Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Special Issue 'New Perspectives in Neuropsychology: From Biology to Society': Research Report

Associations between genetic variations in oxytocin pathway genes and hippocampal volume: Insights from the UK Biobank

Shanshan Xiao [a,b,*], *Natalie C. Ebner* [c,d,e], *Junhua Dang* [f], *Gull Rukh* [b], *Lars Westberg* [g], *Helgi B. Schiöth* [b] and *Håkan Fischer* [a,h,i]

[a] *Department of Psychology, Stockholm University, Stockholm, Sweden*
[b] *Department of Surgical Sciences, Functional Pharmacology and Neuroscience, Uppsala University, Uppsala, Sweden*
[c] *Department of Psychology, University of Florida, Gainesville, USA*
[d] *Cognitive Aging and Memory Program, Clinical Translational Research Program (CAM-CTRP), University of Florida, Gainesville, USA*
[e] *McKnight Brain Institute, University of Florida, Gainesville, USA*
[f] *Institute of Social Psychology, School of Humanities and Social Sciences, Xi'an Jiaotong University, Shaanxi, China*
[g] *Department of Pharmacology, Institute of Neuroscience and Physiology at the Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden*
[h] *Stockholm University Brain Imaging Centre (SUBIC), Stockholm, Sweden*
[i] *Aging Research Center, Karolinska Institutet and Stockholm University, Stockholm, Sweden*

ARTICLE INFO

Article history:
Received 18 April 2024
Reviewed 01 July 2024
Revised 26 July 2024
Accepted 25 November 2024
Published online 17 December 2024

Keywords:
Oxytocin pathway gene
Oxytocin receptor
Hippocampus
Social recognition memory
UK Biobank

ABSTRACT

The role of oxytocin-related genes in social-cognitive function has been previously established, but structural brain mechanisms underlying this link remain poorly understood. Utilizing a substantial dataset from the UK Biobank ($N \approx 30{,}000$), this research determined associations between variations in ten single nucleotide polymorphisms (SNPs) within three oxytocin pathway genes (i.e., the oxytocin/neurophysin I prepropetide gene, the cluster of differentiation 38 glycoprotein gene, the oxytocin receptor gene) and whole-brain gray matter volume. Carriers of the AA or AG genotypes of the oxytocin receptor gene rs237851 SNP exhibited significantly larger hippocampal volume than carriers of the GG genotype. These results support the link between variations in the oxytocin receptor gene and hippocampal structure, with possible impact on social-cognitive function such as social recognition memory.
© 2024 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

This article is part of a special issue entitled: Memory and the social brain published in Cortex.

* *Corresponding author*. Stockholm University, Department of Psychology, Albanovägen 12, SE-114 19, Stockholm, Sweden.
E-mail addresses: shanshan.xiao619@gmail.com (S. Xiao), natalie.ebner@ufl.edu (N.C. Ebner), dangjunhua@gmail.com (J. Dang), gull.rukh@neuro.uu.se (G. Rukh), lars.westberg@pharm.gu.se (L. Westberg), Helgi.Schioth@neuro.uu.se (H.B. Schiöth), hakan.fischer@psychology.su.se (H. Fischer).
https://doi.org/10.1016/j.cortex.2024.11.017
0010-9452/© 2024 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Oxytocin, a pivotal neuropeptide, significantly influences human physiology and social behavior, enhancing social sensitivity, facilitating social processes, including maternal bonding and group affiliation, and supporting social learning and memory (Bartz et al., 2011; Brambilla et al., 2016; Shamay-Tsoory & Abu-Akel, 2016). Produced in the supraoptic and paraventricular nuclei of the hypothalamus (Busnelli & Chini, 2018), oxytocin is distributed for central and peripheral release (Knobloch et al., 2012; Maejima et al., 2014), exerting its effects by binding to its receptors across the brain and the body (Jurek & Neumann, 2018; Quintana & Guastella, 2020). Several vital genes regulate this complex process: the oxytocin/neurophysin I prepropetide (*OXT*) gene, which encodes oxytocin and neurophysin I (Gopal Rao et al., 1992; Xu et al., 2008); the cluster of differentiation 38 glycoprotein (*CD38*) gene, essential for oxytocin's release (Jin et al., 2007); and the oxytocin receptor (*OXTR*) gene, crucial for distribution and availability of the oxytocin receptor (Gimpl & Fahrenholz, 2001; Kimura et al., 1992). These genes contain various single nucleotide polymorphisms (SNPs), contributing to oxytocin's nuanced roles in physiology and social function (Feldman et al., 2016; Prata & Silva, 2022).

Only recently, however, have genetic neuroimaging approaches started to unravel the extent to which specific genetic polymorphisms or genes' methylation status are related to brain structural (e.g., brain volume, cortical thickness) and functional (e.g., task-related, resting-state) phenotypes (Prata & Silva, 2022). This novel approach complements pharmacological neuroimaging, which allows testing the effects of substances on brain structure and function using randomized-controlled trials by determining the impact of naturalistic/endogenous genetic variations on the brain without exogenous manipulation (Gurung & Prata, 2015). Understanding the role of genetic variations on the development of brain structure and the regulation of brain function can be used towards refining pharmacological intervention and will enhance knowledge about the complex process of gene expression and signaling (Prata & Silva, 2022).

Adopting a genetic neuroimaging approach, studies have investigated associations between genetic variations in oxytocin pathway genes and brain structure (Prata & Silva, 2022). The majority of this research has concentrated on *OXTR* SNPs and suggests that specific SNPs within this gene correlate with brain volume in areas critical for social processing and emotional regulation. For instance, variations in the *OXTR* rs2254298 and rs53576 SNPs were associated with differences in hippocampal and amygdala volumes, and these associations were, in some studies, moderated by factors such as emotional neglect or social support (Furman et al., 2011; Inoue et al., 2010; Malhi et al., 2020; Schneider-Hassloff et al., 2016; Tost et al., 2010; Wang et al., 2014; Womersley et al., 2020). The role of *CD38* and *OXT* SNPs on brain structure, in contrast, has yet to be explored (Prata & Silva, 2022). Also, previous studies were often limited by small sample sizes, restricting statistical robustness and obscuring genuine gene variation-brain volume connections.

The current study will examine associations between variations in oxytocin pathway genes and regional brain volumes using a large dataset from the UK Biobank. Our study overcomes several limitations of previous genetic neuroimaging research by analyzing the three oxytocin pathway genes concurrently in the same participant cohort. In particular, the present study will simultaneously examine previously studied SNPs within the *OXT*, *CD38*, and *OXTR* genes, shown to be crucial in human physiology and social behavior (Ebner et al., 2013; Feldman et al., 2016; Seeley et al., 2018). The UK Biobank comprises over 30,000 individuals with both genetic and brain imaging data and thus is significantly larger than previously analyzed datasets, enhancing statistical power of our study to detect even subtle effects of individual SNPs on brain structure across the brain.

2. Methods and materials

With authorization from the National Health Service Research Ethics committees.

(Reference No. 11/NW/0382), this study integrated genetic and neuroimaging data from the UK Biobank (Collins, 2012). Before data collection for the UK Biobank, informed, documented consent was obtained from each participant. This analysis of UK Biobank data was conducted under Application Number 30172, with ethical approval from the Uppsala Regional Ethics Review Board (Dnr 2017/198).

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. *Participants*

In this study, we examined the associations between variations in three oxytocin pathway genes and regional brain volumes across the brain, which required participants to have both T1-weighted MRI scans and genetic data to be included. The UK Biobank contains data from over half a million participants across the United Kingdom whose genetic, health-related, and cognitive data was collected between 2006 and 2014 (Allen et al., 2012; Collins, 2012; Miller et al., 2016; Sudlow et al., 2015). From 2016 to 2022, multimodal brain imaging data were collected on selected participants (Miller et al., 2016). The present analysis incorporated T1-weighted structural images acquired during the first imaging session from 42,789 participants. Of these, not all participants had complete data for all SNPs considered here. To include as many data points in each analysis as possible, we opted against listwise deletion. Instead we utilized the data available, resulting in varying sample sizes for the analysis of each SNP. Additionally, individuals who did not self-identify as white British (referenced in Data-Field 21000, "Ethnic background") and who exhibited more than 5% genotype missingness (specified in Data-Field 22005, "Missingness") were omitted from the sample pool. See Table 1 for details about data inclusion. These inclusion/exclusion criteria were established prior to data analysis.

Table 1 – Demographic distributions and genetic details for the 10 SNPs analyzed.

Gene	SNP	Chromosome	Position	Major allele	Minor allele	Minor allele frequency (MAF)	Subjects with 0 minor allele	Subjects with 1 minor allele	Subjects with 2 minor alleles	Total sample	Age (M ± SD, in years)	Sex (% females)
OXT	rs4813625	20p13	5′	G	C	.47	7339	13,064	5968	26,371	64.15 ± 7.65	52.88 %
OXT	rs4813627	20p13	3′	A	G	.48	8422	15,533	7022	30,977	64.14 ± 7.65	52.65 %
CD38	rs3796863	4p15	Intronic	C	A	.30	17,552	14,731	3151	35,434	64.16 ± 7.64	52.70 %
OXTR	rs237851	3p25	5′	G	A	.46	10,486	17,509	7562	35,557	64.16 ± 7.65	52.72 %
OXTR	rs2268498	3p25	5′	T	C	.45	10,476	17,271	7179	34,926	64.15 ± 7.64	52.72 %
OXTR	rs53576	3p25	Intron 3	G	A	.31	15,759	14,292	3273	33,324	64.14 ± 7.65	52.73 %
OXTR	rs237887	3p25	Intron 3	A	G	.42	12,212	17,741	6397	36,350	64.16 ± 7.64	52.65 %
OXTR	rs7632287	3p25	3′	G	A	.25	20,286	13,826	2238	36,350	64.16 ± 7.64	52.65 %
OXTR	rs11914885	3p25	3′	A	G	.30	17,515	15,512	3323	36,350	64.16 ± 7.64	52.65 %
OXTR	rs7634632	3p25	3′	T	C	.49	9350	18,032	8640	36,022	64.15 ± 7.64	52.68 %

Abbreviations: M = Means, SD = Standard Deviations.

2.2. *Structural image acquisition and processing*

T1-weighted structural images were obtained on a standard Siemens Skyra 3T scanner with a 32-channel receive head coil. The T1 structural protocol was executed at a 1 mm isotropic resolution utilizing a three-dimensional (3D) MPRAGE acquisition, with inversion and repetition times optimized for maximal contrast (Miller et al., 2016).

Following (Miller et al., 2016), our study utilized T1-weighted structure volumes generated by an image-processing pipeline developed and implemented on behalf of the UK Biobank (Alfaro-Almagro et al., 2018). In brief, the procured 3D MPRAGE T1-weighted volumes underwent pre-processing and analytical procedures using FSL tools. The preprocessing included facial removal for participant anonymization, brain extraction to eliminate non-brain tissue from the image, linear alignment, and nonlinear warping to the standard MNI152 brain template to accommodate significant inter-individual variations in brain structures.

The image-processing pipeline involved several detailed steps to ensure accuracy and standardization of the structural images. Raw original (defaced) T1-weighted structural images, after defacing and reduction of the bias field via the on-scanner "pre-scan normalise" option, were processed without any further correction such as gradient distortion correction. The field-of-view was then reduced to eliminate non-brain tissue using the Brain Extraction Tool and linear alignment with FMRIB's Linear Image Registration Tool, in conjunction with the MNI152 standard-space T1 template. The data was subsequently nonlinearly warped to MNI152 space using FNIRT, generating a warp transform file. A standard-space brain mask was then back-transformed into T1 image space to generate a brain-extracted T1 image.

Tissue-type segmentation was applied using FMRIB's Automated Segmentation Tool (FAST) (Zhang et al., 2001), producing segmentations of cerebrospinal fluid, gray matter, and white matter, as well as partial-volume images for each tissue type. This processing also generated a fully bias-field-corrected version of the brain-extracted T1 image. These data were then used in a SIENAX-style analysis to estimate brain tissue volumes normalized for head size. The FAST gray matter segmentation generated 139 imaging-derived phenotypes by summing gray matter partial volume estimates within 139 regions of interest, defined in MNI152 space. These 139 regional gray matter volumes encompassed both hemispheres for most areas, except certain regions such as the brain stem and various segments of the cerebellum vermis (including VI, Crus I, Crus II, VIIb, VIIIa, VIIIb, IX, and X). Our methodology merged volumes of mirrored regions across hemispheres and incorporated the aforementioned non-lateralized areas, culminating in a comprehensive dataset of gray matter volumes for 74 brain regions. This consolidated dataset was used to explore the associations between SNP variations in the three oxytocin pathway genes (*OXT*, *CD38*, and *OXTR*) and gray matter volumes throughout the brain, covering all 74 identified regions.

2.3. *SNP selection and genotyping*

Before analysis, we conducted stringent quality checks on the genetic data to ensure reliability of the results. A collection of

28 SNPs in the three oxytocin pathway genes was selected based on their links to social behaviors (Ebner et al., 2013; Feldman et al., 2016; Seeley et al., 2018). However, only 20 of these 28 SNPs were available in the UK Biobank (i.e., *OXT*: rs4813625, rs2740210, rs4813627; *CD38*: rs6449197, rs3796863; *OXTR*: rs75775, rs4564970, rs6770632, rs2268490, rs2268493, rs2268494, rs2301261, rs237851, rs4686302, rs2268498, rs53576, rs237887, rs7632287, rs11914885, rs7634632). From these 20 SNPs, we dismissed 3 with minor allele frequencies (MAF) below 10% (*OXTR*: rs4564970, rs2268494, rs2301261) and an additional 7 (*OXT*: rs2740210; *CD38*: rs6449197; *OXTR*: rs75775, rs6770632, rs2268490, rs2268493, rs4686302) that displayed high linkage disequilibrium with other SNPs in our dataset (D' > .8). We assessed genotype distribution for each SNP, ensuring no deviation from expected values under the Hardy–Weinberg equilibrium. None of the SNPs were removed based on $p > .05$. Table 1 documents demographic distributions and genetic details of the 10 selected SNPs.

2.4. Statistical analysis

To test the effect of a specific SNP on a particular brain region, we conducted analyses of variance (ANOVA) using General Linear Model. In this model, brain gray matter volume (measured in cubic millimeters) served as the dependent variable. The SNP (with three genotypes, such as AA, GA, and GG) was entered as a fixed factor, and sex and age were included as random factors (Westberg et al., 2016). To manage potential population stratification, we integrated the first 10 genetic principal components (Data Field 22009) as covariates (Lin et al., 2023), along with whole-brain volume as additional covariate. Statistical analyses were performed in RStudio (software version 4.2.1) using the afex package (version 1.2.1).

As described in section 2.2, we merged volumes of mirrored regions across hemispheres, resulting in a dataset of gray matter volumes for 74 brain regions. Given the 10 identified SNPs, we conducted a total of 740 separate ANOVAs. To control for familywise error rate of multiple comparisons in these analyses, we applied Bonferroni correction, setting the significance level at $p < .05$ (two-tailed) (Benjamini & Hochberg, 1995). Next, we carried out post-hoc comparisons using the emmeans package (version 1.8.1.1) to determine differences among genotypes categorized by SNPs that survived Bonferroni correction.

Finally, to test robustness of our findings, we conducted cross-validation (Song et al., 2021). This method employs two metrics to evaluate how well the proposed model fits the data: R^2 and root mean square error (*RMSE*). R^2 indicates the proportion of the variance in the outcome variable explained by the predictors in the model; and *RMSE* is defined as the square root of the average of the squared differences between expected and observed values, indicating deviation of expected values from observed values. We first calculated R^2 and *RMSE* in the full dataset. Then, we performed k-fold cross-validation, splitting the full dataset into 10 equally sized folds. The proposed model was trained on 9 folds and tested on the remaining fold. This process was repeated 10 times, with each fold serving as the test set once. We then examined the extent to which R^2 and *RMSE* varied from each other across the 10 iterations and if their averages over the 10 iterations were comparable to the R^2 and *RMSE* from the full dataset. If only slight variations exists and averages are comparable to the results from the full dataset, robustness of the proposed model is confirmed.

Our research procedures and analyses were not preregistered. The analytical codes are available at: https://osf.io/7g9j8/.

3. Results

With sex and age as random factors, and the first 10 genetic principal components and whole-brain volume as covariates, our analyses of 10 SNPs across 74 brain regions identified significant results for several ANOVAs (see Supplementary Information 1 for details). However, only one ANOVA result survived Bonferroni correction. Specifically, variations in *OXTR* rs237851 were significantly associated with hippocampus gray matter volume [$F(2, 37115) = 13.00$, $p < .001$; corrected $p = .002$]. In particular and as illustrated in Fig. 1, post-hoc tests showed that AA genotype carriers ($M = 8564.76$, $SD = 853.34$) had larger hippocampal gray matter volumes than GG genotype carriers ($M = 8521.92$, $SD = 832.22$, $z = 4.89$, corrected $p < .001$); and AG genotype carriers ($M = 8550.33$, $SD = 833.68$) had larger hippocampal gray matter volumes than GG genotype carriers ($M = 8521.92$, $SD = 832.22$, $z = 3.75$, corrected $p < .001$). No significant difference in hippocampal gray matter volumes was observed between AA ($M = 8564.76$, $SD = 853.34$) and AG ($M = 8550.33$, $SD = 833.68$) genotype carriers ($z = 2.00$, corrected $p = .138$).

To test robustness of our results, we conducted cross-validation. Using the full dataset, the regression model (with hippocampal volume as the outcome variable, *OXTR* rs237851 as the fixed factor, sex and age as random factors, and the first 10 genetic principal components as well as whole-brain volume as covariates that survived Bonferroni correction) yielded an $R^2 = .4234902$ and an $RMSE = 638.0667$. The two metrics averaged over the 10 iterations ($R^2 = .4234220$, $RMSE = 638.0941$) were very close to those from the full dataset. Further, as shown in Table 2, R^2 and *RMSE* only varied slightly across the 10 iterations, with very small standard deviations for both metrics (SD of $R^2 = .01$, SD of $RMSE = 12.19$). These results confirmed robustness of our findings.

4. Discussion

In the current research, we used a large dataset from the UK Biobank to investigate the links between genetic variations in three oxytocin pathway genes and whole brain structure. We found that variants of the *OXTR* rs237851 SNP were significantly associated with hippocampus gray matter volume. Specifically, A-allele carriers of the *OXTR* rs237851 SNP had larger hippocampal volumes than GG-allele carriers.

Our results are generally consistent with previous literature revealing associations between genetic variations in oxytocin pathway genes and brain structure, in that *OXTR* SNPs were associated with regional gray matter volumes while *OXT* and *CD38* SNPs were rarely associated with gray matter volumes (for a systematic review, see Prata & Silva,

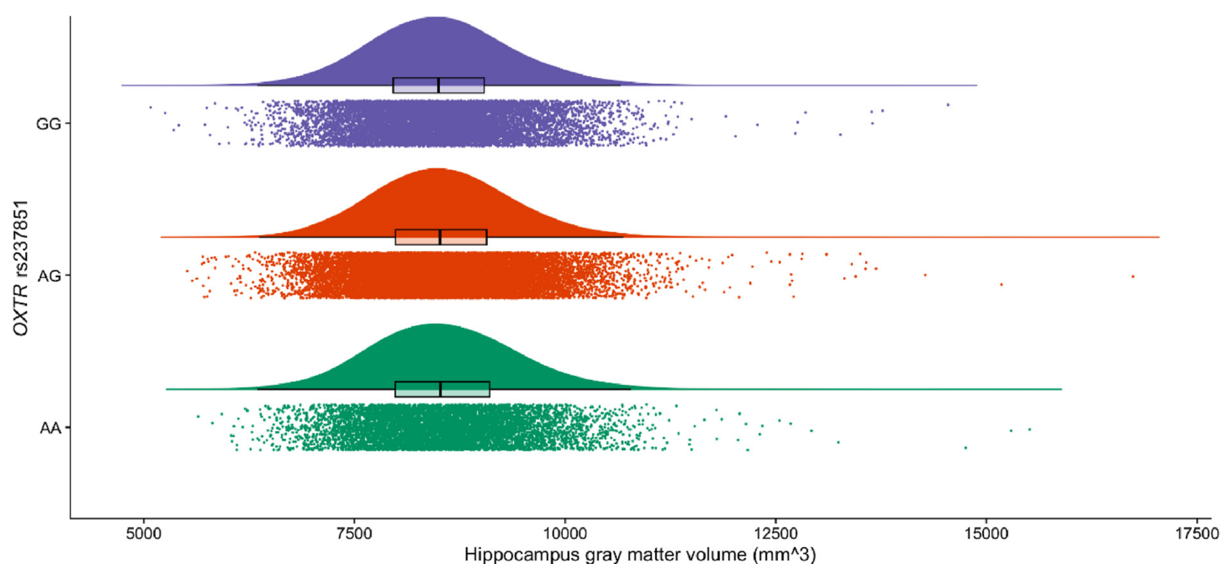

Fig. 1 – Mean hippocampus gray matter volume (mm^3) in the three *OXTR* rs237851 SNP genotypes. Post-hoc analyses showed that AA and AG genotype carriers had larger hippocampus gray matter volumes than GG genotype carriers.

Table 2 – R^2 and *RMSE* resulting from each iteration of the 10-fold cross-validation.

Fold	R^2	RMSE
1	.4234551	645.7849
2	.4109596	644.3961
3	.4495855	613.1766
4	.3943814	654.2020
5	.4242903	635.5500
6	.4254363	646.5815
7	.4159615	648.3620
8	.4307337	634.7326
9	.4305704	628.4495
10	.4288460	629.7057

2022). In particular, the A allele of *OXTR* rs53576 was previously found to be associated with smaller gray matter hippocampus volume (Schneider-Hassloff et al., 2016; Tost et al., 2010) as well as smaller gray matter temporal poles, lingual gyrus, and precuneus volumes (Schneider-Hassloff et al., 2016). Some studies furthermore found that the A allele of *OXTR* rs53576 was associated with smaller bilateral amygdala gray matter volume but only in females (Wang et al., 2014) while it was associated with larger gray matter amygdala volume in males (Tost et al., 2010); and yet other studies reported no significant associations at all (Dannlowski et al., 2016; Inoue et al., 2010; Womersley et al., 2020). In addition, in adolescent carriers of the *OXTR* rs53576 A allele, emotional trauma was associated with reduced gray matter volumes in left hippocampus, with no association for amygdala. However, in adolescent *OXTR* rs53576 A allele carriers who perceived social support from peers, greater volumes in both the hippocampus and the amygdala were observed (Malhi et al., 2020). On the other hand, for the *OXTR* rs2254298 SNP, the A allele was associated with decreased whole-brain gray matter and specifically dorsomedial anterior cingulate cortex volume (Furman et al., 2011), while the link between this same allele and amygdala gray matter volume was mixed (i.e., increased amygdala volume in some studies: Furman et al., 2011; Inoue et al., 2010; Marusak et al., 2015; but decreased amygdala volume in others: Womersley et al., 2020). Finally, in individuals who experienced childhood neglect, the A allele of *OXTR* rs2254298 was associated with decreased hippocampal volume (Womersley et al., 2020). Note that the *OXTR* SNP rs7632287, previously linked with social behavior and amygdala reactivity (Westberg et al., 2016), shows a tentative association with amygdala volume in our sample, but such association did not survive multiple comparisons.

In line with previous studies (e.g., Malhi et al., 2020; Schneider-Hassloff et al., 2016; Tost et al., 2010), we also found that an SNP in the *OXTR* gene (i.e., *OXTR* rs237851) was significantly associated with gray matter hippocampal volume. However, we did not find significant associations between other *OXTR* SNPs and regional volumes. Furthermore, the direction of the effect we observed appears to contradict earlier findings where the A allele of *OXTR* rs53576 was associated with smaller gray matter hippocampal volume (Schneider-Hassloff et al., 2016; Tost et al., 2010). These discrepancies across studies could be attributed to factors such as gene–environment interactions. For example, Malhi et al. (2020) found that the rs53576 A allele was associated with reduced gray matter volume in left hippocampus for adolescents who had experienced emotional trauma, but was associated with larger hippocampal volumes for adolescents who perceived social support. Similarly, it is likely that the rs237851 A allele also interacts with environmental factors, resulting in variations in its effect on hippocampal and other regional volume. Future research will need to delineate the interplay between oxytocin pathway genes and social-cognitive factors on brain structure. Based on feedback from an anonymous reviewer, we conducted a post-hoc analysis in our dataset to determine moderation effects of self-reported childhood trauma and self-reported professionally-diagnosed depression and anxiety on the observed association

between *OXTR* rs237851 genotype and hippocampal volume. Neither childhood trauma nor depression diagnosis moderated the relationship between rs237851 and hippocampal volume. However, the interaction between rs237851 and anxiety was significant. In particular, while anxious versus non-anxious AG or GG carriers did not vary, AA carriers with anxiety had smaller hippocampal volumes than AA carriers without anxiety (see Supplementary Information 2 for details).

Chemogenetic research provides insights on why *OXTR* is associated with hippocampal volume. For example, using a conditional knockout mouse model, Lin et al. (2017) found a role of *OXTR* in regulating neurogenesis in dentate gyrus (a part of the hippocampal trisynaptic circuit). In particular, conditional deletion of the mouse *OXTR* gene from hippocampal excitatory neurons resulted in impaired survival and maturation of newly generated dentate granule cells. Specifically, by binding to oxytocin receptors expressed in hippocampal CA3 pyramidal neurons, endogenous oxytocin increased the excitability of hippocampal CA3 pyramidal neurons, which in turn regulated neurogenesis in the dentate gyrus. Ji et al. (2016), furthermore, found that a 14-day treatment with intranasal oxytocin promoted hippocampal neurogenesis and reduced depressive-like behaviors in adult rats that experienced maternal deprivation. The hippocampus, compared to other brain regions, has higher than average levels of *OXRT* expression in humans (Quintana et al., 2019). Thus it is likely that *OXTR* associates with hippocampal gray matter volume via a similar neuromechanism as suggested by Lin et al. (2017), such that higher levels of *OXRT* expression in hippocampus increase oxytocin bindings and promote neurogenesis of dentate granule cells. Comparatively lower levels of *OXRT* expression in other brain regions may also explain why we did not observe a significant association between *OXRT* gene variations and gray matter volume in regions other than the hippocampus. Our study went beyond most previous work by also examining associations of *OXT* and *CD38* SNPs with brain structure. However, we did not find evidence of a significant link between these two oxytocin pathway genes and gray matter volume across the whole brain. Only the *OXTR* gene demonstrated significant associations with hippocampal volume that survived adequate multiple comparison correction. It is important to note that subcortical regions such as the hippocampus and hypothalamus have several subregions associated with different brain functions and neuropsychiatric behaviors (Chen et al., 2024). Although we did not find significant associations of the *OXT* and *CD38* genes with gray matter volume in the 74 brain regions identified by the UK Biobank, this does not preclude potential links between these genes and other regions and subregions across the brain. Extended future research into this direction could provide a more nuanced conclusion regarding the roles of the *OXT* and *CD38* genes in brain structure.

For a broader picture discussion of our findings, it is pertinent to reflect on our results in light of the broader implications oxytocin and the hippocampus have on social behavior. The hippocampus is instrumental in social recognition memory [i.e., the ability to recognize familiar conspecifics (Diethorn & Gould, 2023; Mundy et al., 2013; Smith et al., 2014); and is crucial in facilitating social interaction (Chen & Hong, 2018). Social recognition memory is supported by a specialized neural network intricately regulated by specific molecules, with oxytocin being the most extensively researched of these molecules (Brennan & Zufall, 2006; Lee et al., 2009; Lopatina et al., 2018)]. Further, research utilizing *OXT* and *OXTR* knockout mice has demonstrated the extent to which *OXTR* signaling, particularly hippocampal *OXTR* signaling (Lin & Hsu, 2018), enhances social recognition memory formation (Oettl et al., 2016; Pobbe et al., 2012; Raam et al., 2017; Takayanagi et al., 2005). For example, the deletion of *Oxtr* in mice in hippocampal CA2/CA3a excitatory neurons has been shown to significantly impact persistence of long-term social recognition memory (Lin & Hsu, 2018).

Taken together, our research advances methodology as well as provides deeper insights into the specific mechanisms of oxytocin pathway genes in brain structure. First, previous studies primarily focused on single *OXTR* SNPs, but here we go beyond this approach by examining a comprehensive array of SNPs across three critical oxytocin pathway genes (*OXT*, *CD38*, and *OXTR*; Ebner et al., 2013; Feldman et al., 2016; Seeley et al., 2018). Second, our study pioneers the integration of genetic and brain imaging data from the large-scale UK Biobank dataset to investigate effects of oxytocin signaling pathway genes on gray matter volumes, encompassing over 30,000 participants, thus surpassing the scope of prior investigations (Prata & Silva, 2022). A recent meta-analysis by Chander et al. (2022) examined the impact of the *OXTR* rs53576 polymorphism on empathy, revealing that individuals with the GG genotype exhibited higher affective empathy compared to other genotypes, with an effect size of Cohen's $d = .12$ (corresponding to a small effect size of $f = .06$ in a one-way ANOVA). In comparison, sensitivity analysis using G*Power showed that our sample size was sufficiently large to detect an effect of $f = .02$ with 99% power at a significance level of .05 for the three genotypes. This large power also reduced the risk of both false positives and false negatives (Christley, 2010), thereby enhancing the robustness of our conclusions. Third, unlike previous studies that typically adopted convenient samples such as college students, the UK Biobank includes middle-aged and older adults (above 40 years old, with a mean age of 64), allowing for an important extension of the current literature on association between oxytocin pathway genes and brain structure.

Although findings from this study generate novel insight into the links between oxytocin pathway gene variations and brain anatomy, the interpretation of results needs to consider some study limitations. First, the UK Biobank is limited to a cohort of white British individuals, aged 40–69 years ($M = 64.15$, $SD = 7.65$), limiting the generalizability of our findings beyond this population. Second, we only examined the relationships between oxytocin pathway genes and gray matter volumes in the brain. Future studies are needed to test other aspects of brain structure, such as white matter tracts. Third, the cross-sectional nature of this study identifies correlations without establishing causality. That is, we cannot infer from our analysis that oxytocin pathway gene variations lead to changes in hippocampal gray matter volume, a link that may also be modulated by other covarying factors such as social and cognitive deficits (Banker et al., 2021). Future

research will benefit from employing longitudinal designs to determine temporal dynamics between genetic variations and brain structure.

5. Conclusion

In summary, our results inform the associations between variations in oxytocin pathway genes and brain structure in a large dataset. Our work suggests specific genetic mechanisms related to variations in the *OXTR* SNP rs237851 in their effect on hippocampal gray matter volume. Increased understanding of the interplay between oxytocin signaling pathway genes and brain structure has potential to informing possible therapeutic targets for enhancing cognitive and social functioning (e.g., social recognition memory and empathy).

Scientific transparency statement

DATA: No raw or processed data supporting this research are publicly available.

CODE: All analysis code supporting this research is publicly available: https://osf.io/7g9j8/

MATERIALS: No study materials supporting this research are publicly available.

DESIGN: This article reports, for all studies, how the author(s) determined all sample sizes, all data exclusions, all data inclusion and exclusion criteria, and whether inclusion and exclusion criteria were established prior to data analysis.

PRE-REGISTRATION: No part of the study procedures was pre-registered in a time-stamped, institutional registry prior to the research being conducted. No part of the analysis plans was pre-registered in a time-stamped, institutional registry prior to the research being conducted.

For full details, see the *Scientific Transparency Report* in the supplementary data to the online version of this article.

CRediT authorship contribution statement

Shanshan Xiao: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Conceptualization. **Natalie C. Ebner:** Writing – review & editing. **Junhua Dang:** Writing – review & editing, Data curation. **Gull Rukh:** Writing – review & editing, Data curation. **Lars Westberg:** Writing – review & editing. **Helgi B. Schiöth:** Writing – review & editing, Funding acquisition. **Håkan Fischer:** Writing – review & editing, Supervision.

Data statement

Data utilized in this study originates from the UK Biobank, subject to a stringent application process ensuring data privacy and ethical use. Due to these governance policies, the dataset cannot be openly accessible. Researchers seeking access must apply directly to the UK Biobank, adhering to its usage guidelines. For application details, visit: (http://www.ukbiobank.ac.uk/enable-your-research/apply-for-access).

Funding

NCE received funding from the National Institute on Aging (Grant R01AG059809), the National Institute on Drug Abuse (Grant R21DA056813), and the U.S. Office of Naval Research (Grant N00014-21-1-2201); JD was funded by the Natural Science Foundation of China (Project 31871098); GR's research is under the auspices of the Swedish Brain Foundation (Grant FO2022-0148); LW received funding from the Swedish Research Council (Grant Dnr 2018-02904); HBS was supported by the Swedish Brain Foundation (Grant FO2023-0090); HF was funded by the Swedish Research Council (Grant Dnr 2013-00854).

Conflict of interest

The authors have nothing to disclose.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2024.11.017.

REFERENCES

Alfaro-Almagro, F., Jenkinson, M., Bangerter, N. K., Andersson, J. L. R., Griffanti, L., Douaud, G., Sotiropoulos, S. N., Jbabdi, S., Hernandez-Fernandez, M., Vallee, E., Vidaurre, D., Webster, M., McCarthy, P., Rorden, C., Daducci, A., Alexander, D. C., Zhang, H., Dragonu, I., Matthews, P. M., … Smith, S. M. (2018). Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. *Neuroimage, 166*, 400–424. https://doi.org/10.1016/j.neuroimage.2017.10.034. October 2017.

Allen, N., Sudlow, C., Downey, P., Peakman, T., Danesh, J., Elliott, P., Gallacher, J., Green, J., Matthews, P., Pell, J., Sprosen, T., & Collins, R. (2012). UK Biobank: Current status and what it means for epidemiology. *Health Policy and Technology, 1*(3), 123–126. https://doi.org/10.1016/j.hlpt.2012.07.003

Banker, S. M., Gu, X., Schiller, D., & Foss-Feig, J. H. (2021). Hippocampal contributions to social and cognitive deficits in autism spectrum disorder. *Trends in Neurosciences, 44*(10), 793–807. https://doi.org/10.1016/j.tins.2021.08.005

Bartz, J. A., Zaki, J., Bolger, N., & Ochsner, K. N. (2011). Social effects of oxytocin in humans: Context and person matter. *Trends in Cognitive Sciences, 15*(7), 301–309. https://doi.org/10.1016/j.tics.2011.05.002

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B: Statistical Methodology, 57*(1). https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

Brambilla, M., Manenti, R., de Girolamo, G., Adenzato, M., Bocchio-Chiavetto, L., & Cotelli, M. (2016). Effects of intranasal oxytocin on long-term memory in healthy humans: A systematic review. *Drug Development Research, 77*(8), 479–488. https://doi.org/10.1002/ddr.21343

Brennan, P. A., & Zufall, F. (2006). Pheromonal communication in vertebrates. In *Nature* (Vol. 444). https://doi.org/10.1038/nature05404. Issue 7117.

Busnelli, M., & Chini, B. (2018). Molecular basis of oxytocin receptor signalling in the brain: What we know and what we need to know. In *Current topics in behavioral neurosciences* (Vol. 35, pp. 3–29). https://doi.org/10.1007/7854_2017_6

Chander, R. J., Mather, K. A., Cleary, R., Grainger, S. A., Thalamuthu, A., Numbers, K., Kochan, N. A., Armstrong, N. J., Brodaty, H., Henry, J. D., & Sachdev, P. S. (2022). The influence of rs53576 polymorphism in the oxytocin receptor (OXTR) gene on empathy in healthy adults by subtype and ethnicity: A systematic review and meta-analysis. In *Reviews in the neurosciences* (Vol. 33). https://doi.org/10.1515/revneuro-2021-0038. Issue 1.

Chen, P., & Hong, W. (2018). Neural circuit mechanisms of social behavior. In *Neuron* (Vol. 98). https://doi.org/10.1016/j.neuron.2018.02.026. Issue 1.

Chen, S. D., You, J., Zhang, W., Wu, B. S., Ge, Y. J., Xiang, S. T., Du, J., Kuo, K., Banaschewski, T., Barker, G. J., Bokde, A. L. W., Desrivières, S., Flor, H., Grigis, A., Garavan, H., Gowland, P., Heinz, A., Brühl, R., Martinot, J. L., … Yu, J. T. (2024). The genetic architecture of the human hypothalamus and its involvement in neuropsychiatric behaviours and disorders. *Nature Human Behaviour, 8*(4). https://doi.org/10.1038/s41562-023-01792-6

Christley, R. M. (2010). Power and error: Increased risk of false positive results in underpowered studies. *Open Epidemiology Journal, 3*. https://doi.org/10.2174/1874297101003010016

Collins, R. (2012). What makes UK Biobank special?. In *The lancet* (Vol. 379). https://doi.org/10.1016/S0140-6736(12)60404-8. Issue 9822.

Dannlowski, U., Kugel, H., Grotegerd, D., Redlich, R., Opel, N., Dohm, K., Zaremba, D., Grögler, A., Schwieren, J., Suslow, T., Ohrmann, P., Bauer, J., Krug, A., Kircher, T., Jansen, A., Domschke, K., Hohoff, C., Zwitserlood, P., Heinrichs, M., … Baune, B. T. (2016). Disadvantage of social sensitivity: Interaction of oxytocin receptor genotype and child maltreatment on brain structure. *Biological Psychiatry, 80*(5), 398–405. https://doi.org/10.1016/j.biopsych.2015.12.010

Diethorn, E. J., & Gould, E. (2023). Development of the hippocampal CA2 region and the emergence of social recognition. In *Developmental neurobiology* (Vol. 83). https://doi.org/10.1002/dneu.22919. Issues 5–6.

Ebner, N. C., Maura, G. M., MacDonald, K., Westberg, L., & Fischer, H. (2013). Oxytocin and socioemotional aging: Current knowledge and future trends. *Frontiers in Human Neuroscience, 7*(AUG), 1–14. https://doi.org/10.3389/fnhum.2013.00487

Feldman, R., Monakhov, M., Pratt, M., & Ebstein, R. P. (2016). Oxytocin pathway genes: Evolutionary ancient system impacting on human affiliation, sociality, and psychopathology. *Biological Psychiatry, 79*(3), 174–184. https://doi.org/10.1016/j.biopsych.2015.08.008

Furman, D. J., Chen, M. C., & Gotlib, I. H. (2011). Variant in oxytocin receptor gene is associated with amygdala volume. *Psychoneuroendocrinology, 36*(6), 891–897. https://doi.org/10.1016/j.psyneuen.2010.12.004

Gimpl, G., & Fahrenholz, F. (2001). The oxytocin receptor system: Structure, function, and regulation. In *Physiological reviews* (Vol. 81). https://doi.org/10.1152/physrev.2001.81.2.629. ssue 2.

Gopal Rao, V. V. N., Loffler, C., Battey, J., & Hansmann, I. (1992). The human gene for oxytocin-neurophysin I (OXT) is physically mapped to chromosome 20p13 by *in situ* hybridization. *Cytogenetics and Cell Genetics, 61*(4). https://doi.org/10.1159/000133420

Gurung, R., & Prata, D. P. (2015). What is the impact of genome-wide supported risk variants for schizophrenia and bipolar disorder on brain structure and function? A systematic review. In *Psychological medicine* (Vol. 45). https://doi.org/10.1017/S0033291715000537. Issue 12.

Inoue, H., Yamasue, H., Tochigi, M., Abe, O., Liu, X., Kawamura, Y., Takei, K., Suga, M., Yamada, H., Rogers, M. A., Aoki, S., Sasaki, T., & Kasai, K. (2010). Association between the oxytocin receptor gene and amygdalar volume in healthy adults. *Biological Psychiatry, 68*(11), 1066–1072. https://doi.org/10.1016/j.biopsych.2010.07.019

Ji, H., Su, W., Zhou, R., Feng, J., Lin, Y., Zhang, Y., Wang, X., Chen, X., & Li, J. (2016). Intranasal oxytocin administration improves depression-like behaviors in adult rats that experienced neonatal maternal deprivation. *Behavioural Pharmacology, 27*(8). https://doi.org/10.1097/FBP.0000000000000248

Jin, D., Liu, H. X., Hirai, H., Torashima, T., Nagai, T., Lopatina, O., Shnayder, N. A., Yamada, K., Noda, M., Seike, T., Fujita, K., Takasawa, S., Yokoyama, S., Koizumi, K., Shiraishi, Y., Tanaka, S., Hashii, M., Yoshihara, T., Higashida, K., … Higashida, H. (2007). CD38 is critical for social behaviour by regulating oxytocin secretion. *Nature, 446*(7131). https://doi.org/10.1038/nature05526

Jurek, B., & Neumann, I. D. (2018). The oxytocin receptor: From intracellular signaling to behavior. *Physiological Reviews, 98*(3), 1805–1908. https://doi.org/10.1152/physrev.00031.2017

Kimura, T., Tanizawa, O., Mori, K., Brownstein, M. J., & Okayama, H. (1992). Structure and expression of a human oxytocin receptor. *Nature,* 356(6369). https://doi.org/10.1038/356526a0

Knobloch, H. S., Charlet, A., Hoffmann, L. C., Eliava, M., Khrulev, S., Cetin, A. H., Osten, P., Schwarz, M. K., Seeburg, P. H., Stoop, R., & Grinevich, V. (2012). Evoked axonal oxytocin release in the central amygdala attenuates fear response. *Neuron, 73*(3). https://doi.org/10.1016/j.neuron.2011.11.030

Lee, H. J., Macbeth, A. H., Pagani, J. H., & Scott Young, W. (2009). Oxytocin: The great facilitator of life. In *Progress in neurobiology* (Vol. 88). https://doi.org/10.1016/j.pneurobio.2009.04.001. Issue 2.

Lin, Y. T., Chen, C. C., Huang, C. C., Nishimori, K., & Hsu, K. S. (2017). Oxytocin stimulates hippocampal neurogenesis via oxytocin receptor expressed in CA3 pyramidal neurons. *Nature Communications, 8*(1). https://doi.org/10.1038/s41467-017-00675-5

Lin, Y. T., & Hsu, K. S. (2018). Oxytocin receptor signaling in the hippocampus: Role in regulating neuronal excitability, network oscillatory activity, synaptic plasticity and social memory. *Progress in Neurobiology, 171*(1), 1–14. https://doi.org/10.1016/j.pneurobio.2018.10.003

Lin, B. D., Pries, L. K., van Os, J., Luykx, J. J., Rutten, B. P. F., & Guloksuz, S. (2023). Adjusting for population stratification in polygenic risk score analyses: A guide for model specifications in the UK Biobank. *Journal of Human Genetics, 68*(9). https://doi.org/10.1038/s10038-023-01161-1

Lopatina, O. L., Komleva, Y. K., Gorina, Y. V., Higashida, H., & Salmina, A. B. (2018). Neurobiological aspects of face recognition: The role of oxytocin. In *Frontiers in behavioral neuroscience* (Vol. 12). https://doi.org/10.3389/fnbeh.2018.00195

Maejima, Y., Sakuma, K., Santoso, P., Gantulga, D., Katsurada, K., Ueta, Y., Hiraoka, Y., Nishimori, K., Tanaka, S., Shimomura, K., & Yada, T. (2014). Oxytocinergic circuit from paraventricular and supraoptic nuclei to arcuate POMC neurons in hypothalamus. *FEBS Letters, 588*(23). https://doi.org/10.1016/j.febslet.2014.10.010

Malhi, G. S., Das, P., Outhred, T., Dobson-Stone, C., Bell, E., Gessler, D., Bryant, R., & Mannie, Z. (2020). Interactions of OXTR rs53576 and emotional trauma on hippocampal volumes and perceived social support in adolescent girls. *Psychoneuroendocrinology, 115*. https://doi.org/10.1016/j.psyneuen.2020.104635. December 2019).

Miller, K. L., Alfaro-Almagro, F., Bangerter, N. K., Thomas, D. L., Yacoub, E., Xu, J., Bartsch, A. J., Jbabdi, S., Sotiropoulos, S. N., Andersson, J. L. R., Griffanti, L., Douaud, G., Okell, T. W., Weale, P., Dragonu, I., Garratt, S., Hudson, S., Collins, R.,

Jenkinson, M., ... Smith, S. M. (2016). Multimodal population brain imaging in the UK Biobank prospective epidemiological study. *Nature Neuroscience, 19*(11), 1523–1536. https://doi.org/10.1038/nn.4393

Mundy, M. E., Downing, P. E., Dwyer, D. M., Honey, R. C., & Graham, K. S. (2013). A critical role for the hippocampus and perirhinal cortex in perceptual learning of scenes and faces: Complementary findings from amnesia and fMRI. *Journal of Neuroscience, 33*(25). https://doi.org/10.1523/JNEUROSCI.2958-12.2013

Oettl, L. L., Ravi, N., Schneider, M., Scheller, M. F., Schneider, P., Mitre, M., da Silva Gouveia, M., Froemke, R. C., Chao, M. V., Young, W. S., Meyer-Lindenberg, A., Grinevich, V., Shusterman, R., & Kelsch, W. (2016). Oxytocin enhances social recognition by modulating cortical control of early olfactory processing. *Neuron, 90*(3). https://doi.org/10.1016/j.neuron.2016.03.033

Pobbe, R. L. H., Pearson, B. L., Defensor, E. B., Bolivar, V. J., Young, W. S., Lee, H. J., Blanchard, D. C., & Blanchard, R. J. (2012). Oxytocin receptor knockout mice display deficits in the expression of autism-related behaviors. *Hormones and Behavior, 61*(3). https://doi.org/10.1016/j.yhbeh.2011.10.010

Prata, D., & Silva, M. (2022). Neuroimaging genetics of oxytocin: A transcriptomics-informed systematic review. *Neuroscience and Biobehavioral Reviews, 142*(August), Article 104912. https://doi.org/10.1016/j.neubiorev.2022.104912

Quintana, D. S., & Guastella, A. J. (2020). An allostatic theory of oxytocin. *Trends in Cognitive Sciences, 24*(7), 515–528. https://doi.org/10.1016/j.tics.2020.03.008

Quintana, D. S., Rokicki, J., van der Meer, D., Alnæs, D., Kaufmann, T., Córdova-Palomera, A., Dieset, I., Andreassen, O. A., & Westlye, L. T. (2019). Oxytocin pathway gene networks in the human brain. *Nature Communications, 10*(1). https://doi.org/10.1038/s41467-019-08503-8

Raam, T., McAvoy, K. M., Besnard, A., Veenema, A., & Sahay, A. (2017). Hippocampal oxytocin receptors are necessary for discrimination of social stimuli. *Nature Communications, 8*(1). https://doi.org/10.1038/s41467-017-02173-0

Schneider-Hassloff, H., Straube, B., Jansen, A., Nuscheler, B., Wemken, G., Witt, S. H., Rietschel, M., & Kircher, T. (2016). Oxytocin receptor polymorphism and childhood social experiences shape adult personality, brain structure and neural correlates of mentalizing. *Neuroimage, 134*, 671–684. https://doi.org/10.1016/j.neuroimage.2016.04.009

Seeley, S. H., Chou, Y. hui, & O'Connor, M. F. (2018). Intranasal oxytocin and OXTR genotype effects on resting state functional connectivity: A systematic review. *Neuroscience and Biobehavioral Reviews, 95*(September), 17–32. https://doi.org/10.1016/j.neubiorev.2018.09.011

Shamay-Tsoory, S. G., & Abu-Akel, A. (2016). The social salience hypothesis of oxytocin. *Biological Psychiatry, 79*(3), 194–202. https://doi.org/10.1016/j.biopsych.2015.07.020

Smith, C. N., Jeneson, A., Frascino, J. C., Brock Kirwan, C., Hopkins, R. O., & Squire, L. R. (2014). When recognition memory is independent of hippocampal function. In *Proceedings of the national academy of sciences of the United States of America* (Vol. 111). https://doi.org/10.1073/pnas.1409878111, 27.

Song, Q. C., Tang, C., & Wee, S. (2021). Making sense of model generalizability: A tutorial on cross-validation in R and shiny. *Advances in Methods and Practices in Psychological Science, 4*(1). https://doi.org/10.1177/2515245920947067

Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., Downey, P., Elliott, P., Green, J., Landray, M., Liu, B., Matthews, P., Ong, G., Pell, J., Silman, A., Young, A., Sprosen, T., Peakman, T., & Collins, R. (2015). UK Biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *Plos Medicine, 12*(3). https://doi.org/10.1371/journal.pmed.1001779

Takayanagi, Y., Yoshida, M., Bielsky, I. F., Ross, H. E., Kawamata, M., Onaka, T., Yanagisawa, T., Kimura, T., Matzuk, M. M., Young, L. J., & Nishimori, K. (2005). Pervasive social deficits, but normal parturition, in oxytocin receptor-deficient mice. In *Proceedings of the national academy of sciences of the United States of America* (Vol. 102). https://doi.org/10.1073/pnas.0505312102, 44.

Tost, H., Kolachana, B., Hakimi, S., Lemaitre, H., Verchinski, B. A., Mattay, V. S., Weinberger, D. R., & Meyer-Lindenberg, A. (2010). A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. In *Proceedings of the national academy of sciences of the United States of America* (Vol. 107). https://doi.org/10.1073/pnas.1003296107, 31.

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 Structure & Function, 219*(5), 1543–1554. https://doi.org/10.1007/s00429-013-0584-9

Westberg, L., Henningsson, S., Zettergren, A., Svärd, J., Hovey, D., Lin, T., Ebner, N. C., & Fischer, H. (2016). Variation in the oxytocin receptor gene is associated with face recognition and its neural correlates. *Frontiers in Behavioral Neuroscience, 10*(SEP), 1–7. https://doi.org/10.3389/fnbeh.2016.00178

Womersley, J. S., Hemmings, S. M. J., Ziegler, C., Gutridge, A., Ahmed-Leitao, F., Rosenstein, D., Domschke, K., & Seedat, S. (2020). Childhood emotional neglect and oxytocin receptor variants: Association with limbic brain volumes. *World Journal of Biological Psychiatry, 21*(7), 513–528. https://doi.org/10.1080/15622975.2019.1584331

Xu, Y., Xue, Y., Asan, Daly, A., Wu, L., & Tyler-Smith, C. (2008). Variation of the oxytocin/neurophysin I (OXT) gene in four human populations. *Journal of Human Genetics, 53*(7). https://doi.org/10.1007/s10038-008-0292-0

Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging, 20*(1). https://doi.org/10.1109/42.906424