Neuroimaging genetics of oxytocin: A transcriptomics-informed systematic review

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ABSTRACT

The last couple of decades have witnessed a rapid accumulation of studies implicating oxytocin (OT) in several neurobiological underpinnings of human behaviour and their impairment in psychiatric illness. Specifically, a neuroimaging genetics approach is helping elucidate the impact of variations in OT pathway genes on the human brain. In this review, we provide the first systematic account and discussion of all previous findings arising from human neuroimaging (epi)genetic studies of OT-related genes. To improve our mechanistic interpretation of such findings, we used data from the Genotype-Tissue Expression project to explore the functional impact the genetic variations may have on the human transcriptome. As a result, we provide an up-to-date summary of brain circuits found to be impacted by OT-relevant (epi)genetic variability, map brain pathways linking OT genes to disease, and highlight several (epi)genetic factors that modulate brain responses to intranasal OT. Finally, we provide some suggestions we believe might improve future research in the field.

1. Introduction

Oxytocin (OT) is a hypothalamic nonapeptide long recognized for its hormonal function during labour and lactation (Grinevich et al., 2016), and for which a prominent role in the development and regulation of human socio-affective behaviour has later been demonstrated, as we and others have reviewed (Miller and Caldwell, 2015;Churchland and Winkelman, 2012; Johnson and Young, 2017; Torres et al., 2018). Further roles of OT include pain regulation (Tracy et al., 2015), food metabolism (Leslie et al., 2018) and neuroinflammation (Kareлина et al., 2011). This expanded importance of OT, namely in brain function, ignited interest in its modulation as a new promising therapeutic strategy for several brain disorders which are currently missing effective treatments (i.e. autism spectrum disorder (Anagnostou et al., 2014), schizophrenia (Shilling and Feifel, 2016), migraine (Tzabazis et al., 2017), stroke (Kareлина et al., 2011), obesity (Olszewski et al., 2017) and Prader-Willi syndrome (Rice et al., 2018)), among others. However, we believe mechanistic pathophysiological questions remain to be answered until OT’s psycho-therapeutic potential can be fully unraveled.

The discovery that intranasal administration is successful in delivering OT to the central nervous system (Lee et al., 2020), and the advancement in human genome mapping, are useful tools to understand the OT system. Respectively, they allow us to assess how variability in human behaviour and cognition, and their neurocorrelates (accessible via functional magnetic resonance imaging (fMRI), electroencephalography (EEG) or positron emission tomography (PET)), may be a function of: (1) acute (via pharmacological potentiation through intranasal OT administration) and (2) chronic (via naturalistic genetic diversity) variability in OTergic tonus. Alongside measurements of OT in biological fluids, these two approaches (pharmaconeuroimaging and neuroimaging genetics) have been at the heart of human OT research.

Neuroimaging (epi)genetics studies, which we herein review, examine if/how a certain genetic polymorphism or gene’s methylation status impacts brain neuroimaging phenotypes, be they functional (task-related, resting-state, or neurochemical (Wandschneider and Koepp, 2016)) or structural (Winterer et al., 2005). This approach complements pharmacological neuroimaging (which has a typical randomized control trial design), by assessing the impact of naturalistic variation between individuals, in a substance’s level and signalling degree which is within normal physiological range and free from artificial manipulation (Gurung and Prata, 2015). Of course, both mentioned approaches can be

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combined, in neuroimaging pharmaco-(epi)genetics designs, to elucidate how the brain’s response to a certain pharmacological manipulation (like intranasal OT) may depend on genetic variations or epigenetic nuances (particularly those directly part of the OT pathway). Nevertheless, interpretation of most findings is strongly limited by the lack of knowledge of the functional consequences of the studied polymorphisms, especially those located in non-coding regions or leading to no amino-acid changes.

Although the vast majority of evidence implicating OT in human physiology has arisen from its pharmacological administration (reviewed elsewhere (Bethlehem et al., 2013; Wigton et al., 2015)), neuroimaging (epi)genetics studies of the OT system have grown considerably over the last five years. Given the resulting plethora of genetic variations, neuroimaging modalities, brain areas and clinical populations investigated, we aim to herein provide a systematic, in-depth and integrated overview of these findings, to better make sense, and increase usefulness, of such research. In the present review, we provide the first comprehensive overview of all OT neuroimaging (epi) genetics advancements to date, to answer the primary question: ‘How does inter-subject genetic variability in the OT system affect brain structure and function?’ and secondary question ‘How are the latter effects altered in psychiatric pathologies?’. (We note that, specifically for the OT’s receptor genotype effects on resting-state functional connectivity, a previous systematic review has been published (Seeley et al., 2018)). We include all single nucleotide polymorphisms (SNPs), and methylation findings reported to date of the three genes coding for main players of the OT pathway (Feldman et al., 2016): the OT/neurophysin I prepropeptide (OXT), the receptor for OT (OXTR) and the cluster of differentiation 38 glycoprotein (CD38) genes. We include studies using any neuroimaging modality (MRI, EEG, magnetencephalography (MEG), PET and single-photon emission computed tomography (SPECT)) and both healthy individuals and clinical samples, in order to better map brain pathophysiological pathways of OT genes. Finally, we also include all pharmaco-neuroimaging (epi)genetics studies using intranasal OT, in order to summarize all (epi)genetics nuances that may affect, and thus help predict, a response. The reviewed findings are discussed and reconciled with current frameworks of OT’s role in human neurophysiology, health and illness; and, as a result, 2) inform the rational design of innovative OTergic neuropharmacological therapies; and 3) foster the development of intranasal OT pharmaco-genetics biomarkers to help us predict who may be more likely to benefit from such therapies.

2. Methods

2.1. Search strategy

We followed the PRISMA guidelines for systematic reviews (Liberati et al., 2009) to identify relevant studies for inclusion in the current review; having started from the initially identified 119 studies down to the 62 included as per flowchart in Fig. 1. A search in Medline was performed to identify all existing neuroimaging (epi)genetics studies of the OT system-related genes in humans, using the query: “oxytocin AND (gene OR genotype OR polymorphism OR genetic marker OR methylation OR epigenetic) AND (neuroimaging OR MRI OR EEG OR MEG OR PET OR SPECT)”. All references in the retrieved articles were also manually checked to detect any previously missed articles. Duplicated studies were removed using ENDNOTE smart group function.

2.2. Selection criteria

Inclusion and exclusion criteria were tailored to obtain all human studies published up to 6th of June of 2021 (irrespective of publication date or subjects’ age, sex or ethnicity), which were original reports on the impact of genetic variations or methylation patterns of the OXT, OXTR, or CD38 genes on human brain structure, function or neurochemistry, in any imaging modality or diagnosis, including OT pharmaco-neuroimaging (epi)genetics. Reports also had to be available in full-text, and published, in English, in a peer-reviewed journal. Exclusion criteria were: being a review or meta-analysis, non-English written, non-peer reviewed, a proceedings publication, an animal-model study, a clinical trial registration, a behavioural genetics study without brain phenotyping or a neuroimaging genetics study not related to the OT system.

Fig. 1. Studies’ selection for systematic review according to PRISMA guidelines.
2.3. Systematic review

For each retrieved study, we recorded the following variables: number, diagnosis (if relevant), sex and ethnicity of participants, genotyping methods, genetic variations analysed, brain (neuroimaging) phenotype and core results. Table 1 lists all SNPs included in this review, Tables 2 and 3 summarize imaging genetics and epigenetics studies, respectively, in the healthy population, Tables 4 and 5 summarise imaging genetics and epigenetics studies, respectively, in clinical samples. Table 6 summarizes OT pharmaco-neuroimaging (epi)genetics studies, where we further extracted information on study design, drug dose, administration route and time interval between administration and neuroimaging data acquisition. We searched for the location (herein listed in Supplemental Material Text T1) and function of each SNP using the UCSC genome browser (https://genome.ucsc.edu), the Pubmed dbSNP browser (https://www.ncbi.nlm.nih.gov/snp) and the Ensemble genome browser (https://www.ensembl.org); using the human assembly of December 2013 (GRCh38/hg38). In Discussion, we report associations always using the minor allele as a reference, so that the directionality of effects can be easily compared between studies. Tables 2–6, referring to the 62 studies’ findings, contain nominally statistically significant results (according to each study’s authors’ criteria), and suggestive but non-significant results were highlighted as ‘trends’.

2.4. Expression Quantitative Trait Loci (eQTL) annotation

We used the publicly available database of The Genotype-Tissue Expression (GTex) project (http://www.gtexportal.org/home/) to ascertain the impact of each of the genetic variations herein reviewed on gene expression in the brain. This database lists the degree of association of quantitative trait loci (QTLs), mostly SNPs, with RNA levels in brain tissue (i.e. expression QTLs or eQTLs) (Consortium, 2013; Nicolae et al., 2010). Specifically, the database holds data for 75 eQTLs of the CD38 gene, although none affecting mRNA expression in the brain; 2179 eQTLs for OXT, of which 304 (14%) act in the brain; and 2509 eQTLs for CD38, of which 228 (9%) act in the brain. We restricted our inspection of RNA levels to genes whose transcription start site is positioned in a window of 1MB from the given genetic variation site (cis-eQTL analysis) (Michaelson et al., 2009). This decision was based on the fact that cis-eQTLs typically have larger (and likely more direct) effect sizes on gene expression than trans-eQTLs (Michaelson et al., 2009). In order to examine whether each of the genetic variations (N = 46) retrieved from the reviewed studies is a cis-eQTL, we manually searched the Gtex eQTL browser, across all the 54 tissues available. Table 1 summarizes the results of this annotation, where we present for each SNP: the identity of the genes whose transcription is affected; the direction and magnitude of this effect; and the body tissue where an association statistically significant after a Bonferroni correction for multiple testing across all 54 tissue types, of an alpha= 0.05, i.e. a p-value < 9.25 × 10^-4, was found. Exact p-values for all the SNPs we investigated, across all body tissues, surviving the above significance threshold, are provided in supplemental Table S3-S5).

2.5. Quality assessment

We appraised each study on an 11-requirement quality score list (detailed in Supplemental Table S1), based on information in its full-text and online supplemental material. For each item, a score of 1–3 depended on whether there was strong (3), some (2), or little or no evidence (1) that it was adhered to. The sum of the 11 items’ scores, divided by the maximum sum applicable to the respective study modality, was then used as an indication of the general quality of the study. No study was discarded from our review on the basis of quality.

3. Results

3.1. Descriptive overview

We reviewed a total of 62 studies, for which we listed all polymorphisms and brain phenotypes, in Table 1; and detailed findings in Tables 2, 3, 4, 5 and 6. Out of those studies: 46 (74%) inspected the impact of OT system-related genes’ variations or methylation on the brain of healthy subjects and 11 (18%) in clinical samples (including ASD, social anxiety disorder (SAD), psychosis and affective disorders), and 5 (8%) explored this impact on brain responses to intranasal OT in healthy subjects. Of the same total, 14 studies (23%) examined the impact of gene methylation of the OXT or OXTR on brain structure and function. Only one study gathered the joint effect of more than one OXTR genetic variation, in the form of an additive polygenic score.

Of the total of 46 genetic variations studied across all studies, the most commonly analysed were the rs53576 (76% of studies), the rs1042778 (20%) and the rs2254298 (34.7%). Most studies focused on OXTR-related variations and methylation (93%). From the reviewed SNPs, only 31 (67%) can be clearly assigned to OXTR, four (9%) to OXT and one (2%) to CD38. The remaining ten variations (22%) have been originally reported as belonging to OXTR but are in fact variations of the neighbouring caveolin-3 (CAV3) and protein-coding Ssu-homolog (SSUH) genes as per the above-mentioned gold-standard gene browsers. CAV3 seems to play a role in neuronal signalling, including that involving the membrane estrogen receptor (Luoma et al., 2008). Not much is known about SSUH, but it is presumed to be involved in cell development, such as in odontogenesis (Xiong et al., 2017).

The studies we reviewed herein varied significantly in the brain phenotypes inspected, spanning brain morphometry (25% of studies), functional and structural connectivity (15%), neurochemistry (6%), and psychological task-based fMRI blood-oxygen-level-dependent (BOLD) (60%), EEG event-related potentials (12%) and functional near-infrared spectroscopy (fNIRS) (2%) responses. A total of 8 studies (12.9%) measured two or three phenotypes simultaneously. From the task-based BOLD studies, the majority addressed emotional face processing (25%), four studies addressed vicarious representation of others’ pain (8%) and three studies addressed cooperation/defection in the Prisoner’s Dilemma paradigm (6%). Other cognitive processes such as those in response to infants or maternal feedback, perspective-taking, response to visual scenes depicting social scenarios, processing of gaze, monetary incentive delay or responses to negative emotion-associated words were addressed in single studies (i.e. one of each kind).

3.2. eQTL annotation

From the total of 46 variations featured, and which we queried in the GTEx browser, 27 (59%) impact on gene transcription (i.e. showed to be eQTLs), irrespective of the tissue. All of these influence OXTR expression, even though some of these variations are better ascribed by contiguity to the CAV3 or SSUH genes, as above mentioned. However, only 13 of these 27 eQTLs are known to affect OXTR transcription in the brain (mainly in the caudate or the putamen). The other 14 affect transcription mainly outside the brain, namely in transformed fibroblasts, aorta and tibial arteries or skeletal muscle. These findings are detailed in Table 1.

3.3. Quality assessment

We present an overview of the combined studies’ compliance with our criteria in Supplemental Table S1, and compliance of each study in Supplemental Table S2.

4. Discussion

Our review provides the first systematic and the most up-to-date overview of brain circuits found to be associated with OT-related (epi)
Table 1
Overview of statistically significant associations between each single oxytocin-related nucleotide polymorphism (SNP) and brain phenotypes examined in the studies reviewed, accompanied by our results of SNPs’ effects on the human transcriptome as per the GTex database (with effect size r, direction and gene affected in 4th column; if surviving Bonferroni correction for the multiple tissues being tested, i.e. threshold of \( p < 9.25 \times 10^{-4} \), and exact p-values provided in supplemental Table S3-S5). We highlighted: 1) in dark blue, putatively functional SNPs based on their location; 2) in light blue, SNPs thought not to be functional based on their location; 3) in dark green, all SNPs’ eQTL effects in brain tissue obtained; 4) in light green, SNPs’ eQTL effects outside brain tissue; 5) in dark purple, all studies reporting significant neuroimaging genetics associations; 6) in light purple, neuroimaging genetics studies showing no significant association; and 7) in pink, some functional studies, at the cellular-level, of the SNP. Labels: SNP – Single Nucleotide Polymorphism; (f)MRI – (Functional) magnetic resonance imaging; EEG – Electroencephalography; SPECT – Single-photon Emission Computed Tomography; PET – Positron Emission Tomography; eQTL – Expression quantitative trait loci; OXT – Oxytocin gene; OT - oxytocin; OXTR – Oxytocin receptor gene; OTR – Oxytocin receptor; CAV3 - Caveolin-3; SSUH and protein-coding Ssu-homolog; RAD18 – RAD18 E3 Ubiquitin Protein Ligase, Nacc – Nucleus accumbens; ACC – Anterior Cingulate; eQTL – Expression quantitative trait loci.

| Gene | SNP ID | Characterist ics | eQTL annotation (effect, in relation to alternative allele, on mRNA levels) | Structural MRI | Functional connectivity | Task-based MRI | EEG | SPECT/ PET |
|------|--------|------------------|-------------------------------------------------|----------------|--------------------------|----------------|-----|-----------|
| OXTR | rs35576 | Introic          | OTR (GG < GA < AA): Caudate (r = -0.54) NAc (r = -0.50) Cortex (r = -0.67) Putamen (r = -0.45) Frontal cortex (BA9) (r = -0.43) Hippocampus (r = -0.41) | Womersley et al., 2019 Na et al., 2018 Dzolczowski et al., 2016 Schmelzer-Haasoff et al., 2016 Wang et al., 2014 Test et al., 2010 | Hernandez et al., 2017 Wang et al., 2014 Verbok et al., 2013 Wang et al., 2013 Test et al., 2010 Zee-Wolf et al., 2020 Catadi et al., 2020 | Chen et al., 2020 Acevedo et al., 2019 Urezovsky et al., 2019 Schmelzer-Haasoff et al., 2016 Dzolczowski et al., 2016 Aupperle et al., 2016 Luo et al., 2015a Luo et al., 2015b Peng et al., 2015 Lausen et al., 2014 Michalska et al., 2014 Test et al., 2010 Zee-Wolf et al., 2020 Acevedo et al., 2020 | Fowler et al., 2018 Luo et al., 2017 Chet et al., 2017 Pushalu et al., 2014 Zee-Wolf et al., 2020 | Chang et al., 2014 |
|      |        |                  |                                           |                |                          |                |      |           |
|      |        |                  |                                           |                |                          |                |      |           |
| OXTR | rs2254298 | Introic          |                                           |                |                          |                |      |           |
|      |        |                  |                                           |                |                          |                |      |           |
| OXTR | rs1042778 | UTR of 3'        |                                           |                |                          |                |      |           |
|      |        |                  |                                           |                |                          |                |      |           |
| OXTR | rs2268408 | Upstream         | OTR (CC > CT > TT): Caudate (r = 0.52) NAc (r = 0.50) Putamen (r = 0.46) Cortex (r = 0.42) Frontal cortex (BA9) (r = 0.39) Hippocampus (r = 0.46) ACC (BA24) (r = 0.55) | Feldman et al., 2012 |                |                          |                |      |           |
|      |        |                  |                                           |                |                          |                |      |           |
| OXTR | rs237897 | Introic          | OTR (GG < GA < AA): Caudate (r = -0.52) Putamen (r = -0.52) NAc (r = -0.50) Cortex (r = -0.48) Frontal cortex (BA9) (r = -0.43) Hippocampus (r = -0.44) ACC (BA24) (r = -0.59) |                |                |                          |                |      |           |
|      |        |                  |                                           |                |                          |                |      |           |
| OXTR | rs237893 | Introic          | OTR (GG < GA < AA): Caudate (r = -0.51) Putamen (r = -0.49) NAc (r = -0.42) Frontal cortex (BA9) (r = -0.38) |                |                |                          |                |      |           |
|      |        |                  |                                           |                |                          |                |      |           |

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Table 1 (continued)

| Genotype | Effect | Description | Gene Symbol | Reference 1 | Reference 2 |
|----------|--------|-------------|-------------|-------------|-------------|
| m127915 Intronic | OTR (CC > CT > TT): Caudate (r = -0.48) Hippocampus (r = -0.40) ACC (r = -0.34) | | | Gonzalez et al., 2019 | Gonzalez et al., 2019 |
| m2228485 Coding sequence, synonymous | OTR (TT > TC > CC): Patellar (r = 0.24) | | | Uzelovsky et al., 2019 |
| m3406675 Upstream | OTR (AA > AG > GG): Caudate (r = -0.09) NAcc (r = 0.50) Patellar (r = 0.52) Cortex (r = -0.47) Frontal cortex (BA9) (r = 0.45) Hippocampus (r = 0.48) ACC (BA24) (r = 0.38) Cultured fibroblasts (r = 0.34) | | | Loth et al., 2014 |
| m35413809 Upstream | OTR (GG < GA > AA): Cerebellar hemisphere (r = -0.52) | | | Loth et al., 2014 |
| m2268495 Intronic | OTR (CC < CT < TT): Cultured fibroblasts (r = -0.17) | | | Damiano et al., 2014 | Westberg et al., 2016 |
| m2268495 Intronic | OTR (GG < GA > AA): Cultured fibroblasts (r = -0.21) | | | | |
| m2279465 Potentially Intronic | OTR (CC > GC > GG): Caudate (r = 0.18) Dorsolateral prefrontal cortex (BA8) (r = 0.22) Cultured fibroblasts (r = 0.22) | | | | |
| m75775 Potentially Intronic | OTR (GG > GT > TT): Cultured fibroblasts (r = 0.25) Auric (r = 0.33) OTR (GG > GT > TT): Cultured fibroblasts (r = 0.25) Auric (r = 0.33) | | | Westberg et al., 2016 | |
| m2268492 Intronic | OTR (TT > CT > CC): Cultured fibroblasts (r = -0.21) | | | Loth et al., 2014 |
| m11711703 Intronic | OTR (GG < GA > AA): Cultured fibroblasts (r = -0.27) | | | Loth et al., 2014 |
| m4686602 Mismatch | OTR (TT < CT < CC): Cultured fibroblasts (r = -0.24) | | | Azevedo et al., 2020 |
| m2301261 UTR of 5' | OTR (TT < CT < CC): Cultured fibroblasts (r = -0.24) | | | Loth et al., 2014 |
| m237987 Intronic | OTR (CC > GT > TT): Cultured fibroblasts (r = 0.25) Auric (r = 0.33) OTR (GG > GT > TT): Cultured fibroblasts (r = 0.25) Auric (r = 0.33) | | | Westberg et al., 2016 | |
| m7632287 UTR of 3' | | | | Westberg et al., 2016 | |
| m9195316 Intronic | OTR (CC > GT > TT): Cultured fibroblasts (r = 0.25) Auric (r = 0.33) OTR (GG > GT > TT): Cultured fibroblasts (r = 0.25) Auric (r = 0.33) | | | Loth et al., 2014 | Uzelovsky et al., 2019 |
| m11711703 Intronic | OTR (GG < GA > AA): Cultured fibroblasts (r = -0.27) | | | | |
| m2268490 Intronic | OTR (TT < CT < CC): Cultured fibroblasts (r = -0.24) | | | | |
| m2268491 Intronic | OTR (CC > GT > TT): Cultured fibroblasts (r = 0.25) Auric (r = 0.33) OTR (GG > GT > TT): Cultured fibroblasts (r = 0.25) Auric (r = 0.33) | | | | |
| m237989 Intronic | OTR (CC > GT > TT): Cultured fibroblasts (r = 0.25) Auric (r = 0.33) OTR (GG > GT > TT): Cultured fibroblasts (r = 0.25) Auric (r = 0.33) | | | | |
| m35408755 Intronic | OTR (CC > GT > TT): Cultured fibroblasts (r = 0.25) Auric (r = 0.33) OTR (GG > GT > TT): Cultured fibroblasts (r = 0.25) Auric (r = 0.33) | | | | |
| m6777726 Potentially Intronic | OTR (CC > GT > TT): Cultured fibroblasts (r = 0.25) Auric (r = 0.33) OTR (GG > GT > TT): Cultured fibroblasts (r = 0.25) Auric (r = 0.33) | | | | |
| m3761248 Upstream | OTR (CC > GT > TT): Liver (r = 0.58) Skin - sun-exposed leg (r = 0.25) | | | Love et al., 2012 |
| m2740210 Downstream | OTR (AA < CA < CC): Cultured fibroblasts (r = -0.24) | | | Love et al., 2012 |
| m4815625 Intronic | OTR (CC > GT > TT): Subcutaneous adipose tissue (r = 0.23) OTR (CC > GT > TT): Subcutaneous adipose tissue (r = 0.23) | | | Love et al., 2012 |

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genetic variations, highlighting those that seem to be implicated in neuropsychiatric disorders. It also gathers the genetic polymorphisms that have been shown to modulate brain responses to intranasal OT. Furthermore, to add a mechanistic understanding of how such variations affect the brain, we describe their influence in the human brain transcriptome. Next, we provide a narrative synthesis of all main (epi)genetics brain associations we gathered. First, we discuss all studies in healthy individuals, then those in clinical samples and then all pharmaco-neuroimaging (epi)genetic studies. Within each of these three sections, we start with the genetic variation findings, followed by the methylation findings. All associations referred to below have surpassed the statistical significance threshold of $p < 0.05$, otherwise specifically referred to as ‘trends’.

4.1. Neuroimaging (epi)genetics in healthy individuals

4.1.1. OXTR

4.1.1.1. rs53576. According to our eQTL annotation, the (minor) allele A of the A/G rs53576 SNP increases OXTR mRNA expression in the caudate, nucleus accumbens (NAcc), cortex, putamen, frontal cortex (BA9) and hippocampus ($p < 0.05$) – which points to this allele being associated with a relatively higher OT signalling capacity, compared to its counterpart.

The intronic rs53576 is until now by far the most studied OT-related genetic variation in the studies reviewed (>50%), probably due to its repeated implication in social cognition across independent studies (Kumsta and Heinrichs, 2013; Li et al., 2015), including in ASD (Wu et al., 2005) although somewhat inconsistently (Michalska et al., 2014, and even though without a clear conclusion regarding the exact allelic direction (Rijlaarsdam et al., 2017).

The association between this SNP and brain structure was researched mostly on regional grey matter volume (GMV), using voxel-based morphometry, with mixed findings. Studies found that the A allele was associated with smaller bilateral amygdala in females (Wang et al., 2014), larger amygdala in males (Tost et al., 2010) or no volume changes were observed (Dannlowski et al., 2016; Inoue et al., 2010; Womersley et al., 2019). The A allele was also associated with a smaller hypothalamus (Tost et al., 2010), left cerebellum, and other regions of the frontal, parietal and temporal cortices (Wang et al., 2014); smaller bilateral temporal poles, right hippocampus, lingual gyrus and precuneus and larger the cerebellar vermis (Schneider-Hassloff et al., 2016). The same allele was also associated with increased structural coupling between the amygdala and the hypothalamus, as well as between dACG and the hypothalamus in a dose-dependent manner (AA > AG > GG) (Tost et al., 2010). In addition to gender, childhood adversity’s effect on GMV may be moderated by this SNP. Insecure childhood attachment and maltreatment were associated with increased left amygdala and decreased right superior parietal, left temporal, and bilateral ventral striatum GMV (Dannlowski et al., 2016) - but only in the absence of the A allele. Emotional trauma in adolescent girls was also found to be associated with smaller left hippocampal volumes only in A homozygotes (with no effect on the amygdala) (Malhi et al., 2020). In the same study, peer-perceived social support in adolescent girls was associated with larger hippocampal and amygdala volumes only in A homozygotes (Malhi et al., 2020). These findings speak in favour of the idea that early life experience may shape further activity of the OT
Table 2

Neuroimaging genetic studies in healthy individuals, with an overview of main findings. Labels: HW – Hardy-Weinberg principle; VBM – Voxel-based morphometry; DRD4 – Dopamine Receptor 4 gene; AVPR1a – Arginine Vasopressin Receptor 1 A gene; N.S. – Not significant; FC – Functional connectivity; GMV – Grey matter volume; OXTRm – Oxytocin receptor methylation; Nacc – Nucleus accumbens, VP – Ventral Pallidium; IPS – Intraparietal Sulcus; DLPFC – Dorsolateral Prefrontal Cortex; GP – Globus Pallidium; ACC – Anterior Cingulate; ITG – Inferior temporal gyrus; MGF – Medial Frontal gyrus; FO – Orbitalfrontal cortex; OCC – Occipital cortex; LPP – Late Positive Potentials; STG – Superior Temporal Gyrus; SN – substantia nigra; VS – Ventral Striatum; VTA – Ventral Tegmental Area; Right - R; Left - left; N.S. - non-significant; N.A. - non-applicable.

| Study                  | SNP ID   | Gene (contiguity) | SNP characteristics | Ethnicity   | Sample size (Males/Females) | HW principle | Genotyping method | Brain phenotype                                                                                       | Main findings (genotype contrast or allelic load correlation) |
|------------------------|----------|-------------------|--------------------|-------------|-----------------------------|--------------|-------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Zeev-Wolf et al. (2020)| rs1042778| OXTR              | Intronic           | Middle eastern | 232 children               | Not deviated | SNaPshot          | Resting state MEG                                                                                     | (-) DMN theta connectivity with social deficit risk composite allelic score. |
|                        | rs2254298| OXTR              | Intronic           |             |                             |              |                   |                                                                                                       |                                                                                                  |
|                        | rs53576  | OXTR              | Intronic           |             |                             |              |                   |                                                                                                       |                                                                                                  |
|                        | rs796863 | OXTR              | Intronic           |             |                             |              |                   |                                                                                                       |                                                                                                  |
|                        | RS3      | AVPR1a            | Promoter           |             |                             |              |                   |                                                                                                       |                                                                                                  |
| Acevedo et al. (2020)  | rs3      | AVPR1a            | Promoter           | Not found    | 19 (11 F/8 M)               | Not deviated | PCR-RFLP          | BOLD response to viewing images of partner vs. familiar faces; at time of wedding (T1) and at 1 year (T2). | Romantic love x AVPR1a rs3: ↑ VTA, periaqueductal gray, hippocampus, occipital (ROIs), STG (long allele, whole-brain; T1/2); ↑ L VTA, caudate, bilateral raphé, hippocampus, L ACC, occipital (ROIs), R lateral geniculate (whole-brain; T2); ↑ R caudate, pons, septum fornix, amygdala/GP (ROIs; T1), bilateral occipital/lingual gyrus (whole-brain; T1). Romantic love x OXTR rs53576: ↑ L VTA/SN, septum/fornix (G allele; T1/2; ROI); ↑ R periaqueductal gray, amygdala, L amygdala, hippocampus (ROIs), L amygdala (whole-brain; G; T1-T2); ↑ L caudate, R amygdala, R intraparietal sulcus, IFG, MFG, STG, L PFC (whole-brain) (G; T2); ↑ bilateral SFG, L MFG (T1, G); ↓ L caudate, AG, somatosensory cortex, geniculate and premotor cortex (T2, G). Romantic love x DRD4-7R: (+) L VTA/SN and posterior insular cortex (7 R number, both faces); (+) bilateral PFC, right PCL (ROIs); entorhinal cortex, L SI, supramarginal gyrus (whole-brain, 7 R number, T1); (+) L somatosensory cortex, DLPFC (whole-brain, 7 R number, T2); (+) L temporal gyrus (T1/2, 7 R number); (+) L hippocampus, R temporal gyrus (T2, 7 R number). Romantic love x COMT rs4680: (+) L SN/ VTA, posterior insular cortex (T1/2, A load); (+) bilateral medial PFC, R primary sensory, L somatosensory cortex, L amygdala (whole-brain, A load; T1); (+) L PCL (ROIs); R VLPPC, DLPFC, posterior cingulate (whole-brain, A load; T2); (+) hippocampus (T1, SN, caudate tail, and dorsal midbrain (T2) (A load) Genotype x paternal care: ↑ R middle frontal gyrus, lateral prefrontal cortex, BA46 (A/A. low care) |
|                        | rs53576  | OXTR              | Intronic           |             |                             |              |                   |                                                                                                       |                                                                                                  |
|                        | rs4680   | OXTR              | Intronic           |             |                             |              |                   |                                                                                                       |                                                                                                  |
|                        | 7R       | DRD4              | Exonic             |             |                             |              |                   |                                                                                                       |                                                                                                  |
| Cataldo et al. (2020)  | rs53576  | OXTR              | Intronic           | Not found    | 134 (84 F/50 M)            | Not deviated | PCR               | fNIRS response                                                                                       | (continued on next page)                                                                         |
| Study                                      | SNP ID       | Gene (contiguity) | SNP characteristics | Ethnicity                                      | Sample size (Males/Females) | HW principle | Genotyping method                      | Brain phenotype                                                                 | Main findings (genotype contrast or allelic load correlation)                                                                 |
|-------------------------------------------|--------------|------------------|---------------------|------------------------------------------------|------------------------------|--------------|----------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Antonucci et al. (2020)                   | rs2268493    | OXTR             | Intronic            | Caucasian                                      | 166 (86 F/80 M)              | Not deviated | Illumina HumanHap550 K/610Quad Bead Chips | Effective connectivity (amygdala–DLPFC) in emotional evaluation                                                                 | R amygdala-to-amygdala (C-carriers, high maternal care); † R amygdala-to-DLPFC (TT, low maternal care)                                                                                          |
| Malhi et al. (2020)                       | rs53576      | OXTR             | Intronic            | European                                        | 219 F                       | Not deviated | Agena Bioscience MassARRAY              | VBM volume (hippocampal, amygdala)                                                                                               | † L hippocampus (high vs. Low emotional trauma-exposed AA)                                                                             |
| (Lee et al., 2020a, 2020b)                | rs3796863    | CD38             | Intronic            | Non-Hispanic European/African/African-American/American Indian | (1) 30 F/34 M, (2) 22 M (3) 276 F/255 M; (4) 26 F/25 M | Not deviated | MassARRAY assay                        | VBM volume (amygdala and hippocampus) Model with genotype and childhood neglect (CN): † R amygdala, L amygdala (trend) (AA/AG vs GG); † hippocampus (trend) (AG/AA) | Model with genotype and childhood neglect (CN): † R amygdala, L amygdala (trend) (AA/AG vs GG); † hippocampus (trend) (AG/AA) |
| Acevedo et al. (2019)                      | rs53576      | OXTR             | Intronic            | 3 Asian American, 3 Hispanic/Latino, 12 White/European-American | 18 (8 M/10 F)               | Not found      | RealSNP and MassARRAY assay            | BOLD response to partner (vs. stranger) faces (Times 1, 2)                                                                  | Genotype x sexual satisfaction: † L NAcc, VP and hypothalamus, R IPS, bilateral DLPFC, hypothalamus, R caudate (G allele); T1: † R VTA/ST, entorhinal area /hippocampus, STG, bilateral PCC, L putamen, mid-insula and SFG (G) T2: † L VTA/ST, Pons/PAG, bilateral GP, R amygdala, lingual gyrus, temporal/auditory cortex (G) Genotype x sexual frequency: † bilateral DLPFC, putamen, ACC, ITG and L MFG (G); T1: † parahippocampal gyrus, insula, IFG and MFG (G) T2: † cingulate gyrus, ACC, thalamus, hippocampus, hypothalamus, MFG, IPS, premotor cortex/caudate (G) Model with genotype and OXTRm: † bilateral amygdala (AG/AA) Model with genotype and OXTRm and CN: † R amygdala, L amygdala (trend) (AG/AA) |
| Womersley et al. (2019)                    | rs2254298    | OXTR             | Intronic            | Caucasian                                      | 63 (28 M/35 F)              | Not deviated | PCR, BamHI and Bsr                      | VBM volume (amygdala and hippocampus) Model with genotype and childhood neglect (CN): † R amygdala, L amygdala (trend) (AA/AG vs GG); † hippocampus (trend) (AG/AA) | Model with genotype and childhood neglect (CN): † R amygdala, L amygdala (trend) (AA/AG vs GG); † hippocampus (trend) (AG/AA) |
|                                         | rs53576      | OXTR             | Intronic            |                                                |                             | Not found      | Pyromark PCR                            | BOLD response, and FC, to emotional faces (angry, fearful)                                                                     | ROI, genotype x economic income: † VS (CT/CC); † VS (TT) Whole-brain, genotype x economic income: † mesolimbic area, motor-cortex, bilateral occipital cortex, L dmPFC (CC/TC vs TT) FC, genotype x economic income: † bilateral VS to VMPFC (CC/CT); † VS to L angular gyrus, R OCG R occipital pole, to R OCG R angular gyrus (CC/CT) | (continued on next page)                                                                                                           |
| Study                      | SNP ID  | Gene (contiguity) | SNP characteristics | Ethnicity | Sample size (Males/ Females) | HW principle | Genotyping method | Brain phenotype                                                                 | Main findings (genotype contrast or allelic load correlation) |
|---------------------------|---------|-------------------|---------------------|-----------|------------------------------|--------------|-------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------|
| Zimmermann et al. (2018)  | rs2254298 | OXTR              | Intronic            | Not found | 143 (52 M/ 91 F)             | Not deviated | Real-time PCR     | Resting state FC (amygdala subdivisions)                                      | L basolateral amygdala: ↑ positive FC to bilateral fusiform, inferior occipital gyrus (TT > CT/CC); L centromedial amygdala: ↑ positive FC to L insula and OFC (CC/CT>TT); ↑ positive FC to L fusiform, lingual gyrus (TT>CC/CT); L superficial amygdala: ↑ positive FC to L fusiform, inferior occipital gyrus (TT>CC/CT); R centromedial amygdala: ↑ positive FC to L putamen, L insula, L IFG (CT/CC>TT); ↑ positive FC to bilateral medial occipital gyrus, to R brainstem (TT>CC/CT) |
| Fowler et al. (2018)      | rs53576  | OXTR              | Intronic            | Not found | 47                           | Not deviated | TaqMan            | LPP amplitude in response to emotional faces (neutral, positive, negative)    | Genotype x valence: ↑ to negative images (GG > AA/GA) |
| Luo et al. (2017)          | rs53576  | OXTR              | Intronic            | Chinese   | 48 F                         | Not found    | TaqMan            | N1, N2, P3 amplitude in response to emotional faces (painful vs neutral)      | Genotype x valence: ↑ P3 for painful > neutral (GG > AA) |
| Wang et al. (2017)         | rs7634632 | OXTR              | Intronic            | European  | 328 (123 M/ 205 F)           | Not deviated | Human610-Quad BeadChip (Illumina) | Resting-state FC of PCC/precuneus; VBM                                      | N.S.                                                                 |
|                           | rs11914885 | SSSUH2             | Intronic            |           |                              |              |                   |                                                                                |                                                                 |
|                           | rs151462  | CAV3/ SSSUH2      | Intronic            |           |                              |              |                   |                                                                                |                                                                 |
|                           | rs237875  | CAV3/ SSSUH2      | Intronic            |           |                              |              |                   |                                                                                |                                                                 |
|                           | rs6791619 | CAV3/ RAD18       | Intrinsic           |           |                              |              |                   |                                                                                |                                                                 |
|                           | rs2270465 | OXTR              | Intronic            |           |                              |              |                   |                                                                                |                                                                 |
|                           | rs237888  | OXTR              | Intronic            |           |                              |              |                   |                                                                                |                                                                 |
|                           | rs2254298 | OXTR              | Intronic            |           |                              |              |                   |                                                                                |                                                                 |
|                           | rs237897  | OXTR              | Intronic            |           |                              |              |                   |                                                                                |                                                                 |
|                           | rs237851  | OXTR              | Intronic            |           |                              |              |                   |                                                                                |                                                                 |
| Choi et al. (2017)         | rs53576  | OXTR              | Intronic            | Japanese  | 88 M                         | Not deviated | TaqMan            | N1, N2, LPP amplitude in response to emotional human, animal and object pictures | N1: ↑ negative deflection (GG>GA>AA) N2, genotype x content: ↑ negative deflection for humans (GG vs AA); ↑ negative deflection for humans vs. objects (GG); ↑ negative for objects vs. humans (AA) |
| Westberg et al. (2016)     | rs75775  | OXTR              | Intergenic (5' region OXTR) | Caucasian | 54 (25 M/ 29 F)             | Not found    | KASPar             | BOLD response to faces encoding                                                 | N.S.                                                                 |
|                           | rs2270465 | OXTR              | Intronic            |           |                              |              |                   |                                                                                |                                                                 |
|                           | rs2268498 | OXTR              | Intronic            |           |                              |              |                   |                                                                                |                                                                 |
|                           | rs237897  | OXTR              | Intronic            |           |                              |              |                   |                                                                                |                                                                 |
|                           | rs53576   | OXTR              | Intronic            |           |                              |              |                   |                                                                                |                                                                 |
|                           | rs2268493 | OXTR              | Intronic            |           |                              |              |                   |                                                                                |                                                                 |

(continued on next page)
| Study                                | SNP ID        | Gene characteristics | Ethnicity                        | Sample size (Males/ Females) | HW principle | Genotyping method | Brain phenotype                                                                 | Main findings (genotype contrast or allelic load correlation)                                                                 |
|--------------------------------------|---------------|----------------------|----------------------------------|-----------------------------|--------------|-------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| Dannlowski et al. (2016)             | rs237887      | Intronic             | European                         | 309 (138 M/171 F)           | Not deviated | Multiplex assay iPLEX | VBM volume                                                                | ↑ R amygdala for incidental encoding of faces (GA vs GG); ↑ R amygdala for faces later remembered (GA vs GG)                        |
|                                      | rs1042778     | 3' UTR               |                                   |                             |              |                   | BOLD response to emotional face-matching                                   | Genotype x maltreatment: ↓ VS with increasing maltreatment score (GG) Whole-brain, genotype x maltreatment: ↑ SMC (AA/AG); ↓ SMC (GG) ROI: ↑ amygdala to angry and fearful faces (GG vs GA/AA) |
|                                      | rs7632287     | 3' UTR               |                                   |                             |              |                   |                                                                             |                                                                                                                               |
| Waller et al. (2016)                 | rs53576       | OXTR                 | Non-Hispanic Caucasians          | 406 (193 M/213 F)           | Not deviated | Custom illumina arrays        | BOLD response to emotional face-matching                                   | ↑ R amygdala to angry > neutral faces in men - trend (TT vs GT/GG) N. S.                                                                                                     |
|                                      | rs1042778     | 3' UTR               |                                   |                             |              |                   |                                                                             |                                                                                                                               |
|                                      | rs53576       | Intrinsic            |                                   |                             |              |                   |                                                                             |                                                                                                                               |
|                                      | rs2254298     | Intrinsic            |                                   |                             |              |                   |                                                                             |                                                                                                                               |
| Schneider-Hassloff et al. (2016)     | rs53576       | OXTR                 | Western or Middle-European’      | 195 (98 M/97 F)            | Not significantly deviated | Real-Time PCR using TaqMan                           | BOLD response to Prisoner’s dilemma                                                                                       | Whole brain: ↑ bilateral temporal poles, R hippocampus, lingual gyrus, precuneus (GG > AG/AA); ↓ cerebellar vermis (GG > AG/AA) Whole brain, genotype x childhood attachment: ↑ fronto-parietal network (including L SMG) (GG); ↓ fronto-parietal regions except for L SMG (AA/AG); ↓ L hippocampus, amygdala (GG) Whole brain, genotype x childhood attachment x sex: ↑ R STG, SMG, SFG, SMedG with secure childhood attachment in men vs. women (GG vs GA/AA) Whole brain, genotype x sex: ↓ postcentral gyrus, superior parietal lobe, calcarine gyrus, in men vs women (GG vs AA/AG) ROI, genotype x childhood attachment: ↑ L basolateral amygdala with insecure childhood attachment (GG vs GA/AA) Genotype x childhood attachment: ↑ R frontal (inc. R superior and middle frontal gyri, bilateral paracentral lobules), bilateral parieto-temporo-occipital (inc. bilateral temporal poles, precuneus) during mentalizing with insecure childhood attachment (GG vs GA/AA) Parent’s genotype x maternal feedback: ↑ R amygdala for praise (AA/AG vs GG); ↓ R amygdala for critical statements - trend (AA/AG vs GG) |
|                                      | rs53576       | Intrinsic            |                                   |                             |              |                   |                                                                             |                                                                                                                               |
| Aupperle et al. (2016)               | rs53576       | OXTR                 | 22.2% European American, 33.3% Afro-American, 22.2% Native American, 22.2% Other Caucasian | 18 F                      | Not found     | TaqMan                     | BOLD response to maternal feedback                                      | Experiment 1 and 2, hemisphere x genotype: ↑ R lateralization (AA/AG) Experiment 2, genotype x hemisphere x                                      |
|                                      |               |                      |                                   |                             |              |                   |                                                                             |                                                                                                                               |
| Munk et al. (2016)                   | rs53576       | OXTR                 |                                   | 163 (86 M/77 F)            |              |                   | BOLD response to Prisoner’s dilemma                                        |                                                                                                                               |

(continued on next page)
| Study | SNP ID | Gene (contiguity) | SNP characteristics | Ethnicity | Sample size (Males/Females) | HW principle | Genotyping method | Brain phenotype | Main findings (genotype contrast or allelic load correlation) |
|-------|--------|------------------|---------------------|-----------|----------------------------|--------------|-------------------|-----------------|---------------------------------------------------------------|
|       |        |                  |                     |           |                            |              |                   |                 |                                                                |
| Table 2 (continued) |        |                  |                     |           |                            |              |                   |                 |                                                                |
| Maruak et al. (2015) | rs3796863 | CD38 | Intronic | 23 African American, 18 Caucasian, 7 mixed, 2 Hispanic, 5 not reported | 55 (21 M/34 F) | Not deviated | 5'-nuclease assay | VBM volume, BOLD response to emotional faces | emotion: ↓ N170 latency in R hemisphere for upright angry faces (AA/AG) Experiment 1, genotype x stimulus x position: ↓ N170 latency for inverted chairs (CC); ↓ N170 latency for inverted faces (AC/AA) Experiment 2, genotype x hemisphere x position x perspective: ↑ R lateralization to upright and inverted faces (CC) Experiment 2, genotype x perspective x emotion: ↑ N170 latency for angry inverted faces vs neutral or happy (CC) Whole brain, face-categorization Stroop task: ↑ insula, amygdala, hippocampus, R MTG, R MFG, L SPL, R thalamus, L postcentral gyrus, L IPL, midbrain, brainstem in incongruent vs. congruent trials (AA/GA vs GG) Whole brain, face-matching task: ↑ amygdala, L insula, R parahippocampal gyrus, L MTG, R IFG for neutral faces (AA/GA vs GG) ↓ L putamen, R caudate, L STG, bilateral IPL for neutral faces (AA/GA vs GG) ROI, face-categorization Stroop task, main effect of genotype: ↑ amygdala for incongruent vs congruent trials (AA/GA vs GG); ↑ amygdala for incongruent vs congruent trials (GG); ↑ R amygdala (AA/AG) ROI, face-matching task, main effect of genotype: ↑ amygdala for neutral faces (AA/GA vs GG) VBM, main effect of genotype: ↑ amygdala (AA/AG vs GG) ROI, genotype x pain x race: ↑ ACC/SMA for painful videos of Asian vs Caucasian faces (GG); ↑ ACC/SMA with stronger racial bias (GG vs AA); ROI, genotype x pain x race: ↑ NAcc for painful (vs. non-painful) stimuli applied to Caucasian vs. Asian models (AA); ↑ NAcc with stronger racial bias (AA vs GG) Whole-brain, pain vs non-painful stimuli, asian faces: ↑ ACC/SMA, AI, parietal operculum, SII, L inferior temporal cortex (GG & AA); ↑ R MFG, R superior parietal cortex and cerebellum (GG); ↑ middle insula and L OCC (AA) Whole-brain, pain vs non-painful stimuli, caucasian faces: ↑ ACC/SMA, R |
| Luo et al. (2015a) | rs2254298 | OXTR | Intronic | Chinese | 60 (32 M/28 F) | Not deviated | TaqMan | BOLD response to video depicting pain vs non-painful stimulation Asian vs. Caucasian | Whole-brain, pain vs non-painful stimuli, asian faces: ↑ ACC/SMA, AI, parietal operculum, SII, L inferior temporal cortex (GG & AA); ↑ R MFG, R superior parietal cortex and cerebellum (GG); ↑ middle insula and L OCC (AA) Whole-brain, pain vs non-painful stimuli, caucasian faces: ↑ ACC/SMA, R |
| Study                | SNP ID    | Gene (contiguity) | SNP characteristics | Ethnicity   | Sample size (Males/ Females) | HW principle  | Genotyping method | Brain phenotype                                                                 | Main findings (genotype contrast or allelic load correlation)                                                                 |
|---------------------|-----------|-------------------|---------------------|-------------|------------------------------|---------------|-------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Luo et al. (2015b)  | rs53576   | OXTR Intronic     | Chinese             | 60 (32 M/ 28 F) | Not deviated                | TaqMan        |                   | BOLD response to racial in- and out-group painful pictures                      | IF, parietal operculum/SII (AA & GG); ↑ L IFC, R MFG, R inferior temporal cortex, L OCC lobe (GG); ↑ bilateral insula (AA); Whole-brain, pain x race: ↑ ACC/SMA for painful vs non-painful in Asian vs. Caucasian faces (GG); ↑ L NAcc for painful vs non-painful in Caucasian vs Asian faces (AA); (+) ACC/SMA in painful vs non-painful for Asians vs Caucasian face, with implicit race attitude scores and (GG); (-) NAcc with altruistic motivation toward racial outgroup (AA) |
| Laursen et al. (2014)| rs2268498 | OXTR Promoter     | Not found           | 50 F         | Not deviated                | TaqMan        |                   | BOLD response to painful facial expressions                                    | Genotype x interdependence, Asian: ↑ bilateral insula, bilateral amygdala, bilateral STG for painful vs non-painful (GG) (+) R STS with empathic accuracy (CC/CT); (-) R STS with empathic accuracy (TT) (+) R STS with empathic accuracy – trend (AA/AG vs GG) (+) R insula with A allele load |
|                     | rs53576   | OXTR Intronic     | Japanese            | 135 (79 M/ 56 F) | Not found                  | TaqMan        |                   | VBM volume                                                             |                                                                                                                                   |
| Saito et al. (2014) | rs2254298 | OXTR Intronic     | Japanese            | 135 (79 M/ 56 F) | Not found                  | TaqMan        |                   | VBM volume                                                             |                                                                                                                                   |
| Loth et al. (2014)  | rs7632287 | OXTR 3’ UTR       | European            | 1445 (697 M/ 748 F) | Not deviated               | Illumina      | HumanHap610 and HumanHap660 Bead-Chips | BOLD response to angry faces (VS, amygdala)                                   | N. S.                                                                                                                                 |
|                     | rs1042778 | rs11706648        | Intrinsic           | 3’ UTR       | Not deviated               | Illumina      | HumanHap610 and HumanHap660 Bead-Chips | BOLD response to angry faces (VS, amygdala)                                   | N. S.                                                                                                                                 |
|                     | rs237887  | rs2268490         | Intrinsic           | 3’ UTR       | Not deviated               | Illumina      | HumanHap610 and HumanHap660 Bead-Chips | BOLD response to angry faces (VS, amygdala)                                   | N. S.                                                                                                                                 |
|                     | rs226491  | rs226492          | Intrinsic           | 3’ UTR       | Not deviated               | Illumina      | HumanHap610 and HumanHap660 Bead-Chips | BOLD response to angry faces (VS, amygdala)                                   | N. S.                                                                                                                                 |
|                     | rs226494  | rs2254298         | Intrinsic           | 3’ UTR       | Not deviated               | Illumina      | HumanHap610 and HumanHap660 Bead-Chips | BOLD response to angry faces (VS, amygdala)                                   | N. S.                                                                                                                                 |
|                     | rs237889  | rs11131149        | Intrinsic           | 3’ UTR       | Not deviated               | Illumina      | HumanHap610 and HumanHap660 Bead-Chips | BOLD response to angry faces (VS, amygdala)                                   | N. S.                                                                                                                                 |
|                     | rs53576   | rs35498753        | Intrinsic           | 3’ UTR       | Not deviated               | Illumina      | HumanHap610 and HumanHap660 Bead-Chips | BOLD response to angry faces (VS, amygdala)                                   | N. S.                                                                                                                                 |
|                     | rs237915  | rs17171703        | Intronic            | 3’ UTR       | Not deviated               | Illumina      | HumanHap610 and HumanHap660 Bead-Chips | BOLD response to angry faces (VS, amygdala)                                   | N. S.                                                                                                                                 |
|                     | rs4686302 | rs35413809        | Intronic            | 3’ UTR       | Not deviated               | Illumina      | HumanHap610 and HumanHap660 Bead-Chips | BOLD response to angry faces (VS, amygdala)                                   | N. S.                                                                                                                                 |
|                     | rs2301261 | rs3806675         | Intronic            | 3’ UTR       | Not deviated               | Illumina      | HumanHap610 and HumanHap660 Bead-Chips | BOLD response to angry faces (VS, amygdala)                                   | N. S.                                                                                                                                 |
|                     | rs1465386 | rs7777726         | Intronic            | 3’ UTR       | Not deviated               | Illumina      | HumanHap610 and HumanHap660 Bead-Chips | BOLD response to angry faces (VS, amygdala)                                   | N. S.                                                                                                                                 |
| Wang et al. (2014)  | rs53576   | OXTR Intronic     | Han Chinese         | 290 (136 M/ 154 F) | Not deviated               | PCR - RFLP    |                   | VBM volume (amygdalar subdivisions)                                             | Whole-brain: ↑ bilateral amygdala, l. cerebellum, l. IPG, R lingual gyrus, R amygdalar subdivisions |
| Study                  | SNP ID   | Gene (contiguity) | SNP characteristics | Ethnicity       | Sample size (Males/Females) | HW principle | Genotyping method | Brain phenotype                                                                 | Main findings (genotype contrast or allelic load correlation)                                                                 |
|-----------------------|----------|-------------------|---------------------|-----------------|-----------------------------|--------------|-------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Chang et al. (2014)   | rs53576  | OXTR              | Intronic            | Han Chinese     | 82 (37 M/45 F)              | Not deviated | TaqMan            | Striatal DAT availability by [99mTc]TRODAT-1 SPECT                             | \(\dagger\) DAT availability (AA vs AG/GG); \(+\) DAT availability with plasma OXT (GG); \(+\) DAT availability with neuroticism in low plasma OXT (AA) |
|                       | rs2254298| OXTR              | Intronic            | 95.8% Caucasian | 48 (25 M/23 F)              | Not deviated | Real-Time PCR      | N170 amplitude and latency in response to faces                              | N.S.                                                                                                                        |
|                       | rs53576  | Intrinsic         | SNP                 | Caucasian       | 94 F (48 mothers/46 non-mothers) | Deviated     | TaqMan            | N1, N170, EPN, LPP latency in response to infant/adult emotional faces        | Genotype x attention x intensity for infant faces; \(\dagger\) N1 latency of infants for strong vs mild intensity infant facial expressions (GG) |
|                       | rs1042778| Intrinsic         | 3’ UTR              | Caucasian       | 31 (14 M/17 F)              | Not deviated | GoldenGate assay w/ Illumina BeadXPressplatform | BOLD response to monetary incentive delay | N. S.                                                                 |
|                       | rs237887 | Intrinsic         |                     |                 |                             |              |                   |                                                                                |                                                                                                                              |
| Michalska et al. (2014)| rs53576  | OXTR              | Intronic            | 21 European American, 15 African-American | 36 mothers   | Not deviated | TaqMan            | BOLD response to own vs other children, and to inappropriate vs neutral child behaviour | ROI: \(+\) bilateral OFC, L ACC, with A load, for own > other child (trend); \(+\) R hippocampus, with A load, for inappropriate > appropriate behavior (trend) |
|                       | rs1042778| Intrinsic         | 3’ UTR              |                 |                             |              |                   |                                                                                |                                                                                                                              |
| Verbeke et al. (2013) | rs53576  | OXTR              | Intronic            | Caucasian       | 21 (13 M/8 F)               | Not deviated | TaqMan            | BOLD response to emotional faces effective connectivity                     | ROI: \(+\) R hippocampus with T load, for inappropriate > appropriate behavior (trend) |
| Wang et al. (2013)    | rs53576  | OXTR              | Intronic            | Chinese Han     | 270 (125 M/145 F)          | Not found but not deviated | PCR-RFLP | Resting-state FC, including density (FCD)                                      | \(\dagger\) amygdala to: insula, pars opercularis, mPFC, premotor cortex (GG vs GA/AA) Whole-brain: \(\dagger\) FCD of hypothalamus (AA vs AG/GG); Whole-brain, genotype x gender; \(\dagger\) FC of hypothalamus with L DLPFC (male AA vs male GG/GA) |
| Love et al. (2012)    | rs4813625| OXT               | Intronic            | 66% European, 14% African, 10% Asian, 6% Mid, 2% Far Eastern | 55 (23 M/32 F) | Not deviated | Illumina GoldenGate platform | Dopamine release - D2/D3 availability (PET) during pain-stress                | \(\dagger\) stress-induced dopamine release in R ventromedial caudate (GC/CC vs GG); Genotype x gender: \(\dagger\) dopamine release in R ventromedial caudate in females (CC vs GG/GG); \(\dagger\) dopamine release in R ventromedial caudate in females vs males (GC/CC/GG) |

(continued on next page)
Table 2 (continued)

| Study | SNP ID | Gene (contiguity) | SNP characteristics | Ethnicity | Sample size (Males/Females) | HW principle | Genotyping method | Brain phenotype | Main findings (genotype contrast or allelic load correlation) |
|-------|--------|-------------------|---------------------|-----------|-----------------------------|--------------|-------------------|----------------|---------------------------------------------------------------|
| Furman et al. (2011) | rs877172, rs3761248 | OXTR Intronic | Not found | 5 F | Not deviated | PCR | Manual volume tracing, VBM volume | | ROI, manual tracing: ↓ amygdala (GG vs GA) Whole brain, VBM: ↑ dorsomedial ACC (GG vs GA/AA); ↑ posterior brainstem (GA vs GG) N. S. |
| Inoue et al. (2010) | rs1042778, rs237887, rs918316 | OXTR 3' UTR Intronic | Japanese | 208 (143 M/65 F) | Not deviated | TaqMan | VBM volume (amygdala, hippocampus) | | ↓ bilateral amygdala (TCG or CTG haplotype – independent of T or C); ↓ bilateral amygdala (TCG or CTG haplotype – independent of T or C); ↑ bilateral amygdala (AA/AG vs GG); ↑ bilateral amygdala (TCG or CTG haplotypes containing G) N. S. |
| Tost et al. (2010) | rs53576, rs2268495 | OXTR Intronic | European Caucasians | 212 (103 M/109 F) | Not deviated | TaqMan | VBM volume | | ↓ hypothalamus (AA < AG < GG); ↑ R amygdala in males (AA > AG > GG); ↑ structural connectivity of hypothalamus with amygdala and dACG (AA > AG > GG) |
| | rs53576 | OXTR Intronic | 228 (102 M/126 F) | BOLD response to emotional faces | | | ↓ amygdala (AA < AG < GG); ↑ coupling of hypothalamus and amygdala (AA > AG > GG) | |
Table 3
Neuromaging methylation studies in healthy individuals, with an overview of main findings. Labels: FC – Functional connectivity; VBM – Voxel-based morphometry; EN – Emotional Neglect; IF – Inferior Frontal Cortex; DLPPC; ITG – Inferior Temporal gyrus; DLPFC – Dorsolateral Prefrontal cortex; STG – Superior Temporal Gyrus; IFG – Inferior Frontal Gyrus; STS – Superior Temporal Sulcus; dACC – Dorsal anterior Cingulate; TPJ – Temporo-parietal junction; VS – Ventral Striatum; Right – R; Left – L; N.S. – non-significant; N.A. – non-applicable.

| Study | Gene (contiguity) | Ethnicity | Sample size (Males/ Females) | Biological sample | DNA methylation method | Brain phenotype | Main findings (correlation with methylation) |
|-------|------------------|-----------|------------------|------------------|----------------------|----------------|---------------------------------------------|
| Hirakawa et al. (2016) | OXT | Japanese | 57 F | Saliva | Bisulfite pyrosequencing | VBM volume | (-) IFG |
| Puglia et al. (2020) | OXTR | Caucasian | 81 infants (41 F/40 M); 65 infants (31 F) | Saliva, whole blood | Bisulfite pyrosequencing | EEG response to human vocalizations; facial/ object viewing; human/water sounds | (+) brain signal entropy during social perception, accounting for social behavior in the 1st year of life |
| Fujiwara et al. (2019) | OXTR | Japanese | 85 (55 M/30 F) | Saliva | Bisulfite pyrosequencing | VBM volume | Child maltreatment x methylation: (-) OFC (insecure attachment) |
| Krol et al. (2019) | OXTR | Caucasian | 98 infants (49 M/49 F) | Saliva | Bisulfite pyrosequencing | fNIRS response to emotional faces | (+) R IF for happy; (+) R IF for fearful and angry |
| Womersley et al. (2019) | OXTR | Caucasian | 63 (28 M/35 F) | Whole blood | Bisulfite pyrosequencing | VBM volume (amygdala, hippocampus) | N.S. |
| Lancaster et al. (2018) | OXTR | Caucasian | 79 (35 M/44 F) | Whole blood | Bisulfite pyrosequencing | VBM volume (amygdala) | (+) R amygdala |
| Puglia et al. (2018) | OXTR | Caucasian | 54 (31 M/23 F) | Whole blood | Bisulfite pyrosequencing | BOLD response to social/non-social visual stimuli | (+) Attentional control network (incl. bilateral DLPF and parietal lobe) for social; (+) FC between DLPFC and salience network (incl. R insula and bilateral STG) for social |
| Haas et al. (2016) | OXT | 59 White, 24 Black, 18 Asian, 4 Hispanic, 2 Pacific Island, 12 Mixed, 2 Other | 121 (54 M/69 F) | Buccal cells | Mass spectrometry-based bisulfite sequencing (EpiTYPER) | BOLD response to emotional perspective-taking; (+) R fusiform gyrus volume; (-) association with R STS, R fusiform gyrus/middle occipital gyrus, R IFG, L fusiform during emotion attribution | (-) STS during emotional perspective-taking; (+) R fusiform gyrus volume; (-) association with R STS, R fusiform gyrus/middle occipital gyrus, R IFG, L fusiform during emotion attribution |
| Jack et al. (2012) | OXTR | 28 Caucasian, 7 Asian, 4 Black, 3 Mixed origin | 42 (23 M/19 F) | Blood (mononuclear cells) | Bisulfite pyrosequencing | BOLD response to visual animations | (+) STG, SMG at TPJ and dorsal ACC activations for social scenes |

Findings from functional neuroimaging studies have also been heterogeneous to some extent. Of note, the A allele was dose-associated with a decreased amygdala response towards fearful and angry faces (Dannowski et al., 2016; Tost et al., 2010). This is consistent with its putative association with A’s abovementioned higher OT signalling capacity (i.e. OXTR gene expression) and with widely replicated evidence showing intranasal OT to decrease in amygdalar response to fearful faces (Ellenbogen, 2018), despite the well replicated modulatory effects of OT on facial emotion recognition (as shown in pharmacological studies with intranasal OT (Leppanen et al., 2017; Shabrestani et al., 2013)). As such, these findings support the idea that one of the mechanisms through which OT might impact on social human behaviour is through down-regulating the brain’s anxiogenic response to others’ negative emotions (Olf et al., 2013). Nevertheless, three studies in this review have not found a significant association between this SNP and BOLD responses during facial emotional face processing (Loth et al., 2014; Waller et al., 2016; Westberg et al., 2016).

Using the same above paradigm, the A allele was also associated with increased functional, besides structural, connectivity between the amygdala and the hypothalamus (Tost et al., 2010), and decreased with other key social cognition areas, such as the insula or the mPFC (Verbeke et al., 2013). In resting-state studies, sex modulated this SNP’s effect on functional connectivity. As for volumes above, the A allele was associated with decreased dorsolateral prefrontal cortex (DLPPC) functional connectivity with the amygdala in females (Wang et al., 2014); and with the hypothalamus in males (Wang et al., 2013). These studies illustrate the need to carefully consider sex when investigating associations between OT-related polymorphisms and brain phenotypes. The mechanisms underlying this gender dimorphism remain to be fully clarified, but most likely include interactions with other sex hormones, such as testosterone (Crespi, 2016) or estradiol (Berio et al., 2017), which can modulate the response of the oxytocin receptor (OTR) to OT binding.

In brain function during an empathy task, similarly to above mentioned structural findings, childhood adversity was found to modulate this SNP’s genotype effect. A positive association was found between childhood trauma and supplementary motor cortex (SMC) activation in allele A carriers, but not in G homozygotes (Dannowski et al., 2016). In a racial in/out-group paradigm the A allele was associated with lower anterior cingulate (AC) and SMA activation in response to racial in-group members’ facial expression of pain; but with higher NAcc activity in response to racial outgroup members’ pain. Moreover, such ACC/SMC activity positively predicted participants’ racial in-group bias in implicit attitudes and NAcc activity negatively predicted participants’ motivations to reduce racial outgroup members’ pain (Luo et al., 2015a). In another study with a similar paradigm, the same research group found the A allele to be associated with a weaker association between cultural interdependence values and insula, amygdala and superior temporal gyrus response to painful expression from in-group members (Luo et al., 2015b). These two studies match well previous pharmacological evidence suggesting that OT influences behaviour towards others dependently of their perceived group membership (De Dreu et al., 2011) (Stallen et al., 2012). As such, OT’s role may be to contribute to generating/exacerbating intrinsic in-group bias which enhances group cohesion and shaped the evolution of human societies towards parochialism (De Dreu et al., 2011).
Table 4
Neuroimaging genetics studies in psychiatric populations, with an overview of main findings. Labels: ASD – Autism spectrum isorders; MDD – Major depressive disorder; AN – Anorexia Nervosa; SCZ – Schizophrenia; AD – Affective spectrum disorders; N. S. – Not significant; FC - Functional Connectivity; RMET – Reading the mind in the eyes test; Nacc – Nucleus accumbens; SMG – Supramarginal gyrus; ACC – Anterior cingulate; mPFC – Medial Prefrontal Cortex; IPL – Inferior Parietal lobe; NAA – N-Acetyl-Aspartate; Cr – Creatine; DG – Dentate gyrus; PCC – Posterior Cingulate Cortex.

| Diagnosis | study | SNP ID | Gene (continguity) | SNP characterists | Ethnicity | Sample size (Males/ Females) | HW principle | Genotyping method | Brain phenotype | Main findings (genotype contrast or allelic load correlation) |
|-----------|-------|--------|-------------------|------------------|-----------|-----------------------------|--------------|-----------------|-----------------|-----------------------------------------------|
| ASD       | Uzefovsky et al. (2019) | rs53576 | OXTR | Intronic | Not found | ASD: 38 (28 M/ 10 F); HC: 33 (16 M/ 17 F) | Not found | PCR-based KASP | BOLD response to RMET | ↑ R SMG and R IPL (GG vs AG/AA) Genotype x diagnosis: ↑ R SMG and R IPL in HC only (GG vs AG/AA) |
|           |       |        |                   |                  |           |                             |              |                 |                               | N. S. |
|           |       | rs2268491 | Intrinsic | | | | | | | |
|           |       | rs2254298 | Intrinsic | | | | | | | |
|           |       | rs7632287 | Intrinsic | (3' UTR) | Synonymous | | | | | N. S. |
|           | Hernandez et al. (2017) | rs2228485 | OXTR | Intronic | | | | | | ASD: 1 FC of NAcc with striatal and bilateral caudate, putamen and ACC (poly-SNP risk-allele score) |
|           |       | rs1042778 | Intrinsic | | | | | | | HC: ↑ FC of NAcc with mPFC (poly-SNP risk-allele score) |
|           |       | rs2254298 | Intrinsic | | | | | | | |
|           |       | rs53576 | OXTR | Intronic | | | | | | |
|           |       | rs237887 | OXTR | Intronic | | | | | | |
|           | Egawa et al. (2014) | rs9840864 | CAV3 | Intrinsic | Not found | ASD: 26 (21 M/ 5 F); HC: 0 | Not found | TaqMan (rs53576, rs2254298); Illumina Omni-1 or Omni-2.5-exome platforms (rs237887, rs1042778) | Resting-state FC | ↑ N-acetylaspartate to creatine (NAA/Cr) |
|           |       | rs11706648 | OXTR | | | | | | | |
|           | MDD   | Na et al. (2018) | rs53576 | OXTR | Intronic | Not found | MDD: 47 F; HC: 30 F | Not deviated | TaqMan | Hippocampal subfield volumes |
|           |       |        |                   |                  |           |                             |              |                 |                               | N. S. |
|           |       |        |                   |                  |           |                             |              |                 |                               | ↓ R medial temporal lobe (amygdala and hippocampus) trend (AA vs GA/ GG; AA vs AC/CC) |
|           |       |        |                   |                  |           |                             |              |                 |                               | |
|           |       |        |                   |                  |           |                             |              |                 |                               | |
|           |       |        |                   |                  |           |                             |              |                 |                               | |
|           |       |        |                   |                  |           |                             |              |                 |                               | |
|           |       |        |                   |                  |           |                             |              |                 |                               | |
|           |       |        |                   |                  |           |                             |              |                 |                               | |
|           | SCZ and AD | Haram et al. (2016) | rs53576 | OXTR | Intronic | Not found | AN: 49 F; HC: 0 | Not found | DNA Sanger Sequencing | BOLD response, and FC, during socia/non-social movement |
|           |       | rs2254298 | OXTR | Intronic | | | | | | |
|           |       | rs237902 | CAV3 | Synonymous | | | | | | |
|           | AN    | Sala et al. (2018) | rs53576 | OXTR | Intronic | Not found | SCZ: 104 (63 M/ 41 F); AD:100 (43 M/ 57 F); HC: 142 (84 M/ 58 F) | Not deviated | Affymetrix Human SNP Array 6.0 | BOLD response during emotional faces |
|           |       | rs2254298 | OXTR | Intronic | | | | | | |
|           |       | rs237902 | CAV3 | Synonymous | | | | | | |

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disruptions in DMN connectivity, which, in turn, was associated with adolescents presenting increased right amygdala activation (Michalska et al., 2014). In another study, the parents hippocampus BOLD response to positive statements from their children might indicate stronger resilience to stress and anxiety, a known anxiety disorder in later childhood and avoidant symptoms in early childhood (Zeev-Wolf et al., 2020). Higher paternal care was also found to increase the positive effect of the A allele on the middle frontal gyrus and ventromedial orbital regions of PFC, at high CU HC: (−) high or moderate CU; (+) with FC for high or moderate CU; (−) with FC at low CU (above areas) Emotion resonance, methylation x CU traits x diagnosis: CD: (+) midcingulate cortex and supplementary motor regions for high CU; (−) for low CU; (−) with FC between basolateral amygdala with precentral and temporoparietal regions for high CU; (+) neural activity at low CU levels HC: (−) neural activity for high or moderate CU; (+) with FC for high or moderate CU. Methylation x sex: SCZ: (−) R hippocampus in females only SCZ-AFF: L MTG and L SFG in females only HC: (−) R hippocampal, L MTG and R IFG in females only SAD: (−) amygdala for social phobia-related words

### Table 5

| Diagnosis | Study | Gene (contiguity) | Ethnicity | Sample size (Males/Females) | Biological sample | DNA methylation method | Brain phenotype | Main findings (association with methylation) |
|-----------|-------|------------------|-----------|-----------------------------|------------------|------------------------|----------------|------------------------------------------|
| PTSD      | Nawijn et al. (2019) | OXTR | Caucasian | PTSD: 31 (17 M/14 F); HC: 36 (17 M/19 F) | Whole blood | Bisulfite pyrosequencing | BOLD response to emotional faces | (+) L amygdala for negative emotions in PTSD females (trend) |
| CD        | Aghajani et al. (2018) | OXTR | Northwestern European (8CD/17HC); Non-Northwestern European (31CD/10 HC) | CD: 39 M; HC: 27 M | Saliva | Bisulfite pyrosequencing | BOLD response, and FC, to emotional faces | Emotion recognition, methylation x CU traits x diagnosis: CD: (+) midcingulate, insular, temporoparietal and precentral cortices and supplementary motor region, for high CU; (−) with FC between centromedial amygdala and ventro/medial orbital regions of PFC, at high CU HC: (−) high or moderate CU; (+) with FC for high or moderate CU; (−) with FC at low CU (above areas) |
| Psychosis | Rubin et al. (2016) | OXTR | 137 White, 71 Black, 25 Other | Psychotic: 167 (75 M/92 F); HC: 75 (37 M/38 F) | Whole blood | Bisulfite pyrosequencing | VBM volume | |
| SAD       | Ziegler et al. (2015) | OXTR | Caucasian | SAD: 110 (34 M/77 F); HC: 111 (33 M/77 F) | Whole blood | Bisulfite pyrosequencing | BOLD response to social phobia-related vs negative or neutral words | |
| ASD       | Andari et al. (2020) | OXTR | 68 Caucasian (28ASD/40HC); 26 African (8ASD/18HC); 10 Asian (HC); 9 Other (4ASD/6HC) | ASD: 40 M; HC: 74 (57 M/17 F) | Saliva | PicoGreen dsDNA Assay | Resting state FC | |

Mentalizing neurocorrelates has also been researched. For instance, an interaction between genotype and sex frequency/satisfaction has been reported to predict BOLD responses to the picture of a partner (Acevedo et al., 2019): the A allele was associated with weaker associations between sexual satisfaction/frequency and activation of a range of areas including the NAcc, ventral pallidum, caudate, hypothalamus, insula and DLpFC, ACC and parietal and temporal cortex (Acevedo et al., 2019). Supporting current hypotheses which postulate OT as a facilitator of human maternal bonding (Feldman, 2012), the A allele in parents was found to be associated with increased left ACC and right hippocampus BOLD response to positive statements from their children (Michalska et al., 2014). In another study, the parents’ A allele was associated with adolescents presenting increased right amygdala activation during their positive statements (Aupperle et al., 2016). In turn, the A allele in parents was associated with reduced amygdala activation in adolescents during critical statements (Aupperle et al., 2016), which might indicate stronger resilience to stress and anxiety, a known anxiolytic effect of intranasal OT. The A allele was also associated with disruptions in DMN connectivity, which, in turn, was associated with anxiety disorders in later childhood and avoidant symptoms in early childhood (Zeev-Wolf et al., 2020). Higher paternal care was also found to increase the positive effect of the A allele on the middle frontal gyrus fNIRS activation in response to stress, which authors defend represents a less adaptive response to social stressors (Cataldo et al., 2020). In the Prisoner’s Dilemma game, the A allele was associated with increased activation in the right frontal gyrus and in a bilateral parieto-temporo-occipital network during mentalizing, but only in those with secure childhood attachment (Schneider-Hassloff et al., 2016).

Overall, although some MRI studies seem to support current theories of OT as a reinforcer of social reward learning (i.e. as in attachment) and supporting current hypotheses which postulate OT as a facilitator of human maternal bonding (Feldman, 2012), the A allele in parents was found to be associated with increased left ACC and right hippocampus BOLD response to positive statements from their children (Michalska et al., 2014). In another study, the parents’ A allele was associated with adolescents presenting increased right amygdala activation during their positive statements (Aupperle et al., 2016). In turn, the A allele in parents was associated with reduced amygdala activation in adolescents during critical statements (Aupperle et al., 2016), which might indicate stronger resilience to stress and anxiety, a known anxiolytic effect of intranasal OT. The A allele was also associated with disruptions in DMN connectivity, which, in turn, was associated with anxiety disorders in later childhood and avoidant symptoms in early childhood (Zeev-Wolf et al., 2020). Higher paternal care was also found to increase the positive effect of the A allele on the middle frontal gyrus fNIRS activation in response to stress, which authors defend represents a less adaptive response to social stressors (Cataldo et al., 2020). In the Prisoner’s Dilemma game, the A allele was associated with increased activation in the right frontal gyrus and in a bilateral parieto-temporo-occipital network during mentalizing, but only in those with secure childhood attachment (Schneider-Hassloff et al., 2016).

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Event-related potentials (ERP) studies using facial emotion paradigms have equally shown heterogeneity in main effects of genotype. On the one hand, these studies reported an effect of genotype in early stages.
| Study                  | SNP ID       | Gene (contiguity) | SNP characteristics | Ethnicity                       | Sample size (Males/Females) | HW principle | Genotyping method | OXT Dose | Design                              | Brain phenotype                                                                 | Main findings (genotype contrast or allelic load correlation)                                                                                   |
|------------------------|--------------|-------------------|---------------------|---------------------------------|-----------------------------|---------------|------------------|-----------|---------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Chen et al. (2020)     | rs53576      | OXTR              | Intronic            | African American, 61 Asian, 66 Caucasian, 9 Latino, 12 Other | 182 (92 M/90 F)             | Not deviated  | TaqMan           | 24IU       | Double-blind, placebo-controlled, between-subject                               | BOLD response to Prisoner’s dilemma                                                                                                        |
|                        |              |                   |                     |                                 |                             |               |                  |           | Study SNP ID (allele) |                                              | Cooperation, IN-OXT x OXTR methylation (OXTRmeth): IN-OXT ↑ L occipital pole in women with low methylation (OXTRmeth) (& vice-versa). |
|                        |              |                   |                     |                                 |                             |               |                  |           | Study SNP ID (allele) |                                              | Cooperation in rs53576 GG, IN-OXT x OXTRmeth: IN-OXT ↑ lateral septum, lateral OCC and L postcentral gyrus in women and precuneus in men with low OXTRmeth (& vice-versa). |
|                        |              |                   |                     |                                 |                             |               |                  |           | Study SNP ID (allele) |                                              | Defection, IN-OXT x OXTRmeth: IN-OXT ↑ R precuneus, L postcentral gyrus, R occipital pole in men with low OXTRmeth (& vice-versa). |
|                        |              |                   |                     |                                 |                             |               |                  |           | Study SNP ID (allele) |                                              | Defection in rs53576 GG carriers, IN-OXT x OXTRmeth: IN-OXT ↑ visual cortex in men with low OXTRmeth (& vice-versa). |
|                        |              |                   |                     |                                 |                             |               |                  |           | Study SNP ID (allele) |                                              | Whole-brain, drug x sex x genotype: Females: IN-OXT ↑ ventral caudate nucleus, NAcc, STG, MTG, ACC and PFC for human partners (GG); IN OXT ↓ NAcc, putamen and insula for computer partners (GG) |
| Feng et al. (2015)     | rs53576      | OXTR              | Intronic            | Not found                        | 204 (104 M/100 F)          | Not deviated  | TaqMan           | 24IU       | Double-blind, placebo-controlled, between-subject                               | BOLD response to Prisoner’s dilemma                                                                                                        |
| Montag et al. (2013)   | rs2268498    | OXTR              | Intronic            | European Causasian               | 55 M                        | Deviated      | Real-time PCR     | 25IU       | Double-blind, placebo-controlled, crossover                                    | BOLD response (amygdala) to processing of gaze                                                                                               |
|                        | rs180789     | CAV3              | Intronic            | European                        |                             |               |                  |           | Study SNP ID (allele) |                                              | N. S.                                                                                                                                        |
|                        | rs401015     | CAV3              | Promoter            |                                 |                             |               |                  |           | Study SNP ID (allele) |                                              | N. S.                                                                                                                                        |
| Sauer et al. (2013)    | rs3796863    | CD38              | Intronic            | European                        | 55 M                        | Not deviated  | Real-time PCR     | 25IU       | Double-blind, placebo-controlled, crossover                                    | BOLD response to emotional faces                                                                                                          |
|                        | rs4680       | COMT              | Missense            |                                 |                             |               |                  |           | Study SNP ID (allele) |                                              | IN-OXT x COMT x CD38 genotypes: ↑ amygdala in val/val (vs. met/met) and A carriers, only in Placebo.                                      |
| Sauer et al. (2012)    | rs3796863    | CD38              | Intronic            | European                        | 55 M                        | Not deviated  | Real-time PCR     | 25IU       | Double-blind, placebo-controlled, crossover                                    | BOLD response to emotional faces with eye-tracking,                                                                                           |
|                        |              |                   |                     |                                 |                             |               |                  |           | Study SNP ID (allele) |                                              | Whole-brain: ↑ L fusiform gyrus for social vs non-social (combined or separate) (CC vs AC/AA); IN-OXT ↑ L fusiform gyrus (CC vs AC/AA) for social vs non-social (combined or separate) |
|                        |              |                   |                     |                                 |                             |               |                  |           | Study SNP ID (allele) |                                              | ROI: ↑ bilateral amygdala for direct vs averted gaze (AA/AC vs CC); IN-OXT ↑ fusiform gyrus for direct vs averted gaze (CC vs AC/AA); IN-OXT ↑ L amygdala for direct vs averted gaze (AA/AC > CC) |
of visual processing, with the A allele associated with decreased negative N1 deflection when watching human, animal or object pictures in a dose dependent manner (Choi et al., 2017), and decreased N1 latency when attending infants’ strong versus mild facial expressions (Peltola et al., 2014). The allele was also associated with a longer N170 latency in response to emotional inverted faces, but replication failed (Munk et al., 2016). The A allele was also associated to a smaller negative N1 amplitude in response to images of both humans and objects, and N2’s, in response to images of humans (and not objects); suggesting a socially preferential SNP effect on mid-to-late visual cues processing but not social-exclusive in early processing (Choi et al., 2017). Although the latter study did not find an effect on later potentials, such as the late positive potential (LPP), other studies reported SNP effects only for late-stage emotional visual processing, with the A allele being associated with shorter LPP amplitude (Fowler et al., 2018), and P3 amplitude preferentially during painful image viewing (Luo et al., 2017). The fact that rs53576 impacts social visual stimuli processing is compatible with the well-known social salience hypothesis of OT (Shamay-Tsoory and Abu-Akel, 2016).

One [99mTc] TRODAT-1 SPECT study found that the A allele was associated with increased striatal dopamine transporter (DAT) availability (Chang et al., 2014), which means lower dopaminergic tone. This is consistent with an independent finding of its association with lower activation of the dopamine-rich ventral tegmental area during viewing of their lover’s image (and with a lower sense of sociality, empathy and altruism toward the partner) (Acevedo et al., 2020). Both these studies’ findings follow well from non-human animal evidence demonstrating OT to regulate the amount of dopamine that is released in response to rewarding stimuli and support the current robust hypothesis of an OT-dopamine interplay in the human brain (Baskerville and Douglas, 2010), which for now is still in requirement of direct evidence. Such theory is furthermore in line with our eQTL analysis showing the same allele to be associated with increased OXTR mRNA levels in the basal ganglia.

4.1.1.2. rs2254298. Despite its popularity in neuroimaging genetics studies, our eQTL analysis did not retrieve any association between this SNP and gene transcription in any of the tissues included in the Gtex database.

The intronic rs2254298 has attracted considerable attention (figuring in about 25% of all studies reviewed herein) probably because its minor allele A has been associated with higher OT plasma levels in healthy individuals (Feldman et al., 2012) and with protection against an ASD diagnosis in Caucasian individuals (Jacob et al., 2007) (studies in Asian samples have instead reported an association between the minor allele A and ASD diagnosis (Liu et al., 2010)).

Morphometric studies reported mixed findings regarding the association between this SNP and regional brain volumes. The A allele was repeatedly found to present associated with increased amygdala volume (Furman et al., 2011; Inoue et al., 2010; Marusak et al., 2015). However, allele A has also been associated with decreased right amygdalar volume, only in those with childhood early neglect, and decreased bilateral amygdalar volume when simultaneously accounting for OXTR methylation (Womersley et al., 2019). However, a haplotype analysis found a positive association of the A allele with the bilateral amygdala volume (Inoue et al., 2010). Additionally, the A allele was associated with decreased whole brain grey matter volume and dorsomedial ACC volume (Furman et al., 2011). In men, but not in women, it was associated with thinner cortical grey matter in the dorsal ACC bilaterally (Wang et al., 2017) and with a larger right insular cortex GMV (Saito et al., 2010) – suggesting this SNP may affect the structure of the brain predominantly in men.

In terms of MRI resting state functional connectivity, the A allele was associated with a decrease between the posterior cingulate cortex and a set of other brain regions, extending from the right fronto-insular cortex to subcortical structures (such as the putamen, the globus pallidus and the bilateral dorsal ACC) (Wang et al., 2017), but an increase between all three amygdalar sub-nuclei and the visual processing areas. Interestingly, A allele was associated with reduced coupling of the centromedial amygdala with higher-order cognitive processing regions, such as the frontal cortex (Zimmermann et al., 2018). In another study, that allele was also associated with reduced DMN connectivity, which in turn has been associated with avoidance symptoms in early childhood and anxiety disorders in later childhood (Zeev-Wolf et al., 2020).

Only one study found significant association between genotype and brain activation during salience processing of emotional faces. In this case, the A allele was associated with increased BOLD response in different cortical and subcortical regions during emotional face categorization or matching (though this effect depended on the context and emotional expression of the stimuli) (Marusak et al., 2015). An additional region of interest analysis revealed an intersection between genotype and task condition, which was mainly driven by an association between the A allele and increased amygdala activity during incongruent trials (vs. congruent trials) – or neutral faces – as compared to shapes, during the same tasks (Marusak et al., 2015). In contrast, other studies did not find any effects of genotype on BOLD responses (Loth et al., 2014; Waller et al., 2016) or ERPs (Slane et al., 2014) during emotional face processing.

A fNIRS study found that the A allele was associated with increased brain activation in channels 10 and 15 – related to awareness and inferential reasoning - during low maternal care (Cataldo et al., 2020). Higher maternal care also corresponded itself to higher activation in these channels, suggesting that it is associated with a higher readiness to act in social situations and a more efficient response to stressful stimuli (Cataldo et al., 2020).

4.1.1.3. rs1042778. We did not find any association between this SNP and gene transcription in our eQTL analysis.

As an exonic rs1042778 and 3’ untranslated region (UTR) variation of the OXTR gene has been assumed to play an important role in the regulation of the transcription and translation of OXTR, including in allelic expression imbalance in the amygdala (Israel et al., 2009; Tansey et al., 2010). Furthermore, its minor allele T has also been linked to lower OT levels in the healthy individuals (Feldman et al., 2012) and also with a higher risk for autism and reduced empathy (Zeev-Wolf et al., 2020).

In line with the effects on allelic expression imbalance in the amygdala, two studies found a trend for an association of T allele with increased right amygdala reactivity during emotional faces (Waller et al., 2016), and significantly increased left hippocampal response to own vs other children pictures (Michalska et al., 2014). Further morphometric (Inoue et al., 2010), fMRI (Damiano et al., 2014; Loth et al., 2014; Westberg et al., 2016) and EEG (Slane et al., 2014) studies did not find any significant association.

4.1.1.4. rs2268498, rs237897. In our eQTL annotation, we found the C allele of rs2268498 to be associated with an increase of OXTR transcription in the caudate, NAcc, putamen, hippocampus, ACC, frontal cortex and the total cortex, and the same pattern in the same regions for the (minor) allele A of rs237897.

The upstream gene variation of the 5’ rs2268498 and the intronic rs237897 are thought to impact considerably on OXTR expression. For instance, carriers of the intronic C allele were shown to have increased OXTR expression in the hippocampus (Reuter et al., 2017). This association was further confirmed using in vitro human cell lines. Furthermore, rs2268498 is located within a CTICF (zinc finger protein) transcription factor binding motif, which is recognized as a transcriptional regulator protein able to activate or repress transcription (Schuschl et al., 2015).

Despite robust evidence suggesting a functional role for both SNPs,
all neuroimaging genetics studies evaluating the impact of rs237897 variation on brain’s structure (voxel-based morphometry (Wang et al., 2017)) or function (resting-state connectivity of the precuneus) (Wang et al., 2017), EEG (Slane et al., 2014) or fMRI responses during a face encoding task (Westberg et al., 2016) have not found any significant association. For rs2268498, the same fMRI face encoding study also did not find any significant association (Westberg et al., 2016). However, in an empathy task, the C allele was positively associated with right STS activation and empathic accuracy when observing painful face expressions (Laursen et al., 2014).

4.1.1.5. rs237893, rs237915, rs3806675, rs35413809. The intronic SNPs rs237893 and rs237915 and the rs3806675 and rs35413809 upstream variations showed in our eQTL annotation, impact on OXTR transcription in the brain. Via our eQTL analysis, for instance, we found the alternative alleles G and C of rs237893 and rs237915, respectively, to decrease OXTR transcription in the caudate, NAcc, frontal cortex and total cortex, and additionally in the putamen, hippocampus and ACC for rs237893. Whereas the allele G of rs35413809 was linked with a decrease in OXTR transcription in the cerebellar hemisphere, the allele A of rs3806675 was associated with an increase in caudate, NAcc, putamen, hippocampus, ACC, frontal and total cortex, and in cultured fibroblasts. In line with our eQTL annotation, one functional imaging study investigating the effects of interactions between genotype and economic income on brain responses during emotional face matching found that the C allele was associated with decreased ventral striatum activation and increased connectivity between the ventral striatum and ventromedial prefrontal cortex in those with past increased economic privilege; with lower striatal activation predicting increased social anxiety (Gonzalez et al., 2019). These findings support the idea that economic privilege and rs237915 genotype might calibrate social motivational neural systems. The biological mechanisms underlying such interaction remain unknown but might involve further interactions with stress exposure and epigenetic shaping of the activity of the OT system (Baker et al., 2017).

In another study, the minor rs237915C and rs237893 A alleles were associated with decreased ventral striatum responses to angry faces (Loth et al., 2014). The same study did not find any association involving rs3806675 or rs35413809 genotypes (Loth et al., 2014). The absence of significant results on ventral striatum activation for the OXTR SNP rs3806675 is surprising, considering that local effects on OXTR transcription were identified in our eQTL annotation analysis. Nevertheless, the sample size used in this study was small, raising the question of whether effects might have been missed due to lack of statistical power. Therefore, further adequately powered studies revisiting this finding are needed before we assume that this variation is not associated with striatal responses.

4.1.1.6. rs2268493, rs2268495, rs2270465, rs75775. The intronic rs2268493, rs2268495, rs2270465 and rs75775 showed no effect on transcription in brain tissue from our eQTL analysis. However, in cultured fibroblasts, while the minor allele C of rs2268493 was associated with decreased transcription of OXTR, for the minor alleles C of rs2270465, G of rs75775, and A of rs2268495, we found increased OXTR transcription. Additionally, our eQTL annotation also found, for rs2268495 G a decrease in OXTR transcription in coronal arteries; for rs2270465 an increase in the tibial artery and oesophagus mucosa; and for rs75775 G, an increase in the coronal arteries and a decrease in the tibial nerve. While effects on brain tissue were not identified, it is not impossible that these SNPs might still affect OXTR transcription in the brain with smaller effects that were not captured by our eQTL analyses. Morphometric studies did not find any significant association between rs2268493 or rs2268495 (Inoue et al., 2010) or rs2270465 (Wang et al., 2017) and brain structure. However, one study found that rs2268493 was associated with amygdala bilateral volume in a haplotype analysis (Inoue et al., 2010).

In a functional study using the monetary incentive delay task, the minor rs2268493C allele was associated with increased BOLD response during monetary reward anticipation, but not receipt, in the left NAcc, left orbital frontal cortex, left thalamus and in the left cingulate gyrus (Damiano et al., 2014). However, a face encoding MRI study did not find any significant association between rs2268493, rs2270465 and rs75775 and BOLD response (Westberg et al., 2016). In an explicit emotion processing fMRI study, the C allele and high maternal care were associated with higher right top-down DLPPC-to-amygdala effective connectivity, suggesting a gene by environment interaction mediated by the oxytocin receptor emotion processing response (Antonacci et al., 2020).

4.1.1.7. rs2268492, rs11171703, rs4686302, rs2301261. For the intronic rs2268492 and rs11171703, the rs2301261 UTR variation of the 5’ and rs4686302 missense variation, in our eQTL analysis, the alternative alleles were found to be associated with OXTR transcription in cultured fibroblasts. However, we could not identify any effects on brain transcription. In line with the absence of significant effects on transcription in the brain, no significant association between rs2268492, rs11171703, rs4686302 and rs2301261 (among other SNPs) and ventral striatum and amygdala responses to angry faces has been found (Loth et al., 2014).

4.1.1.8. rs237887, rs918316, rs237888, rs7632287. The intronic rs237887, rs918316, rs237888 and rs11706648, and the rs7632287 UTR variation of the 3’ were found not to impact on transcription, in our eQTL annotation analysis.

Only one haplotype analysis yielded a significant association between rs918316 and amygdala volume (bilaterally), but not for rs237887 (Inoue et al., 2010). For rs237888 there was no effect of genotype on the GMV or functional connectivity of the precuneus in one study (Wang et al., 2017). In another study, (minor) rs7632287 A was associated with higher BOLD response in the right amygdala during face encoding task (Westberg et al., 2016). rs237887 (minor) G allele was associated with increased BOLD responses during monetary reward anticipation, but not receipt, in frontal and occipital regions as well as in right precuneus and supramarginal gyrus (Damiano et al., 2014). Further studies did not find any significant associations between genotype and functional activity in task-based studies for rs237887 (Loth et al., 2014; Westberg et al., 2016), or for rs7632287 and rs237888 (Loth et al., 2014).

4.1.1.9. rs11706648, rs2268490, rs2268491, rs2268494, rs1465386, rs11131149, rs237889, rs35498753, rs6777726. For rs1465386 upstream variation, and intronic rs11706648, rs2268490, rs2268491, rs2268494, rs2268495, rs11131149, rs237889, rs35498753, rs6777726, we could not find any effects on gene transcription via our eQTL analysis. In line with the absence of significant effects on transcription, the only study investigating associations between genotype and the neural responses of the ventral striatum and amygdala to angry faces did not find any significant association (Loth et al., 2014).

4.1.2. OXT

4.1.2.1. rs3761248, rs877172, rs2740210, rs4813625. Our eQTL analysis showed neither of the rs3761248, rs877172, rs2740210, rs4813625 SNPs to have a significant impact on OXT transcription in brain tissue. However, the alternative alleles C and G of rs3761248 and rs877172, respectively, increased the transcription of OXT in the liver and skin (sun-exposed leg). In turn, the (minor) allele A of rs2740210 decreased OXT transcription in cultured fibroblasts and, the (minor) allele C of the rs4813625 increased OXT transcription in the subcutaneous adipose tissue and decreased it in the liver.
The rs3761248 upstream variation, and rs2740210 downstream/upstream variation have been associated with whole-brain serotonin levels and rs877172 (minor) G allele additionally with decreased plasma OT (Francis et al., 2016).

By evaluating the dopamine D2 and D3 receptor occupancy during a pain stress challenge, a PET study examined the association of these four OXT SNPs with stress-induced dopamine release (Love et al., 2012): in females only, the rs4813625 (minor) C allele was associated with an increase of dopamine release in the right ventromedial caudate during pain. Unfortunately, we could not explore whether rs4813625 impacts OXT transcription in the substantia nigra, one of the local sources of dopamine in the brain (Xiao et al., 2017), since substantia nigra samples in the Gex database were too few to conduct reliable regional eQTL analyses (Consortium, 2013). Nevertheless, in rodents, OT signalling at dopamine-producing neurons was shown to increase the synthesis and release of dopamine (Charlet and Grinevich, 2017; Xiao et al., 2017). Therefore, the abovementioned increases in dopamine release in the caudate may reflect direct effects of rs4813625 A allele on OXT transcription in dopamine-producing neurons, i.e. of the ventral tegmental area (VTA) and/or substantia nigra.

4.1.3. CD38

4.1.3.1. rs3796863. We did not find any significant effects on mRNA transcription in any of the brain tissues of our eQTL annotation, but allele A is associated with decreased CD38 mRNA levels in the tibial nerve.

The intronic rs3796863’s minor allele A was associated with higher OT plasma levels (Feldman et al., 2012), and increased expression of CD38 in ASD subjects (a population which showed decreased CD38 expression) (Lerer et al., 2010), and with protection against disruptions in the DMN theta connectivity (Zeev-Wolf et al., 2020). The same allele has also been associated with decreased alcohol self-administration, dopamine alcohol release, ventral striatum response to positive feedback, and resting state functional connectivity between the ventral striatum and the cingulate cortex, suggesting it may impair (the dopamine-related) reward (Lee et al., 2020a, 2020b). This SNP was also investigated in one facial processing EEG study which reported no effect (Munk et al., 2016).

4.1.4. CAV3

4.1.4.1. rs6791619, rs237851, rs151462, rs237875. Among intronic rs6791619, rs237851, rs151462 and rs237875, in our eQTL annotation, we found the minor allele T of rs6791619 to be associated with an increased OXTR transcription in the spinal cord, NAcc, putamen, hypothalamus, amygdala, caudate and frontal cortex, and a decreased outside the brain, in the oesophagus mucosa. For the rs237851, we found a significant effect of the minor allele G, but mainly outside of the brain: increasing OXTR transcription in cultured fibroblasts and the tibial and coronary arteries but decreasing it in the tibial nerve and cerebellum. For rs151463, we found the minor allele G to decrease OXTR transcription in the skeletal muscle. rs237875 was not found to impact gene transcription.

Despite significant effects of some of these SNPs on gene transcription, the only study examining the effects of these variations on brain morphometry and resting-state functional connectivity did not find any significant association (Wang et al., 2017).

4.1.5. SSUH2

4.1.5.1. rs11914885, rs7634632. For intronic rs11914885 and rs7634632, our eQTL annotation did not retrieve any significant effects on gene transcription in any of the tissues included in the Gex database. In line with this, the only study examining the effects of these variations on brain morphometry and resting-state connectivity did not find any significant association (Wang et al., 2017).

4.1.6. OXT and OXTR Methylation

Although still few (n = 6), some studies evaluating the effects of methylation of the OXT (n = 1) and OXTR (n = 5) genes on brain structure and function in healthy individuals have been reported (Table 3). The only three structural studies conducted so far have investigated mostly associations between OXTR (n = 2) methylation and the amygdala, which is a key-hub of the OT system (Martins et al., 2020; Quintana et al., 2019; Rosenfeld et al., 2011). OXTR methylation degree has been associated with increased right amygdala GMV (Lancaster et al., 2018) and decreased right fusiform gyrus GMV (Haas et al., 2016), whilst another did not report any significant association (Womersley et al., 2019).

Functional studies have mostly investigated associations between OXTR or OXT methylation and brain responses to facial affect processing, emotional perspective-taking and social perception. One fNIRS study in infants found a negative and a positive association between OXTR methylation and the right inferior frontal gyrus response to happy and to angry/fearful faces, respectively (Krol et al., 2019). Another study also found a negative association between OXT methylation and BOLD responses of several brain areas involved in mentalizing and facial processing (such as the right STS, fusiform gyrus bilaterally, inferior frontal gyrus) during an emotional attribution task (Haas et al., 2016), and in the STS during emotional perspective-taking (Haas et al., 2016). Another study found OXT methylation degree to be positively associated with personal distress empathy in mothers with young children, and negatively with right inferior temporal gyrus volume, illustrating a connection between maternal empathy, structural variation, and the OXT gene (Hiraoaka et al., 2021).

Regarding OXTR, two studies investigating social perception reported its methylation degree to be positively associated with: (i) decreased functional coupling between regions of salience and attention control salience (Puglia et al., 2018); and (ii) increased neural response within BOLD response in regions of the attentional control network (Jack et al., 2012). The third study found increased brain signal entropy during social perception partially due to epigenetic modification to OXTR in two individual infant samples, accounting for individual differences in social behavior during the first year of life (Puglia et al., 2018). Higher OXTR methylation has also been associated with childhood maltreatment and with a decreased left OFC volume. The latter was concluded to be a mediator between the higher methylation effect and more insecure attachment style (Fujisawa et al., 2019).

Altogether, these studies provide multi-modal evidence supporting a link between OXT/OXTR epigenetic regulation, human social cognition and its neural correlates. The mechanisms underlying these relationships remain to be clarified; nevertheless, it is tempting to speculate that increased OXT/OXTR methylation, by decreasing gene expression, may impair social cognitive abilities and decrease their associated neural efficiency.

4.2. Neuroimaging (epi)genetics in clinical samples

Imaging (epi)genetic studies of OT-related genes have been on the agenda as an attempt to better understand OT’s (dys)function in psychiatric disorders. Below, we summarize both genetic (Table 4) and methylation (Table 5) findings for each of the disorders investigated so far, separately (grouping across diagnosis when appropriate).

4.2.1. Autism spectrum disorder

ASD has been identified as one of the most promising clinical applications of exogenous OT. OXTR SNPs have been associated with diagnosis status and social cognition in ASD, across different samples, although null-findings have also been reported. Three studies investigated a total of nine SNPs (rs53576, rs2268491, rs2254298, rs7632287,
rs2228485, rs1042778, rs237887, rs9840864 and rs11706648) of the OXTR/CAV3 gene. In one study, rs53576, rs2268491 and rs2254298 (but not rs7632287 or rs2228485) were found to interact with diagnosis to explain BOLD response during the Reading the Mind in the Eyes task in the right supramarginal gyrus and inferior parietal lobe (Uzefovsky et al., 2019). The interaction was driven by a genotype effect of these polymorphisms in the control group, that was not present in the ASD group, suggesting that some unknown aspect of this clinical condition nullifies a naturally occurring effect of the gene on brain function during that cognitive empathy process. In another study, ASD risk alleles for rs1042778, rs2254298, rs53576 and rs237887 of the OXTR gene were all dose-dependently associated with decreased functional connectivity between NAcc and other mesolimbic areas in ASD individuals, and with functional connectivity of the NAcc with the medial prefrontal cortex in neurotypically developing individuals (Hernandez et al., 2017). Finally, an MRS study found OTR rs9840864/rs11706648 minor allele C to be associated with decreased ratio of N-acetyl-aspartate/Creatine (a marker of neuronal function and viability) in the right medial temporal lobe (amygdala and hippocampus) in ASD (Egawa et al., 2014). However, these associations did not survive correction for multiple testing and should therefore be considered preliminary.

OXTR hypermethylation was also suggested as a potential biomarker for adults with ASD with impairments in theory of mind and self-awareness (Andari et al., 2020). In this population, higher OXTR methylation levels: (i) in intron 1, was associated with clinical symptoms and hyperconnectivity between cortico-cortical brain areas involved with theory of mind, and (ii) in exon 1, was associated with deficits in social responsiveness and hyperconnectivity between striatal and cortical areas.

4.2.2. Major depressive, social anxiety and post-traumatic stress disorders

Three studies have investigated an association between OXTR (epi) genetics variation and structure or function of the brain in major depressive (MDD) (1 genetics study), SAD (1 methylation study) and posttraumatic stress (PTSD) (1 methylation study) disorders. rs53576 (minor) A allele was associated with a larger hippocampal volume in females; with no effect found in MDD females (Na et al., 2018). In PTSD, OXTR methylation degree was found to be associated with left amygdala BOLD response to negative emotional faces in females; although this did not survive correction for multiple comparisons (Nawijn et al., 2019). In contrast, another study found OXTR methylation degree was associated with decreased amygdala responses to social phobia words (vs. other negative or neutral words) in SAD (Ziegler et al., 2015). Given the known anxiolytic role of OT, these findings may sound paradoxical. However, the same study also reported decreased OXTR methylation in patients with SAD. Assuming that decreased OXTR methylation can increase OXTR expression, these findings may reflect a compensatory upregulation for pathologically reduced oxytocin levels in these patients. However, the authors did not measure OT, which makes the full interpretation of these findings challenging.

4.2.3. Psychosis

We could only find two studies investigating associations between OXTR (epi)genetics variation and brain structure or function during emotional face matching in patients with psychosis. The (minor) rs237902 G allele was dose-dependently associated, in schizophrenia patients, with decreased amygdala BOLD response to negative emotional faces (Urama et al., 2016). This association was more present in healthy controls or patients with affective spectrum disorders. The same study did not find associations for rs53576 or rs2254298. A VBM study found complex associations between OXTR methylation, diagnosis and gender for a number of structures of the frontal and temporal lobes (Rubin et al., 2016). In healthy women and women with schizophrenia, but not men, OXTR methylation degree was associated with smaller right hippocampal volumes and, only in healthy women, also with left medial temporal (MTG) and right inferior frontal (IFG) gyri volumes. In contrast, in women, but not men with schizoaffective disorder, OXTR methylation degree was associated with larger left MTG and superior frontal gyrus (SFG) volumes. These studies exemplify well the need to consider sex when investigating the putative role of OT in psychosis psychopathology (Rubin et al., 2017).

4.2.4. Anorexia nervosa

We found one study investigating an association between rs53576 and rs2254298 and BOLD response to movement in anorexia nervosa (AN): therein, in AN women, the rs2254298 (minor) A allele was associated with decreased BOLD responses in the posterior cingulate (PCC) and medial prefrontal cortex (mPFC), as well as more negative functional connectivity between the PCC and the occipital lobe, in response to social (vs. non-social) movement (Sala et al., 2018). rs53576 did not reveal any effects. This study, albeit isolated, supports current hypotheses about a potential contribution of OT system dysfunction to the socioemotional difficulties exhibited by AN patients (Giel et al., 2018).

4.2.5. Conduct disorder

One recent study investigated whether OXTR methylation may modulate the association between callous-unemotional (CU) traits in youths with conduct disorder (CD) and brain function during the recognition of, and resonance (i.e. subjective emotional empathy), to distressing socio-affective stimuli (angry and fearful faces) (Aghajani et al., 2018). First, both OXTR methylation and CU levels in CD youths were positively associated with mid-cingulate hyperactivity during both facial emotion resonance and with insular, temporoparietal and pre-cuneal hyperactivity during emotion recognition. Second, interactions between OXTR methylation and CU levels in CD youths predicted centromedial amygdala decoupling from the ventromedial/orbitofrontal regions during recognition and basolateral amygdala decoupling from the precuneus and temporoparietal regions during resonance.

Collectively, the evidence accumulated until now is still insufficient to support a direct role of OT-related genetic and epigenetic variations in the brain function, structure and neurochemical psychopathological mechanisms in neuropsychiatric disorders, but suggestive. Although preliminary, these studies support current theories suggesting that OT dysfunction may contribute to the disruption of emotional and social processing observed during a number of disorders. The neural circuits involved in the pathways from OT-related (epi)genetic variation to disorder seem to mostly include areas of the limbic system (amygdala, hippocampus, basal ganglia), mentalizing network (i.e. supramarginal gyrus, medial prefrontal cortex) or cognitive control (i.e. frontoparietal network). The fact that these variations can present with differential effects during health and illness suggests that disease-specific factors might render patients more susceptible to the beneficial or detrimental effects of OT-related (epi)genetic variations. These studies also highlight the importance of considering sex, given that some of these effects seem restricted to a specific gender (and in these studies, significant associations were more likely to emerge in women).

4.3. Pharmacoco-neuroimaging (epi)genetics of intranasal oxytocin

From the five SNPs (rs53576, rs2268498, rs180789, rs401015 and rs3796863) inspected so far, studies only found significant moderation of intranasal OT effects on brain responses during social cooperation/defection, gaze processing and emotional face processing for rs53576, rs401015 and rs3796863. Indeed, we found rs53576 to be associated with OXTR transcription across a wide range of brain areas, including the basal ganglia where at least one study (Feng et al., 2015) has reported significant moderation effects of this variation. Therein, the A allele was associated with a decreased left ventral caudate nucleus activation during reciprocated cooperation, in response to intranasal OT, in men (but not women) – suggesting rs53576 genotype is an important variable to consider in clinical efficacy studies of this potential treatment.
In addition, we found rs401015 to impact OXTR mRNA expression in the brain, including in the cortex and basal ganglia – which was also implicated by another study: therein, the minor C allele was associated with higher amygdala BOLD activation during direct (vs. averted) gaze, after intranasal OT (Montag et al., 2013), with no effect of rs2268498 or rs180789. In sum, such genetic moderations may even exist via causing inter-individual differences in the amount of OTR in the brain, which in turn may amplify or attenuate responses to exogenous OT.

We found that rs3796863 was associated with CD38 transcription, in the tibial nerve but not in the brain. In line with the role of this gene in OT release, its minor allele T was also associated with higher OT plasma levels in healthy individuals (Feldman et al., 2012). Furthermore, a main effect of this SNP in the left fusiform gyrus and amygdala BOLD activation (Sauer et al., 2013), and an epistatic effect with a catechol-o-methyltransferase (COMT) genotype in the amygdala (Sauer et al., 2012) was found during a face matching task. However, no interaction with intranasal OT administration was found. While the exact mechanisms through which CD38 genetic variation can moderate the neuromodulatory effects of intranasal OT remain unknown, at least two possible mechanisms might be involved. First, it is possible that differences in baseline OTeergic neurotransmittonitus associated with CD38-genetically determined differences in OT release might induce downstream compensatory adaptations of the number of OT receptors available for OT binding, which in turn would lead to differences in response to intranasal OT. Second, if the effects of intranasal OT on the brain require, to some extent, engagement of endogenous OT release, then CD38-genetically related differences in endogenous OT release could influence the effects of intranasal OT in the brain.

Only one study investigated moderator effects of OXTR methylation on intranasal OT effects on brain responses, and it was regarding social cooperation/defection (Chen et al., 2020). Since increased OXTR methylation is associated with decreases in OTXTR expression, one would mostly predict it leading to attenuated intranasal OT responses. This study nevertheless indicates that the picture may be way more complex. OXTR methylation did not modulate OT effects within brain regions where the authors previously reported OT effects in response to reciprocated (caudate) and unreciprocated cooperation (amygdala and anterior insula). However, it modulated OTXTR effects on the response to both reciprocated and unreciprocated cooperation in other brain regions such as the precuneus and visual cortex. Furthermore, the same study also showed a three-way interaction between OXTR methylation, OXTR rs53576 genotype and gender, which suggested that genetic and epigenetic differences in endogenous OT release could influence the effects of intranasal OT in the brain.

4.4. Appraisal of study design

In regards to our quality assessment criteria, most studies (i.e. > 70%) compiled with using paradigms and neuroimaging techniques - for which data acquisition and statistical methods and significance thresholds were well outlined - appropriate or consensusal to addressing the proposed research questions. However, and although eligibility criteria were also well described in most, attempts – which we recommend - to homogenize and/or account for high sample demographic heterogeneity and bias, to have appropriate sample size, to report effect sizes, or to clearly describe aims and hypotheses, were not as often as desirable (<70%). The latter impairs a correct appraisal of the findings’ magnitude and power calculations in posterior studies, and their reliability as true positives. Further recommendations in regards to neuroimaging genetics are available elsewhere (Gerber et al., 2009; Meyer-Lindenberg et al., 2008).

The rationale behind applications of the neuroimaging genetics approach can be highly hypothesis-based, wherein specific polymorphisms are chosen because of previous evidence of their functional impact on transcriptomic (see next section), proteomic, cellular, or clinical phenotypes; and specific tasks, brain markers and neuroimaging modalities are chosen based on evidence of behavioural or neurodevelopmental impairments associated with the cognitive process under study. Nevertheless, researchers often chose to ‘escape’ such evidence-based ‘restrictions’ and explore polymorphisms and/or neuroimaging phenotypes which are not clearly related a priori. The preference for the latter design has become quite evident in our review, since we found a diverse plethora of SNPs as well as tasks, brain areas, and functional or structural measures being used as dependent variables. Unfortunately, this is the design that, although of course brimming with innovation (and hence attractive to funding agencies and journals), is putatively more likely to lead to false positives, given the known sample size limitations in neuroimaging (due to scanning and recruitment costs) and the associated low statistical power. As well argued (Cremers et al., 2017) this is particularly problematic in between-subject and massive univariate whole-brain analyses, and for expected weak (as for most SNPs) and spatially distributed (as in across the brain) effects – all contingencies which coincide with a typical neuroimaging genetics study herein reviewed. Thus, especially in neuroimaging genetics, but also in OT administration studies (Quintana, 2020; Walum et al., 2016), replication attempts, and null effect findings, are paramount to consolidate any true findings in the literature and should be incentivized by funding bodies and journals. Unfortunately, it was hard to find a study, in this review, which set out to replicate another (using the same variables, i.e. SNP/methylation, and task paradigm and neuroimaging technique and, if the case, ROI). Some, for example, only apparently did so: for example some (Choi et al., 2017; Fowler et al., 2018; Luo et al., 2017) found the same allelic direction GG>A for OXTR rs53576 for an amplitude increase for negative images in a ‘genotype x valence’, but for different ERPs (P3, N1, and LPP, respectively); and others have used a highly overlapping sample ([(Inoue et al., 2010; Saito et al., 2014) and (Chen et al., 2020; Feng et al., 2015)]. In the few (2 in 62 studies) which replicated the same research question as a previous study - (Womersley et al., 2020) after (Lancaster et al., 2018) and (Hiraoaka et al., 2021) after (Fujisawa et al., 2019) - the replication was unsuccessful. In the first case, a negative association of OXTR methylation with amygdalar gray matter was not confirmed. In the second case, one (Fujisawa et al., 2019) found a negative association between OXTR methylation and the left OFC; whilst the other (Hiraoaka et al., 2021) found it in the right ITG volume but independent of child maltreatment (these being the closest two findings we saw among all studies). Such overall degree of inconsistency in findings seriously limited our capacity to extract conclusive interpretations in our review, leaving it rather more as a synthesis of pilot studies, proofs of concept and preliminary findings.

4.5. The added value of gene – transcriptomic data for OT neuroimaging genetics

Our eQTL annotation suggested that most of the polymorphisms with effects on brain neuroimaging phenotypes indeed affect the transcription of genes of the OT pathway. However, some can affect the transcription of other genes outside of the OT pathway, such as CAV3, which is expressed in the brain and was shown to participate in neural signalling. Hence, while our eQTL annotation suggests that a big part of the gene-brain associations summarized herein are likely to involve interindividual differences in some element of the OT pathway, some caution is needed when inferring effects of genetic variability on target
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At the same time, a high number of the SNPs we reviewed herein do not seem to influence the transcription of any of the genes of the OT pathways in brain tissue, but still were associated to brain phenotypes. Possible explanations for such effects in the absence of transcription regulation may include effects on other gene regulatory mechanisms not directly affecting genes transcription levels, such as alternative splicing, post-transcriptional mechanisms, protein-protein interactions or others (Albert and Kruglyak, 2015; Koester and Insel, 2016), or, of course, they were false positive findings. Although this was not the main focus of our analysis, we note that none of the SNPs we reviewed herein seem to be a splicing-QTL in any of the body tissues incorporated in the GTEx database. Since information about the proteome is not available in this dataset, we should not draw strong conclusions about the extent to which these variations affect protein levels or other post-transcriptional modifications. Inferring variation in protein expression from mRNA might be problematic, since variation in mRNA levels may not be paralleled by changes in protein expression (Schindler et al., 1990). Further studies shedding light on the mechanisms by which these variations may influence brain structure and function through OT’s pathway regulation would be welcome. Meanwhile, prioritizing SNPs whose impact on mRNA transcription can be determined based on large-scale human gene-transcriptome initiatives, such as the Gtex project, could be a good way forward.

Following this line of thought, and to help future study design and present literature interpretation, we provide, in this manuscript, an extensive list of all genetic variations impacting on the transcription of OT-related genes as listed in the GTEx database. Except for the OXT gene, several SNPs seem to be linked to the transcription of OXTR, and CD38 across different areas of the brain. These OXT-related genes’ eQTLs, specifically those with effects in the brain tissue mRNA levels, represent preferable targets for neuroimaging genetics studies because they maximize the likelihood and plausibility of an effect. Indeed, by making the choice of SNPs in the study design more hypothesis-based (i.e. on previous gene expression evidence), the risk of false positive findings is reduced. Another manner by which one can further avoid false positive findings emerging from multiple SNP testing, in candidate gene studies, is by using polygenic/poly-SNP eQTLs-based scores capturing multivariate effects on gene transcription (Dudbridge, 2013), such as the PrediXcan tool (Tavares et al., 2021). Ultimately, the inclusion of brain transcriptomic data could considerably expand the insights our OT neuroimaging genetics efforts may have to offer by helping to bridge the gap between genetic and neuroimaging analysis, with an additional level of evidence related to intermediate phenotype such as mRNA expression level.

5. Overview

Taken together, the findings from the studies we reviewed herein show that neuroimaging (epi)genetics approaches are suitable to: i) provide insights about the neurobiology of the OT system in humans; ii) map brain pathways linking OT genes to disease, and iii) identify (epi) genetic factors that can help to explain inter-individual differences in the neuromodulatory effects of intranasal OT across different subjects. The reviewed studies also highlight some factors such as gender, culture, and early environment that moderate (epi)genetics – brain associations and often impair attempts to replicate original findings. Overall, the field seems to be still in its early stages. Indeed, even though the yearly number of OT (epi)genetics studies including neuroimaging have doubled in the last ten years, the total number of studies conducted in this field is still relatively sparse when compared to other neurochemical systems, such as dopamine or serotonin. Even if associations between genotype and structure/function/neurochemistry seem to consistently emerge for a number of brain areas, such as the amygdala, basal ganglia or the mentalizing networks, the inconsistency of findings (likely due to the use of relatively small sample sizes) alongside with methodological differences in study design and analysis, make it difficult to draw firm conclusions about effects of genes of the OT pathway in the human brain and about what impact these (epi)genetics – brain associations might have on behavioural phenotypes and clinical conditions.

We also noted that, to some extent, the imaging (epi)genetics findings we reviewed are only broadly consistent with existing theories for OT’s modus operandi in social cognition. These herein partially-supported theories include hypotheses that OT enhances the salience of social stimuli (Shamay-Tsoory and Abu-Akel, 2016) (i.e. the Social Salience Hypothesis of OT) and increase the reward value of affiliative interactions (Scheele et al., 2013). These theories have indeed have now replaced the initial theory that OT lead to purely pro-social behaviour. A more recent theory, the General Approach-Withdrawal Hypothesis – which states that OT heightens the salience of ‘personally relevant or emotionally evocative stimuli’, regardless of their, socialness (Harari-Dahan and Bernstein, 2014), may explain findings where no specificity of OT-related effects were found, however this theory has still to be adequately juxtaposed with the social salience theory since studies which have compared OT’s effects on the salience of both social and non-social stimuli(Eckstein et al., 2019), have not disassociated socialness from relevance. The latter is paramount because a stimulus’s socialness can be confounded by its relevance, especially for faces (Hesselso, 2020; Leopold and Rhodes, 2010; Ro et al., 2007; Yarbus, 1967), which are inherently more relevant than non-social stimuli. Orthogonalizing their socialness and relevance in future studies, including imaging genetics ones, is thus warranted. Another recent theory, also posing its non-specificity to social contexts, is the Allostatic Hypothesis (Quintana and Guastella, 2020), postiting OT promotes the maintenance of stability of one’s status by facilitating the anticipation of future changes in the environment (social or non-social) and responding accordingly (e.g. via cognitive or emotional) empathic behaviour). However, as an overarching theory, by design, it should be ‘broken down’ into specific hypotheses for specific states and environments in order to be tested.

Finally, our review is a good showcase of how greatly large-scale gene transcriptomic initiatives (such as the Gtex) may help us improve our mechanistic understanding of existing and future OT neuroimaging genetics findings, and to identify polymorphisms impacting the expression of candidate genes in the brain that we could prioritize in future similar efforts.

CRediT authorship contribution statement

DP wrote the manuscript and supervised all contributions. MS contributed with literature search, co-writing and proofreading.

Conflict of interest

None declared.

Data Availability

No data was used for the research described in the article.

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Appendix A. Supporting information
Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104912.

References
Acevedo, B.P., Poulin, M.J., Heber, G., Grafton, S., Brown, L.L., 2019. The neural and genetic correlates of satisfying sexual activity in heterosexual pair-bonds. Brain Behav. Sci. 9, e1286.

Acevedo, B.P., Poulin, M.J., Collins, N.L., Brown, L.L., 2020. After the honeymoon: neural and genetic correlates of romantic love in newlyweds. Front. Psychol. 11. https://doi.org/10.3389/fpsyg.2020.00634.

Aghajani, M., Klapwijk, E.T., Collin, G.F., Ziegler, C., Domschke, K., Vermeiren, R., van der Wee, N.J.A., 2018. Interactions between oxytocin receptor gene methylation and callous-unemotional traits impact socioaffective brain systems in conduct-disordered offenders. Biol. Psychiatry Cogn. Neuroimaging. Neuroimaging 3, 579–591.

Aldao, A., Sotres-Albeniz, X., Vidal-Torres, M., Manoliu, T., Sotres-Bayon, F., 2013. The role of regulatory variation in complex traits and disease. Nat. Rev. Genet. 16, 197–212.

Angugno, B., Sooka, L., Brian, J., Dupuis, A., Mankad, D., Smile, S., Jacob, S., 2014. Intraoral oxytocin in the treatment of autism spectrum disorders: a review of experimental and early clinical efficacy data in youth. Brain Res. 1580, 188–190.

Andari, E., Nishitani, S., Kaundinya, G., Caceres, G.A., Morrier, M.J., Ousley, O., Smith, A.K., Cubells, J.F., Young, I.J., 2020. Epigenetic modification of the oxytocin receptor gene: implications for autism spectrum behavior and brain functional connectivity. Neuropsychopharmacology 45 (7), 1150–1158. https://doi.org/10.1038/s41386-020-0610-6.

Antonacci, L.A., Pergola, G., Passiatore, R., Tursiasono, P., Quarto, T., Disopo, E., Rampino, R., Bertolino, A., Carabia, R., Balsi, G., 2020. The interaction between OXTR rs2268493 and perceived maternal care is associated with amygdala dorsolateral prefrontal effective connectivity during explicit emotion processing. Eur. Arch. Psychiatry Clin. Neurosci. 270 (5), 553–565.

Appel, R.L., Morris, A.S., Silk, L.S., Cries, M.M., Judah, M.R., Eagleton, S.G., Kircil, N., Byrd-Craven, J., Phillips, R., Alvarez, R.P., 2016. Neural responses to maternal praise and criticism: Relationship to depression and anxiety symptoms in high-risk adolescent girls. Neuroimage Clin. 11, 548–554.

Baker, M., Lindell, S.G., Driscoll, C.A., Zhou, Z., Yuan, Q., Schwandt, M.L., Miller-Crews, I., Simpson, E.A., Faulkner, A., Ferrari, P.F., Sindhu, R.K., Razagzari, M., Sommer, W.H., Lopez, J.F., Thompson, R.C., Goldman, D., Heilieg, M., Higley, J.D., Suomi, S.J., Barr, C.S., 2017. Early rearing history influences oxytocin receptor epigenetic regulation in rhesus macaques. Proc. Natl. Acad. Sci. USA 114, 11769–11774.

Baskerville, T.A., Douglas, A.J., 2010. Dopamine and oxytocin interactions underlying auto-aggressive behavior. Front. Neurosci. 4, 105.

Bhat, S., Amin, S., Dimov, C., Studer, C., Gruber, C., Schaub, M., Berti, M., 2021. The impact of oxytocin on the neural response to social cooperation in humans. Genes Brain Behav. 14, 1065–1076.

Bilkey, R.A., van Honk, J., Anyung, B., Baron-Cohen, S., 2013. Oxytocin, brain physiology, and functional connectivity: a review of intranasal oxytocin fMRI studies. Psychoneuroendocrinology 38, 962–974.

Cataldo, I., Neoh, M.I.Y., Chew, W.F., Foo, J.N., Iepri, B., Esposito, G., 2020. Oxytocin receptor gene and parental bonding module preferential responses to cues: a NIRS Study. Sci. Rep. 10 (1) https://doi.org/10.1038/s41598-020-65582-0.

Chang, W.H., Lee, I.H., Chen, K.C., Chi, M.H., Chiu, N.T., Yao, W.J., Lu, R.B., Yang, Y.K., Li, D., Liao, Y., 2012. Regulation of this review was there any theoretical or concrete influence from these sponsors.

Chang, W.H., Lee, I.H., Chen, K.C., Chi, M.H., Chiu, N.T., Yao, W.J., Lu, R.B., Yang, Y.K., Li, D., Liao, Y., 2012. Regulation of this review was there any theoretical or concrete influence from these sponsors.

Chang, W.H., Lee, I.H., Chen, K.C., Chi, M.H., Chiu, N.T., Yao, W.J., Lu, R.B., Yang, Y.K., Li, D., Liao, Y., 2012. Regulation of this review was there any theoretical or concrete influence from these sponsors.

Chang, W.H., Lee, I.H., Chen, K.C., Chi, M.H., Chiu, N.T., Yao, W.J., Lu, R.B., Yang, Y.K., Li, D., Liao, Y., 2012. Regulation of this review was there any theoretical or concrete influence from these sponsors.

Chang, W.H., Lee, I.H., Chen, K.C., Chi, M.H., Chiu, N.T., Yao, W.J., Lu, R.B., Yang, Y.K., Li, D., Liao, Y., 2012. Regulation of this review was there any theoretical or concrete influence from these sponsors.
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Karelina, K., Stuller, K.A., Jarrett, B., Zhang, N., Wells, J., Norman, G.J., DeVries, A.C., 2011. Oxytocin mediates social neuroprotection after cerebral ischemia. Stroke 42, 3608–3611.

Koester, S.E., Insel, T.R., 2016. Understanding how non-coding genomic polymorphisms affect gene expression. Mol. Psychiatry 21, 448–449.

Krol, K.M., Puglia, M.H., Morris, J.P., Connolly, J.J., Grossman, T., 2017. Estrogen mTOR pathway: a sex-dependent signaling cascade. Mol. Cell Endocrinol. 439, 1–10.

Krol, K.M., Puglia, M.H., Morris, J.P., Connolly, J.J., Grossman, T., 2018. DNA methylation of OXTR is associated with paraspinal sympathetic nervous system activity and amygdala morphology. Soc. Cogn. Affect Neurosci. 13, 1155–1162.

Lautzenhiser, L.R., Sieben, A., Mowery, T., Maden, R., Haddow, O., Hennessey, S., 2014. Variation in the oxytocin receptor gene is associated with behavioral and neural correlates of empathy and affect. Front. Behav. Neurosci. 8, 423.

Lee A.M., Shatiko, T.A., Blue, S.W., Kaucher, A.V., Winchell, A.J., Erikson, D.W., Grant, K.A., Leggo, L., 2020a. Labeled oxytocin administered via the intranasal route reaches the brain in rhesus macaques. Nat. Commun. 11, 2783.

Lee, M.R., Shin, J.H., Deschaine, S., D’Amor, A.M., Stangl, B.L., Yan, J., Ramchandani, V.A., Schwaab, M., Grodin, E.N., Momemian, R., Corral-Frias, N., Hariri, A.R., Bogdan, R., Alvarez, V.A., Leggo, L., 2020b. A role for the CD38 rs3796863 polymorphism in alcohol and monetary reward: evidence from CD38 knockout mice and alcohol self-administration. Am. J. Drug Alcohol Abuse. 46, 167–179.

Leppanen, J., Ng, K.W., Tchanturia, K., Treasure, J., 2017. Meta-analysis of the effects of oxytocin on brain reward circuitry to social cues and response to stressful life events. Biol. Psychiatry 81, 13. Article in Press.

Lerer, E., Levi, S., Israel, S., Yaari, M., Nemanov, L., Mankuta, D., Nurit, Y., Ebstein, R.P., 2011. Oxytocin mediates social neuroprotection after cerebral ischemia. Stroke 42, 1602–1606.

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P., déClercq, E., 2018. A systematic review and meta-analysis of the effects of oxytocin receptor gene (OXTR) polymorphisms with autism spectrum disorder (ASD) in the Japanese population. J. Hum. Genet. 55, 137–141.

Logothetis, K.E., Pauls, T., Augath, M., Trinath, T., Oeltermann, A., 2001. Brain imaging studies using functional magnetic resonance imaging (fMRI). Annu. Rev. Neurosci. 24, 571–626.

Lorenz, K., Johnson, R., 2014. Oxytocin and social behavior: the neuroscience of empathy. In: Social Neuroscience: An Integrative Approach. Oxford University Press, Oxford, pp. 337–358.

Ludermir, T., Brusciano, F., Brusciano, N., 2012. Estrogen mTOR pathway: a sex-dependent signaling cascade. Mol. Cell Endocrinol. 360, 1162–1167.

Luo, J., Bouwland, M.A., Mezelstein, P.G., 2008. Cavolin proteins and estrogen signaling in the brain. Mol. Cell. Endocrinol. 290, 8–13.

Malhi, G.S., Das, P., Outhred, T., Dobson-Stone, C., Bell, E., Gessler, D., Bryant, R., Luoma, J.I., Boulware, M.I., Mermelstein, P.G., 2008. Osteoporosis, osteopenia, and estrogen mTOR pathway: a sex-dependent signaling cascade. Mol. Cell Endocrinol. 290, 8–13.

Marusak, H.A., Furman, D.J., Kuruvadi, N., Shattuck, D.W., Joshi, S.H., Joshi, A.A., Mannie, Z., 2020. Genotype–phenotype interaction of OXTR rs53576 and emotional trauma on effects of stress on human neuroendocrine function. Front. Endocrinol. (Lausanne) 11, 604912.

Maurer, C.D., Giardino, A.P., Joshi, S., Spence, L., Peckham, T., Krug, J., Costanzo, M.C., 2015. Autism spectrum disorder: evidence from a pharmacogenetic imaging genetics study. BMC Evol. Biol. 15, 85.

Maurer, C.D., Giardino, A.P., Joshi, S., Spence, L., Peckham, T., Krug, J., Costanzo, M.C., 2015. Autism spectrum disorder: evidence from a pharmacogenetic imaging genetics study. BMC Evol. Biol. 15, 85.

Mason, S.D., Chronis-Tuscano, A., Waldman, I.D., Lahey, B.B., 2014. Genetic imaging of the ventral striatum to social cues and response to stressful life events. Biol. Psychiatry 81, 13. Article in Press.

Maurer, C.D., Giardino, A.P., Joshi, S., Spence, L., Peckham, T., Krug, J., Costanzo, M.C., 2015. Autism spectrum disorder: evidence from a pharmacogenetic imaging genetics study. BMC Evol. Biol. 15, 85.

Maier, W., Hurlemann, R., 2013. Oxytocin enhances brain reward system responses in healthy humans. J. Neurosci. Res. 91, 1450–1456.

Maier, W., Hurlemann, R., 2013. Oxytocin enhances brain reward system responses in healthy humans. J. Neurosci. Res. 91, 1450–1456.

McEwen, B.S., 1998. Stress and the brain: stress and the brain. In: The stress of life. McGraw Hill, New York, pp. 473–520.

McEvoy, L.P., Glatt, S.J., Price, L.H., 2008. A meta-analysis of the effects of social context on the processing of threatening social stimuli. Biol. Psychiatry 64, 75–82.

Mendlewicz, J., 1982. Social anxiety and social phobia: a review of the literature. Acta Psychiatr. Scand. 65, 269–279.

Merchant, J.C., Ramsey, K., Sweet, J.M., 2012. FINK: a pharmacogenetic imaging genetics study. Neuroimage 59, 491–496.

Merchant, J.C., Ramsey, K., Sweet, J.M., 2012. FINK: a pharmacogenetic imaging genetics study. Neuroimage 59, 491–496.
Schindler, R., Clark, B.D., Dinarello, C.A., 1990. Dissociation between interleukin-1 beta mRNA and protein synthesis in human peripheral blood mononuclear cells. J. Biol. Chem. 265, 10232–10237.

Schneider-Hassloff, H., Kircher, T., 2016. Oxytocin receptor polymorphism and childhood social experiences shape adult personality, brain structure and neural correlates of mentalizing. Neuroimage 134, 671–684.

Seeley, S.H., Chou, Y.H., O’Connor, 2018. Intrasal oxytocin and OXTR genotype effects on resting state functional connectivity: A systematic review. Neurom. Biobehav Rev. 95, 17–32.

Shahrestani, S., Kemp, A.J., Guastella, A.J., 2013. The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: a meta-analysis. Neuropsychopharmacology 38, 1929–1936.

Shamay-Tsoory, S.G., Abu-Akel, A., 2016. The social salience hypothesis of oxytocin. Biol. Psychiatry 79, 194–202.

Shilling, P.D., Feifel, D., 2016. Potential of oxytocin in the treatment of schizophrenia. CNS Drugs 30, 193–208.

Slade, M.M., Lusk, L.G., Boomer, K.B., Jansen, A., Nuscheler, B., Wemken, G., Witt, S.H., Schneider-Hassloff, H., Straube, B., Jansen, A., Nuscheler, B., Wemken, G., Witt, S.H., 2014. Social oxytocin receptor polymorphism and childhood social experiences shape adult personality, brain structure and neural correlates of mentalizing. Neuroimage 134, 671–684.

Snodgrass, N.J., Correa, C., Manering, N., Carson, D., Mechoux, V., Ziegler, C., Dannlowski, U., Brauer, D., Stevens, S., Laeger, I., Wittmann, H., Kugel, H., W., 2016. An oxytocin receptor polymorphism predicts amygdala reactivity and antisocial behavior in men. Soc. Cogn. Affect Neurosci. 11, 1218–1226.

Wandersdorfer, B., Koepp, M.J., 2016. Pharmaco fMRI: Determining the functional anatomy of the effects of medication. Neuroimage Clin. 12, 691–697.

Wang, J., Qin, W., Liu, B., Wang, D., Zhang, Y., Jiang, T., Yu, C., 2013. Variant in OXTR gene and functional connectivity of the hypothalamus in normal subjects. Neuroimage 81, 199–204.

Wang, J., Qin, W., Liu, B., Zhou, Y., Wang, D., Zhang, Y., Jiang, T., Yu, C., 2014. Neural mechanisms of oxytocin receptor gene mediating anxiety-related temperament. Brain Struct. Funct. 219, 1543–1554.

Wang, J., Braskie, M.N., Hafzalla, G.W., Faskowitz, J., McMahon, K.L., de Zubicaray, G.I., Wright, M.J., Yu, C., Thompson, P.M., 2017. Relationship of a common OXTR gene variant to brain structure and default mode network function in healthy humans. Neuroimage 147, 500–506.

Westberg, L., Henningsson, S., Zettergren, A., Svahn, J., Hörvall, D., Ebner, N.C., Fischer, H., 2016. Variation in the oxytocin receptor gene is associated with face recognition and its neural correlates. Front. Behav. Neurosci. 10, 178.

Wigston, R., Radua, J., Allen, P., Averbeck, B., Meyer-Lindenberg, A., McGuire, P., Shergill, S.S., Fusar-Poli, P., 2015. Neurophysiological effects of acute oxytocin administration: systematic review and meta-analysis of placebo-controlled imaging studies. J. Psychiatry Neurosci. 40, E1–E22.

Winterer, G., Hariri, A.R., Goldman, D., Weinberger, D.R., 2005. Neuroimaging and human genetics. Int. Rev. Neurobiol. 67, 325–383.

Womersley, J.S., Hemmings, S.M.J., Ziegler, C., Guittridge, A., Ahmed-Leitao, F., Eisen, J., Ziegler, C., Dannlowski, U., Brauer, D., Stevens, S., Laeger, I., Wittmann, H., Kugel, H., W., 2018. Intranasal oxytocin and OXTR genotype effects on resting state functional connectivity in trauma-exposed youth. Front. Endocrinol. 11. https://doi.org/10.3389/fendo.2020.00335.

Zee-Wolf, M., Levy, J., Ebstein, R.P., Feldman, R., 2020. Cumulative risk on oxytocin-pathway genes impairs default mode network connectivity in trauma-exposed youth. Front. Endocrinol. 11. https://doi.org/10.3389/fendo.2020.00335.

Ziegler, C., Dannlowski, U., Brauer, D., Stevens, S., Laeger, I., Wittmann, H., Kugel, H., Dohel, C., Hurlembre, B., Reif, A., Lesch, K.P., Heindel, W., Kirschbaum, C., Arolt, V., Gerlach, A.L., Hoyer, J., Deckert, J., Zwaninger, P., Domschke, K., 2015. Oxytocin receptor gene methylation: converging multilevel evidence for a role in social anxiety. Neuropsychopharmacology 40, 1528–1538.

Zimmermann, J., Derix, N., Montag, C., Reuter, M., Fellen, A., Becker, B., Weber, B., Markett, S., 2018. A common polymorphism on the oxytocin receptor gene (rs2268498) and resting-state functional connectivity of amygdala subregions - a genetic imaging study. Neuroimage 171, 1–10.