The Neurobiology of Attachment and Psychosis Risk – A Theoretical Integration

Benjamin K. Brent, MD, MS[1], Martin Debbané[2,3,4], Ph.D., Peter Fonagy, FmedSci, Ph.D.[3]

[1] The Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, U.S.A., [2] Developmental Clinical Psychology Research Unit, Faculty of Psychology and Educational Sciences, University of Geneva, Switzerland [3] Research Department of Clinical, Educational and Health Psychology, University College London, United Kingdom, [4] Office Médico-Pédagogique Research Unit, Department of Psychiatry, University of Geneva School of Medicine, Switzerland

Correspondence should be addressed to: Benjamin K. Brent, M.D., Massachusetts General Hospital, Freedom Trail Clinic, 25 Staniford Street-2nd Floor, Boston, MA 02114. E-mail: bbrent@partners.org

Introduction

The last decade has witnessed a significant growth of research and clinical interest in understanding how the vicissitudes of attachment relationships may play a part in the development and course of psychotic-spectrum disorders (Berry, Barrowclough, & Wearden, 2007; B. K. Brent, Holt, Keshavan, Seidman, & Fonagy, 2014). This has been motivated by several considerations. First, there is a large body of evidence suggesting that childhood adversity broadly speaking (i.e., exposure to stressors such as living in an urban environment, or minority group status) is an indicator of psychosis risk (van Os, Kenis, & Rutten, 2010). Second, several studies have shown that dysfunction specific to the childhood caregiving environment (e.g., aberrant relationships with caregivers and trauma) confers greater vulnerability to psychosis (Cannon et al., 2002; Jones, Rodgers, Murray, & Marmot, 1994; Wahlberg et al., 1997). Third, recent studies have linked attachment insecurity with increased symptom levels and poorer social function in people with a diagnosis of schizophrenia (Berry, Barrowclough, & Wearden, 2008; Gumley, Taylor, Schwannauer, & MacBeth, 2014).

Importantly, attachment insecurity is viewed not as a causal variable in the etiology of psychotic-spectrum disorder, but rather as an environmental risk factor that likely interacts with an underlying genetic diathesis to potentiate psychosis risk (B. K. Brent & Fonagy 2014). The hypothesis that attachment could modulate the expression of the genetic vulnerability to psychosis is consistent with evidence from animal research showing that the quality of the caregiving environment can influence gene expression and, as a result, the development of behavioral patterns and biological systems (Sullivan, 2012). The goal of this chapter is to discuss possible interactions between disruptions in the neurobiology of attachment and psychosis.

Determining the biological mechanisms linking attachment disturbances to psychosis may be critical for refining predictions about the effects of the attachment environment on the pre-psychosis development of youth at risk for psychotic disorders. It may also contribute to the development of treatment interventions that could help prevent, or delay psychosis onset in at-risk youth, and/or to improve clinical outcomes among people with established psychotic-spectrum diagnoses. We begin by reviewing the neural underpinnings of the attachment system. This is followed by a discussion of how disruptions within the neural circuitry mediating attachment might interact with the neurobiology of the symptoms and social cognitive deficits associated with a psychotic-spectrum diagnosis. Finally, we consider some of the therapeutic implications of the neurobiological interconnections between disturbances of the attachment system and the phenomenology of psychotic disorders.

Neurobiology of Attachment

An extensive body of animal research has provided considerable insight into the neural basis of attachment-related behavior (e.g., social bonding, affiliation, or caregiving). A comprehensive review of the neural circuitry implicated in attachment is beyond the scope of this chapter. Here, we highlight evidence supporting the involvement of three key neural systems in attachment-related behavior: the oxytocinergic/arginine vasopressinergic, dopaminergic, and hypothalamic-pituitary-adrenal (HPA) stress-response systems.

Oxytocinergic/Arginine Vasopressinergic System

Oxytocin and arginine vasopressin (AVP) are neuropeptide hormones/neurotransmitters synthesized primarily in the paraventricular and supraoptic nuclei of the hypothalamus and

stored in the pituitary. Animal studies suggest that the oxytocinergic/AVP neural circuitry comprises several central brain areas, including the ventral striatum (nucleus accumbens [NAcc]), ventral tegmental area (VTA), medial preoptic area, and the bed nucleus of the stria terminalis (Strathearn, 2011). The role of oxytocin and AVP in the attachment-related behavior of rodents (e.g., the formation of adult attachment [pair bonding] and caregiving behavior) has been particularly well studied. Experiments in prairie voles (small rodents indigenous to North America), for example, have shown that intracerebral oxytocin and/or AVP infusion can induce partner preference in the absence of prior mating (a key facilitator in partner bonding in voles) (Young, Liu, & Wang, 2008).

Consistent with these findings, studies in humans link peripheral measures of oxytocin to a wide range of mental processes that foster social affiliation (e.g., social perception, social cognition, social memory) (Sobrian & Holson, 2011), as well as to maternal and paternal bonding behaviors (e.g., greater closeness and warmth during parent-infant interactions) (Gordon, Martin, Feldman, & Leckman, 2011). For one example, Gordon and colleagues have shown that increased levels of peripheral oxytocin predicted greater physical proximity and affectionate touch between parents and their first child at six month of age (Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010). The role of AVP in caregiving and other social behavior has been less studied, but initial research in humans also parallels findings in the animal literature (Sobrian & Holson, 2011). Intranasal AVP administration, for example, has been linked with increased social cooperation in men (Rilling et al., 2012), and variance in the AVP receptor is associated with the likelihood of monogamy and marital satisfaction in males (Walum et al., 2008). Additionally, as reviewed by Strathearn (Strathearn, 2011), neuroimaging studies have shown: 1) engagement of oxytocin-

associated neural circuitry during attachment-related processing (e.g., mothers' responses to hearing their infant's cries); 2) reduced levels of oxytocin in adulthood in association with deficits in the childhood caregiving environment (e.g., emotional neglect and maltreatment); and 3) aberrant activation of oxytocinergic-related brain regions in response to infantile attachment-seeking behavior in insecurely attached mothers.

Dopaminergic System

Animal research has also provided a strong empirical basis for linking attachment-related behavior to the dopamine (DA) mesocorticolimbic reward system – a neural system that includes the VTA, NAcc, and prefrontal cortex (PFC). In particular, it has been suggested that mesocorticolimbic DA may mediate the motivational drive necessary for the initiation and maintenance of caregiving and affiliative behaviors (Insel, 2003). For example, activation of DA receptors in the NAcc has been implicated in the facilitation of maternal behaviors in rats, while infusion of DA antagonists in the NAcc of postpartum rats has been linked with the disruption of pup retrieval (i.e., maternal rodent behavior that involves locating and bringing back newborn pups who have strayed from the litter) (Stoesz, Hare, & Snow, 2013). Notably, disruption of the early caregiving environment in rodents (e.g., maternal separation) is also associated with long-term, chronic dysfunction of the DA system; such as, increased DA levels and greater DA release in response to stress in adulthood (Strathearn, 2011).

Consistent with research in animals, fMRI studies in humans have demonstrated the engagement of DA reward circuitry during maternal responses to infant stimuli (e.g, viewing photographs of one's own baby), suggesting its role in caregiving behavior (Strathearn, 2011). Further, several

fMRI studies have linked neural activity in the mesolimbic DA reward circuitry with love between romantic partners (for review see: (Strathearn, 2011)). Bartels and Zeki, as well as Aron and colleagues, have shown in separate studies that people who are in love demonstrate increased activation of DA-rich brain areas (e.g., VTA and anterior cingulate gryus) when viewing pictures of their beloved (Aron et al., 2005; Bartels & Zeki, 2004). Taken together with the evidence from animal studies, these findings are thought to support the role of the dopaminergic reward system in human attachment (Gordon et al., 2011).

HPA Stress-Response System

Animal research has identified the HPA stress-response system as a third key contributor to the neurobiology of attachment. Psychological, or physiological stress triggers the release of stress hormones (corticotrophic-releasing hormone [CRH] and AVP) from the paraventricular nucleus of the hypothalamus into the hypophyseal portal system where they then stimulate the anterior pituitary gland to release adrenocorticotrophin hormone (ACTH) into the bloodstream. ACTH travels to the adrenal cortex, initiating the release of glucocorticoids (cortisol, in humans). Under normal conditions, cortisol facilitates adaptive responses to stress while also exerting an inhibitory effect on the stress-response system via a negative feedback mechanism.

Several lines of evidence implicate HPA axis activity in the development and maintenance of attachment bonds. For example, in male prairie voles, the enhancement of partner bond formation has been associated with stimulation of CRH receptors in the NAcc (a central brain area in the mesolimbic DA reward circuitry as described above) (Lim et al., 2007). Further, HPA axis activation in response to stress in rodents may mediate the association between depressive-

like behavioral symptoms and attachment loss (Burkett & Young, 2012). By pairing an aversive state with the disruption of attachment relationships, HPA axis activity may provide an important neurobiological basis for the motivation to re-establish attachment bonds after separation and, thus, to maintain attachment bonds over time. Additionally, studies in rats have shown that while rat pups' exposure to prolonged maternal separation is associated with elevation of corticosterone (the rodent equivalent of cortisol), the presence of the mother suppresses corticosterone levels in rat pups during social stress ("social buffering") (Johnson & Young, 2015). Conversely, disturbances of the early care environment of rodents have been linked with long-term HPA axis system dysfunction and chronically elevated corticosterone levels (Sullivan, 2012).

In humans, a growing number of studies have shown associations between HPA axis activity and attachment-related behavior (e.g., romantic love, development of adult attachment, and maternal caregiving) (Gordon et al., 2011). For example, maternal behavior and infant responsiveness (Fleming, Steiner, & Corter, 1997) have been linked with increased levels of HPA-associated cortisol release, as has the initial phase of pair bonding (falling in love) (Marazziti & Canale, 2004). Additionally, reviews of the literature suggest that while a sensitive caregiving environment is associated with adaptive responses to stress and may help protect the HPA axis during early development, childhood maltreatment is consistently correlated with HPA axis dysfunction (Nemeroff, 2004; Toth, Gravener-Davis, Guild, & Cicchetti, 2013).

Disruptions of the Attachment System and the Neurobiology of Psychotic Disorders

Clearly, alterations of the neurobiology of attachment cannot be sufficient to cause psychosis, as disturbances of the attachment system are implicated in many other psychiatric disorders, particularly borderline personality disorder (Fonagy & Luyten, 2009). Nevertheless, growing evidence supports several plausible interactions between disturbances of the neural systems mediating attachment and positive symptoms (e.g., delusions, hallucinations), negative symptoms (e.g., asociality, affective blunting), and social cognitive impairments (e.g., theory of mind [ToM]) in people diagnostic criteria for schizophrenia. Below, we highlight some of these putative interactions.

Positive Symptoms

The notion that dysregulation of striatal DA plays a central role in the positive symptoms of schizophrenia and related psychotic disorders is broadly supported by over four decades of research (Howes & Kapur, 2009). According to contemporary neurodevelopmental models, the abnormal function of striatal DA gives rise to a vulnerability to positive symptoms that is initially held in check, or modulated, because of relatively intact PFC inhibitory control over subcortical (striatal) DA (Keshavan, 1999). During adolescence, however, aberrant synaptic pruning may lead to excessive cortical (PFC) gray matter loss and, consequently, to subcortical disinhibition (Keshavan, 1999). In conjunction with heightened social stress, the erosion of PFC inhibitory control over striatal DA could then lead to the emergence of positive symptoms.

How might disturbances of the neurobiology of attachment contribute to the emergence of positive symptoms? As described above, animal studies have shown that disruption of the early attachment environment (e.g., maternal separation) is associated with persistently elevated DA

levels and heightened DA release during stress (Strathearn, 2011). Dysregulation of striatal DA, however, could be additionally affected by depletion of available oxytocin and over-activation of the HPA axis system, which both have been associated with a dysfunctional early care environment. Oxytocin, for example, has been shown to have a modulatory effect on excessive mesolimbic DA in rodents receiving psychostimulants, leading to the suggestion that oxytocin may have intrinsic antipsychotic properties (Rich & Caldwell, 2015). Additionally, over-activation of the HPA axis has been associated with elevated DA synthesis and alterations of striatal DA receptors (Walker & Diforio, 1997). We suggest that, taken together, early neurobiological alterations of the attachment system could increase the likelihood that a premorbid susceptibility to striatal DA dysregulation and, therefore, increase the risk of psychosis during later adolescent/early adult development.

Negative Symptoms

Alterations of a number of different brain areas involved in social and emotional processing, such as PFC and amygdala, have been implicated in the neurobiology of negative symptoms (i.e., asociality, anhedonia, avolition, alogia, and blunted affect) (Millan, Fone, Steckler, & Horan, 2014). For example, it is thought that elevated striatal DA may induce reductions in PFC function and, thus, social deficits, as a result of indirect communications from the striatum to the PFC by way of the thalamus (Fusar-Poli et al., 2011). This view is in part based on animal studies showing that excessive striatal DA can lead to deficits of PFC DA activity in conjunction with behavioral inflexibility (Kellendonk et al., 2006). Evidence that the level of striatal DA is negatively correlated with PFC activation in prodromal individuals (Fusar-Poli et al., 2011)

further supports the possibility that the neurobiology of positive symptoms (excessive striatal DA) and negative symptoms (reduced PFC DA; "hypofrontality") may be inter-related.

An alternative (though not mutually exclusive) model, however, suggests that overactivity of the amygdala may generate inappropriate responses (e.g., heightened fear and anxiety) to neutral, or benign social stimuli and, thus, mediate the asocial dimension of negative symptoms in schizophrenia (Sobota, Mihara, Forrest, Featherstone, & Siegel, 2015). Consistent with this model, animal studies in rats have shown that phencyclidine (PCP)-induced amygdylar hyperactivity is associated with significant disruptions of socially interactive behavior (Katayama et al., 2009). Further, neuroimaging studies in people with a schizophrenia diagnosis have demonstrated that increased amygdylar activity is associated with aberrant responses to social and emotional stimuli (Holt et al., 2006; Satterthwaite et al., 2010).

Based on these findings, alterations of the neural system mediating attachment could contribute to both hypofrontal and hyperamygdylar pathways to negative symptoms. First, as previously discussed, disturbances of the early attachment environment may lead to chronic dysfunction of striatal DA, and, thus, indirectly, to impairments of social functioning, given the potential contribution of elevated striatal DA to reductions in PFC DA function. Rodent research, for example, has showed that adult rats exposed to disruptions in their early maternal care environment exhibit aberrant social behavior and increased anxiety that is similar to negative symptoms (Rich & Caldwell, 2015).

Additionally, however, the oxytocinergic system is densely interconnected with the amygdala and is thought to exert much of its "prosocial" effects by way of dampening down amygdylar activity (Sobota et al., 2015). Attachment-related alterations of the oxytocinergic system (oxytocin depletion) could, therefore, lead to a greater likelihood of amygdylar overactivation during social interactions and, consequently, greater social inhibition and anxiety. Suggestive evidence along these lines comes from a study of rats, in which PCP-induced negative-symptom-like social deficits were reversed by injection of oxytocin into the central nucleus of the amygdala (Lee, Brady, Shapiro, Dorsa, & Koenig, 2005). Implicitly, therefore, attachment-related alterations of oxytocinergic regulation over amygdalar activity could contribute to an increased vulnerability to negative symptoms.

Social Cognition

Impaired social cognition – i.e., the capacity to perceive, interpret, and respond to the behavior of other people – is recognized as a distinct component of the phenomenology of schizophrenia and related psychotic-spectrum disorders (Mehta et al., 2013). Here, we focus on one aspect of social cognitive dysfunction associted with psychosis that may be closely tied to the quality of attachment relationships; namely, mentalization – i.e., the ability to think about states of mind in the self and others. Mounting evidence suggests that mentalization deficits (most commonly measured via ToM tasks) confer vulnerability to psychosis and may be among the earliest indicators of the risk for developing a psychotic disorder (for review see (B. K. Brent, Seidman, Thermenos, Holt, & Keshavan, 2014).

Numerous functional neuroimaging studies in healthy subjects have shown that the retrieval of information about the self and/or other people engages a neural system that includes cortical midlines structures ([CMS]; i.e., medial PFC (MPFC) and posterior cingulate cortex [PCC]), as well as parts of the lateral temporal cortex ([LTC]; e.g., superior temporal gyrus [STG]) (for review see: (B. K. Brent, Seidman, Coombs, et al., 2014). These same brain areas show increased activity when people are not engaged in any goal-directed tasks – i.e., during the so-called resting state. In people with a schizophrenia diagnosis, fMRI studies have shown aberrant engagement of CMS and/or LTC structures during mentalizing tasks, as well as abnormal functional connectivity of CMS during the resting state (Bosia, Riccaboni, & Poletti, 2012). These findings suggest that mentalization deficits associated with psychosis may be mediated by an overall change in the coordinated function of this network of CMS and LTC brain areas.

A significant body of evidence links the development of self and other understanding with the quality of attachment relationships (Dykas & Cassidy, 2011). Evidence exists for the link between attachment security and mentalizing in infants (Laranjo, Bernier, Meins, & Carlson, 2014) and pre-adolescent children (Harris, de Rosnay, & Pons, 2005). Further, many studies support the suggestion that secure children are better than insecure children at mentalization tasks (see, e.g., de Rosnay & Harris, 2002). Additionally, maltreated children have shown delays in the successful acquisition of basic ToM abilities (Cicchetti, Rogosch, Maughan, Toth, & Bruce, 2003; Pears & Fisher, 2005a), and studies suggest that the capacity to discern complex and emotionally charged representations of the parent and of the self may even deteriorate with development (Toth, Cicchetti, Macfie, Maughan, & VanMeenen, 2000).

A growing body of evidence indicates that childhood maltreatment can have a negative impact on several aspects of developing social-cognitive capacities, including: less symbolic and child-initiated dyadic play (Valentino, Cicchetti, Toth, & Rogosch, 2011), failing to show empathy when witnessing distress in other children (Klimes-Dougan & Kistner, 1990), and fewer references to internal states (Shipman & Zeman, 1999). Findings concerning significant developmental delay in the emotional understanding of maltreated young children are quite consistent (Pears & Fisher, 2005b), if somewhat reduced when controlling for IQ and socioeconomic status (Smith & Walden, 1999). Further, a comprehensive, systematic review (Macintosh, 2013) lends support to the assumption that mentalizing mediates the relationship between attachment and/or adversity and adult functioning. However, more research is clearly needed in this area, as we do not fully understand the nature of mentalizing deficits associated with childhood maltreatment. Regardless of the specific mechanism, if the maltreatment is perpetrated by a family member, it can contribute to an acquired partial "mind-blindness" (i.e., the inability to understand mental states in the self and/or others) by compromising open, reflective communication between parent and child. Maltreatment may also undermine the benefit derived from learning about the links between internal states and actions in attachment relationships (e.g., the child is told that he/she "deserves", "wants", or even "enjoys" the abuse). In such a situation the child finds that reflective discourse does not correspond to his/her feelings, a consistent misunderstanding that could reduce the child's ability to understand and mentalize verbal explanations of other people's actions.

Somewhat paradoxically, activation of the attachment system (e.g., during exposure to physical or psychological threat) is thought to have an inhibitory, deactivating effect on the mentalizing

network, as heightened emotional arousal associated with the engagement of the attachment system could disrupt the function of the higher cortical brain areas (MPFC, PCC, STG) within the mentalizing network (Fonagy & Luyten, 2009). The functioning of the oxytocin system, however, provides an obvious account for the replicated association between attachment security and the development of mentalization competencies (Heinrichs, von Dawans, & Domes, 2009). Oxytocin facilitates empathic facial recognition and in-group trust (Bakermans-Kranenburg & van, 2013); it also increases perceived salience of social cues (Shamay-Tsoory et al., 2009) and improves empathic accuracy in less socially skilled individuals (Bartz et al., 2010). Further, by enhancing activity in the insula and inferior frontal gyrus, oxytocin improves understanding of others' emotions, and it reduces anxiety by decreasing amygdalar activity, facilitating contingent responses of help and compassion (Bakermans-Kranenburg & van, 2013). A secure attachment, therefore, may function to optimize the balance between engagement of the attachment and mentalizing neural systems, leading to the eventual ability to keep mentalizing online during relational stress and to integrate attachment needs with appropriate social judgment and socio-emotional understanding.

Alternatively, in the setting of attachment insecurity, underlying disruption of regulatory controls over stress and/or emotional arousal may lead to imbalance, or dyscoordination of the attachment and mentalizing systems (Fonagy & Luyten, 2009). Attachment history may moderate the effects of oxytocin as well as the setting of the "switch" that turns the mentalizing system from planned, controlled, and organized cognition to automatic processing with narrowed, poorly sustained attention, and increased vigilance for attachment disruptions such as rejection and abandonment (Cullen et al., 2011). This is in line with our previous suggestion that secure

attachment requires the simultaneous (and paradoxical) activation of components that are normally reciprocally activated – mentalizing and reward-salience associated regions of the brain (Fonagy & Bateman, 2006). These observations are also in line with the assumption that secure attachment consists of a combination of low anxiety and low avoidance. Avoidant attachment may reflect a maladaptive attempt to regulate attachment-related anxiety through prolonged deactivation of the attachment system in conjunction with hyperactivation of the mentalizing network. Anxious resistant attachment, in which anxiety may be regulated through repeated efforts to maintain physical proximity to an attachment figure, could involve repeated hyperactivation of the attachment system together with hypoactivation of the mentalizing network.

These proposed interactions between the functioning of the neural systems mediating attachment and mentalization remain to be empirically tested in children. However, neuroimaging studies have shown that post-traumatic stress disorder (PTSD) in adults is associated with altered resting-state functional connectivity of key nodes within the mentalizing network (e.g., MPFC and PCC) (Bluhm et al., 2009; Sripada et al., 2012). These findings in PTSD, though indirect and correlational, support the possibility that significant stress exposure could link dysregulation of anxiety and emotional distress (as is thought also to occur in an insecure attachment) with dysfunction of the mentalizing network. In the context of an underlying psychosis diathesis, attachment-related stress and poor modulation of subcortical brain areas associated with emotional arousal could predict dysfunction of the mentalizing system and heightened vulnerability to impairments of self and other understanding during early development.

Therapeutic Implications

Several therapeutic implications follow from the foregoing considerations. First, as discussed above, attachment-related alterations in the oxytocinergic system could contribute to dysregulation of striatal DA and amygdalar activity, both of which are implicated in the symptoms and social cognitive impairments associated with psychotic disorders. Pharmacotherapy with oxytocin, therefore, may offer a promising approach to reducing the symptoms and social disability in people with psychosis. Indeed, over the last decade a growing number of clinical trials of intranasal oxytocin administration in schizophrenia have shown reductions in positive and negative symptoms, and improvements in socio-emotional processing (K. Macdonald & Feifel, 2012).

Second, there is mounting case-report evidence that psychotherapeutic treatments that target mentalizing deficits within attachment-related contexts could contribute to improvements in social functioning in people diagnosed with schizophrenia (e.g., mentalization-based treatment for psychosis (B. Brent, 2009), metacognitive psychotherapy (Lysaker et al., 2010), and compassion focused psychotherapy (Braehler & Schwannauer, 2012). The neural mechanisms that might be facilitated by these psychotherapeutic approaches are not known. However, one recent study has shown that people with a diagnosis of schizophrenia who completed a six-month-long cognitive training program that included mentalizing exercises exhibited significant recovery of social function in conjunction with improvement in MPFC activation during a reality monitoring task (Subramaniam et al., 2012). One possibility is that psychotherapies that focus on engaging the mentalizing system during relational stress could enhance PFC function and (eventually) the capacity to manage anxiety/negative social stimuli, given the role of the PFC in

modulating subcortical (e.g., amygdalar) activity. These psychotherapeutic interventions, therefore, may provide a valuable additional approach to the improvement of interpersonal relatedness among people with a diagnosis of schizophrenia.

Third, although we focused on the possible negative effects of insecure attachment, it is equally possible that attachment security could have a protective effect with respect to psychosis risk. By facilitating the regulation of striatal DA, HPA axis, and amygdalar activity, and fostering mentalization, secure attachment could attenuate the likelihood that an underlying vulnerability for psychosis will become expressed. A large body of evidence suggests that secure attachment is an important resilience factor in childhood mental health, protecting the developing brain against the potentially adverse effects of psychological stress and negative social experience (Schore, 2001). Youth at familial high-risk (FHR) for schizophrenia (i.e., offspring of a parent with a schizophrenia diagnosis) may be particularly likely to benefit from early interventions that foster sensitive caregiving. Research suggests, for example, that mothers with a diagnosis of schizophrenia frequently struggle with the demands of parenting and that FHR youth are at increased risk not only for receiving a schizophrenia diagnosis, but also for a wide range of poor developmental outcomes (Gearing, Alonzo, & Marinelli, 2012). However, there is also evidence that a healthy parent-child relationship, social support during adolescence, or the presence of a positive relationship with a highly-involved non-patient parent can help prevent the risk of a poor developmental course (Gearing et al., 2012). Home-based interventions to foster attachment security in mothers-infant dyads (e.g., Minding the Baby®) have shown promising initial results in young, first-time mothers in terms of the development of more sensitive parenting and less externalizing behaviors in children during the first three years of life (Ordway et al., 2014; Sadler

et al., 2013). Whether similar interventions could be successfully adapted to aid mothers with a diagnosis of schizophrenia with the challenges of parenting, however, remains to be tested.

Conclusion

In this chapter, we reviewed the evidence supporting interactions between alterations of the neural system mediating attachment and the neurobiology of psychosis-spectrum disorders. Preclinical and human studies linking attachment insecurity with dysfunction of the mesocorticolimbic DA, oxytocinergic, and HPA axis systems suggest that attachment-related disturbances in childhood could potentiate the vulnerability to positive symptoms, negative symptoms, and social cognitive impairments in the context of a psychosis diathesis. Several valuable clinical interventions could follow from the potential interconnections between disturbances of the neural systems mediating attachment and psychosis, such as: 1) pharmacotherapy with oxytocin to reduce symptoms and social deficits among people diagnosed with a psychotic disorder; 2) psychotherapies that target deficits of mentalization within attachment contexts to bolster resilience to social stress and foster the recovery of interpersonal relatedness; and 3) family-based interventions to address disturbances in parent-child interactions in genetic high-risk youth that could facilitate greater caregiver sensitivity and attenuate the risk of poor developmental outcomes.

Significant evidence implicates genetic factors in the etiology of developing a schizophrenia diagnosis (approximately 40%-60% of the liability to a schizophrenia diagnosis is estimated to be owing to genes (A. W. MacDonald & Schulz, 2009)). Further, structural and functional alterations of the same brain areas involved in attachment-related behavior are commonly found

in people with psychosis (B. K. Brent, Thermenos, Keshavan, & Seidman, 2013). Thus, the possibility cannot be excluded that the relationship between attachment disturbances and schizophrenia could be epiphenomenal – i.e., a byproduct of genetically-mediated dysmaturational processes that are thought to be part of the pathoetiology of schizophrenia. Nevertheless, there is increasing recognition that environmental risk factors (particularly those related to the early social environment, such as childhood adversity (Varese et al., 2012), while not sufficient to cause the symptoms of schizophrenia, may interact with susceptibility genes to heighten psychosis risk (van Os et al., 2010). Future longitudinal research in high-risk youth, however, is needed to determine the extent to which the attachment environment is associated with the structural/functional development of brain areas mediating the key symptoms and social dysfunction associated with psychotic disorders and to examine interactive effects of attachment on the trajectory of psychosis risk.

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