Comprehensive Psychoneuroendocrinology 17 (2024) 100224

Contents lists available at ScienceDirect

Comprehensive Psychoneuroendocrinology

journal homepage: www.sciencedirect.com/journal/comprehensive-psychoneuroendocrinology

Serotonin 4 receptor brain binding and oxytocin-promoted affective and social cognition in healthy women – A randomized controlled trial

Vibeke Høyrup Dam [a,*,1], Sidsel Høgsgaard Andersen [a,d,1], Sofie Trolle Pedersen [a], Dea Siggaard Stenbæk [a,b,d], Vibe Gedsoe Frokjaer [a,b,c]

[a] Neurobiology Research Unit, The Neuroscience Centre, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[b] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[c] Mental Health Services in the Capital Region of Copenhagen, Denmark
[d] Department of Psychology, University of Copenhagen, Copenhagen, Denmark

ARTICLE INFO

Keywords:
Affective cognition
Social cognition
Oxytocin
Serotonin 4 receptor
EMOTICOM

ABSTRACT

Background: Oxytocin is a neuropeptide known for its prosocial properties and role in social bonding, and intervention with intranasal oxytocin is posited to modulate affective and social cognition (i.e., hot cognition). Serotonin (5-HT) neurotransmission is also involved in emotional and social behaviors and appear to work in concert with oxytocin. However, this interaction so far remains elusive in humans. Therefore, we here investigate the relation between brain 5-HT 4 receptor (5-HT_4R) levels and oxytocin-modulated hot cognition.
Methods: Using a double blind, placebo-controlled, randomized crossover design, 35 healthy women received a dose of 24 IU intranasal oxytocin or placebo one month apart. The women were naturally cycling and to control for hormonal fluctuations across the menstrual cycle, intervention days were placed during the early follicular phase. Following intervention cognitive domains including affective memory, affective bias in emotion processing, moral emotions and social information preference were assessed. In a subgroup (n = 25), Positron Emission Tomography (PET) was used to image 5-HT_4R brain binding at baseline with the [^{11}C]SB207145 radiotracer.
Results: No effect of oxytocin intervention relative to placebo was observed for any of the cognitive outcomes. Likewise, regional brain 5-HT_4R binding at baseline was not associated with cognitive responses to oxytocin intervention.
Conclusion: Our data suggest that intervention with intranasal oxytocin does not have an overall effect on hot cognition in healthy women and further that 5-HT_4R brain architecture does not mediate cognitive effects of oxytocin in the healthy state.

1. Introduction

Oxytocin is a neuropeptide colloquially known as the "love hormone" because of its putative prosocial properties and central role in human bonding. Intranasal interventions with oxytocin has been proposed to exert effects on so-called 'hot' cognitive functions, i.e. reward-, social and affective-related mental processes [1] with some studies reporting altered performance on emotion recognition, memory, judging of social situations and social economic games [2–4] while other studies show little or no effect [5–7].

Serotonin (5-HT) neurotransmission is strongly involved in human social and emotional functioning and has also been related to several psychiatric and neurodevelopmental disorders with pronounced disorganization of hot cognitive functioning including depression and autism spectrum disorder [7]. Pharmacological enhancement of synaptic brain 5-HT levels has been found to promote prosocial behavior, e.g. by enhancing empathy in humans [8], and functional imaging studies (fMRI) show that 5-HT modulates the neural responses to reward and punishment in humans [9], indicating that the 5-HT system plays a critical role in orchestrating motivated behaviors.

Notably, 5-HT neurotransmission is involved in the same emotional and social behaviors as oxytocin and their neuronal pathways show

* Corresponding author. Neurobiology Research Unit, Rigshospitalet, Section 8057, 9 Blegdamsvej, DK-2100 Copenhagen East, Denmark.
E-mail address: vibekedam@nru.dk (V.H. Dam).
[1] Authors contributed equally.

https://doi.org/10.1016/j.cpnec.2023.100224
Received 29 December 2023; Accepted 29 December 2023
Available online 5 January 2024

large overlap in the brain [10]. Coordinated oxytocin and serotonin signaling may be involved in, and even necessary, for certain social behaviors [4,10]. For example, rodent work has shown that stimulation of the serotonin 1B receptor (5-HT_{1B}R) in the nucleus accumbens, a key hub in the reward system, is needed for prosocial action of oxytocin [10]. Additionally, rodent work strongly suggest that 5-HT modulates reward-related behaviors in a receptor subtype specific manner [11] including the 5-HT 4 receptor (5-HT_4R) which is expressed with high density in key sites of the reward system [12]. To date, no human studies have addressed if oxytocin effects depend on serotonin architecture in humans and if the social reward system findings generalize to social and affective cognition. However, the 5-HT_4R has been proposed as a promising antidepressant target, particularly for the treatment of cognitive dysfunction [13]. In healthy volunteers, pharmacological stimulation of the 5-HT_4R specifically enhances memory performance and reward-learning behaviors [14], and in patients with major depression disorder impaired memory function has been linked to lower 5-HT_4R brain levels [15]. Rodent studies also show that the 5-HT_4R is critically involved in learning and memory functions [16–18].

In the present study we (1) assess the effect of oxytocin nasal spray on a range of hot cognitive functions and (2) investigate if oxytocin effect on cognition is influenced by cerebral 5-HT_4R levels.

2. Materials and methods

2.1. Participants

We recruited 35 healthy Danish women (age range 20–39) from a previously established database of healthy volunteers or through internet advertisements. We choose to use women in this study to avoid assuming uniformity of neuroendocrine responses across sexes and to contribute to the inclusion of women in clinical research. Exclusion criteria for the study were: history of psychiatric disorders (DSM-IV Axis I Disorders); significant somatic illness; brain trauma; use of psychotropic medication; use of illicit drugs; use of hormonal contraception; irregular menstrual cycle; pregnancy or breastfeeding; and non-fluency in Danish. Written informed consent was obtained from all participants and the study was registered and approved by the Health Research Ethics Committee of the Capital Region of Denmark (protocol: H-15004506 and H-15017713).

2.2. Study design

We used a randomized double-blind placebo-controlled crossover design. On test days, participants received 24 IU of oxytocin (Syntocinon®) or placebo via self-administered nasal spray. Randomization and administration of the intervention was conducted by research administrators not otherwise involved in the study to preserve blinding. After a wait period of 40 min participants completed a fixed series of well-validated neuropsychological tasks assessing emotion processing, affective memory, social information processing and moral emotions [19–21]. The 40-min wait-period was chosen based on pharmacokinetic studies investigating peak oxytocin levels following intranasal administration and align with standard practice in the literature [22,23]. The average length of the test sessions was 1 h 28min ±10min. To minimize the potential influence of natural fluctuations in hormonal cycle, both test sessions were conducted during the latter part of the follicular phase (days 5–12) and were placed a least one month apart (mean days between intervention sessions 28.8 ± 2.6), all participants were natural cycling. The participants were randomly assigned to either oxytocin-placebo test order (n = 19) or placebo-oxytocin test order (n = 16) using block randomization. The study was originally planned to include 45 participants, but recruitment was halted after 35 for logistical reasons. Our sample size was chosen to be able to reliably detect ~10% change in cognitive performance and were based on previously reported effect sizes from similar studies investigating oxytocin intervention and cognition [24,25].

A subset of participants (n = 25) also underwent Positron Emission Tomography (PET) scan with the [11C]SB207145 radioligand, assessing 5-HT_4R binding in the brain. All PET scans were acquired close to either the first or second test session but never on the same day as the experimental oxytocin/placebo intervention. The mean number of days between PET scan and an intervention day was 5.9 (SD = 8.4). Due to technical issues, one PET scan had to be rescheduled and was therefore acquired 35 days after the last intervention. In the PET subgroup, 14 participants were randomized to oxytocin-placebo test order while 11 were randomized to placebo-oxytocin test order.

2.3. Neuropsychological tests

Table 1 provides an overview of the cognitive test domains and

Table 1
Neuropsychological tests overview.

Emotion Recognition Task	*Description* Assessment of emotion recognition. A series of emotional faces showing only eyes appear briefly (for 250 ms) and the participant is asked to identify the expressed emotion (happy, sad, angry, or fearful). *Primary outcomes* Accuracy in identification of each emotion calculated as hit rate (%).
Emotional Intensity Morphing Task	*Description* Assessment of perceptual threshold for emotion detection. A face with a slowly morphing emotional expression is shown and the participant must indicate when they can detect no longer perceive an emotion. The emotional expressions include happy, sad, angry, fearful, and disgusted. *Primary outcomes* Average intensity threshold for detection of each emotion.
Moral Emotion Task	*Description* Assessment of emotional reactions to moral social situations. The participant is presented with cartoons of moral scenarios in which one character intentionally or unintentionally harms another. The participant must rate how guilty, shameful, annoyed, and bad they would feel if they were either the victim or the agent (i.e., the victimizer). *Primary outcomes* Average ratings of guilt and shame for victim and agent scenarios.
Social Information Preference Task	*Description* Assessment of preference for different types of information. The participant is shown a socially ambiguous situation in which nine pieces of information (faces, thoughts, and facts/objects) are hidden from view. The participant is instructed to pick four pieces of information to help them decide between three different interpretations of the situations; a positive, neutral, and negative. *Primary outcomes* Information sampling preference for social information over non-social information calculated as percentage of factual information pieces picked subtracted from percentage of social (faces and thoughts) information pieces picked. In addition bias in interpretation calculated as percentage negative interpretations picked subtracted from positive interpretation picked.
Verbal Affective Memory Task	Assessment of learning and immediate short term and delayed recall memory of affective stimuli. The participant is shown a list of words, 10 positive, 10 negative and 6 neutral, on a computer screen and instructed to recall as many as possible. This procedure is repeated five times (learning condition) after which an interference list is shown, and the participant is asked to recall as many words from the original list as possible (immediate recall condition). Lastly, after a delay of 30 min the test participant is asked to perform a surprise recall of the original list (delated recall condition). *Primary outcomes* The average number of words correctly recalled in each word category (positive, negative, and neutral) across learning and immediate and delayed recall conditions.

outcomes. All testing was conducted in standardized test rooms by trained neuropsychological testers at the Copenhagen University Hospital Rigshospitalet, Denmark.

2.4. PET acquisition

The synthesis of [^{11}C]SB207145 was performed according to previously described procedures [26]. Participants were scanned on a High Resolution Research Tomograph (HRRT) with an estimated in-plane resolution of 2 mm. Immediately following the intravenous bolus injection of [^{11}C]SB207145, a 120-min dynamic 3D PET scan (6 × 5 s, 10 × 15 s, 4 × 30 s, 5 × 120 s, 5 × 300 s, and 8 × 600 s) was conducted. The acquired PET data was reconstructed as described by Fisher et al. [27].

MRI was obtained using a 3T Siemens Magnetom Trio scanner (Erlangen, Germany). 2D T2-weighted and high-resolution 3D T1-weighted sequences (matrix 256 × 256; 1 × 1 × 1 mm voxels) were acquired and corrected for non-uniformity and spatial distortions. Using SPM5 (Welcome Department of Cognitive Neurology, London, UK), T1-weighted images were segmented into gray matter, white matter, and cerebrospinal fluid. Each voxel was assigned to the tissue class with the highest probability and this segmentation was applied afterwards for delineation of the region of interest. The T2-weighted images were used for brain masking.

Pvelab was used to automatically outline regions from the structural MRI scan and subsequently determine time-activity curves within each region [28]. The non-displaceable binding potential (BP_{ND}) of [^{11}C]SB207145 was modeled with the simplified reference tissue model using PMOD (PMOD Technologies, Zurich, Switzerland) employing cerebellum as a reference region [26], defined as: $BP_{ND} = f_{ND} \times B_{avail} \times (1/K_D)$, where f_{ND} is the free fraction of ligand in the nondisplaceable tissue compartment, K_D is the dissociation constant and B_{avail} is the concentration of receptors available for binding. Three regions of interest (ROIs) were included in our model: Frontal cortex, hippocampus and amygdala, as these regions are critically involved in the brain's emotional circuitry.

2.5. Statistics

As a majority of the primary cognitive outcomes exhibited non-parametric distributions, the main effect of oxytocin intervention on memory, affective and social cognition was assessed using Wilcoxon signed-rank test. To test the association between 5-HT$_4$R binding and the effect of oxytocin intervention on memory, affective and social cognition, a simple linear regression model was used with 5-HT$_4$R binding and intervention order as independent variables and effect of oxytocin intervention on cognition defined as percentage change in performance between placebo and oxytocin condition (ΔOT=(score$_{placebo}$–score$_{OT}$)/score$_{placebo}$ × 100) as the dependent variable. The study includes 15 individual cognitive outcomes, so to minimize type 1 error rates, we used a Bonferroni corrected threshold of p-value <0.003.

3. Results

3.1. Descriptive statistics

The age range of participants was 20–39 years (25.0 ± 4.7, mean ± SD). There were no significant differences between intervention order groups (placebo/oxytocin vs. oxytocin/placebo) on age ($p = 0.15$) or education level ($p = 0.58$) (see Table S1). Likewise, there were no significant differences between the whole sample and the subgroup that was PET-scanned on age ($p = 0.33$) or education ($p = 0.94$) (see Table S2).

To test the blinding procedure, both participants and the neuropsychological tester guessed the intervention (placebo vs oxytocin) after each test session: the rate of correct guesses were 45% for the participants and 61% for the tester on the first intervention day and 67% for participants and 58% for the tester on the second intervention day. Thus, while the tester blinding appears to have been successful, we did observe a 22% point increase in correct guesses from the first to the second intervention in participants, suggesting that some participants were able to distinguish between the intervention conditions.

3.2. Effect of oxytocin on cognition

Table 2 shows the effect of oxytocin intervention on hot cognitive performance. We found no statistically significant evidence of an effect of oxytocin on any of the individual cognitive outcomes (all $p > 0.07$).

3.3. Mediating role of 5-HT$_4$R on oxytocin effect on hot cognition

Table 3 shows the associations between the neuropsychological outcomes and 5-HT$_4$R binding in brain ROIs. Given our significance threshold of $p < 0.003$, we found no evidence that the effect of oxytocin on hot cognition was dependent on 5-HT$_4$R levels (all $p > 0.02$). However, 5-HT$_4$R binding in the hippocampus and amygdala appeared, at a trend-level, to mediate the effect of oxytocin intervention on guilt ratings in the moral emotions task (hippocampus, $p = 0.03$; amygdala, $p = 0.02$) while preference for social information over factual information in the social information preference task similarly at a trend-level appeared to be mediated by 5-HT$_4$R levels in the amygdala ($p = 0.02$) and hippocampus ($p = 0.02$).

Table 2
Effect of oxytocin on hot cognition.

	Oxytocin		Placebo		p-value
	Mean ± SD	Range	Mean ± SD	Range	
Emotion Recognition Task					
Happiness hit rate (%)	77.7 ± 16.3	35–100	75.7 ± 13.9	30–100	0.22
Sadness hit rate (%)	81.7 ± 14.8	25–100	79.7 ± 18.9	15–100	0.74
Anger hit rate (%)	73.6 ± 12.6	40–100	68.9 ± 13.1	40–100	0.07
Fear hit rate (%)	74.0 ± 13.0	45–100	76.1 ± 11.8	50–100	0.37
Intensity Morphing Task					
Happiness threshold	5.1 ± 1.4	2.8–8.0	4.7 ± 1.6	2.0–8.0	0.20
Sadness threshold	5.0 ± 1.5	2.0–7.8	4.8 ± 1.5	1.7–8.3	0.57
Anger threshold	4.5 ± 1.2	1.3–7.3	4.2 ± 1.3	1.0–8.0	0.13
Fear threshold	4.7 ± 1.4	2.0–7.5	4.5 ± 1.3	2.3–7.3	0.38
Moral Emotion Task					
Guilt rating	3.9 ± 0.4	3.2–5.0	4.0 ± 0.7	2.7–7.0	0.49
Shame rating	4.0 ± 0.6	3.0–5.6	4.1 ± 0.7	2.8–7.6	0.99
Social Information Preference Task					
Information sampling (%)	37.4 ± 18.0	−6.3–68.8	37.2 ± 18.4	−3.1–68.8	0.93
Interpretation bias (%)	12.8 ± 21.9	−66.7–50.0	8.2 ± 19.2	−44.4–50.0	0.24
Verbal Affective Memory Task-26					
Positive word recall	7.4 ± 1.2	4.6–9.0	7.4 ± 1.5	3.7–9.7	0.87
Negative word recall	7.0 ± 1.4	3.1–9.0	7.2 ± 1.6	2.7–9.4	0.38
Neutral word recall	4.9 ± 0.6	3.6–6.0	4.9 ± 0.7	3.3–6.0	0.93

Table 2. Effect of oxytocin intervention (oxytocin vs placebo condition) on hot cognition assessed with Wilcoxon signed rank test.

Table 3
Association between 5-HT$_4$R binding and oxytocin-promoted changes in cognition.

	Prefrontal cortex		Amygdala		Hippocampus	
	β	*p*-value	β	*p*-value	β	*p*-value
Emotion Recognition Task						
Happiness	−6.69	0.35	−0.93	0.85	−1.65	0.67
Sadness	−63.22	0.22	−48.43	0.18	−33.52	0.23
Anger	−34.30	0.41	−23.00	0.43	0.15	1.00
Fear	−10.44	0.36	−2.99	0.71	−0.42	0.95
Intensity Morphing Task						
Happiness	1.42	0.72	4.14	0.12	3.27	0.11
Sadness	3.45	0.28	4.25	0.05	2.54	0.13
Anger	2.64	0.45	2.38	0.33	3.33	0.06
Fear	0.12	0.97	−0.34	0.86	0.06	0.97
Moral Emotion Task						
Guilt	0.78	0.39	1.39	0.02	1.00	0.03
Shame	1.97	0.08	1.10	0.16	1.10	0.06
Social Information Preference Task						
Information sampling	7.18	0.84	56.43	0.02	41.15	0.02
Interpretation bias	0.05	1.00	−20.98	0.46	−22.73	0.29
Verbal Affective Memory Task-26						
Positive word recall	2.41	0.12	−0.33	0.76	−0.01	0.99
Negative word recall	2.15	0.23	1.44	0.25	1.46	0.12
Neutral word recall	1.63	0.17	1.63	0.04	1.03	0.10

Table 3. Associations between regional serotonin 4 receptor (5-HT$_4$R) binding and oxytocin-promoted changes in performance across cognitive domains. Using Bonferroni correction for 15 tests, significance threshold is set at $p > 0.003$.

4. Discussion

We here investigated the effects of oxytocin on hot cognition and the possible interaction between the serotonin system in terms of 5-HT4R availability and oxytocin in a double-blind randomized placebo-controlled study. We did not observe any main effects of oxytocin on hot cognition nor did oxytocin's effect on cognition appear to be influenced by cerebral 5-HT$_4$R levels.

Previous studies investigating effects of intranasal oxytocin interventions have so far yielded mixed findings. Interestingly, studies using healthy samples have found that oxytocin improved performance on social tasks specifically among individuals with lower levels of self-reported social cognitive abilities [29,30] while two meta-analyses found effects of intranasal oxytocin on hot cognitive functions in people with neurodevelopmental disorders [6,31]. In contrast, studies in healthy populations show that intranasal oxytocin interventions may have limited effects on hot cognition [30,32]. Thus, it is likely that oxytocin can 'rescue' function in populations who experience some degree of impaired social and affective cognition but has little to no effect on high-functioning individuals. This may explain why we did not observe a main effect of oxytocin intervention in our sample of highly educated and healthy young women.

We did not find any significant associations between 5-HT$_4$R binding and effect of oxytocin intervention. However, we noted a trend for higher 5-HT$_4$R binding being related to higher guilt and shame ratings in the moral emotions task as well as preference for social and emotional information over factual information in the social information preference task, when the participant had received oxytocin. This could indicate that high 5-HT$_4$R binding may mediate the effect of oxytocin on higher complex social cognition. Importantly, we did not observe any strong main effect of oxytocin in our sample of young and healthy women who we speculate may be so high-functioning that it is difficult to improve their cognitive functioning and therefore to detect pro-cognitive effects. Thus, we cannot exclude that an interaction between 5-HT$_4$R binding and oxytocin effects may be detectable and more pronounced in individuals who are more sensitive to oxytocin intervention. Future studies should therefore investigate the interplay between oxytocin and the 5-HT system in cohorts with pronounced hot cognitive disturbances (e.g. depression, schizophrenia or autism) as well as look at different 5-HT receptors. For example, 5-HT$_{1B}$R is one interesting target of investigation, as rodent studies of social interaction show that oxytocin and 5-HT interplay in the nucleus accumbens specifically implicate signaling via 5-HT$_{1B}$R ([10]; Celada et al., 2013).

In conclusion, our data suggest that intervention with intranasal oxytocin does not influence hot cognition in healthy women, also not when taking individual 5-HT$_4$R brain architecture into account. On a positive note, this may reflect a robust cognitive system in healthy individuals, which is stable in function when manipulated pharmacologically with a single, smaller dose of oxytocin administered exogenously. Future studies must elucidate the interplay between serotonin and oxytocin in larger cohorts and relevant clinical groups for example postpartum women with depressive symptoms, ideally with interventions that trigger endogenous release of oxytocin.

4.1. Methodological considerations

We used a single, conventional dose of 24 IU intranasal oxytocin in accordance with the literature, however, it cannot be ruled out that a higher dose would have yielded different results. We did not include peripheral oxytocin measures as this is not a currently well validated as a marker of central oxytocin levels [33,34]. Therefore, future studies should explore associations between central and peripheral levels of oxytocin in healthy populations. To examine differences in effects of pharmacologically applied and endogenously released oxytocin, it is also highly relevant to investigate oxytocin effects using other methods than intranasal administration such as breast feeding, physical contact, or sexual stimuli, known to be endogenous oxytocin release mechanisms that are potentially more potent and more naturalistic.

Using a cross-over design, the results as reported in Table 1 refer to the compiled oxytocin intervention group and compiled placebo group. Thus, the order of the cross over administration of oxytocin and placebo is not taken into consideration and a potential indirect learning effect of the order of oxytocin vs. placebo administration has not been tested. An indirect learning effect is, however, not expected considering that no significant effect of the oxytocin-intervention was observed for any of the cognitive outcomes (all $p > 0.07$).

Funding

This study was funded by the Independent Research Fund Denmark (ID 4183-00420B). The funders had no role in the design and conduct of the study, collection, management, analysis and interpretation of the data preparation, review or approval of the manuscript.

CRediT authorship contribution statement

Vibeke Høyrup Dam: Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Sidsel Høgsgaard Andersen:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Sofie Trolle Pedersen:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Dea Siggaard Stenbæk:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Vibe Gedsoe Frokjaer:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Within the last 5 years VGF has received honorarium as speaker for

Lundbeck Pharma A/S, Jannsen-Cilag A/S, and Gedeon Richter, DSS has received honorarium as speaker for Lundbeck Foundation, and STP is currently employed at ALK Abello A/S. All other authors declare no conflict of interest.

Acknowledgements

We would like to thank all the participants and Dorthe Givard, Peter Jensen, Lone Freyr, Bente Dall and Gerda Thomsen for their assistance with the data collection and data management. We would also like to acknowledge and thank The John and Birthe Meyer Foundation for the donation of the Cyclotron and PET scanner.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpnec.2023.100224.

References

[1] M.A. Salehinejad, E. Ghanavati, H.A. Rashid, M.A. Nitsche, Hot and cold executive functions in the brain: A prefrontal-cingular network, Brain Neurosci. Adv. (2021). https://doi.org/10.1177/23982128211007769.
[2] A. Bozorgmehr, F. Alizadeh, B. Sadeghi, A. Shahbazi, S. Norouzi Ofogh, M. T. Joghataei, S. Razian, F. Heydari, M. Ghadirivasfi, Oxytocin moderates risky decision-making during the Iowa Gambling Task: a new insight based on the role of oxytocin receptor gene polymorphisms and interventional cognitive study, Neurosci. Lett. 708 (2019) 134328, https://doi.org/10.1016/j.neulet.2019.134328.
[3] H.-J. Lee, A.H. Macbeth, J. Pagani, W.S. Young, Oxytocin: the great facilitator of life, Prog. Neurobiol. (2009), https://doi.org/10.1016/j.pneurobio.2009.04.001.
[4] N. Striepens, A. Matusch, K.M. Kendrick, Y. Mihov, D. Elmenhorst, B. Becker, M. Lang, H.H. Coenen, W. Maier, R. Hurlemann, A. Bauer, Oxytocin enhances attractiveness of unfamiliar female faces independent of the dopamine reward system, Psychoneuroendocrinology 39 (2014) 74–87, https://doi.org/10.1016/j.psyneuen.2013.09.026.
[5] R. Hurlemann, V. Grinevich (Eds.), Behavioral Pharmacology of Neuropeptides: Oxytocin, vol. 35, Springer International Publishing, 2018, https://doi.org/10.1007/978-3-319-63739-6.
[6] B. Keech, S. Crowe, D.R. Hocking, Intranasal oxytocin, social cognition and neurodevelopmental disorders: a meta-analysis, Psychoneuroendocrinology 87 (2018) 9–19, https://doi.org/10.1016/j.psyneuen.2017.09.022.
[7] F. Zhao, H. Zhang, P. Wang, W. Cui, K. Xu, D. Chen, M. Hu, Z. Li, X. Geng, S. Wei, Oxytocin and serotonin in the modulation of neural function: neurobiological underpinnings of autism-related behavior, Front. Neurosci. 16 (2022), https://doi.org/10.3389/fnins.2022.919890.
[8] M.J. Crockett, L. Clark, M.D. Hauser, T.W. Robbins, Serotonin selectively influences moral judgment and behavior through effects on harm aversion, Proc. Natl. Acad. Sci. USA 107 (40) (2010) 17433–17438, https://doi.org/10.1073/pnas.1009396107.
[9] J. Macoveanu, Serotonergic modulation of reward and punishment: evidence from pharmacological fMRI studies, Brain Res. 1556 (2014) 19–27, https://doi.org/10.1016/j.brainres.2014.02.003.
[10] G. Dölen, A. Darvishzadeh, K.W. Huang, R.C. Malenka, Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin, Nature 501 (7466) (2013) 179–184, https://doi.org/10.1038/nature12518.
[11] D.J. Hayes, A.J. Greenshaw, 5-HT receptors and reward-related behaviour: a review, Neurosci. Biobehav. Rev. 35 (6) (2011) 1419–1449, https://doi.org/10.1016/j.neubiorev.2011.03.005.
[12] L. Marner, N. Gillings, K. Madsen, D. Erritzoe, W.F.C. Baaré, C. Svarer, S. G. Hasselbalch, G.M. Knudsen, Brain imaging of serotonin 4 receptors in humans with [11C]SB207145-PET, Neuroimage 50 (3) (2010) 855–861, https://doi.org/10.1016/j.neuroimage.2010.01.054.
[13] S.E. Murphy, L.C. Wright, M. Browning, P.J. Cowen, C.J. Harmer, A role for 5-HT $_4$ receptors in human learning and memory, Psychol. Med. 50 (16) (2020) 2722–2730, https://doi.org/10.1017/S0033291719002836.
[14] A.N. de Cates, L.C. Wright, M.A.G. Martens, D. Gibson, C. Türkmen, N. Filippini, P. J. Cowen, C.J. Harmer, S.E. Murphy, Déjà-vu? Neural and behavioural effects of the 5-HT4 receptor agonist, prucalopride, in a hippocampal-dependent memory task, Transl. Psychiatry 11 (1) (2021) 497, https://doi.org/10.1038/s41398-021-01568-4.
[15] K. Köhler-Forsberg, V.H. Dam, B. Ozenne, A. Sankar, V. Beliveau, E.B. Landman, S. V. Larsen, A.S. Poulsen, C.-T. Ip, A. Jørgensen, M. Meyer, D.S. Stenbæk, H.R. L. Eiberg, J. Madsen, C. Svarer, M.B. Jørgensen, V.G. Frokjaer, G.M. Knudsen, Serotonin 4 receptor brain binding in major depressive disorder and association with memory dysfunction, JAMA Psychiatr. 80 (4) (2023) 296, https://doi.org/10.1001/jamapsychiatry.2022.4539.
[16] H. Hagena, D. Manahan-Vaughan, The serotonergic 5-HT4 receptor: a unique modulator of hippocampal synaptic information processing and cognition, Neurobiol. Learn. Mem. 138 (2017) 145–153, https://doi.org/10.1016/j.nlm.2016.06.014.
[17] M. King, C. Marsden, K. Fone, A role for the 5-HT1A, 5-HT4 and 5-HT6 receptors in learning and memory, Trends Pharmacol. Sci. 29 (9) (2008) 482–492, https://doi.org/10.1016/j.tips.2008.07.001.
[18] A. Quiedeville, M. Boulouard, K. Hamidouche, V. Da Silva Costa-Aze, G. Nee, C. Rochais, P. Dallemagne, F. Fabis, T. Freret, V. Bouet, Chronic activation of 5-HT4 receptors or blockade of 5-HT6 receptors improve memory performances, Behav. Brain Res. 293 (2015) 10–17, https://doi.org/10.1016/j.bbr.2015.07.020.
[19] A.R. Bland, J.P. Roiser, M.A. Mehta, T. Schei, H. Boland, D.K. Campbell-Meiklejohn, R.A. Emsley, M.R. Munafo, I.S. Penton-Voak, A. Seara-Cardoso, E. Viding, V. Voon, B.J. Sahakian, T.W. Robbins, R. Elliott, EMOTICOM: a neuropsychological test battery to evaluate emotion, motivation, impulsivity, and social cognition, Front. Behav. Neurosci. 10 (2016). https://www.frontiersin.org/articles/10.3389/fnbeh.2016.00025.
[20] V.H. Dam, C.K. Thystrup, P.S. Jensen, A.R. Bland, E.L. Mortensen, R. Elliott, B. J. Sahakian, G.M. Knudsen, V.G. Frokjaer, D.S. Stenbæk, Psychometric properties and validation of the EMOTICOM test battery in a healthy Danish population, Front. Psychol. 10 (2019). https://www.frontiersin.org/articles/10.3389/fpsyg.2019.02660.
[21] V.H. Dam, C. Langley, D.S. Stenbæk, B.J. Sahakian, EMOTICOM test battery, in: G. J. Boyle, Y. Stern, D.J. Stein, C.J. Golden, B.J. Sahakian, T.M.-C. Lee, S.-H.A. Chen (Eds.), The SAGE Handbook of Clinical Neuropsychology: Clinical Neuropsychological Assessment and Diagnosis, SAGE, 2023.
[22] A. Gossen, A. Hahn, L. Westphal, S. Prinz, R.T. Schultz, G. Gründer, K. N. Spreckelmeyer, Oxytocin plasma concentrations after single intranasal oxytocin administration – a study in healthy men, Neuropeptides 46 (5) (2012) 211–215, https://doi.org/10.1016/j.npep.2012.07.001.
[23] Y. Paloyelis, O.M. Doyle, F.O. Zelaya, S. Maltezos, S.C. Williams, A. Fotopoulou, M. A. Howard, A spatiotemporal profile of in vivo cerebral blood flow changes following intranasal oxytocin in humans, Biol. Psychiatr. 79 (8) (2016) 693–705, https://doi.org/10.1016/j.biopsych.2014.10.005.
[24] M.A. Ellenbogen, A.-M. Linnen, R. Grumet, C. Cardoso, R. Joober, The acute effects of intranasal oxytocin on automatic and effortful attentional shifting to emotional faces, Psychophysiology 49 (1) (2012) 128–137, https://doi.org/10.1111/j.1469-8986.2011.01278.x.
[25] A.A. Marsh, H.H. Yu, D.S. Pine, R.J.R. Blair, Oxytocin improves specific recognition of positive facial expressions, Psychopharmacology 209 (3) (2010) 225–232, https://doi.org/10.1007/s00213-010-1780-4.
[26] L. Marner, N. Gillings, R.A. Comley, W.F.C. Baaré, E.A. Rabiner, A.A. Wilson, S. Houle, S.G. Hasselbalch, C. Svarer, R.N. Gunn, M. Laruelle, G.M. Knudsen, Kinetic modeling of ^{11}C-SB207145 binding to 5-HT $_4$ receptors in the human brain in vivo, J. Nucl. Med. 50 (6) (2009) 900–908, https://doi.org/10.2967/jnumed.108.058552.
[27] P.M. Fisher, K.K. Holst, D. Adamsen, A.B. Klein, V.G. Frokjaer, P.S. Jensen, C. Svarer, N. Gillings, W.F.C. Baare, J.D. Mikkelsen, G.M. Knudsen, BDNF Val66met and 5-HTTLPR polymorphisms predict a human in vivo marker for brain serotonin levels: genetic Predictors of Human Brain Serotonin Marker, Hum. Brain Mapp. 36 (1) (2015) 313–323, https://doi.org/10.1002/hbm.22630.
[28] C. Svarer, K. Madsen, S.G. Hasselbalch, L.H. Pinborg, S. Haugbøl, V.G. Frøkjær, S. Holm, O.B. Paulson, G.M. Knudsen, MR-based automatic delineation of volumes of interest in human brain PET images using probability maps, Neuroimage 24 (4) (2005) 969–979, https://doi.org/10.1016/j.neuroimage.2004.10.017.
[29] J.A. Bartz, J. Zaki, N. Bolger, E. Hollander, N.N. Ludwig, A. Kolevzon, K. N. Ochsner, Oxytocin selectively improves empathic accuracy, Psychol. Sci. 21 (10) (2010) 1426–1428, https://doi.org/10.1177/0956797610383439.
[30] J.A. Bartz, J.P. Nitschke, S.A. Krol, P.-P. Tellier, Oxytocin selectively improves empathic accuracy: a replication in men and novel insights in women, Biol. Psychiatr. 4 (12) (2019) 1042–1048, https://doi.org/10.1016/j.bpsc.2019.01.014.
[31] P.-C. Bürkner, D.R. Williams, T.C. Simmons, J.D. Woolley, Intranasal oxytocin may improve high-level social cognition in schizophrenia, but not social cognition or neurocognition in general: a multilevel Bayesian meta-analysis, Schizophr. Bull. 43 (6) (2017) 1291–1303, https://doi.org/10.1093/schbul/sbx053.
[32] M.A. Straccia, A.R. Teed, P.L. Katzman, K.M. Tan, M.H. Parrish, M.R. Irwin, N. I. Eisenberger, M.D. Lieberman, B.A. Tabak, Null results of oxytocin and vasopressin administration on mentalizing in a large fMRI sample: evidence from a randomized controlled trial, Psychol. Med. 53 (6) (2023) 2285–2295, https://doi.org/10.1017/S0033291721004104.
[33] A. Lefevre, R. Mottolese, M. Dirheimer, C. Mottolese, J.-R. Duhamel, A. Sirigu, A comparison of methods to measure central and peripheral oxytocin concentrations in human and non-human primates, Sci. Rep. 7 (1) (2017), https://doi.org/10.1038/s41598-017-17674-7.
[34] M. Valstad, G.A. Alvares, O.A. Andreassen, L.T. Westlye, D.S. Quintana, The relationship between central and peripheral oxytocin concentrations: a systematic review and meta-analysis protocol, Syst. Rev. 5 (1) (2016), https://doi.org/10.1186/s13643-016-0225-5.