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Epigenetic variability in the human oxytocin receptor (*OXTR*) gene: A possible pathway from early life experiences to psychopathologies

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ABSTRACT

The human oxytocin (OXT) system is implicated in the regulation of complex social behaviors, as well as in psychopathologies characterized by social deficits. Emerging evidence suggests that variation in epigenetic regulation of the oxytocin receptor gene (*OXTR*) provides the oxytocin system with flexibility in response to environmental events, especially those occurring during early childhood. Changes in DNA methylation patterns of *OXTR* associated with these events may reflect biological alterations of social sensitivity. This is often related to an increased risk of developing mental disorders later in life. Here, we systematically reviewed all human studies (n = 30) discussing *OXTR* methylation in relation to socio-behavioral phenotypes. As such, we provide a complete and up-to-date overview of the literature that will aid future research in the interdisciplinary field of epigenetics and socio-behavioral sciences.

1. Introduction

The oxytocin (OXT) system has a central role in the regulation of a broad range of complex social and emotional behaviors, including attachment and bonding, social perception and recognition, as well as social stress and anxiety. Functioning of the OXT system is also associated with a wide variety of psychopathologies characterized by social deficits (Bakermans-Kranenburg and van IJzendoorn, 2014). The key hormone of this pathway, OXT, mainly exerts its effects through the oxytocin receptor (OXTR). This receptor is encoded by the OXTR gene, located on chromosome 3p25.3 (GRCh38/hg38 assembly, 3:8750408-8769628 according to Ensembl:ENSG00000180914), and contains three introns and four exons (Fig. 1) (Inoue et al., 1994). Inter-individual phenotypic variations may be partially explained by single nucleotide polymorphisms (SNPs). Human studies highlight two *OXTR* SNPs, rs53576 (hg38, 3:8762685; G/A) and rs2254298 (hg38, 3:8760542; G/A), implicated in parenting and pair-bonding behaviors, empathy, stress reactivity and social recognition. These *OXTR* SNPs are also linked to significant structural and functional differences in the limbic circuitry, including the amygdala, hypothalamus and cingulate gyrus (Furman et al., 2011; Inoue et al., 2010; Tost et al., 2011, 2010), that are potentially related to the neurobiology of social behaviors, as well as to the etiology of autism spectrum disorders (LoParo and Waldman, 2015), depressive disorders (McQuaid et al., 2014) and schizophrenia (Montag et al., 2013). However, studies on *OXTR* SNPs in relation to social (dys)functioning are inconclusive and more importantly, the exact functional relevance of these genetic variants on *OXTR* expression and function is poorly understood. Furthermore, a recent meta-analysis reported that the SNPs rs53576 and rs2254298 do not significantly correlate with social functioning nor with related psychopathologies (Bakermans-Kranenburg and van IJzendoorn, 2014). However, in addition to genetic variation, changes in the activity of *OXTR* may be related to other non-genetic regulatory mechanisms of transcription.

One such additional mechanism is epigenetics, which refers to dynamic, structural adaptations of chromosomal regions while preserving the underlying genetic composition (Bird, 2007; Dupont et al., 2009). The most common and well-studied epigenetic process is DNA methylation, which entails a chemical modification of the genome by the covalent attachment of methyl groups to cytosines primarily located in cytosine-guanine (CpG) sequences (Szyf, 2011), although the role of methylation outside CpG rich regions or of other sequences has become increasingly clear (Jang et al., 2017; Patil et al., 2014). Genomic regions relatively enriched in CpG sites, termed CpG islands, are often

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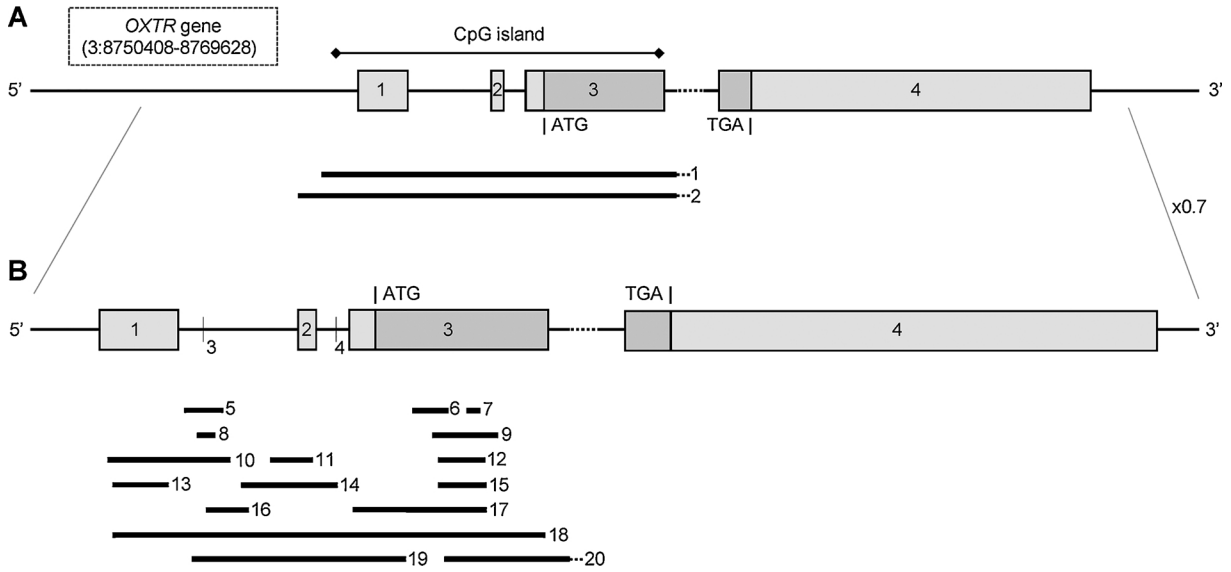

Fig. 1. Genomic organization of the OXTR gene.
The OXTR gene is located on chromosome 3p25-3p26.2 (hg38, 3:8750408-8769628), spans 17 kb and contains four exons (boxes) and three introns. Exon III and IV contain the protein-coding region (gray), starting with the translation start codon ATG and ending with the stop codon TGA. Panel **A** shows the location of *OXTR* CpG island, which stretches from 140 bp upstream from and 2338 bp downstream of the transcription start site (TSS; hg38, 3:8768045-8770525). The horizontal black lines in panel **A** and the enlarged (x 0.7) section in panel **B** indicate the regions that were investigated in the reviewed studies. The numbers refer to the following studies: 1. Gouin et al. (2017), 2. Smearman et al. (2016); Moore et al. (2017), 3. Bell et al. (2015); Ebner et al. (2018); Jack et al. (2012); Puglia et al. (2018, 2015); Rubin et al. (2016), 4. Kimmel et al. (2016), 5. Dadds et al. (2014), 6. King et al. (2017), 7. Nawijn et al. (2018), 8. Gregory et al. (2009), 9. Cappi et al. (2016); Chagnon et al. (2015), 10. Kim et al. (2014), 11. Rijlaarsdam et al. (2017), 12. Ziegler et al. (2015); Aghajani et al. (2018), 13. Simons et al. (2017), 14. Milaniak et al. (2017), 15. Unternaehrer et al. (2016), 16. Ein-Dor et al. (2018), 17. Unternaeher et al. (2012, 2015), 18. Cecil et al. (2014), 19. Reiner et al. (2015), 20. Galbally et al. (2018).

associated with the transcription start site of the particular gene (Gardiner-Gardern and Frommer, 1987; Illingworth and Bird, 2009; Jones, 2012). Although most CpG islands remain unmethylated (Bird et al., 1985), enhanced DNA methylation across these CpG islands is traditionally associated with transcriptional repression (Dor and Cedar, 2018; Moore et al., 2013). The OXTR gene also contains such a CpG island (hg38, 3:8768045-8770525; Fig. 1A) and methylation within this region has been shown to negatively impact *OXTR* transcription across tissues (Gouin et al., 2017; Gregory et al., 2009; Kusui et al., 2001). Interestingly, it is well documented that physical, biological and social environmental factors have stable and long-lasting effects on biological systems via epigenetic control of gene expression (for reviews on this topic see Kofink et al., 2013; Kundakovic and Champagne, 2015; Szyf & Bick, 2012).

The research on the impact of *OXTR* methylation variability on human functioning has gained increased attention and the literature on epigenetic regulation of socio-behavioral phenotypes has extensively expanded especially in the last few years (Kumstra et al., 2013; Maud et al., 2018). Two key OXT pathway genes have particularly been subject of study; *OXT* which codes for oxytocin itself and *OXTR* which codes for the receptor that senses the oxytocin signal. Since there is currently only one study examining the role of epigenetic regulation of *OXT* in human sociability (Haas et al., 2016), *OXTR* is to date the more interesting candidate for review. Therefore, this current article systematically reviews all studies on the association between epigenetic variability of *OXTR* and its phenotypical outcomes, aiming to facilitate and stimulate future research to unravel the socio-biological consequences of *OXTR* methylation.

2. Methods

2.1. Search strategy and study selection

A computerized search of two electronic databases, PudMed and EMBASE, was conducted to identify relevant literature. The search strategies were composed of the keywords “oxytocin receptor” and “DNA methylation” or “epigenetics” with associated synonyms, using the terms appropriate to each database (see Supplementary Table 1). These keywords were used as title/abstract words, as well as MeSH/Emtree terms. This review is restricted to published literature, with the last search conducted on 23-11-2018.

All articles were imported into reference manager Mendeley, after which duplicates were removed, yielding a total of 123 articles. Eligibility of the retrieved articles was independently assessed on title and abstract by two authors (EJK and HS). All articles describing the influence of epigenetic variability of *OXTR* on socio-behavioral phenotypes were included, thereby excluding literature on animal subjects ($n = 26$) and articles that either described phenotypes unrelated to the social domain ($n = 10$) or did not included epigenetics ($n = 1$). Furthermore, only English literature was included, with no limitations on either date or journal of publication. Review articles ($n = 27$), conference abstracts ($n = 22$) and types of publications other than experimental articles ($n = 7$) were excluded. Subsequently, full text screening was conducted by two authors independently (EJK and HS). Disagreements between authors were resolved by consensus, after which the included articles ($n = 30$) were categorized by phenotype.

2.2. Categorization

The following phenotypical categories of outcome assessments were identified: social perception and cognition ($n = 4$), social attachment ($n = 2$), autism spectrum disorder ($n = 3$), internalizing disorders ($n = 9$) and externalizing disorders ($n = 4$). The category ‘internalizing disorders’ covers psychopathologies such as anorexia nervosa, social anxiety disorder (SAD), depressive disorders, posttraumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD), whereas the category ‘externalizing disorders’ includes conduct problems (CP), callous-unemotional (CU) traits and psychopathy. Lastly, the category

Table 1
Extracted values from the included articles.

Article	Sample			Epigenetic measures					Genetic measures	
Author (year of publication)	Sex	Ethnicity	Phenotype	# CpG(s)	Novel coordinates (hg38)	Original coordinates (*)	Tissue	Analysis	SNPs	Coordinates (hg38)
Aghajani et al. (2018)	male	mixed	externalizing disorders (CP)	12 CpGs	8767595-8767848	8809281-8809534	saliva	bisulfate sequencing	rs53576	8762685
Bell et al. (2015)	female	Caucasian	social perception and cognition	1 CpG	8769121	8810807	blood	pyrosequencing	rs53576, rs2254298	8762685, 8760542
Cappi et al. (2016)	mixed	Latino	internalizing disorders (OCD)	9 CpGs	8767526-8767880	8809212-8809566	blood	bisulfite sequencing		
Cecil et al. (2014)	mixed	Caucasian	externalizing disorders (CP)	12 CpGs	8767276-8769594	8808962-8811280	blood	Infinium Human Methylation 450 K BeadChip		
Chagnon et al. (2015)	female	Caucasian	internalizing disorders (anxiety / depression)	9 CpGs	8767526-8767880	8809212-8809566	saliva	pyrosequencing	rs53576	8762685
Dadds et al. (2014)	male	ns.	externalizing disorders (CP)	5 CpGs	8768994-8769204	8810680-8810890	blood	EpiTYPER		
Ebner et al. (2018)	mixed	Caucasian	social attachment	1 CpG	8769121		blood	pyrosequencing		
Ein-Dor et al. (2018)	mixed	ns.	social attachment	4 CpGs	8768866-8769098	8810552-8810784	saliva	OneStep qMethyl kit		
Elagoz Yuksel et al. (2016)	mixed	Caucasian	autism spectrum disorders	ns.	ns.	ns.	blood	INFINITY UV transilluminator		
Galbally et al. (2018)	female	ns.	internalizing disorders (depression)	22 CpGs	8767815-8768964	8809501-8810650	placenta	EpiTYPER		
Gouin et al. (2017)	mixed	Caucasian	biological link	16 CpGs	8765201-8769915	8806887-8811601	blood	pyrosequencing		
Gregory et al. (2009)	mixed	Caucasian	autism spectrum disorders	5 CpGs	8769047-8769146	8785733-8785832 **	blood	bisulfite sequencing		
Jack et al. (2012)	mixed	mixed	social perception and cognition	1 CpGs	8769121	8810807	blood	pyrosequencing		
Kim et al. (2014)	female	Asian	internalizing disorders (anorexia nervosa)	35 CpGs	8768966-8769624	8810652-8811310	buccal cells	bisulfite sequencing		
Kimmel et al. (2016)	female	mixed	internalizing disorders (depression)	2 CpGs	8768382, 8768391	8810068, 8810077	blood	bisulfite sequencing	rs53576	8762685
King et al. (2017)	mixed	mixed	biological link	22 CpGs	8767620-8767815	8809306-8809501	saliva	MiSeq System		
Milaniak et al. (2017)	mixed	mixed	externalizing disorder (CP)	3 CpGs	8768391, 8768453, 8768906	8810077, 8810139, 8810592	(cord) blood	Infinium Human Methylation450 BeadChips	rs237900, rs62243375	8767010, 8768776
Moore et al. (2017)	mixed	mixed	biological link	7 CpGs	8764631-8770072	8806317-8811758	buccal cells	Infinium Human Methylation450 BeadChips	rs53576, rs7632287	8762685, 8749760
Nawijn et al. (2018)	mixed	ns.	internalizing disorder (PTSD)	8 CpGs	8767702-8767777	8809388-8809463	blood	Illumina Miseq 300V2		
Puglia et al. (2015)	mixed	Caucasian	social perception and cognition	1 CpG	8769121	8810807	blood	pyrosequencing		
Puglia et al. (2018)	mixed	Caucasian	social perception and cognition	1 CpG	8769121		blood	pyrosequencing		
Reiner et al. (2015)	female	Caucasian	internalizing disorders (depression)	43 CpGs	8768022-8769171	8743773-8744922 ***	blood	bisulfite sequencing	rs53576	8762685
Rijlaarsdam et al. (2017)	mixed	Caucasian	biological link	3 CpGs	8767620, 8767815, 8767850	8809306, 8809501, 8809536	(cord) blood	Infinium Human Methylation 450 K BeadChip	rs53576	8762685
Rubin et al., (2016)	mixed	mixed	social perception and cognition	1 CpG	8769121	8810807	blood	pyrosequencing		
Simons et al. (2017)	female	African American	internalizing disorders (depression)	4 CpGs	8769294, 8769318, 8769406, 8769593	8810980, 8811004, 8811092, 8811279	blood	Infinium Human Methylation 450 K BeadChip		
Smearman et al. (2016)	mixed	African American	biological link	18 CpGs	8764631-8770072	8806317-8811758	blood	Infinium Human Methylation 450 K BeadChip	44 SNPs	
Unternaehrer et al. (2012)	mixed	Caucasian	biological link	61 CpGs	8767589-8768307	8809275-8809993	blood	EpiTYPER		
Unternaehrer et al. (2015)	mixed	Caucasian	biological link	66 CpGs	8767589-8768307	8809275-8809993	blood	EpiTYPER		

(*continued on next page*)

Table 1 (*continued*)

Article	Sample			Epigenetic measures					Genetic measures	
Author (year of publication)	Sex	Ethnicity	Phenotype	# CpG(s)	Novel coordinates (hg38)	Original coordinates (*)	Tissue	Analysis	SNPs	Coordinates (hg38)
Unternaehrer et al. (2016)	female	Caucasian	biological link	13 CpGs	8767589-8767848	8809275-8809534	(cord) blood	EpiTYPER		
Ziegler et al. (2015)	mixed	Caucasian	internalizing disorders (SAD)	12 CpGs	8767595-8767848	8809281-8809534	blood	bisulfite sequencing	rs53576	8762685

Abbreviations: CpG, 5′-C-phosphate-G-3′; CP, conduct problems; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; ns., not specified; SAD, social anxiety disorder; SNPs, single nucleotide polymorphisms.
*: according to GRCh37/hg19 assembly (GCF_000001405.13).
**: according to NCBI36 assembly (GCF_000001405.12).
***: according to HuRef assembly (GCF_000002125.1).

'biological link' (n = 8) contains all studies that describe *OXTR* methylation as mediator between pre- or postnatal environmental events or factors and socio-behavioral phenotypes.

2.3. Data extraction

The following variables were extracted: first name of author and year of publication, demographic features of participants (sex, ethnicity and phenotypic category), epigenetic measures (investigated CpG sites, coordinates (GRCh38/hg38 and original assemblies), tissue and analyses) and genetic measures (SNPs and coordinates). The extracted variables are shown in Table 1 (for a more detailed overview of the genomic coordinates and locations of the individual CpG sites, see Supplementary Table 2 and Supplementary Fig. 1). A schematic overview of the genomic organization of the OXTR gene and investigated genomic regions is shown in Fig. 1.

3. Results

3.1. Social perception and cognition

Basic, low-level (social) processes like social perception and cognition are thought to facilitate higher-order, more complex social behaviors such as empathy and mentalizing (Decety and Svetlova, 2012; Kraaijenvanger et al., 2017). Therefore, inter-individual variations in these basic perceptual processes due to epigenetic variability of *OXTR* may profoundly impact the overall repertoire of human social behaviors, as well as alter the susceptibility to psychopathologies characterized by social deficits.

The study by Jack et al. (2012) sought to investigate this relation between variations in social perception and variability in *OXTR*. Therefore, the brain's sensitivity to displays of animacy as neural measure of social perception was related to blood DNA methylation levels of *OXTR* CpG site -934 (hg38, 3:8769121). Data from 42 participants collectively revealed a significant positive interaction between DNA methylation levels and neural activity to the perception of animacy as compared to random movements. This enhanced neural activity was found in a network of brain structures involved in social perception and mentalizing abilities, including the temporal parietal junction and the dorsal anterior cingulate cortex (dACC). Besides demonstrating that DNA methylation levels were associated with individual differences in brain activity in neural areas underlying social perceptual processes, these results also indicate that peripheral *OXTR* methylation may serve as a proxy for variability in epigenetic regulation of *OXTR* within the brain that can influence behavioral phenotypes (Jack et al., 2012).

A core component of social cognition is the recognition and processing of emotional facial expressions. Although the involvement of the OXT system in this process has been suggested by previous neuroimaging studies (Bethlehem et al., 2013; Wang et al., 2017), results were inconsistent. This may be due to neglect of epigenetic variability. Therefore, Puglia et al. (2015) examined whether *OXTR* methylation variability impacts individual differences in neural responses to the perception of emotional facial expressions in a validated emotional face-matching fMRI task (as described by Hariri et al., 2002). Neural activity patterns were assessed from 98 healthy participants, as well as blood *OXTR* methylation levels at CpG site -934 (hg38, 3:8769121). A significant association was found between higher *OXTR* methylation levels and increased neural activity in brain areas important for face perception and emotion regulation, including the amygdala, fusiform gyrus, insular cortex and dorsal anterior cingulate cortex (ACC). Furthermore, functional connectivity between the amygdala and the brain areas supporting social perception was negatively affected by higher DNA methylation levels, which was especially evident in response to negative social stimuli like angry and fearful expressions. This indicates that lower *OXTR* promotor methylation, which has been related to

altered OXTR gene expression (Kusui et al., 2001), may provide one with an enhanced ability to appropriately regulate affective responses to negative stimuli.

A more recent study by Puglia et al. (2018) further investigated neural responses to human faces, which are considered highly salient social stimuli. Individual differences in the intrinsic saliency of such social cues, and thus in underlying neural responses, might result from variability in the OXT system (social salience hypothesis (Shamay-Tsoory and Abu-Akel, 2016)). A sample of 54 participants was subjected to a selective attention fMRI task in which they were presented with images of human faces and houses, and *OXTR* methylation levels at CpG site -934 were assessed from peripheral blood mononuclear cells (PBMCs) (hg38, 3:8769121). When focusing on human faces, higher *OXTR* methylation levels were positively associated with neural activity in regions of the face perception network and the attentional control network, and negatively with the functional connectivity between the attentional control network and the salience network. Based on similar neuroimaging results in individuals with autism, the authors conclude that enhanced *OXTR* methylation is associated with lower intrinsic salience during selective attention to social cues (Puglia et al., 2018).

As mentioned, deficits in social perception and cognition are often associated with psychopathologies characterized by aberrant functioning in social domains. Rubin et al. (2016) examined the interaction between *OXTR* methylation and such social cognition deficits in individuals suffering from (non-)affective psychotic disorders. Therefore, 167 patients with bipolar disorder or schizophrenia and 75 healthy controls participated in a validated facial emotion recognition task (Penn Emotion Recognition Test; Gur et al., 2002) while undergoing structural imaging (n = 190). *OXTR* methylation levels from CpG site -934 (hg38, 3:8769121) and plasma OXT levels were assessed from whole blood samples. Overall, higher *OXTR* methylation levels significantly correlated with a decreased ability to recognize emotional faces, as well as with smaller volumes of brain structures underlying emotion regulation in schizophrenia patients - however only in females. This sexual dimorphic effect was also shown for mean DNA methylation levels of CpG site -934, similar to the findings in healthy individuals by Puglia et al. (2015), which indicates that DNA methylation at *OXTR* CpG site -934 may be a general sex-specific effect. Furthermore, no significant associations were found between *OXTR* methylation and OXT plasma levels in whole blood samples of both patients and controls. This result indicates that the effects of differential DNA methylation may not be mediated by effects on neuropeptide synthesis but rather influences *OXTR* functioning itself.

3.2. Social attachment

The formation and maintenance of close relationships and social attachments are central to human physical and psychological wellbeing across the lifespan (Bos, 2017; McWilliams and Bailey, 2010; Nolte et al., 2011; Pietromonaco and Beck, 2018; Puig et al., 2013; Stanton and Campvell, 2014). Studies on the neuropeptide regulation of social attachment have repeatedly highlighted the importance of the vasopressin system and the OXT system (Carter, 2017; Nishitani et al., 2017; Walum et al., 2012). Based on previous reports of the effect of DNA methylation variability on social attachment (Bosmans et al., 2018; Haas et al., 2016; Jones-Mason et al., 2016; Mulder et al., 2017; van IJzendoorn et al., 2010), the study by Ebner et al. (2018) was the first to examine the relation between attachment behavior and *OXTR* methylation. To study this association across adulthood, 22 young-adults (20–31 years) and 34 elderly participants (63–80 years) were subjected to the short form of the Experiences in Close Relationship Scale (ECR-S; Wei et al., 2007) to assess self-reported attachment anxiety and avoidance. Blood samples were collected to measure plasma OXT levels and *OXTR* methylation levels at CpG site -934 (hg38, 3:8769121). Analyses revealed a significant association between adult attachment and *OXTR* methylation, however, only in young adults. More specifically, low *OXTR* methylation and high plasma OXT was associated with lower self-reported attachment anxiety and low *OXTR* methylation was also associated with higher self-reported attachment avoidance. While both the observed age-differences and associations between the OXT system and attachment anxiety are in line with literature (Baltes, 1997; Wu and Zhang, 2014 and Haas et al., 2016, respectively), the direction of the interaction between *OXTR* methylation and attachment avoidance contradicted the hypothesis.

Similarly, Ein-Dor et al. (2018) investigated the relation between attachment anxiety and avoidance and epigenetic regulation of two genes linked to attachment behavior and stress-coping, *NR3C1* and *OXTR* (Bosmans et al., 2018; Ein-Dor et al., 2018; Haas et al., 2016). Self-reported attachment avoidance and anxiety was measured in 109 participants with questions derived from the Adult Attachment Scale (AAS; Collins and Read, 1990), and saliva samples were collected to assess DNA methylation patterns of *NR3C1* and *OXTR* (hg38, 3:8768866-8769098; four CpG sites located in intron I). In general, high attachment avoidance scores were related to high DNA methylation levels of both *NR3C1* and *OXTR*. Among participants with low attachment anxiety scores, a significant positive relation between attachment avoidance and *OXTR* methylation levels was also reported. These results are in line with established attachment theories (Ein-Dor et al., 2018; Taylor, 2006), and imply that the reluctance to seek social proximity in stressful situations may arise from a hampered OXT system as well as from a less efficient stress regulation system. However, these results do contradict the findings by Ebner et al. (2018), who reported an association between low *OXTR* methylation and high attachment avoidance scores in young-adults, although this might be explained by a difference in both location and number of assessed *OXTR* CpG sites. Considering the limited number of studies, future studies on the role of the OXT system in human attachment behaviors may offer more clarity on the subject.

3.3. Autism spectrum disorders

Autism Spectrum Disorders (ASDs) comprise a heterogeneous group of disorders characterized by impairments in social interactions and communication, as well as repetitive behaviors and restricted interests (American Psychiatric Association, 2013). These autistic traits typically become evident in early childhood, indicative of a possible origin in early brain development. ASDs are highly heritable (Hallmayer et al., 2011; Lichtenstein et al., 2010; Sandin et al., 2017; Tick et al., 2016), however, the heterogeneous nature of ASDs limits the research on genetic factors underlying the etiology of ASDs.

The OXT system, and particularly genomic variation in *OXTR*, is a candidate for explaining genetic vulnerability to autistic social behavior (Yamasue, 2013), based on multiple genetic studies linking variations in *OXTR* with ASDs (de Oliveira Pareira Ribeiro et al., 2018; Jacob et al., 2007; Lerer et al., 2008; Liu et al., 2010; Ocakoğlu, Köse et al., 2018; S. Wu et al., 2005; Ylisaukko-oja et al., 2006; Yrigollen et al., 2008), as well as studies reporting ameliorating effects of OXT on core autistic traits (Andari et al., 2010; Guastella et al., 2010; Hollander et al., 2007, 2003; Kosaka et al., 2012). However, some genetic studies failed to show significant associations between *OXTR* SNPs and ASDs (Campbell et al., 2011; Tansey et al., 2010). Meta-analytic reviews also demonstrated contradictive findings about *OXTR* SNPs in relation to ASDs and associated autistic traits (Bakermans-Kranenburg and van IJzendoorn, 2014; LoParo and Waldman, 2015). This raises the question whether disregard of the influence of epigenetic variability might have contributed to these negative findings. To date, three articles investigated the role of *OXTR* methylation variability in autism and ASDs (Elagoz Yuksel et al., 2016; Gregory et al., 2009; Rijlaarsdam et al., 2017).

The study by Gregory et al. (2009) started with a genetic study in autistic individuals, which revealed a heterozygous deletion of *OXTR* (3p25.3) in an autistic boy as most significant result. The association

between *OXTR* and autism was further investigated, with a specific focus on epigenetic variability in the promoter region of *OXTR*. PBMCs were collected from the affected individual and all first-degree relatives, after which analyses showed that the participant's affected sibling did not inherit the deletion but did display DNA hypermethylation of CpG sites -901, -924 and -934 (hg38, 3:8769088, 8769111, 8769121; located in intron I) as compared to a non-affected relative. Thereafter, analyses were extended beyond this family and *OXTR* methylation levels were assessed from PMBCs of 20 patient-control pairs. Similarly, significant DNA hypermethylation was observed for CpG sites -860 and -934 in male patients (hg38: 3:8769047and 8769121) and for CpG site -959 in female patients (hg38: 3:8769146) as compared to healthy controls. This DNA methylation pattern in autistic individuals was further confirmed in an independent sample of eight patient-control pairs, demonstrating significant DNA hypermethylation of CpG sites -860, -901, -924 and -934 (hg38, 3: 8769047, 8769088, 8769111, 8769121) in postmortem temporal cortex tissue. Higher *OXTR* methylation levels of temporal cortex DNA, especially of CpG site -934 (hg38, 3:8769121), functionally correlated with decreased *OXTR* mRNA expression. These results not only suggest functional importance of epigenetic variability of *OXTR* in the etiology of autism, but underscore the modulating effects of DNA methylation at these CpG on *OXTR* expression as well.

Likewise, Elagoz Yuksel et al. (2016) examined the relation between *OXTR* methylation and ASDs. Peripheral blood samples were collected from 66 infants, of which 27 with ASDs according to the DSM-IV (American Psychiatric Association, 2000), to assess DNA methylation levels of four consecutive regions (coined MT1, MT2, MT3 and MT4, in accordance with Kusui et al. (2001)) in *OXTR* promoter region. Analysis revealed significant DNA hypomethylation of one CpG site and four CpG sites in regions MT1 (containing exon I) and MT3 (containing intron I, exon II and intron II), respectively, but not of CpG sites located in regions MT2 and MT4 in autistic children as compared to healthy controls. This first report of *OXTR* hypomethylation further implicates dysregulation of epigenetic regulation as mechanism underlying the etiology of autism. However, the current findings are inconsistent with the study by Gregory et al. (2009), who reported DNA hypermethylation of CpG sites located in the MT2 region. Important to note is that the included CpG sites in the MT2 region in these two studies are different and not directly comparable due to methodological differences in assessing DNA methylation (Elagoz Yuksel et al., 2016; Gregory et al., 2009). This discrepancy may underlie the inconsistent findings reported here. Another confounding factor may be the ethnic differences in sample groups, thereby underscoring the clinically and genetically heterogeneity of autism.

Rijlaarsdam et al. (2017) investigated the interactive effects of *OXTR* SNP rs53576 and neonatal *OXTR* methylation on child autistic traits, thereby extending the relation between the OXT system and ASDs by including genetic variability as well. A subsample of 743 children from the Generation R Study (Jaddoe et al., 2012) was included of which child autistic traits were assessed at age six with maternal ratings on the Social Responsiveness Scale (SRS; Constantino et al., 2003) and the Pervasive Developmental Problems scale of the Child Behavior Checklist (CBCL; Achenbach and Rescorla, 2000). Cord blood samples collected at birth were used to assess genotype measures as well as *OXTR* methylation levels at three CpG sites located in intron I and exon II (hg38, 3:8767620, 8767815 and 8767850). Overall, *OXTR* methylation levels were positively associated with child autistic traits in *OXTR* rs53576 homozygous G-allele children. After separate analyses, this interaction remained significant for one CpG site (hg38, 3:8767620). As argued by the authors, these results may indicate that increased DNA methylation levels of CpGs associated with the rs53576 protective G-allele elevates the risk for autistic traits by decreasing the overall expression of *OXTR*.

Collectively, both DNA hypermethylation (Gregory et al., 2009; Rijlaarsdam et al., 2017) and DNA hypomethylation (Elagoz Yuksel et al., 2016) of specific *OXTR* CpG sites have been reported in relation to autism and ASDs. Importantly, this inconsistency in *OXTR* methylation patterns may arise from the assessment of CpG sites located at different regions of *OXTR*. Nonetheless, the results support the suggested involvement of the OXT system, and more specifically of *OXTR*, in the etiology of autism and ASDs. These findings are however in dire need of replication in larger and more homogeneous samples, especially given the highly heterogeneous nature of autism and ASDs.

3.4. Internalizing disorders

3.4.1. Anorexia nervosa

The eating disorder anorexia nervosa (AN) is characterized by abnormal eating patterns and disturbances in body image, as well as comorbid symptoms like anxiety, social deficits and rigid behavioral patterns (Maguire et al., 2013). The OXT system has been implicated in the psychopathology of AN, given its involvement in socio-emotional functioning as well as in food intake (Blevins and Baskin, 2015; Lawson, 2017). Aberrant OXT function has indeed been shown in patients with AN (Maguire et al., 2013), reporting lower OXT levels in both CSF (Demitrack et al., 1990) and blood (Lawson et al., 2011; Schmelkin et al., 2017) of AN patients compared to healthy controls. Based on previous reports of epigenetic variability in eating disorders, Kim et al. (2014) sought to investigate the relation between *OXTR* methylation and AN psychopathology. Buccal cells from 51 women, including 15 A N patients according to DSM-IV (MBSR First et al., 2002), were collected to assess *OXTR* methylation levels (hg38, 3:8768966-8769624). Various markers of disease severity were examined, including clinical features (EDE-Q; Fairburn and Beglin, 1994), autistic traits (AQ; Baron-Cohen et al., 2001), depression (BDI; Beck et al., 1961) and anxiety (STAI; Spielberger et al., 1983). Five CpG sites located in exon I and the MT2 region (Kusui et al., 2001), were hypermethylated in AN patients compared to healthy controls, which negatively correlated with body mass index (BMI) as index of disease severity. Furthermore, positive correlations were found between DNA methylation at specific CpG sites and autistic traits, depression and anxiety. These results indicate that differential *OXTR* promoter methylation is indeed implicated in AN psychopathology, which may act via the suppression of OXTR gene expression (Gregory et al., 2009; Kusui et al., 2001). It must however be noted that epigenetic variability in AN patients might be a secondary consequence of food deprivation (Choi et al., 2013; Yi et al., 2000), although this has never been tested for *OXTR*.

3.4.2. Social anxiety disorder

Individuals with social anxiety disorder (SAD) display substantial fear for and avoidance of social interactions. SAD has been associated with OXT functioning on multiple levels (Guastella et al., 2009; Hoge et al., 2008; Labuschagne et al., 2010). Further elucidating this association, Ziegler et al. (2015) thoroughly investigated the role of *OXTR* methylation in phenotypes of SAD. Peripheral blood samples were collected from 110 patients with SAD according to DSM-IV (Wittchen, 1997) and 110 matched healthy controls to assess both genotype (SNP rs53576) and *OXTR* methylation levels (hg38, 3:8767595-8767848; 12 CpG sites in exon III). Additionally, fMRI measurements were collected from a subsample of 25 female SAD patients to assess amygdala responsiveness to social phobia-related verbal stimuli (as described by Laeger et al., 2014). Overall, mean *OXTR* methylation levels were lower in SAD patients compared to healthy controls and negatively correlated with disease severity as assessed with the Social Phobia Scale and Social Interaction Anxiety Scale (SPS and SIAS; Stangier et al., 1999). These findings were particularly significant for one CpG site (hg38, 3:8767751) after Bonferroni correction. The authors suggest that *OXTR* hypomethylation and thus enhanced OXTR expression (Kusui et al., 2001) may indicate a compensatory mechanism to counteract the pathologically low OXT plasma levels in SAD patients (Hoge et al., 2008).

It must however be mentioned that the studied CpG sites are located in *OXTR* exon III rather than in the promoter region and may therefore also differentially relate to *OXTR* transcription (Ball et al., 2009). Furthermore, overall *OXTR* hypomethylation was associated with enhanced amygdala responsiveness to social phobia-related stimuli in SAD patients compared to healthy controls. These findings not only replicate previous studies (Laeger et al., 2012; Schmidt et al., 2010), but may also serve as a biological explanation for the disease-related, negative bias towards social interactions as a result of social anxiety.

3.4.3. Obsessive-compulsive disorder

The chronic condition obsessive-compulsive disorder (OCD) is highly heterogeneous in clinical symptoms (e.g. fears, repeating rituals and checking behaviors), as well as in comorbidity patterns with other neuropsychiatric conditions (e.g. depression, anxiety and eating disorders) (Bloch et al., 2008). Being the first to study the involvement of *OXTR* methylation in OCD psychopathology, Cappi et al. (2016) collected peripheral blood samples from 42 OCD patients and 31 healthy controls. DNA methylation levels of nine CpG sites located in exon III (hg38, 3:8767526-8767880) were assessed, as well as OCD symptom severity by using the Beck Depression Inventory (BDI; Beck and Beamesderfer, 1974), the Beck Anxiety Inventory (BAI; Beck et al., 1988) and the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989). Overall, higher global *OXTR* methylation levels were observed in OCD patients as compared to healthy controls, as well as a positive correlation between enhanced *OXTR* methylation and OCD symptom severity. These findings provide a first indication of the involvement of differential *OXTR* methylation patterns in OCD psychopathology.

3.4.4. Posttraumatic stress disorder

Various key features of posttraumatic stress disorder (PTSD) arise from an enhanced salience processing and reduced inhibitory control over fear responses upon the experience of a traumatic event (Koch et al., 2014b; Rothbaum and Davis, 2003). These PTSD characteristics implicate the involvement of the OXT system (Olff et al., 2010), which indeed has been shown (Frijling et al., 2015; Koch et al., 2014a; Nawijn et al., 2016). Since DNA methylation may mediate between trauma experiences and PTSD (Klengel et al., 2014), the study by Nawijn et al. (2018) sought to investigate the role of *OXTR* methylation in the etiology of PTSD. Whole blood samples from 31 PTSD patients and 36 trauma-exposed controls were collected to assess *OXTR* methylation levels (hg38, 3: 8767702–8767777; 8 CpG sites located in exon III). Interestingly, only female PTSD patients showed significantly higher methylation levels of two CpG sites (hg38, 3: 8767727 and 8767751), which was related to high anhedonia and low left amygdala reactivity towards negative faces in a validated fMRI paradigm (as described by Hariri et al., 2002) – although not significantly after correction for multiple comparisons. These results confirm both study hypothesis and the sexually dimorphic pattern of *OXTR* methylation as reported by previous studies (Gouin et al., 2017; Gregory et al., 2009; Puglia et al., 2015; Rubin et al., 2016), and suggest that *OXTR* hypermethylation in PTSD patients may underlie the observed reduced sensitivity to social cues. In addition, it importantly indicates that the neurobiological correlates of PTSD may differ between males and females – which may further contribute to elucidating the mechanisms underlying the sex-differences in PTSD.

3.4.5. Depressive disorders

Depressive disorders are among the most prevalent mental disorders, significantly affecting quality of life by impairing both cognitive and social functioning (Lépine and Briley, 2011). The OXT system has been implicated in depression-related feelings like loneliness, negativity and distrust, and it has been suggested that this involvement is highly influenced by environmental factors through epigenetic mechanisms (Schroeder et al., 2010).

Reiner et al. (2015) directly compared *OXTR* methylation levels between clinically depressed patients and healthy controls, and assessed whether differences were influenced by genotype. A sample of 43 patients with depression according to DSM-IV (Wittchen et al., 1997) and 42 healthy controls were included, and venous blood samples were collected to assess genotype (*OXTR* SNP rs53576) and DNA methylation levels from 43 *OXTR* CpG sites located in exon I and II. Analyses revealed a significant DNA hypomethylation of CpG sites in exon I in depressed patients compared to healthy controls. This effect was mainly present in patients homozygous for the G-allele compared to patients that carried an A-allele. These results suggest an exon-specific DNA methylation pattern that can distinguish depressed patients from healthy controls.

Additionally, Chagnon et al. (2015) examined the influence of *OXTR* epigenetic variability in participants with depression and comorbid anxiety disorders. These highly comorbid psychiatric disorders both share a significant hereditary component, indicative of a mutual genetic origin (Neale and Kendler, 1995; Roy et al., 1995). Saliva samples were collected from 43 older women, of which 19 participants with previous anxiety disorder and/or depression, to assess both genetic (*OXTR* SNP rs53576) and epigenetic (hg38, 3:8767526-8767880; nine CpG sites located in exon III) measures. Overall, a significant hypermethylation of one CpG site (hg38, 3:8767869) was reported in patients, but only in homozygous carriers of the A-allele. It must however be noted that this significant change in DNA methylation did not survive post-hoc analyses.

A history of depressive symptoms is a strong predictor of the development of postpartum depression (PPD) (Field, 2011). The OXT system is implicated in this, since reduced maternal plasma OXT levels during pregnancy are associated with an enhanced risk for PPD development (Skrundz et al., 2011). Further examining this, Bell et al. (2015) investigated whether this increased risk for PPD is related to DNA methylation of *OXTR* CpG site -934 (hg38, 3:8769121), and whether this association is modulated by *OXTR* genotype (SNPs rs53576 and rs2254298). A subsample of 269 women with PPD were selected based on scores on the validated Edinburg Postnatal Depression Scale (EPDS; Evans et al., 2001) at eight weeks postpartum. Genetic and epigenetic data was assayed from whole blood samples collected during mid-pregnancy. A significant interaction was found between DNA methylation levels at CpG site -934, the rs53576 genotype and the presence of PPD. More specifically, women with no depressive symptoms during pregnancy with the homozygous risk phenotype (rs53576_GG) as well as high DNA methylation levels were found to have a nearly three-fold higher risk for the development of PPD.

The study by Kimmel et al. (2016) similarly tested the hypothesis that PPD is associated with *OXTR* methylation at two functionally relevant CpG sites located in intron II (hg38, 3:8768383 and 8768392). To this aim, 51 women with PPD provided blood samples during pregnancy which were (epi-)genetically analyzed. Overall, *OXTR* methylation levels and *OXTR* expression levels were significantly lower in patients as compared to healthy controls after multiple test correction. Notably, the association between *OXTR* methylation and expression levels and PPD was only significant in women that were also prenatally depressed. This contradicts the findings by Bell et al. (2015), who specifically reported a PPD specific *OXTR* hypermethylation in GG homozygotes of the *OXTR* SNP rs53576 in women that were not prenatally depressed. Given that the locations of the assessed CpG sites in these two studies were over 1 kb apart, these differences may suggest a distinct regulatory role of each locus in *OXTR*. Interestingly, the CpG sites in this study are located in close proximity of two estrogen response elements (ERα and a SP1 transcription factor binding site). Since previous studies showed the occurrence of estrogen mediated epigenetic reprogramming of *OXTR* (Bartella et al., 2012; Fleming et al., 2006; Harony-Nicolas et al., 2014; Vivar et al., 2010), this may indicate that differential DNA methylation at these CpGs has functional relevance to *OXTR* gene expression.

As DNA methylation levels can profoundly affect *OXTR* expression (Gregory et al., 2009; Kusui et al., 2001), these results suggest that a dysfunction in the OXT system is possibly associated with the pathology of PPD, or as Kimmel et al. (2016) alternatively states, with a depressed state in general. Of note, although all four studies indicate that epigenetic variation of *OXTR* is likely associated with the psychopathology of depressive disorders, the reported DNA methylation patterns across studies differ. Whereas the studies by Bell et al. (2015) and Chagnon et al. (2015) report a significant DNA hypermethylation of CpG sites of *OXTR*, Kimmel et al. (2016) and Reiner et al. (2015) demonstrated a significant DNA hypomethylation in relation to depressive disorders. Although these studies assessed DNA methylation levels from different regions of *OXTR,* thereby making the results not directly comparable, these inconsistencies in DNA methylation patterns highlight the complexity of the suggested association between the OXT system and the psychopathology of depressive disorders.

3.5. Externalizing disorders

Children that present a stable pattern of antisocial behavior, collectively termed callous-unemotional (CU) traits, are at risk for early-onset and persistent conduct problems (CP) (Rowe et al., 2010) and adult psychopathy (Frick and Viding, 2009). Given the fundamental role of the OXT system in social behaviors, it has been suggested that alterations in OXT functioning may underlie the core characteristics of CU traits and psychopathy. Indeed, lower salivary OXT levels were correlated with CP severity (Levy et al., 2015) and genetic studies demonstrated associations between *OXTR* SNPs and high levels of CU traits in CP individuals (Beitchman et al., 2012; Dadds et al., 2014; Malik et al., 2012).

Further investigating this relation between the OXT system and CU traits in CP individuals, Dadds et al. (2014) examined 156 young males with CPs as assessed with the Diagnostic Interview Schedule for Children, Adolescents, and Parents (DISCAP; Holland and Dadds, 1997). The severity of CU traits was measured using the Antisocial Process Screening Device (APSD; Frick and Hare, 2001) and the prosocial subscale of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). Circulating OXT blood levels ($n = 95$) and DNA methylation levels ($n = 98$) in intron I of *OXTR* (hg38, 3:8768994-8769204) were assessed as well ($n = 37$ for both OXT and *OXTR* measures). Significant associations were found between the severity of CU traits and both higher plasma OXT levels and higher *OXTR* methylation levels at two CpG sites (hg38, 3:8769147 and 8769177) in the CP sample group comprising 9- to 16-year old males, although only one CpG site remained significant after multiple test correction (hg38, 3:8769147). Importantly, a significant negative association was found between plasma OXT levels and *OXTR* methylation levels in the older children, thereby adding to the literature on functional relevance of *OXTR* methylation (Gregory et al., 2009; Kusui et al., 2001; Rubin et al., 2016).

Likewise, Aghajani et al. (2018) studied the link between *OXTR* methylation and CU traits in CP young-adults, and moreover, aimed to unravel how this interaction might impact neural systems involved in processing distressing social information. Therefore, 39 juvenile offenders with CD, according to the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997) and 27 matched controls were subjected to an explicit socio-affective processing fMRI task (as described by Klapwijk et al., 2016) in which participants were presented with negative facial expressions (angry and fearful). In addition, CU traits (YPTI; Andershed et al., 2002), antisocial tendencies and externalizing and internalizing symptomology were assessed, as well as salivary *OXTR* methylation values (hg38, 3:8767595-8767848; 12 CpG sites located in exon III). Analyses revealed that a positive interaction between *OXTR* methylation and CU trait severity significantly impacted the processing of distressing social information, as indicated by frontoparietal hyperactivity and reduced amygdala-frontoparietal connectivity in CP individuals. Interestingly, the healthy control group showed the exact opposite activation pattern. This prompts new research questions for future studies, as this discrepancy in brain activation between healthy and affected individuals is currently poorly understood.

The longitudinal study by Cecil et al. (2014) extended previous studies by investigating the relation between *OXTR* methylation and pre- and postnatal environmental risk exposure to elucidate the etiological pathways leading to CU traits and CPs. Cord blood samples at birth and peripheral blood samples at age seven and nine were collected from 84 CP individuals from the ongoing Avon Longitudinal Study of Parents and Adolescents (ALSPAC; Fraser et al., 2013; Relton et al., 2015) to assess *OXTR* methylation levels (hg38, 3:8767276-8769594; spanning from exon I to exon III). The severity of CU traits (SDQ; Goodman, 1997, as described in Moran et al., 2008), internalizing problems (DAWBA; Goodman et al., 2011) and environmental risk scores were assessed at age 13. Results showed that higher *OXTR* methylation levels at birth were significantly associated with higher CU traits at age 13, but only in the low internalizing subgroup ($n = 39$). Also prenatal parental risks (e.g. substance abuse, parental psychopathology or criminal involvement) were significantly associated with *OXTR* methylation at birth in this group. This not only replicates Dadds et al. (2014) and Aghajani et al. (2018) by showing an association between high *OXTR* methylation and high CU traits, but also underscores the impact of pre- and postnatal experiences on mental health in later stages of life.

In a similar study paradigm, Milaniak et al. (2017) sought to examine the impact of prenatal environmental stressors on *OXTR* methylation in CP individuals. To this aim, a subset of 91 young-adults with established CPs were included from the ALSPAC (Fraser et al., 2013; Relton et al., 2015), of which cord blood samples were collected at birth to assess *OXTR* methylation levels (hg38, 3:8768391, 8768453, 8768906; spanning from intron I to intron II). Pre- and postnatal environmental risk scores, assessments of internalizing and externalizing problems at age 7,8,10, 12 and 13 and psychosocial functioning at age 13 (SDQ; Goodman, 1997) were assessed as well. Significantly enhanced *OXTR* methylation across all individual CpG sites was related to higher resilience to CPs at age 13. Interestingly, this contradicts previous findings by Dadds et al. (2014), Aghajani et al. (2018) and Cecil et al. (2014), all reporting a positive relation between *OXTR* methylation levels and CU trait severity. Nevertheless, the current results do highlight the critical impact of prenatal environmental factors on the development of child psychopathologies, and furthermore put forward DNA methylation as mechanism by which early childhood experiences might become biologically embedded.

3.6. Epigenetics as biological link between (early) environment and disease susceptibility

Differential DNA methylation patterns of *OXTR* have been repeatedly linked to psychiatric disorders characterized by deficits in social cognition and functioning, as extensively described in the sections above. Several studies hinted towards the impact of environmental events on DNA methylation patterns. Implicitly, this suggests that epigenetic variability may not only influence interpersonal variability in disease susceptibility, but that these epigenetic mechanisms themselves are under influence of etiological factors. In other words, *OXTR* methylation may be dynamically responsive to the environment. In this way, epigenetic variability may serve as biological link between environmental events and disease susceptibility later in life.

In an effort to demonstrate that environmental events indeed dynamically alter *OXTR* methylation, Unternaehrer et al. (2012) subjected 76 participants to the Trier social stress test (Kirschbaum et al., 1993). Peripheral blood samples were taken right before, 10 minutes after and 90 minutes after stress exposure and *OXTR* methylation levels were assessed for 35 CpG sites located in exon III (hg38, 3:8767589-

8768307). Analysis revealed that mean DNA methylation levels increased directly after stress exposure and then significantly decreased even below baseline 90 minutes after stress exposure. Although it cannot be excluded that this may partly reflect changes in blood cell composition (Dhabhar et al., 1995; Zhu et al., 2012), the authors state that this overcompensating mechanism after exposure to an environmental event, such as acute social stress, may indicate that the OXT system functions as a dynamic buffering system to cope with the event and to support physiological recovery afterwards. It must however be mentioned that these findings should be interpreted with caution as they are not replicated and report only small methylation changes (0.38% increase and 1.04% decrease) based on a single measurement. The reported differences may therefore lie within the error range of the assay.

Whereas short exposure to such adverse events may be neutralized, extended exposure to adverse environments may evolve to more pathological conditions. Especially when chronic adversities occur during critical periods of development like early childhood, this may have long-lasting consequences on autonomic, immune, neuroendocrine and neural functioning (Danese and McEwen, 2012), given that early life is a critical period for the offspring's health as well as for the cognitive and social-emotional development of the child (Beck, 1998; Bos, 2017; Field, 2011; Rilling and Young, 2014).

One of the main predictors of epigenetic variation in human newborns is prenatal exposure to maternal adversities like distress, depression and anxiety (Lutz and Turecki, 2014). Based on the animal finding that prenatal stress can induce variations in the OXT system as well as in social behaviors (de Souza et al., 2013), Unternaehrer et al. (2016) investigated whether human maternal adversities during pregnancy predicted variations in *OXTR* methylation in offspring. Various measures of maternal adversities of 100 pregnant women, including life changing events prior to the pregnancy, chronic stress experiences during pregnancy and maternal depressive symptoms during the last stage of pregnancy were related to cord blood *OXTR* methylation measurements of 13 *OXTR* CpG sites located in exon III (hg38, 3:8767589-8767848). Interestingly, some but not all indicators of maternal adversities predicted cord blood *OXTR* methylation in offspring. For example, the total number of stressful events prior to pregnancy did predict decreased DNA methylation levels, as opposed to chronic stress experiences during pregnancy. This may indicate a stronger relevance of stressful life events rather than subjective experiences of stress for DNA methylation status, which is in line with previous literature (Cao-Lei et al., 2014). Furthermore, maternal depressive symptoms during the final stage of pregnancy predicted lower *OXTR* methylation. The authors suggest that this may indicate that *OXTR* methylation could provide an adaptive mechanism that enables a more flexible regulation of *OXTR* expression in a postnatal environment that is characterized by restricted maternal care due to maternal depressive symptoms (Lovejoy et al., 2000; Unternaehrer et al., 2016).

Likewise, Rijlaarsdam et al. (2017) examined the interaction between *OXTR* SNP rs53576 and variability in neonatal *OXTR* methylation in relation with prenatal exposure to maternal stress. Cord blood samples from 743 children were collected at birth to assess genotypic (*OXTR* SNP rs53576) and epigenetic measures (hg38, 3:8767620, 8767815, 8767850; located in intron I and exon II), as well as maternal reports of prenatal stress exposure. Overall, no significant association was found between prenatal maternal stress exposure and *OXTR* methylation for both *OXTR* rs53576 G- and A-allele carriers, as well as between prenatal stress exposure and *OXTR* methylation. This result attenuates the suggested mediating role of *OXTR* methylation between prenatal exposure and the offspring's social and cognitive development (Monk et al., 2012; Rijlaarsdam et al., 2017).

Galbally et al. (2018) sought to investigate the impact of perinatal depression and antidepressant medication use on *OXTR* methylation status of the developing fetus (termed 'fetal programming', for a review see Novakovic and Saffery, 2012). A subsample of 239 women from the Mercy Pregnancy and Emotional Wellbeing Study (Galbally et al., 2017), of which 52 with MDD according to the DSM-IV (First et al., 1997), was included. Third semester depressive symptoms were assessed (EPDS; Cox, Holden, & Sagovsky, 1987), as well as plasma antidepressant medication levels and placental *OXTR* methylation values (hg38, 3: 8767815–8768964; 22 CpG sites in exon III and intron III) collected at delivery. Interestingly, whereas perinatal depression was not related to changes in placental *OXTR* methylation levels, cord blood antidepressant medications levels were associated with enhanced placental *OXTR* methylation levels at one CpG site (hg38, 8810731) – which might stimulate new research into the effect of prenatal (antidepressant) medication use on the psychosocial development of the offspring.

In addition, King et al. (2017) examined the intergenerational transmission of DNA methylation patterns from mother to child by studying the association between perinatal depression and DNA methylation patterns of three oxytocin-related genes among mothers and their children. Besides exon III of the OXTR gene (hg38, 3:8767620-8767815; 22 CpG sites), DNA methylation patterns of two intergenic regions (IGRs) between the OXT gene and the vasopressin (AVP) gene were assessed from saliva samples of 220 mother-child dyads. Overall, mothers with persistent perinatal depressive symptoms according to the EPDS, demonstrated significant hypermethylation of *OXTR* and significant hypomethylation of the AVP IGR after multiple test correction, as well as higher DNA methylation of the OXT IGR, although not statistically significant. In addition, while none of the results did reach significance, DNA methylation levels were highest in children exposed to persistent perinatal depressive symptoms for all three genomic regions.

Interestingly, and perhaps somewhat surprising, results from the studies described above are inconsistent in reporting significant associations between the exposure to prenatal adversities and changes in *OXTR* methylation patterns in the offspring. Whereas two studies were successful in demonstrating substantial changes in *OXTR* methylation patterns upon prenatal exposure to maternal depression (King et al., 2017; Unternaehrer et al., 2016), three reported an absence of such effects of either prenatal exposure to maternal stress (Rijlaarsdam et al., 2017; Unternaehrer et al., 2016) or to maternal depression (Galbally et al., 2018). This is in line with the results from studies on the effect of adverse prenatal exposures on *OXTR* methylation in relation to CP etiology, reporting either no associations (Milaniak et al., 2017) or signitificant associations between high prenatal parental risk and lower *OXTR* methylation (Cecil et al., 2014). Such a discrepancy in results may arise from differences in sample groups, as well as from variation in *OXTR* CpG locations across studies given that not all CpGs of a specific gene are equally related to functional changes in gene expression (Lam et al., 2012; Milaniak et al., 2017). In addition, the more traditional view on the functional effect of DNA methylation, that is, highly methylated genes are expressed at low levels, was challenged by a human epigenetic population study that showed that a substantial part of the investigated human genes diverged from this pattern, both within an individual and across individuals. Again, this was mainly driven by the genomic context of a given CpG (Lam et al., 2012). This even further emphasizes the complexity and difficulty in interpreting the impact of DNA methylation on human behavioral phenotypes.

Variations in *OXTR* methylation patterns of the offspring due to exposure to prenatal adversities are mostly maintained in the (early) postnatal period, mediated by variations in the quality of dyadic mother-infant interactions and parenting style. To illustrate, depressed mothers exhibit reduced responsiveness, attachment and maternal sensitivity towards their child (Bos, 2017; Field, 2010; Monk et al., 2012). Given the critical impact of the quality of caregiving behavior on the healthy development of the child, one could speculate that variations in caregiving behavior might influence susceptibility to a wide variety of (adult) psychopathologies by inducing long-term changes in epigenetic regulation of OXT functioning.

Investigating such a mediating role of *OXTR* methylation role, Unternaehrer et al. (2015) sought to investigate the association between childhood maternal care and *OXTR* methylation patterns in adulthood. A subsample of 84 participants was equally divided into two groups, according to retrospective childhood maternal care experiences assessed with the Parental Bonding Instrument (PBI; Parker et al., 1979). DNA methylation levels of 23 CpG sites located in *OXTR* exon III (hg38, 3:8767589-8768307) were assessed from blood samples. Overall, exposure to low childhood maternal care was associated with DNA hypermethylation of one of the two target regions of *OXTR* (hg38, 3:8767824-8768307; 17 CpG sites), compared to exposure to high childhood maternal care. This confirms the hypothesis that early life adversities are associated with changes in DNA methylation patterns.

Moore et al. (2017) further examined the importance of mother-infant interactions in early life by studying the relation between early postnatal tactile contact and socio-cognitive development of the child as mediated by DNA methylation patterns across *NR3C1*, *OPRM1*, *BDNF* and *OXTR* (hg38, 3: 8764631–8770072; 7 CpG sites across the entire CpG island) – candidate genes relevant to the neurobiological encoding of tactile contact. Caregiving reports of infant distress and tactile contact at five weeks of age (Baby's Day Diary; Barr et al., 1988; St.James-Roberts and Plewis, 1996) and buccal epithelial cells and saliva samples to assess both genotype and DNA methylation were collected at the age of 4–5 from 94 children. Overall, no significant association could be found between postnatal contact and either genotype or DNA methylation patterns of all four candidate genes. An additional genome wide DNA methylation assay did however reveal three differently methylated genes between low and high tactile contact groups (*LDHAL, HLA-DRB5, ZFAND2A*). The functional relevance of this in terms of mediating the link between caregiving behaviors and the offspring's healthy development, however, is unknown and should be further investigated.

Additionally, Gouin et al. (2017) investigated the association between exposure to early life adversities (ELA), childhood trajectories of anxiousness and *OXTR* methylation frequency in adulthood. A subsample of 46 adult participants from a longitudinal study provided a blood sample for epigenetic analysis (hg38, 3:8765201-8769146; 16 CpG sites). Prospectively collected indicators of childhood socio-economic status (SES), self-reported exposure to physical and sexual abuse (combined from the Parent-Child Conflict Tactics Scale (Straus et al., 1996); Adverse Childhood Experiences Questionnaire (Felitti et al., 1998) and the Sexually Victimized Children Questionnaire (Finkelhor, 1979)) and teacher-rated childhood trajectories of anxiousness and disruptiveness (Social Behavior Questionnaire; Masse and Tremblay, 1997) were assessed as well. Analyses revealed a positive relation between exposure to ELA and DNA methylation at one CpG site in the first intron (hg38, 3:8769047) in females, as well as between childhood anxiousness and DNA methylation at one CpG site in the promoter region (hg38, 3:8769857) in females, but again not in males. Both associations remained significant after multiple test correction. Interestingly, these sexually dimorphic effects of *OXTR* methylation parallel the sex-specific associations between *OXTR* methylation and emotion regulation as reported by Rubin et al. (2016) and add to the literature about sex-specific effects of the OXT system (Ditzen et al., 2013; Fischer-Shofty et al., 2013; Rilling et al., 2014; Tseng et al., 2014). The implications of this, however, are currently unknown and need to be addressed in future studies. Moreover, Gouin et al. (2017) examined the functional significance of *OXTR* methylation in an *in vitro* luciferase experiment. It revealed that higher *OXTR* methylation in the promoter region resulted in lower *OXTR* expression, thereby complementing previous results (Gregory et al., 2009; Kusui et al., 2001).

Smearman et al. (2016) examined the impact of childhood abuse on the mental health developmental trajectory of children. A sample of 393 patients was included, of which genetic (44 SNPs) and epigenetic (hg38, 3:8764631-8770072, 18 CpG sites located across the entire CpG island) measures of *OXTR* were assessed from whole blood samples. These biological measures were combined with self-reported measures of trauma with the Child Trauma Questionnaire (CTQ; Bernstein et al., 2003) and the Traumatic Events Inventory (TEI; Schwartz et al., 2005), as well as current depressive (BDI; Beck et al., 1961) and anxiety symptoms (HAM-A; Maier et al., 1988). Although *OXTR* methylation did not mediate the relation between childhood abuse and psychiatric symptoms, childhood abuse and *OXTR* methylation of three CpG sites (hg38, 3: 8764631, 8769294 and 8769318) interacted to predict depression and anxiety in adulthood – maintaining significance after multiple test correction. Interestingly, the pattern of interaction was location specific, a similar finding as reported in previous studies (Bell et al., 2015; Kimmel et al., 2016). When exploring the interaction between genetics, DNA methylation and early environment, *OXTR* SNPs rs53576 and rs2254298 did not interact with childhood abuse to predict adult psychiatric outcomes. In contrast, *OXTR* methylation at associated CpG sites did, which may suggest that DNA methylation has an important mediating role between genetic variation and actual gene expression, and consequently the biological effect of such a variation.

Showing that the impact of adversities on the OXT system is not limited to childhood experiences, Simons et al. (2016) investigated the effect of persistent adverse environments on the negative cognitive bias characteristically associated with a depressive phenotype. A subsample of 100 females was included of which peripheral blood samples were collected to assess *OXTR* methylation levels of four CpG sites (hg38, 3:8769294, 8769318, 8769406 and 8769593; located in exon I). Various self-reported measures of internalizing problems were assessed, including distrust (ECR-R; Fraley et al., 2000), pessimism (LOT; Scheier and Carver, 1985) and depression (Mini-MASQ; (Clark and Watson, 1995), as well as self-reported measures of adult adversity, including unmet material needs and neighborhood disorder (Conger and Elder, 1994; Sampson et al., 1997). Overall, results demonstrated that the negative effect of adverse events in adulthood on feelings of pessimism and distrust are partially mediated through *OXTR* methylation, and that the effect of *OXTR* methylation on depression is fully mediated by the association with feelings of pessimism and distrust. In other words, adverse events appear to have a long-lasting impact through changes in *OXTR* methylation, thereby establishing a negative cognitive bias and enhancing the risk on development of depression.

Altogether, these studies demonstrate that epigenetic regulation serves as a molecular mechanism by which environmental events or factors can become biologically embedded, thereby altering an individuals' vulnerability for a wide variety of psychopathologies (Meaney, 2010; Szyf, 2011; Szyf and Bick, 2013). As suggested by various studies, these dynamic changes in *OXTR* methylation patterns may be key in calibrating the sensitivity of the OXT system in response to an individual's environment. Interestingly, the plasticity of the OXT system is not limited to (early) childhood, but remains functional throughout life, as demonstrated by Simons et al. (2016).

4. Discussion and future directions

4.1. Genetics and epigenetics

Whereas studies on the relation between epigenetics and socio-behavioral phenotypes is relatively new, the influence of genetic variations of *OXTR* on these phenotypes preceded these studies (Bakermans-Kranenburg and van IJzendoorn, 2014). However, recent developments point out that to enhance our understanding of the complex interplay between genomic factors and social behaviors, other levels of genomic variation need to be incorporated at the same time (Bonder et al., 2017; Vermunt et al., 2016). Here, the minority of studies investigated both epigenetic and genetic measures of *OXTR* (Aghajani et al., 2018; Bell et al., 2015; Chagnon et al., 2015; Kimmel et al., 2016; Milaniak et al., 2017; Moore et al., 2017; Reiner et al., 2015; Rijlaarsdam et al., 2017; Smearman et al., 2016; Ziegler et al., 2015). As some of the authors argue, the additional layer of epigenetic regulation may either mask or reveal associations between underlying SNPs and social phenotypes.

Recent studies indeed suggest that *OXTR* methylation is influenced by the underlying genotype. For example, Smearman et al. (2016) showed that *OXTR* genotype interacts with *OXTR* methylation of specific CpG sites and that specific SNPs interacted with *OXTR* methylation to predict phenotypical outcomes. Similarly, Rijlaarsdam et al. (2017) demonstrated allele-specific effects of DNA methylation, indicative of an interaction between *OXTR* methylation and genotype, which has also been observed in the studies by Chagnon et al. (2015), Bell et al. (2015), Reiner et al. (2015) and Moore et al. (2017). Ultimately, future studies investigating the effect of an individual's genome on socio-behavioral phenotypes should integrate both genotypic and epigenetic measures to fully understand and interpret the complex interaction between inherited and environmental components that collaboratively determine the phenotypic outcome.

4.2. Sources of inter-individual variation of DNA methylation

Subject to debate is whether and to what extent the DNA methylation pattern in peripheral tissues (blood, saliva or buccal cells) is an accurate reflection of the DNA methylation pattern in the brain, given that DNA methylation is highly tissue-specific (Byun et al., 2009; Illingworth et al., 2008; Ladd-Acosta et al., 2007). Due to difficulties with procuring human brain tissue, human psychosocial studies are often restricted to the assessment of DNA methylation from peripheral tissues, of which blood is the most widely used option. Several studies correlating DNA methylation patterns in blood and (postmortem) brain tissue suggest large differences in general (Walton et al., 2015) but consistency in DNA methylation patterns for some regions in the genome (Davies et al., 2012; Farré et al., 2015; Horvath et al., 2012; Kaminsky et al., 2012; Sullivan et al., 2006; Yuferov et al., 2011). Another source of variation is the cellular heterogeneity of biological samples that can have substantial influence on DNA methylation patterns (Adalsteinsson et al., 2012; Holbrook et al., 2017; Jaffe and Irizarry, 2014; Wang et al., 2012). It has been reported that both stress (Zhu et al., 2012) and adverse childhood experiences (Surtees et al., 2003) are associated with variations in blood cell distribution, and this phenomenon may at least partially underlie the observed interactions between environmental events and differential *OXTR* methylation patterns. Although some studies control for cellular heterogeneity (Kimmel et al., 2016; Moore et al., 2017; Nawijn et al., 2018; Puglia et al., 2018; Rijlaarsdam et al., 2017; Simons et al., 2017; Smearman et al., 2016; Unternaehrer et al., 2012, 2015), it thus remains a potential source of bias that may have implications for the interpretation of interindividual variation in DNA methylation across multiple biological samples (Holbrook et al., 2017). To reduce such inter-individual variability due to cellular heterogeneity, more homogeneous samples are needed (e.g. using fractionated blood, adjustments for cell count or statistical approaches (Lin et al., 2016)). It also has been suggested that buccal cells are better surrogates than blood samples for the investigation of non-blood based phenotypes (Lowe et al., 2013), but only five articles in this review assessed *OXTR* methylation measures from either buccal cells or saliva samples (Aghajani et al., 2018; Ein-Dor et al., 2018; Kim et al., 2014; King et al., 2017; Moore et al., 2017). Although a detailed analysis of the implications of cell- and tissue-specificity of DNA methylation is beyond the scope of this review, it is a serious limitation of the study field. It has, however, been suggested that by prioritizing CpG sites that highly correlate across tissue types, future studies investigating DNA methylation may partially eliminate tissue-specificity as source of inter-individual variability (Walton et al., 2015).

Demographical and lifestyle characteristics of the sample can also account for substantial variation in DNA methylation, including age, ethnicity, gender and smoking (Kader and Ghai, 2017). For example, aging is strongly correlated with alterations in DNA methylation patterns (Fraga et al., 2005; Heyn et al., 2012) and in general with the establishment of global DNA hypermethylation of CpG sites located in a CpG island (Horvath et al., 2012; Johnson et al., 2012). Genetic ancestry is another potential confounder in DNA methylation studies, and this ethnic disparity in DNA methylation is already present at birth (Adkins et al., 2011). Therefore, most studies have included an ethnically homogenous sample to exclude potential confounding effects of ethnicity. However, this significantly decreases the generalizability of the obtained results. Moreover, although the studies on autism by Elagoz Yuksel et al. (2016) and Gregory et al. (2009) both included Caucasian individuals, Turkish and American respectively, they report inconsistent findings with respect to *OXTR* methylation. This shows that even within ethnic populations, significant differences in DNA methylation patterns do exist and this indicates that future studies should either further restrict the sample group, e.g. Caucasians of European descent (Puglia et al., 2018), or should include multiple ethnic groups and control for genetic differences between groups. In addition, DNA methylation is subject to gender differences (Boks et al., 2009). These sexually dimorphic effects of *OXTR* methylation on socio-behavioral phenotypes are indeed demonstrated by various studies included in this review (Gouin et al., 2017; Gregory et al., 2009; Nawijn et al., 2018; Puglia et al., 2015; Rubin et al., 2016). Generally, these studies mostly reported higher sensitivity of female subjects as compared to male subjects, which is broadly in line with the literature on sex-specificity of the OXT system (Dumais and Veenema, 2016). A final confounder is the strong correlation between smoking and variation in DNA methylation (Breitling et al., 2011; Zeilinger et al., 2013). Even prenatal exposure to smoking significantly alters DNA methylation patterns in the offspring (Joubert et al., 2012; Markunas et al., 2014; Terry et al., 2008). Notably, the influence of smoking on DNA methylation also varies between ethnic groups, which is likely due to genetics, lifestyle, diet and behavioral differences (Breitling et al., 2011; Elliott et al., 2014; Zeilinger et al., 2013). Whereas many studies included in this review do control for the abovementioned potential confounders (age, ethnicity, sex and cell count), they often do not include smoking status. Future studies investigating the impact of DNA methylation on phenotypes should therefore include this relatively new confounding factor as control variable as well.

These potential confounds of the relation between *OXTR* methylation and socio-behavioral phenotypes are especially important when examining potential therapeutic interventions targeting epigenetic regulation of *OXTR* expression. For example, it is most likely that not all individuals are equally sensitive to the consequences of *OXTR* methylation and the presumed functional effects on OXT sensitivity (Bos, 2017). Following this line of reasoning, potential future therapeutic strategies interfering with *OXTR* methylation may not exert the anticipated beneficial effects across individuals – comparable with the gender-specific beneficial effects of intranasal OXT on social functioning (Rilling et al., 2014).

Lastly, results from previous studies on DNA methylation in relation to social phenotypes and psychopathologies are often not directly comparable with results from present studies. This is mainly because different CpG sites are assessed, as well as different techniques and nomenclature are used across studies. To enable comparison across all studies in this field, it is crucial to decide on a standard set of CpG sites that will be investigated in future studies. This review aims to facilitate this process by providing a starting point by directly comparing all results from past studies and more importantly, by conversion of the locations and coordinates of the investigated CpG sites according to the most recent genetic assembly, GRCh38. This enables future studies to directly compare their own results to previous findings and to make substantiated conclusions about their results.

4.3. Replication and addressing heterogeneity

As argued by most authors of the included articles in this review, independent replications of the presented findings in larger samples are required. There is a case for homogeneous samples in order to reduce confounding and increase power, however, to advance the field in

general, large heterogeneous samples are important (Ioannidis et al., 2001). Increasing the heterogeneity of the sample group will not only enhance the generalizability of the results, but also allows for comparisons within and between genders and age- and ethnic groups. Moreover, many studies specifically include physically and psychologically healthy individuals or base their sample groups on extreme phenotypic indications. It is therefore possible that different patterns of results may emerge among individuals that display less or moderate phenotypic characterizations, especially given the highly heterogeneous nature of many of the discussed psychopathologies. This aspect should be addressed in future studies, preferably by including a normally distributed participant sample. Additionally, longitudinal studies could provide unique insight in causal relations between *OXTR* methylation patterns and socio-behavioral phenotypes and enables the investigation of actual changes in DNA methylation patterns due to exposure to environmental events or factors.

Another phenomenon advocating for validation and replication of reported findings relates to the statistical issues that inevitably arise when analyzing and interpreting DNA methylation patterns in relation to psychosocial traits or psychopathologies (Jones et al., 2018). One of these important issues is the strength of the reported associations. Similar to genetic studies in the early days there is an element of type I error inflation (false positives) due to candidate gene approaches and publication bias. In absence of large epigenome wide studies of homogeneous phenotypes it cannot be ascertained whether the relationship between *OXTR* methylation and behavioral phenotypes survives epigenome wide multiple testing correction. This is particularly important given that the majority of studies described here have examined DNA methylation patterns across a large number of gene regions and individual CpG sites while not adjusting for multiple comparisons in the statistical analyses (Aghajani et al., 2018; Cappi et al., 2016; Cecil et al., 2014; Chagnon et al., 2015; Gregory et al., 2009; Milaniak et al., 2017; Reiner et al., 2015; Rijlaarsdam et al., 2017; Simons et al., 2017; Unternaehrer et al., 2015, 2012). Future studies should be attentive to such statistical issues and should strive for replication of their findings in independent datasets. Meta-analyses might provide a useful tool to validate prior findings and confirm reliable results across studies (Jones et al., 2018; Lin et al., 2016).

In addition, while most studies solely focus on *OXTR* when investigating the role of the OXT system in socio-behavioral phenotypes, it would be interesting to include DNA methylation measures of other genes within the same functional circuitry, such as *OXT, LNPEP* and *CD38*, or genes related to the vasopressinergic system (Ebstein et al., 2012; Feldman et al., 2016), as done in the study by King et al. (2017). To date, one study investigated the interaction between *OXT* methylation and human social behavior (Haas et al., 2016), showing that DNA hypomethylation of the promoter region of *OXT* correlated with higher sociability, as indicated by a more secure attachment style, improved ability of facial recognition, larger fusiform gyrus gray matter volume and greater STS activity during social-cognitive fMRI tasks (Haas et al., 2016). This is in line with the majority of literature on *OXTR* methylation above described: lower levels of promoter DNA methylation, presumably yielding higher gene expression and OXT pathway functioning, associates with higher social sensitivity.

4.4. Functional significance of OXTR methylation

Although the amount of studies investigating the relation between *OXTR* methylation and socio-behavioral phenotypes has intensively increased in the last years, the relevance of these studies would markedly increase if the functional significance of epigenetic variation in *OXTR* was clearer. In other words, it is of great importance to understand the actual impact of alterations in DNA methylation patterns on gene expression, protein levels and functionality of the OXT system. Since most studies in this review do not assess *OXTR* expression or protein levels, most functional explanations of reported alterations in *OXTR* methylation remain speculative. In this current review, only four studies assessed the relation of changes in *OXTR* methylation patterns with *OXTR* expression (Gouin et al., 2017; Gregory et al., 2009) or with peripheral OXT levels (Dadds et al., 2014; Rubin et al., 2016). Future studies should prioritize the precise specification of the functional relevance of epigenetic variability of the OXTR gene, given that this fundamental aspect of epigenetic regulation of phenotypic outcomes is an underexposed subject in the current literature. As of now, such associative epigenetic patterns in relation to psychopathologies are probably best understood as potential biomarkers (Jones et al., 2018). Future studies on the underlying molecular mechanisms of these epigenetic patterns might provide further understanding of functional effects. In this respect, results from animal studies could serve as guideline for future human studies (Harony-Nicolas et al., 2014; Mamrut et al., 2013).

5. Conclusions

A growing body of evidence suggests that epigenetic variability of *OXTR* is related to inter-individual differences in socio-behavioral phenotypes and susceptibility to psychopathologies characterized by social deficits. Epigenetic regulation of OXT function may provide this neurobiological system with a considerable flexibility in response to environmental events, especially those that occur during early childhood. By impacting *OXTR* methylation, these environmental events may become biologically embedded and have lasting consequences on an individual's social sensitivity. Here, we systematically reviewed all articles that discuss the epigenetic variability of *OXTR* in relation to human socio-behavioral phenotypes and as such, provided a comprehensive overview that will aid future research in the interdisciplinary field of epigenetics and socio-behavioral science.

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Appendix A. Supplementary data

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