Neurobiology of Disorganized Attachment: A Review of Primary Studies on Human Beings

Neuroscience Insights
Volume 18: 1–10
© The Author(s) 2023
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/26331055221145681

Marcelo Arancibia[1], Mariane Lutz[1], Álvaro Ardiles[1,2,3] and Camila Fuentes[4]

[1]Interdisciplinary Centre for Health Studies (CIESAL), School of Medicine, Faculty of Medicine, Universidad de Valparaíso, Viña del Mar, Chile. [2]Synaptopathy Lab, School of Medicine, Faculty of Medicine, Universidad de Valparaíso, Valparaíso, Chile. [3]Centro Interdisciplinario de Neurociencias de Valparaíso (CINV), Faculty of Sciences, Universidad de Valparaíso, Valparaíso, Chile. [4]Faculty of Sciences, Universidad de Valparaíso, Valparaíso, Chile.

ABSTRACT: This article describes and analyzes various aspects related to the neurobiology of disorganized attachment (DA), which is associated with personality, eating, affective, dissociative, and addictive disorders. We included primary studies in humans, published in PubMed from 2000 to 2022. Eight genetic and one epigenetic study were considered. Three molecular studies describe possible roles of oxytocin and cortisol, seven neurophysiological studies investigated functional correlates, and five morphological studies describe anatomical changes. Findings in candidate genes involved in dopaminergic, serotonergic, and oxytonergic systems have not been able to be replicated in large-scale human studies. Alterations in the functioning of cortisol and oxytocin are preliminary. Neurophysiological studies show changes in subcortical structures (mainly in the hippocampus) and occipital, temporal, parietal, and insular cortices. Since there is a lack of robust evidence on the neurobiology of DA in humans, the possible inferences of these studies are preliminary, which restricts their translation to clinical parameters.

KEYWORDS: Neurobiology, neurophysiology, review, psychology

RECEIVED: May 25, 2022. **ACCEPTED:** November 28, 2022.

TYPE: Review

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Marcelo Arancibia, Interdisciplinary Centre for Health Studies (CIESAL), School of Medicine, Faculty of Medicine, Universidad de Valparaíso, Angamos 655, Viña del Mar, Valparaíso 2540064, Chile. Email: marcelo.arancibiame@uv.cl

Significance Statement

- Candidate genes refer mainly to variants in the dopaminergic, serotonergic, and oxytonergic systems. However, studies have failed in demonstrating consistent results regarding disorganized attachment (DA) and are currently being replaced by the polygenic risk scores approach.
- At the molecular level, findings on the hypothalamic-pituitary-adrenal axis are preliminary.
- fMRI studies have shown that amygdala, hippocampus, prefrontal and anterior cingulate cortices, and temporal sulcus would be involved in DA.
- Structural findings would demonstrate changes in hippocampal volume.
- Available evidence still lacks robustness to draw clear conclusions about the neurobiology of DA with clinical application.

Introduction

Adverse and favorable early experiences in the life cycle, even from intrauterine life, exert an impact on neurobiological development and, therefore, on the psychological and psychopathological development of children and adults. These observations were collected early by authors such as Bowlby,[1] who developed the attachment theory and then evaluated it under experimental conditions in both animal and human models. Initially, attachment was classified according to different categories inferred indirectly from physiological and behavioral changes.[2] These categories included secure attachment, insecure anxious-ambivalent and insecure-avoidant attachment. Subsequently, Main et al[3,4] introduced a new classification of infantile attachment, which considered organized (the one that includes the aforementioned forms) and disorganized attachment (DA), also known as disoriented or unresolved, which collects characteristics of anxious-ambivalent and insecure attachment. Children with DA show a series of strange, disoriented, and openly contradictory behaviors in the presence of their parents, who become both a source of comfort and alarm.[5] As a consequence, in stressful episodes, the need to approach the parents in search of comfort and to flee from them because of fear coexists in these children.[6] Disorientation can be expressed through angry feelings or unexpected crying after being calm, which denotes an alteration of emotional regulation in general. The theory proposes that the attachment style patterns that children establish with their primary caregivers can be maintained throughout adult life, fluctuating according to lived experiences, and established relationships. In this sense, in adults who established DA, contradictory tendencies may be evident, such as the desire for proximity together with actions of withdrawal and avoidance,[6] and their interpersonal relationships are usually unstable and chaotic. In summary, child development includes mental schemes of response and relationships with the environment and with others, that persist to a significant degree in adult life. These processes would involve deep brain structures that contribute to preconscious emotional responses.[7]

In the fields of psychology and psychiatry, attachment study methods aim to measure its behavioral, cognitive, affective, and physiological repercussions and associations, which adds up to a high level of complexity, related to the heterogeneity of existing approaches and definitions. There are different instruments for the assessment of attachment. Among the most commonly used are the Strange Situation Method (SSM),[8] a laboratory procedure to study the mother-child relationship during the first year of life, the Adult Attachment Interview (AAI),[4] which evaluates the memories an adult has of their relationships with the attachment figures in childhood, and the Adult Attachment Projective Picture System (AAP),[9] which measures the representation of adult attachment based on the narrative analysis of a set of seven standardized images of attachment scenes. Attachment styles have been characterized as both protective and risk factors for mental health. DA has been associated with personality disorders with borderline and antisocial patterns,[10,11] affective, addictive, eating[12] and dissociative disorders,[13] among others. Although the biological basis of attachment styles has been of great interest to research over the past few years, the greatest concern has been received by organized patterns of attachment. Due to the relevance of DA in the constitution of child and adult psychopathology, this review synthesizes and analyzes studies in humans that investigate the neurobiology of DA.

Materials and Methods

A narrative review was carried out around the neurobiological bases of the DA. We included primary articles in humans, published in PubMed from 2000 to March 2022, without language restriction. Narrative reviews were excluded. The search algorithm ((attachment[tiab]) AND (neur*[tiab])) was used. As a secondary search method, we checked the references of the included articles.

Results

We obtained 6804 articles, from which we selected 24 primary studies with humans. Table 1 summarizes the included studies, classified into the categories of genetic, molecular, and neurophysiology studies (Figure 1).

Genetic Studies

We included eight genetic studies and one epigenetic study. The *DRD4* gene exhibits a diversity that results from the presence of single nucleotide polymorphisms (SNPs), among others. Two functional variants have been analyzed: one of 7 repetitions (7R) or long, and one of 4 repetitions (4R) or short. Lakatos et al[14] established an association between these two variants and the predisposition to DA. The results show that the presence of at least one of the alleles of the *DRD4-7R* variant was found in 71% (n = 12) of the study population with AD versus 29% (n = 21) without AD. Further analysis for the same sample of participants verified that the presence of two alleles of the *DRD4* gene produces a significant increase in DA.[15] However, Graffi et al[16] found that children without the *DRD4-7R* allele presented more frequently with DA, so the authors postulate that it would act as a protective factor. The same authors[17] constructed a multivariate model of gene-environment interaction, corroborating that the presence of the *DRD4-7R* allele was associated with a lower frequency of DA. This type of attachment was also associated with maternal depression and mothers who frequently looked away from the newborn. Wazana et al[18] studied maternal sensitivity to the newborn evaluating mother-child interaction behavior, by measuring its frequency and duration. In particular, the study covers the interaction between two environmental risk factors: maternal sensitivity and birth weight, with the *DRD4-7R* since both relate to DA at 36 months of age. The authors describe a negative association between the presence of *DRD4-7R* and AD, a result that again suggests a protective effect of this allele. On the other hand, Luijk et al[19] analyzed the effects of the interaction of genetic variants of dopaminergic (*DRD4* 48 bp VNTR, *DRD2* rs1800497 and *COMT* Val158Met rs4680), serotonergic (*HTTLPR*) and oxytonergic systems (*OXTR* rs53576 and rs2254298) with parental quality on attachment (NICHD Study of Early Child Care and Youth Development—SECCYD). The authors found no consistent additive genetic associations but did verify that carriers of the *COMT* Val/Met genotype exhibited higher levels of disorganization. Consistently, Leerkes et al[20] did not find significant effects of different variants of *DRD2, DRD4, COMT, 5HTTLPR*, and *OXTR* on levels of disorganization in a sample of 200 infants, using additive, dominant, and homozygous models. Finally, in the seminal article by Roisman et al,[21] the aforementioned findings are confirmed; based on the data from the SECCYD, as well as the study by Luijk et al,[19] in which the authors showed that the effect of dopaminergic, serotonergic, and oxytonergic gene variants on infant attachment security and disorganization was not significant.

During gestation, gene expression is regulated by environmental conditions, through prenatal epigenetic modifications that can affect susceptibility or resilience to future neuropsychiatric conditions. Garg et al[22] evaluated the relationship between genome-wide methylation patterns and attachment at 36 months of age. By comparing by attachment style (secure vs disorganized), the authors established significant differences in the methylation patterns of promoter regions associated with genes coding for glucocorticoid receptor (eg, *NR3C1*), estrogen (eg, *ESR1*), and glucocorticoid signaling (such as *SKG, FKBP5*, and *POMC*).

Molecular Studies

We selected three studies, which focus on oxytocin and cortisol. In the first of them, Bergman et al[23] measured the levels of cortisol in blood and amniotic fluid in pregnant women and the child development of their children between 14 and 19 months of age. Additionally, they analyzed the type of

Table 1. Synthesis of the included studies.

STUDY	PARTICIPANTS	ATTACHMENT INSTRUMENT	METHODOLOGY	MAIN RESULTS
Genetic studies				
Lakatos[14]	52 boys, 38 girls 12-13 mo (n = 90)	SSM	Genotypification by PCR (Exon III *DRD4* 48 pb).	17 participants with DA and 73 without DA. 71% with DA had at least one *DRD4-7R* allele vs 29% without DA. Estimated relative risk of DA in children with the allele was 4.15.
Lakatos[15]	Children 12-13 mo (n = 95)	SSM	Genotypification by PCR (Exon III *DRD4* 48 pb and SNP-521 CT).	With two risk alleles, odds ratio for DA increased 10 times.
Graffi[16]	Mother-child dyads (n = 251)	SSM	Effect of birth weight and genotype *DRD4-7R* on development of DA in children at 36 mo of age.	Birth weight did not affect attachment style. Genotype: children lacking the 7E allele would be more protected of developing DA.
Graffi[17]	Mother-child dyads (n = 655)	SSM	*DRD4* genotype was classified according to the presence of 7R, considering birth weight, maternal depression, maternal attention, interaction, and attachment.	Presence of *DRD4-7R* is associated with less DA. Women with depression and frequent gaze-aloof behavior generated higher probability of DA.
Wazana[18]	Mother-child dyads (n = 650)	SSM	Possible bi- and tridirectional SNP interactions of presence of *DRD4-7R*, birth weight and early mother care (6 mo) to predict DA at 36 mo of age. Maternal behavior: video record (20 min of mother-child interaction). Style of attachment at 36 mo of age.	Interaction of birth weight and frequency of maternal attention al 6 mo predicted DA in logistic regression methods adjusted for socio-demographic variables. Children in the middle range of birth weight were more prone to DA with lesser maternal attention. The association was reverted with extreme birth weights (low and high). *DRD4-7R* was associated with non-DA (protective). Children lacking *DRD4-7R*: higher probability of DA classification.
Garg[22]	Newborn and 36 mo (n = 226)	SSM	Complete genome methylation and genetic variations. Association of attachment style with cognitive and behavioral development at 36 mo of age. Cognitive development according to Bayley Scale.	Attachment style: moderated the effects of prenatal adverse environmental conditions at 36 mo of age. Principal components analysis: direct association between attachment type and variations in DNA methylome. Effects were more evident comparing children with secure attachment vs DA, and more pronounced in girls. The attachment style predicted the cognitive development and behavior of children under stressing stimuli.
Luijk et al[19]	Individuals participating in two studies (n~1000): 1.Generation R Study (GenR); a prospective cohort study investigating development from fetal life into young adulthood (Netherlands) 2. The NICHD Study of Early Child Care and Youth Development (SECCYD); a prospective study following children from birth to 17.5 yof age (US)	SSM	GenR: DNA from cord blood samples at birth; SECCYD: DNA from buccal cheek cells at 15 y of age. n = 506-n = 547 for specific SNPs and VNTRs.	In both cohort studies, no consistent evidence emerged for additive effects of candidate genes putatively involved in attachment security and disorganization. Carriers of the *COMT* Val/Met genotype had higher levels of disorganization.
Leerkes et al[20]	Infants; assessments at 1 and 2 y of age (n = 200)	SSM	DNA genotyping: saliva samples from children during a subsequent 2 y laboratory visit.	No significant two-way interactions between candidate genes and maternal sensitivity were identified when predicting disorganization. No significant interactions between candidate genes and overtly negative maternal behavior were identified when predicting attachment security or disorganization.
Roisman[21]	The NICHD Study of Early Child Care and Youth Development (SECCYD); a prospective study following children from birth to 17.5 y of age (US) (n = 674)	SSM	DNA from buccal cheek cells at 15 y of age.	The average effect of "usual suspect" polymorphisms on infant attachment security and disorganization is approximately zero.

(Continued)

Table 1. (Continued)

STUDY	PARTICIPANTS	ATTACHMENT INSTRUMENT	METHODOLOGY	MAIN RESULTS
Molecular studies				
Bergman[23]	Mother-child dyads (n = 125)	SSM	Prospective study of mothers and children with normal development from pregnancy until 17 mo. Samples of amniotic fluid and blood at 17.2 gestation wks; analysis of cortisol levels. Children: evaluated at 17 mo of age with Bayley Scale.	Prenatal exposure to cortisol predicts negatively the cognitive capacity of the newborn, independently of prenatal, obstetrical and socio-economic factors. The association is moderated by mother-child attachment. Insecure attachment: significative reduction of cognitive capacity. Secure attachment: no association.
Luijk et al[24]	GenR Study: Mother-child dyads (n = 369)	SSM	Attachment assessment and saliva samples at 14 mo of age.	DA infants had a more flattened slope of the diurnal rhythm than non-DA children.
Pierrehumbert[25]	Adults (n = 74)	AAI	Influence of type of attachment on subjective endocrine response patterns to stress in 28 community adults and 46 adults sensitive to stress, by exposition to childhood or adolescence trauma. Trier test (experimental psychosocial challenge). Cortisol level in saliva and plasma ACTH and oxytocin before, during and after the procedure.	The response to stress relates with the attachment style. Subjects with secure attachment: relatively low stress, moderate response of HPA axis (ACTH and cortisol), high oxytocin levels. Subjects with avoiding attachment: high subjective stress, HPA response is blocked, moderate levels of oxytocin.
Neurophysiological studies				
Buchheim[26]	Adult women (n = 11)	AAP	The test was applied (7 drawings stimulating attachment system) in healthy adult women while measuring fMRI, and a subjective assessment questionnaire for anxiety.	Five women presented DA. Only women with DA exhibited higher activation of the temporal medial regions, including the amygdala and the hippocampus.
Buchheim[27]	Adult women (n = 28, 11 borderline personality disorder, 17 healthy or control)	AAP	Difference in narrative and neuronal responses to monadic images (characters challenged by attachment threats alone) and dyadic images (interaction between characters within an attachment context).	Borderline personality disorder—monadic images: higher activation of the anterior cingulate cortex—Dyadic images: higher activation of the right superior temporal cliff and less activation of the right para-hippocampus gyrus.
Petrowski[28]	Healthy adults, 21-71 y of age (n = 38)	AAP	Aggrupation according to attachment type: secure (n = 14), insecure (n = 15), and DA (n = 9). Images showing faces of attachment figures (romantic couple or parents) and unknown subjects were shown; neural response measured by fMRI.	Secure attachment: higher activity in left cerebellum/ vermis, left inferior parietal lobule, left superior temporal gyrus, right anterior/media cingulated cortex, left insula, compared to subjects with DA. Insecure attachment: higher activity in right inferior frontal gyrus, left inferior parietal lobule, right putamen and right cingulated medial cortex.
Moutsiana[29]	Newborns at 18 mo and 22 y of age (n = 59)	SSM	Impact of maternal postpartum depression on infant development. Attachment state of the infant (24 with secure attachment, 35 with insecure attachment, including DA) at 18 mo of age. The fMRI evaluations were completed at 22 y of age.	Insecure children attachment (including DA) was associated with higher volumes of amygdala in young adults, effect that is not explained by maternal depression. The early infant attachment state did not predict hippocampal volumes.
Biro[30]	Follow-up of children at 10 and 12 mo of age (n = 70)	SSM	EEG of children in front of animations that involve a distressing separation event, and that end with comforting or ignorant behavior. Analysis: frontal asymmetry of EEG and attachment style.	DA: less or lack of frontal asymmetry of the right side of EEG compared with secure or insecure attachment.

(Continued)

Table 1. (Continued)

STUDY	PARTICIPANTS	ATTACHMENT INSTRUMENT	METHODOLOGY	MAIN RESULTS
Spitoni[33]	Adults (n=63)	AAI	Subjects were divided into two groups: organized attachment (n=46) and DA (n=17). Responses of CT fibers activation to stimuli "like a caress" were recorded, combining clinical psychology, psychophysics and neuroimage methods.	Unlike organized adults, the responses of adults with DA to CT and non-CT stimulation activated the limbic and paralimbic structures.
Tharner[34]	Infants of 6 wk of age (n=629)	SSM	Prospective cohort study. Ultrasound: the diameter of the ganglio-thalamus ovoid of infants at 6 wk and the attachment classification at 14 mo of age were measured.	Infants with larger ganglio-thalamus ovoid at 6 wk of age exhibited less risk of DA at 14 mo of age. The volume of lateral ventriculi (indicative of general brain development) was not associated with DA.
Moutsiana[35]	Follow-up of children at 18 mo and adults at 22 y of age (n=59)	SSM	Prospective longitudinal study of children born from women with postpartum depression. Attachment: evaluated at 18 mo (24 secure, 35 insecure) Neural fundamentals of the active regulation of caring (fMRI) was measured at 22 y of age.	Young adults with insecure attachment (including DA) when babies showed increased volume of the amygdala, without changes in the hippocampus.
Cortes Hidalgo et al[37]	Follow-up of children at 14 mo and at 10 y old (n=551)	SSM	Paternal-filial attachment at 14 mo of age. fMRI at 10 y of age.	Children with DA showed higher volume of hippocampus than those with organized attachment style. No other morphological differences were observed.
van Hoof[38]	Adolescents (n=74)	AAI	Mixed group; 21 with infant sexual abuse, 28 anxiety and/or depression, and 25 non-clinical, to categorize styles of attachment. Neuroimages by fMRI.	DA was associated with smaller volume of the left hippocampus (no effect on right side or amygdala) and higher functional connectivity between hippocampus, medial temporal gyrus and lateral occipital cortex.
Massullo[31]	Adults from 18 to 30 y of age (n=50)	AAI	EEG (functional connectivity through network analysis).	Lesser global efficiency after AAI in subjects with DA.
Lyons-Ruth[36]	Follow-up of children at 8 mo and adults at 29 y of age (n=18)	SSM	Attachment assessment at 8 mo followed by fMRI at 29 y of age.	67% (n=12) infants presented DA and 61% (n=11) mothers were classified as disrupted in their responses to their infants' attachment cues. Larger left amygdala volume in adults was strongly related to dissociative symptoms (partial and limbic irritability).

Abbreviations: SSM, strange situation method; AAI, adult attachment interview; AAP, adult attachment projective picture system; DA, disorganized attachment; EEG, electroencephalography; fMRI, functional magnetic resonance; HPA, hypothalamus-pituitary-adrenal; *OXTR*, oxytocin receptor; PCR, polymerase chain reaction test; SNP, single nucleotide polymorphism; VNTR, variable number tandem repeat.

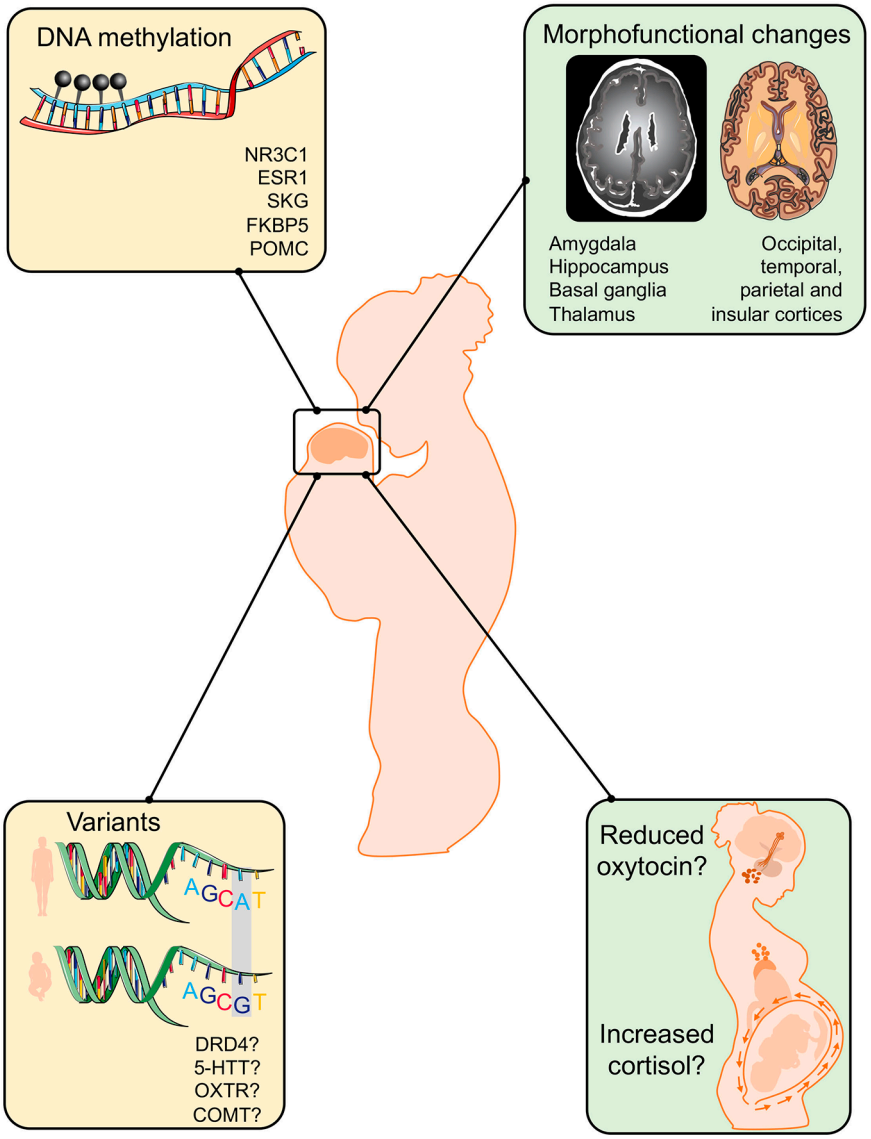

Figure 1. Summary of the main findings according to genetic, molecular and neurophysiology studies.

attachment using the SSM. The authors concluded that cortisol level in amniotic fluid, which reflects prenatal cortisol exposure, negatively predicts the child's cognitive ability, and that this association is moderated by attachment style, with a negative and statistically significant correlation in the insecure attachment group, which includes those with DA. Similarly, Luijk et al[24] analyzed 369 mother-infant dyads from the Generation R Study, a prospective cohort. Saliva cortisol levels were analyzed and parent-infant assessment was tested through the SSM when the infant was about 14 months of age. The results showed that DA infants had a more flattened slope of the diurnal rhythm than non-DA children.

Pierrehumbert et al[25] studied the secretion patterns of oxytocin and adrenocorticotropin (ACTH) in adults with and without childhood trauma. Although no biological responses differentiated according to the presence of childhood trauma were found, those who demonstrated DA when subjected to the stress test presented a suppressed response of the hypothalamic-pituitary-adrenal axis and moderate levels of oxytocin secretion, which did not differ significantly from those presented by subjects with other styles of attachment.

Neurophysiology Studies

Twelve studies were incorporated, which can be classified according to their focus of analysis: seven investigated functional correlates and five morphological correlates.

Functional Findings

The first authors to examine neural correlates of attachment in adult women were Buchheim et al,[26] who analyzed the neural correlate of attachment narratives using functional magnetic resonance imaging (fMRI). The authors applied the AAP for the evaluation, which consists of the construction of narratives in front of seven images that show situations associated with attachment. Participants with DA showed increased activation of medial temporal regions, including the amygdala and

hippocampus. Using narrative techniques and fMRI, Buchheim et al[27] studied the functional neuroanatomy of DA in people with borderline personality disorder. Group differences in narrative responses and neural activity were analyzed in the face of "monadic" images (characters who individually face attachment threats) and "dyadic" images (interaction between characters in an attachment context). Narrative data showed that monadic imaging was significantly more traumatic for participants with personality disorders than for controls, as they showed greater activation of the anterior cingulate cortex. In response to the dyadic images, the subjects showed greater activation of the right upper temporal sulcus and less activation of the right para-hippocampal gyrus.

Petrowski et al[28] observed that individuals with secure attachment showed significantly higher brain activity in the left cerebellum/cerebellar vermis, left inferior parietal lobe, left superior temporal gyrus, right anterior/medial cingulate cortex, and left insula, compared to individuals with DA. Those with insecure attachment, on the other hand, showed greater neuronal activity in the right inferior frontal gyrus, the left inferior parietal lobe, the right putamen and the right medial cingulate cortex compared to individuals with DA. In this study, participants were shown a series of facial photographs of attachment figures (parents and romantic partner), followed by facial photographs of unknown people (in this case, clinical staff members), while observing neural responses using fMRI.

Moutsiana et al[29] conducted a 22-year longitudinal study to examine the influence of early child-mother attachment, observing that the state of attachment at 18 months of age predicts neuronal response during the regulation of positive affects 20 years later. Adults who had insecure attachment at an early age showed greater activation in the prefrontal regions involved in cognitive control and reduced coactivation of the nucleus accumbens with the prefrontal cortex in attempting to regulate positive emotions upward.

Biro et al[30] performed an electroencephalographic analysis of frontal asymmetry, an indicator of emotional and motivational tendencies in the face of SSM type animations, which represent episodes of distressing separation and behavior of support or omission (absence of response) in infants at 10 months of age. Those with DA had none or less frontal asymmetry on the right side of electroencephalography, compared to safe and unsafe infants. Therefore, infants with DA did not respond in the same way as those organized to the animations to which they were exposed. Likewise, Massullo et al[31] performed an electroencephalographic analysis on 50 adults classified according to organized attachment and DA. Records were conducted before and after applying the AAI. The results showed a significant decrease in global efficiency (a functional integration measurement of brain networks) after administration of the attachment instrument, that is, exposure to the memory of traumatic attachment memories.

In another order of ideas, affective touch contributes to the establishment of filial bonds and social cognition. The activity of nerve fibers associated with affective touch has been the target of study in the context of the style of attachment. The emotional valence that is assigned to touch involves the optimal activation of type C (CT) tactile nerve fibers.[32] Tactile deficiencies are common in the psychiatric population, but also in healthy people with DA. Spitoni et al[33] propose that affective difficulties in adults with DA could be reflected in an altered perception of affective touch. In their study, the authors observed that, unlike organized adults, the responses of subjects with DA to stimulation of CT and non-CT fibers activated limbic and paralimbic structures in a fight-or-flight form.

Morphological Findings

A different approach has been examined to describe whether early structural differences in the ganglio-thalamic ovoid (ie, basal nuclei and thalamus) are involved in the etiology of DA. Tharner et al[34] measured ovoid volume in 6 week-old infants, noting that those with a higher volume ovoid had a lower risk of DA at 14 months of age. Lateral ventricle volume as an indicator of overall brain development was not associated with DA. In this line, Moutsiana et al[35] proposed that the quality of the early environment influences the development of regions related to the affective response, mainly the amygdala. The authors conducted an fMRI prospective study that evaluated the volumes of structures related to emotional regulation, at 18 months and 22 years of age. Attachment was assessed using the SSM at 18 months. They concluded that, at 22 years of age, the insecure attachment group, which included participants with DA, was associated with larger amygdala volumes; however, attachment style did not predict hippocampal volume. Lyons-Ruth et al[36] obtained similar results by assessing amygdala volumes in infants and following them longitudinally to adulthood. In infancy, they showed DA behavior and disrupted maternal communication; during adulthood, they exhibited increased left amygdala volume. This modification was further associated with dissociation and limbic irritability, mediating the prediction from DA in infancy to limbic irritability in adulthood. The authors hypothesized that the amygdala would be most affected by the quality of early care, based mainly on evidence that the tissue has high glucocorticoid receptor density and develops rapidly after birth. In contrast, Cortes Hidalgo et al,[37] in a large-sample study, found that AD at 14 months of age was associated with greater hippocampal volume at 10 years of age. This observation has not been consistently demonstrated; such is the result of van Hoof et al,[38] who associated DA with a lower left hippocampal volume and with greater functional connectivity between the hippocampus, the median temporal gyrus, and the lateral occipital cortex.

Discussion

The development of socio-cognitive skills in childhood is subject to an intricate interaction between the maturation of neural systems and environmental information. This relationship has been extensively studied in animal models,[39] however, human studies are scarce and show great heterogeneity. It is widely accepted that attachment style develops early in life, especially (but not solely) from bonding experiences, and determines individual differences in the processing of emotions, cognitions, and interpersonal relationships.[40]

Our review found evidence that DA is related to genetic, epigenetic, molecular and neurophysiological alterations. At the molecular level, changes in cortisol physiology have been studied, but the results show only partial differences between DA and non-DA children.[24] Most of the empirical evidence involving the association of dopaminergic, serotonergic, and oxytonergic gene variants with DA has been obtained from small-sample genetic studies; however, the association has been difficult to replicate and lacks robustness when the studies are replicated in large-scale assays. According to this statement, Luijk et al[19] assessed a variety of possible genes involved in the domain of social-emotional development in 2 large cohorts of infants, including attachment studies. For this, the authors selected gene variants in the dopaminergic, serotonergic, and oxytonergic systems to explore whether they are associated with the infants' attachment behavior. In both cohort studies, no consistent evidence was observed for the effects of candidate genes involved in DA, and the authors are aware of the limitations of the studies. Also, Roisman et al[21] analyzed 674 participants at 15 years of age, who had previously participated as infants with their mothers in a study on DA at 15 months of age. The authors genotyped for markers in the dopaminergic (*DRD2* rs1800497, *DRD4* 48 bp VNTR, *DRD4* rs1800495, *COMT* rs4680), serotonergic (*5HTT* VNTR), and the oxytonergic (*OXTR* rs53576, *OXTR* rs2254298) systems, obtaining results with little or null consistency to support the significant findings of small-size candidate gene studies. Consequently, they recommend maintaining sample sizes above 700 individuals. This article stresses the relevance of theoretical, methodological, and statistical considerations related to study design, sample sizes, and inheritance models used. Additionally, Leerkes et al[20] did not observe any interactions between the same candidate genes and maternal sensitivity when predicting disorganization, arguing that in large samples the effect is missing just as stated early by Luijk et al[19] and Roisman et al.[21] Moreover, Leerkes et al[20] hypothesize that if there is any effect of these genes on attachment, it could be through an indirect role, via genetically linked individual social aspects such as affect and cognition, which may play influence parent-child interactions, and perhaps the child's interpretation and representation of such interactions.

DA corresponds to a category of attachment that is conceptualized after its initial typification. Consequently, many of the early studies conducted in insecure attachment probably classified participants with DA as having an insecure attachment. However, the definition of the concept of secure/organized attachment has been rather constant, persistently considered as a protective factor against stress and environmental adversity, and therefore, associated with good outcomes in mental health. More specifically, Garg et al[22] have stated that secure attachment can mitigate some early adverse effects, such as prenatal maternal anxiety. The authors highlight the interaction between infant attachment and DNA methylation patterns, especially those related to dopamine and serotonin signaling pathways.

The newborn DNA methylome is highly sensitive not only to early stress, but also to early care. Therefore, it can be modified with early socialization experiences. One of the most studied neuropeptides in attachment has been oxytocin, synthesized by hypothalamic neurons that exert an effect on the amygdala and brainstem. These neurons exert main roles in emotional regulation, at the central and autonomic level, with substantial repercussions on social bonding and attachment. Proper functioning of the oxytocin system is associated with mental health, allowing the expression of positive social behaviors and creating selective bonds.[2] On the contrary, experiences of child abuse are linked to epigenetic modifications that alter the functioning of the oxytocin receptor (OXTR). Multiple studies have pointed to the role of this hormone as a mediator of processes involving social cognition, such as empathy and attachment. Fujisawa et al[41] studied differences in *OXTR* gene methylation in the saliva of Japanese children with and without child abuse and its impact on brain structures using imaging and clinical data. Abused children exhibited increased methylation and a negative correlation with gray matter volume in the left orbitofrontal cortex. Additionally, it was confirmed that the alteration of the oxytocin signaling pathway by hypermethylation generates an atypical development of the left orbitofrontal cortex. Our review did not find any study describing genetic or epigenetic modifications in oxytocin physiology linked to DA itself.

The dopaminergic system is involved in attentional, motivational, emotional and reward processes. Therefore, it has been postulated as part of the biological basis of the attachment system.[14] The functioning of *DRD4* was analyzed by eight studies included in this review. *DRD4-7R* has been associated with less inhibition of neuronal firing at the prefrontal cortex level and greater dopaminergic stimulation.[40] However, the clinical correlate is less certain, since it has been postulated as a protective[18] and risk[15] factor for AD. In the latter case, some authors argue that the *DRD4-7R* is linked to increased susceptibility to environmental influences and, therefore, to early adverse experiences, which would indirectly increase the risk of DA.[42] Conversely, the presence of the allele would also favor positive outcomes in terms of mental health when it occurs in children who develop in safe and caring environments. Belsky et al[43] describe the relevance of a positive environment versus susceptibility to the negative effects of an adverse environment and,

consequently, the example of the *DRD4-7R* allele highlights the putative importance of the gene-environment interaction studied by differential sensitivity models. However, as mentioned above, a series of studies considering multiple candidate genes, among them *DRD4*, have failed to replicate these findings.

Neurophysiological studies, developed mostly through fMRI techniques, show morpho-functional changes in subcortical structures such as the amygdala, hippocampus, basal nuclei and thalamus, and occipital, temporal, parietal and insular cortices, all involved in the processing of sensory, nociceptive, emotional, and cognitive information. These findings are very heterogeneous and cover different levels, which makes it difficult to elucidate the relevance of one finding over another with greater consistency. Some coincidences point to increased activity of the anterior cingulate cortex in subjects with DA[27,28] and the amygdala.[26] The latter structure has been shown to possess a higher volume in a prospective study that included 22 years old adults[35] with DA. However, the result comes from the analysis of a group of participants with insecure attachment that included people with DA. In animal models, the results obtained indicate that the neural substrates of emotion regulation may be persistently altered by early environmental exposure,[35] proposing that similar processes occurring in human development could have a significant effect since the ability to regulate emotional states is critical for adaptation. Therefore, it is not striking to confirm that the limbic and paralimbic regions are functionally and morphologically involved with the neurophysiology of DA. From another point of view, the results of Massullo et al[31] highlight that the activation of attachment memories (associated with events), could trigger "disintegrative processes" that alter emotional and executive regulatory functions, which translate into difficulties in social cognition. However, these results are incipient and do not allow a direct psychopathological translation. White et al[44] have proposed the neuro-anatomical model of disrupted attachment (NAMDA), as a complement for the previous neuro-anatomical model of attachment NAMA, which neglected the DA dimension. Briefly, the authors propose two main neurobiological phenotypes for AD, characterized by hypo-arousal and hyper-arousal. Each one would present differential alterations according to the following neural dimensions: aversion, approach, emotion (self)regulation, and mental state representation. NAMDA provides a theoretical framework that homogenizes the different definitions and taxonomies in the study of AD on a robust neurobiological assumption.

Human evidence regarding the neurobiology of DA is scarce and, consequently, the inferences obtained are preliminary in nature and not very robust. In this sense, translation to clinical and therapeutic parameters is restricted. Since the DA construct does not appear with the first conceptualization of attachment styles, some results come from samples of participants with categories that include DA, but simultaneously involve other types of attachment. Similarly, some publications including people with AD may have been excluded from this review for not explicitly pointing this out.

Conclusions

DA is a complex process that has a significant impact on various cognitive, affective, and behavioral aspects. Studies that attempt to establish correlates between DA and genetic (or epigenetic), molecular and neurophysiological changes carried out in humans are scarce, and the methodologies applied are varied and complex. Most studies aim to measure their repercussions and behavioral, cognitive, affective and physiological associations, using a wide variety of approaches. Additionally, authors use a diversity of terminologies or definitions. Although this work covers a review of the publications of primary studies carried out in humans over a period of more than 20 years, their number is low and there is a lack of robustness of the available evidence.

The results of the review allow us to conclude that: (1) findings in candidate genes involved in dopaminergic, serotonergic, and oxytonergic systems have not been able to be replicated in large-scale studies; (2) evidence for the effect of epigenetic regulation by DNA methylation is still very scarce in the period studied, although it represents an important possibility of interaction effect with the environment, especially in early life; (3) among the molecules closely associated with DA, the dysregulation of the hormone systems cortisol and oxytocin could be involved, both related to the stress response and exerting a critical role in neurodevelopment; (4) functional neuroimaging techniques have established that in humans morpho-functional changes associated with DA occur, especially in the hippocampus, which corroborates other techniques such as EEG and others that account for neurophysiological changes; and (5) the available evidence still lacks robustness to apply clinically.

Author Contributions

All authors contributed to the planning and writing of the original manuscript. MA, ML and AA performed the search of the available articles. MA and ML developed Table 1. AA elaborated Figure 1.

ORCID iD

Marcelo Arancibia https://orcid.org/0000-0003-2239-6248

REFERENCES

1. Bowlby J. The Bowlby-Ainsworth attachment theory. *Behav Brain Sci*. 1979;2:637-638.
2. Carter CS. The role of oxytocin and vasopressin in attachment. *Psychodyn Psychiatry*. 2017;45:499-517.
3. Main M, Solomon J. Discovery of a new, insecure-disorganized/disoriented attachment pattern. In: Yogman M, Brazelton T, eds. *Affective Development in Infancy*. Ablex; 1986;95-124.
4. Main M, Kaplan N, Cassidy J. Security in infancy, childhood, and adulthood: a move to the level of representation. *Monogr Soc Res Child Dev*. 1985;50:66-104.

5. Main M, Hesse E. Parents' unresolved traumatic experiences are related to infant disorganized attachment status: is frightened and/or frightening parental behavior the linking mechanism? In: Greenberg M, Cichetti D, Cummings E, eds. *Attachment in the Preschool Years: Theory, Research, and Intervention*. The University of Chicago Press; 1990;161-182.
6. Lyons-Ruth K, Jacobvitz D. Attachment disorganization: unresolved loss, relational violence, and lapses in behavioral and attentional strategies. In: Cassidy J, Shaver P, eds. *Handbook of Attachment: Theory, Research, and Clinical Applications*. The Guildford Press; 1999;520-554.
7. Soon CS, Brass M, Heinze HJ, Haynes JD. Unconscious determinants of free decisions in the human brain. *Nat Neurosci*. 2008;11:543-545.
8. Ainsworth MS, Bowlby J. An ethological approach to personality development. *Am Psychol*. 1991;46:333-341.
9. George C, West M. The development and preliminary validation of a new measure of adult attachment: the adult attachment projective. *Attach Hum Dev*. 2001;3:30-61.
10. Crawford TN, John Livesley W, Jang KL, Shaver PR, Cohen P, Ganiban J. Insecure attachment and personality disorder: a twin study of adults. *Eur J Pers*. 2007;21:191-208.
11. Buchheim A, George C. Attachment disorganization in borderline personality disorder and anxiety disorder. In: Solomon J, George C, eds. *Disorganized Attachment and Caregiving*. Guilford Press; 2011;343-382.
12. Amianto F, Daga GA, Bertorello A, Fassino S. Exploring personality clusters among parents of ED subjects. Relationship with parent's psychopathology, attachment, and family dynamics. *Compr Psychiatry*. 2013;54:797-811.
13. Farina B, Liotti M, Imperatori C. The role of attachment trauma and disintegrative pathogenic processes in the traumatic-dissociative dimension. *Front Psychol*. 2019;10:933.
14. Lakatos K, Toth I, Nemoda Z, Ney K, Sasvari-Szekely M, Gervai J. Dopamine D4 receptor (DRD4) gene polymorphism is associated with attachment disorganization in infants. *Mol Psychiatry*. 2000;5:633-637.
15. Lakatos K, Nemoda Z, Toth I, et al. Further evidence for the role of the dopamine D4 receptor (DRD4) gene in attachment disorganization: interaction of the exon III 48-bp repeat and the –521 C/T promoter polymorphisms. *Mol Psychiatry*. 2002;7:27-31.
16. Graffi J, Moss E, Jolicoeur-Martineau A, et al. Preschool children without 7-repeat DRD4 gene more likely to develop disorganized attachment style. *McGill Sci Undergr Res J*. 2015;10:31-36.
17. Graffi J, Moss E, Jolicoeur-Martineau A, et al. The dopamine D4 receptor gene, birth weight, maternal depression, maternal attention, and the prediction of disorganized attachment at 36 months of age: a prospective gene×environment analysis. *Infant Behav Dev*. 2018;50:64-77.
18. Wazana A, Moss E, Jolicoeur-Martineau A, et al. The interplay of birth weight, dopamine receptor D4 gene (DRD4), and early maternal care in the prediction of disorganized attachment at 36 months of age. *Dev Psychopathol*. 2015;27:1145-1161.
19. Luijk MP, Roisman GI, Haltigan JD, et al. Dopaminergic, serotonergic, and oxytonergic candidate genes associated with infant attachment security and disorganization? In search of main and interaction effects. *J Child Psychol Psychiatry*. 2011;52:1295-1307.
20. Leerkes EM, Gedaly LR, Zhou N, Calkins S, Henrich VC, Smolen A. Further evidence of the limited role of candidate genes in relation to infant-mother attachment outcomes. *Attach Hum Dev*. 2017;19:76-105.
21. Roisman GI, Booth-Laforce C, Belsky J, Burt KB, Groh AM. Molecular-genetic correlates of infant attachment: a cautionary tale. *Attach Hum Dev*. 2013;15:384-406.
22. Garg E, Chen L, Nguyen TTT, et al. The early care environment and DNA methylome variation in childhood. *Dev Psychopathol*. 2018;30:891-903.
23. Bergman K, Sarkar P, Glover V, O'Connor TG. Maternal prenatal cortisol and infant cognitive development: moderation by infant-mother attachment. *Biol Psychiatry*. 2010;67:1026-1032.
24. Luijk MP, Saridjan N, Tharner A, et al. Attachment, depression, and cortisol: deviant patterns in insecure-resistant and disorganized infants. *Dev Psychobiol*. 2010;52:441-452.
25. Pierrehumbert B, Torrisi R, Ansermet F, Borghini A, Halfon O. Adult attachment representations predict cortisol and oxytocin responses to stress. *Attach Hum Dev*. 2012;14:453-476.
26. Buchheim A, Erk S, George C, et al. Measuring attachment representation in an FMRI environment: a pilot study. *Psychopathology*. 2006;39:144-152.
27. Buchheim A, Erk S, George C, et al. Neural correlates of attachment trauma in borderline personality disorder: a functional magnetic resonance imaging study. *Psychiatry Res*. 2008;163:223-235.
28. Petrowski K, Wintermann GB, Hübner T, Smolka MN, Donix M. Neural responses to faces of attachment figures and unfamiliar faces: associations with organized and disorganized attachment representations. *J Nerv Ment Dis*. 2019;207:112-120.
29. Moutsiana C, Fearon P, Murray L, et al. Making an effort to feel positive: insecure attachment in infancy predicts the neural underpinnings of emotion regulation in adulthood. *J Child Psychol Psychiatry*. 2014;55:999-1008.
30. Biro S, Peltola MJ, Huffmeijer R, Alink LRA, Bakermans-Kranenburg MJ, van IJzendoorn MH. Frontal EEG asymmetry in infants observing separation and comforting events: the role of infants' attachment relationship. *Dev Cogn Neurosci*. 2021;48:100941.
31. Massullo C, Imperatori C, De Vico Fallani F, et al. Decreased brain network global efficiency after attachment memories retrieval in individuals with unresolved/disorganized attachment-related state of mind. *Sci Rep*. 2022;12:4725.
32. Krahé C, von Mohr M, Gentsch A, et al. Sensitivity to CT-optimal, affective touch depends on adult attachment style. *Sci Rep*. 2018;8:14544.
33. Spitoni GF, Zingaretti P, Giovanardi G, et al. Disorganized attachment pattern affects the perception of affective touch. *Sci Rep*. 2020;10:9658.
34. Tharner A, Herba CM, Luijk MP, et al. Subcortical structures and the neurobiology of infant attachment disorganization: a longitudinal ultrasound imaging study. *Soc Neurosci*. 2011;6:336-347.
35. Moutsiana C, Johnstone T, Murray L, et al. Insecure attachment during infancy predicts greater amygdala volumes in early adulthood. *J Child Psychol Psychiatry*. 2015;56:540-548.
36. Lyons-Ruth K, Pechtel P, Yoon SA, Anderson CM, Teicher MH. Disorganized attachment in infancy predicts greater amygdala volume in adulthood. *Behav Brain Res*. 2016;308:83-93.
37. Cortes Hidalgo AP, Muetzel R, Luijk MPCM, et al. Observed infant-parent attachment and brain morphology in middle childhood- a population-based study. *Dev Cogn Neurosci*. 2019;40:100724.
38. van Hoof MJ, Riem M, Garrett A, et al. Unresolved-disorganized attachment is associated with smaller hippocampus and increased functional connectivity beyond psychopathology. *J Trauma Stress*. 2019;32:742-752.
39. Meaney MJ. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annu Rev Neurosci*. 2001;24:1161-1192.
40. Erkoreka L, Zumarraga M, Arrue A, et al. Genetics of adult attachment: an updated review of the literature. *World J Psychiatry*. 2021;11:530-542.
41. Fujisawa TX, Nishitani S, Takiguchi S, Shimada K, Smith AK, Tomoda A. Oxytocin receptor DNA methylation and alterations of brain volumes in maltreated children. *Neuropsychopharmacology*. 2019;44:2045-2053.
42. Bakermans-Kranenburg MJ, van IJzendoorn MH, Caspers K, Philibert R. DRD4 genotype moderates the impact of parental problems on unresolved loss or trauma. *Attach Hum Dev*. 2011;13:253-269.
43. Belsky J, Bakermans-Kranenburg MJ, van IJzendoorn MH. For better and for worse: differential susceptibility to environmental influences. *Curr Dir Psychol Sci*. 2007;16:300-304.
44. White LO, Schulz CC, Schoett MJS, et al. Conceptual analysis: a social neuroscience approach to interpersonal interaction in the context of disruption and disorganization of attachment (NAMDA). *Front Psychiatry*. 2020;11:517372.