in order to regulate the effects of negative emotions. The activation of orbito-frontal cortex has been previously associated with efforts in maintaining and sustain attention while distractors intervene (D'Esposito, Detre et al. 1995) and with efforts in suppressing negative emotions (Depue, Curran et al. 2007).

All these data suggest that differences in terms of attachment experiences with respect to the memories of maternal care and maternal sensitivity are reflected at multiple level: emotional, cognitive, neurobiological. The processing of emotions, especially those with negative valence, seem to be strongly modulated by the attachment style and the perceived maternal care. Individual differences measured in this context are also reflected in different patterns of activation and elicitation of key-areas of the limbic system.

The importance of the study of neurobiological correlates of adult attachment style is further corroborated by a series of studies which demonstrate that adverse parenting experiences during childhood not only are more likely to be associated to insecure patterns of adult attachment (Main et al. 1985), but also to a dysregulated neurobiological strategy of coping with stress experiences expressed in terms of an increase of cortisol release (Carpenter and Stacks 2009). In this context, a recent line of research has the aim of investigating the modulation of attachment anxiety and avoidance on the hypothalamus-pituitary-adrenal (HPA) axis activity, which depends on the cortisol release and which has been previously associated with several stress-related illnesses (Claes 2004, Narita, Fujihara et al. 2012). An increase in cortisol release in humans and animals has been previously correlated with significant gray matter reductions (Sheline 2003). Other studies on patients suffering from stress-related diseases have indicated that subjects highly

exposed to stressful experiences could exhibit brain atrophy (Gross 2008), suggesting that investigating the environmental variables which contribute in increasing level of experienced stress both at perceived and physiological level. In this line of reasoning, a recent study (Quirin, Gillath et al. 2010) has shown that also attachment anxiety has been previously associated with stress-related cortisol release (Gillath, Mikulincer et al. 2006), (Powers, Gunlicks et al. 2006, Quirin, Pruessner et al. 2008): subjects underwent an MRI and Voxel-Based Morphometry was conducted on to investigate the gray matter distribution in the brain. The authors hypothesized that attachment insecurity (expressed in terms of avoidance or anxiety) would be inversely correlated with grey matter density in hippocampus, which had been previously identified as a key area in modulating the specific relationship between attachment insecurity and HPA activity because of its ability to reduce negative feedback related to HPA activity after stressful events (Jacobson and Sapolsky 1991). The authors found that both attachment anxiety and avoidance were associated with a selective reduction of gray matter in the hippocampus, inferring that this abnormality could reflect difficulties in insecure individuals in regulating their emotional response to stressful experiences (Mikulincer and Shaver, 2007) and that the neurobiological influences of adult attachment style on neurobiological mechanisms are not only reflected on functional anomalies of specific loci, but also at a core, structural and anatomical level.

Other studies have investigated adult attachment dynamics through the use of tasks involving visual and/or acoustic features related to children, with special attention to cues related to the one's own child. It has been previously reported that stimuli related to somebody's own infant can elicit the attachment system and its related behaviors. Moreover, they are thought to be strongly rewarding and, for this reason, the exposure to these cues is associated with the involvement of the so-called, "reward system", which seems to be activated in order to reach goals, incentives, awards. In this network, especially globus pallidus, nucleus accumbens and other regions seem to be strongly related to both attachment behavior and reward (Bartels and Zeki 2004, Northoff and Hayes 2011). Infant-related stimuli have been used in previous studies in different ways.

Both visual and acoustic exposure to infant-related stimuli seem to be a reliable strategy to investigate the neural basis of attachment behavior. Strathearn et al. (Strathearn, Li et al. 2008) exposed mothers to pictures of their own child and of an unknown child during an fMRI session, counterbalancing stimuli for the emotional valence (happy, sad neutral), suggesting that the view of pictures of their own babies elicited in mothers the activation of several cerebral loci and suggesting the implication of different systems in the attachment behavior. Consistently, the authors found widespread activations in limbic system (medial prefrontal cortex, anterior cingulate, insula), reward system (ventral striate, putamen, caudate head, ventral-tegmental area and substantia nigra) and key-areas for cognitive processing (dorsolateral prefrontal cortex). These data are coherent with the hypothesis that attachment behavior relies on different and multiple mental processes and that, while mothers are watching an emotion on their child's face, they need to operate an integration of all the information necessary to respond to that emotion (affective, cognitive, motivational). Particularly, the activation of key-areas for the dopaminergic release, such as substantia nigra and ventral-tegmental area, while watching happy faces suggests that the child's face could be, for his mother, a highly positive rewarding stimulus and could therefore activate dopaminergic pathways. Since previous studies on animals have demonstrated the relationship between dopaminergic release and positive maternal behaviors (Champagne, Chretien et al. 2004), it could be argued that a positive expression on the face of a child could induce in his mother a higher dopamine release and, therefore, increase the chance of a positive maternal behavior. Differences in terms of limbic system activation with respect to the attachment state of mind and to the attachment style, as measured by AAI, are also found in nulliparous women, suggesting that infant-related stimuli are relevant even in absence of parenting experiences. Lenzi et al. (Lenzi, Trentini et al. 2013) found that, while subjects were watching infant faces with the request of "empathize" with the babies, dismissing women exhibited greater activation of several limbic areas than secure women, while secure women showed an increase in the activation of fronto-medial areas, such as the medial orbito-frontal cortex. In dismissing women, the increase of activation in limbic areas could be interpreted as a sign of affective

dysregulation, while the decrease of activation in orbito-frontal cortex, which is tightly connected to reward areas (i.e., ventral striatum) and to the amygdala, and which is also considered a crucial area for emotion modulation and for reinforcing positive behaviors (Nitschke, Nelson et al. 2004), could be interpreted as the neural correlate of the typical emotion regulation style related to attachment avoidance, expressed in terms of a decreased capacity of emotion regulation. Orbito-frontal cortex activation, in fact, is tightly related to monetary and non-monetary reward (Breiter, Aharon et al. 2001), to positive experiences (Anderson, Christoff et al. 2003, O'Doherty, Kringelbach et al. 2001, Zalla, Koechlin et al. 2000), and to the exposure to positive attachment-related stimuli (Nitschke et al. 2004). Therefore, this seems to be a key-area for the detection of positive emotions (Rolls 2000), evidence points to the fact that secure subjects, who show greater orbito-frontal activation than insecure ones while watching positive emotions on infant faces, succeed more than insecure subjects in keeping track of positive moods of infants' faces. Future research should assess whether this ability is somewhat connected to maternal sensitivity, maternal care and higher quality of parenting.

Other studies have investigated the neurobiology of attachment behavior and attachment style using acoustic infant-related stimuli, especially infant cry. Infant cry seems to be a relevant type of stimulus because it elicits empathy and sensitive behaviors. For these reasons, it could be considered a fundamental variable in shaping the attachment bond. On the other hand, it also seems to elicit negative feelings, irritation, anger and stressful sensations (Dix 1991). Through the use of tasks based on infant cry stimuli, previous literature has demonstrated that perceived maternal care (assessed through the use of the PBI) could modulate neurobiological activation in response to infant cry: mothers who had high levels of perceived maternal care showed higher cortical activation (middle frontal gyrus, superior temporal gyrus), while subjects with low maternal care scores exhibited increased hippocampal activation (Kim, Trickett et al. 2011), suggesting that differences in retrospective maternal care could be found not only at a behavioral level, but also at a neurobiological level. A recent study by Riem et al. (Riem, Bakermans-Kranenburg et al. 2012) has enlarged and clarified these differences using adult attachment as measured by

the AAI in order to investigate potential differences in amygdala activation related to being exposed to infant cry. They found that insecurely (preoccupied and dismissing) attached individuals, when exposed to infant crying, had increased amygdala activation than secure subjects. Moreover, they tend to report greater levels of irritation when exposed to infant cry. Amygdala activation has been previously associated with negative emotions, such as anger and fear (Bertolino, Arciero et al. 2005, Blasi, Hariri et al. 2009) and its activation seems to be particularly elicited by maternal behaviors, especially in recognizing signals of alert and indicating the need of sensitive behaviors (Barrett, Wonch et al. 2012). Furthermore, this region seems to be tightly connected to several brain loci which are part of the reward network: previous studies have shown amygdala to be strongly interconnected especially to nucleus accumbens, in order to process the value of stimuli which come from the baby and with the objective of allocating or re-allocating the parent's attention and sensitivity in order to fulfill the child's needs (Numan and Woodside 2010). Some evidence has also suggested that amygdala hyperactivation is associated to several pathological conditions, especially with anxiety and stress-related disorders (Monk 2008, Stein, Goldin et al. 2002, Stein, Simmons et al. 2007).

On the other hand, previous studies have reported hypoactivation of the amygdala, especially when the studies involved people who have been exposed to trauma several times (Frewen and Lanius 2006, Lanius, Frewen et al. 2010), suggesting that this could be interpreted as a strategy of defense from the prolonged exposure to trauma (Bowlby 1988, Vanderlinden, Spinhoven et al. 1995).

Despite the fact that results from literature are not fully coherent and that amygdala has been reported as hyper or hypo-activated in insecure people and especially in people exposed to trauma, it could be argued that several stressful events occurred during life, such as stressful experiences related to the mother-child attachment relationship and trauma occurred in this relational context, could be reflected in abnormal activation of amygdala. Unresolved trauma in mothers, which could be experienced in a way which is close to Post-Traumatic Stress Disorder symptomatology (Lyons-Ruth 2008, Solomon and George 2011), could have serious and lifelong consequences that could be reflected in

forms of disorganized attachment in children. Similarly, the neurobiology of the brain could be influenced by a large series of factors, including stress and mood fluctuations. Taking into account that experiences of trauma in the context of attachment bond are often prolonged in exposure, early-onset and reflected in altered maternal sensitivity and responsiveness (Frewen and Lanius, 2006, Fonagy et al. 1995), it could be hypothesized that brain mechanisms are strongly influenced by environmental factors and that stressful experiences could modify and modulate the neurobiology of the brain. In a very recent study, Kim et al, (Kim, Fonagy et al. 2014) focused their attention on the neural correlates of trauma regarding insecure forms of attachment and abnormal familiar and personal relationships. Using the AAI in order to investigate unresolved/disorganized experiences of loss, abuse or trauma, subjects underwent a fMRI session while watching happy and sad infant faces which included faces of the mothers' own children. The authors found that mothers with unresolved/disorganized experiences, in the context of attachment system activation (while seeing their own babies' face when sad), exhibited decreased amygdala activation. This could be interpreted as a strategy of suppression of negative emotions generated by their infant's facial expressions of distress. Non-traumatized mothers, oppositely, showed greater amygdala activation than insecure mothers, confirming the key role of this area in responding to alerting signals, such as sad faces, and confirming that amygdala is a cerebral locus of strong interest in the context of the investigation of neurobiological modulations of adult attachment style. The decreased activity found in amygdala in traumatized mothers could be then interpreted as the neurobiological reflection of a series of behavioral coping strategies that these mothers use to protect themselves from re-experiencing negative feelings in the context of attachment (such as suppression of emotions).

All these studies have contributed to shed light on the neurobiological dynamics of adult attachment style and on the neurobiological correlates of attachment behaviors related to the exposure to emotions represented on infants' faces (known vs. unknown). However, research lacks in evidence elucidating whether the neurobiological differences related to the adult attachment style are potentially connected with infant-related output measures

and have influence on the intergenerational transmission of attachment security or insecurity, such as infant attachment style. At this point, there is only one study (Laurent and Ablow 2012) which directly investigated neural response of mothers while exposed to infant cry and the relationship between mothers' neural response and their infants' attachment style, in order to verify the existence of a neurobiological intergenerational transmission of attachment. The authors found that mother of infants with scores which pointed to attachment insecurity exhibited greater activation of key areas for emotion processing and regulation while exposed to infant cry, such as parahippocampal gyrus, ventral amygdala and posterior insula, suggesting that mothers of infants more likely to be classified as insecure tend to fail in deactivating some key-regions for cognitive emotion-related functions, and this strategy could reflect a tendency to be hyper-reactive (as witnessed by Amygdala hyperactivation) to stimuli belonging to their own infants.

3.1.2 The role of the genetics: the oxytocinergic system and its interaction with attachment style on emotion processing

The posterior pituitary neuropeptide hormone, oxytocin (OXT) is a well-recognized component of the complex biobehavioral system at the basis of mother-infant bonding (Ross and Young, 2009). Several studies have strongly elucidated that this hormone has a crucial role in the facilitation of positive maternal parenting, due to its capacity to influence estrogen and progesterone levels during pregnancy and labor (Champagne, Diorio et al. 2001, Champagne, Weaver et al. 2003, Champagne 2008, Rosenblatt, Olufowobi et al. 1998).

Studies on rats have in fact demonstrated that the inhibition of postpartum maternal behavior was facilitated by OXT antagonists injections (van Leengoed, Kerker et al. 1987) and that, on the other hand, OXT injections seemed to increase positive maternal behaviors (Pedersen and Prange 1979). Consistently, studies on humans have demonstrated that higher levels of OXT receptors were seen in brain regions implicated in the expression of maternal behaviors during pregnancy, parturition and while nursing, such as the central nucleus of amygdala and the hypothalamus (Champagne et al. 2001). Furthermore, other studies have elucidated that mother with higher levels of plasma OXT

reported higher maternal fetal attachment during the postpartum (Levine, Zagoory-Sharon et al. 2007) and had higher positive maternal postpartum behaviors, such as gaze, vocalizations, positive affect (Feldman et al. 2007) and higher synchrony with the signals expressed by the infant (Atzil, Hendler et al. 2011).

Interestingly, OXT has been examined also in relationship with mothers' attachment experiences: here, studies have demonstrated that higher plasma OXT were reported following mother-infant physical interactions in mothers reporting a secure attachment regarding their proper childhood experiences, when compared to those with an insecure attachment pattern (Strathearn, Fonagy et al. 2009). Furthermore, OXT levels have been positively correlated with self-reported experiences of positive maternal and parental care (Feldman, Zagoory-Sharon et al. 2012, Gordon, Zagoory-Sharon et al. 2008).

OXT seems also to be strongly involved in stress regulation, and literature fairly agrees that higher OXT seems to reduce stress and anxiety (Ayers, Missig et al. 2011, Ishak, Kahloon et al. 2011). Interestingly, studies revealed that the relation between OXT and stress seems to be potentially mediated by individual difficulties in interpersonal relationships (Tabak, McCullough et al. 2011), both with primary caregivers (Taylor, Gonzaga et al. 2006) and romantic partners (Marazziti, Dell'Osso et al. 2006). Here, authors found a positive relationship between plasma and urinary OXT and stress during social interactions, raising the hypothesis that OXT levels can be considered an index of the need to affiliate with others (Taylor, Saphire-Bernstein et al. 2010).

Research has also elucidated that OXT is strongly implicated in social skills, especially in emotion recognition (Melchers, Montag et al. 2013). OXT has been strongly associated with empathy, bonding, nurturing, altruism and prosocial behaviors both in animals and humans (Bosch 2011, Campbell 2008, Da Costa, Guevara-Guzman et al. 1996, Galbally, Lewis et al. 2011, Heinrichs, von Dawans et al. 2009). Accordingly, recent studies are consistent in revealing that intranasal OXT infusions can enhance the whole OXT activity in the central nervous system. This increased activity seems to be positively correlated with greater ability to recognize emotions on facial expressions (Domes, Heinrichs et al. 2007, Lischke, Berger et al. 2012, Schulze, Lischke et al. 2011, Van Ijzendoorn and

Bakermans-Kranenburg 2012). Moreover, intranasal OXT infusions seem to modulate brain activity in response to emotional faces (Kirsch, Esslinger et al. 2005). In this context, Atzil et al. (2011) presented to 28 mothers a video made of infant-mother interactions vignettes while they were laying still in the scanner. The interaction could involve both unfamiliar infants and their own infant. The maternal care style and sensitivity behavior were assessed through techniques of micro-codification of videos representing mother-child interactions conducted at home. On these basis, mothers could be classified as synchronous or intrusive (Feldman, Eidelman et al. 2004). Using venipuncture, in Atzil et al. study (2011) oxytocin levels were measured both for synchronous and intrusive mothers. Results indicated that synchronous mothers, while processing cues related to their own infant, had greater activation of the left nucleus accumbens than of the amygdala. On the other hand, intrusive mothers displayed hyperactivation of amygdala. Moreover, this group activated the nucleus accumbens to a lesser extent than the group of synchronous mothers. This reversed pattern of activation between synchronous and intrusive mothers could suggest that the processing of facial cues related to own children involves both cognitive and emotional abilities and, while in synchronous mothers this ability relies mostly on areas which are part of the reward network (supporting the hypothesis that reading ad interpreting correctly the signals expressed by the infant could be considered an ability which implies the reward - i.e., incentive, motivation - of having a baby whose needs are fulfilled), in intrusive mothers the hyperactivation of amygdala supports the hypothesis that a less-sensitive style of maternal care is reflected – at a neurobiological level – by the elicitation of a key area for anxiety and fear cues processing. Moreover, the authors found that in the synchronous mothers, the left nucleus accumbens is functionally connected to dorsomedial prefrontal cortex and subcallosal anterior cingulate cortex, which animal models have defined as areas involved in reward, motivation and incentivation processes (Lorberbaum, Newman et al. 2002), and which studies involving humans have demonstrated as areas strongly involved in the Theory of Mind processes (Gallagher and Frith 2003). In this context, synchronous mothers showed greater functional connectivity between amygdala and regions like insula, inferior frontal

gyrus and superior temporal gyrus, than intrusive mothers. These areas are known to be involved in cognition (Sidhu, Stretton et al. 2013), imitation (Chaminade, Leutcher et al. 2013) and interoceptive awareness (Ernst, Boker et al. 2014, Farb, Segal et al. 2013). These data about functional coupling between areas could be read in terms of a greater ability of the synchronous mothers to understand, recognize, read and respond to a wide variety of signals expressed on the baby's face. Mostly important, the authors found that oxytocin levels were correlated with nucleus accumbens and amygdala activation in the synchronous mothers. In fact, Shahrokh et al. (2010) indicated that OXT infusions in ventral tegmental area of rats were associated with an increase in dopamine levels in nucleus accumbens and with greater maternal behavior (Shahrokh, Zhang et al. 2010).

Taken together, these studies support the hypothesis that not only the reward system is crucially implicated in the attachment system and related behaviors, but also that its activation and functioning is in a tight relationship with the oxytocinergic system, linking in a strict bond of interdependence the three faces of maternal behavior: molecular, neurobiological and behavioral.

In subjects without offspring, studies are fairly consistent and revealed that the anxiolytic effect of OXT may be associated with the modulation of amygdala activation. fMRI studies in fact have elucidated that, in healthy male subjects, reduced amygdala activation was found after OXT infusions when fear-inducing visual stimuli (angry or frightened faces) had to be matched with an identical stimulus (Kirsch et al. 2005), while in the placebo condition subjects showed greater amygdala activation for fear-inducing stimuli.

Whether OXT reduces arousal or downregulates fear may be derived from experiments with positive emotional signals such as infant laughter. Healthy female adults (without offspring) listened in the fMRI scanner to brief episodes of infant laughter and scrambled control sounds (Riem, van et al. 2012). OXT infusions reduced amygdala activation when individuals listened to infant laughter compared with control sounds. In addition, OXT infusions increased functional connectivity between the amygdala and neural reward regions, the orbital frontal cortex and the caudal anterior cingulated cortex. Increased functional connectivity between the orbital frontal cortex, anterior cingulate cortex and

amygdala may enhance cognitive control over arousal and at the same time increase the incentive salience of infant laughter (Berridge 2007, Kringelbach 2005).

A more complicated picture emerged from a study on activation of different subregions of the amygdala to negative and positive stimuli. Participants were instructed to classify briefly presented negative (fearful), positive (happy) or neutral facial expressions as quickly and accurately as possible (Gamer and Buchel 2009). OXT decreased activity in lateral and dorsal regions of the anterior amygdala when viewing fearful faces, and stimulated activity in these parts in response to happy faces. OXT also increased the proportion of gaze changes toward the eyes across negative as well as positive expressions, and this effect was mediated by enhanced coupling between the posterior amygdala and superior colliculus. OXT might thus facilitate the detection of fear or happiness from subtle cues around the eyes (Bakermans-Kranenburg and van 2013).

Other studies revealed increased amygdala activation in female participants who watched fearful faces (Domes, Lischke et al. 2010) or threatening scenes (Lischke et al. 2012) after OXT administration. However, reduced amygdala activation in response to infant cry sounds has also been observed among female participants. Female twins, without children of their own and in good health, listened to a series of short cry bouts of varying pitch and to scrambled control sounds in the fMRI scanner, either after OXT administration or a placebo (Riem, Bakermans-Kranenburg et al. 2011). OXT administration was related to reduced right amygdala activation and enhanced insula and inferior frontal gyrus activation when exposed to infant crying compared with control sounds. This is particularly relevant since the insula is involved in the perception of the own infant's sad faces (Strathearn et al. 2009) and the inferior frontal gyrus has been associated with empathic prosodic comprehension. (Leitman, Wolf et al. 2011). Empathy has been found related with parental responsiveness to infant signals (Feldman, Weller et al. 2007). It is based on a neural simulation mechanism that is activated both when subjected to an emotion and when observing someone else experiencing the emotion, thus enabling humans to understand others' emotions (Gallese, Keysers et al. 2004, Iacoboni 2009). The insula and inferior frontal gyrus are suggested to have an important role in this simulation

process (Jabbi, Swart et al. 2007). Decreased amygdala activation might promote responsiveness to infant crying by preventing parents from being overwhelmed by anxious or aversive feelings. This fits well with findings of stress-reducing effects of OXT in lactating mothers (Heinrichs, Meinlschmidt et al. 2001, Heinrichs, Baumgartner et al. 2003).

Furthermore, childhood experiences may moderate the effect of intranasal OXT administrations on both behavior and neural activity. A wide variety of studies in fact demonstrated that the prosocial effects of OXT administrations are stronger or even limited to individuals who received support, care and comfort by caregivers during childhood (Bakermans-Kranenburg et al. 2013). In a double-blind, randomized controlled trial, Riem et al. (Riem, van et al. 2013) investigated OXT effects on prosocial behaviors, finding that the positive effects of OXT on prosocial behavior towards a victim of social exclusions during a ball-tossing game were limited to individuals with supportive family backgrounds. Furthermore, OXT increased the participants' willingness to donate money to charity but only in participants who experienced low levels of parental love-withdrawal (Van Ijzendoorn et al. 2012). In another study, authors (Bakermans-Kranenburg, van Ijzendoorn et al. 2012) tested the effect of intranasal OXT administration and experiences with harsh parental discipline during childhood on the use of excessive force in a parenting context, finding that participants'experiences with harsh parental discipline during childhood moderated the effect of OXT on the use of excessive force during exposure to infant crying: participants whose parents did not discipline harshly used less excessive force in the OXT conditions, but in subjects disciplined harshly there was no difference between the OXT and the placebo conditions.

All these studies indicate therefore that OXT administration does not generate positive effects in individuals who experienced unfavorable early caregiving, who therefore may have a bias towards negative interpretation of social cues (Bakermans-Kranenburg et al. 2013). As an alternative, untoward childhood experiences may interfere with the

oxytocinergic system on a more fundamental level, affecting for example the biological pathway of the OXT receptor (OXTR) gene.

3.1.2.1. The oxytocin receptor gene: modulation on social phenotypes, emotions, neurobiological variables and mental illness

An elegant method to demonstrate the role of OXT in shaping individual differences in emotion processing is the use of gene markers. The OXT receptor (OXTR) gene is located on chromosome 3p25, spans ~19 kbp and contains 4 exons and 3 introns. It is a 389-amino-acid polypeptide with 7 transmembrane domains belonging to the class I G-protein-coupled receptor family (Bartholomeusz, Ganella et al. 2015). Given the well-documented role of OXT in mammalian social behaviors, and the previously mentioned effects of OXT administration on social abilities in humans, it is perhaps not surprising that OXTR single nucleotide polymorphisms (SNPs) have been associated with a range of general social phenotypes in the healthy population, including emotional processing, empathy, reward dependence, prosocial behavior, positive affect, stress reactivity, moral judgement, theory of mind and global social cognition (Meyer-Lindenberg, Domes et al. 2011). The rationale of these studies consisted mainly in the goal of investigating risk for social cognitive and behavioral deficits and related psychiatric conditions (Cochran, Fallon et al. 2013). The strongest evidence supports OXTR polymorphisms as being significantly associated with risk for autism spectrum disorders and autistic traits (rs2268493, (Liu, Kawamura et al. 2010, Di Napoli, Warrier et al. 2014). However, variations in OXT SNPs rs4813625, rs4813626 and rs3761248 (Souza, Ismail et al. 2010, Teltsh, Kanyas-Sarner et al. 2012) and OXTR SNPs rs53576, rs237885 (Souza et al. 2010, Montag, Brockmann et al. 2013), have been linked to risk for schizophrenia.

With the aim of investigating whether and how OXT and OXTR may be involved in psychosis and schizophrenia risk, several studies have demonstrated that OXTR SNPs have been associated with symptoms severity of overall psychopathology (rs237885, rs237887), and general (rs53576, rs2254298), positive (rs11706648, rs4686301, rs237899) and negative (rs237902, rs2740204) symptoms in schizophrenia (Souza et al. 2010, Montag,

Brockmann et al. 2012, Montag, Brockmann et al. 2013). Davis et al. (2014) recently found the rs2268493 T-allele (one of 7 SNPs investigated) was associated with poorer social performance measured through a composite social cognition index, as well as on individual measures of theory of mind and social perception in schizophrenia. However, they failed to find any SNP association with symptomatology. This limited body of literature is highly variable and discrepancies are likely related to variation in participants' ancestry and sample size.

fMRI studies have therefore tried to investigate the potential modulatory role of OXTR SNPs on plausible neurobiological phenotypes of psychosis. The limited studies in this area have primarily focused on structural differences in social brain regions in healthy samples and in relation to OXTR risk variants for autism spectrum disorders using MRI (Zink and Meyer-Lindenberg 2012). In healthy samples, OXTR variants have been linked with differences in amygdala and anterior cingulated cortex volume, functional activation and connectivity of the amygdala and hypothalamus, among other neurobiological phenotypes. Studies in healthy participants also point towards potential intermediate functional phenotypes that link OXTR genotype with social cognition and emotion processing and, to a lesser extent, social behavior. For example, the rs53576 AA genotype has been associated with reduced amygdala activation during emotional face processing (Tost, Kolachana et al. 2010). As mentioned earlier, the amygdala is typically under-activated during such tasks in schizophrenia, thus it may be that higher A allelic load for this SNP is a contributing factor to this abnormal activation, especially given that the A allele of this SNP has been linked to risk for schizophrenia and general psychopathology (Bartholomeusz et al. 2015). A recent study in a large sample of healthy adolescents showed that variation in rs237915 had a significant effect on activation in the striatum, cingulate cortex, inferior frontal gyrus, thalamus and cerebellum during emotion processing of angry facial expressions (Loth, Poline et al. 2014). Moreover, Loth et al. (2014) not only found that C-allele homozygotes displayed lower ventral striatum activations compared to T allele carriers, but that this reduced emotion processing-related activity in C-allele homozygotes was significantly related to more social problems with

peers. Thus, putatively the rs237915 C-allele may be a significant risk biomarker, given that these same brain regions are structurally and functionally abnormal in schizophrenia, and that social-emotional disturbances are inherent to psychotic illness. These findings support therefore a model whereby OXTR variants, and to a lesser extent OXTR variants, could potentially moderate the relationship between social brain function and social cognitive/behavioral outcomes.

Interestingly, studies have revealed that attachment security may be modulated by OXTR rs53576 (Costa, Pini et al. 2009). Therefore, gene by environment (GxE) studies (Figure 3.3) appear to be promising in increasing the chance to identify new behavioral and neurobiological phenotypes of risk for mental disorders, as well as in testing candidate predictors of illness.

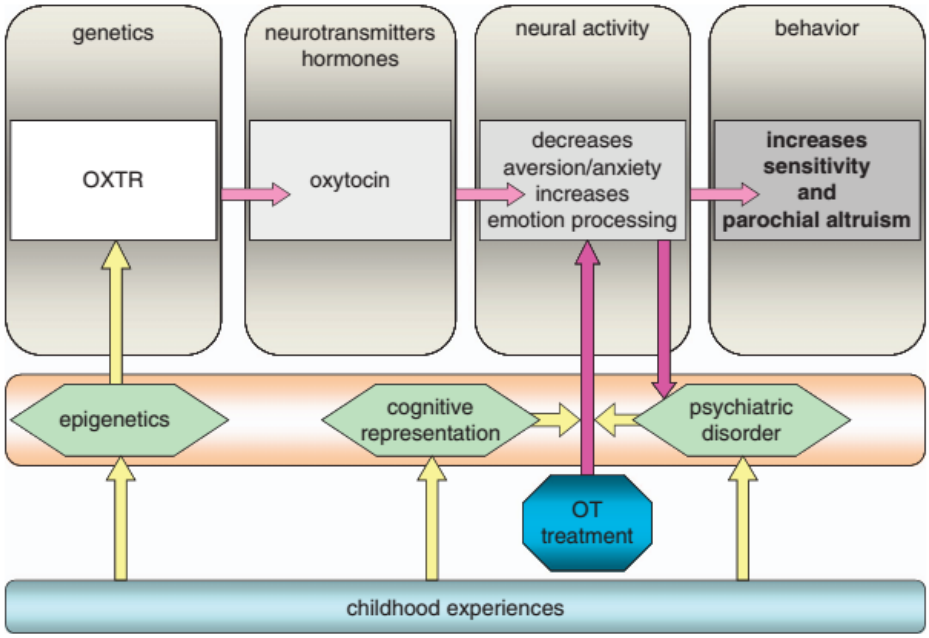

Figure 3.3: a neurobiological model of the OXT role in psychiatric disorders, modulated by childhood experiences (Bakermans-Kranenburg et al. 2013).

Results from animal and human studies have in fact demonstrated that the oxytocinergic system is shaped by early life experiences, especially in the context of the caregiver-infant interactions (Bales and Perkeybile 2012, Ross and Young 2009): studies in rats have

demonstrated that maternal care modulates long term OXTR expression in the amygdala and social behavior (Champagne 2011, Francis, Young et al. 2002, Lukas, Bredewold et al. 2010), thus accounting for an epigenetic effect of maternal care on gene expression (Schneider-Hassloff, Straube et al. 2016). Furthermore, child maltreatment has been associated with alterations in peripheral OXT levels and with OXT-induced modulations of functional connectivity between brain regions implicated in social cognition in and fMRI experiment (Riem, van et al. 2013). Interestingly, studies have demonstrated an interaction between OXTR rs53576 and childhood experiences (such as infant attachment security and child maltreatment) on emotion regulation and internalizing symptoms (Bradley, Westen et al. 2011, Hostinar, Cicchetti et al. 2014, Raby, Cicchetti et al. 2013). Furthermore, OXTR rs53576 GG subjects seemed to be susceptible to the quality of the childhood family environment (Bradley, Davis et al. 2013), differently from AA subjects. Therefore, OXTR genetic variations seem to interact with childhood experiences in modulation social phenotypes. To our knowledge, only one study has investigated the interaction effects of OXTR genetic variations and early environmental factors on social neural correlates. In this context, Schneider-Hassloff et al. (2016) found that, in healthy adult subjects, OXTR rs53576 interacts with childhood attachment security in modulating personality traits that are crucial for emotion processing and regulation, such as alexithymia. Furthermore, authors found that, in GG subjects but not in A-carriers subjects, insecure childhood attachment was associated with high attachment-related anxiety, higher brain gray matter volume of amygdala and lower superior parietal lobule and temporal pole volumes. Furthermore, they found that GG subjects with insecure childhood attachment had higher mentalizing-related neural activity in bilateral temporal pole, precuneus, middle and superior frontal gyrus. Therefore, these data suggest that OXTR rs53576 GG homozygotes subjects are more susceptible to childhood attachment experiences than subjects with other genotype combinations.

Other studies focused on the investigation of the OXTR rs2268493 genetic variation on behavioral and brain phenotypes which may be linked to psychiatric conditions. Specifically, Kawamura et al. (2011) found that a specific haplotype, comprising

rs62243370, rs62243369, rs13316193, rs2254298, rs2268493, and rs2268491 (GGTGTC, corrected p=0.0016) was associated with the attention switching autistic trait in healthy controls. Furthermore, Campbell et al. (2011) reported that rs2268493 modulated social phenotypes of autism spectrum disorders.

Furthermore, emerging evidence raises the necessity to understand whether and how this genetic variation is involved in the risk mechanisms of schizophrenia. In fact, Davis et al. (Davis, Green et al. 2014, Davis, Horan et al. 2014) found in patients with schizophrenia that the OXTR rs2268493 allele was significantly associated with poorer performance on a composite social cognition index, as well as specific tests of mentalizing and social perception, thus suggesting the possibility to test whether and how this genetic variant, interacting with other environmental factors, may be involved in the risk mechanisms of psychosis. This results, although preliminary, are significant due to the fact that psychosis spectrum disorders, especially schizophrenia, are often defined as "brain diseases" because of the strong neurodevelopmental hypotheses explaining their risk trajectories and defining their closest phenotypic correlates (Weinberger et al. 1987), and because it is well known that a large amount of the variance regarding the risk of developing psychotic disorders is attributable to genetic factors (Gottesman et al. 1987). These genetic factors may interact with environmental variables in determining an increase of susceptibility for psychosis. Therefore, gene by environment (GxE) studies appear to be promising in increasing the chance to identify new behavioral and neurobiological phenotypes of risk for mental disorders, as well as in testing candidate predictors of illness.

3.2 Goal of the project

- **AIM:** several studies have demonstrated that not only attachment security may be modulated by OXTR, but also that untoward childhood experiences may interfere with the oxytocinergic system affecting biological pathways (i.e., the OXTR system) which may have a potential role in the genetic trajectories of neurodevelopmental disorders, such as autism and schizophrenia. Therefore, the aim of the study is to investigate the potential interaction between perceived maternal care and OXTR rs2268493 (which has been previously associated with autisms spectrum disorders but also with social cognition and emotion regulation strategies in patients with schizophrenia) on behavior and brain activity of normal control subjects while they underwent a fMRI session in which they were asked to perform an explicit emotion processing paradigm.
- **EXPECTED RESULTS:** we expect to find a significant gene by environment interaction in key areas of the emotion processing and regulation system.

3.3 Materials and methods

3.3.1. Sample characteristics

This study included 166 healthy controls, whose demographic information are reported in Table 3.1. This sample is partially overlapping with the Study 1 sample. All subjects had undergone an extensive clinical interview in order to assess the absence of any psychiatric diagnosis through the Structured Clinical Interview for DSM-IV (First et al. 1996). Additional exclusion criteria were presence of head trauma with loss of consciousness, presence of any pharmacological treatment that could influence cerebral metabolism or blood flow, presence of any neurological or psychiatric disorder and of any other medical condition and history of significant drug or alcohol abuse (no active drug use in the past year). All subjects were given a complete description of the study and its procedures. Written informed consent was obtained only after full comprehension of the protocol.

	Whole sample (mean±SD)	OXTR rs2268493 TT (mean±SD)	OXTR rs2268493 Ccar (mean±SD)
N	166	87	79
Gender ratio (M/F)	80/86	41/46	39/40
Age	27.54±6.93	27.1±7.05	25.83±6.77
Socio-Economic Status	39.93±15.97	37.84±14.9	42.24±16.87
Handedness	0.74±0.4	0.76±0.37	0.71±0.44

Table 3.1: *demographic information of Study 3 sample.*

N=sample size; SD=Standard Deviation; Ccar=C carriers subjects. Age is reported in years.

3.3.2. Instruments

3.3.2.1.Evaluation of perceived maternal care

Perceived maternal care was measured using the Parental Bonding Instrument (PBI), which is based on the subjects'memories of their parents during the first 16 years of life (Parker et al. 1980). According to the principles of attachment theory, Parker (1980) posits that nurturing and parenting abilities may influence the quality of the mother-child relationship. The perception of a loving and emotionally close parent seems to favor the

development of a secure attachment in the child. On the other hand, a perceived cold and intrusive parent can lead to a problematic child development and to subsequent psychological disorders (George et al. 1985).

The PBI is a 25-item self-report questionnaire investigating two main dimensions, "care" and "overprotection". The "care" dimension reflects perceived parental warmth, affection, and involvement in contrast to coldness, indifference, and rejection. On the other hand, the "overprotection" dimension reflects perceived parental psychological control and intrusion in contrast to the encouragement of autonomy and independence. Subjects were asked to score their mother's attitudes using a 4-point scale.

In this study, we focused on the continuous scores of maternal care for analysis purposes.

3.3.3. Genotyping procedures

Participants underwent blood withdrawal for subsequent DNA extraction from peripheral blood mononuclear cells. To this aim, approximately 20ml of fresh blood was obtained through a conventional venous blood collection with 10ml EDTA Vacutainer Venous Blood Collection Glass Tubes (Vacutainer ®). Approximately 200 ng DNA was used for genotyping analysis. DNA was concentrated at 50ng/μl (diluted in 10 mM Tris/1mM EDTA) with a Nanodrop Spectrophotometer (ND-1000). We used Illumina HumanHap550K/610Quad Bead Chips (San Diego, California) to genotype our sample. Briefly, each 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 GenomeStudio (Illumina, v.2010.1) with cluster position files provided by Illumina, and fluorescence intensities were converted into OXTR rs2268493 genotypes. After genotypes were called and the pedigree file was assembled, we removed SNPs showing minor allele frequency <1%, genotype missing rate >5%, or deviation from Hardy-Weinberg equilibrium ($p<0.0001$). Individuals were also removed if their overall genotyping rate was

below 97%. Sample duplications and cryptic relatedness were ruled out through identity-by-state (IBS) analysis of genotype data.

3.3.4. fMRI procedures

3.3.4.1.Explicit emotion processing assessment: the FACES task

The event-related FACES fMRI paradigm (Blasi, Hariri et al. 2009, Blasi, Lo Bianco et al. 2009) consisted of the presentation of faces with angry, fearful, happy and neutral emotional expressions from a validated set of facial pictures (Tottenham, Tanaka et al. 2009). Subjects were instructed to decide whether they would "approach" or "avoid" the actor in the picture. Each stimulus was presented for 500 ms, with an interstimulus interval (ISI) randomly jittered between 2 s and 7 s. The order of facial emotional stimuli was pseudo-randomized across the session (Friston et al. 1999). The stimuli used were pictures of faces with four different expressions. In particular, the same 40 faces were presented with each of the expressions used. The total number of stimuli was 144: 30 angry, 39 fearful, 37 happy and 38 neutral faces. A fixation cross hair was presented during ISI. Total duration of the task was 6 min and 8 s.

3.3.4.2. fMRI acquisition parameters

Blood Oxygen Level Dependent (BOLD) fMRI was performed on a GE Signa 3T scanner (gradient echo-planar imaging sequence, TR/TE 2000/28 ms, 24 interleaved slices, thickness 4 mm, gap 1 mm, voxel size 3.75 x 3.75 x 5 mm, scan repetitions 180, flip angle 908, field of view 24 cm, matrix 64x64) while subjects performed the task. The first four scans were discarded to allow for signal saturation. Stimuli were presented via a back-projection system and responses were recorded through a fiber optic response box which allowed measurement of behavioral data as number of approached and avoided stimuli and reaction time (RT). fMRI responses were modeled using a canonical hemodynamic response function and temporally filtered using a high-pass filter of 128 Hz to minimize scanner drift.

3.3.4.3. fMRI data preprocessing pipeline

Analysis of the fMRI data were completed using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm). For each subject, images were realigned to the first

volume in the time series and movement parameters were extracted to check for excessive head motion (> 2 mm of translation, > 1.5° rotation). Images were then re-sampled to a 3.75 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. FMRI responses were modeled using a canonical hemodynamic response function (HRF) at each voxel. Vectors were created for approached and avoided stimuli, irrespectively of the emotion that individuals were exposed to. Residual movement was modeled as regressor of no interest. 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., approach and avoid stimuli versus fixation crosshairs.

3.3.5. Data analysis

The interaction between OXTR rs2268493 and PBI maternal care on behavior (respectively, approached and avoided number of responses and related RT) was tested through general regressions models in which OXTR rs2268493 was inserted as categorical predictor and PBI maternal care as continuous predictor. Age and gender were inserted in the models as nuisance covariates.

A flexible factorial model was performed through the software Statistical Parametric Mapping (SPM) 12. PBI maternal care was used as covariate of interest, while OXTR rs2268493 genotype (TT vs. Ccarrier - Ccar- subjects) was used as categorical between-subjects factor, and the explicit emotion processing (i.e., fMRI contrasts of the approach and the avoid conditions) was inserted as within factor. Age and gender were inserted in the statistical model as nuisance covariates, since genotypic groups differed significantly for age (see Results section) and since the majority of studies investigating OXT-related biological mechanisms recommend to control for gender (Rubin, Connelly et al. 2016). Blood Oxygen Level Dependent (BOLD) signal change arbitrary units, representing the change in activation and engagement of brain areas while performing a neuropsychological task, were extracted through Marsbar toolbox from significant clusters

in which a significant PBI x OXTR rs2268493 was present. Results were thresholded at $p<0.05$, Family-Wise Error (FWE) corrected for an activity mask obtained through the sum of the activated voxels in both the "approach" and the "avoid" conditions ($p<0.005$). To further characterize our results, Pearson's r correlation analyses were conducted to test the relationship between:

a. BOLD signal change arbitrary units of significant clusters and behavioral emotion processing indices (i.e., number of total approached stimuli and related reaction time (RT) and number of total avoided stimuli and related RT,
b. BOLD signal change arbitrary units of significant clusters and personality dimensions measured through the Temperament and Character Inventory (Cloninger et al. 1994) (respectively, Harm Avoidance and Novelty Seeking).

3.4. Results

3.4.1. Behavioral results

General regression models indicated the presence of a significant interaction between OXTR rs2268493 and PBI maternal care on:

4. Number of approached stimuli (R^2= 0.107, p=0.002, Figure 3.4/a),
5. Number of avoided stimuli (R^2= 0.102, p=0.003, Figure 3.4/b),

Analysis on approach and avoid RT revealed no significant results (p>0.05).

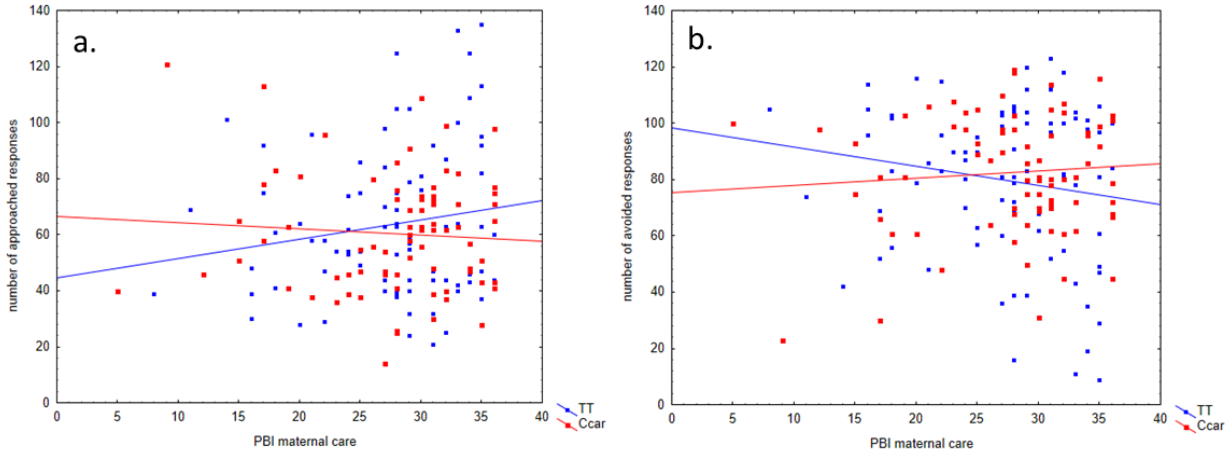

Figure 3.4: *scatterplots of the significant interaction between OXTR rs2268493 and PBI maternal care on (a) number of approached responses during the fMRI task, (b) number of avoided responses during the fMRI task.*

3.4.2. fMRI flexible factorial model results

fMRI results revealed a significant interaction between OXTR rs2268493 and PBI maternal care located in left thalamus (MNI coordinates x= 4, y= -7, z=-2, FWE corrected p= 0.029, Z=4.27, k=127, Figure 3.5/a). Replication of the statistical model performed through a general regression model in which the mean BOLD thalamic signal change between the approach and the avoid condition was inserted as dependent variable revealed a significant interaction between OXTR rs2268493 and PBI maternal care (p=0.008, Figure 3.5/b).

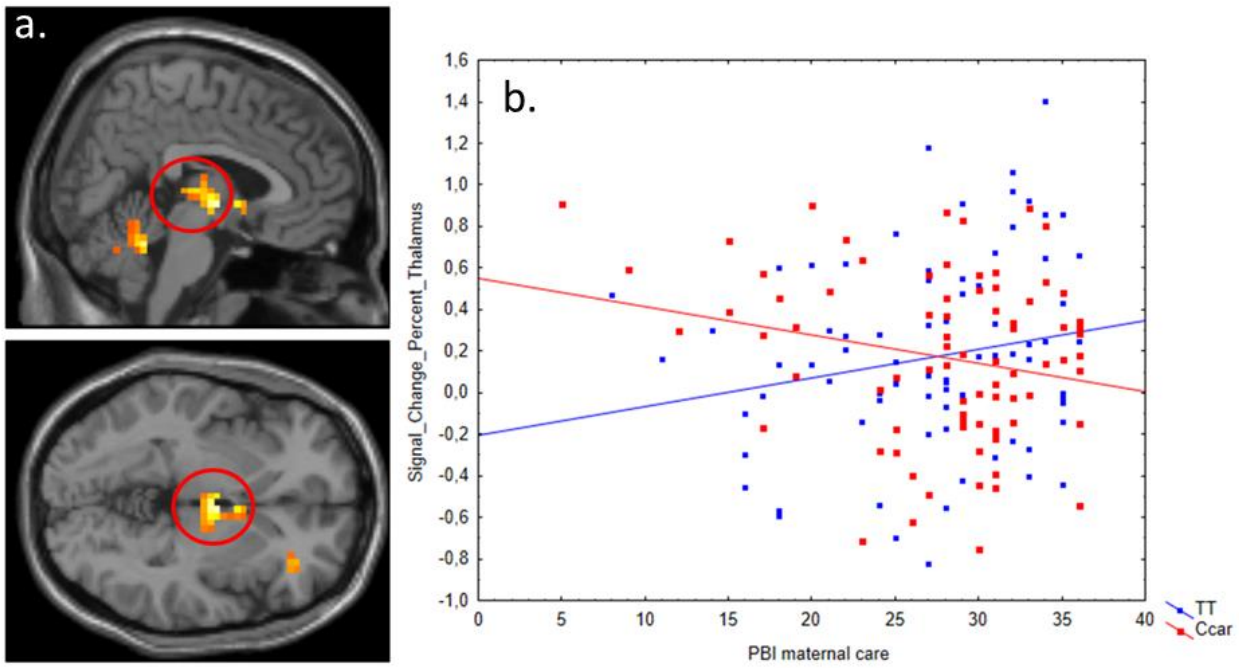

Figure 3.5: *(a) interaction between OXTR rs2268493 and PBI maternal care on brain activity during explicit emotion processing located in thalamus, (b) scatterplots of the significant interaction between OXTR rs2268493 and PBI maternal care on the mean BOLD signal change extracted from the cluster depicted in (a).*

3.4.3. Correlation analysis

Correlation analysis between BOLD signal change arbitrary units of significant clusters and behavioral emotion processing indices did not reveal any significant association (all $p>0.05$).

On the other hand, correlation analysis between TCI Harm Avoidance scale and BOLD thalamic signal change during the avoid condition revealed a negative association, statistically significant at a trend level, only in the OXTR rs2268493 Ccar group ($r= -0.2066$, $p=0.068$, Figure 3.6). Correlation analysis between BOLD thalamic signal change and TCI Novelty Seeking revealed no significant results ($p>0.05$).

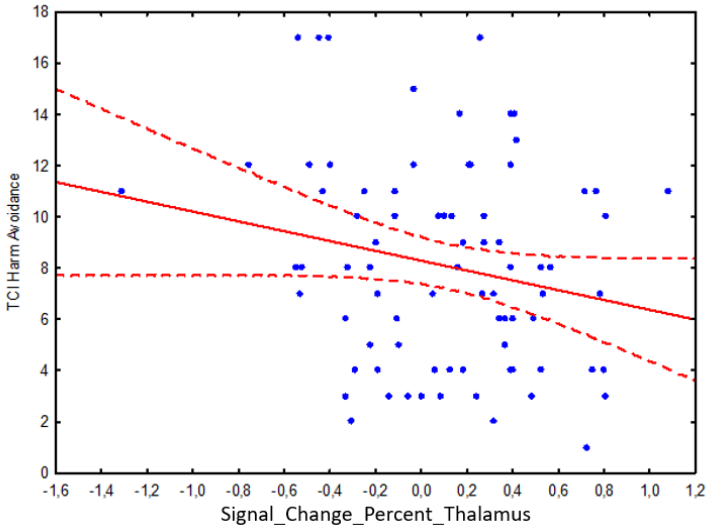

Figure 3.6 : *scatterplot of the relationship between BOLD thalamic signal change during the avoid condition and TCI Harm Avoidance in Ccar subjects.*

3.5. Discussion

Our Study 3 aimed to investigate the potential interaction between perceived maternal care and OXTR rs2268493 (which has been previously associated with social cognition and emotion regulation strategies in patients with schizophrenia) on behavior and brain activity of normal control subjects while they underwent a fMRI session in which they were asked to perform an explicit emotion processing task.

At a behavioral level, results revealed the presence of a significant interaction between OXTR rs2268493 and perceived maternal care, assessed through the PBI maternal care scores, on both number of approached and avoided stimuli. Specifically, in Ccar subjects the more the maternal care score, the less the number of approached stimuli (and the more the number of avoided stimuli) during the explicit emotion processing task. On the other hand, in TT subjects the relationship between the variables was opposite, that is, the more the maternal care score, the more the number of approached stimuli (and the less the number of avoided stimuli). As previously reported, OXT is involved in complex social behavior and social cognition in humans (Buchheim, Heinrichs et al. 2009, Tops, van Peer et al. 2007), in social memory (Bartz et al. 2011), emotion recognition (Shahrestani, Kemp et al. 2013) and mentalizing (Domes, Heinrichs et al. 2007). In this framework, our approach/avoid paradigm leads to test subjects'ability to modulate the behavioral and physiological response tendencies activated by emotional faces. Being able to approach positive and attractive stimuli and to avoid negative or punitive emotional stimuli or situations is a crucial aspect of the effective emotion process because it is a fundamental element in the ability to resist temptations or to face dangerous and difficult situations (Bamford, Broyd et al. 2015, Gross, Drummond et al. 2015). Our results suggest that OXTR rs2268493 seems to modulate the effect of maternal care on the emotion regulation strategies, therefore subjects carrying the OXTR rs2268493 allele and having low scores of perceived maternal care seem to be those who approach less and avoid more emotional stimuli, irrespectively of the emotion seen on the screen, thus suggesting that rs2268493 modulates emotion processing. This is in line with previous studies that found that

rs2268493 genotype modulates social functioning in autism spectrum disorders patients (Campbell, Datta et al. 2011, Yrigollen, Han et al. 2008) and with studies assessing that the quality of the parent-child relationship may shape the understanding of emotions (Cassidy, Parke et al. 1992). Our data therefore suggest that the pattern shown by TT subjects with low maternal care score may be interpreted as a specific pattern of hypervigilance to the vision of facial expressions, with no respect for their emotional valence, as shown by previous literature on subjects with attachment insecurity (Niedenthal, Brauer et al. 2002).

fMRI results revealed a statistically significant interaction between OXTR rs2268493 and perceived maternal care on brain activation during explicit emotion processing located in thalamus. In detail, OXTR rs2268493 genotype seems to modulate the relationship between perceived maternal care and thalamic signal change: while in Ccar subjects the relationship is negative (that is, the low the perceived maternal care, the more the thalamic activation during explicit emotion processing), in TT subjects the relationship is opposite (the low the perceived maternal care, the low the activation of thalamus during explicit emotion processing). Our data therefore suggest that TT subjects who perceived less maternal care during childhood exhibit hypo-activation of thalamus relative to the other three groups.

Our finding is in line with previous evidence testifying the key role of thalamus in emotion-attention processing (Sun, Perakyla et al. 2015), due to several thalamic sub-structures involved in the emotional pathways, such as the mammillothalamic tract (Mac 1949, Papez, 1937) and the pulvinar nucleus (Arend, Henik et al. 2015, Ward, Calder et al. 2007), which our cluster partially overlaps with. The pulvinar is hypothesized to mediate the processing of emotional information through the colliculo–pulvino–amygdalar pathway (LeDoux 2012, Morris, Ohman et al. 1999, Tamietto and Morrone 2016). It was further claimed that the pulvinar is not a passive relay nucleus but has an important role in coordinating multimodal signals and highlighting information that are significant to the individual (Padmala, Lim et al. 2010, Pessoa and Adolphs 2010, Pessoa, Padmala et al.

2012). Furthermore, the thalamus may play a key role in emotion recognition when subjects are exposed to facial expressions (Cheung, Lee et al. 2006) due also to single case studies demonstrating that patients with partial or total loss of one of the thalamic nuclei, such as the pulvinar, were impaired in emotional processing. These patients also showed deficits in other functions, such as response interference (selective attention) and eye movements to visual targets (Ward, Danziger et al. 2005, Ward, Calder et al. 2007).

Specifically,, the gene by environment interaction that we found located in thalamus suggests that OXTR rs2268493 genotype differentially influences the relationship between perceived maternal care and thalamic activation during emotion processing. Recent experimental findings on proximity seeking in adult attachment suggest that anxious individuals' motivation for closeness and intimacy is primarily operating in an automatic mode (Dewitte, De Houwer et al. 2008, Donges, Kugel et al. 2012). Therefore, our results are consistent with literature demonstrating that attachment avoidance and anxiety differentially modulated the brain response to masked sad faces, consistently with the idea that people who withdraw from close relationships respond spontaneously to a lesser extent to negative interpersonal emotional signals than securely attached individuals. Furthermore, brain imaging studies have correlated negative childhood experiences with changes in both task-related (Mueller, Maheu et al. 2010, Thomaes, Dorrepaal et al. 2012) and intrinsic brain activity (Bluhm, Williamson et al. 2009, McFarlane, Clark et al. 2005), finding significant alterations in cognitive function (Gould, Clarke et al. 2012, Majer, Nater et al. 2010), neuroendocrine stress responses (Carpenter, Shattuck et al. 2011), microstructural white matter (Lu, Wei et al. 2013), as well as resting state (Howells, Stein et al. 2012) and emotion-related (Dannlowski, Stuhrmann et al. 2012, Dannlowski, Kugel et al. 2013, Hentze, Walter et al. 2016) brain function in healthy humans. These results, together with our findings, suggest therefore that negative childhood experiences can predict changes in brain structure, function and behavior during adulthood.

Furthermore, the relationship between thalamic activation and perceived maternal care that we found matches the results of studies indicating that insecure attachment is

associated with increased suppression of negative feelings and dysregulated emotional response (Cassidy and Kobak 1988). Thalamic hypo or hyper-activation, therefore, may be interpreted as a mechanism of suppression of the valence of feelings that could emerge in the context of task performance (Roisman, Tsai et al. 2004).

This relationship may be clarified by the examination of the role of the OXTR rs2268493 genotype in shaping the PBI – thalamic activation relationship. OXTR rs2268493 is included in intron 3 of OXTR and it localizes 5930 bp upstream of the intron 3-exon 4 splice junction. Functional annotation indicates that this genetic variation alters six different transcription factor-binding sites (Di Napoli, Warrier et al. 2014). Specifically, Di Napoli et al. (2014) found that OXTR rs2268493 is significantly associated with Asperger Syndrome in a Caucasian sample, and found OXTR rs2268493 to be located in five haplotypes associated with Asperger Syndrome (Bonferroni corrected).

Moreover, rs2268493 and haplotypes that include this variant have been reported to be associated with autism spectrum disorders in earlier reports (Campbell, Datta et al. 2011, Yrigollen, Han et al. 2008). OXTR has four splice variants and three of them are protein-coding, one transcript includes four exons and three introns, another variant is composed of the first three exons (1, 2 and 3) and introns 1 and 2, and the other two variants include exon 1, intron 1 and part of exon 2. Genetic variations that disrupt regulatory regions can affect gene expression in a time- and tissue-specific manner. Molecular studies are needed to understand this further.

While the biological and functional mechanisms of OXTR rs2268493 are still unknown, studies have focused their attention on understanding the implications of genetic variations of this SNP on behavioral and brain phenotypes. Kawamura et al. (2011) found that a specific haplotype, comprising rs62243370, rs62243369, rs13316193, rs2254298, rs2268493, and rs2268491 (GGTGTC, corrected $p = 0.0016$) was associated with the attention switching autistic trait in healthy controls. In this haplotype, the T allele (which is in our study associated with a positive relationship between maternal care and thalamic activation) was associated with excessive attention switching, consistently with another

study (Campbell et al. 2011) which reported that rs2268493 modulated social phenotypes of autism spectrum disorders. Interesting, in another report (Ayaz, Karkucak et al. 2015) children with Attention Deficit/Hyperactivity Disorder (ADHD) and normal controls were compared in order to test social functioning according to the polymorphism of three oxytocin receptor (OXTR) genes (rs53576, rs13316193, and rs2268493). Results revealed that the allele distribution of the OXTR gene SNP rs2268493 was significantly different in the ADHD group, compared to the control group.

Only one study has investigated the effect of OXTR rs2268493 on fMRI phenotypes. Here (Damiano, Aloi et al. 2014) the authors found that T homozygotes of the rs2268493 SNP demonstrated relatively decreased activation in mesolimbic reward circuitry (including the nucleus accumbens, amygdala, insula, thalamus and prefrontal cortical regions) during the anticipation of reward, while allelic variation of the rs1042778 and rs237887 SNPs did not moderate mesolimbic activation during reward processing. Here authors suggest that, in light of these results, OXT and mesolimbic dopamine systems may act reciprocally and become linked through early social experiences (Baskerville and Douglas 2010, Melis, Melis et al. 2007, Shahrokh, Zhang et al. 2010, Smeltzer, Curtis et al. 2006).

Our results therefore are consistent with previous literature, revealing that early social experiences of maternal care, interacting with a genetic variant of OXTR, modulate key areas for explicit emotion processing. However, only few studies have been conducted in order to understand the role of rs2268493 on brain and behavior emotion-related phenotypes, and future studies are warranted in order to understand the biological functioning of this SNP.

It is important to note that, while some studies point to the fact that OXTR rs2268493 may be involved in the pathophysiology of autism spectrum disorder (Campbell et al. 2011, Di Napoli et al. 2014), emerging evidence raises the necessity to understand whether and how this genetic variation is involved in the risk mechanisms of schizophrenia. In fact, Davis et al. (Davis, Green et al. 2014, Davis, Horan et al. 2014) found in patients with schizophrenia that the OXTR rs2268493 allele was significantly associated with poorer performance on a

composite social cognition index, as well as in specific tests of mentalizing and social perception. As stated before, the genetic mechanism by which rs2268493 variants could affect social cognitive processes is not known, but it is possible that this variant alters OXTR expression. In this context, differences in regional OXTR expression density have been found to affect the processing of social information and affiliative behaviors in animals (Ross and Young 2009).

These results and implications are of particular interest, in the light also of the results of Study 1 and 2 of the current project, due to the fact that literature fairly agrees on the fact that clinical features such as psychosis, mood dysregulation and cognitive impairments transcend diagnostic categories. Doubt remains about the boundaries between the syndromes and the degree to which they signify entirely distinct entities, disorders that have overlapping foundations, or different variants of one underlying disease (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Such debates have intensified especially for what concerns the overlapping between schizophrenia and autism spectrum disorders. Autism was once known as childhood schizophrenia and the two disorders were not clearly differentiated until the 1970s. Findings from the past few years have emphasized phenotypic and genetic overlap between autism spectrum disorders and schizophrenia (King and Lord 2011, Rapoport, Chavez et al. 2009, Rapoport 2009), including identification of copy number variants conferring risk of both (Levinson, Duan et al. 2011).

Therefore, future studies are warranted to understand how OXTR rs2268493, which has been previously associated with autism spectrum disorders, may be implicated in the pathophysiology of schizophrenia, also by the investigation of schizophrenia-related brain and behavior phenotypes. In this framework, our results may confirm that OXTR rs2268493, in interaction with perceived maternal care, modulates the activation of a region whose altered connectivity was found to be linked with familial risk for schizophrenia. In fact, in our previous study (Antonucci et al. 2016), we found that both patients with schizophrenia and their unaffected siblings exhibited thalamic hypo-

connectivity within an attentional control network when compared to normal controls. For this reason, we may hypothesize that OXTR rs2268493, together with maternal care, modulates a key brain phenotype for schizophrenia.

Future directions

Following the prevention-based framework of the entire current project, which is to understand whether and how early attachment experiences may shape risk for psychosis by influencing personality traits (Study 1), parenting abilities (Study 2) and brain activity during emotion processing (Study3), future research should investigate whether and how OXTR rs2268493, together with childhood attachment experiences which may also involve the investigation of maltreatment and trauma experiences, may modulate brain and behavior psychosis-related phenotypes in subject at risk mental state for the disorder, who are experiencing the prodromal phase but without fully manifesting the full blown schizophrenia symptomatology (Yung et al. 2005). Furthermore, machine learning prediction analysis may be informative of whether and how the genetic and environmental factors here investigated, alone or in combination with each other or with other risk factors, may predict the transition to psychosis from the prodromal phase. This type of analysis would provide relevant information about the amount of risk for psychosis that each variable explains, giving therefore intriguing novel insight about (a) potential new target genes involved in the biologic mechanisms of psychosis, and (b) potential new target variables to be considered when planning psychoeducative, psychoterapic and familiar interventions in young people with psychosis or at risk for the disease.

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