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Dysfunctions in the Oxytocinergic System and Network Alterations in the Psychotic Brain: A Translational Paradigm of Interpersonal Neuromodulation

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Resumo

A oxitocina é um neuropéptido produzido nos núcleos paraventricular e supra-óptico do hipotálamo e libertado tanto centralmente como na circulação periférica. Desde a sua descoberta em 1906 pelas equipas de Dale e du Vigneaud, a oxitocina tem sido amplamente estudada pela sua ação uterotónica e na lactação, mas apenas nas últimas décadas se reconheceu o seu papel como neuromodulador de comportamentos sociais e emocionais. Em animais, demonstrou-se que a administração central de oxitocina reforça ligações sociais — nomeadamente a formação de pares em roedores monogâmicos — e modula a resposta ao stress através do eixo hipotálamo–hipófise–adrenal. Em humanos, estudos subsequentes validaram a sua influência na confiança interpessoal, na empatia e na perceção de expressões faciais, situando a oxitocina no cerne da neurobiologia das interações sociais.

As perturbações psicóticas, em especial a esquizofrenia, caracterizam-se por défices acentuados na cognição social, na integração sensorial e na regulação emocional. Nesta perturbação, sintomas como anedonia, alogia e retraimento social associam-se a disfunções de conectividade em redes frontolímbicas — envolvendo a amígdala, hipocampo e córtex pré-frontal — assim como a alterações de plasticidade sináptica em vias glutamatérgicas e dopaminérgicas. Estas alterações sugerem um comprometimento dos mecanismos que, noutros contextos, são modulados pela oxitocina para promover a coesão social e a adaptação emocional.

No presente trabalho, propõe-se rever e sintetizar a evidência científica relativa à influência do sistema oxitocinérgico na fisiopatologia da psicose e a sua potencial aplicação como intervenção terapêutica adjuvante. Para tal, foi conduzida uma revisão sistemática de estudos publicados entre 2010 e 2024, com pesquisa estruturada nas bases de dados PubMed, Scopus e PsycINFO. Utilizaram-se termos MeSH e palavras-chave como “oxytocin”, “schizophrenia” e “social cognition”, de modo a identificar estudos clínicos que avaliem a modulação oxitocinérgica em indivíduos com perturbações psicóticas.

Este trabalho pretende, assim, traçar um panorama do papel da oxitocina na regulação de redes neuronais sociais e emocionais e a sua utilidade como adjuvante terapêutico no cérebro psicótico.

Palavras-Chave

Oxitocina; esquizofrenia; cognição social; conectividade frontolímbica; plasticidade sináptica; neuromodulação

Abstract

Oxytocin is a neuropeptide produced in the paraventricular and supraoptic nuclei of the hypothalamus and released both centrally and into the peripheral circulation. Since its discovery in 1906 by the teams of Dale and du Vigneaud, oxytocin has been widely studied for its uterotonic and lactation action, but only in recent decades has its role as a neuromodulator of social and emotional behaviour been recognized. In animals, central administration of oxytocin strengthens social bonds - particularly pair-bonding in monogamous rodents - and modulates the stress response via the hypothalamic-pituitary-adrenal axis. In humans, subsequent studies have validated its influence on interpersonal trust, empathy and the perception of facial expressions, placing oxytocin at the heart of the neurobiology of social interactions.

Psychotic disorders, especially schizophrenia, are characterized by marked deficits in social cognition, sensory integration and emotional regulation. In this disorder, symptoms such as anhedonia, alogia and social withdrawal are associated with connectivity dysfunctions in frontolimbic networks - involving the amygdala, hippocampus and prefrontal cortex - as well as alterations in synaptic plasticity in glutamatergic and dopaminergic pathways. These alterations suggest an impairment of the mechanisms that, in other contexts, are modulated by oxytocin to promote social cohesion and emotional adaptation.

This paper aims to review and synthesize the scientific evidence on the influence of the oxytocinergic system on the pathophysiology of psychosis and its potential application as an adjuvant therapeutic intervention. To this end, a systematic review of studies published between 2010 and 2024 was conducted, with a structured search in PubMed, Scopus and PsycINFO databases. MeSH terms and keywords such as “oxytocin”, “schizophrenia” and “social cognition” were used to clinical studies evaluating oxytocinergic modulation in individuals with psychotic disorders.

This work thus aims to provide a comprehensive overview of the role of oxytocin in the regulation of social and emotional neuronal networks and its usefulness as a therapeutic adjuvant in the psychotic brain.

Keywords

Oxytocin; schizophrenia; social cognition; frontolimbic connectivity; synaptic plasticity; neuromodulation

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1. Introdução

A oxitocina foi descoberta no início do século XX como um agente uterotónico, sendo Du Vigneaud quem descreveu a sua estrutura em 1953. Durante décadas, o seu estudo centrou-se nas funções reprodutivas, mas desde os anos 1950 que investigadores começaram a observar efeitos comportamentais ligados ao seu papel no sistema nervoso central (1). Em roedores monogâmicos, a administração central de oxitocina mostrou reforçar a formação de laços sociais, enquanto em primatas verificou-se influência na regulação do stress através da modulação do eixo hipotálamo–hipófise–adrenal (HPA) (2). Estes achados pré-clínicos criaram as bases para o interesse translacional na área psiquiátrica, onde se procurou explorar a capacidade deste neuropéptido em promover comportamentos pró-sociais e reduzir resposta ao medo.

Em 2010, Feifel et al. publicaram o primeiro ensaio clínico randomizado sobre o impacto da administração de oxitocina intranasal na esquizofrenia, demonstrando uma redução significativa dos sintomas psicóticos em doentes estáveis, o que constituiu um marco na investigação do potencial terapêutico da oxitocina em perturbações psicóticas (3). No mesmo ano, estudos genéticos revelaram que variantes no gene da oxitocina (OXT) e no recetor de oxitocina (OXTR) estavam associadas à gravidade dos sintomas da esquizofrenia e à resposta terapêutica a fármacos como a clozapina, sugerindo que predisposições individuais na sinalização oxitocinérgica podem influenciar o curso clínico da esquizofrenia (4).

Posteriormente, investigações observacionais evidenciaram que doentes com esquizofrenia apresentavam níveis plasmáticos de oxitocina inferiores quando comparados com controlos saudáveis, e que estes níveis se correlacionavam inversamente com a presença de sintomas da esquizofrenia, apontando para uma disfunção crónica do eixo oxitocinérgico nesta população (5). Estudos de neuroimagem funcional associaram a administração aguda de oxitocina à normalização de conectividade em repouso entre a amígdala e o córtex pré-frontal medial – circuitos envolvidos na cognição social e regulação emocional, frequentemente deteriorados na esquizofrenia (6) Estes resultados fortaleceram a hipótese de que a oxitocina não só intervém na neurobiologia das interações sociais, mas pode também atenuar défices interpessoais típicos da psicose.

As perturbações psicóticas, em especial a esquizofrenia, manifestam-se por delírios, alucinações e défices marcantes na cognição social, integração sensorial e modulação emocional. Estas disfunções têm sido atribuídas a alterações de plasticidade sináptica e

a um desequilíbrio na conectividade das redes frontolímbicas — envolvendo a amígdala, o hipocampo e o córtex pré-frontal — áreas particularmente ricas em recetores de oxitocina (7). A relação entre a sinalização oxitocinérgica e a homeostase emocional sugere um mecanismo em que a oxitocina permitiria a restauração parcial da função destas redes, otimizando processos de teoria da mente, reconhecimento de expressões faciais e confiança interpessoal.

Diversos ensaios clínicos têm explorado o impacto da oxitocina em domínios cognitivos específicos para além da cognição social pura. Feifel et al. (2012) demonstraram que, após três semanas de administração intranasal de 40 UI duas vezes ao dia, os doentes com esquizofrenia exibiram melhorias significativas na aprendizagem verbal imediata e na recuperação de curto prazo, medidas pelo California Verbal Learning Test (CVLT) e pela tarefa Letter Number Sequencing(8). Estas descobertas sugerem um efeito potencial da oxitocina na memória de trabalho e no processamento verbal na psicose.

Outros estudos focaram a perceção e discriminação de afetos faciais, essenciais para a integração sensorial e a regulação emocional. Goldman et al. (2011) realizaram um estudo de doses comparativas (10 UI versus 20 UI) em doentes esquizofrénicos, encontrando efeitos divergentes: a dose mais baixa aumentou a intensidade percebida de expressões emocionais, enquanto a dose mais elevada normalizou enviesamentos na deteção de medo, particularmente em doentes com polidipsia psicogénica comorbida (9). Averbeck et al. (2012) confirmaram que uma dose única de 24 UI melhora modestamente o reconhecimento de emoções em faces alteradas, embora sem corrigir integralmente o défice observado face a controlos saudáveis(10).

Estudos de tarefas de reconhecimento de medo sublinharam o papel estabilizador da oxitocina na reatividade emocional. Fischer-Shofty et al. (2013) mostraram que 24 UI intranasais aumentaram significativamente a precisão no reconhecimento de expressões de medo em doentes com esquizofrenia, sobretudo naqueles com desempenho basal mais baixo, indicando que a oxitocina pode beneficiar especialmente os subgrupos com défices mais graves (11).

Além de domínios cognitivos tradicionais, investigações integraram medidas de integração sensorial olfativa como indicador de plasticidade fronto-límbica. Num ensaio placebo-controlado, Oxytocin intranasal (20 UI) melhorou significativamente a pontuação total no University of Pennsylvania Smell Identification Test (UPSIT) em doentes hospitalizados, correlacionando-se com redução de sintomas negativos (12). Estes resultados sugerem que a oxitocina pode modular circuitos sensoriais elementares,

estendendo o seu alcance terapêutico para além das redes estritamente visuais e emocionais.

Perspetivas complementares de intervenção foram exploradas num estudo de terapias não farmacológicas. Jayaram et al. (2013) verificaram que um programa de yoga terapêutico de um mês elevou os níveis plasmáticos de oxitocina em doentes com esquizofrenia e melhorou o desempenho em tarefas de reconhecimento de emoções, ainda que não existisse correlação direta estatisticamente significativa entre as variações de oxitocina e a performance (13). Este trabalho aponta para a viabilidade de estratégias integrativas que potenciem a libertação endógena de oxitocina.

Finalmente, investigações de associação genética reforçam a complexidade individual da sinalização oxitocinérgica. Montag et al. (2012) associaram o alelo A do SNP rs2254298 em *OXTR* a maiores scores de “empathic concern”, enquanto variantes em *OXT* correlacionaram-se com severidade de sintomas positivos e negativos, indicando que o genótipo pode moldar a responsividade aos efeitos comportamentais e neurofisiológicos da oxitocina (14).

Este conjunto de evidências multidimensionais — desde memória e aprendizagem verbal, discriminação afetiva, tarefas sensoriais olfativas, até variações genéticas e abordagens de intervenção comportamental — sublinha o vasto potencial da oxitocina como neuromodulador na esquizofrenia, mas também evidencia a necessidade de calibrar protocolos de dose, registo de efeitos farmacocinéticos e estratificação genotípica dos doentes.

2. Metodologia

2.1. Questão de investigação

O presente trabalho procura explorar o impacto da modulação do sistema oxitocinérgico na cognição social, integração sensorial e conectividade frontolímbica em indivíduos com perturbações psicóticas. Pretende-se, também, identificar as principais lacunas metodológicas nos protocolos de administração de oxitocina e apontar diretrizes para futuras investigações clínicas e translacionais.

2.2. Objetivos

O principal objetivo desta revisão sistemática é avaliar e sintetizar a evidência científica relativa à influência da oxitocina sobre o funcionamento neurocognitivo e social em indivíduos com perturbações psicóticas, focando-se na modulação da plasticidade sináptica dos circuitos frontolímbicos. Mais concretamente, pretender-se-á (1) Determinar se a modulação do sistema oxitocinérgico resulta em melhorias significativas nos sintomas psicossociais e cognitivos dos doentes com esquizofrenia. (2) Analisar a eficácia da oxitocina como intervenção terapêutica adjuvante, com especial foco na correção das disfunções em áreas cerebrais críticas, nomeadamente a amígdala e o córtex pré-frontal. (3) Explorar o papel da oxitocina na integração sensorial e na conectividade neuronal, contribuindo para a compreensão dos mecanismos neurobiológicos que fundamentam a psicose.

2.3. Pesquisa de artigos

A pesquisa de literatura foi realizada nas bases de dados PubMed, Scopus e Google Scholar, privilegiando artigos publicados entre 2010 e 2024. Recorrendo a termos MeSH e palavras-chave — incluindo “oxitocina”, “perturbações psicóticas”, “esquizofrenia”, “neuroplasticidade”, “cognição social”, “integração sensorial” e “modulação frontolímbica” — procedeu-se a combinações booleanas que abrangiam sinergias temáticas (por exemplo, “oxitocina AND esquizofrenia”, “oxitocina AND frontolimbic connectivity”). Após a obtenção dos resultados iniciais, empregou-se um processo de filtragem para retirar duplicados e estudos claramente irrelevantes pelo título.

2.4. Critérios de inclusão e exclusão

Foram incluídos estudos originais que tivessem como foco principal a avaliação dos efeitos da oxitocina — endógena ou exógena — sobre a cognição social, a integração sensorial ou a conectividade neuronal em contextos de psicose, preferencialmente através de ensaios clínicos randomizados, estudos observacionais ou investigações genéticas. Também se aceitaram pesquisas que realizassem análises de neuroimagem

funcional ou medições de biomarcadores relacionados com plasticidade sináptica em redes frontolímbicas. Excluíram-se relatos de caso únicos sem análise neurobiológica aprofundada, revisões de literatura sem dados empíricos, bem como qualquer trabalho centrado em populações saudáveis sem comparação direta com grupos psicóticos ou sem exploração clara dos domínios de interesse.

2.5. Recolha de dados

Os dados foram extraídos de forma padronizada, através de grelha construída ad hoc. Para cada estudo registou-se o tipo de desenho — ensaio clínico, estudo observacional ou análise genética —, a caracterização da amostra (número de participantes, sexo, diagnóstico), o protocolo de administração de oxitocina (via, dose, frequência, duração), as técnicas de avaliação empregues (neuroimagem, testes comportamentais, biomarcadores), e os principais resultados reportados. Adicionalmente, catalogaram-se aspetos metodológicos relevantes, como o método de randomização, a utilização de duplo-cego e as correções estatísticas para comparações múltiplas. Esta abordagem permitiu uma síntese rigorosa dos achados e a identificação de variáveis críticas para a reproduzibilidade e comparabilidade entre estudos.

2.6 Avaliação do risco de viés

A avaliação crítica da qualidade metodológica dos estudos incluídos foi realizada com recurso à ferramenta *RoB 2 (Revised Cochrane risk-of-bias tool for randomized trials)* para os ensaios clínicos randomizados, que avalia o risco de viés em cinco domínios principais: (1) processo de randomização, (2) desvios da intervenção, (3) dados de desfecho ausentes, (4) mensuração dos desfechos, e (5) seleção dos resultados reportados. Cada domínio foi classificado como "*baixo risco*", "*algumas preocupações*" ou "*alto risco de viés*" conforme as orientações do *Cochrane Handbook* (15).

Para os estudos observacionais de tipo transversal, como estudos de biomarcadores ou estudos genético-associativos, foi utilizada a ferramenta de avaliação crítica da *JBI (Joanna Briggs Institute)* para estudos transversos. Esta ferramenta contempla critérios como a clareza dos critérios de inclusão, validade e confiabilidade na medição da exposição e dos desfechos, adequação dos métodos estatísticos, e identificação e controlo de fatores de confusão. (16)

Cada estudo foi avaliado por dois revisores de forma independente, com resolução de discrepâncias por consenso. A classificação final do risco de viés foi usada para interpretar os resultados com maior precaução quando se tratavam de estudos com alto risco metodológico. Cada critério foi pontuado qualitativamente como "*sim*", "*não*" ou

"*não claro*", permitindo avaliar a robustez metodológica dos estudos transversais incluídos.

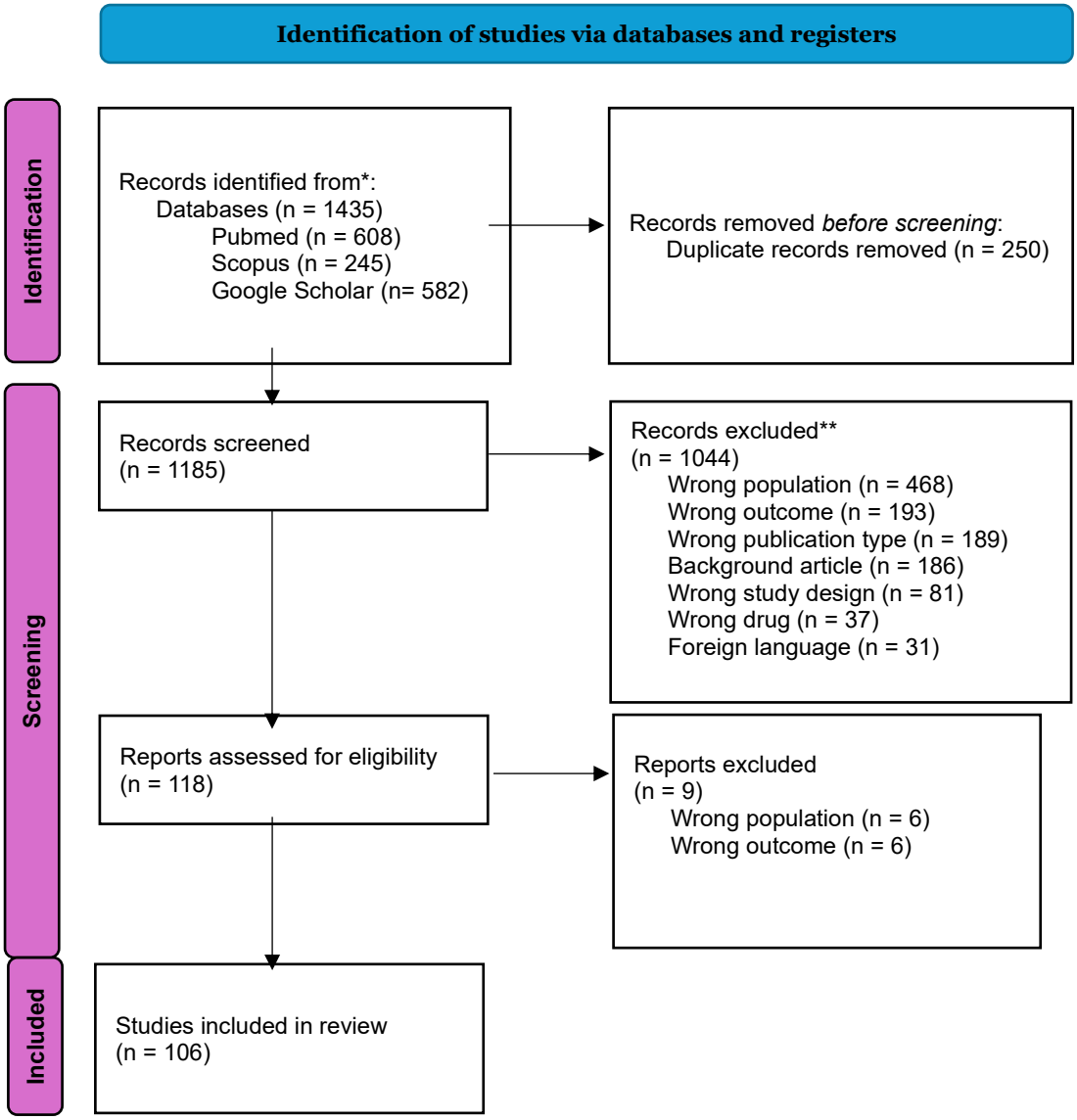

Fig. 1. Flowchart mostrando o processo de seleção de estudos para revisão sistemática de acordo com as diretrizes PRISMA

3.Resultados

Encontram-se no apêndice 3 um resumo de todos os artigos resultantes da pesquisa efetuada.

3.1 Seleção de estudos

De um total de 1 435 artigos inicialmente identificados (608 em PubMed, 245 em Scopus e 582 no Google Scholar), foram removidos 250 duplicados, restando 1 185 registos para triagem. Após leitura de títulos e resumos, 1 044 artigos foram excluídos por se referirem a populações erradas, desfechos não relevantes, tipo de publicação ou metodologia inadequada. Dos 118 artigos avaliados em texto completo, 12 não cumpriam os critérios de elegibilidade (população ou desfecho incorretos), resultando em 106 estudos incluídos na revisão (Fig. 1).

3.2 Caracterização dos estudos

Os 106 artigos incluídos podem ser organizados em três categorias principais. A primeira abrange 19 estudos genéticos e moleculares, nos quais se investigaram associações entre polimorfismos em *OXT*, *OXTR* e outros genes do eixo oxitocinérgico e fenótipos de esquizofrenia ou resposta a antipsicóticos, exemplificados por Souza et al. (2010), Montag et al. (2012) e Teltsh et al. (2012). (17–19)

A segunda categoria reúne 35 estudos observacionais que avaliaram níveis basais de oxitocina, seja sérico ou no líquor, e de vasopressina, bem como a sua relação com sintomas positivos, negativos e medidas de cognição social, como descrito por Rubin et al. (2010), Sasayama et al. (2012) e Strauss et al. (2015). (5,20,21)

A terceira e mais numerosa inclui 52 ensaios clínicos randomizados de oxitocina intranasal, nos quais se testaram doses que variaram de 10 a 80 UI diárias, administradas durante períodos que iam de uma dose única até 16 semanas, em doentes com esquizofrenia ou psicose precoce. Esses ensaios investigaram desfechos que vão desde a sintomatologia psicótica (PANSS, BPRS) e a cognição social (RMET, TASIT, ER-40, UPSIT), até à memória verbal (CVLT), integração sensorial (UPSIT, limiares olfativos), teoria da mente e abordagens de aproximação-evitação social (SVT, AAT).

3.3 Principais achados

3.3.1 Associação genética

No âmbito da associação genética, variantes em *OXTR* (rs2254298 e rs53576) mostraram-se ligadas a diferenças em “empathic concern” e à severidade dos sintomas

negativos e gerais, conforme relatado por Montag et al. (2012) e Teltsh et al. (2012). (22,23) Haplótipos em *OXT* correlacionaram-se com melhor resposta à clozapina e redução de sintomas negativos, como evidenciado por Souza et al. (2010). (4)

3.3.2 Níveis periféricos de oxitocina

Quanto aos níveis periféricos de oxitocina, doentes com esquizofrenia apresentaram concentrações plasmáticas significativamente inferiores às de controlos, inversamente correlacionadas com sintomas positivos e negativos, segundo Rubin et al. (2010) e Jobst et al. (2014). (5,24) No líquor, Sasayama et al. (2012) observaram que o fluxo de oxitocina se correlacionava negativamente com sintomas negativos em doentes do sexo masculino. (25)

3.3.3 Ensaios de oxitocina intranasal

Nos ensaios clínicos de oxitocina intranasal, vários RCTs demonstraram reduções modestas, embora consistentes, nas pontuações de PANSS e BPRS após administração de 40–48 UI diárias durante três a oito semanas; contudo, esses efeitos mostraram-se heterogéneos e dependentes de dose e duração (3,26,27). Melhores desempenhos em tarefas de cognição social e teoria da mente foram registados em estudos cruzados que administraram uma dose única de 24–40 UI, sobretudo em doentes com défices mais acentuados. (28,29) No domínio do processamento afetivo, doses baixas (10–20 UI) aumentaram a perceção da intensidade emocional (30), e doses superiores (40 UI) normalizaram enviesamentos na deteção de medo. (11) A integração sensorial olfativa foi também beneficiada pela administração de oxitocina intranasal: Lee et al. (2013) e Woolley et al. (2014) relataram melhorias no desempenho do UPSIT e na sensibilidade a odores em doentes hospitalizados. (12,31)

Por fim, intervenções combinadas, como o programa de yoga terapêutico estudado por Jayaram et al. (2013), mostraram que abordagens comportamentais podem elevar níveis endógenos de oxitocina e melhorar o reconhecimento emocional, sugerindo sinergias potenciais entre estratégias farmacológicas e não farmacológicas. (13)

3.4 Variabilidade metodológica e lacunas

Apesar do volume crescente de estudos, observou-se grande heterogeneidade nos protocolos de dose (10–80 UI), regimes de administração (única dose vs. semanas/meses), medidas de desfecho (diversos testes comportamentais e de imagem) e composição amostral (sexo, fase da doença, comorbilidade). Apenas uma minoria dos ensaios aplicou correções rigorosas para comparações múltiplas ou avaliou a durabilidade dos efeitos no seguimento a longo prazo.

4. Discussão

Nesta revisão, evidenciou-se que o sistema oxitocinérgico exerce múltiplas ações sobre circuitos neuronais e processos cognitivo-comportamentais envolvidos na esquizofrenia.

4.1 Evidência genética e predisposição individual

A variabilidade observada na eficácia da oxitocina intranasal em esquizofrenia reflete a complexa interação entre fatores genéticos, epigenéticos, neurobiológicos e imunológicos, indicando que qualquer abordagem terapêutica deve ser rigorosamente estratificada e multimodal.

Em primeiro lugar, há evidências farmacogenómicas de que polimorfismos em *OXT* modulam a resposta a antipsicóticos. Souza et al. (2010) mostraram que os single nucleotide polimorphism (SNP) rs2740210 e rs2740204 em *OXT* conferem maior probabilidade de remissão de sintomas negativos sob clozapina, sugerindo uma influência direta na farmacodinâmica dos neuromoduladores endógenos. (4) Por sua vez, variantes de *OXTR* (rs24298 e rs53576) explicam diferenças marcantes em "*empathic concern*" e na gravidade sintomática geral, nos pacientes que possuiam essas variantes, nomeadamente terem "empathetic concern" e sintomatologia geral segundo PANSS. Assim, reforça-se a hipótese de a oxitocina não ser apenas um transmissor passivo, mas, juntamente com o OXTR possam ser moduladores ativos da plasticidade sináptica e do comportamento social (14).

Os mecanismos epigenéticos emergem como um segundo nível de modulação: alterações na metilação de *OXTR*, possivelmente induzidas por fatores ambientais, parecem silenciar ou potenciar a expressão destes receptores, criando subgrupos de doentes hipersensíveis ou resistentes à oxitocina exógena . Embora estudos dirigidos à metilação em esquizofrenia ainda sejam escassos, dados de populações com outras patologias psiquiátricas indicam que a adversidade precoce altera permanentemente a resposta ao neuropeptídeo, o que explica a menor eficácia clínica observada em alguns indivíduos.

Num nível funcional, estudos de neuroimagem revelam que a oxitocina intranasal atua em escalas temporais e topológicas distintas: doses únicas (24–40 UI) normalizam a hiperatividade amigdalar a expressões ameaçadoras e melhoram a conectividade inibitória amígdala–córtex pré-frontal em minutos a horas (32), enquanto regimes prolongados (40–48 UI diárias, 3–8 semanas) promovem mudanças mais lentas na coesão dos circuitos frontolímbicos, traduzidas em reduções de sintomas negativos e ganhos em confiança interpessoal (3,27).

No domínio da cognição social, frequentemente debilitada na esquizofrenia, a neuromodulação oxitocinérgica revela impactos preferenciais: estudos cruzados indicam que doentes com défices severos em teoria da mente e reconhecimento afetivo

experimentam melhorias no RMET, TASIT ou no Brüne Task após dose única de OXT (28–30). A extensão destes ganhos a tarefas de integração sensorial, como a identificação olfativa, sublinha um papel potencial da oxitocina na sincronização de múltiplas modalidades sensoriais, podendo mitigar a fragmentação perceptiva típica da psicose (12,33).

Para além disto, estudos genético-observacionais reforçam a noção de que variantes de *OXTR* modulam tanto a resposta à oxitocina intranasal como a perceção social basal. Veras et al. identificaram que variantes raras de *OXTR* em doentes com esquizofrenia se associam a diferenças em cognição social e história de trauma infantil, salientando a necessidade de personalização terapêutica (34) Tais dados apontam para a relevância de definir perfis genéticos dos doentes de modo a otimizar as intervenções baseadas em oxitocina.

Assim, o uso racional da oxitocina em esquizofrenia deverá basear-se em perfis farmacogenómicos e epigenómicos individuais, integrando avaliação genética, marcadores inflamatórios, neuroimagem funcional e técnicas de formulação avançadas.

4.1.1 Afetação genética na apresentação da doença

A investigação genética da esquizofrenia tem destacado o papel central dos polimorfismos no gene do receptor de oxitocina na predisposição e modulação clínica da doença. Goh et al. (2024), analisando 560 indivíduos, identificaram sete SNPs no gene OXTR (rs2254298, rs237885, rs237887, rs237899, rs53576, rs9840864, rs13316193, rs7632287, rs1042778, e rs237895). Dentro desta população, os pacientes que possuiam estes SNPs também tinham um Additive Genetic Risk Score (AGRS) mais elevado, quando comparados com indivíduos saudáveis associando assim o aumento de AGRS com a presença de doença esquizofrénica.(35) A presença destes SNPs implicava assim um risco aumentado de 1.118 vezes de diagnóstico de esquizofrenia por cada unidade na escala de AGRS. (35) Para além disso, também identificaram uma relação entre trauma infantil, níveis de OXT e a pontuação da AGRS. Foi observado ainda que na presença de uma pontuação no AGRS alta, a ocorrencia de trauma infantil causa uma diminuiçao nos niveis de OXT, de acordo com o CTQ-SF, não havendo associação quando a pontuação de AGRS era baixa (35) Assim percebemos o impacto que a variação na apresentação genética da OXT e OXTR possui na própria existência da esquizofrenia e ainda como estas variações podem potenciar o efeito de causas ambientais, como o trauma infantil, nas alterações da função social.

Congruentemente, Haram et al. (2016) correlacionou o polimorfismo rs237902 à diminuição da ativação da amígdala durante o processamento emocional negativo e o

diagnóstico de perturbações do espetro da esquizofrenia (36)indicando uma base genética para deficiências cognitivas sociais na esquizofrenia e que a parte genética associada à OXT está intimamente relacionada com a esquizofrenia.

Teltsh et al. (2012) identificaram, numa grande população árabe-israelense, variantes no cluster OXT-AVP com impacto funcional direto sobre a expressão gênica, destacando mecanismos biológicos específicos associados ao risco genético para esquizofrenia. (22) Nomeadamente os SNPs rs4813626 , rs2740204 e AVP3011589 estavam associados à presença de uma perturbação do espetro da esquizofrenia. (22) Estes resultados reforçam o papel funcional dos neuropeptídeos associados à via da oxitocina e destacam o potencial de novas estratégias terapêuticas focadas na modulação da expressão génica.

Yang et al. (2017) demonstraram aumento significativo da expressão de mRNA de OXT e OXTR em pacientes com primeiro episódio de esquizofrenia em comparação a controlos saudáveis, tal como Liu et al. (2019). (37,38) Assim, podemos observar um padrão na apresentação inicial de esquizofrenia que pode ser estudado futuramente como possível marcador inicial de doença esquizofrénica.

Por outro lado, Lee et al. (2018), em análise de tecido cerebral pós-mortem, verificaram que o uso crônico de antipsicóticos, transtornos do humor e histórico de abuso de substâncias elevam a expressão de mRNA de OXTR enquanto Eghtedarian et al. (2022) mostraram, em células de pacientes de primeiro episódio, subexpressão de ITPR1 e superexpressão de FOS, genes associados à via da oxitocina, sendo a alteração de FOS particularmente importante devido seu papel imune e regulador de neuroplasticidade. Estas alterações sugerem ajustes compensatórios na sinalização intracelular. (39,40) e demonstram o papel fulcral da medicação e de mecanismos adaptativos na modulação da via da oxitocina em esquizofrenia.

4.1.2. Polimorfismos \ genética e sintomatologia em esquizofrenia

No que toca à sintomatologia na esquizofrenia, algumas variações genéticas foram associadas à sua presença e maior intensidade. Em particular, o estudo realizado por Teltsh et al. destacou o haplótipo específico (GGAAGGT), cuja frequência elevada estava correlacionada significativamente com sintomas negativos como isolamento social, embotamento afetivo e diminuição das habilidades sociais, destacando o papel funcional dessas variantes na modulação fenotípica da doença.(22)

Em paralelo, Montag et al. também identificaram associações significativas entre variantes do gene receptor de oxitocina, particularmente os polimorfismos rs53576 e rs237885, e a esquizofrenia. Pacientes com o alelo A no locus rs53576 apresentaram maior risco para desenvolver esquizofrenia, com diferenças na frequência alélica sendo

mais pronunciadas no grupo masculino. Além disso, o polimorfismo rs53576 correlacionou-se significativamente com as pontuações de psicopatologia geral na escala PANSS, enquanto o polimorfismo rs237902 foi associado especificamente a sintomas negativos(41). Esses resultados sugerem que diferentes polimorfismos no sistema oxitocinérgico têm influência clínica diferenciada em pacientes esquizofrênicos, refletindo uma complexa interação gene-fenótipo.

Por fim, estudos conduzidos por Haram et al. e Lv et al. exploraram detalhadamente o impacto funcional dos polimorfismos OXTR em aspectos específicos da esquizofrenia. Haram et al. reportaram que o polimorfismo rs53576 foi associado a um maior grau de retraimento emocional, enquanto outro estudo do mesmo grupo destacou o envolvimento do rs237902 na ativação reduzida da amígdala esquerda, um achado significativo, considerando o papel desta estrutura cerebral em processos emocionais e sociais frequentemente comprometidos na esquizofrenia (36,42). Complementando esta associação, Lv et al. revelaram que o polimorfismo rs2268490 influencia significativamente a resposta terapêutica a antipsicóticos, especialmente quanto à melhora dos sintomas negativos relacionados à apatia e abulia (43). Em conjunto, esses resultados reforçam a relevância dos polimorfismos oxitocinérgicos como alvos potenciais para intervenções personalizadas na esquizofrenia

Em Ortega, Miguel A et al. (2023), ao observar-se a expressão de OXT e do seu receptor OXTR em placentas de mulheres com primeiro episódio psicótico (FEP) versus controlos, utilizando RT-qPCR e imunohistoquímica, notou-se um aumento significativo dos níveis de mRNA e de proteína de OXT/OXTR em vilosidades placentárias e células deciduais. (44) Esses achados sugerem uma hiperatividade paracrina/endócrina placentária associada ao FEP, potencialmente contribuindo para stresse oxidativo, inflamação e alterações histopatológicas previamente descritas, com impacto negativo no bem-estar materno-fetal, sendo possiveis consequências do neurodesenvolvimento associadas a este impacto um tema importante para futuras investigações

4.1.3 Polimorfismos genéticos e sintomatologia

No que toca à sintomatologia Davis et al. genotiparam sete SNPs de OXTR em 74 pacientes esquizofrénicos submetidos a testes de cognição social (mentalização, percepção social e inteligência emocional). Nesse estudo, destacou-se o polimorfismo rs2268493 que se associou a pior desempenho no índice composto de cognição social, segundo as escalas The Awareness of Social Inference Test — Part III (TASIT) e Half-Profile of Nonverbal Sensitivity (PONS) (45)Montag et al., avaliaram outro aspeto da cognição social, a empatia via Interpersonal Reactivity Index (IRI), mostrando que portadores de um ou dois alelos A do rs2254298 apresentaram classificações mais altas

na escala geral de psicopatologia da PANNS e ainda um maior “empathetic concern” segundo a Interpersonal Reactivity Index (IRI). (23) Assim, percebemos o impacto que estes genes associados à oxitocina podem ter na capacidade de socialização dos indivíduos com esquizofrenia, tornando-se potenciais focos de estudo para uma melhor compreensão da causa específica destes défices nesta população.

Adicionando ao previamente referido, Giralt-López et al., demonstraram ainda que, em pessoas saudáveis, um valor alto no questionário sobre personalidade esquizotípica estava associado a uma baixa performance em processos de teoria da mente, quando a variante de OXTR com o SNP rs53576 era tida em conta, reforçando seu papel como endofenótipo de esquizofrenia . (46)

Nakata et al. descobriram ainda que o SNP rs53576, em pacientes com esquizofrenia resistente ao tratamento e em remissão, tem impacto na memória de trabalho e na pontuação da tarefa de inteligência emocional utilizada - a Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT). Especificamente, portadores do alelo minor G tinham piores resultados na avaliação de cognição e cognição social, comparativamente a não portadores desse alelo. (47) Assim, voltamos a perceber o impacto deste polimorfismo nos aspetos cognitivo-sociais da esquizofrenia, tornando-o bastante importante na caracterização desta doença e de subtipos da mesma.

Além dos SNPs comuns, Veras et al. identificaram cinco variantes raras de missense no gene do OXTR na sua população de 48 pessoas com esquizofrenia. Os portadores exibiram sintomas negativos e psicopatologia geral significativamente menos graves, porém maior déficit em cognição não-verbal, nomeadamente em tarefas de organização perceptual e velocidade de processamento mais baixa que os controlos. (34) Este estudo adiciona assim um possivel fenótipo da esquizofrenia, em que certas variações genéticas de OXTR podem estar associadas a apresentações clínicas específicas, tais como uma menor sintomatologia mas pior capacidade de cognição

Por fim, integrando genética e ambiente, Goh et al. relacionam a presença de alelos de risco em sete SNPs de OXTR (incluindo rs2254298, rs53576 e rs237899) com níveis plasmáticos de oxitocina mais baixos, e maiores scores de trauma infantil segundo o Childhood Trauma Questionnaire, e piores scores de funcionamento social segundo Social Functioning Scale (SFS). Curiosamente, ao realizarem um modelo multinível de previsão do efeito de trauma, oxitocina e AGRS explicaram conjuntamente 82,5% da variância de funcionamento social, com o trauma infantil tendo o maior peso.(35)

Em síntese, variantes genéticas de OXTR — de SNPs comuns a raras missense — influenciam sintomas negativos, dimensões afetivas da empatia, teoria da mente,

percepção social e funcionamento interpessoal na esquizofrenia, frequentemente mediadas por níveis reduzidos de oxitocina e moduladas por experiências de trauma infantil, ressaltando uma complexa interação gene-ambiente na etiopatogenia dos déficits sociais dessa doença.

4.1.4 Metilaçao Genética e sintomatologia

No que toca à metilação e sintomatologia em esquizofrenia, Rubin et al. mostraram que mulheres, saudáveis e com esquizofrenia, com maiores níveis de metilação no gene de OXTR em -934 tinham uma capacidade menor de reconhecimento de expressões faciais, tais como raiva, tristeza e felicidade.(48) Especificamente em mulheres com esquizofrenia, foi observada uma maior metilação quando comparado com homens com esquizofrenia, sendo a mesma associada a volumes diminuídos no hipocampo direito.(48) Esta associação pode justificar esta incapacidade de reconhecer emoções e demonstra uma diferença entre géneros na apresentação e caracterização da esquizofrenia.

Em contraste, Bang et al. encontraram hipometilação de 3 CpGs em OXTR1 e 8 em OXTR2 em indivíduos com risco elevado de desenvolver psicose (UHR) e esquizofrenia de início recente (ROS).(49) Adicionalmente também foi observada uma diferença entre géneros, sendo que as mulheres com ROS e UHR, com o mesmo grau de sintomatologia negativa e de metilação, possuíam uma associação inversa entre a metilação no CpG1 e as classificações em anedonia e insociabilidade. Também observaram que existia ainda uma relação positiva entre o aumento da conectividade funcional na rede estriato-amigdalar e o nível de metilação de CpG1 no OXTR1.(49)

Integrando esses achados, observa-se um padrão bidirecional em que hipometilação precoce predispõe ao isolamento social, concluindo que a hipermetilação tardia compromete o processamento emocional, sendo estes processos mais comuns no sexo feminino.

No domínio cognitivo, Grove et al. demonstraram que a metilação no CpG Chr3:8767638 estava associada a uma menor capacidade de cognição, afetando memória verbal, velocidade de processamento e função executiva na população estudada. (50). Piao et al. identificaram 2912 CpGs diferencialmente metilados associados a pacientes com psicose recente (ROP). Destes CpGs, identificaram nos pacientes uma associação positiva entre cg13562874 e história de trauma e uma associação negativa entre cg13810931 e cg18128437 com o score total na escala PANSS.(51) Estes resultados demonstram que a disfunção cognitiva na esquizofrenia tem uma base epigenética multifocal na via da

oxitocina, podendo estar associada desde à presença em si da doença, a sua gravidade clinica e cognitivo-social e ainda com fatores ambientais.

4.1.5 Sintomatologia e mrna

Relacionando alterações da expressão de mRNA com sintomatologia, Broniarczyk-Czarniak et al. avaliaram a expressão de mRNA de OXT, OXTR, AVP e AVPR1a, mostrando redução significativa de OXT mRNA em pacientes com diagnóstico realizado após 10 a 15 anos de doença (G1) (0,17 ± 0,03) e com diagnóstico realizado após 2 anos de doença (G2) (0,19 ± 0,03) versus controles (0,32 ± 0,04; $p<0,001$), ao passo que OXTR e AVP mRNA estavam elevados e AVPR1a reduzido em pacientes. Crucialmente, apenas os níveis de OXT (mRNA e proteína) em G2 correlacionaram-se positivamente com a gravidade dos sintomas depressivos avaliados pela CDSS ($q=0,42$; $p=0,011$; $q=0,37$; $p=0,028$) (52), evidenciando que a diminuição da expressão transcricional de OXT acompanha de modo específico a intensidade da sintomatologia depressiva na fase inicial da doença.

4.1.6 Genética e terapêutica

Em estudos post-mortem de indivíduos com esquizofrenia, Lee et al. não encontraram diferenças basais na expressão de mRNA de OXTR versus controles, mas observaram que o uso de antipsicóticos e de abuso de substâncias se associou a um aumento significativo dessa expressão, enquanto que os estabilizadores de humor exerceram o efeito oposto, reduzindo os níveis de OXTR mRNA, e ainda que (39) Esses achados sugerem que, embora a sinalização oxitocinérgica cortical não esteja intrinsecamente alterada na esquizofrenia crônica, ela é sensível ao perfil farmacológico, abrindo a possibilidade de modular a expressão de OXTR com agentes adjuvantes para reforçar a eficácia social e cognitiva dos antipsicóticos.

Lv et al., por sua vez, relacionaram polimorfismos em OXTR (por ex., rs237899, rs13316193, rs2268490) à gravidade sintomática—incluindo sintomas globais, hostilidade e ansiedade—e demonstraram que o alelo de rs2268490 previu melhora nos sintomas negativos após seis semanas de tratamento antipsicótico. (43) . Adicionalmente, Souza et al. observaram que a variante rs2740204 em OXT associou-se à resposta clínica a clozapina ($p = 0,042$), e que outros polimorfismos em OXTR apresentaram associações nominais com redução de sintomas positivos e negativos porém sem significância pós-correção. Estes dados reforçam a viabilidade de estratégias de medicina personalizada em esquizofrenia, nas quais o genótipo do sistema oxitocinérgico oriente a seleção e o ajuste de doses de antipsicóticos, potencialmente melhorando tanto a remissão sintomática quanto a recuperação funcional.

4.2 Biomarcadores periféricos de oxitocina

A caracterização do eixo oxitocinérgico em esquizofrenia através de marcadores periféricos tem revelado disfunções sustentadas que se relacionam com sintomas clínicos, género e até mecanismos de stress, sugerindo que medidas estáticas de oxitocina não capturam toda a sua dinâmica patobiológica.

Num dos primeiros estudos, Rubin et al. (2010) compararam 50 doentes crónicos com 58 controlos e encontraram concentrações plasmáticas de oxitocina significativamente mais baixas nos doentes, com correlações inversas moderadas a fortes com sintomas positivos ($r \approx -0{,}30$) e gerais ($r \approx -0{,}50$) do PANSS. (5)

Jobst et al. (2014) corroboraram estas diferenças, mostrando que tanto oxitocina como vasopressina estavam reduzidas em plaquetas de doentes masculinos, o que reforça a noção de um défice neuropeptídico crónico e sistémico na esquizofrenia (24).

Ao nível central, Sasayama et al. (2012) mediram oxitocina no líquor de 27 doentes masculinos e observaram uma correlação negativa significativa com os sintomas negativos do PANSS ($r = -0{,}38$; $p = 0{,}05$), indicando que a disfunção do eixo oxitocinérgico também se manifesta no compartimento cerebroespinhal (25).

A influência do género e do ciclo menstrual foi aprofundada por Rubin et al. (2011), que constataramque, apesar de não haver flutuações cíclicas de oxitocina, níveis mais elevados de OXT em mulheres se associaram a melhor perceção de felicidade em rostos e a menores sintomas negativos, enquanto em homens verificou-se associação com parâmetros de prosocialidade, evidenciando dimorfismo sexual na função neuropeptídica (53).

Strauss et al. (2015) exploraram o conceito de biomarcadores, demonstrando que níveis basais de oxitocina previam a precisão em tarefas de reconhecimento de pistas sociais (gaze bias, ToM bias) e a identificação olfativa em esquizofrenia, sugerindo que OXT periférica funciona como indicador de capacidade de processamento de estímulos sociais e sensoriais (12,54). Essa mesma equipa verificou que a correlação entre OXT e *performance* sensorial era mais robusta em subgrupos sem delírios, apontando para interação com fenótipos clínicos específicos. (54)

Walss-Bass et al. (2013) investigaram simultaneamente oxitocina e nove citocinas pró-inflamatórias, concluindo que doentes com delírios apresentavam correlações positivas entre OXT e enviesamento de teoria da mente, enquanto que doentes sem delírios apresentavam correlações negativas entre OXT e capacidade de *gaze*, sugerindo que a

correlação entre OXT e resposta inflamatória pode diferir conforme o subtipo psicótico (55).

Em primeiros episódio psicóticos ou primeiros surtos, Rubin et al. (2013) compararam 38 doentes não medicados com 38 controlos e encontraram níveis de OXT semelhantes, mas elevação de vasopressina correlacionada com sintomas positivos e défices de memória verbal só na população feminina com esquizofrenia, indicando que os desequilíbrios peptidérgicos podem surgir precocemente e serem modulados por género (56).

Finalmente, abordagens recentes como a de Rubin et al. (2014) mostraram que não só a oxitocina periférica, mas também a vasopressina, modulam seletivamente redes cerebrais envolvidas na empatia e perceção social, reforçando que medições conjuntas de ambos os peptídeos podem fornecer um perfil biomarcador mais completo (57).

Em conjunto, esses estudos salientam que a avaliação de oxitocina — tanto em plasma como em líquor — deve ser acompanhada de medições funcionais (comportamentais, sensoriais e neuroimagiológicas) e de marcadores inflamatórios, de forma a capturar a dinâmica e os efeitos moduladores do eixo oxitocinérgico em diversos subtipos de esquizofrenia.

4.2.1 Oxitocina e substâncias da sua via como biomarcadores de sintomatologia

Rubin et al. (2010, 2014) mostraram resultados contraditórios no que toca à associação entre níveis de OXT e sintomatologia. No estudo de 2010, Rubin et al. mostraram que níveis elevados de oxitocina estavam associados com pontuações mais baixas no PANSS. (5) Porém, em 2014, Rubin et al. identificaram o contrário, tendo observado uma correlação entre níveis elevados de OXT e sintomas positivos mais severos, algo para o qual não conseguiram encontrar uma causa definitiva. (57)

De forma complementar, a Rubin et al. (2010), também Strauss et al. (2015) observaram que níveis plasmáticos de OXT se correlacionavam negativamente com sintomatologia negativa. (54) Jobst et al. (2014), além de ter observado a mesma associação que Strauss et al. (2015), identificou ainda, em homens com esquizofrenia, níveis plasmáticos significativamente menores de oxitocina e de AVP em comparação a controlos, e que niveis reduzidos de OXT associam-se a aumento na pontuação da subescala de sintomas negativos da PANSS (24), confirmando que défices de oxitocina implicam um agravamento da sintomatologia negativa da esquizofrenia.

Rubin et al. (2013) destacaram que, em pacientes com esquizofrenia com primeiro episódio psicótico, a arginina-vasopressina (AVP) estava elevada. Especificamente em

pacientes do sexo feminino, correlacionaram também níveis elevados de AVP a um aumento da severidade de sintomas positivos na PANSS, sem evidência de alterações clínicas associadas aos níveis de oxitocina na população total. (56) Estes resultados sugerem que a vasopressina pode ter papel predominante nos estágios iniciais da psicose e que a oxitocina intervenha em fases mais tardias da doença.

Guzel et al. (2018) relataram que, na fase aguda da esquizofrenia, pacientes apresentaram oxitocina reduzida e AVP elevado. Essas alterações refletem piores pontuações na PANSS total e na Clinical Global Impression (CGI), indicando maior gravidade sintomatológica e pior prognóstico clínico.(58)

Hidalgo-Figueroa et al. (2022), ao investigar indivíduos com primeiro episódio psicótico, não encontrou nenhuma associação entre OXT e sintomatologia, mas correlacionou níveis elevados de prolactina, uma hormona que interage com oxitocina e tem efeitos no controlo de resposta ao stress,(59) com uma maior pontuação na escala de PANSS em homens, (60) reforçando o impacto que a disfunção da via oxitocinérgica tem na sintomatologia em estágios iniciais da doença.

Chen et al. (2024) e Yu et al. (2023) por sua vez investigaram a associação entre oxitocina, α-MSH, neurotensina, orexina-A e substância P e a sintomatologia em pacientes com esquizofrenia. Chen et al. (2024) observaram uma correlação negativa entre níveis de OXT e todas as escalas de PANSS exceto a que aborda sintomas positivos. (61) Yu et al. (2023), ao avaliarem a presença das substâncias supramencionadas em líquido cefalorraquidiano evidenciaram que níveis menores de oxitocina correlacionam-se a maiores scores positivos na PANSS e na BPRS e que maiores níveis de substância P estão associados a uma maior falta de enegria, segundo a BPRS (62), confirmando que múltiplas vias neuroendócrinas influenciam diretamente a expressão de sintomas.

Rodrigues et al. (2024) associaram sintomatologia não só com oxitocina, mas com outros parâmetros biológicos. Mostraram assim que níveis de oxitocina correlacionam-se negativamente com abulia, porém outras substâncias e células também tinham correlação com a sintomatologia. Valores de TSH elevados associaram-se a uma maior falta de angústia. A relação neutrófilos-linfócitos por sua vez correlaciona-se positivamente com anedonia, insociabilidade e abulia, enquanto a contagem de eritrócitos correlacionou-se negativamente com esses domínios e com um maior embotamento afetivo. Rodrigues et al. (2024) demonstraram ainda correlações positivas entre o volume corpuscular médio e abulia, e correlações negativas entre o número de linfócitos e gravidade de embotamento afetivo e alogia. Observou-se ainda uma associação negativa entre a amplitude de distribuição eritrocitária e insociabilidade.

Todas estas alterações representam o impacto que a esquizofrenia tem parâmetros não só hormonais, mas também hematológicos e imunes, e que ao ter em consideração estes parâmetros consegue-se uma caracterização mais aprofundada desta doença. (63)

Daimei Sasayama et al. (2012) avaliaram níveis de oxitocina no líquido cefalorraquidiano (LCR) em pacientes com esquizofrenia, medindo a severidade sintomática pela PANSS. Nos seus resultados, reportam uma correlação negativa significativa entre os níveis de OXT presentes no LCR e sintomas negativos da PANSS, apesar de não haver diferença entre os níveis de OXT no LCR entre pacientes e controlos saudáveis. (25) Estes resultados demonstram que na presença do diagnóstico de esquizofrenia, os níveis de oxitocina presentes no LCR são um indicador da severidade dos sintomas negativos experienciados pelos doentes com esta patologia.

Por último, Elena R. Popescu et al. (2021) investigaram 28 pacientes psicóticos não medicados e correlacionaram os níveis de cortisol e de oxitocina séricos a tipos de agressão avaliados pelo Overt–Covert Aggression Inventory e pelo Modified Overt Aggression Scale. Pacientes com maior agressividade discreta exibiam níveis de cortisol significativamente reduzidos e níveis de oxitocina elevados. Segundo o estudo, estes dois resultados combinados podiam prever e explicar a presença de uma elevada agressividade internalizada. A possibilidade de identificar este tipo de agressividade antes que esta se torne externalizada seria benéfico na diminuição do risco de violência e intervenção precoce. (64)

4.2.3 Oxitocina e substâncias da sua via e função social

A oxitocina e outras substâncias neuroendócrinas mostram-se promissoras como biomarcadores da função social na esquizofrenia, embora os seus efeitos variem com o sexo e o contexto experimental. Os estudos seguidamente discutidos exploram essas relações sob diversos ângulos, estabelecendo conexões robustas e nuances interessantes quanto à interação desses marcadores biológicos com o comportamento social.

Rubin et al. (2014) destacam que, embora os níveis de oxitocina não sejam significativamente diferentes entre indivíduos com transtornos psicóticos e controlos saudáveis, há uma clara dissociação entre níveis fisiológicos de OXT e sua eficácia moduladora sobre cognição social em pacientes, uma vez que apenas em indivíduos saudáveis existia uma associação entre níveis elevados de OXT e capacidade mais elevada de reconhecer emoções faciais. Esta dissociação sugere uma disrupção na capacidade da OXT de modular adequadamente processos sociais em indivíduos psicóticos. (57) Spilka et al. (2022) corroboram esta observação, relatando que níveis mais baixos de OXT plasmática estão associados a um reconhecimento emocional facial reduzido em

indivíduos com esquizofrenia, indicando que variações endógenas da OXT são preditoras de habilidades sociais básicas. (65)

Já Tas et al. (2018), ao investigarem a relação entre OXT, libertação de cortisol perante indução de stress em ambiente social e esquizofrenia, relataram ausência de associação direta entre níveis de OXT e cortisol. No entanto, observaram um aumento da capacidade de cognição social, particularmente no que toca a comunicação interpessoal e atividades recreativas, em pacientes que tinham aumento nos níveis de cortisol, demonstrando um potencial uso do cortisol como biomarcador de função social em esquizofrenia. (66)

Em relação ao género, Rubin et al. (2018) e Rubin et al. (2011) enfatizaram que efeitos da OXT são sexualmente dimórficos, com influências diferentes sobre a atividade cerebral regional e a perceção emocional em homens e mulheres com esquizofrenia. Especificamente, na perceção emocional, mulheres com níveis de OXT elevados mostraram terem uma perceção de caras como mais felizes, algo não observado na população masculina. (53) Relativamente à atividade cerebral regional, apesar de não ter sido observada correlação entre níveis de OXT e reconhecimento de emoções, o estudo imagiológico dos pacientes revelou que a região cerebral em que havia alterações na função cerebral e os défices cognitivo-sociais associados eram dependentes de género, demonstrando uma dicotomia da apresentação da esquizofrenia. (67)

Montag et al. (2020) acrescentaram uma dimensão importante, relatando que níveis elevados de OXT após estímulo emocional apresentam uma correlação inversa à empatia cognitiva, potencialmente refletindo uma hiper-reatividade maladaptativa do sistema da OXT em contextos sociais exigentes em pacientes com esquizofrenia. (68)

Além disso, Brown et al. (2014) mostraram que níveis mais elevados de OXT endógena relacionam-se com uma maior tendência para evitar emoções negativas como raiva, particularmente em pacientes com maiores níveis de paranoia, reforçando o papel protetor, embora paradoxal, deste neuropeptídeo frente a ameaças sociais percebidas. (69)

Strauss et al. (2015) complementeam esses resultados ao relacionar a OXT com a perceção de emoções expressas com o corpo, indicando que níveis elevados de OXT estão associados a melhor reconhecimento emocional, especialmente em mulheres. Este achado reforça os resultados de Rubin et al. (2011), sugerindo uma especificidade sexual importante na ação da OXT sobre habilidades sociais. (70)

Pek et al. (2019) destaca a relação entre níveis periféricos de OXT e AVP e ANP, e a sua modulação funcional no contexto da esquizofrenia, porque, embora os níveis gerais possam não ser distintamente alterados em comparação aos controles saudáveis, a

capacidade moduladora dessas substâncias sobre a cognição social e emocional está significativamente comprometida nestes pacientes. Este fenómeno é observado por a OXT, AVP e ANP não se associarem a nenhuma medida de função social em pacientes, exceto a associação positiva entre níveis de OXT e tempo de reconhecimento de expressões faciais. Por outro lado, os indivíduos saudáveis demonstraram mais associações entre as hormonas supramencionadas e os testes de cognição social. (71)

Strauss et al. (2015) sugerem que níveis plasmáticos elevados de OXT correlacionam-se positivamente com uma melhor identificação de social cues concretas em indivíduos com esquizofrenia, sugerindo uma facilitação no processamento imediato e objetivo das interações sociais por parte da OXT. (54) Em consonância, o estudo de Strauss et al. (2015) demonstra igualmente uma relação significativa entre menores níveis de oxitocina e deficiências na identificação olfativa, uma função sensorial básica com implicações em comportamentos sociais mais complexos, reforçando o papel amplo desta substância nas interações interpessoais e sociais. (72)

No entanto, a complexidade da relação entre oxitocina e função social torna-se mais evidente quando consideramos os trabalhos de Goh e Lu (2022) e Walss-Bass et al. (2013). Ambos destacam uma interação diferenciada da oxitocina com subdomínios específicos da cognição social, sugerindo que níveis plasmáticos deste peptídeo podem modular de formas distintas componentes afetivos e cognitivos da teoria da mente. (55,73)A pesquisa de Goh e Lu (2022) realça que a oxitocina possui uma associação particularmente forte com o componente afetivo da teoria da mente, (73)sublinhando o papel do neuropeptídeo na empatia e compreensão emocional dos estados internos dos outros. Em Walss-Bass et al. (2013) observa-se que a presença de delírios tem impacto na relação entre níveis de OXT e teoria da mente, implicando um efeito positivo da oxitocina no viés da teoria da mente mas negativo na capacidade dos doentes serem capazes de inferir crenças, intenções e estados mentais dos outros com base no seu comportamento. (55)

Adicionalmente, os resultados apresentados por Aydın et al. (2018) indicam que níveis reduzidos de oxitocina relacionam-se diretamente com défices metacognitivos na esquizofrenia (74)sugerindo que a oxitocina não influencia apenas processos perceptivos imediatos, mas também a capacidade mais integrativa e complexa de refletir sobre o self e os outros no contexto social. Corroborando estas observações, Balikci et al. (2018) salientam ainda a relevância dos níveis endógenos de oxitocina, associando-os positivamente à cognição social.(75)

A evidência reunida sublinha o forte potencial da oxitocina como biomarcador da disfunção social na esquizofrenia: os seus níveis plasmáticos traduzem-se em diferenças mensuráveis no reconhecimento emocional, na teoria da mente e na metacognição. Com protocolos standardizados de medição e a incorporação de variáveis (sexo, perfil sintomático, contexto), a oxitocina poderá tornar-se, num futuro próximo, num indicador fiável para rastreio clínico e monitorização do tratamento destas funções sociais..

4.2.4 Oxitocina e substâncias da sua via e cognição

A associação entre a OXT e outras substâncias neuropeptídicas, como a AVP e a neurotensina, com aspectos específicos da cognição e função executiva em indivíduos com esquizofrenia, é uma área promissora, embora complexa e ainda parcialmente incompreendida algo que iremos abordar nesta secção.

Rubin et al. (2018) indicam que baixos níveis periféricos de OXT estão relacionados com atividade cerebral reduzida no tálamo, levando a uma influência indireta sobre capacidades cognitivas como aprendizagem verbal e velocidade de processamento de informação. Quando tendo em conta o género do doente, Rubin et al. (2018) obtiveram resultados que demonstram défices cognitivos específicos associados a áreas cerebrais distintas. Indivíduos do sexo masculino com esquizofrenia apresentavam uma maior atividade cerebral no giro frontal medial direito associada a uma menor fluência verbal, e maior atividade cerebral no tálamo estava associada a uma capacidade diminuída de aprendizagem verbal e de velocidade de processamento de informação. (67)

Em contraste, as mulheres com esquizofrenia demonstraram uma associação entre uma elevada atividade cerebral nos córtices cerebelares e menor fluência semântica. (67) Adicionalmente, Rubin et al., (2013) revelou uma correlação negativa entre AVP e aprendizagem verbal em mulheres durante o primeiro episódio psicótico. (56)

No contexto das funções cognitivas executivas, Yu et al. (2023) salientam uma relação relevante entre neuropeptídeos reduzidos, incluindo a OXT, e uma pior performance cognitiva em pacientes com esquizofrenia. (62) Estes achados destacam o potencial destes neuropeptídeos enquanto marcadores biológicos promissores não apenas para diagnóstico, mas também para monitorização clínica.

No entanto, nem todos os estudos encontram relações diretas ou consistentes. Pek et al. (2019), observou que no grupo de doentes com esquizofrenia, apenas o ANP mostrou uma associação estatisticamente relevante negativa com a memória de longo prazo e positiva com o tempo de execução do TMT-B. Oxitocina e vasopressina não se

correlacionaram de modo significativo com as medidas de neurocognição ou função executiva avaliadas. Estas observações sublinham o uso do ANP como um biomarcador mais específico para certas áreas da neurocognição. (71)

É também notável que a associação entre OXT e cognição não é uniforme em todos os estudos, o que sugere uma modulação complexa, possivelmente influenciada por variáveis demográficas, metodológicas ou pela heterogeneidade clínica da esquizofrenia. Por exemplo, em Hidalgo-Figueroa et al. (2022), níveis plasmáticos mais baixos de oxitocina associaram-se a melhor desempenho executivo. No domínio da atenção, em mulheres, níveis de OXT diminuídos relacionaram-se com menor capacidade de atenção sustentada e, em homens, com maior capacidade de atenção sustentada. Adicionalmente, níveis elevados de prolactina correlacionaram-se com pior memória de trabalho, especificamente no sexo feminino, e com melhor tempo de reação à atenção no sexo masculino. (60)

Sun et al.(2024) revelam que os níveis de β-endorfinas (BE) e de neurotensina (NT) apresentaram correlações positivas com uma melhor pontuação nos domínios visuoespacial e construcional avaliados pelo RBANS, sugerindo um efeito sinérgico na modulação dopaminérgica de circuitos pré-frontais. Por outro lado, α-MSH correlacionou-se negativamente com o domínio da linguagem, apontando para potenciais efeitos diferenciados dos peptídeos investigados na função executiva.(76)

Rubin et al. (2015) demonstraram que as diferenças sexuais na cognição, em que notou-se que mulheres com esquizofrenia tinham melhores pontuações em tarefas verbais, enquanto que os doentes do sexo masculino tiveram mais sucesso em tarefas visuoespaciais, permanecem intactas em pacientes com esquizofrenia, mesmo diante das alterações de estradiol e progesterona associadas ao ciclo menstrual. A ausência de modulação cognitiva pela fase folicular ou lútea sugere que esses vieses refletem organização neurobiológica precoce. Além disso, a correlação positiva entre oxitocina endógena e desempenho verbal em mulheres com esquizofrenia destaca seu potencial como alvo terapêutico cognitivo. (77)

Concluindo, cada peptídeo relatado aparenta apresentar um perfil de biomarcador específico. OXT para reconhecimento emocional e metacognição, AVP e ANP para memória e aprendizagem verbal, cortisol para plasticidade social sob stress, neurotensina e βendorfinas em cognição visuoespacial e prolactina em memória de trabalho e atenção. A combinação desses marcadores, aliados a protocolos padronizados, poderá fornecer um painel biomolecular robusto para avaliação clínica na esquizofrenia.

4.2.5 Biomarcadores e outras associações

Em Wehring et al. (2018), ao investigar a associação entre OXT e comportamentos sexuais em indivíduos com esquizofrenia, não se observou associações em homens, mas nas mulheres níveis mais altos de oxitocina correlacionaram-se positivamente com maior disfunção sexual total e nos domínios de desejo, excitação, lubrificação/ereção e orgasmo ($rs=0,63–0,75$; $p\leq0,04$). Estes resultados reforçam a noção de impactos específicos e distintos da oxitocina periférica nos dois sexos, possivelmente ligado a mecanismos compensatórios ou a influências hormonais e terapêuticas.(78)

Aydın et al. (2019) por sua vez analisaram indivíduos com esquizofrenia, os seus irmãos e indivíduos saudáveis, os seus estilos de vínculo afetivo utilizando o ECR-R, perceção de atitudes parentais utilizando o s-EMBU e OXT plasmática. Nos pacientes, níveis reduzidos de OXT correlacionaram-se positivamente com maior ansiedade e evasão de vínculo (ECRR) e com perceções elevadas de rejeição parental. Em suma, estes achados sugerem que poderá existir uma relação de causalidade ou potenciação entre os níveis oxitocinérgicos e a sintomatologia ou capacidade de vinculação dos doentes, nomeadamente perceções de rejeição parental. (79)

4.3 Modulação de sintomas psicóticos e cognitivos

Vários estudos têm investigado como o sistema oxitocinérgico pode modular sintomas psicóticos, positivos e negativos, e défices cognitivos em esquizofrenia. Em ensaios clínicos controlados, a administração intranasal de oxitocina demonstrou atenuar sintomas positivos em alguns relatos iniciais: Feifel et al.(2010) observaram redução significativa nas pontuações de PANSS quando oxitocina foi adicionada ao tratamento habitual. (3) Além disso, há evidências de melhoria em domínios cognitivos específicos; por exemplo, Feifel et al. (2012) relataram que doses únicas de oxitocina melhoraram a memória verbal em doentes com esquizofrenia(8).

No que toca a efeitos associados à cognição, Porffy et al. (2020) demonstraram que uma dose única de 40 UIs de OXT aumentou o número de fixações, a dispersão do olhar e a amplitude de sacadas, e reduziu a duração média das fixações em tarefa de rastreamento ocular com faces e imagens-controlo, sugerindo modulação aguda de atenção social, ainda que sem especificidade para emoções faciais e requerendo investigação sobre a duração e relevância comportamental desses efeitos.(80)

Lee et al. (2016) não observaram elevação periférica de oxitocina nem correlações com scores de BPRS/SANS após 3 semanas de 40 UI diárias, atribuindo os resultados à baixa potência estatística, limitações de sensibilidade dos ensaios e variabilidade de adesão, e recomendaram amostras maiores e métodos analíticos mais precisos. (81)

İmamoğlu et al. (2024) submeteram 67 participantes a 12 semanas de 48 UIs diárias, e, apesar de melhora global no RBANS, não encontraram efeitos específicos de oxitocina em memória imediata, atenção, memória tardia ou linguagem, apenas estabilização visuoespacial frente ao declínio do placebo, algo que atribuíram à ausência de correlação entre o tempo de toma de OXT e o tempo em que os instrumentos de medição foram utilizados.(82)

Notamos assim uma falta de uniformidade nos resultados. Alguns ensaios encontraram apenas efeitos modestos ou nulos. Rubin et al. correlacionaram níveis periféricos de oxitocina à severidade de sintomas, sugerindo relação inversa (mais oxitocina, menos sintomas), mas estudos de intervenção controlada nem sempre confirmaram melhorias clínicas robustas (5). Goldman et al. (por ex., uso de diferentes doses de oxitocina) e Woolley et al. (2014) não observaram ganhos estatisticamente significativos em sintomas psicóticos ou cognitivos gerais, embora este último tenha notado melhora em estratégias controladas de cognição social (9,31).

Parece também haver uma segurança associada a administração de oxitocina, uma vez que em estudos de uso prolongado, Busnelli et al. (2016) relataram ausência de alterações em oxitocina e vasopressina plasmáticas, osmolaridade, sódio, pressão arterial e IMC após 4 meses de 40 UI diárias, demonstrando que esta hormona não afeta outros parâmetros da nossa biologia (26)

Alguns ensaios clínicos de curta duração suportam o potencial sintomático da oxitocina (ex. redução de sintomas positivos e melhoria de memória), mas resultados inconsistentes e amostras pequenas limitam conclusões firmes. A heterogeneidade entre estudos (uso de diferentes scores de sintomas, subgrupos de doentes, regimes de dose) dificulta sínteses diretas.

4.4 Cognição social, percepção afetiva e integração sensorial

No que toca à parte de cognição social e modulação da mesma, a OXT demonstra um efeito mais promissor e consistente. Nomeadamente, Hennig-Fast et al. (2023) e Korann et al. (2022) que investigaram, respectivamente, os efeitos de níveis endógenos e da administração intranasal de oxitocina na esquizofrenia, focando-se no seu efeito na

modulação de redes fronto-parieto-estriatais ligadas à regulação emocional, motivação e função executiva.

Em Hennig-Fast et al., 20 pacientes esquizofrénicos masculinos e 20 controles realizaram tarefa de fMRI com imagens a demonstrar vínculo. Os pacientes apresentaram níveis plasmáticos de oxitocina reduzidos, maior vínculo inseguro e hiperativações em várias zonas do cérebro, como o pré-cuneo, ínsula, junção temporo-parietal (JTP) e córtex pré-frontal medial (c-PFm), e uma associação positiva entre níveis de OXT e ativação do pré-cuneo e da JTP bilateralmente, sugerindo um processamento compensatório diante de estímulos afetivos e um efeito regulador e até amenizador de défices por parte da OXT nas vias cerebrais.(83) Korann et al. aplicaram 24 UI intranasais de oxitocina ou placebo em 31 pacientes e 21 controles antes de realizarem uma ressonância magnética funcional em repouso. No estado basal, observaram conectividade efetiva reduzida do núcleo caudado esquerdo para SMA e áreas pré-frontais, déficit este revertido pela oxitocina, que restaurou essas conexões e correlacionou-se com melhor insight cognitivo e menor sintomatologia negativa. Assim, administração de OXT mostrou-se benéfica ao restaurar a conectividade fronto-estriatal e ao associar-se a melhora no insight cognitivo e redução de sintomas negativos.(84) Esses achados confirmam seu potencial terapêutico imediato, embora a magnitude da resposta varie entre os indivíduos.

Shin et al. (2015) e Wynn et al. (2019) convergem ao demonstrar a importância da dose para efeitos neurais: enquanto Shin mostrou que 40 IU normalizam a reatividade amigdalar a emoções negativas e positivas(85), Wynn identificou que 36–48 IU otimizam a supressão do ritmo mu, sugerindo que essa faixa de dose é a mais eficaz a afetar o processamento de estímulos sociais. Juntos, esses achados indicam uma janela terapêutica comum para modular circuitos subcorticais e cortical-somatomotores envolvidos em percepção social.(86)

Os resultados de Woolley et al. (2017) sobre o efeito inexistente da oxitocina na classificação da fiabilidade de outros complementam Chuang et al. (2020), que não encontraram mudanças no reconhecimento de prosódia auditiva.(87,88) Apesar disso, Woolley et al. demonstraram que a oxitocina aumenta a frequência total de expressões nos pacientes com SCZ, com um impacto especifico nas expressões negativas, estando estes aumentos negativamente correlacionados com sintomatologia geral e positiva. Ressalta-se assim que a administração de oxitocina pode só afetar certos aspetos da cognição social, tais como a expressão social, e que estes efeitos são condicionados por

vários fatores como sintomatologia e medicação, enquanto outros aspetos da cognição social podem não estar associados a esta hormona. (87,88)
Andari et al. (2021) e De Coster et al. (2019) ilustram que administração oxitocinérgica em contextos interativos e tarefas de mentalização revelam benefícios mais robustos: Andari encontrou melhoria no reconhecimento de emoções em pacientes com esquizofrenia, enquanto De Coster mostrou uma melhoria na precisão de SCZ após OXT em aspetos como crença, pensamento e emoção, estando esta melhoria associada a um maior ativação neuronal na junção temporoparietal e o córtex prefrontal medio comparativamente a quando os indivíduos tomaram placebo.(89,90) A convergência desses dados sugere que a oxitocina potencializa inferências sociais de alto nível quando o cenário envolve interações ativas ou demandas de mentalização,melhorando assim a teoria da mente nos indivíduos esquizofrenicos.

Em contraste, Lee et al. (2019) não observaram qualquer efeito em teoria da mente, reconhecimento de emoções e estilos atributivos após 40 IUs por dia por três semanas, tal como Dwyer et al. (2020) não viram mudança em indicadores de afiliação social com 48 IUs por dia por seis semanas.(91,92). Tal ausência de alteração pode dever-se aos métodos utilizados, nomeadamente a possibilidade dos mesmos não serem os mais adequados para testar o impacto especifico da oxitocina em certas áreas da cognição social.Também Halverson et al. (2019), com um regime prolongado de 48 IUs por dia por doze semanas, encontrou apenas uma melhoria na capacidade de tomar prespetivas.(93) Observamos assim que a administração intranasal de oxitocina atua preferencialmente em circuitos neurais de alto nível e comportamentos sociais interativos, especialmente dentro de uma faixa de dose de 36–48 IU. Efeitos em domínios de baixo nível ou medidas de proximidade social parecem depender de contextos mais envolventes, doses mais altas/cronogramas prolongados ou complementação com treinamentos psicossociais.
Continuando, Mouchlianitis et al. (2022) observaram aumento de atividade no córtex parietal lateral direito durante a fase de investimentos , em um jogo de recompensação com múltiplas rondas, e maior sinalização do caudado ventral e ínsula, com redução da reatividade amigdalar em reembolsos humanos, (94) indicando recrutamento de circuitos antecipatórios e de monitoramento atencional mais proeminente com a administração de oxitocina.

Em 20 pacientes, Wigton et al. (2021) mostraram que 40 IUs de OXT aboliram o viés de seleção de felicidade e evitação de raiva em decisões com faces emocionais, sem afetar estímulos neutros. Neuralmente, OXT suprimiu atividade na junção temporo-parietal,

córtex cingulado posterior, precuneus, ínsula e amígdala,(95) sugerindo atenuação de circuitos avaliativos e recalibração da atribuição de saliência social.Esses resultados indicam que a OXT atua preferencialmente em vias cerebrais de atenção e antecipação (córtex parietal lateral e estriado ventral), circuitos de saliência e emoção (ínsula e amígdala) e redes associativas de mentalização (TPJ e PCC/precuneus), promovendo um reequilíbrio entre processos antecipatórios e avaliativos.

Em 2019, Strauss et al. investigaram o impacto de 72 IUs de oxitocina intranasal antes de sessões de *cognitive behavioural social skills training* (CBSST) em que também se avaliou a cognição social em indivíduos esquizofrénicos. Os resultados demonstraram primeiramente, que não houve melhoria na cognição social com o tratamento conjunto de psicoterapia e oxitocina, mas também um aumento no tempo de permanência do olhar em caras felizes ao longo do estudo e do tratamento. (96) Assim, a associação entre psicoterapia e oxitocina, apesar de parecer um bom próximo passo a tomar na melhoria da cognição social, ainda precisa de ser aperfeiçoada para se perceber em que áreas especificas esta hormona pode ajudar. Browne et al., por sua vez, tentaram perceber o impacto de 24 semanas sob CBBST e 72 IUs de oxitocina diária em vários aspetos da vida da população estudada, como atividades humor e relações interpessoais. De facto, indivíduos que tomaram esquizofrenia reportaram maior atividade física, afeto positivo mais elevado, tal como confiança e gentileza nas interações que tinham, sugerindo um impacto positivo da oxitocina adjuvante a CBBST na melhoria da capacidade do individuo esquizofrénico conseguir estar presente em contexto social com um maior conforto (97)

Na esquizofrenia, a oxitocina tem-se revelado um modulador promissor de vários domínios da cognição social, da perceção afetiva e da integração sensorial. Os primeiros ensaios centraram-se no reconhecimento de emoções faciais, mostrando que a administração intranasal de oxitocina pode melhorar a discriminação de expressões emocionais específicas.

Fischer-Shofty et al. demonstraram que, em doentes com esquizofrenia, um único spray intranasal de 24 IU de oxitocina aumentou significativamente a precisão no reconhecimento de expressões de medo, sem alterar outros tipos de emoção. (11) Num estudo subsequente, os mesmos autores verificaram que essa dose melhorava também o desempenho na identificação de relações sociais — parentesco e intimidade — em tarefas de perceção social, sugerindo que a oxitocina potencia a capacidade de inferir estados mentais alheios (30,98).

Paralelamente, Woolley et al. mostraram que 40 IU de oxitocina, administrados em regime duplo-cego cruzado, aumentaram de forma robusta a performance em tarefas de cognição social controlada, como o *The Awareness of Social Inference Test* (TASIT), que avalia inferências mentais mais deliberadas (31). Guastella et al. confirmaram estes achados, evidenciando que uma dose única de 24 IU de oxitocina melhora o desempenho em testes de teoria da mente de nível superior, incluindo a detecção de *faux pas* e a leitura de intenções nos olhos (29). Contudo, Davis et al. não observaram alteração significativa na acuidade global de reconhecimento emocional após 40 IU, embora tenha havido tendências para melhoria em subtarefas de sarcasmo, o que sublinha a variabilidade de resposta ao peptídeo (99).

A heterogeneidade dos efeitos parece refletir a dependência do contexto social e de fatores individuais. Bradley et al. aplicaram métodos computacionais para quantificar o viés afetivo e reportaram que a oxitocina atenua vieses negativos no reconhecimento facial, mas apenas em situações com reforço social positivo (100). Este grupo descobriu ainda que a oxitocina aumenta o tempo de fixação no olhar, índice de atenção social, em doentes com estilos de vinculação mais seguros e sintomatologia negativa moderada (101). Em tarefas de competição social, os estudos de Bradley et al. mostraram que a oxitocina eleva a disposição para participar em comportamentos dispendiosos quando existe recompensa social, sugerindo um reforço da motivação social (102). Por sua vez, as mulheres com esquizofrenia não beneficiaram de melhoria significativa em mentalização após oxitocina, evidenciando possíveis diferenças sexuais na eficácia do tratamento (103).

Para além das tarefas comportamentais, a oxitocina influencia padrões de ativação neural associados ao processamento social. Estudos de neuroimagem revelam que a administração intranasal de oxitocina pode atenuar a hiperreatividade da amígdala a expressões negativas e reforçar a conectividade com o córtex pré-frontal medial, embora muitas destas alterações careçam de significância estatística robusta (32). Singh et al., por EEG, observaram que 24 IU de oxitocina aumentam a supressão mu em resposta a movimento biológico, sugerindo melhor integração de pistas visuais de ação social (104). Complementarmente, Strauss et al. associaram níveis endógenos de oxitocina à capacidade de reconhecer emoção em expressões corporais dinâmicas, reforçando o papel do peptídeo na integração sensório-emocional. (70)

Em intervenções mais prolongadas e em combinação com treino cognitivo social, a oxitocina tem mostrado benefícios adicionais. Pedersen et al. administraram 48 IU diários durante duas semanas e relataram melhorias significativas em teoria da mente e perceção social, concomitantes à redução de sintomas psicóticos (28). Gibson et al.

realizaram um ensaio piloto de seis semanas combinando oxitocina (24 IU duas vezes ao dia) com treino de competências sociais, encontrando ganhos em expressividade facial e empatia autorrelatada (105). Davis et al. demonstraram que 40 IU de oxitocina antes de sessões de treino grupal de cognição social potenciam a aprendizagem em tarefas de reconhecimento facial, inferência de estados mentais e inteligência emocional, com efeitos mantidos até um mês após o fim do programa (106). Cacciotti-Saija et al. verificaram que jovens com psicose precoce beneficiam de 24 IU duas vezes ao dia durante seis semanas em tarefas de teoria da mente e funções sociais, com efeitos persistentes aos três meses (107).

Outros ensaios exploraram populações específicas e resultados complementares. Jarskog et al. prolongaram o tratamento para 12 semanas (24 IU duas vezes ao dia), documentando melhorias consistentes em tarefas de cognição social como o *Emotion Recognition-40* (ER-40), *Reading the Mind in the Eyes test* (RMET) e *Ambiguous Intentions Hostility Questionnaire* (AIHQ), bem como ganhos em níveis de funcionamento social (108). Buchanan et al. compararam oxitocina com galantamina, ambos isoladamente e em combinação, tendo observado que 24 IU de oxitocina duas vezes ao dia durante seis semanas reduzem sintomas negativos e melhoram capacidades cognitivas mensuradas pela MATRICS (109). Abu-Akel et al. demonstraram que 24 IU de oxitocina aumentam respostas empáticas ao sofrimento de membros de *out-groups* conflituais em doentes com esquizofrenia, sugerindo ação sobre mecanismos de empatia intergrupal (110). Por outro lado, Horta de Macedo et al. não encontraram efeitos em tarefas de *matching emocional*, indicando limites no alcance da intervenção (111). Caravaggio et al. reforçaram este ceticismo ao mostrar ausência de impacto sobre o "*jumping to conclusions*", embora tenham notado interações com volume caudado e funcionamento social basal (112).

Em amostras de doentes crónicos em regime aberto, Ota et al. descreveram benefícios modestos em funções sociais e cognitiva após 12 IU duas vezes ao dia, sem relato de eventuais efeitos adversos significativos (113) Fulford et al. demonstraram que 40 IU de oxitocina aumentam o vigor em tarefas incentivadas socialmente, confirmando a sua ação motivacional em contextos pragmáticos de reforço (114).

Warren et al. (2018), por sua vez, avaliaram o impacto de 24 UI de oxitocina intranasal na sinalização de saciedade em 16 indivíduos com esquizofrenia. Embora os efeitos da terapêutica sobre o consumo alimentar e o autorrelato de saciedade não tenham sido estatisticamente significativos, observaram-se reduções significativas dos níveis de leptina após administração única de 24 UI de oxitocina intranasal, em comparação com o placebo. A constatação destas alterações leptínicas sem modificações na glicémia,

insulina ou na sensibilidade gustativa e olfativa sugere que a oxitocina poderá regular aspetos metabólicos independentes da ingestão imediata, apontando para investigações com doses e regimes mais intensivos.(115)

A literatura demonstra que a oxitocina intranasal pode melhorar de forma específica e dependente de contexto diversos domínios da cognição social e da integração sensorial na esquizofrenia. Os benefícios mais consistentes ocorrem em tarefas de reconhecimento de medo, teoria da mente e motivação social, mas a heterogeneidade de respostas — influenciada por sexo, genética, sintomatologia e tipo de tarefa — impõe cautela e aponta para a necessidade de abordagens personalizadas e de estudos de larga escala, idealmente com critérios genéticos e psicossociais pré-definidos.

4.5 Abordagens integrativas e não farmacológicas

Além das intervenções farmacológicas, abordagens não medicamentosas têm vindo a ganhar relevo na melhoria dos sintomas negativos, da cognição social e do funcionamento global em indivíduos com esquizofrenia. Estas intervenções são frequentemente integradas como complementos ao tratamento habitual com antipsicóticos, visando potenciar melhorias clínicas através de mecanismos neurobiológicos e psicossociais complementares.

Diversas terapias corpo-mente, nomeadamente o yoga, têm demonstrado potencial clínico significativo. Jayaram et al. realizaram um estudo no qual a prática regular de yoga terapêutico resultou em melhorias objetivas no reconhecimento de emoções faciais, redução de sintomas negativos, e aumento dos níveis plasmáticos de oxitocina endógena em doentes com esquizofrenia estabilizada (13). De forma semelhante, a meditação baseada em mindfulness (MBGT, mindfulness-based group therapy) surge como intervenção promissora, com Zierhut et al. a demonstrarem que esta abordagem, quando combinada com oxitocina intranasal, melhora não apenas a empatia autorreportada, como também reduz sintomas negativos em pacientes com perturbações do espectro esquizofrénico (116). Böge et al. reforçaram ainda esta noção, mostrando que programas de mindfulness se associam a aumentos mensuráveis nos níveis periféricos de oxitocina, correlacionando-se positivamente com ganhos em medidas neurocognitivas e sociais (117).

A combinação estruturada de terapias psicossociais com administração intranasal de oxitocina também tem vindo a ser amplamente investigada. Saporta-Wiesel et al., num ensaio randomizado, concluíram que a associação de oxitocina com treino estruturado de competências sociais resultou numa maior eficácia comparativamente à administração isolada de placebo ou oxitocina, evidenciando sinergias benéficas entre

intervenções farmacológicas e comportamentais (118). Buchanan et al., num estudo semelhante, reportaram melhorias sustentadas nas capacidades sociais e redução dos sintomas negativos em indivíduos tratados simultaneamente com oxitocina intranasal e treino cognitivo-comportamental especializado, sugerindo que esta combinação poderá maximizar ganhos terapêuticos (119).

Além das intervenções estruturadas acima descritas, outros autores exploraram ainda abordagens menos convencionais. Fulford et al. testaram intervenções que associam a administração de oxitocina à terapia ocupacional focada em recompensas sociais, reportando melhorias na motivação social e redução de sintomas negativos secundários, indicando que a estimulação social positiva pode ser um elemento crítico na reabilitação psicossocial (114).

Em contraste, programas clássicos de remediação cognitiva, treino vocacional e grupos de apoio, apesar de amplamente recomendados em guidelines clínicas, permanecem pouco explorados diretamente em associação com intervenções farmacológicas como a oxitocina, representando uma lacuna na literatura atual que necessita de maior investigação futura.

4.6 Heterogeneidade metodológica e limitações

Apesar dos resultados encorajadores, a literatura sobre o uso de oxitocina e intervenções integrativas na esquizofrenia revela considerável heterogeneidade metodológica, impondo cautela à interpretação dos achados.

A diversidade metodológica manifesta-se em vários níveis: desenho dos estudos (cruzado versus paralelo), dose e duração da intervenção (dose única versus administração prolongada), seleção de participantes (estabilizados versus agudos), e coexistência de medicação concomitante.

Por exemplo, enquanto alguns ensaios usaram administrações únicas de oxitocina (29,99), outros envolveram regimes de longa duração com dosagens repetidas (27).

Adicionalmente, o tamanho amostral limitado constitui uma limitação persistente, com a maioria dos estudos envolvendo menos de 30 participantes por braço, comprometendo o poder estatístico (12,31). Muitos ensaios também carecem de seguimento de longo prazo, impedindo conclusões sobre a estabilidade dos efeitos clínicos (105,120).

Outra importante fonte de heterogeneidade reside na variabilidade das medidas de desfecho utilizadas. Alguns estudos priorizaram instrumentos padronizados como PANSS, BPRS ou SANS, enquanto outros empregaram testes neuropsicológicos específicos ou métodos neurofisiológicos (eye-tracking, EEG, fMRI), o que dificulta a

comparação entre resultados. A variabilidade no contexto experimental (ambiente laboratorial versus socialmente ecológico) constitui igualmente uma preocupação importante. Bradley et al. destacaram que diferenças subtis no contexto social durante a testagem podem influenciar a resposta à oxitocina, sugerindo que efeitos contextuais e expectativas dos participantes são determinantes não negligenciáveis dos resultados (100,102).

Face a estas limitações, estudos futuros devem adotar protocolos padronizados, com amostras maiores, abordagens multicêntricas, seguimento a longo prazo e instrumentos padronizados e validados, permitindo uma comparação robusta e uma meta-análise precisa dos resultados.

4.7 Implicações para a prática clínica

Os achados disponíveis atualmente fornecem implicações clínicas cautelosas, mas relevantes. Apesar do interesse crescente na oxitocina intranasal como potencial adjuvante no tratamento da esquizofrenia, os dados atuais são insuficientes para sustentar recomendações para a sua implementação clínica imediata fora de contextos de investigação controlados. As melhorias modestas e inconsistentes, aliadas à heterogeneidade metodológica, desaconselham, por ora, o seu uso clínico rotineiro, especialmente sem critérios rigorosos de seleção de doentes.

Contudo, abordagens não farmacológicas estruturadas, como programas de mindfulness, yoga terapêutico e treino de competências sociais, evidenciam resultados consistentemente positivos, sobretudo em sintomas negativos, cognição social e qualidade de vida geral, sugerindo que podem desempenhar um papel complementar robusto à medicação antipsicótica padrão (13,117,118).

No contexto clínico atual, portanto, é recomendável encorajar intervenções psicossociais bem validadas e estruturadas como complemento essencial à terapêutica farmacológica tradicional. As práticas baseadas em mindfulness e técnicas corporais como yoga ganham especial relevância, dada a robustez crescente dos resultados empíricos favoráveis.

Quanto à investigação com oxitocina, permanece promissora mas claramente experimental, exigindo maior estratificação clínica e genética dos participantes. Futuros protocolos de tratamento deverão ser personalizados, baseados em perfis farmacogenómicos e neurocognitivos, bem como na identificação de subgrupos específicos que possam beneficiar particularmente de uma intervenção combinada. Neste cenário, os avanços metodológicos permitirão, eventualmente, um uso clínico mais direcionado, racional e seguro da oxitocina intranasal.

5.Conclusão

A presente revisão sistemática confirmou e destacou a relevância fundamental do sistema oxitocinérgico na modulação de processos sociais e emocionais frequentemente comprometidos em indivíduos com perturbações psicóticas, particularmente na esquizofrenia. O principal objetivo do estudo foi avaliar a influência da oxitocina sobre o funcionamento neurocognitivo e social em pacientes com esquizofrenia, centrando-se na plasticidade sináptica e na conectividade das redes frontolímbicas.

Entre os achados genéticos mais comuns e importantes, destacam-se as associações consistentes entre polimorfismos nos genes da oxitocina (OXT) e do receptor de oxitocina (OXTR) com a suscetibilidade à esquizofrenia e à gravidade clínica. Polimorfismos como rs2254298 e rs53576 no gene OXTR revelaram ligações robustas à sintomatologia negativa e geral, assim como ao desempenho em tarefas de cognição social e emocional. Particularmente notáveis foram os estudos que demonstraram a influência dos fatores genéticos no desenvolvimento e na expressão fenotípica da doença, incluindo interações gene-ambiente, como a influência de traumas precoces que afetam significativamente os níveis de oxitocina e a severidade dos sintomas sociais.

A análise dos biomarcadores periféricos revelou consistentemente que níveis reduzidos de oxitocina plasmática são observados em indivíduos com esquizofrenia, correlacionando-se inversamente com a intensidade dos sintomas negativos e positivos. Estes níveis mais baixos de oxitocina também foram ligados a uma menor capacidade de reconhecimento emocional e a dificuldades na integração sensorial, como identificado nos testes olfativos e de reconhecimento facial. A oxitocina, portanto, parece representar um biomarcador promissor para monitorizar a gravidade clínica e os efeitos terapêuticos na esquizofrenia.

Relativamente ao efeito exógeno da oxitocina, numerosos ensaios clínicos controlados evidenciaram benefícios na administração intranasal deste neuropeptídeo. Melhorias significativas foram reportadas na cognição social, com particular destaque para a teoria da mente, reconhecimento de emoções, interpretação de social cues e aumento da saliência social. Estes efeitos foram frequentemente acompanhados por uma normalização parcial da conectividade frontolímbica alterada, sobretudo entre a amígdala e o córtex pré-frontal medial. Uma janela terapêutica entre 36 e 48 unidades internacionais (UI) diárias foi identificada como particularmente eficaz para esses domínios. Contudo, os resultados variaram amplamente entre os estudos, refletindo uma significativa heterogeneidade metodológica quanto à dose, duração e técnicas de avaliação utilizadas.

Apesar destas descobertas promissoras, diversas limitações foram identificadas. A heterogeneidade metodológica significativa, a ausência frequente de ajustes rigorosos para comparações múltiplas e a falta de uniformidade na caracterização clínica das amostras limitam a comparabilidade dos resultados. Além disso, poucos estudos exploraram profundamente os efeitos a longo prazo da administração de oxitocina, sugerindo que o impacto sustentado desta intervenção permanece subexplorado.

Achados mais particulares também emergiram nesta revisão, como o potencial da oxitocina em melhorar aspectos específicos da integração sensorial, nomeadamente através da modulação olfativa e visual, assim como o papel das abordagens não farmacológicas complementares, como programas de yoga terapêutico, na elevação dos níveis endógenos de oxitocina e consequente melhoria no desempenho social e emocional.

Diante destas limitações e dos achados particulares identificados, propõe-se uma série de recomendações para futuras investigações. É essencial que estudos subsequentes implementem protocolos padronizados para administração e medição da oxitocina, incluindo medidas rigorosas e consistentes de efeitos farmacocinéticos e farmacodinâmicos. Além disso, deve ser dada atenção à estratificação genética e epigenética detalhada dos participantes, o que pode permitir intervenções personalizadas mais eficazes. A utilização combinada de técnicas avançadas de neuroimagem funcional com medidas de biomarcadores periféricos poderá ainda contribuir para uma compreensão mais completa dos mecanismos neurobiológicos subjacentes à ação terapêutica da oxitocina.

Em conclusão, o sistema oxitocinérgico apresenta-se como um alvo terapêutico promissor na esquizofrenia, particularmente no que diz respeito à melhoria da cognição social, incluindo teoria da mente, reconhecimento emocional, percepção de social cues e aumento da saliência social. A concretização deste potencial, contudo, requer esforços continuados para esclarecer a variabilidade genética, otimizar protocolos de administração e explorar abordagens combinadas e integrativas que maximizem os benefícios.

6. Referências

1. Du Vigneaud V. Trail of sulfur research: From insulin to oxytocin. Science (1979) [Internet]. 1956 [citado 11 de Maio de 2025];123(3205):967–74. Disponível em: https://pubmed.ncbi.nlm.nih.gov/13324123/

2. Ross HE, Young LJ. Oxytocin and the neural mechanisms regulating social cognition and affiliative behavior. Front Neuroendocrinol [Internet]. 1 de Outubro de 2009 [citado 11 de Maio de 2025];30(4):534–47. Disponível em: https://www.sciencedirect.com/science/article/pii/S0091302209000284

3. Feifel D, MacDonald K, Nguyen A, Cobb P, Warlan H, Galangue B, et al. Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients. Biol Psychiatry [Internet]. 1 de Outubro de 2010 [citado 11 de Maio de 2025];68(7):678–80. Disponível em: https://pubmed.ncbi.nlm.nih.gov/20615494/

4. Souza RP, De Luca V, Meltzer HY, Lieberman JA, Kennedy JL. Schizophrenia severity and clozapine treatment outcome association with oxytocinergic genes. International Journal of Neuropsychopharmacology [Internet]. Julho de 2010 [citado 11 de Maio de 2025];13(6):793–8. Disponível em: https://pubmed.ncbi.nlm.nih.gov/20196918/

5. Rubin LH, Carter CS, Drogos L, Pournajafi-Nazarloo H, Sweeney JA, Maki PM. Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. Schizophr Res [Internet]. 2010 [citado 26 de Junho de 2025];124(1–3):13–21. Disponível em: https://pubmed.ncbi.nlm.nih.gov/20947304/

6. Sripada CS, Phan KL, Labuschagne I, Welsh R, Nathan PJ, Wood AG. Oxytocin enhances resting-state connectivity between amygdala and medial frontal cortex. International Journal of Neuropsychopharmacology [Internet]. Março de 2013 [citado 11 de Maio de 2025];16(2):255–60. Disponível em: https://pubmed.ncbi.nlm.nih.gov/22647521/

7. Bjorkquist OA, Olsen EK, Nelson BD, Herbener ES. Altered amygdala-prefrontal connectivity during emotion perception in schizophrenia. Schizophr Res [Internet]. 1 de Agosto de 2016 [citado 11 de Maio de 2025];175(1–3):35–41. Disponível em: https://pubmed.ncbi.nlm.nih.gov/27083779/

8. Feifel D, MacDonald K, Cobb P, Minassian A. Adjunctive intranasal oxytocin improves verbal memory in people with schizophrenia. Schizophr Res [Internet]. 1 de Agosto de 2012 [citado 11 de Maio de 2025];139(1–3):207–10. Disponível em: https://www.sciencedirect.com/science/article/pii/S0920996412003118?via%3Dihub

9. Goldman MB, Gomes AM, Carter CS, Lee R. Divergent effects of two different doses of intranasal oxytocin on facial affect discrimination in schizophrenic patients with and without polydipsia. Psychopharmacology (Berl) [Internet]. Julho de 2011 [citado 11 de Maio de 2025];216(1):101–10. Disponível em: https://pubmed.ncbi.nlm.nih.gov/21301811/

10. Averbeck BB, Bobin T, Evans S, Shergill SS. Emotion recognition and oxytocin in patients with schizophrenia. Psychol Med [Internet]. Fevereiro de 2012 [citado 11 de Maio de 2025];42(2):259–66. Disponível em: https://www.cambridge.org/core/journals/psychological-medicine/article/emotion-recognition-and-oxytocin-in-patients-with-schizophrenia/FA84D94AF328EA067FDAC3FE2A547F29

11. Fischer-Shofty M, Shamay-Tsoory SG, Levkovitz Y. Characterization of the effects of oxytocin on fear recognition in patients with schizophrenia and in healthy controls. Front Neurosci [Internet]. 18 de Julho de 2013 [citado 11 de Maio de 2025];7(7 JUL):50402. Disponível em: www.frontiersin.org

12. Lee MR, Wehring HJ, McMahon RP, Linthicum J, Cascella N, Liu F, et al. Effects of adjunctive intranasal oxytocin on olfactory identification and clinical symptoms in schizophrenia: Results from a randomized double blind placebo controlled pilot study. Schizophr Res [Internet]. Abril de 2013 [citado 11 de Maio de 2025];145(1–3):110–5. Disponível em: https://pubmed.ncbi.nlm.nih.gov/23415472/

13. Jayaram N, Varambally S, Behere R V., Venkatasubramanian G, Arasappa R, Christopher R, et al. Effect of yoga therapy on plasma oxytocin and facial emotion recognition deficits in patients of schizophrenia. Indian J Psychiatry [Internet]. Julho de 2013 [citado 11 de Maio de 2025];55(7). Disponível em: https://journals.lww.com/indianjpsychiatry/fulltext/2013/55003/effect_of_yoga_therapy_on_plasma_oxytocin_and.19.aspx

14. Montag C, Brockmann EM, Lehmann A, Müller DJ, Rujescu D, Gallinat J. Association between Oxytocin Receptor Gene Polymorphisms and Self-Rated 'Empathic Concern' in Schizophrenia. PLoS One [Internet]. 20 de Dezembro de 2012 [citado 11 de Maio de 2025];7(12):e51882. Disponível em: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0051882

15. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. The BMJ [Internet]. 2019 [citado 26 de Junho de 2025];366. Disponível em: https://pubmed.ncbi.nlm.nih.gov/31462531/

16. Barker TH, Hasanoff S, Aromataris E, Stone JC, Leonardi-Bee J, Sears K, et al. The revised JBI critical appraisal tool for the assessment of risk of bias for analytical cross-sectional studies. JBI Evid Synth [Internet]. 10 de Junho de 2025 [citado 26 de Junho de 2025]; Disponível em: https://pubmed.ncbi.nlm.nih.gov/40521701/

17. Souza RP, De Luca V, Meltzer HY, Lieberman JA, Kennedy JL. Schizophrenia severity and clozapine treatment outcome association with oxytocinergic genes. International Journal of Neuropsychopharmacology [Internet]. 2010 [citado 26 de Junho de 2025];13(6):793–8. Disponível em: https://pubmed.ncbi.nlm.nih.gov/20196918/

18. Montag C, Brockmann EM, Lehmann A, Müller DJ, Rujescu D, Gallinat J. Association between Oxytocin Receptor Gene Polymorphisms and Self-Rated 'Empathic Concern' in Schizophrenia. PLoS One [Internet]. 2012 [citado 26 de Junho de 2025];7(12):e51882–e51882. Disponível em: https://pmc.ncbi.nlm.nih.gov/articles/PMC3527477/

19. Teltsh O, Kanyas-Sarner K, Rigbi A, Greenbaum L, Lerer B, Kohn Y. Oxytocin and vasopressin genes are significantly associated with schizophrenia in a large Arab-Israeli pedigree. International Journal of Neuropsychopharmacology [Internet]. 2012 [citado 26 de Junho de 2025];15(3):309–19. Disponível em: https://pubmed.ncbi.nlm.nih.gov/21899794/

20. Sasayama D, Hattori K, Teraishi T, Hori H, Ota M, Yoshida S, et al. Negative correlation between cerebrospinal fluid oxytocin levels and negative symptoms of male patients with schizophrenia. Schizophr Res [Internet]. 2012 [citado 26 de Junho de 2025];139(1–3):201–6. Disponível em: https://pubmed.ncbi.nlm.nih.gov/22742979/

21. Strauss GP, Keller WR, Koenig JI, Gold JM, Frost KH, Buchanan RW. Plasma oxytocin levels predict social cue recognition in individuals with schizophrenia. Schizophr Res [Internet]. 1 de Março de 2015 [citado 26 de Junho de 2025];162(1–3):47–51. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25673435/

22. Teltsh O, Kanyas-Sarner K, Rigbi A, Greenbaum L, Lerer B, Kohn Y. Oxytocin and vasopressin genes are significantly associated with schizophrenia in a large Arab-Israeli pedigree. International Journal of Neuropsychopharmacology [Internet]. 2012 [citado 4 de Junho de 2025];15(3):309–19. Disponível em: https://pubmed.ncbi.nlm.nih.gov/21899794/

23. Montag C, Brockmann EM, Lehmann A, Müller DJ, Rujescu D, Gallinat J. Association between Oxytocin Receptor Gene Polymorphisms and Self-Rated «Empathic Concern» in Schizophrenia. PLoS One [Internet]. 20 de Dezembro de 2012 [citado 6 de Junho de 2025];7(12). Disponível em: https://pubmed.ncbi.nlm.nih.gov/23284802/

24. Jobst A, Dehning S, Ruf S, Notz T, Buchheim A, Henning-Fast K, et al. Oxytocin and vasopressin levels are decreased in the plasma of male schizophrenia patients. Acta Neuropsychiatr [Internet]. 19 de Junho de 2014 [citado 13 de Maio de 2025];26(6):347–55. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25288094/

25. Sasayama D, Hattori K, Teraishi T, Hori H, Ota M, Yoshida S, et al. Negative correlation between cerebrospinal fluid oxytocin levels and negative symptoms of male patients with schizophrenia. Schizophr Res [Internet]. Agosto de 2012 [citado 12 de Maio de 2025];139(1–3):201–6. Disponível em: https://pubmed.ncbi.nlm.nih.gov/22742979/

26. Busnelli M, Dagani J, de Girolamo G, Balestrieri M, Pini S, Saviotti FM, et al. Unaltered Oxytocin and Vasopressin Plasma Levels in Patients with

Schizophrenia After 4 Months of Daily Treatment with Intranasal Oxytocin. J Neuroendocrinol [Internet]. 2016 [citado 26 de Junho de 2025];28(4). Disponível em: https://pubmed.ncbi.nlm.nih.gov/26715485/

27. Modabbernia A, Rezaei F, Salehi B, Jafarinia M, Ashrafi M, Tabrizi M, et al. Intranasal oxytocin as an adjunct to risperidone in patients with schizophrenia: An 8-week, randomized, double-blind, placebo-controlled study. CNS Drugs [Internet]. Janeiro de 2013 [citado 28 de Maio de 2025];27(1):57–65. Disponível em: https://pubmed.ncbi.nlm.nih.gov/23233269/

28. Pedersen CA, Gibson CM, Rau SW, Salimi K, Smedley KL, Casey RL, et al. Intranasal oxytocin reduces psychotic symptoms and improves Theory of Mind and social perception in schizophrenia. Schizophr Res [Internet]. Outubro de 2011 [citado 12 de Maio de 2025];132(1):50–3. Disponível em: https://pubmed.ncbi.nlm.nih.gov/21840177/

29. Guastella AJ, Ward PB, Hickie IB, Shahrestani S, Hodge MAR, Scott EM, et al. A single dose of oxytocin nasal spray improves higher-order social cognition in schizophrenia. Schizophr Res [Internet]. 1 de Novembro de 2015 [citado 13 de Maio de 2025];168(3):628–33. Disponível em: https://pubmed.ncbi.nlm.nih.gov/26150070/

30. Fischer-Shofty M, Brüne M, Ebert A, Shefet D, Levkovitz Y, Shamay-Tsoory SG. Improving social perception in schizophrenia: The role of oxytocin. Schizophr Res [Internet]. Maio de 2013 [citado 13 de Maio de 2025];146(1–3):357–62. Disponível em: https://pubmed.ncbi.nlm.nih.gov/23433504/

31. Woolley JD, Chuang B, Lam O, Lai W, O'Donovan A, Rankin KP, et al. Oxytocin administration enhances controlled social cognition in patients with schizophrenia. Psychoneuroendocrinology [Internet]. 2014 [citado 13 de Maio de 2025];47:116–25. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25001961/

32. Abram S V., De Coster L, Roach BJ, Mueller BA, Van Erp TGM, Calhoun VD, et al. Oxytocin Enhances an Amygdala Circuit Associated with Negative Symptoms in Schizophrenia: A Single-Dose, Placebo-Controlled, Crossover, Randomized Control Trial. Schizophr Bull [Internet]. 10 de Abril de 2020 [citado 13 de Maio de 2025];46(3):661–9. Disponível em: https://pubmed.ncbi.nlm.nih.gov/31595302/

33. Woolley JD, Lam O, Chuang B, Ford JM, Mathalon DH, Vinogradov S. Oxytocin administration selectively improves olfactory detection thresholds for lyral in patients with schizophrenia. Psychoneuroendocrinology [Internet]. 1 de Março de 2015 [citado 28 de Maio de 2025];53:217–22. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25637811/

34. Veras AB, Getz M, Froemke RC, Nardi AE, Alves GS, Walsh-Messinger J, et al. Rare missense coding variants in oxytocin receptor (OXTR) in schizophrenia cases are associated with early trauma exposure, cognition and emotional processing. J Psychiatr Res [Internet]. 1 de Fevereiro de 2018 [citado 12 de Maio de 2025];97:58–64. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29190530/

35. Goh KK, Kanahara N, Chiu YH, Lu ML. The impact of childhood trauma exposure on social functioning in schizophrenia: The moderated mediation role of oxytocin and oxytocin receptor gene polymorphisms. Psychol Med [Internet]. 18 de Abril de 2024 [citado 4 de Junho de 2025];54(5):980–92. Disponível em: https://pubmed.ncbi.nlm.nih.gov/37721215/

36. Haram M, Bettella F, Brandt CL, Quintana DS, Nerhus M, Bjella T, et al. Contribution of oxytocin receptor polymorphisms to amygdala activation in schizophrenia spectrum disorders. BJPsych Open [Internet]. Novembro de 2016 [citado 4 de Junho de 2025];2(6):353–8. Disponível em: https://pubmed.ncbi.nlm.nih.gov/27847593/

37. Yang X, Tang Y, Wei Q, Lang B, Tao H, Zhang X, et al. Up-regulated expression of oxytocin mRNA in peripheral blood lymphocytes from first-episode schizophrenia patients. Oncotarget [Internet]. 2017 [citado 26 de Junho de 2025];8(45):78882–9. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29108272/

38. Liu Y, Tao H, Yang X, Huang K, Zhang X, Li C. Decreased serum oxytocin and increased homocysteine in first-episode schizophrenia patients. Front Psychiatry [Internet]. 2019 [citado 6 de Junho de 2025];10(APR). Disponível em: https://pubmed.ncbi.nlm.nih.gov/31024366/

39. Lee MR, Sheskier MB, Farokhnia M, Feng N, Marenco S, Lipska BK, et al. Oxytocin receptor mRNA expression in dorsolateral prefrontal cortex in major psychiatric disorders: A human post-mortem study. Psychoneuroendocrinology [Internet]. 1 de Outubro de 2018 [citado 6 de Junho de 2025];96:143–7. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29940428/

40. Eghtedarian R, Akbari M, Badrlou E, Mahmud Hussen B, Eslami S, Akhavan-Bahabadi M, et al. Assessment of expression of oxytocin-related lncRNAs in schizophrenia. Eur J Pharmacol [Internet]. 15 de Outubro de 2022 [citado 6 de Junho de 2025];932. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35987251/

41. Montag C, Brockmann EM, Bayerl M, Rujescu D, Müller DJ, Gallinat J. Oxytocin and oxytocin receptor gene polymorphisms and risk for schizophrenia: A case-control study. World Journal of Biological Psychiatry [Internet]. Setembro de 2013 [citado 4 de Junho de 2025];14(7):500–8. Disponível em: https://pubmed.ncbi.nlm.nih.gov/22651577/

42. Haram M, Tesli M, Bettella F, Djurovic S, Andreassen OA, Melle I. Association between genetic variation in the oxytocin receptor gene and emotional withdrawal, but not between oxytocin pathway genes and diagnosis in psychotic disorders. Front Hum Neurosci [Internet]. 23 de Janeiro de 2015 [citado 4 de Junho de 2025];9(JAN):1–7. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25667571/

43. Lv X, Hou Y Sen, Zhang ZH, Yue WH. OXTR polymorphisms associated with severity and treatment responses of schizophrenia. Schizophrenia [Internet]. 1 de

Dezembro de 2024 [citado 4 de Junho de 2025];10(1). Disponível em: https://pubmed.ncbi.nlm.nih.gov/38184684/

44. Ortega MA, García-Montero C, Fraile-Martinez Ó, De Leon-Oliva D, Boaru DL, Bravo C, et al. Assessment of Tissue Expression of the Oxytocin–Vasopressin Pathway in the Placenta of Women with a First-Episode Psychosis during Pregnancy. Int J Mol Sci [Internet]. 1 de Junho de 2023 [citado 6 de Junho de 2025];24(12). Disponível em: https://pubmed.ncbi.nlm.nih.gov/37373400/

45. Davis MC, Horan WP, Nurmi EL, Rizzo S, Li W, Sugar CA, et al. Associations between oxytocin receptor genotypes and social cognitive performance in individuals with schizophrenia. Schizophr Res [Internet]. 1 de Novembro de 2014 [citado 6 de Junho de 2025];159(2–3):353–7. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25244972/

46. Giralt-López M, Miret S, Soler J, Campanera S, Parellada M, Fañanás L, et al. The role of schizotypal traits and the OXTR gene in theory of mind in schizophrenia: A family-based study . European Psychiatry [Internet]. 2020 [citado 6 de Junho de 2025];63(1). Disponível em: https://pubmed.ncbi.nlm.nih.gov/32093796/

47. Nakata Y, Kanahara N, Kimura A, Niitsu T, Komatsu H, Oda Y, et al. Oxytocin system dysfunction in patients with treatment-resistant schizophrenia: Alterations of blood oxytocin levels and effect of a genetic variant of OXTR. J Psychiatr Res [Internet]. 1 de Junho de 2021 [citado 4 de Junho de 2025];138:219–27. Disponível em: https://pubmed.ncbi.nlm.nih.gov/33866050/

48. Rubin LH, Connelly JJ, Reilly JL, Carter CS, Drogos LL, Pournajafi-Nazarloo H, et al. Sex and Diagnosis-Specific Associations between DNA Methylation of the Oxytocin Receptor Gene with Emotion Processing and Temporal-Limbic and Prefrontal Brain Volumes in Psychotic Disorders. Biol Psychiatry Cogn Neurosci Neuroimaging [Internet]. 1 de Fevereiro de 2016 [citado 6 de Junho de 2025];1(2):141–51. Disponível em: https://pubmed.ncbi.nlm.nih.gov/26977453/

49. Bang M, Kang JI, Kim SJ, Park JY, Kim KR, Lee SY, et al. Reduced DNA Methylation of the Oxytocin Receptor Gene Is Associated with Anhedonia-Asociality in Women with Recent-Onset Schizophrenia and Ultra-high Risk for Psychosis. Schizophr Bull [Internet]. 2019 [citado 26 de Junho de 2025];45(6):1279–90. Disponível em: https://pubmed.ncbi.nlm.nih.gov/31220321/

50. Grove TB, Burghardt KJ, Kraal AZ, Dougherty RJ, Taylor SF, Ellingrod VL. Oxytocin Receptor (OXTR) Methylation and Cognition in Psychotic Disorders. Mol Neuropsychiatry [Internet]. 2016 [citado 6 de Junho de 2025];2(3):151–60. Disponível em: https://pubmed.ncbi.nlm.nih.gov/27867940/

51. Piao YH, Cui Y, Rami FZ, Li L, Karamikheirabad M, Kang SH, et al. Methylome-wide Association Study of Patients with Recent-onset Psychosis. Clinical Psychopharmacology and Neuroscience [Internet]. 1 de Agosto de 2022

[citado 6 de Junho de 2025];20(3):462–73. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35879030/

52. Broniarczyk-Czarniak M, Szemraj J, Śmigielski J, Gałecki P. The Role of OXT, OXTR, AVP, and AVPR1a Gene Expression in the Course of Schizophrenia. Curr Issues Mol Biol [Internet]. 2022 [citado 26 de Junho de 2025];44(1):336–49. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35723404/

53. Rubin LH, Carter CS, Drogos L, Jamadar R, Pournajafi-Nazarloo H, Sweeney JA, et al. Sex-specific associations between peripheral oxytocin and emotion perception in schizophrenia. Schizophr Res [Internet]. Agosto de 2011 [citado 12 de Maio de 2025];130(1–3):266–70. Disponível em: https://pubmed.ncbi.nlm.nih.gov/21684122/

54. Strauss GP, Keller WR, Koenig JI, Gold JM, Frost KH, Buchanan RW. Plasma oxytocin levels predict social cue recognition in individuals with schizophrenia. Schizophr Res [Internet]. 1 de Março de 2015 [citado 12 de Maio de 2025];162(1–3):47–51. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25673435/

55. Walss-Bass C, Fernandes JM, Roberts DL, Service H, Velligan D. Differential correlations between plasma oxytocin and social cognitive capacity and bias in schizophrenia. Schizophr Res [Internet]. Julho de 2013 [citado 13 de Maio de 2025];147(2–3):387–92. Disponível em: https://pubmed.ncbi.nlm.nih.gov/23628601/

56. Rubin LH, Carter CS, Bishop JR, Pournajafi-Nazarloo H, Harris MSH, Hill SK, et al. Peripheral vasopressin but not oxytocin relates to severity of acute psychosis in women with acutely-ill untreated first-episode psychosis. Schizophr Res [Internet]. Maio de 2013 [citado 13 de Maio de 2025];146(1–3):138–43. Disponível em: https://pubmed.ncbi.nlm.nih.gov/23465965/

57. Rubin LH, Sue Carter C, Bishop JR, Pournajafi-Nazarloo H, Drogos LL, Kristian Hill S, et al. Reduced levels of vasopressin and reduced behavioral modulation of oxytocin in psychotic disorders. Schizophr Bull [Internet]. 1 de Novembro de 2014 [citado 13 de Maio de 2025];40(6):1374–84. Disponível em: https://pubmed.ncbi.nlm.nih.gov/24619535/

58. Guzel D, Yazici AB, Pek TM, Doganay S, Simsek ABS, Saglam K, et al. Atrial natriuretic peptide and posterior pituitary neurohormone changes in patients with acute schizophrenia. Neuropsychiatr Dis Treat [Internet]. 2018 [citado 26 de Junho de 2025];14:1855–60. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30038496/

59. Yashwini K, Shivam Alpeshkumar P, Vinyas M. Prolactin and Oxytocin in Psychiatry: A Review. International Journal of Zoological Investigations [Internet]. 2024 [citado 26 de Junho de 2025];10(1):766–74. Disponível em: https://doi.org/10.33745/ijzi.2024.v10i01.083

60. Hidalgo-Figueroa M, Salazar A, Romero-López-Alberca C, MacDowell KS, García-Bueno B, Bioque M, et al. The Influence of Oxytocin and Prolactin

During a First Episode of Psychosis: The Implication of Sex Differences, Clinical Features, and Cognitive Performance. International Journal of Neuropsychopharmacology [Internet]. 1 de Agosto de 2022 [citado 26 de Junho de 2025];25(8):666–77. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35353882/

61. Chen YJ, Lu ML, Chiu YH, Chen C, Santos VHJ, Goh KK. Linking childhood trauma to the psychopathology of schizophrenia: the role of oxytocin. Schizophrenia [Internet]. 1 de Dezembro de 2024 [citado 26 de Junho de 2025];10(1). Disponível em: https://pubmed.ncbi.nlm.nih.gov/38388569/

62. Yu H, Ni P, Zhao L, Tian Y, Li M, Li X, et al. Decreased plasma neuropeptides in first-episode schizophrenia, bipolar disorder, major depressive disorder: associations with clinical symptoms and cognitive function. Front Psychiatry [Internet]. 2023 [citado 26 de Junho de 2025];14. Disponível em: https://pubmed.ncbi.nlm.nih.gov/37275985/

63. Rodrigues A, Santos HC, Ferreira S, Diogo V, Costa M, Brissos S, et al. An exploration of blood-based biomarkers of negative symptoms of psychosis in men. J Psychiatr Res [Internet]. 1 de Setembro de 2024 [citado 26 de Junho de 2025];177:256–63. Disponível em: https://pubmed.ncbi.nlm.nih.gov/39047549/

64. Popescu ER, Semeniuc S, Hritcu LD, Horhogea CE, Spataru MC, Trus C, et al. Cortisol and oxytocin could predict covert aggression in some psychotic patients. Medicina (Lithuania) [Internet]. 2021 [citado 26 de Junho de 2025];57(8). Disponível em: https://pubmed.ncbi.nlm.nih.gov/34440968/

65. Spilka MJ, Keller WR, Buchanan RW, Gold JM, Koenig JI, Strauss GP. Endogenous oxytocin levels are associated with facial emotion recognition accuracy but not gaze behavior in individuals with schizophrenia. Acta Psychiatr Scand [Internet]. 1 de Maio de 2022 [citado 26 de Junho de 2025];145(5):494–506. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35243618/

66. Tas C, Brown EC, Eskikurt G, Irmak S, Aydın O, Esen-Danaci A, et al. Cortisol response to stress in schizophrenia: Associations with oxytocin, social support and social functioning. Psychiatry Res [Internet]. 1 de Dezembro de 2018 [citado 26 de Junho de 2025];270:1047–52. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29960725/

67. Rubin LH, Li S, Yao L, Keedy SK, Reilly JL, Hill SK, et al. Peripheral oxytocin and vasopressin modulates regional brain activity differently in men and women with schizophrenia. Schizophr Res [Internet]. 1 de Dezembro de 2018 [citado 26 de Junho de 2025];202:173–9. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30539769/

68. Montag C, Schöner J, Speck LG, Just S, Stuke F, Rentzsch J, et al. Peripheral oxytocin is inversely correlated with cognitive, but not emotional empathy in schizophrenia. PLoS One [Internet]. 2020 [citado 26 de Junho de 2025];15(4). Disponível em: https://pubmed.ncbi.nlm.nih.gov/32255800/

69. Brown EC, Tas C, Kuzu D, Esen-Danaci A, Roelofs K, Brüne M. Social approach and avoidance behaviour for negative emotions is modulated by endogenous oxytocin and paranoia in schizophrenia. Psychiatry Res [Internet]. 30 de Novembro de 2014 [citado 26 de Junho de 2025];219(3):436–42. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25048758/

70. Strauss GP, Keller WR, Koenig JI, Sullivan SK, Gold JM, Buchanan RW. Endogenous oxytocin levels are associated with the perception of emotion in dynamic body expressions in schizophrenia. Schizophr Res [Internet]. 1 de Março de 2015 [citado 26 de Junho de 2025];162(1–3):52–6. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25620121/

71. Mutu Pek T, Yazici E, Guzel D, Kose E, Yazıcı AB, Erol A. The relationship between oxytocin, vasopressin and atrial natriuretic peptide levels and cognitive functions in patients with schizophrenia. Psychiatry and Clinical Psychopharmacology [Internet]. 2 de Outubro de 2019 [citado 26 de Junho de 2025];29(4):798–810. Disponível em: http://psychiatry-psychopharmacology.com/en/the-relationship-between-oxytocin-vasopressin-and-atrial-natriuretic-peptide-levels-and-cognitive-functions-in-patients-with-schizophrenia-13393

72. Strauss GP, Keller WR, Koenig JI, Gold JM, Ossenfort KL, Buchanan RW. Plasma oxytocin levels predict olfactory identification and negative symptoms in individuals with schizophrenia. Schizophr Res [Internet]. 1 de Março de 2015 [citado 26 de Junho de 2025];162(1–3):57–61. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25583247/

73. Goh KK, Lu ML. Relationship between the domains of theory of mind, social dysfunction, and oxytocin in schizophrenia. J Psychiatr Res [Internet]. 1 de Novembro de 2022 [citado 26 de Junho de 2025];155:420–9. Disponível em: https://pubmed.ncbi.nlm.nih.gov/36182771/

74. Aydın O, Lysaker PH, Balıkçı K, Ünal-Aydın P, Esen-Danacı A. Associations of oxytocin and vasopressin plasma levels with neurocognitive, social cognitive and meta cognitive function in schizophrenia. Psychiatry Res [Internet]. 1 de Dezembro de 2018 [citado 26 de Junho de 2025];270:1010–6. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29609987/

75. Balikci K, Aydin O, Tas C, Danaci AE. Oxytocin and social cognition in patients with schizophrenia: Comparison with healthy siblings and healthy controls. Psychiatry and Clinical Psychopharmacology [Internet]. 2018 [citado 26 de Junho de 2025];28(2):123–30. Disponível em: http://psychiatry-psychopharmacology.com/en/oxytocin-and-social-cognition-in-patients-with-schizophrenia-comparison-with-healthy-siblings-and-healthy-controls-13500

76. Sun W, Jin T, Yang H, Li J, Tian Q, Gao J, et al. Alterations of serum neuropeptide levels and their relationship to cognitive impairment and psychopathology in male patients with chronic schizophrenia. Schizophrenia [Internet]. 1 de Dezembro de 2024 [citado 26 de Junho de 2025];10(1). Disponível em: https://pubmed.ncbi.nlm.nih.gov/38172494/

77. Rubin LH, Carter CS, Drogos LL, Pournajafi-Nazarloo H, Sweeney JA, Maki PM. Effects of sex, menstrual cycle phase, and endogenous hormones on cognition in schizophrenia. Schizophr Res [Internet]. 2015 [citado 27 de Junho de 2025];166(1–3):269–75. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25990704/

78. Wehring HJ, Buchanan RW, Feldman S, Carpenter WT, McMahon RP, Weiner E, et al. Oxytocin and sexual function in males and females with schizophrenia. Schizophr Res [Internet]. 1 de Setembro de 2018 [citado 26 de Junho de 2025];199:431–2. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29551232/

79. Aydın O, Balıkçı K, Taş C, Ünal-Aydın P, Taneli F, Esen-Danacı A. Assessing the relationship between attachment, parental attitude and plasma oxytocin in schizophrenia patients and their unaffected siblings. Nord J Psychiatry [Internet]. 2 de Janeiro de 2019 [citado 26 de Junho de 2025];73(1):51–7. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30636461/

80. Porffy LA, Bell V, Coutrot A, Wigton R, D'Oliveira T, Mareschal I, et al. In the eye of the beholder? Oxytocin effects on eye movements in schizophrenia. Schizophr Res [Internet]. 2020 [citado 26 de Junho de 2025];216:279–87. Disponível em: https://pubmed.ncbi.nlm.nih.gov/31836261/

81. Lee MR, Wehring HJ, McMahon RP, Liu F, Linthicum J, Verbalis JG, et al. Relationship of plasma oxytocin levels to baseline symptoms and symptom changes during three weeks of daily oxytocin administration in people with schizophrenia. Schizophr Res [Internet]. 2016 [citado 26 de Junho de 2025];172(1–3):165–8. Disponível em: https://pubmed.ncbi.nlm.nih.gov/26879587/

82. İmamoğlu A, Stiles BJ, Jarskog LF, Pedersen CA, Elliott T, Penn DL. The effect of intranasal oxytocin on neurocognition in people with schizophrenia: A randomized controlled trial. J Psychiatr Res [Internet]. 2024 [citado 26 de Junho de 2025];171:95–8. Disponível em: https://pubmed.ncbi.nlm.nih.gov/38262165/

83. Hennig-Fast K, Meissner D, Steuwe C, Dehning S, Blautzik J, Eilert DW, et al. The Interplay of Oxytocin and Attachment in Schizophrenic Patients: An fMRI Study. Brain Sci [Internet]. 1 de Agosto de 2023 [citado 27 de Junho de 2025];13(8). Disponível em: https://pubmed.ncbi.nlm.nih.gov/37626482/

84. Korann V, Jacob A, Lu B, Devi P, Thonse U, Nagendra B, et al. Effect of Intranasal Oxytocin on Resting-state Effective Connectivity in Schizophrenia. Schizophr Bull [Internet]. 2022 [citado 26 de Junho de 2025];48(5):1115–24. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35759349/

85. Shin NY, Park HY, Jung WH, Park JW, Yun JY, Jang JH, et al. Effects of oxytocin on neural response to facial expressions in patients with schizophrenia. Neuropsychopharmacology [Internet]. 2015 [citado 26 de Junho de 2025];40(8):1919–27. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25666311/

86. Wynn JK, Green MF, Hellemann G, Reavis EA, Marder SR. A dose-finding study of oxytocin using neurophysiological measures of social processing. Neuropsychopharmacology [Internet]. 1 de Janeiro de 2019 [citado 27 de Junho de 2025];44(2):289–94. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30082892/

87. Woolley JD, Chuang B, Fussell C, Scherer S, Biagianti B, Fulford D, et al. Intranasal oxytocin increases facial expressivity, but not ratings of trustworthiness, in patients with schizophrenia and healthy controls. Psychol Med [Internet]. 2017 [citado 26 de Junho de 2025];47(7):1311–22. Disponível em: https://pubmed.ncbi.nlm.nih.gov/28091349/

88. Chuang BJ, Campellone TR, Woolley JD. Oxytocin does not improve emotional prosody recognition in schizophrenia-spectrum disorders. Compr Psychoneuroendocrinol [Internet]. 2020 [citado 26 de Junho de 2025];4. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35755629/

89. Andari E, Massa NM, Fargotstein MD, Taylor NB, Halverson DM, Owens A V, et al. Effects of Oxytocin on Emotion Recognition in Schizophrenia: A Randomized Double-Blind Pilot Study. J Clin Psychopharmacol [Internet]. 2021 [citado 26 de Junho de 2025];41(2):103–13. Disponível em: https://pubmed.ncbi.nlm.nih.gov/33587397/

90. De Coster L, Lin L, Mathalon DH, Woolley JD. Neural and behavioral effects of oxytocin administration during theory of mind in schizophrenia and controls: a randomized control trial. Neuropsychopharmacology [Internet]. 2019 [citado 26 de Junho de 2025];44(11):1925–31. Disponível em: https://pubmed.ncbi.nlm.nih.gov/31103018/

91. MR L, HJ W, RP M, F L, J L, RW B, et al. The Effect of Intranasal Oxytocin on Measures of Social Cognition in Schizophrenia: A Negative Report. J Psychiatr Brain Sci [Internet]. 2019 [citado 26 de Junho de 2025];4(1). Disponível em: https://pubmed.ncbi.nlm.nih.gov/31037274/

92. Dwyer KR, Andrea AM, Savage CLG, Orth RD, Shan L, Strauss GP, et al. A Randomized Clinical Trial of Oxytocin or Galantamine in Schizophrenia: Assessing the Impact on Behavioral, Lexical, and Self-Report Indicators of Social Affiliation. Schizophr Bull Open [Internet]. 2020 [citado 26 de Junho de 2025];1(1). Disponível em: https://pubmed.ncbi.nlm.nih.gov/32803156/

93. Halverson T, Jarskog LF, Pedersen C, Penn D. Effects of oxytocin on empathy, introspective accuracy, and social symptoms in schizophrenia: A 12-week twice-daily randomized controlled trial. Schizophr Res [Internet]. 2019 [citado 26 de Junho de 2025];204:178–82. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30243853/

94. Mouchlianitis ED, Tracy DK, Wigton R, Vanes LD, Fett AK, Shergill SS. Neuroimaging oxytocin modulation of social reward learning in schizophrenia. BJPsych Open [Internet]. 2022 [citado 26 de Junho de 2025];8(5). Disponível em: https://pubmed.ncbi.nlm.nih.gov/36156189/

95. Wigton R, Tracy DK, Verneuil TM, Johns M, White T, Michalopoulou PG, et al. The importance of pro-social processing, and ameliorating dysfunction in schizophrenia. An FMRI study of oxytocin. Schizophr Res Cogn [Internet]. 2022 [citado 26 de Junho de 2025];27. Disponível em: https://pubmed.ncbi.nlm.nih.gov/34660212/

96. Strauss GP, Granholm E, Holden JL, Ruiz I, Gold JM, Kelly DL, et al. The effects of combined oxytocin and cognitive behavioral social skills training on social cognition in schizophrenia. Psychol Med [Internet]. 2019 [citado 26 de Junho de 2025];49(10):1731–9. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30180918/

97. Browne J, Harvey PD, Buchanan RW, Kelly DL, Strauss GP, Gold JM, et al. A Longitudinal Examination of Real-World Sedentary Behavior in Adults with Schizophrenia-Spectrum Disorders in a Clinical Trial of Combined Oxytocin and Cognitive Behavioral Social Skills Training. Behavioral Sciences [Internet]. 2022 [citado 26 de Junho de 2025];12(3). Disponível em: https://pubmed.ncbi.nlm.nih.gov/35323379/

98. Navarro E. What is theory of mind? A psychometric study of theory of mind and intelligence. Cogn Psychol [Internet]. 1 de Agosto de 2022 [citado 26 de Junho de 2025];136:101495. Disponível em: https://www.sciencedirect.com/science/article/pii/S0010028522000329?via%3Dihub

99. Davis MC, Lee J, Horan WP, Clarke AD, McGee MR, Green MF, et al. Effects of single dose intranasal oxytocin on social cognition in schizophrenia. Schizophr Res [Internet]. Julho de 2013 [citado 13 de Maio de 2025];147(2–3):393–7. Disponível em: https://pubmed.ncbi.nlm.nih.gov/23676253/

100. Bradley ER, Portanova J, Woolley JD, Buck B, Painter IS, Hankin M, et al. Quantifying abnormal emotion processing: A novel computational assessment method and application in schizophrenia. Psychiatry Res [Internet]. 1 de Junho de 2024 [citado 13 de Maio de 2025];336. Disponível em: https://pubmed.ncbi.nlm.nih.gov/38657475/

101. Bradley ER, Seitz A, Niles AN, Rankin KP, Mathalon DH, O'Donovan A, et al. Oxytocin increases eye gaze in schizophrenia. Schizophr Res [Internet]. 1 de Outubro de 2019 [citado 13 de Maio de 2025];212:177–85. Disponível em: https://pubmed.ncbi.nlm.nih.gov/31416746/

102. Bradley ER, Brustkern J, De Coster L, Van Den Bos W, McClure SM, Seitz A, et al. Victory is its own reward: Oxytocin increases costly competitive behavior in schizophrenia. Psychol Med [Internet]. 1 de Março de 2020 [citado 13 de Maio de 2025];50(4):674–82. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30944045/

103. Bradley ER, Tai M, Hankin M, Woolley JD. Preliminary evidence that oxytocin does not improve mentalizing in women with schizophrenia. Horm Behav

[Internet]. 1 de Fevereiro de 2021 [citado 13 de Maio de 2025];128. Disponível em: https://pubmed.ncbi.nlm.nih.gov/33340522/

104. Singh F, Nunag J, Muldoon G, Cadenhead KS, Pineda JA, Feifel D. Effects of intranasal oxytocin on neural processing within a socially relevant neural circuit. European Neuropsychopharmacology [Internet]. 1 de Março de 2016 [citado 13 de Maio de 2025];26(3):626–30. Disponível em: https://pubmed.ncbi.nlm.nih.gov/26727038/

105. Gibson CM, Penn DL, Smedley KL, Leserman J, Elliott T, Pedersen CA. A pilot six-week randomized controlled trial of oxytocin on social cognition and social skills in schizophrenia. Schizophr Res [Internet]. 2014 [citado 13 de Maio de 2025];156(2–3):261–5. Disponível em: https://pubmed.ncbi.nlm.nih.gov/24799299/

106. Davis MC, Green MF, Lee J, Horan WP, Senturk D, Clarke AD, et al. Oxytocin-Augmented Social Cognitive Skills Training in Schizophrenia. Neuropsychopharmacology 2014 39:9 [Internet]. 18 de Março de 2014 [citado 13 de Maio de 2025];39(9):2070–7. Disponível em: https://www.nature.com/articles/npp201468

107. Cacciotti-Saija C, Langdon R, Ward PB, Hickie IB, Scott EM, Naismith SL, et al. A Double-Blind Randomized Controlled Trial of Oxytocin Nasal Spray and Social Cognition Training for Young People with Early Psychosis. Schizophr Bull [Internet]. 1 de Março de 2015 [citado 13 de Maio de 2025];41(2):483–93. Disponível em: https://pubmed.ncbi.nlm.nih.gov/24962607/

108. Jarskog LF, Pedersen CA, Johnson JL, Hamer RM, Rau SW, Elliott T, et al. A 12-week randomized controlled trial of twice-daily intranasal oxytocin for social cognitive deficits in people with schizophrenia. Schizophr Res [Internet]. 1 de Julho de 2017 [citado 28 de Maio de 2025];185:88–95. Disponível em: https://pubmed.ncbi.nlm.nih.gov/28094169/

109. Buchanan RW, Kelly DL, Weiner E, Gold JM, Strauss GP, Koola MM, et al. A Randomized Clinical Trial of Oxytocin or Galantamine for the Treatment of Negative Symptoms and Cognitive Impairments in People with Schizophrenia. J Clin Psychopharmacol [Internet]. 1 de Agosto de 2017 [citado 13 de Maio de 2025];37(4):394–400. Disponível em: https://pubmed.ncbi.nlm.nih.gov/28590362/

110. Abu-Akel A, Fischer-Shofty M, Levkovitz Y, Decety J, Shamay-Tsoory S. The role of oxytocin in empathy to the pain of conflictual out-group members among patients with schizophrenia. Psychol Med [Internet]. 6 de Dezembro de 2014 [citado 13 de Maio de 2025];44(16):3523–32. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25065955/

111. Horta de Macedo LR, Zuardi AW, Machado-de-Sousa JP, Chagas MHN, Hallak JEC. Oxytocin does not improve performance of patients with schizophrenia and healthy volunteers in a facial emotion matching task. Psychiatry Res [Internet].

15 de Dezembro de 2014 [citado 13 de Maio de 2025];220(1–2):125–8. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25190346/

112. Caravaggio F, Gerretsen P, Mar W, Chung JK, Plitman E, Nakajima S, et al. Intranasal oxytocin does not modulate jumping to conclusions in schizophrenia: Potential interactions with caudate volume and baseline social functioning. Psychoneuroendocrinology [Internet]. 1 de Julho de 2017 [citado 13 de Maio de 2025];81:80–7. Disponível em: https://pubmed.ncbi.nlm.nih.gov/28431278/

113. Ota M, Yoshida S, Nakata M, Yada T, Kunugi H. The effects of adjunctive intranasal oxytocin in patients with schizophrenia. Postgrad Med [Internet]. 2 de Janeiro de 2018 [citado 13 de Maio de 2025];130(1):122–8. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29105546/

114. Fulford D, Treadway M, Woolley J. Social motivation in schizophrenia: The impact of oxytocin on vigor in the context of social and nonsocial reinforcement. J Abnorm Psychol [Internet]. 1 de Janeiro de 2018 [citado 13 de Maio de 2025];127(1):116–28. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29369669/

115. Warren KR, Wehring HJ, Liu F, McMahon RP, Chen S, Chester C, et al. Effects of intranasal oxytocin on satiety signaling in people with schizophrenia. Physiol Behav [Internet]. 15 de Maio de 2018 [citado 27 de Junho de 2025];189:86–91. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29524451/

116. Zierhut M, Bergmann N, Hahne I, Wohlthan J, Kraft J, Braun A, et al. The combination of oxytocin and mindfulness-based group therapy for empathy and negative symptoms in schizophrenia spectrum disorders – A double-blinded, randomized, placebo-controlled pilot study. J Psychiatr Res [Internet]. 1 de Março de 2024 [citado 28 de Maio de 2025];171:222–9. Disponível em: https://pubmed.ncbi.nlm.nih.gov/38309212/

117. Böge K, Bergmann N, Zierhut M, Hahne I, Braun A, Kraft J, et al. The relationship between mindfulness and empathy with the oxytocinergic system in persons with schizophrenia spectrum disorders – A proof-of-concept randomized controlled trial (OXYGEN). International Journal of Clinical and Health Psychology [Internet]. 1 de Julho de 2024 [citado 28 de Maio de 2025];24(3):100503. Disponível em: https://www.sciencedirect.com/science/article/pii/S1697260024000681

118. Saporta-Wiesel L, Feldman R, Levi L, Davidson M, Burshtein S, Gur R, et al. Intranasal Oxytocin Combined With Social Skills Training for Schizophrenia: An Add-on Randomized Controlled Trial. Schizophr Bull Open [Internet]. 1 de Janeiro de 2024 [citado 28 de Maio de 2025];5(1). Disponível em: https://pubmed.ncbi.nlm.nih.gov/39502135/

119. Buchanan RW, Kelly DL, Strauss GP, Gold JM, Weiner E, Zaranski J, et al. Combined Oxytocin and Cognitive Behavioral Social Skills Training for Social Function in People with Schizophrenia. J Clin Psychopharmacol [Internet]. 1 de

Maio de 2021 [citado 28 de Maio de 2025];41(3):236–43. Disponível em: https://pubmed.ncbi.nlm.nih.gov/33783399/

120. Dagani J, Sisti D, Abelli M, Di Paolo L, Pini S, Raimondi S, et al. Do we need oxytocin to treat schizophrenia? A randomized clinical trial. Schizophr Res [Internet]. 1 de Abril de 2016 [citado 28 de Maio de 2025];172(1–3):158–64. Disponível em: https://pubmed.ncbi.nlm.nih.gov/26883950/

7. Apêndice

Apêndice 1 –Viés dos estudos transversais, de acordo com a ferramenta JBI

JBI TOOL	1. Os critérios de inclusão na amostra foram claramente definidos?	2. Os participantes do estudo e o contexto foram descritos em detalhe?	3. A exposição foi medida de forma válida e fiável?	4. Foram utilizados critérios objetivos e padronizados para medir a condição?	5. Foram identificados os fatores de confusão?	6 Foram indicadas estratégias para lidar com os fatores de confusão??	7. Os desfechos foram medidos de forma válida e fiável?	8. Foi utilizada uma análise estatística adequada?
Souza, RP et al. (2010)	Sim	Sim	Sim	Sim	Sim	No	No	Sim
Rubin, LH et al. (2010)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Rubin, LH et al. (2011)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Montag, C et al. (2012)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Teltsh, Omri et al. (2012)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Sasayama, D et al. (2012)	Sim	Sim	Sim	Sim	No	No	Sim	Sim
Rubin, LH et al. (2013)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Walss-Bass, Cet al. (2013)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Montag, C. et al. (2012)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Rubin, LH et al. (2014)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Davis, MC et al. (2014)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Brown, EC et al. (2014)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Jobst, A et al. (2014)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Haram, M et al. (2015)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Strauss, GP et al. (2015a)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Strauss, GP et al. (2015b)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Strauss, GP et al. (2015c)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Rubin, LH et al. (2015)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Rubin, LH et al. (2016)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Grove, TB et al. (2016)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Haram, M et al. (2016)	Sim	Sim	Sim	Sim	Incerto	Incerto	Sim	Sim

JBI TOOL	1. Os critérios de inclusão na amostra foram claramente definidos?	2. Os participantes do estudo e o contexto foram descritos em detalhe?	3. A exposição foi medida de forma válida e fiável?	4. Foram utilizados critérios objetivos e padronizados para medir a condição?	5. Foram identificados os fatores de confusão?	6. Foram indicadas estratégias para lidar com os fatores de confusão?	7. Os desfechos foram medidos de forma válida e fiável?	8. Foi utilizada uma análise estatística adequada?
Yang, X et al. (2017)	Sim	Sim	Sim	Sim	Sim	Sim	Incerto	Sim
Balikci K et al. (2018)	Sim	Sim	Sim	Sim	Sim	Incerto	Não	Sim
Veras, AB et al. (2018)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Guzel, D et al. (2018)	Sim	Sim	Sim	Sim	Incerto	Incerto	Sim	Sim
Wehring, HJ et al. (2018)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Rubin, LH et al. (2018)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Tas, C et al. (2018)	Sim	Sim	Sim	Sim	Incerto	Incerto	Sim	Sim
Aydın, O et al. (2018)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Aydın, O et al. (2019)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Tugba, MP et al (2019)	Sim	Sim	Sim	Sim	Incerto	Incerto	Sim	Sim
Liu, Y et al. (2019)	Sim	Sim	Sim	Sim	Sim	Incerto	Sim	Sim
Bang, Met al. (2019)	Sim	Sim	Sim	Sim	Incerto	Incerto	Sim	Sim
Montag, Cet al. (2020)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Giralt-López, M et al. (2020)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Nakata, Yet al. (2021)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Popescu, ER et al. (2021)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Broniarczyk-Czarniak, M et al. (2022)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Spilka, MJ et al. (2022)	Sim	Sim	Sim	Sim	Não	Não	Sim	Sim
Hidalgo-Figueroa, M et al. (2022)	Sim	Sim	Sim	Sim	Não	Não	Sim	Sim
Piao, YH et al. (2022)	Sim	Sim	Sim	Sim	Não	Não	Sim	Sim
Eghtedarian, Ret al. (2022)	Sim	Sim	Sim	Sim	Não	Não	Sim	Sim
Goh, KK et al. (2022)	Sim	Sim	Sim	Sim	Não	Não	Sim	Sim
Yu, H et al. (2023)	Sim	Unclear	Sim	Sim	Não	Não	Sim	Sim
Ortega, MA et al. (2023)	Sim	Sim	Sim	Sim	Não	Sim	Sim	Sim

JBI TOOL	1 Os critérios de inclusão na amostra foram claramente definidos?	2. Os participantes do estudo e o contexto foram descritos em detalhe?	3. A exposição foi medida de forma válida e fiável?	4. Foram utilizados critérios objetivos e padronizados para medir a condição?	5. Foram identificados os fatores de confusão?	6. Foram indicadas estratégias para lidar com os fatores de confusão?	7. Os desfechos foram medidos de forma válida e fiável?	8. Foi utilizada uma análise estatística adequada?
Hennig-Fast, K et al. (2023)	Incerto	Sim	Sim	Não	Não	Sim	Sim	Sim
Lezheiko, TV, et al. (2024)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Sun, W et al. (2024)	Sim	Sim	Incerto	Sim	Não	Não	Sim	Sim
Lv, X et al. (2024)	Sim	Sim	Incerto	Sim	Sim	Sim	Não	Sim
Chen, YJ et al. (2024)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim
Goh, KK et al. (2024)	Incerto	Sim	Sim	Sim	Não	Não	Incerto	Sim
Rodrigues, A et al. (2024)	Sim	Sim	Sim	Sim	Sim	Sim	Sim	Sim

Anexo 2 – Tabela de risco de viés para os estudos clínicos randomizados, segundo a ferramenta RoB 2 for RCTs

Identificação do estudo	D1	D2	D3	D4	D5	Geral
Feifel et al. 2010	Baixo	Baixo	Baixo	Baixo	Baixo	Baixo
Goldman, MB et al. 2011	Baixo	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Pedersen, CB et al 2011	Alguma preocupação	Baixo	Baixo	Baixo	Baixo	Alguma preocupação
Averbeck, BB et al. 2011	Baixo	Baixo	Baixo	Baixo	Baixo	Baixo
Alguma preocupação	Baixo	Alguma preocupação	Baixo	Baixo	Baixo	**Some concerns**
Fischer-Shofty, M et al. 2013	Baixo	Baixo	Baixo	Baixo	Some concerns	**Some concerns**
Modabbernia, A et al. 2013	Baixo	Baixo	Baixo	Baixo	Baixo	Baixo
Lee, MR et al. 2013	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Fischer-Shofty, M et al. 2013b	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Davis, MC et al. 2013	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Jayaram, N et al. 2013	Alguma preocupação	Alto	Alto	Alguma preocupação	Alguma preocupação	Alto
Gibson, CM et al. 2014	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Davis, MC et al. 2014	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Woolley, JD et al 2014	Baixo	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Abu-Akel, A et al. 2015	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Horta de Macedo, LR et al. 2014	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Woolley, JD et al. 2015	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Cacciotti-Saija, C et al. 2015	Baixo	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Shin, NY et al. 2015	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação

Identificação do estudo	D1	D2	D3	D4	D5	Geral
Guastella, AJ et al. 2015	Baixo	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Singh, F et al. 2016	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Dagani, J et al. 2016	Baixo	Baixo	Baixo	Baixo	Baixo	Baixo
Lee, MR et al. 2016	Baixo	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Busnelli, M et al. 2016	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Woolley, JD et al. 2017	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Caravaggio, F et al. 2017	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Jarskog, LFet al. 2017	Baixo	Baixo	Baixo	Baixo	Baixo	Baixo
Buchanan et al. 2017	Baixo	Baixo	Baixo	Baixo	Baixo	Baixo
Ota, M et al. 2018	Alto	Alto	Baixo	Alto	Alguma preocupação	Alto
Fulford, D et al. 2018	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Warren, KR et al. 2018	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Lee, M et al 2019	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Wynn, JK et al. 2019	Baixo	Baixo	Baixo	Baixo	Baixo	Baixo
Halverson, T et al. 2019	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Strauss, GP et al. 2019	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
De Coster, Let al. 2019	Baixo	Baixo	Baixo	Baixo	Baixo	Baixo
Bradley, ER et al. 2019	Baixo	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Dwyer, KR et al. 2020	Baixo	Baixo	Alguma preocupação	Baixo	Alguma preocupação	Alguma preocupação
Porffy, LA et al. 2020	Baixo	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação

Identificação do estudo	D1	D2	D3	D4	D5	Geral
Abram, SV et al. 2020	Baixo	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Chuang, BJ et al. 2020	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Bradley, ER et al. 2020	Baixo	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Bradley, ER et al. 2021	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Andari, E et al. 2021	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Buchanan, RW et al. 2021	Baixo	Baixo	Baixo	Baixo	Baixo	Baixo
Wigton, R et al. 2021	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Browne, J et al. 2022	Alguma preocupação	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Korann, V et al. 2022	Alguma preocupação	Baixo	Baixo	Baixo	Baixo	Alguma preocupação
Mouchlianitis, ED et al. 2022	Alguma preocupação	Baixo	Baixo	Baixo	Baixo	Alguma preocupação
Saporta-Wiesel, L et al. 2024	Baixo	Baixo	Baixo	Baixo	Alguma preocupação	Alguma preocupação
İmamoğlu, A et al. 2024	Baixo	Alguma preocupação	Baixo	Baixo	Alguma preocupação	Alguma preocupação
Zierhut, M et al. 2024	Baixo	Baixo	Baixo	Baixo	Baixo	Baixo
Bradley, ER et al. 2024	Baixo	Baixo	Baixo	Alguma preocupação	Baixo	Alguma preocupação
Böge, K et al. 2024	Baixo	Baixo	Baixo	Baixo	Baixo	Baixo

Anexo 3 – Resultados resumidos

Autor Ano Nome do Artigo	Tipo de Estudo\ Método	Objetivo do estudo	Participantes	Intervenção	Principais resultados
Souza, Renan P et al. (2010)	Genetic Association Study	To understand if genetic variants in the oxytocinergic system were associated with schizophrenia severity and clozapine response.	140 adult individuals with schizophrenia (96 male 44 female)	> Clozapine treatment for a minimum of 6 months > Monitoring of Clozapine blood levels > Brief Psychiatric Rating Scale (BPRS) > Basal four-item positive symptom subscale (BPOS) > Basal three-item negative symptom subscale (BNEG) > Genotyping of Oxytocin and Oxytocin receptor SNPs	> Clozapine (CZP) response was nominally associated with two variants in Oxytocin (OXT): SNP4 and SNP6 > SNP6 showed nominal significant association with improvement of negative symptoms on the BNEG score > The haplotypes composed by SNP4 and SNP6 were nominally associated with clozapine response > Oxytocinergic receptor (OXTR) polymorphisms presented nominal significant effects on the severity of overall symptoms, namelly SNP9 AND SNP11, on the BPRS score as well as on the improvement of the positive symptoms, namelly SNP10, SNP13, SNP20 on the BPOS score > SNP10 and SNP13 presented high Linkage disequilibrium (LD)
Feifel, David et al. (2010)	Randomized Clinical Trial	To assess if oxytocin can reduce symptoms of schizophrenia	15 adult individuals with schizophrenia	3 weeks of daily intranasal oxytocin (titrated to 40 IU twice a day) and 3 weeks of daily placebo,both adjunctive to their antipsychotics, with 1-week washout between treatments. Positive and Negative Syndrome Scale (PANSS) Clinical Global Impressions-Severity (CGI-S) Urine and Blood Sampling and testing	> PANSS total scores improved significantly more across visits with OXT compared with placebo > PANSS scores were significantly lower with OXT versus placebo at the end point (week 3) visit with no significant difference at baseline, week 1, or week 2. > PANSS negative subscale scores were significantly lower for OXT versus placebo at week 3 only > PANSS positive scores were

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					significantly lower with oxytocin treatment when it was the first treatment but not when it was the second treatment > The CGI-I scores revealed a drug by treatment week interaction that approached significance. > The CGI-I was significantly lower for oxytocin versus placebo at week 3 but not at baseline, week 1, or week 2. > OXT scores were significantly lower than placebo scores at week 3 but not at baseline, week 1, or week 2.
Rubin, Leah H et al. (2010)	Cross- -Sectional Study	To assess the effects of menstrual cycle phase and related fluctuations in peripheral hormone levels on clinical symptoms in women with chronic schizophrenia.	108 adult individuals 50 patients with schizophrenia (23 women, 27 men) 58 controls (31 women, 27 men).	> Women were evaluated once during the early follicular phase (Day 2–4; low estradiol/progesterone) and once during the midluteal phase. Sessions were held during two separate cycles about 42 days apart. Men were tested in separate sessions approximately 42 days apart. > PANSS > Serum hormone assays of estradiol, prolactin, sex hormone binding globulin, Free testosterone and Oxytocin	> OXT levels did not change significantly across the cycle. > OXT levels did not differ between female groups. > Free testosterone levels were lower in male patients compared to controls (pb0.05), but estradiol and OXT levels did not differ between the two groups. > Higher levels of OXT were associated with lower scores on the total symptom, and positive, general psychopathology, and prosocial measures > A trend for higher OXT levels to be related to lower negative symptom scores in women was found. > In men, higher OXT levels were associated with better prosocial scores. > In female patients, higher levels of OXT were significantly associated

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					with better clinical symptoms on delusions, hallucinatory behavior, suspiciousness/paranoia, passive social withdrawal, and tension.
Goldman, Morris B et al. (2011)	Randomized Clinical Trial	To explore if oxytocin reverses impaired facial affect discrimination in schizophrenic patients with, relative to that in patients without, polydipsia.	24 adult individuals 5 patients with schizophrenia with polydipsia 8 patients with schizophrenia without polydipsia 11 healthy controls	> Urine osmolality > 10 IU, or 20 IU of oxytocin or placebo, on three separate occasions, approximately 7 days apart. > Rating of 36 photos of actors expressing one of six normative emotions (six photos each of fear, happiness, sadness, surprise, disgust, or anger) with pictures from a subset of Ekman and Friesen > The Benton Facial Discrimination Test	> Perceived intensity increased further following the lower dose (10 IU) of intranasal OXT in polydipsic patients relative to healthy controls, but did not differ in the two patient groups > Higher OXT dose (20 IU) was associated with no difference in polydipsic patients relative to healthy controls, but was associated with diminished intensity in polydipsic relative to nonpolydipsic patients > Higher OXT dose diminished fear intensity ratings in polydipsic relative to nonpolydipsic patients > Intensity ratings fell slightly with repeat exposure on subsequent trial days, but not specifically for fear. > Recognition (i.e., percent correct) following the lower dose of OXT worsened in the polydipsic group relative to healthy controls, but the effects were similar in the two patient groups. > The change in recognition with the higher dose did not differ between the polydipsic group and controls, but improved in polydipsic relative to nonpolydipsic patients. > Following the lower dose of OXT, undetected emotions diminished

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					across groups relative to the placebo condition indicating an improved hit rate > Misidentified emotions increased on the lower dose of OXT in the polydipsic group relative to healthy controls > Following the higher dose, misidentified errors showed a trend toward diminishing in polydipsic patients relative to controls, and fell significantly in polydipsic relative to nonpolydipsic patients > The higher dose improved recognition of fear in polydipsic relative to nonpolydipsic patients > The higher dose nearly normalized polydipsic patients bias to detect fear in nonfearful faces > Performance (percent correct, misidentified emotions) improved slightly for all emotions over subsequent trials (order effects=2–3%), but not significantly for fear, per se.
Rubin, Leah H et al. (2011)	Cross--Sectional Study	To assess the influence of sex, sex steroid hormone fluctuations, and peripheral oxytocin levels on emotional processing in men and women with schizophrenia.	105 adult individuals 48 patients with schizophrenia (26 Male 22 Female) 57 controls (26 Male 31 Female)	> All participants were tested in two separate sessions, approximately 42 days apart, to assess females across menstrual cycles once during the early follicular phase (Days 2–4; low estradiol/progesterone) and once during the midluteal phase (Days 20–22; high estradiol/progesterone) , and males in parallel. > Penn Emotion Acuity Test at the start	> Although OXT did not fluctuate across phases, higher average OXT levels related to perceiving faces as happier in both groups of women, but not in men (In patients, this pattern of effects remained significant after controlling for negative symptoms, suspiciousness/paranoia, and antipsychotic medication dose (Chlorpromazine equivalents))

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				> Plasma hormone assays assessed estrogen, progesterone, testosterone, and oxytocin.	
Pedersen, Cort A et al. (2011)	Randomized Clinical Trial	To assess if sustained daily intranasal administration of Oxytocin (OT) would improve social cognition as well as reduce psychotic symptoms in schizophrenia.	20 adult individuals with schizophrenia 11 individuals on oxytocin treatment 9 individuals on placebo	2-week treatment trial, with daily administration of 48 international units (IUs) of oxytocin or placebo > Blood and urine laboratory tests, ECGs and body weights obtained at screening and treatment day 14 in all subjects and also on treatment days 3 and 7 in inpatients. > Social cognition measures and psychiatric ratings were repeated beginning 50 min after the AM dose of study medication on treatment day 14. > Brüne Theory of Mind Picture Stories Task > Trustworthiness Task > Positive and Negative Symptom Scale (PANSS) > Paranoia Scale	> OXT group had significant improvements from baseline to treatment day 14 in accurate identification of second order false belief in the Brüne Task as well as significant reductions in PANSS total, positive subscale, general subscale, suspiciousness/persecutory item, anxiety item and Paranoia Scale scores. > OXT recipients showed trends toward significant improvement in accurate recognition of deception in the Brüne Task, rating untrustworthy faces (faces rated by a normative sample as untrustworthy) as less untrustworthy and reductions in PANSS negative subscale scores. > In the placebo group, the only significant change during the treatment period was a decline in PANSS suspiciousness item scores > The OXT group, compared to the placebo group, had a significantly greater decline in PANSS total scores. > A trend toward a significantly greater decline in PANSS general subscale scores for the OXT group compared to placebo was found.

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Montag, Christiane et al. (2012)	Genetic Association Study	To assess the influence of two single nucleotide polymorphisms (SNPs) within the oxytocinocinergic receptor (OXTR) gene on a measure of socio-emotional functioning in schizophrenic patients.	290 adult individuals 145 patients with schizophrenia: 128 paranoid, 5 undifferentiated, 4 disorganized, 3 catatonic, 1 residual, and 4 schizoaffective disorder 145 Healthy controls .	> Positive and Negative Syndrome Scale PANSS > Genotyping > Interpersonal Reactivity Index (IRI) assesses aspects of empathic responding, > A multiple choice vocabulary test (Mehrfachwahlwortschatztest, MWT-B) was applied to estimate verbal intelligence.	> In the patients group, the AA- or AG-genotype of rs2254298 was significantly more common in males than in females > Significant overall effects were detected for OXTR rs2254298, diagnostic group, and IQ; the interaction between OXTR rs2254298 genotype and diagnosis was significant > Post-hoc analyses indicated higher IRI 'empathic concern' in the combined OXTR AA/AG-genotype compared to GG > Diagnosis showed no significant main effect on 'empathic concern', but schizophrenic patients carrying one or two A-alleles of OXTR rs2254298 showed highest 'empathic concern' compared to all the other groups. > While females showed significantly higher values of IRI 'empathic concern' and 'personal distress', the significant impact of OXTR rs2254298 on 'empathic concern' remained > There was no significant interaction between gender and OXTR rs2254298. > Regarding the impact of OXTR SNPs rs2254298 and rs53576 on psychopathological symptom severity, t-tests for independent samples indicated significantly higher values on the PANSS general psychopathology score in patients

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					endowed with one or two A-alleles of rs2254298 > Regarding the IRI 'empathic concern', the model predicted 18.1% of total variance. Significant predictors of 'empathic concern' were OXTR rs2254298 genotype, age at first manifestation, PANSS negative score and PANSS general psychopathology score. > OXTR rs2254298 significantly predicted PANSS general psychopathology scores, but it showed only a trend on PANSS negative symptoms and no effect on age of onset of schizophrenia > Comparisons of the direct effects of OXTR rs2254298 on IRI 'empathic concern' and b-values from simultaneous regression of IRI 'empathic concern' on OXTR rs2254298 including each of the 3 potential mediators as additional independents did not indicate mediation effects
Averbeck, B B et al. (2012)	Randomized Clinical Trial	To assess if (1) patients with schizophrenia would have a deficit relative to a control group on recognizing emotions; and if (2) oxytocin could ameliorate some of this deficit.	1 59 adult individuals 30 patients with schizophrenia (24 male 6 female) 29 control participants (18 male 11 female) 2 21 patients with schizophrenia (all male, 11 from the 1st study)	Both Studies: > PANSS on the first day > Hexagon emotion discrimination task using faces drawn from the Ekman series with both morphed and unmorphed faces being used 2. > Two sessions of testing separated by	1. No results related to OXT 2. > Effects of OXT on emotion discrimination. Analysis of the fraction correct data of each participant, comparing OXT with placebo, morphed with non-morphed trials for each emotion showed main effects of drug, morph and emotion

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			11 oxytocin first (5 from 1st study) 10 placebo first (6 from 1st study)	7 or 8 days >Upon arrival, the participant self-administered either 24 IU oxytocin or saline placebo. > All individuals received both oxytocin and placebo and the order in which they received them was randomized. > Following administration, behavioral testing commenced after a 50-min delay. > Brief Mood Inventory Scale before testing began, 50 min after drug delivery, on both the drug and placebo visit.	> Although the overall performance was generally improved on OXT , none of the individual emotions showed a significant difference, although fear showed a trend in the unmorphed condition > Performance of the patients on OXT was still lower than the performance of the control group, as there was still a main effect of group > The control group performed at 72% correct, the patient group off OXT in the second experiment at 54% correct and the patient group on OXT at 58% correct.
Teltsh, Omri et al. (2012)	Genetic Association Study	To explore whether the PANK2, ATRN, AVP and OXT genes are associated with schizophrenia in an large inbred Arab-Israeli pedigree, and search for disease-causing variants. To study the possible functional role of these variants by examining their correlation with the expression of OXT and AVP in the brain.	1. Arab-Israeli families 56 individuals from one clan, 25 with schizophrenia spectrum disorders. 2. 52 nuclear families of Arab-Israeli origin - 186 individuals 90 with schizophrenia spectrum disorders 25 arab unrelated controls 274 healthy unrelated jewish individuals 60 unaffected caucasians 3. 272 adult jewish patients with schizophrenia (177 male 95 female, 136 Ashkenazi ancestry)	> Mutation screening - genes ATRN, PANK2, AVP and OXT > Genotyping - seven SNPs > Expression analysis of AVP and OXT - Microarray expression levels of OXT and AVP, genomic DNA samples we received from SMRI for genotyping the SNPs of interest in OXT and AVP,	> Two SNPs are located in the first (rs6139004) and second (rs34097556) introns of OXT and the remaining three are located in the first (rs3787482 and rs2282018) and second (AVP3011589) introns of AVP > Two more SNPs on the disease-associated haplotype: rs4813626 in the region upstream of OXT and rs2740204 downstream of AVP > The OXT related SNPs rs4813626 , rs2740204 and AVP3011589, were significantly associated with schizophrenia, even after multiple testing correction. > In the Arab nuclear family sample, three SNPs were nominally associated with disease compared to normal controls. One of these

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			273 adult unrelated israeli jew controls (137 male 136 female, 173 Ashkenazi ancestry) Expression study (post mortem). 104 subjects, 35 individuals with schizophrenia 34 with bipolar disorder 35 were unaffected controls		associations remained significant after correction for multiple testing. This SNP, rs4813626, is one of the SNPs that were significantly associated in the extended pedigree. >In the Jewish case-control replication sample, two SNPs were found to be nominally associated with schizophrenia in men only. One of these, rs4813626, was still significant after correction for multiple testing. > The 'GGAAGGT haplotype,' which had a frequency of 0.44 among the affected individuals, was nominally associated with disease compared to the unaffected family group and was still significant after multiple testing correction compared to healthy unrelated controls from the general population. > Linkage disequilibrium (LD) analysis of the affected members from this sample revealed one main LD block of 2.4 kb from rs2740204 to rs2282018 and an additional block of 0.3 kb which contained rs6139004 and rs34097556. > In the extended pedigree, there were significantly more affected men than women who carried the haplotype, and more women than men who carried the haplotype but did not develop schizophrenia. > Examination of the clinical diagnoses of all the affected individuals in the pedigree that carry

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					the 7-SNP haplotype in the OXT and AVP cluster revealed that almost all of them had predominant negative symptoms, including social isolation, affective flattening and decrease in social skills.
Feifel, David et al. (2012)	Randomized Clinical Trial	To explore the effects of oxytocin on cognition	15 adult individuals with schizophrenia (12 male, 3 female)	>3 weeks of daily intranasal oxytocin (titrated to 40 IU twice a day) (20 IU twice daily for 1 week, then 40 IU twice daily thereafter)\ and 3 weeks of daily placebo,both adjunctive to their antipsychotics. Order of intranasal treatment was randomly assigned and there was a 1-week washout between treatments. >PANSS Patients performed the following assessments at baseline and at the last visit (week 3) of each treatment period. >California Verbal Learning Test (CVLT) and >Letter Number Sequencing (LNS) task	> None of the ANOVAs performed on the CVLT measures revealed a significant main effect of treatment sequence or a significant interaction between drug X treatment sequence >There were significant effects of drug for total recall trials 1–5, short delayed free recall, and total recall discrimination, but not for long delay free recall, or total recognition discriminability. > Post-hoc paired t-test performed on the measures that produced a significant drug effect revealed that OXT scores were significantly higher than placebo scores for total recall trials 1–5, for short delayed free recall and total recall discrimination but not for long delay free recall, or total recognition discriminability.
Sasayama, Daimei et al. (2012)	Cross--Sectional Study	To assess if cerebrospinal fluid oxytocin levels would be lower in patient groups compared to healthy controls and if symptom severity would be negatively correlated with the oxytocin levels.	58 male adult individuals 27 patients with schizophrenia 17 patients with major depressive disorder (MDD) 21 healthy controls	> Lumbar puncture and oxytocin assay Immediatly after: > PANSS > GRID Hamilton Depression Rating Scale, 17-item version (HAMD-17)	> A one-way ANOVA using the transformed oxytocin levels as the dependent variable indicated no significant difference between diagnostic groups. > The transformed OXT levels were significantly negatively correlated with negative subscale of PANSS. > The transformed OXT levels in

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					schizophrenic patients were significantly negatively correlated with chlorpromazine equivalents of total antipsychotic dose and second generation antipsychotic (SGA) dose, but not with chlorpromazine equivalents of first generation antipsychotic (FGA) dose. > Those prescribed SGA had significantly lower CSF OXT levels compared to those not prescribed SGA. > Partial correlation between transformed OXT levels and negative subscale of PANSS, removing the linear effects of total antipsychotic dose, was statistically significant. > Removing the linear effects of SGA dose instead of total antipsychotic dose also resulted in significant correlation of transformed CSF OXT levels with negative subscale as well as with total PANSS score.
Fischer-Shofty, Meytal et al. (2013)	Randomized Clinical Trial	To examine the effect of intranasal oxytocin (IN OT) on fear recognition in individuals with schizophrenia	65 adult individuals 30 patients with schizophrenia (27 male and 3 female) 35 healthy individuals (32 male and 3 female)	> two sessions, one after IN OT administration ((24 IU) and the other 7 days later, following placebo administration. Half of the participants were randomly assigned to receive IN OT in the first session, and half began with placebo administration. Behavioral tasks began 45 min after substance administration . > PANSS > Clinical Global Impression scale (CGI)	>Overall, both patients and healthy control participants were more accurate in recognizing fearful facial expressions, but not happy faces, following intranasal oxytocin (IN OT) administration compared to placebo. >IN OT did not differentially affect emotion recognition in patients and healthy controls. >A significant improvement in fear recognition following IN OT administration was observed only

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				> Vocabulary subtest > Abstract test of the Shipley Institute of Living Scale >Facemorphing task (test recognition of emotional facial expressions) >Depression Adjective Check Lists (DACL)	among individuals whose baseline performance was below the median, regardless of psychiatric status. >No overall treatment effect or mood type interaction was found for mood ratings after IN OT administration. >A significant interaction between treatment and emotional facial expression was found, showing differential effects of IN OT and placebo on fear (but not happiness) recognition. >Patients with schizophrenia had significantly higher negative mood ratings than controls, though positive mood ratings did not differ. >Reaction time to fearful faces was significantly longer than for happy faces; patients also had longer reaction times overall than controls. >The regression analysis indicated that lower placebo performance predicted a greater improvement in fear recognition following IN OT administration. >The above-median baseline performance group showed no significant difference between IN OT and placebo trials. >No significant moderating effect of psychiatric status (patient vs control) on the drug effect was found.
Modabbernia, Amirhossein et al. (2013)	Randomized Clinical Trial	To assess the efficacy and tolerability of oxytocin intranasal spray (given as an	40 adult patients with schizophrenia (33 male 7 female) 20 with oxytocin treatment (17	>Participants were inpatients on a stable dose of risperidone (5 or 6 mg/day) for a minimum of 4 weeks	> There was a significant effect for time X treatment interaction on the PANSS total, positive, negative and

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		adjuvant to risperidone) in patients with schizophrenia.	male 3 female) 20 with placebo (16 male 4 female)	prior to entry. The patients were randomly assigned to oxytocin IN spray or placebo IN spray containing normal saline for 8 weeks. Oxytocin spray was administered as 20 IU twice a day for the first week followed by 40 IU twice a day for the following 7 weeks. >PANSS at baseline and at weeks 2, 4, 6 and 8 > Extrapyramidal Symptom Rating Scale (ESRS) at baseline and at weeks 1, 2, 4, 6 and 8	general psychopathology subscale scores. > By week 8, patients in the OXT group showed significantly greater improvement on the positive , negative and general psychopathology subscales and total PANSS scores than the placebo group. >At the end of the trial, changes of 6.7 (11.2 % reduction from the baseline) and 1.6 (1.7 % reduction from the baseline) in the total score were observed in the OXT and the placebo groups, respectively >At the end of week 8, changes of 3.3 (20 % reduction from the baseline) and 0.7 (4 % reduction from the baseline) in the positive subscale score were observed in the OXT and the placebo groups, respectively > At the end of the trial, changes of 1.3 (7 % reduction from the baseline) and 0.3 (2 % reduction from the baseline) in the negative subscale score were observed in the OXT and the placebo groups, respectively > At the end of the trial, changes of 2.0 (8 % reduction from the baseline) and 0.6 (2 % reduction from the baseline) in the general psychopathology subscale score were observed in the OXT and the placebo groups, respectively

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Lee, Mary R et al. (2013)	Randomized Clinical Trial	To assess the effect of intranasal oxytocin on olfactory identification using the UPSIT. To investigate concomitant changes in negative and positive symptoms, as well as their relationship to performance on the UPSIT as a consequence of oxytocin administration.	28 adult patients with schizophrenia or schizoaffective disorder (20 male 8 female) 13 with oxytocin treatment 15 with placebo	> 3 week treatment with adjunctive intranasal 20 IU oxytocin or placebo twice daily in people with SZ. Patients went a two week lead in stabilization period prior to randomization in the 3 week study and and then followed with weekly study visits. > University of Pennsylvania Smell Identification Test (UPSIT) >The Brief Psychiatric Rating Scale (BPRS) total score > The modified Scale for the Assessment of Negative Symptoms (SANS) > The Clinical Global Impression (CGI) > BPRS, SANS, and CGI were obtained at baseline, week 1 and after the last dose of study medication.	>Regarding total BPRS, there was a significant treatment × time interaction favoring placebo during the study in the repeated measures analysis. > There was a treatment × time interaction for the SANS total scores. However, on exploratory analysis of treatment setting, there was a treatment group × setting interaction favoring OXT in the inpatient setting. > At week 3, there was a significant difference between treatment groups for the inpatient mean total SANS scores only: OXT : 25.5 ± 7.2, placebo: 38.7 ± 7.4, difference = – 8.0 ± 3.4, t = – 2.3, df = 33.8. >SANS subscore showed significant improvement in the OXT group in the inpatient setting. >There was a significant treatment group × time interaction such that there was a significant improvement in total UPSIT score in the OXT group relative to placebo from baseline to endpoint. > There was a treatment group × time interaction for pleasant smell UPSIT subscore only such that the OXT group improved significantly with no significant treatment effects found for neutral or unpleasant smells. Although performance deficits on the UPSIT have been shown to be associated with negative symptoms, we found no correlation overall at baseline or, for either treatment

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					group, between negative symptom change and UPSIT total score change or for subscore changes.
Fischer-Shofty, M et al. (2013)	Randomized Clinical Trial	To examine the effect of oxytocin (OT) on social perception among patients with schizophrenia.	83 adult individuals 35 patients with schizophrenia (31 men and 4 women) 48 psychologically healthy participants (39 men and 9 women)	> Participants were randomly assigned into groups for the first administration, of either 24 IU OT or placebo 45 min prior to performing the behavioral task(Interpersonal Perception Task). Seven days later at the second session of the experiment, participants underwent the same procedure with the other substance. > Positive and Negative Symptoms of Schizophrenia (PANSS) scale > Clinical Global Impression (CGI) > Shipley Institute of Living Scale > Interpersonal Reactive Index (IRI) >Interpersonal Perception Task (IPT) > Depression Adjective Check Lists (DACL)	> Patients with schizophrenia had significantly lower empathy scores than the healthy controls on the IRI perspective-taking subscale > A significant treatment effect was found, indicating that the mean of performance in the task was higher following the administration of OXT as compared to the placebo. > A significant relationship category effect was found, indicating that the participants were generally better in recognizing kinship as compared to intimacy. > No overall group differences were found, indicating that although the patients scored lower in the task than the controls, these differences did not reach significance. > For the patient group, both a significant treatment effect and a significant relationship category effect were found. > Follow-up t-tests revealed a significant difference between the OXT and the placebo treatments only in the recognition of kinship, but not intimacy. > For the control group, a significant condition effect and a marginally significant treatment effect were found.

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Rubin, Leah H et al. (2013)	Cross--Sectional Study	To compare the concentration of peripheral OT and AVP levels in unmedicated, acutely-ill first-episode schizophrenia patients to healthy controls. To evaluate whether peripheral OT and AVP levels are associated with positive symptom severity and verbal learning in these patients.	76 adult individuals (48 male and 28 female) 38 adult patients (24 men and 14 women) with schizophrenia (n = 34; 90%) or schizoaffective disorder depressed type (n = 4; 10%) 38 healthy controls (14 women, 24 men)	>PANSS >California Verbal Learning Test (CVLT) >WAIS-R Digit Span >Trail Making Test >WMS-III Spatial Span Test >Serum hormone assays of OT and AVP	> Patients demonstrated increased AVP levels compared to healthy controls > The two subject groups showed similar levels of OT. No hormone levels differed as a function of sex and there were no sex by group interactions. > OXT and AVP were not associated in patients, but there was a trend for higher levels of AVP to relate to OT in controls. > Higher AVP levels were associated with more severe positive symptoms and lower verbal learning scores in female, but not in male, patients. > These differences were significant for verbal learning and marginally significant for positive symptoms. > Exploratory analyses on individual PANSS items on the positive subscale indicated that in female patients, higher levels of AVP were significantly associated with greater grandiosity. > There was also a trend for higher levels of AVP to relate to suspiciousness > AVP was not associated with any of the secondary cognitive outcomes > OXT was not associated with clinical symptoms or cognitive functioning in female or male patients. OT was also not associated with verbal learning in female or male controls.

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Davis, Michael C et al. (2013)	Randomized Clinical Trial	To determine if a single dose of intranasal oxytocin acutely improves social cognitive functioning in schizophrenia	23 adult male patients with schizophrenia 11 with oxytocin treatment 12 with placebo	Inicial assessment: >PANSS > CGI > MIRECC Global Assessment of Functioning (MIRECC GAF) >Social cognition assessment battery: (1)Theory of mind using Part III of The Awareness of Social Inference Test; 2)Empathy using the Emotional Perspective Taking Task; 3) Social perception using the Half Profile of Nonverbal Sensitivity; 4) Facial affect recognition was assessed by asking participants to identify facial expressions of emotion in still images from the standardized stimulus set developed by Ekman >One week after inicial assessment, subjects were randomized to receive either intranasal OT(total dose of 40 IU) or placebo. Thirty minutes after treatment, each subject completed the same assessments in the same order as in their baseline visit. At the conclusion of the visit, participants were interviewed regarding their subjective experiences of the treatment (Subjective experience assessment)	>OXT did not significantly improve performance relative to placebo on the total social cognition composite measure >OXT significantly improved performance in high-level social cognition with a large effect size. >OXT treatment did not improve performance on any individual social cognition measure when compared to placebo, though it reached a trend level of significance in improving the TASIT III sarcasm score. >In general, patients later randomized to receive OXT scored lower on baseline social cognition measures, particularly the EPTT and Ekman facial affect recognition tasks. >There were no significant differences in clinical symptom improvement between subjects treated with OXT vs. placebo, as assessed by PANSS, CGI-S, and CGI-I ratings >Side effects of nasal spray treatment were reported in 2/12 subjects receiving placebo (rhinorrhea and mild nasal irritation) and in 2/11 subjects receiving OxT (mild tingling on nasal inhalation and mild drowsiness).
Walss-Bass, Consuelo et al. (2013)	Cross--Sectional Study	To identify relevant associations between oxytocin and both social cognitive capacity and bias.	80 adult individuals 60 patients with schizophrenia (36) or schizoaffective disorder (24), 21 of those patients being	> Blood measurements of OXT levels and 39 inflammatory markers,of which nine were chosen for principal component analysis (PCA) (	> Patients and controls differed significantly in terms of education and performance on the HVLT, Category Verbal Fluency Tasks

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		To examine the potential role of inflammation in these processes.	defined as having clinically significant delusions, and 39 as non-delusional. (45 male 15 female) 20 healthy controls (14 male 6 female)	(interleukin-1β [IL-1β], IL-1 receptor antagonist [IL-1RA], IL-2, soluble IL-2 receptor [sIL-2R], IL-6, IL-8, IL-10, tumor necrosis factor-α [TNF-α] and interferon-γ [IFN-γ]) > Waiting Room Task (WRT) > Hopkins Verbal Learning Test (HVLT)—Revised , Phonemic (letter) and Category (animals and occupations) tests > Trail Making Test Parts A and B > Brief Psychiatric Rating Scale (BPRS) > Negative Symptom Assessment—16-item version (NSA-16)	and Trail Making Test > Patients without delusions scored lower on the BPRS (mean = 46.44 [SD = 9.98] vs. 53.71 [9.98], Z = – 2.483, p = 0.013) and NSA-16 (41.13 [9.53] vs. 46.76 [11.19], Z = – 2.025, p = 0.043) scales. > Patients without delusions performed better on neurocognitive measures than did patients with delusions: 1) HVLT: mean = 18.97 (6.15) vs. 14.43 (SD = 4.39), t = 2.995, p = 0.004; 2) Letter fluency: 34.79 (13.35) vs. 28.15 (8.34), Z = – 1.835, p = 0.066; 3) Animal category fluency: 17.28 (7.26) vs. 12.52 (5.59), Z = – 2.533, p = 0.011; 4) Occupations category fluency: 12.15 (4.79) vs. 10.38 (4.42), Z = – 1.454, p = 0.146; and 5) Trail Making Test: 165.24 (56.15) vs. 213.76 (48.92), t = – 3.076, p = 0.003. > Controls performed significantly better than the full patient group on the WRT: 1) Gaze capacity: Z = – 2.798, p = 0.005; 2) Gaze bias: Z = – 2.343, p = 0.019; 3) ToM capacity: – 3.260, p = 0.001; and 4) ToM bias: Z = – 2.463, p = 0.014. > Controls also performed significantly better than each patient subgroup on all WRT variables, with no significant differences in WRT scores between patients with and without delusions. > Levels of OXT were significantly lower in controls compared to

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					patients without delusions (Z = –2.658, p = 0.008) > Patients without delusions had significantly lower levels of OXT than did patients with delusions (Z = –2.085, p = 0.037). > Social cognitive capacity and bias were strongly correlated in all three groups, for both subscales > Significant positive correlations between OXT and ToM bias and significant negative correlations between OXT and both gaze and ToM capacity in patients with delusions were found >No significant correlations were identified between OXT and any of the social cognitive capacity or bias subscales in patients without delusions. > In controls, significant correlations were found between OXT and social cognitive bias, but not between OXT and social cognitive capacity. > No significant differences in inflammatory marker levels between the three groups were found > PCA revealed the presence of two factors: 1) Factor 1 included IL-2, IL-6, IL-8, TNF-α and IFN-γ, and accounted for 48.59% of the total variance; 2) Factor 2 included IL-1β, IL-1RA, sIL-2R and IL-10, and accounted for 28.78% of the total variance. Factor 1 was significantly positively correlated with OXT in patients without delusions, but was

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					uncorrelated with OXT in controls and in patients with delusion > Significant correlations were found between Factor 1 and ToM capacity in the control group (r = – 0.462, p = 0.007) and Factor 2 and ToM bias in patients with delusions (r = 0.395, p = 0.017,= not significant after Holm–Bonferroni correction [adjusted alpha = 0.013]).
Jayaram, N et al. (2013)	Randomized Clinical Trial	To study the effect of yoga therapy on facial emotion recognition deficits (FERD), negative symptoms and social-occupational functioning as add on treatment in antipsychotic stabilized schizophrenia patients as compared to a waitlist group. To study the effect of yoga therapy on plasma oxytocin levels and its correlation with FERD.	27 adult patients with schizophrenia (19 male 8 female) 15 were in the yoga group(12 male 3 female) 12 were in the waitlist group (7 male 5 female)	>The patients in the yoga group received yoga therapy along with antipsychotic medication for a period of 1 month while patients in the waitlist group continued antipsychotic medication alone without any additional intervention. Assessments performed at baseline were repeated after a period of 1 month in all subjects. >Scale for assessment of positive symptoms (SAPS) >Scale for assessment of negative symptoms (SANS) >Socio-occupational functioning scale (SOFS) >Tool for recognition of emotions in neuropsychiatric disorders (TRENDS) >Blood sample was drawn to assess the plasma oxytocin levels.	>On comparison of baseline and follow-up variables, both groups showed significant improvement in negative symptoms and positive symptoms (P<0.001). > However only the yoga group showed a significant improvement in SOFS scores (P<0.001), TRENDS accuracy score (TRACS) (P<0.001), TRENDS over identification score (TOI) (P=0.03) and plasma oxytocin level (P=0.01) >On correlation analysis no significant correlation was found between plasma oxytocin levels and TRACS or TOI.
Montag, C. et al. (2012)	Genetic Association Study	To investigate associations between genetic variants of the oxytocinergic system and schizophrenia.	406 adult individuals with shizophrenia 406 normal controls	>Positive and Negative Syndrome Scale (PANSS) >Genotyping	> Chi-squared tests revealed significantly different genotype frequencies between groups (schizophrenic patients and healthy controls) with respect to rs53576 and

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					rs237885 with rs53576(AG) and rs237885(TT) being more common and rs53576(GG) being less common in the schizophrenia sample compared to controls. > When males and females were tested separately for the distribution of genotypes, all group differences between schizophrenic patients and healthy controls were attributable to the male sample (OXTR rs53576: genotype frequencies: χ2 6.114, P 0.047; allele frequencies A/G: χ2 5.142, P 0.023; OR(95%CI) 1.347(1.041 – 1.743); OXTR rs237885: genotype frequencies: χ2 7.777, P 0.020; allele frequencies G/T: χ2 4.401, P 0.036; OR(95%CI) 0.776(0.612 - 0.983). > Allele frequencies differed significantly with respect to rs53576; the A-allele carriers were of higher risk of belonging to the schizophrenia group compared to non-A-carriers. > There was a significant association between the studied genotypes and schizophrenia risk for rs53576 (z 2.448, P(asymptotic) 0.014, two-sided). > OXTR SNP rs237885 (GG vs. GT/ TT) significantly predicted status as a patient or control (Wald 9.381, df 1, P 0.0022). > There was a significant association between OXTR rs53576 and PANSS general psychopathology score (GG: 37.8 1.3, AG: 34.2 1.4, AA: 30.9 2.8, F

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					2.315 [6;620], P 0.032). > Post-hoc testing revealed higher PANSS general scores in GG- than in AA-genotype patients (F 3.479 [2;311]; P 0.032, pairwisecomparisons AA GG: P(Bonferroni) 0.054). > PANSS negative scores were associated with OXTR SNP rs237902 (GG: 21.1 0.9, AG: 19.6 0.9, AA: 17.5 1.5; F 1.891 [6;620], P 0.080, post-hoc: F 3.433 [2;311], P 0.034, pairwise comparisons GG AA: P(Bonferroni) 0.041). > PANSS positive scores were associated with age (F 4.434, df [1;311], P 0.036).
Gibson, Clare M et al. (2014)	Randomized Clinical Trial	To explore whether oxytocin can improve social cognition and social skills in individuals with schizophrenia over a six-week period.	14 adult individuals with schizophrenia 8 with oxytocin treatment 6 with placebo	> Patients self-administered intranasal study drug twice daily ,the total insufflation at each dose being approximately 24 international units (IU) of OT or placebo > PANSS score > The Emotion Recognition-40 (ER-40), > Theory of Mind Picture Stories Task, > The Reading the Mind in the Eyes Test, > The Interpersonal Reactivity Index (IRI), > The Trustworthiness Task , > The Ambiguous Intentions Hostility Questionnaire-Abbreviated Version (AIHQ). > Social skills were assessed with a role-	> The placebo group had significantly greater positive symptoms at baseline > Within group analyses revealed a significant improvement in fear recognition in the OT sample [t(7) = 2.37, p = .05] and a corresponding large effect size. > Both groups significantly improved on Theory of Mind (ToM) as measured by the Brune total score [OT: t(7) = 2.82, p = .03; PL: t(5) = 2.95, p = .03]. > Both groups demonstrated trend level improvements for the ToM sub-score, deception detection [OT t(7) = 2.05, p = .08; PL: t(5) = 2.24, p = .08].

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				play measure administered at the baseline and six-week visits.	> The OT group showed a trend level improvement for third order ToM [t(7) = 1.93, p = .10] and the PL group showed a trend level improvement for second order ToM [t(5) = 2.24, p = .08]. > Both groups generally showed large effect size improvements on the Brune indices. > No significant within group changes on the Trustworthiness Task for either group > The OT group showed a significant increase in self-reported perspective taking (PT) at six weeks [t(4) = 3.26, p = .03]. > Both groups showed a significantly reduced hostility bias at six weeks [OT: t(7) = – 2.80, p = .03; PL: t(5) = – 4.34, p = .007]; > The OT group had a significant decrease on all PANSS sub-scores [positive: t(7) = – 3.64 p = .008; negative: t(7) = – 5.00, p = .002; and general symptom scores: t(7) = – 2.51, p = .04)] at six weeks. > The PL group showed a significant decrease in PANSS positive [t(5) = – 2.62 p = .05] and general symptoms scores [t(5) = – 3.16, p = .025] and no significant change on negative symptom ratings.
Davis MC, Green MF, Lee J, et al. (2014)	Randomized Clinical Trial	To assess whether intranasal oxytocin (OT), given before social cognitive training,	27 male patients with schizophrenia	One week before the intervention: >the MATRICS Consensus Cognitive Battery (MCCB)	> Regarding the social-cognition composite score, a significant main effects of time was found, indicating

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		enhances learning of social cognitive skills.	13 with oxytocin treatment 14 with placebo	>Brief Psychiatric-Rating Scale (BPRS) >Clinical-Assessment Interview for Negative Symptoms (CAINS) >One week later, subjects began social cognitive training skills (SCST) in groups that included individuals receiving OT (40 IUs) or placebo 30 min before the SCST. The trial took 6 weeks, with 12 SCST sessions in between. The social-cognition measures and the MCCB were administered at 1 week before the first intervention and then at 1 week and 1 month after the final SCST session. The BPRS and the CAINS were re-administered at 1 week post-treatment. > Facial affect recognition Profile of Nonverbal Sensitivity (PONS) > The empathic accuracy task >Mayer–Salovey–Caruso emotional intelligence test (MSCEIT) > The Awareness of Social Inference Test (TASIT) > Side effect checklist > Columbia Suicide Severity Rating Scale (C-SSRS)	improvement across the combined-treatment groups (p=0.03 at 1 week posttreatment and p<0.01 at 1 month) > Significant main effects of time on individual measures of facial affect recognition (p<0.0001 at 1 week and 1 month posttreatment); the MSCEIT Managing Emotions total score (p=0.01 at 1 week posttreatment and p=0.03 at 1 month); and the PONS total score (p=0.04 at 1 month posttreatment) on the combined-treatment groups. > Regardning empathic accuracy it was found that subjects assigned to OT demonstrated significantly greater improvements than placebo on the total posttreatment (p=0.03, d=0.92) and at 1 month (p=0.03, d=0.98) > There were no effects of OT on basic neurocognition as measured by the MCCB nonsocial composite score. > There was a main effect of time (across the combined-treatment groups) on the MCCB nonsocial composite score between baseline and 1 month follow up (p<0.01), suggesting overall improvement that may have been related to SCST and/or practice effects.

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Woolley JD, Chuang B, Lam O, et al. (2014)	Randomized Clinical Trial	To assess oxytocin's effects on automatic and controlled social cognition in male patients with chronic schizophrenia (SZ) and age-matched healthy controls (HC).	60 adult male individuals 29 patients with a chronic psychotic disorder (22 with schizophrenia and 7 with schizoaffective disorder) 31 healthy controls	> 2 testing days separated by at least one week. On each test day, 40 IU of OT or saline placebo (PCB) was self-administered via nasal spray > Reading the Mind in the Eyes Test" (RMET) > The Awareness of Social Inference Test (TASIT) > Positive And Negative Symptom Scale (PANSS) to a subset of 19 patients	> There was a significant Drug × Task × Group interaction, F(1, 58) = 8.75, p = 0.004, Cohen's d = 0.78 (Fig. 1). > There was a main effect for Group (F(1, 58) = 45.85, p < 0.001) reflecting the fact that patients with SZ showed worse performance overall compared to HC's on our tests of social cognition, but no significant main effect for Drug (F(1, 58) = 2.94, p = 0.09). > For low-level, automatic social cognition, there was no significant Drug × Group interactions for the composite score or for any of the five subscales > For high-level, controlled social cognition,there was a significant Drug × Group interaction (F(1, 58) = 8.55, p = 0.005) for the composite score. Thus, OT appears to have differential effects on controlled social cognition in SZ and HC. In follow-up analysis, a significant Drug effect for SZ, (F(1, 28) = 12.39, p = 0.001) was found, but not for HC, reflecting the fact that OT administration selectively improved performance on controlled social cognition in patients with SZ. > On secondary analyses, it was found that OT significantly improved performance for SI-E "think" verbal, F(1, 28) = 7.16, p = 0.01 and "say", F(1, 28) = 7.64, p = 0.01) subscales in

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					patients with SZ. > Groups did not significantly differ in performance on the control task (F(1, 59) = 0.04, p = 0.85)
Rubin, Leah H et al. (2014)	Cross--Sectional Study	To examine alterations in oxytocin (OT) and vasopressin (AVP) levels and the relation of endocrine levels to behavior and cognition in patients with schizophrenia, schizoaffective disorder, and psychotic bipolar disorder and in their first-degree family members.	427 adult individuals (163 male 264 female) 57 patients with schizophrenia (35 male 22 female) 34 patients with schizoaffective disorder (26 with the bipolar type) (15 male 19 female) 75 patients with psychotic bipolar disorder (24 male 51 female) 61 first-degree relatives without a history of psychosis of the patients with schizophrenia (15 male 46 female) 43 first-degree relatives without a history of psychosis of the patients with schizoaffective disorder (14 male 29 female) 91 first-degree relatives without a history of psychosis of the patients with psychotic bipolar disorder (32 male 59 female) 66 healthy controls (28 male 38 female)	> PANSS > Montgomery Asberg Depression Rating scale > Young Mania Rating scale. > The Penn Emotion Recognition-40 test (PENN ER-40) > The Brief Assessment of Cognition in Schizophrenia (BACS) >Serum Hormone Assays for OT and AVP	> There were significant group differences on the BACS composite and in community functioning (P's < .001). > All proband groups performed worse than healthy controls on both measures (P's < .001). > Schizophrenia probands performed worse than bipolar probands on both measures (P's < .05). > On the PENN ER-40, schizophrenia probands (P < .001) performed worse than healthy controls and bipolar probands (P = .04). > Schizophrenia probands (B = −0.44, SE = 0.14, P = .002) and their relatives (B = −0.37, SE = 0.12, P = .002) showed lower AVP but not OT levels, compared with controls. > Bipolar probands (B = −0.27, SE = 0.13, P = .03) also had lower levels of AVP but not OT, compared with controls. > Relatives of bipolar probands showed a trend for lower levels of AVP but not OT, compared with controls (B = −0.20, SE = 0.11, P = .07). > Post hoc comparisons yielded no

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					significant differences in peptides between proband groups or first-degree relative groups. > All proband and relative groups showed a higher proportion of individuals with lower levels of AVP (ie, <1 SD from controls), compared with controls using the Lambda statistic. > There were more schizophrenia probands than bipolar probands with low levels of AVP (P = .04) > Familiality estimates were highly significant for both OT (h 2 = 0.79, SE = 0.08, P = 3.97e−15) and AVP (h 2 = 0.78, SE = 0.10, P = 3.93e−12) in the pooled data of proband families. > Higher levels of OT were associated with better emotion recognition accuracy in healthy controls (β = 0.40, B = 3.76, SE = 1.13, P < .001) but not in patients with schizophrenia or their relatives > Higher levels of OT in healthy individuals were associated with better emotion recognition of neutral (β = 0.35, B = 7.17, SE = 2.64, P < .01), happy, (β = 0.27, B = 1.44, SE = 0.69, P = .04), and sad faces (β = 0.26, B = 6.03, SE = 2.96, P = .04). > Higher levels of OT were associated with better global neuropsychological performance in healthy controls (β = 0.26, B = 0.36, SE = 0.17, P = .04) but not in any proband or relative group.

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					> In schizophrenia, higher levels of OT, but not AVP, were associated with more severe positive symptoms (β = 0.32, B = 2.67, SE = 1.17, P = .02). > In schizoaffective probands, those with lower AVP levels had more severe manic (β = −0.50, B = −4.06, SE = 1.29, P = .002) and positive symptoms (β = −0.40, B = −2.68, SE = 1.12, P = .02).
Davis, Michael C et al. (2014)	Genetic Association Study	To assess the relationship of OXTR in schizophrenia and social cognition.	74 adult patients with schizophrenia (53 male 21 female)	> Genotyping 7 oxytocin receptor OXTR single nucleotide polymorphisms SNPs > Half-Profile of Nonverbal Sensitivity (PONS) The Awareness of Social Inference Test — Part III (TASIT) > Mayer–Salovey–Caruso Emotional Intelligence 2.0 (MSCEIT) > Brief Psychiatric Rating Scale (BPRS) > Scale for the Assessment of Negative Symptoms (SANS)	> Only one SNP (rs2268493) showed statistically significant (p < .05) differences among allele subgroups on the social cognitive measures. > Rs2268493 genotypes showed significant differences on the social cognition summary score, as well as the TASIT and PONS. > Participants with the 'TT' genotype (n = 50), the identified risk allele, performed more poorly across these measures than those in the combined 'CC + CT' group (n = 23). > None of the SNPs we genotyped were significantly associated with BPRS positive symptoms or SANS scores > There were trend level associations for the rs1042778 genotype with the SANS expression subscore (p=.087)
Brown, Elliot C et al. (2014)	Cross--Sectional Study	To investigate the role of endogenous oxytocin in social	28 right-handed adult patients with schizophrenia (15 male 13 female)	> PANSS > Joystick based The Approach-Avoidance Task (AAT)	> Significant inter-correlations between happy straight and happy averted AAT effect scores (rs

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		Approach and Avoindance behaviour in schizophrenia.		> Face Emotion Identification Task (FEIT) >Face Emotion Discrimination Task (FEDT) >The Paranoia Scale >Blood sample collection and assessment	(28)=0.51; p=0.006) were found. > Significant inverse correlations between AAT scores for angry-straight vs. happy-straight (rs (28)= −0.479, p=0.01) and angry-straight vs. happy-averted (rs (28)= −0.413, p=0.03) were found. > Significant main effects of gaze direction (Wald-χ2=4.90, p=0.02), response (Wald-χ2=15.13, p=≤0.001) and basal oxytocin levels (Wald-χ2=7.51, p=0.006) were found. > Significant 2-way interaction effects between emotion and response (Wald-χ2=18.33, p=≤0.001) and response and oxytocin level (Wald-χ2=5.96, p=0.015)Wwere found > A significant 3-way interaction between gaze direction, emotion and oxytocin level (Wald-χ2=22.94, p=≤0.001) was found. > The 4-way interaction between gaze direction, emotion, response and oxytocin level was significant (Wald-χ2=8.19, p=0.004) >The group differences in performance on the face discrimination and face recognition tasks were not significant. > Levels of oxytocin were negatively correlated with AAT effect scores for angry faces with direct gaze (rs(28)= −0.396, p=0.04). However, the correlation between basal oxytocin and AAT effect scores for angry faces

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					with an averted gaze did not reach significance (rs (28)= −0.188, p=0.35) > Significant correlations between paranoia and AAT effect scores for angry averted-gaze (rs (28)= −0.422, p=0.03) but not between angry straight-gaze (rs (28)= −0.155, p=0.44) were found.
Jobst, Andrea et al. (2014)	Cross--Sectional Study	To assess whether young men with schizophrenia show alterations in both plasma OT and plasma AVP levels compared with HC To assess whether male schizophrenia patients with higher scores for 'autism' PANSS items show lower OT and AVP levels than male schizophrenia patients without such 'autism' symptoms	86 male adult individuals 41 patients with schizoprenia 45 healthy controls	> Plasma OT and AVP assessement > PANSS > CGI > Sociodemographic characteristics were recorded; they included information about childhood, severe life events, number of important attached persons, social network, and partnerships	1. Lower plasma oxytocin (OT) and arginine-vasopressin (AVP) levels in schizophrenia patients than in healthy controls (HC); 2. OT plasma levels associated with severe life events and fewer important attached persons; and 3. OT plasma levels associated with negative symptoms of schizophrenia. > Schizophrenia patients had grown up significantly more often with only one parent or not with their parents ($\chi 2$ 1 = 4.893; p = 0.027*) and more often reported a severe life event ($\chi 2$ 1 = 8.950; p = 0.003*) compared with HC. > The patients reported significantly more often having no former or current partnerships ($\chi 2$ 1 = 17.628; p<0.001*). > The schizophrenia group had significantly fewer (3.2±2.19, range 0–10) important attached persons than the HC (4.9±2.19, range 2–10; U = 3.479; p<0.001*)

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					> The schizophrenia patients had significantly lower plasma OT levels (median 225.70 pg/ml) than the HC (median 292.60 pg/ml; U = 2.754; p = 0.006) > AVP levels showed a similar trend, with lower levels in the patient group (median 45.48 pg/ml in schizophrenia patients and median 55.36 pg/ml in HC; U = 1.946; p = 0.052; > Severe life events (U = – 2.757; p = 0.006*) and fewer important attached persons (ρ = – 0.278; p = <0.010*) were associated with lower OT levels. > Lower OT levels correlated with growing up with only one parent or without parents (Kruskal- –Wallis Test: χ2 3 = 13.098; p = <0.001*). > Higher OT levels were found in participants who had grown up with both parents. > There was a negative association between the PANSS negative scale score and OT levels (ρ = – 0.413; p = 0.007*): Patients with a high PANSS negative scale score had lower plasma OT levels. > The most dominant 'autistic' symptoms 'preoccupation' (G15; ρ = – 0.537; p<0.001*), 'emotional withdrawal' (N2, ρ = – 0.531; p<0.001*), and 'passive/apathetic social withdrawal' (N4, ρ = – 0.509; p = 0.001*) were negatively correlated with OT levels

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					> Regression analysis with OT as the independent (predictor) variable and PANSS negative scale score as the dependent (outcome) variable showed a significant association (β: –0.420; t1 = – 2.894; p = 0.006*) > Schizophrenia patients with former relationships showed higher AVP levels than patients without former relationships (U = 1.978; p = 0.048*)
Abu-Akel, A et al. (2014)	Randomized Clinical Trial	To determine the effect of oxytocin on the patients' empathic responses to pain experienced by in-group, conflictual out-group and neutral out-group members	55 male adult participants 28 patients with schizophrenia 27 healthy controls	> Participants were randomly assigned to groups for the first administration of either OT or placebo 45 min prior to performing the behavioral task. Those initially receiving OT were administered a single intranasal dose of 24 IU. Seven days later, the second session of the experiment, participants underwent the same procedure with the other substance (i.e. placebo or OT) > PANSS > CGI > Shipley Institute of Living Scale (SILS) > The Pain Evaluation Task	>There was a significant treatment by target effect (F2,53 = 6.74, p= 0.002, ηp 2 = 0.21) indicating that, in the healthy controls, the treatment differentially affected the pain ratings of the different target groups. > OT had a significant effect on increasing the pain rating for the Arab protagonists (t26 = 2.06, p= 0.049) but it did not affect the pain rating for the European (t26 =–0.59, p= 0.56) or Jewish targets (t26 =–0.56, p= 0.58). > In the no-pain condition, OT had a significant effect on increasing the empathy to pain ratings for the Arab targets (t26 = 3.27, p= 0.003) and for the European targets (t26 = 2.31, p= 0.029) but nonsignificantly for the Jewish targets (t26 = 1.37, p= 0.18). > Under the OT condition, the patients, but not the controls, rated the non-painful stimuli differently across the targets. Paired t tests

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					reveal that the Jewish targets received significantly higher ratings than both the Arab targets (t27 = 3.17, p= 0.004) and the European targets (t27 = 2.38, p= 0.024). The European targets also received higher rating than the Arab targets, but the difference did not reach significance (t27 = 1.34, p= 0.19).
Horta de Macedo, Ligia R et al. (2014)	Randomized Clinical Trial	To evaluate the effects of intranasal oxytocin in a facial emotion matching task in patients with schizophrenia and healthy volunteers.	40 adult male participants 20 patients with schizophrenia 20 healthy controls	> All participants received 48 IU intranasal oxytocin and placebo in two sessions, within a time interval of 15 days between sessions.Fifty minutes after the administration of the drug, subjects performed the tests >Facial-emotion matching and control tests (using faceidentities, colors and shapes) > PANSS-negative > BPRS	> For the emotion-matching task, a main effect of diagnosis ($F_{1,36}=5.76$; $p=0.022$) was found, showing that patients with schizophrenia performed worse than healthy volunteers. > There was also a main effect of emotion ($F_{5,180}=57.54$; $p<0.001$) due to a difference in how accurately emotions were matched. > Both groups were more accurate when neutral faces were used as target stimuli ($p<0.001$) and made more mistakes when matching faces expressed sadness and anger ($p<0.001$) > There were no effects of treatment on the matching of identity ($F_{1,35}=0.09$; $p=0.924$) and of shapes and colors ($F_{1,36}=2.359$; $p=0.133$). > There were no differences between groups of patients receiving oxytocin or placebo in the psychopathology scales BPRS ($F_{1,38}=2.441$; $p=0.126$) and PANSS-negative ($F_{1,18}=0.117$; $p=0.737$)

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Haram, Marit et al. (2015)	Genetic Association Study	To explore the relationship between oxytocin pathway genes and symptoms related to social dysfunction in patients with psychotic disorders.	1154 individuals 734 subjects with psychotic spectrum disorders 420 healthy controls were included.	> PANSS (two positive symptoms (p) and two negative symptoms (n): Suspiciousness/Persecution (p6) ; Hostility (p7) Emotional Withdrawal (n2) and Passive/Apathetic Social Withdrawal (n4) > Gene selection and genotyping > Imputation of SNPs > Polygenic risk score(PGRS)	> There was statistically significant association between rs53576 and the level of Emotional Withdrawal (n2) (nominal $p = 0.007$; $p = 0.084$ after Bonferroni correction taking into consideration the four PANSS items and the three SNPs) > There were no other associations between single SNPs and the other symptom scores > Multiple regression analyses indicated a significant association between rs53576 and the level of Emotional Withdrawal (nominal $p = 0.00225$; $p = 0.009$ after Bonferroni correction taking into consideration the four PANSS items) > Having the risk allele A in rs53576 was associated with higher scores on Emotional Withdrawal as measured by the PANSS.
Strauss, Gregory P et al. (2015a)	Cross--Sectional Study	To determine if there is an association between endogenous oxytocin levels and lower- and higher-level social cognition	62 adult individuals (43 male 19 female) 40 individuals diagnosed with either schizophrenia(35) or schizoaffective disorder(5) (SZ) (28 male 12 female) 22 healthy controls (CN) (15 male 7 female)	> Brief Negative Symptom Scale > Brief Psychiatric Rating Scale > Level of Function Scale > Plasma oxytocin levels > Social Cue Recognition Test (SCRT)	> One-way ANOVA indicated that participants with SZ had significantly higher plasma oxytocin levels than CN, $F (1, 60) = 6.69$, $p < 0.02$ > MANOVA examining false positive rates revealed a significant overall Group effect, $F (2, 59) = 10.41$, $p < 0.001$, as well as significant individual effects for concrete, $F (1, 60) = 19.30$, $p < 0.001$, and abstract, $F (1, 60) = 9.49$, $p < 0.01$, cues. > MANOVA also revealed a significant Group effect for sensitivity (A′) scores, $F (2, 59) =$

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					9.59, p < 0.001, with significant group differences for both abstract, F(1, 60) = 9.60, p < 0.001, and concrete, F (1, 60) = 19.35, p < 0.001, cues. > Spearman correlations indicated that higher plasma oxytocin levels were associated with higher (better) sensitivity scores for abstract cues in CN and a higher rate of false positives for concrete cues in individuals with SZ > A significant association was only observed between endogenous oxytocin levels and concrete cues. The significant correlation observed in the SZ group is consistent with past studies reporting an association between endogenous oxytocin and lower-level social cognition in SZ using measures of facial affect perception > In CN, lower endogenous oxytocin was associated with poorer performance on abstract cues, which require higher-level social cognition.
Woolley, J D et al. (2015)	Randomized Clinical Trial	to determine if the administration of intranasal oxytocin would improve olfactory deficits in schizophrenia	65 adult individuals 31 patients with a schizophrenia spectrum illness(21 with schizophrenia, 9 with schizoaffective disorder, and 1 with schizophreniform disorder) (25 male and 6 female) 34 healthy controls (32 male 2 female)	> 2 testing days separated by at least one week. At each testing session, 40 IU of oxytocin was self-administered intranasally from drug administration to olfactory testing was 139 min >PANSS before nasal administration > Munich olfaction test with serial dilutions of lyral and anise odors	> Oxytocin induced significantly greater improvement in detection of lyral in the SZ than in the HC group (U = 374, Z = −2.01, p = 0.04) > Follow-up within-group analyses revealed a significant oxytocin-induced improvement in detection thresholds for lyral in SZ (Z = −3.0, p = 0.003) but not in HCs (Z = −0.21, p = 0.84)

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					> In terms of the oxytocin vs. placebo z-difference scores in patients (normed to the HC placebo day thresholds), the effect of oxytocin was significantly greater for lyral than for anise (z-difference score mean (SD); lyral: −0.33 (0.83), anise: 0.28 (0.94)); Z = −3.01, p = 0.003).
Strauss, Gregory P et al. (2015b)	Cross--Sectional Study	To examine the association between plasma oxytocin, social functioning, symptoms, olfactory identification, and olfactory hedonic judgments	60 adult individuals 39 patients with schizophrenia (28 male 11 female) 21 healthy controls (14 male 7 female)	> Brief Negative Symptom Scale (BNSS) > Brief Psychiatric Rating Scale (BPRS) > Level of Function Scale (LOF) > The University of Pennsylvania Smell Identification Test (UPSIT) > Measurement of plasma oxytocin levels by radioimmunoassay	> One-way ANOVA indicated that people with schizophrenia had significantly higher plasma oxytocin levels than controls, $F(1, 59) = 6.93$, $p < 0.01$) > MANOVA investigating accuracy across valence conditions indicated a significant overall effect, $F(1, 59) = 6.16$, $p < 0.001$),as well as significant individual effects for pleasant: $F(1, 59) = 15.22$, $p < 0.001$) and unpleasant odors: $F(1, 59) = 8.46$, $p < 0.01$). > There was a trend toward participants with schizophrenia being less accurate than controls for neutral odors: $F(1, 59) = 3.75$, $p = 0.058$) > There was a significant overall effect for how negative individuals with schizophrenia and controls reported feeling to unpleasant, neutral, and pleasant stimuli, $F(3, 56) = 3.25$, $p < 0.03$), such that participants with schizophrenia reported more negative emotion than controls.

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					> There was a significant individual effect for pleasant odors, F(1, 58) = 4.84, p < 0.04) > In participants with schizophrenia, lower plasma oxytocin levels were significantly associated with poorer identification accuracy for all UPSIT items and unpleasant items > Self-reports of how positive participants with squizophrenia felt in relation to neutral stimuli were significantly associated with lower oxytocin levels > In participants with schizophrenia, significant associations were observed between plasma oxytocin levels and the BNSS total score, BNSS asociality, BPRS negative symptom factor, LOF total, and LOF social outcome, but not LOF work outcome, BPRS positive, BPRS disorganized, or BPRS total scores > In both CN and SZ, higher ratings of positive emotion were associated with better accuracy (SZ: r = 0.17, p < 0.001; CN: r = 0.17; p < 0.001) and higher ratings of negative emotion were associated with poorer accuracy (SZ: r = − 0.14, p < 0.001; CN: r = − 0.08, p = 0.015).
Cacciotti-Saija, Cristina et al. (2015)	Randomized Clinical Trial	To investigate the efficacy of an oxytocin nasal spray treatment course, combined with targeted social cognitive training(SCT), in an early psychosis population.	52 patients (aged 16–35 years) with an early psychosis schizophrenia-spectrum illness (36 male 16 female) 27 for Social cognitive training +	> 6 weeks of intranasal oxytocin (24 IU) or placebo, administered twice-daily (48 IUs daily) An additional 24 IU was administered 15 minutes prior to each weekly social	> There were no significant changes over time, or interaction with drug condition, on the RMET or the SFS > A significant main effect of time for both positive (F(2, 100) = 5.77, P =

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			placebo (18 male 9 female) 25 Social cognitive training + oxytocin (18 male 7 female)	cognitive training session Measurements obtained at baseline, post-intervention, and 3-month follow-up: Reading the Mind in the Eyes Test (RMET) > Scale for the Assessment of Positive and Negative Symptoms (SAPS and SANS) > Social Functioning Scale (SFS) > Facial Expressions of Emotions Task (FEEST) > The Movie Stills Task > False Belief Picture Sequencing Task > The Faux Pas Task > The Empathy Quotient > Ambiguous Intentions Hostility Questionnaire > Repeatable Battery for the Assessment of Neuropsychological Status > Depression, Anxiety, and Stress Scale (DASS 21-item version) > Kessler Psychological Distress Scale (K-10) > Social Interaction Anxiety Scale (SIAS) > Clinical Global Impression-Severity scale (CGI-S) > Social Skills Performance Assessment (SSPA) > Interpersonal Competence Questionnaire (ICQ) > Sheehan Disability Scale (SDS)	.004, η 2 p = .10) and negative (F(2, 100) = 8.17, P = .001, η 2 p = .14) symptoms indicated significantly fewer psychotic symptoms reported over time. > A main effect of drug condition also indicated that the SCT + oxytocin group reported significantly higher ratings of positive symptoms compared with SCT + placebo, on average (F(1, 50) = 5.58, P = .02, η 2 p = .10), with no significant interaction with time. > Post hoc pairwise comparisons, with Bonferroni corrections, suggested that this significant main effect was due primarily to the placebo group tending to decrease reports of positive symptoms over time, particularly between baseline and post assessments (P = .03), whereas there were no significant differences at any time point for the oxytocin group > There were no significant main effects of drug condition on negative symptoms (F(1, 50) = 1.12, P = .30, η 2 p = 02) > Comparison of effect sizes between baseline and post-treatment assessments, using Cohen's d for repeated measures, on the primary outcomes revealed small to moderate effects on both positive and negative symptoms in both groups (positive symptoms: oxytocin d = 0.27, placebo d = 0.62; negative

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					symptoms: oxytocin d = 0.31, placebo d = 0.53). > Smaller effect sizes were observed on the social cognition and functioning primary outcomes (RMET: oxytocin d = 0.05, placebo d = 0.19; SFS: oxytocin d = .04, placebo d = 0.13). > Significant main effects of time on some social cognition outcomes suggested potential improvements on social-cognitive performance, averaged across drug condition. This included improved emotion recognition from faces using the FEEST ($F(2, 96) = 19.83$, $P < .001$, $\eta 2 p = .29$), recognition of emotions in scenes using the Movie Stills task ($F(1.77, 86.76) = 5.86$, $P = .01$, $\eta 2 p = .11$), and understanding of false beliefs ($F(2, 96) = 9.41$, $P < .001$, $\eta 2 p = .16$). > Significant reductions were also observed in interpreting ambiguous situations as hostile ($F(1.69, 81.01) = 5.83$, $P < .01$, $\eta 2 p = .11$) and a trend towards less aggressive attributions ($F(1.77, 84.99) = 2.76$, $P = .07$, $\eta 2 p = .05$) over time. > Significant main effects were observed for depression, anxiety, and social interaction anxiety. Although SIAS scores significantly decreased over time ($F(2, 96) = 3.57$, $P = .03$, $\eta 2 p = .07$), depression and anxiety exhibited significant quadratic trends, indicating initial reductions

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					in symptoms and then a return to baseline levels by the follow-up assessment >Assessor-rated severity of illness, using the CGI, also indicated significant reductions in the severity of illness over time ($F(2, 100) = 7.65$, $P = .001$, $\eta 2 p = .13$), with no differences between groups. > Significant improvements in social functioning were observed on the SSPA ($F(2, 100) = 6.55$, $P < .01$, $\eta 2 p = .12$) and SDS ($F(2, 94) = 5.82$, $P < .01$, $\eta 2 p = .11$) that did not significantly interact with drug condition. > A significant main effect of time emerged on general neurocognition ($F(2, 100) = 20.63$, $P < .001$, $\eta 2 p = .29$), indicating improved cognitive performance over time. > Significant associations were found between spray usage and changes in negative symptoms in the oxytocin condition only > A series of Pearson's correlations explored potential associations between change scores from baseline at post and follow-up assessments on the primary and secondary outcomes, across the 3 domains (social cognition, symptom severity, and social functioning). However, no significant differences in these associations emerged between drug groups. Further analyses examining the number of individuals who had

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					positively responded to treatment on any of the primary outcomes at the post assessment also indicated no differences between drug groups, all P -values >.05.
Strauss, Gregory P et al. (2015c)	Cross--Sectional Study	To determine whether associations between oxytocin and emotion perception are specific to facial affect processing	63 adult individuals 41 patients with schizophrenia (SZ) (29 male 12 female) 22 healthy controls (CN) (15 male 7 female)	> Brief Negative Symptom Scale(BNSS) > Brief Psychiatric Rating Scale(BPRS: > Level of Function Scale (LOF) >Measurement of plasma oxytocin levels via radioimmunoassay > Forced-choice affective body expression classification	> One-way ANOVA revealed that individuals with schizophrenia had significantly higher endogenous oxytocin levels than healthy controls, $F(1,60) = 2.84$, $p < 0.02$. > A 2 Group (SZ, CN) × 4 Emotion (Happiness, Sadness, Anger, Neutral) mixed-models ANOVA revealed a significant effect of Group, $F(1,61) = 15.6$, $p < 0.001$, and a significant within-subjects effect of emotion, $F(3,183) = 13.6$, $p < 0.001$ > SZ were less accurate at identifying happiness, $F(1,60) = 9.92$, $p < 0.01$, and sadness $F(1,60) = 19.15$, $p < 0.001$, and were less accurate overall, $F(1,60) = 21.41$, $p < 0.001$, than CN > Groups did not differ in accuracy for neutral, $F(1,60) = 1.64$, $p = 0.21$, or anger, $F(1,60) = 3.60$, $p = 0.063$. > Higher endogenous oxytocin levels were associated with better total accuracy in both CN and SZ. > Additionally, higher plasma oxytocin concentrations were associated with better accuracy for neutral stimuli in CN, and better accuracy for sadness in SZ. > In SZ, poorer identification of sadness was associated with greater

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					severity of BNSS negative symptoms ($r = -0.32$, $p < 0.05$) and poorer functional outcome ($r = 0.37$, $p < 0.02$). > Male CN had better total emotion recognition than male SZ, $F(1,43) = 7.52$, $p < 0.01$, and female CN had better total emotion recognition than female SZ, $F(1,18) = 19.12$, $p < 0.001$. > There were no sex differences in overall accuracy for CN, $F(1,20) = 1.63$, $p = 0.22$ > Higher endogenous oxytocin was associated with better accuracy for anger stimuli and total accuracy in females. > Sex-specific associations between oxytocin and accuracy were also evident in CN, where males with higher oxytocin had higher happiness, neutral, and total score accuracy, as well as poorer sadness accuracy; > There were no significant associations between oxytocin and emotion recognition in CN females
Shin, Na Young et al. (2015)	Randomized Clinical Trial	To assess the effect of a single dose of intranasal oxytocin on brain activity in patients with schizophrenia using an implicit facial emotion-recognition paradigm	32 mostly adult male individuals 16 patients with schizophrenia 16 healthy controls	>Subjects self administered 40 IUs of intranasal oxytocin and then underwent functional magnetic resonance imaging (fMRI) on two occasions 1 week apart. The order of the drug administration was counterbalanced. > Relationship Style Questionnaires (RSQ)	> A main effect of emotional valence was significant in the PANAS ($F1,29=5.90$, $p=0.022$), indicating reduction of negative affects after drug administration > Attachment style data revealed that secure attachment scores were significantly lower ($t29=3.00$, $p=0.006$) in patients with

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				> Interpersonal Reactivity Index (IRI) The Positive and Negative Affect Schedule (PANAS) > Visual analog scale (VAS) > Region of interest (ROI) analysis was performed on the left and right amygdala regions	schizophrenia than control subjects after Bonferroni correction (p=0.01) > Patients had significantly higher scores for personal distress (t29=−3.95, p<0.001) than did control subjects > Patients with schizophrenia showed greater activation for fearful faces in left cerebellum than healthy controls in the placebo condition. However, amygdala activation did not significantly differ between the two groups in the same contrast. > Patients with schizophrenia displayed an increased activation in the left amygdala (p<0.05 corrected within an amygdala ROI) and greater activation in the right superior orbitofrontal cortex than controls for the neutral faces in the placebo condition. > For happy faces, the patient group had greater activation than in the control group in right cerebellum > There was a significant main effect of emotional valence (F2,58=4.98, p=0.010, ηp2=0.25), denoting less amygdala activity to neutral relative to emotional faces. > A significant interaction of the drug × group (F1,29=7.61, p=0.010, ηp2=0.21) was found in the first run, indicating differential effects of oxytocin between the patient and control groups > There were significant group differences in oxytocin-induced

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					signal change (t29=2.76, p=0.01), indicating that the patient group showed slightly attenuated activation following oxytocin treatment (mean±SD; −0.03±0.10), whereas the control group exhibited increased activation > A significant drug × emotional valence interaction (F2,58=6.64, p=0.003, ηp2=0.32 was found > There was attenuated activation in response to the fearful faces and increased activation in response to happy faces comparing oxytocin to placebo > There was significantly more left amygdala activation in control than in patient groups (t29=2.10 p=0.049), but no significant difference in right-amygdala activation between the groups (t29=0.42 p=0.676). >A significant negative correlation was found between the oxytocin(happy-baseline)>placebo(happy-baseline) contrast in the right amygdala during the first run and the RSQ preoccupied attachment score in control subjects (r=−0.733, p=0.002; Figure 4) after Bonferroni correction (p=0.005), indicating less degree of activation increase following oxytocin in persons who have preoccupied attachment style.

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Rubin, Leah H et al. (2015)	Cross--Sectional Study	To assess sex differences in cognition in patients with schizophrenia and controls To evaluate whether cognitive performance varies across the menstrual cycle in women with and without schizophrenia in relation to levels of estradiol, progesterone, and oxytocin.	108 adult individuals 50 patients with schizophrenia or schizoaffective disorder (27 male 23 female) 58 controls (27 male 31 female)	> Participants were assessed in two separate sessions, approximately 42 days apart > Women were evaluated during the early follicular phase (days 2–4; low estradiol/progesterone) and the midluteal phase (days 20–22; high estradiol/progesterone) estrogen progesterone and serum prolactin were assessed > Men were also tested in separate sessions approximately 42 days apart and free testosterone and oxytocin were assessed Female dominant tests: > California Verbal Learning Test (CVLT) > WAIS-R Digit Symbol Substitution Subtest (DSST) > Grooved Pegboard Test (GPEG) Male dominant test: > Card rotations test	> There was a statistically significant difference between sexes, validating the designation of tests as “female” or “male” > Follow-up analyses indicated that women (patients and controls) showed an advantage on the “female-dominant” composite ($p < 0.01$) whereas men (patients and controls) showed an advantage on the “male-dominant” score ($p < 0.05$) > Of the “female-dominant” tests, women showed an advantage on all measures (ps < 0.05) except the verbal fluency composite ($p = 0.44$) > Patients performed more poorly than controls, $F(2, 102) = 28.98$, $p < 0.001$, Wilk's $\Lambda = 0.63$. > Estradiol and progesterone levels were significantly higher during the midluteal versus follicular phase (ps < 0.001) whereas testosterone and oxytocin levels were stable across the cycle (ps > 0.48) > Progesterone levels were also lower in patients compared to controls ($p = 0.003$), but only during the midluteal phase ($p < 0.001$) > Sexually dimorphic cognitive abilities did not change significantly across the menstrual cycle in women with or without schizophrenia > In men, only free testosterone levels were lower in male patients compared to controls ($p < 0.05$). > No hormone levels differed as a function of test session in males and

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					sexually dimorphic cognitive abilities did not differ significantly across sessions > In female patients, higher levels of oxytocin were associated with better performance on the "female-dominant" composite (r = 0.46, p = 0.04;) > A follow-up analysis of individual tests comprising the female composite suggested that those effects were driven by verbal memory (CVLT long delay free recall, r = 0.45, p = 0.04) and semantic fluency (r = 0.46, p = 0.04). > Oxytocin was not associated with cognitive performance in female controls.
Guastella, Adam J et al. (2015)	Randomized Clinical Trial	To further explore the different domains of social cognition in patients with schizophrenia following intranasal administration of oxytocin.	21 male patients with schizophrenia	> Participants received either 24 international units (IU) of oxytocin or placebo at each administration. After a standard wait-period of 45 min after oxytocin or placebo administration, experimental tasks and side effect reports were completed. Two weeks later, participants returned to receive the alternative nasal spray and complete the experimental measures. > Diagnostic Interview for Psychoses (DIP) > The Scales for the Assessment of Positive and Negative Symptoms (SAPS/SANS) > Wechsler Abbreviated Scale of Intelligence	> Overall analysis did not show a main effect of oxytocin in comparison to placebo on lower order social cognition performance F(4, 16) = 2.71, p = 0.07, no main effect of drug order, F(4, 16) = 1.13, p > 0.05, and no interaction with order of drug administration F(4, 16) = 1.19, p > 0.05. > Considering the individual variables using a linear contrast of the effect of drug, only performance on the DANVA paralinguistic scale showed significant improvement of oxytocin above placebo, F (1,19) = 7.81, p = 0.01 > There was a significant main effect

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				>Diagnostic Analysis of Non-Verbal Accuracy (DANVA) > Facial Expressions of Emotions Task (FEEST) > Reading the Mind in the Eyes Task (RMET) > False Belief Picture Sequencing Task (FBPSTL) > The Faux Pas Recognition Task > Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	of drug, suggesting that oxytocin significantly improved higher order social cognition performance above placebo, F (4, 16) = 4.05, p = 0.02. >There was a main effect of drug order, F(4, 16) = 3.22, p = 0.04, such that those participants who received oxytocin last performed better overall. > There was no significant interaction of the main drug effect with order of actual drug administration, F (4, 16) = 2.97, p > 0.05. > Follow-up contrasts for the effect of drug on each of the individual test scores showed a significant improvement from oxytocin versus placebo on both the Hinting Task F (1, 19) = 5.38, p = 0.03, and the non faux pas condition of the Faux Pas Recognition Task F(1,19) = 6.37, p = 0.02 > Side effects included tiredness and relaxation (19% of sessions), followed by increased alertness 7%, and non-specific awareness of something being different (4.7%).
Singh, Fiza et al. (2016)	Randomized Clinical Trial	To investigate the effects of two different OT doses on biological motion-induced mu suppression in SCZ and healthy subjects.	32 individuals 17 patients with schizophrenia (9 male, 8 female) 15 Controls (6 male, 9 female)	> All participants were pretreated with a single administration of IN placebo, low-dose OT (24IU) or high-dose OT (48IU) prior to viewing videos of biological and non-biological motion. Subjects received each drug condition in randomized order, separated by one	> A significant three-way interaction was found between treatment×sex×diagnostic group (F (2, 54)=4.1, p≤0.05, η2=0.13]), but no main effect of treatment (F (2, 54)=1.9, p=0.16, η2=0.07) or electrode site (F (1, 27)=0.132, p=0.7,

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				OT-free week >EEG cap and electrodes were applied for testing. >Mu suppression social index (MSSI) was calculated to obtain a quantitative measure that reflected OT′s specific effect on social motion processing (biological motion video) versus non-specific motion processing (non-biological motion video)	η2=0.01) > Treatment×sex×diagnostic group interaction, followed up by 2 factor RM-ANOVAs (treatment×diagnostic group) in males (F (2, 30)=2.2, p=0.1, η2=0.14]) and females (F (2, 24)=2.0, p=0.1, η2=0.13]) demonstrated medium effect sizes, though did not reach significance. > 2 factor RM-ANOVA for treatment×sex in HC (F (2, 24)=1.6, p=0.2, η2=0.12) and SCZ subjects (F (2, 30)=2.7, p=0.08, η2=0.15) also demonstrated medium effect sizes, but was statistically non-significant. > There was a significant treatment effect in SCZ males (F (2, 16)=3.6, p<0.05, η2=0.3) with a large effect size. > Single factor RM-ANOVAs in HC males (F (2, 8)=0.6, p=0.5, η2=0.15), HC females (F (2, 16)=2, p=0.2, η2=0.2) and SCZ females (F (2, 14)=1.1, p=0.4, η2=0.14), revealed medium effect sizes, though did not reach statistical significance. > Follow-up paired samples t-tests in SCZ males comparing placebo to 24IU (t (8)=1.0, p=0.3, Cohen′s d=0.4) and 48IU OT (t (8)=−1.7, p=0.1, Cohen′s d=1.3) revealed a large effect size at the higher dose, although statistical significance was not reached.

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Rubin, Leah H et al. (2016)	Genetic Association Study	To assess the difference between OXTR DNA methylation from whole blood in individuals with psychotic disorders and matched healthy controls	242 mostly adult individuals (112 male 130 female) 167 patients with affective and nonaffective psychotic disorders (75 male 92 female) - 57 with schizophrenia (35 male 22 female) ; 34 with schizoaffective disorder (15 male 19 female); 76 with bipolar disorder (25 male 51 female) 75 (37 male 38 female) healthy controls	Emotion processing > SFS=Social Functioning Scale > PANSS=Positive and Negative Syndrome Scale > YMRS=Young Mania Rating Scale > MADRS=Montgomery Asberg Depression Rating Scale > The Penn Emotion Recognition-40 Test (ER-40) > Epigenotyping procedures - Genomic DNA was isolated; Cytosine methylation was measured at site -934 upstream of the OXTR start codon > Plasma hormone assays > Measurement of oxytocin using immunoassay > Structural magnetic resonance imaging procedure and measurement - The regions of interest (ROI) were four prefrontal regions (superior frontal, middle frontal, inferior frontal, orbital frontal gyri), and six temporal-limbic regions (parahippocampal, middle temporal, and fusiform gyri, hippocampus, amygdala, and insula)	> Only individuals with schizophrenia showed higher levels of methylation compared to controls (B=2.29, SE=1.15, p=0.04; Cohen's d=0.33) > Patients with greater similarity to prototypic schizophrenia compared to those with bipolar features (B=0.36, SE=0.15, p=0.02) had higher levels of methylation; > Greater methylation at OXTR site -934 was observed in females patients overall compared to male patients (p=0.005) as seen in controls. > Associations between DNA methylation levels and peripheral OT levels were in opposite directions for male (r=-0.24, p=0.04) and female (r=0.23, p=0.03) patients > Among all women(did not differ between patient and control), but not men, greater methylation was associated with poorer recognition of emotional expressions (p<0.001) > In women, higher methylation was associated with greater difficulties identifying angry (p<0.001), sad (p=0.006), happy (p=0.02) as well as low- (p<0.001) and high-intensity facial expressions (p=0.004) [trend on fear p=0.07] > In healthy females, greater methylation was associated with smaller volumes in the right hippocampus (β=-0.29, p=0.04), left middle temporal gyrus (β=-0.28, p=0.04), and right inferior frontal

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					gyrus (β=-0.34, p=0.008). > In females with schizophrenia, higher methylation was also associated with smaller volumes of right hippocampus (β=-0.29, p=0.04) > In females with schizoaffective disorder, greater methylation was associated with larger volumes in the left middle temporal gyrus (β=0.61, p=0.007) and left superior frontal gyrus (β=0.47, p=0.01). > In men (combined patients and controls), DNA methylation was positively associated with volumes of left middle frontal gyrus (p=0.04) and left insula (p=0.04)
Dagani, Jessica et al. (2016)	Randomized Clinical Trial	To test the efficacy of oxytocin, as augmentation therapy, in a sample of patients with schizophrenia.	32 adult patients with schizophrenia with short-medium illness duration (< 11 years)	>Subjects self-administered 4 months of daily 40 IUs of intranasal oxytocin and 4 months of daily intranasal placebo, with one week of washout in between. The main evaluation time-points were T0, T1 (4 months of treatment, before washout) and T2 (8 months of treatment, end of treatment) > PANSS > CGI-S > Personal and Social Functioning scale (FPS) > Specific Levels of Functioning (SLOF) > Premorbid Adjustment Scale (PAS). > Hamilton Depression Scale (HAM-D) > State Trait Anger Expression Inventory2 (STAXI 2) > World Health Organization (WHO)	> All PANSS scores decreased over time. General psychopathology was the subscale with the smallest decrease between T0 to T2, with both experimental groups' scores decreased just of about 20%, whilst a higher decrease (25.9%) was detected in positive subscales, group Placebo–Oxytocin. The effect of treatment was not significant in any of the subscales (p > 0.05) > A highly significant period effect was found on the State Anger scale (p = 0.006) and on Anger Control Out scale (p = 0.006). > HAM-D total score showed a significant period effect (p = 0.007) coupled with a significant treatment

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				Quality of Life Instrument (WHOQOL-Bref) > Self Esteem Rating Scale (SERS) > Questionnaire on the social network (SNQ) > Dosage Record Treatment Emergent Symptom Scale (DOTES) > Physical examinations > Electrocardiograms > Female participants underwent a pregnancy test	effect (p = 0.04), indicating a higher anti-depressant effect for placebo compared to the oxytocin. > Assessment tools (e.g., CGI, WHOQOL-Bref, SERS and SNQ) results do not point to any significant treatment or period effects. > No serious adverse events reported during the study > No significant differences between oxytocin and placebo in all of the measured blood chemistry or osmolality tests, and these remained within normal laboratory range at all timepoints for both study groups
Lee, Mary R et al. (2016)	Randomized Clinical Trial	To examine the effects of repeated OT dosing versus placebo on peripheral OT levels and the relationship between changes in peripheral OT levels and changes in clinical symptoms.	28 adult patients with schizophrenia or schizoaffective disorder (20 male 8 female) 13 with oxytocin treatment 15 with placebo	> Each participant was instructed to administer 20 IU of OT or PBO intranasally twice daily during 3 weeks. Symptom measures were administered at baseline, before the first dose of OT/PBO and at endpoint, after the last dose of OT/PBO > BPRS > SANSS > Measurement of plasma OT levels	> At baseline, there were no significant treatment group differences in symptom measures (Lee et al., 2013), OT levels, or significant correlations between baseline OT levels and symptom measures. > After 3 weeks, there was neither a significant treatment group difference in the change in plasma OT level ($F = 0.71$, $df = 1,22$, $p = 0.41$) nor a significant interaction with treatment setting ($F = 0.00$, $df = 1,22$, $p = 0.98$). > There was no significant treatment group difference in the magnitude of the correlation between change in OT level and change in BPRS total score (Table 2, Fig. 1a) or change in BPRS negative symptom score

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Busnelli, M et al. (2016)	Randomized Clinical Trial	To assess the effect of 4 months of chronic daily treatment of intranasal OXT in patients with schizophrenia on peripheral levels of endogenous OXT and the related neuropeptide vasopressin (AVP)	32 adult patients with schizophrenia for at least 1 year (27 male 5 female)	> Patients self-administered 4 months of daily intranasal 40 IUs of OXT and 4 months of daily intranasal placebo with 1 week of washout inbetween > Blood samples for laboratory tests were collected for each patient at 1 week prior to the start of the treatment (t0); in the last week of the first phase of the treatment (t1); and in the last week of the second phase of the treatment (t2) for OXT and AVP measurements through radioimmunoassays > Plasma osmolality assessment > Systolic blood pressure measurement > Body mass index (BMI)	Coefficient Variation values varied from 38% to 59% for OXT and from 25% to 56% for AVP > Comparison between Coefficient Variation values of AVP and OXT was not significantly different (P > 0.05) > At t0, the mean +\- SD plasma OXT concentration was 1.62 +\- 0.68 pg/ml (n = 31), a value within the normal range for endogenous OXT (0–10 pg/ml) as determined by a radioimmunoassay (RIA) > The mean +\- SD AVP plasma level was 2.40 +\- 1.26 pg/ml (n = 31), which again is compatible with values currently reported as normal (< 5 pg/ml) > A significant correlation between AVP and OXT plasma levels is present only at t0 (r = 0.48; P < 0.001) > AVP values, show significant correlations both between t0 and t1 (r = 0.78; P < 0.001) and t1 and t2 (r = 0.53; P = 0.002), indicating that AVP plasma levels show a discrete intra-subject repeatability. This means that, despite the high dispersion of the data, as quantified by the high CV values, each patient tends to maintain constant AVP levels. > Mean values of osmolality, plasma Na+ and systolic blood pressure did not demonstrate any significant clinical variation from the normal reference parameters at any time point, indicating that the chronic

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					treatment with OXT had no effect on these biochemical and clinical parameters > No effect of chronic OXT was observed on BMI values at any time point. > There were no serious adverse events reported during the study
Grove, Tyler B et al. (2016)	Genetic Association Study	To investigate the relationship of OXTR DNA methylation and general cognition in a sample of participants with schizophrenia, schizoaffective disorder, or psychotic disorder not otherwise specified	164 adult individuals (97 male 67 female) 101 participants with a psychotic disorder (56 male 45 female) - 32 with schizophrenia; 59 with schizoaffective disorder; 10 with psychotic disorder not otherwise specified 63 controls (41 male 22 female)	> DNA Methylation Analysis > The Brief Assessment of Cognition in Schizophrenia (BACS)	> The investigated sites were 'lowly' methylated (average methylation of sites ~20%), which is in agreement with healthy control studies investigating OXTR methylation within and near this region > A significant negative Pearson correlation was observed between Chr 3:8767638 site and BACS composite z-score Chr 3:8767742, which was positively correlated with BACS composite z-score > The multiple regression analyses showed that only OXTR methylation site Chr3:8767638 explained a significant amount of variance in BACS composite z-score, along with Verbal Memory, Symbol Coding, and Tower of London z-scores, independent of level of education, antipsychotic type, and smoking status, even after correcting for multiple testing
Haram, Marit et al. (2016)	Genetic Associantion Study	To identify potential different contributions of three oxytocin receptor polymorphisms	346 adult individuals (190 male 156 female) 104 patients with schizophrenia	> Blood was drawn for genotyping of oxytocin receptor polymorphisms (rs53576, rs237902, rs2254298).> A	> Differences in amygdala activation (left hemisphere: χ^2=0.73, P=0.69; right hemisphere: χ^2=0.19, P=0.91)

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		(rs53576, rs237902 and rs2254298) between patients with schizophrenia spectrum disorders (SCZ), affective spectrum disorders (AD) and healthy controls (HC).	spectrum disorders (SCZ) (63 male 41 female) 100 patients with affective spectrum disorders (AD) (43 male 51 female) 142 healthy controls (HC) (84 male 58 female)	paradigm was employed to elicit amygdala activation were participants selected which of two stimuli matched a target stimulus > Participants then underwent a task-based MRI scan (using BOLD fMRI) while performing a matching task designed to elicit amygdala activation"	or accuracy rate (χ^2=0.29, P=0.87) were not detected between diagnostic subgroups, but in response time. > Among patients with SCZ, rs237902 was significantly associated with left amygdala activation, whereas the rs237902G allele displayed increased risk of low amygdala activation (P=0.014, Bonferroni corrected P=0.04) > There was a significant effect of having a diagnosis of SCZ compared with HC on the association between rs237902 and amygdala activation
Woolley, J D et al. (2017)	Randomized Clinical Trial	To assess the effects of a single-dose of oxytocin on blunted affect and ratings of facial trustworthiness	68 adult individuals (63 male 5 female) 33 patients with schizophrenia (30 male 3 female) 35 healthy controls (33 male 2 female)	> Two testing days separated by at least one week. On each test day, 40 IU of oxytocin or placebo was self administered via nasal spray. On each testing day, participants completed behavioral testing and were simultaneously video-recorded , 60 minutes post-administration and continued for no longer than 120 minutes. > Social Judgment Task(SJT) -> participants rate the trustworthiness of faces after the presentation of an affective 'prime' photograph just prior to presentation of the face photograph > Facial Expressivity Coding > quantified using videos of participants while they completed > PANSS on a subset of 23 patients	> SZ participants displayed fewer total (both negative and positive valence) facial expressions while viewing emotionally evocative pictures compared to HCs on the placebo day (p's<0.01) > Compared to placebo, oxytocin administration significantly increased the frequency of total facial expressions in SZ (Z=−2.33, p=0.02) and non-significantly in HC (Z=−1.87, p=0.06) > Oxytocin significantly increased the frequency of negative valence facial expressions in SZ (Z=−2.67, p<0.008), but not in HC (Z=−1.18, p=0.24), and had no significant effect on the frequency of positive expressions in either group > Oxytocin-induced increases in facial expressivity for negative

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					valence expressions were non-significantly greater than for positive expressions in patients with SZ (Z=−2.05, p=0.04) > Twenty-three of the 33 individuals with SZ (70%) and 12 of the 35 HC (34.3%) had zero expressions on at least one testing day. For the ones that did have at least one expression on both testing days, > Oxytocin did not have an effect on average duration per expression in SZ vs placebo or controls > Oxytocin did not have an effect on intensity per expression in SZ (oxytocin: 1.27(0.13) vs. placebo 1.50(0.22); p=0.15) or HC (oxytocin: 1.31(0.05) vs. placebo: 1.35(0.06); p=0.56) > SZ did not differ from HC on these measures on the placebo day (p's>0.4). > The frequency of negative expressions was still significantly greater while on oxytocin than placebo for SZ (Z=−2.24; p=0.03), but the total and positive expressions were not (p's>0.07) > Pairwise comparisons revealed that in both groups, and across Drug conditions, negative primes were associated with significantly lower trust ratings than were neutral or positive primes. > The main effect of Prime was significant in both SZ and HC (p's<0.001)

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					> Within-subject contrasts revealed that in both groups, negative primes were associated with significantly lower trust ratings than in both the positive and neutral primes (p's<0.001), while trust ratings during the positive and neutral primes did not differ (p=0.67) > There were no significant main effect for Drug nor were there any significant Drug x Prime, Drug x Group , or Drug x Prime x Group > SZ had significantly greater frequency of positive expressions on the first day (p=0.04) and HC had significantly higher positive, negative and total expressions on the first day (p's<0.02) > Oxytocin-induced increases in negative and total expressivity were negatively correlated with positive and general symptoms as well as antipsychotic dosage
Caravaggio, Fernando et al. (2017)	Randomized Clinical Trial	To understand whether intranasal oxytocin could reduce jumping to conclusions in stable, medicated patients with SCZ and healthy controls (HCs) To understand whether striatal volume, clinical symptoms, and baseline social functioning (SF) was related to jumping to conclusions (JTC) performance	59 adult male individuals 43 schizophrenia patients 16 healthy controls	> Beads Task on two separate visits (minimum 20 days apart) 60 min after nasal spray administration of either intranasal oxytocin (50IU in solution) or intranasal placebo (saline). > 20 of the SCZ patients and all sixteen HCs also provided T1 MRIs > SAPS > SANS > Social Functioning Scale	> Under the placebo condition, patients with schizophrenia used significantly fewer draws-to-decision (DTD) compared to HCs (t(57) = 2.78, p = 0.007), replicating the greater jumping to conclusions (JTC) bias observed in patients and held within the sub-sample of patients who completed the MRI imaging (t(34) = 2.30, p = 0.03) > Oxytocin did not significantly alter the number of DTD in HCs (t(15) =

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					−0.62, p = 0.55), nor in patients with schizophrenia (t(42) = −1.11, p = 0.27). Thus, given oxytocin, patients continued to use significantly fewer beads to make a decision (t(57) = 2.5, p = 0.02) > In patients with schizophrenia, post-commissural caudate volume was negatively correlated with DTD on placebo (r(18) = −0.50, p=0.03); i.e., patients with worse JTC performance had larger ventral caudate volumes (this finding did not survive Bonferroni correction for multiple comparisons.) > Dorsal caudate volume in HC's was positively correlated with the with percent change (%Δ) in DTD (r(14) = 0.58, p = 0.03), but not in patients with schizophrenia. However, this also did not survive correction for multiple comparisons. > %Δ in DTD was negatively correlated with independence performance (r(41) = −0.36, p = 0.02) and recreational activity levels (r(41) = −0.36, p = 0.02) > Oxytocin significantly increased DTD (5.33 ± 2.10 vs. 7.0 ± 2.92) in patients within the first quartile of independence performance (t(11) = −2.50, p = 0.03; n = 12; score cut-off ≤26). > Oxytocin did not significantly change DTD (7.85 ± 3.76 vs. 7.23 ±

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					3.17) for those within the fourth quartile of independence performance (t(12) = 0.65, p = 0.53; n = 13; score cut-off ≥35). > Oxytocin significantly increased DTD (6.25 ± 4.0 vs. 9.0 ± 3.52) in patients within the first quartile of recreational activity levels (t(11) = −2.30, p = 0.04; n = 12; score cut-off ≤14), but failed to change DTD (6.92 ± 4.27 vs. 6.0 ± 3.65) for those within the fourth quartile of recreational activity levels (t(12) = 0.75, p = 0.47; n = 13; score cut-off ≥24). > ~50% of participants employed more DTD, while ~30% used less, after oxytocin. > Patients whose DTD performance improved after oxytocin (n = 22), versus those whose performance worsened (n = 13), had lower baseline levels of independence (t(33) = −2.28, p = 0.03) and prosocial functioning (t(33) = −2.34, p = 0.03), with a trend level relationship for reduced recreational activity levels (t(33) = −1.75, p = 0.09).
Jarskog, L Fredrik et al. (2017)	Randomized Clinical Trial	To better understand the therapeutic potential of oxytocin on social cognition in people with schizophrenia and schizoaffective disorder by extending the treatment duration to 12 weeks	62 individuals (47 male 15 female) - 39 patients with schizophrenia; 23 patients with schizoaffective disorder 32 were assigned oxytocin (24 male 8 female) - 19 patients with schizophrenia; 20 patients with schizoaffective disorder	> Intranasal study drug was self-administered twice daily for 12 weeks. each dose was approximately 24 international units (IU) of oxytocin or placebo (48 IUs daily) Primary outcome measures assessed at baseline, 6 and 12 weeks: > Emotion Recognition-40 Task (ER-	> Although several measures of social cognition demonstrated within-group changes for oxytocin and placebo groups, no measure (ER-40, Brüne Theory of Mind task, Eyes Test, Trustworthiness Task and AIHQ) demonstrated significant between-group change at 6 or at 12

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			30 were assigned placebo (23 male 7 female) - 13 patients with schizophrenia; 10 patients with schizoaffective disorder	40) > Brüne Theory of Mind Stories Task > Reading the Mind in the Eyes Test (Eyes Test) > Trustworthiness Task > Ambiguous Intentions Hostility Questionnaire (AIHQ) Secondary outcome measures assessed at baseline and 12 weeks: > Specific Levels of Functioning Scale (SLOF) > Social Skills Performance Assessment (SSPA) modified to evaluate empathy in social situations > The PANSS was administered at baseline, 2, 6, 9 and 12 weeks > Laboratory/safety measures	weeks > Only those subjects with at least 60% adherence to study drug showed no differential effect of oxytocin over placebo. > Small but significant interactions were found between AIHQ and treatment group for patients taking antidepressants (p = 0.04) and between Brüne-A total score and treatment group for patients taking benzodiazepines (p = 0.045) > For SLOF participant IP (interpersonal relationship) rating, the between-group comparison suggested an advantage for oxytocin over placebo at a statistical trend level (p = 0.096) > On the SSPA modified role-play task, there were statistically significant group differences at 6 weeks only on the VSS and GSS in favor of placebo. > ANSS total, positive, negative and general psychopathology subscales demonstrated no significant between-group differences at any time point > Significant within-group negative symptom improvement in the oxytocin arm was seen at 2 weeks (p = 0.024) and 6 weeks (p = 0.044), with a statistical trend at 9 weeks (p = 0.099) and 12 weeks (p = 0.051), while the placebo group showed no within-group change at any time point

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					> A significant between-group advantage for oxytocin emerged on PANSS negative scores in subjects with schizophrenia at 6 weeks (p = 0.029), and a statistical trend was seen at 9 weeks (p = 0.096). In the schizoaffective disorder subgroup, no between-group advantage for oxytocin was seen at any point.
Buchanan, Robert W et al. (2017)	Randomized Clinical Trial	To test whether similar or different pathways were associated with the treatment of negative symptoms and cognitive impairments by determining the effect of intranasal oxytocin and galantamine on these two domains.	50 adult patients with either schizophrenia or schizoaffective disorder 17 treated with galantamine (11 male 6 female) 15 treated with oxyticn (13 male 2 female) 18 placebo (15 male 3 female)	> 4-week Evaluation Phase and a 6-week Double-Blind Treatment Phase. Participants who met inclusion criteria entered the 6-week Double-Blind Treatment Phase and were randomized to one of three treatment regimens: active intranasal oxytocin and placebo galantamine; placebo intranasal oxytocin and active galantamine; or placebo intranasal oxytocin and placebo galantamine. The intranasal oxytocin dose was 24 IU twice a day.The galantamine target dose was 12 mg twice a day Measures at beggining and end of the Evaluation Phase and biweekly during the Double-Blind Treatment Phase: > SANS > BPRS > Calgary Depression Scale (CDS) > Clinical Global Impression (CGI) Administered at the end of the Evaluation and Double-blind Phases: > MATRICS Consensus Cognitive	> In the oxytocin versus placebo comparison, the MM-ANCOVA treatment × week interaction was not significant (F=0.19, df=2,47.4, p=0.83) > The oxytocin versus placebo week 6 SANS total score comparison was also not statistically significant (Cohen's d = -0.10, estimated mean difference in total scores ± s.e.: -1.02±1.55; t= -0.66, df=46.9, p=0.51). > In the galantamine versus placebo comparison, the MM-ANCOVA treatment × week interaction was not significant (F=0.41, df=2,52.5, p=0.67), > The week 6 galantamine versus placebo contrast (Cohen's d= -0.15, estimated mean difference in total scores ± s.e.: -1.45±1.39; t= -1.04, df= 46.9, p=0.30) was not significant. > There were no significant galantamine/placebo or oxytocin/placebo group differences for any of the individual measure that

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				Battery (MCCB) > The Rapid Visual Information Processing Test (RVIP) > The modified version of the UCSD Performance-Based Skills Assessment (UPSA)32, the UPSA-2 > Safety Assessments > Plasma oxytocin levels determined via radioimmunoassay	comprised the composite measure > There were no significant galantamine/placebo (t=0.49; df=42.0; p=0.63; Cohen's d=0.09) or oxytocin/placebo (t=0.78; df=42.0; p=0.44; Cohen's d=0.15) group differences > There were also no significant group differences in the UPSA-2 total score: galantamine versus placebo: t= -0.69; df=44; p=0.49; and oxytocin versus placebo: t= 1.25; df=44; p=0.22 > There were also no significant group differences in the CGI severity of illness item > There were no significant week 6 group differences in oxytocin levels (F=0.42; df=2,36; p=0.66)
Yang, Xiudeng et al. (2017)	Cross--Sectional Study	To examine the relative mRNA expression of OXT, OXTR, AVP, AVPR1a and CD38 in HC and first-episode, unmedicated schizophrenia (FES) patients To compare the gender-associated mRNA expression in HC and FES patients	90 individuals (56 male 34 female) 43 patitents with first-episode schizophrenia (FES) (27 male 16 female) 47 healthy controls (HC) (29 male 18 female)	> PANSS The peripheral mRNA expression of OXT, OXT receptor (OXTR), AVP, AVP 1a receptor (AVPR1a) and CD38 was determined by real-time quantitative polymerase chain reaction (RT-qPCR): > RNA isolation from lymphocytes. > cDNA synthesis > Primer design > Quantitative PCR	> Levels of OXT and OXTR mRNA were significantly higher (P=0.015 and P=0.037, respectively) in FES patients (0.2725 ± 0.1879 and 0.1945 ± 0.1229, respectively) than that in HC (0.1846 ± 0.0896 and 0.1443 ± 0.0156, respectively). > The expression of AVP and CD38 mRNA was significantly decreased (P=0.001 and P=0.012, respectively) in FES patients (0.7359 ± 0.4639 and 1.0861 ± 0.4564, respectively) compared with those in HC (1.0378 ± 0.4905 and 1.3830 ± 0.6691, respectively). > There was no difference (P=0.300)

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					for the levels of AVPR1a mRNA between FES patients (3.1512 ± 1.6290) and HC (3.0950 ± 2.0266) > The intra-group comparisons of mRNA expression between males and females showed no difference both in FES patients and HC group > Female FES patients (0.6571 ± 0.5457 and 1.0331 ± 0.4190, respectively) showed significantly decreased (P=0.003 and P=0.002, respectively) AVP and CD38 mRNA than female HC (1.1096 ± 0.5325 and 1.6094 ± 0.8156, respectively)
Balikci, Kuzeymen et al. (2018)	Cross- -Sectional Study	To assess the role of oxytocin in social cognition in schizophrenia.	81 individuals 27 patients with schizophrenia (19 male 8 female), 27 healthy siblings (HS) of the patients(11 male 16 female) 27 psychologically healthy controls (HC) (12 male 15 female)	> PANSS > Wisconsin Card Sorting Test WCST, used for executive functioning > Wechsler Adult Intelligence Scale-Revised > Vocabulary Subtest > RMET > Assessment of blood samples	> Mean PANSS scores were 21.55 ± 4.40 in PANSS-Negative, 12.29 ± 4.65 in PANSS-positive, and 38.00 ± 8.70 in PANSS-General > A statistically significant difference was foundbetween the groups in the scores of RMET Easy Items, RMET Total Scores, WCST's Categories achieved, Perseverative errors, and Number of correct (healthy controls performed better in all of them compared to schizophrenia patients , WCST's Categories number correct and preservative errors > In healthy control group, there was positive correlation between blood OT levels and RMET's difficult items subtest (r = .461, n = 27, p = .01), total score subtest (r = .415, n = 27, p = .03), and WCST's categories achieved (r = .416, n = 27, p = .03).

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					A statistically significant correlation was found between blood OT levels and all subtests of RMET [easy items subtest (r = .272, n = 81, p = .01), difficult items subtest (r = .216, n = 81, p = .05), total score subtest (r = .281, n = 81, p = .01)]. > There is a statistically significant difference between high and low OT groups with regard to social cognition in all subtests of the RMET. > When participants were divided into three groups as patients with SCH, HS, and control group, only a statistically significant difference was observed in the control group in all subtests of the RMET [RMET Easy items(t = 2.01, df = 25, p = .05), RMET Difficult items(t = 4.07, df = 25, p < .01), RMET Total score(t = 3.09, df = 25, p < .01)]. > In HS, there was a statistically significant difference in easy items subtest (t = 2.03, df = 25, p = .05) and total score subtest (t = 2.19, df = 25, p = .03).
Ota, Miho et al. (2018)	Randomized Clinical Trial	To assess the safety and efficacy of intranasal oxytocin on the cognition, appetite, and psychotic symptoms in patients with schizophrenia To determine the possible relationship between treatment response to oxytocin and brain	16 patients with chronic schizophrenia (7 men and 9 women)	> Non-randomized, open-label 12-week treatment trial with 12 international units (IUs) of oxytocin intranasally twice daily (24 IUs daily) > Screening of subjects included a review of psychiatric and medical history, physical examination, and blood collection(at weeks 2, 6, and 12) for standard laboratory tests	> A significant reduction of PANSS total score (f value = 20.4, partial η2 = 0.58, p < 0.001) as significant reductions of the positive (f value = 7.3, partial η2 = 0.33, p < 0.001), negative (f value = 17.9, partial η2 = 0.54, p < 0.001), and general (f value = 13.1, partial η2 = 0.47, p < 0.001) scale scores was observed.

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		structure assessed by magnetic resonance imaging		> PANSS at weeks 2, 6, and 12 at baseline and at week 12 : > Brief Assessment of Cognition in Schizophrenia-Japanese (BACS-J) > RMET > Autism-Spectrum Quotient > Social Responsiveness Scale > Life Skills Profile > MR imaging was performed for 15 out of 16 subjects before the beginning of oxytocin administration.	> There was a significant reductions of the blunted affect (f value = 20.4, partial η2 = 0.58, p < 0.001), emotional withdrawal (f value = 7.0, partial η2 = 0.32, p = 0.001), and lack of spontaneity and flow of conversation (f value = 7.0, partial η2 = 0.32, p = 0.001) >There was a significant increase of category fluency derived from BACS during the oxytocin treatment (t = −2.86, p = 0.012 by paired t-test, effect size [Δ] = 0.53;) > Negative correlations between the gray matter volume/ intracranial volume and the changes of PANSS negative score in the right cortical gyrus around the horizontal ramus of the lateral sulcus (correlation coefficient = −0.71, p = 0.004) and left dorsal anterior cortex (anterior midcingulate cortex, correlation coefficient = −0.74, p = 0.003; posterior midcingulate, correlation coefficient = −0.74, p = 0.003) were found, meaning the larger these regions are before oxytocin treatment, the better the negative symptoms become by the oxytocin administration
Fulford, Daniel et al. (2018)	Randomized Clinical Trial	To develop a task that incorporated social encouragement as reinforcement for effortful behavior	85 adult individuals (60 male 25 female) 42 patients with schizophrenia (31 male 11 female)	At a separate session in the week prior to the first testing session: > PANSS >CGI	SZ group had lower personal education than the HC group The SZ group reported significantly lower empathy on the EQ, but no significant differences on the ECR

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		To test the effects of a manipulation of the oxytocin system—a neuropeptide implicated in social behavior—on effort in the context of social encouragement.	43 healthy controls (29 male 14 female)	> Two testing days separated by at least one week, that consisted of the Social Vigor Task (SVT) (56 trials of the SVT on each testing day). At the beginning of each testing day, 40 IU of oxytocin or saline placebo was self-administered via nasal spray. >Empathy Quotient (EQ) >Experience of Close Relationships scale (ECR) Social and nonsocial cognition. >TASIT(included the Lie and Sarcasm subscales) > Letter-number sequencing task	> Participant gender was significantly positively associated with change in vigor from placebo to OT day, but only in the SZ group, r = .44, p <.001. > There was a significant main effect of reward type (social vs. points-only). > Across groups, participants displayed higher vigor during social encouragement than during points-only trials (p < .001). There were no main effects of reward rate or trial length. > Across groups and reward conditions, vigor was equal during low and high rate trials and long and short trials. > Although there was a significant Group × Reward Type interaction, planned pairwise comparisons revealed that both SZ (b = −0.052, p <.05) and HC (b = −0.067, p <.05) participants displayed more vigor during social trials than during points-only trials. > A significant three-way interaction among Group, Reward Type, and Reward Rate suggested that social encouragement significantly increased vigor during low rate trials only in the HC group (b = −0.159, p <.05); in the SZ group, social encouragement significantly increased vigor during high rate trials only (b = 0.059, p <.05) >A significant 3-way interaction

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					among group, reward type, and trial length suggested social encouragement significantly increased vigor during short (30 s) trials only in the HC group (b = −0.143, p <.05); in the SZ group, social encouragement significantly increased vigor during long (60 s) trials only (b = 0.079, p <.05) >There was no main effect of drug (b = 0.018, p <.721), nor was there a Group × Drug interaction (b = 0.063, p <.330). Drug also did not interact with reward rate (b = −0.004, p <.969) or trial length (b = 0.046, p <.590). > There was a significant Drug × Reward Type interaction (b = −0.077, p <.005). A visual inspection of marginal means suggested a difference in vigor between social and points-only trials that was present during placebo (Ms = 3.65 for social trials vs. 3.57 for points-only trials), but not during oxytocin (Ms = 3.64 for social trials vs. 3.62 for points-only trials); however, none of the post hoc pairwise comparisons were significant (ps = 0.115–0.127). > There was, however, a significant negative association between PANSS positive symptoms and the social encouragement-points-only difference on vigor during placebo day (r = −0.33, p < 0.05). That is, higher positive symptoms were associated with a diminished impact

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					of social encouragement on vigor during the placebo day. > Given the lack of specificity in negative symptom assessment of the PANSS, two specific symptoms that tap into social/motivational processes were included: passive/apathetic social withdrawal and active social avoidance. In these analyses, higher passive/apathetic social withdrawal was associated with significantly less overall vigor on the SVT (b = −0.35, p <.001), whereas active social avoidance was not significantly related to vigor (b = −0.09, p =.14). These exploratory results suggest that diminished approach motivation influenced performance on the SVT among people with SZ
Veras, Andre B et al. (2018)	Genetic Association Study	To assess if the relationships of OXTR polymorphisms with specific clinical features could aid in evaluating any role of oxytocin in the pathogenesis of schizophrenia	134 individuals 48 patients with schizophrenia 61 other cases (40 male 21 female) 25 controls (13 male 12 female)	> PANSS > Hamilton Depression and Anxiety rating scales > Young Mania Rating Scale > Wechsler Adult Intelligence Scale (WAIS-III) > Early Trauma Inventory (ETI) > Targeted exome capture and variant calling	> Five of the 48 schizophrenia cases carried rare OXTR variants. > Compared to other cases, OXTR variant carriers exhibited milder negative and affective symptoms, demonstrated a specific cognitive profile with lower performance IQ (due to impaired perceptual organization and processing speed), and reported significantly higher exposure to early trauma (physical, emotional, and especially sexual abuse).

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Guzel, Derya et al. (2018)	Cross--Sectional Study	To evaluate oxytocin (OXT), arginine-vasopressin (AVP), and atrial natriuretic peptide (ANP) and assess their interactions with each other, as well as investigate these changes with the manifestations of schizophrenia.	58 male individuals 34 patients with acute schizophrenia 24 healthy individuals as controls	> PANSS > CGI > Global assessment of functionality (GAF) > Laboratory analysis to determine the serum OXT, AVP, and ANP levels	> OXT levels were significantly lower and AVP levels were significantly higher in patients with acute schizophrenia than the individuals in the control group. > ANP levels were not significantly different > OXT was negatively correlated with PANSS positive score and CGI score while it was positively correlated with GAF score. AVP was negatively correlated with CGI score
Warren, Kimberly R et al. (2018)	Randomized Clinical Trial	To determine the effect of intranasal oxytocin on satiety signaling in people with schizophrenia.	16 adult patients with schizophrenia (8 male 8 female)	> Three study visits were performed in this randomized, blind, crossover study: a screening visit and 2 challenge day visits Screening visit: >Complete Metabolic Panel (CBC) >BPRS >SANS > CGI > Calgary Depression Rating Scale (CDS) > Perceived Stress Scale (PSS) On the two challenge day visits : Participants arrived, fasting, in the morning to have an indwelling catheter inserted for blood draws and to undergo the intranasal oxytocin (24 IU) or matching placebo.Baseline ratings for hunger were obtained. At 15-minute following the oxytocin/placebo administration, all participants underwent a preload/test meal	> Ratings during the oxytocin condition compared to placebo had a trend for higher ratings on enjoyment (22% higher; $t = 2.00$, $df = 15$, $p = 0.06$) and to a lesser extent, sweetness (14% higher; $t = -1.42$, $df = 11.2$, $p = 0.18$) > After 30-minute, the oxytocin and placebo groups had mean rating drops of 26% and 21%, respectively. > After 60-minute, the hunger ratings returned to near baseline in the placebo group (4% lower) and slightly attenuated in the oxytocin group (14% lower), however this was not statistically different ($p > 0.05$). > With regards to olfactory and gustatory function there were no between treatment condition differences on the number correct or percentile correct on the BSIT nor the taste strip identification

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				paradigm. This paradigm included administration of a preload and a subsequent test meal measurement > Laboratory assessments of oxytocin, glucose, leptin, and insulin levels were also drawn prior to dosing while fasting and following the preload at 0-, 15-, 30-, and 60-minute.The oxytocin level was drawn again at approximately 75 min > Assessments and outcome measures for satiety and hunger - visual analog scale (VAS) > Gustatory function -spoon-shaped filter paper strips ("Taste Strips") impregnated with four taste qualities (sweet, sour, salty, and bitter) > Olfactory discrimination -Brief Smell Identification Test (BSIT) > The Side Effect Checklist (SEC)	> For leptin, there was a significant difference in baseline values. Thus, controlling for baseline leptin, gender and BMI, we see a significant treatment difference ($F = 5.22$, $df = 1,97.6$, $p = 0.025$) with a decrease in leptin in the oxytocin group post-administration, but no time effect ($F = 1.67$, $df = 6,95.1$, $p = 0.0.180$) or treatment by time interaction ($F = 1.36$, $df = 3,4.16$, $p = 0.261$) > There were no statistically significant correlations between oxytocin level and these outcomes in either the oxytocin or placebo condition ($p > 0.05$) > Side effects were not commonly reported during this single-dose, challenge study
Wehring, H J et al. (2018)	Cross--Sectional Study	To assess the relationship of serum oxytocin levels to sexual behavior in males and females with schizophrenia.	50 patients with schizophrenia or schizoaffective disorder and persistent negative symptoms (40 male 10 female)	> Arizona Sexual Experience Questionnaire (ASEX) > Serum oxytocin levels determined via radioimmunoassay	> ASEX scores were indicative of a group with sexual dysfunction, with a mean of 20.5 (8.3) for females and 19.0 (7.4) for males (in previous schizophrenia studies, cutoff scores of ≥19 were used to identify sexual dysfunction) > There were no significant correlations of serum oxytocin levels to ASEX scores in males, but robust correlations in women for oxytocin and ASEX total score and in 4 of 5 domains were identified, showing higher oxytocin levels associated with increased sexual dysfunction (drive,

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					arousal, vaginal moistness/erection, and reaching orgasm)
Lee, M R et al. (2018)	Genetic Association Study	To assess the expression of oxytocin and oxytocin receptor mRNA in the dorsolateral prefrontal cortex (DLPFC)	581 individuals (postmortem brains) 135 patients with major depressive disorder 57 patients with bipolar disorder 169 patients with schizophrenia\schizoaffective disorder 220 controls	> Tissue retrieval, processing and neuropathology > Antemortem drug exposure > RNA extraction and real time qPCR analysis	> A diagnosis of Major depressive disorder(MDD) and bipolar disorder(BPD) significantly positively predicted normalized OTR mRNA levels On post-hoc testing, log(ln) oxytocine receptor (OTR) mRNA levels were significantly higher for the MDD and BPD groups ($p < 0.001$, Bonferroni corrected) compared to the other 2 groups, whose levels did not significantly differ from each other > The presence of mood stabilizers significantly predicted ln-transformed OTR mRNA levels such that mood stabilizers predicted a reduction of OTR mRNA levels > Presence of antipsychotics also significantly predicted an increase in OTR mRNA > Having a history of substance abuse was a significant positive predictor, such that ln-transformed OTR mRNA levels with a history of substance use predicted higher OTR mRNA levels
Rubin, Leah H et al. (2018)	Cross--Sectional Study	To determine whether hormone-brain physiology associations are altered in men and women with schizophrenia compared to healthy male and female	95 individuals 35 patients with schizophrenia (23 male 12 female) 60 controls (24 male female)	> Serum hormone assays of OT and AVP > Brief Assessment of Cognition in Schizophrenia (BACS) (verbal learning (list learning), verbal fluency (word	> AVP, but not OT levels, were lower in female patients compared to controls ($p = 0.001$) > OT levels were associated with facial emotion recognition in female

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		controls To determine associations of hormone brain physiology findings with symptom severity, cognition, and emotion processing.		generation), and processing speed (symbol-coding)) > Penn Emotion Recognition (ER)-40 TestResting state data acquisition >5 min of scanning using a magnectic resonance (MR) imaging system and an 8-channel phased array head coil.	controls ($r = 0.39$, $p = 0.03$) but not among any other group (p's > 0.07) > In women, lower OT levels were associated with lower amplitude of low-frequency fluctuations (ALFF) in the right superior frontal gyrus, extending to the left superior frontal gyrus and bilateral middle frontal gyrus ($r = 0.71$, $p = 0.01$) and right anterior and posterior cerebellum, extending to left cerebellum in patients ($r = 0.69$ $p = 0.01$) but not controls ($r = -0.09$ and $r = -0.14$, respectively) > The degree to which OT levels were associated with ALFF in frontal and cerebellar cortices differed between female patients and controls ($p = 0.007$ and $p = 0.01$, respectively) > In female patients, but not controls, higher ALFF in frontal and cerebellar cortices were associated with poorer facial emotion recognition (p's < 0.05) and higher ALFF in cerebellar cortices was associated with poorer semantic fluency ($r = -0.61$, $p = 0.04$) > OT levels influenced changes in facial emotion recognition through ALFF in the frontal cortex [69% of the total effect (65%) was explained by the indirect effect] and ALFF in the cerebellum [63% of the total effect (65%) was explained by the indirect effect]. > OT levels influenced changes in

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					semantic fluency through ALFF in the cerebellum [68% of the total effect (55%) was explained by the indirect effect]. > In women, lower AVP levels were associated with higher ALFF in the superior frontal gyri in controls ($r = -0.44$, $p = 0.01$) but not patients ($r = 0.21$, $p = 0.53$). > In female patients, but not controls, ALFF in the frontal cortex were significantly associated with poorer emotion processing ($p = 0.04$) > In men, lower AVP levels were associated with lower ALFF in the right medial frontal gyrus, extending to right cingulate and precentral gyri in patients ($r = 0.52$, $p = 0.01$) but not controls ($r = -0.01$, $p = 0.96$) > In male patients, but not controls, higher ALFF in the right medial frontal gyrus was associated with poorer performance on verbal fluency ($p = 0.02$) for both letter ($r = -0.39$, $p = 0.06$) and category fluency ($r = -0.50$, $p = 0.01$) > In men, lower OT levels were associated with lower ALFF in the right precentral gyrus, extending to middle frontal and cingulate gyri in male patients ($r = 0.48$, $p = 0.02$) but not controls ($r = 0.10$, $p = 0.66$) > Higher OT levels were associated with higher ALFF in bilateral superior/medial frontal gyrus (left hemisphere $r = 0.54$, $p = 0.009$; right

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					hemisphere r = 0.47, p = 0.02) and lower ALFF in the thalamus bilaterally (r = −0.51, p = 0.01) in controls but not patients (r = 0.15, r = 0.004, r = −0.03, respectively) > In male patients, but not controls, higher ALFF in the thalamus was associated with poorer emotion recognition (r = −0.54, p = 0.008), verbal learning (r = −0.49, p = 0.02), and processing speed (r = −0.41, p = 0.05) >OT levels had some influence on emotion recognition, verbal learning, and processing speed through ALFF in the thalamus [46% of the total effect (16%), 92% of the total effect (7%), and 53% of the total effect (13%), respectively)
Tas, Cumhur et al. (2018)	Cross- -Sectional Study	To investigate the association between basal oxytocin and cortisol reactivity to social stress in schizophrenia, and how the cortisol response to stress may be related to social functioning and support	32 patients with schizophrenia (15 male 17 female) 21 patients in the non-responder group 11 patients in the responder group	> PANSS > Social Functioning Scale (SFS) > Medical Outcomes Study Social Support Survey (MOS-SSS) > State–Trait Anxiety Inventory (STAI) > A modified version of the Trier Social Stress Test (TSST) > Blood sample collection and assessment 60 min before and after stress induction test for plasma cortisol and oxytocin assessment > Before and immediately after TSST, the STAI was given to participants > Patients were divided into cortisol responders and non-responders	> For group analyses (responders vs. non-responders) comparing baseline to post-stress levels, separate paired t-tests showed significant differences for plasma cortisol levels (t(1,31) = 2.35, p = 0.03) and heart rate (t(1,31) = 2.86, p = 0.008), but not for behavioral measures of state anxiety (t(1,31) = 0.05, p = 0.96). > The mean baseline and post-stress cortisol levels were 9.91 (SD:3.87) µg/dL and 10.83 (SD:3.97) µg/dL respectively. > Patients in the non-responder group (21 patients) showed a mean percentage decrease in cortisol of

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				according to percentage change following stress induction	−3.62% (SD:7.95; 95% CI [0.00, −7.24]) after the social stress test, relative to baseline, whereas patients in the responder group (11 patients) showed a mean percentage increase in cortisol of 46.17% (SD:49.83; 95% CI [79.65, 12,69]). > ANOVA for cortisol levels using time (baseline and post stress) as the within subjects factor and group (responders and non-responders) as the between subjects factor revealed a main effect of time ($F(1,30) = 30.40$, $p < 0.001$), and a significant interaction between time and group ($F(1,30) = 43.64$, $p < 0.001$). > There was no significant difference between responders and non-responders in baseline cortisol levels ($t = 1.64$, $p = 0.11$) > No significant difference ($t(1,31) = -0.93$, $p = 0.36$) in basal oxytocin levels between cortisol responders ($M = 216.36$, $SD = 102.47$ pg/ml) and non-responders ($M = 260.33$, $SD = 138.20$ pg/ml). > Significantly higher social functioning scores were observed for the cortisol responder group on the interpersonal communication, recreation activities and independence/performance subscales, with prosocial activities at a trend level ($p = 0.06$) > There was a group difference in

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					medication in terms of the chlorpromazine equivalent values ($F(1,31) = 6.13$, $p = 0.019$). > Therewere significant correlations between cortisol responses and State Anxiety scores and Social Functioning Subscales of interpersonal relationships, prosocial activities, recreation and independence performance. > Plasma oxytocin levels did not show any significant linear association with the behavioral outcome variables > There was no significant correlations between any measures of social functioning and social support
Aydın, Orkun et al. (2018)	Cross--Sectional Study	To assess whether levels of neurocognitive, social cognitive and metacognitive function among a group of patients with schizophrenia were differentially related to oxytocin (OT) and vasopressin (VP), and whether relationships between complex patterns of biological processes and more basic cognitive processes could be detected as these could interfere with higher order cognitive processes.	65 individuals (35 male 30 female) 34 patients with schizophrenia (22 male 12 female) 31 healthy controls (13 male 18 female)	> WCST > RMET > Metacognition Assessment Scale-Abbreviated (MAS-A) > Assessment of blood samples for oxytocin and vasopressin	> The schizophrenia group obtained lower mean scores on the RMET, WCST-NC and WCST-CA and a higher mean score for WCST-Perseverative Error(PE). > Univariate testing found the effect to be significant for the RMET ($F(1,61) = 16.18$; $p < 0.001$; $\eta\rho2 = 0.21$), WCST-Number of Correct(NC) ($F(1,61) = 17.22$; $p < 0.001$; $\eta\rho2 = 0.22$), WCST-PE($F(1,61) = 10.55$; $p < 0.01$; $\eta\rho2 = 0.14$), WCST-Categories Achieved (CA) ($F(1,61) = 21.77$; $p < 0.001$; $\eta\rho2 = 0.26$) and plasma OT level ($F(1,61) = 47.32$; $p < 0.001$; but not for plasma VP levels ($F(1,61) = 4.85$; $p = 0.09$; $\eta\rho2 = 0.04$)

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					> In the schizophrenia group, there was a positive correlation between plasma OT level and MAS-A Self reflectivity (SR) ($r = 0.46$, $p < 0.01$), Understanding Other's Mind (UAM) ($r = 0.36$, $p = 0.03$), Decentration (D) ($r = 0.35$, $p = 0.03$), Mastery (M) ($r = 0.39$, $p = 0.02$) and Total score ($r = 0.42$, $p = 0.01$) > All of the MAS-A subdomains except D were correlated negatively with the WCST-PE and they were also associated with the RMET and WCST-NC. The WCST-CA was only correlated with the MAS-A M scale ($r = 0.38$, $p = 0.04$) in a positive direction > There were no significant correlations between plasma OT level and RMET ($r = 0.23$, $p = 0.22$) and WCST-NC ($r = 0.24$, $p = 0.36$), WCST-PE ($r = -0.12$, $p = 0.36$), WCST-CA ($r = 0.23$, $p = 0.42$) scores. > None of the RMET ($r = 0.18$, $p = 0.63$), WCST-NC ($r = -0.13$, $p = 0.45$), WCST-PE ($r = 0.22$, $p = 0.31$), WCST-CA ($r = -0.16$, $p = 0.74$), and MAS-A SR ($r = -0.07$, $p = 0.73$), UAM ($r = -0.13$, $p = 0.95$), D ($r = -0.25$, $p = 0.48$), M ($r = -0.10$, $p = 0.68$) and Total score ($r = -0.12$, $p = 0.54$) were correlated with plasma VP level in the patient group > RMET ($r = 0.36$, $p = 0.04$) and WCST-CA ($r = 0.49$, $p < 0.01$) were positively correlated with OT but not

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					WCST-PE (r = −0.32, p = 0.07) and WCST-NC (r = 0.29, p = 0.10). > VP was not correlated with any of the cognitive parameters > The RMET, WCST-PE and plasma OT level were significantly associated with MAS-A SR and total scores. > The MAS-A UAM score was significantly predicted by the RMET and WCST-PE but not by plasma OT level. > The MAS-A M score was associated with WCST-PE and plasma OT level but not with RMET.
Lee, Mary R et al. (2019)	Randomized Clinical Trial	To assess the effect of oxytocin administration on measures of 4 domains of social cognition, as well as social functioning	28 patients with schizophrenia or schizoaffective disorder (20 male 8 female) 13 with oxytocin treatment (9 male 4 female) 15 with placebo treatment (11 male 4 female)	> 3 week treatment with adjunctive intranasal 20 IU oxytocin or placebo twice daily in people with SZ. Patients went a two week lead in stabilization period prior to randomization in the 3 week study and then followed with weekly study visits Measures of social cognition and social outcomes were performed at baseline (BL) prior to study medication initiation and at endpoint (EP). > BPRS > SANS > CGI > CDSS > Mayer-Salovay Caruso Emotional Intelligence Test (MSCEIT) > Managing Emotions and Understanding Emotions components and the Maryland Assessment of Social Competence (MASC)	> No significant treatment effects were found between the OT-treated and placebo (PBO) groups at the end of study for any primary social cognitive (Mayer-Salovay Caruso Emotional Intelligence Test (MSCEIT), Maryland Assessment of Social Competence (MASC)) or secondary social cognition or anxiety outcomes. > A significant change in the study favoring placebo was found for the MASC effectiveness measure (F = 4.86, df = 1,24; p = 0.037), however, this would not survive correction for multiple testing

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Aydın, Orkun et al. (2019)	Cross--Sectional Study	To examine whether the relationship among attachment styles, perceived parental attitudes and plasma oxytocin levels differ among schizophrenia patients, their healthy siblings, and healthy controls To investigate the relationships among plasma oxytocin levels, attachment styles and perceived parental attitudes among groups To determine whether attachment styles, perceived parental attitudes or plasma oxytocin levels could discriminate the groups from each other.	99 individuals (49 male 50 female) 34 patients with schizophrenia (22 male 12 female) 34 healthy siblings of the schizophrenic patients (14 male 20 female) 31 healthy controls (13 male 18 female)	> PANSS > The experience in close relationships-revised (ECR-R) > My memories of upbringing-short version (Swedish acronym for egna minnen betraffande uppfostran (s-EMBU)) > Assessment of blood samples to measure plasma oxytocin	> The schizophrenia group included a majority of men but gender difference was not significant between the groups (v2 (2)=3.66, p ¼ .16). The mean PANNS scores of schizophrenia sample was 12.17 (SD = 4.42) on the positive subscale, 22.20 (SD = 4.87), on the negative subscale, and 38.08 (SD = 8.13) on the general psychopathology subscale. > Plasma oxytocin levels differed significantly across groups and healthy controls owned the highest mean values followed by healthy siblings and schizophrenia patients, respectively > The healthy sibling group and healthy control group had lower mean scores for ECR-R anxiety/avoidance, s-EMBU rejection/over-protection when compared with schizophrenia patients > No significant differences were observed between healthy controls and healthy siblings in ECR-R and s-EMBU assessments > There was a positive correlation between PANSS-negative and ECR-R avoidance (r ¼ 0.48, p < .01) in patient group. > The ECR-R anxiety was associated with s-EMBU rejection (r ¼ 0.41, p ¼ .04) and s-EMBU over-protection (r ¼ 0.48, p < .01) among patients. > The s-EMBU rejection was

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					positively correlated with s-EMBU over protection (r ¼ 0.40, p ¼ .03) and negatively correlated with s-EMBU emotional warmth (r= 0.47, p < .01) in the patient group. None of the assessed scales were correlated with plasma oxytocin levels in schizophrenia group > Negative correlation was found between s-EMBU over protection and plasma oxytocin levels (r= 0.38, p ¼ .02) for healthy sibling group > In healthy control group ECR-R anxiety and s-EMBU rejection were positively correlated (r ¼ 0.39, p ¼ .03) and negative correlation was shown between s-EMBU over protection and plasma oxytocin levels (r= 0.37, p ¼ .02) > For the healthy sibling group when the mean value of plasma oxytocin levels was entered as a dependent variable into the equation, it was predicted by the independent variable sEMBU over protection significantly (F(1.32)=5.703, p ¼ .02, R2 =0.15). The similar result was duplicated in healthy control group (F(1.29)=4.667, p ¼ .03, R2 =0.10). Regarding the schizophrenia-healthy sibling group, > binary logistic regression indicated that s-EMBU rejection and plasma oxytocin levels were significant predictors in representing the group differences (Chi-Square = 35.659, df ¼ 5, p < .001).

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					>All of the five predictors (s-EMBU over-protection/rejection, ECRR anxiety/avoidance and plasma oxytocin levels) explained 54% of the variability of group difference. s-EMBU rejection (Wald = 7.721, p < .01) and plasma oxytocin levels (Wald = 7.253, p < .01) were significant at the 5% level. > The model correctly predicted 77% of cases whom had schizophrenia diagnosis and 82% of cases whom did not have schizophrenia diagnosis, giving an overall percentage correct prediction rate of 79%. <u>Regarding the schizophrenia-healthy control group,</u> > s-EMBU rejection and plasma oxytocin levels were significant predictors for representing the differences among groups (Chi-Square = 57.102, df ¼ 6, p < .001). > All the six predictors "explained" 78% of the variability of group difference. sEMBU rejection (Wald = 4.328, p ¼ .03) and plasma oxytocin levels (Wald = 10.841, p < .01) were significant at the 5% level. >The model correctly predicted 88% of cases whom had schizophrenia diagnosis and 87% of cases whom did not have schizophrenia diagnosis, giving an overall percentage correct prediction rate of 88% <u>Regarding the healthy sibling-healthy control</u>

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					> Binary logistic regression showed that the mean value of plasma oxytocin levels was only significant predictor for representation of the groups (Chi-Square = 10.268, df ¼ 1, p ¼ .001). >The sole significant predictor (plasma oxytocin levels) explained 20% of the variability of group difference. Plasma oxytocin levels (Wald = 8.104, p ¼ .04) were significant at the 5% level > The model correctly predicted 77% of cases whom were the siblings of schizophrenia patients and 52% of cases whom were not the siblings of the patients, giving an overall percentage correct prediction rate of 65%
Wynn, Jonathan K et al. (2019)	Randomized Clinical Trial	To determine which oxytocin (OT) dose is best for target engagement in pacients with schizophrenia	47 patients with schizophrenia (male 31 female 16)	> BPRS > Participants received either OT or placebo on separate testing days one week apart. Eight doses of OT were used: 8, 12, 24, 36, 48, 60, 72, or 84 IU. Six participants were randomly assigned to each OT/placebo dose. >EEG - Biological motion Mu suppression task where the stimuli consisted of 5 s video clips of point-light walkers simultaneously depicting three different dimensions, each manipulated independently: expression (happy or sad), gender (male or female), or intention (walking towards or away from the viewer).	Mu suppression > All three conditions resulted in significant mu suppression a significant main effect of condition, $F_{2,92} = 3.26$, $p < 0.005$. Follow-up contrasts revealed that this significant main effect was due to significantly less suppression in the gender condition compared to the emotion ($p < 0.03$) condition. > Significant effects of condition ($F_{2,207} = 4.68$, $p = 0.01$) and dose ($F_{8,247} = 2.69$, $p = 0.01$) were observed, but there was no significant interaction between the two ($F_{16,207} = 0.94$, $p = 0.53$).

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				> Facial affect pupillometry task - a 5 s presentation of one stimulus from one of the four conditions (happy, afraid, neutral, or scrambled)after EEG task.	> Post hoc analyses of the condition effect showed that mu suppression during gender identification, −0.05 (0.01), was significantly smaller compared to emotion identification, −0.10 (0.01), $p < 0.01$, and intention identification, −0.08 (0.01), $p = 0.05$. > Mu suppression at doses of 36 IU, −0.14 (0.02), and 48 IU, −0.13 (0.02) was significantly greater compared to the placebo condition, −0.07 (0.01), p's = 0.01 and 0.02, respectively PUPILLOMETRY > The three face conditions resulted in significant pupil dilation, all t's (df = 46) > 2.93, p's < 0.005; pupil dilation to scrambled faces was not significant ($p > 0.45$) >nA repeated-measures ANOVA to determine if there were differences in pupil dilation among the four conditions was performed, revealing a significant main effect of condition $F_{3,138} = 6.81$, $p < 0.001$. > Follow-up contrasts revealed that dilation was significantly smaller to the scrambled face compared to fearful and neutral (p's < 0.06) but not happy faces ($p = 0.21$). OT effects, results of the mixed model analysis did not reveal a significant dose effect, $F_{8,61} = 1.06$, $p = 0.40$.
Tugba Mutu Pek, Esra Yazici, Derya	Cross--Sectional Study	To investigate the relationship between oxytocin (OXT), vasopressin (AVP) and atrial	123 individuals (29 male 64 female) 63 patients with chronic	> Blood was drawn and analysed using ELISA to check OT ANP and AVP levels > Rey Auditory Verbal Learning Test	> Although healthy controls had higher oxytocin, vasopressin, and ANP levels, the differences were not

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Guzel, Elif Kose, Ahmet Bülent (2019)		natriuretic peptide (ANP) levels and cognitive functions in schizophrenia as well as to compare the findings to those in healthy controls.	schizophrenia (35 male 28 female) 60 controls(24 male 36 female)	(VLT) > The Trail Making Test A-B (TMT) > The Stroop Test > The Wechsler Memory Scale-Visual Production Subscale (WMS-V) > Facial Emotion Recognition Test > PANNS > CGI > GAF	statistically significant. > Patients performed significantly worse than controls on several cognitive tests (e.g., Rey Auditory Verbal Learning Test, Wechsler Memory Scale, Trail Making Test, Stroop Test, and Facial Emotion Recognition Test). > A significant negative correlation was found between ANP levels and long-term memory scores (r = –0.321, p = 0.010). > There were significant differences between patients and controls in the correlations of hormone levels (particularly oxytocin and vasopressin) with cognitive measures (e.g., instantaneous memory and emotion recognition response times).
Liu, Yong et al. (2019)	Cross--Sectional Study	To assess the relationship of mRNA expression and serum levels of OXT and OXTR in FES To assess serum OXT, OXTR, IL-6, hsCRP and Hcy levels in FES	52 patients with first-episode schizophrenia (FES) (31 male 21 female) 41 healthy controls (HC) (23 male 18 female)	> Measurement of serum oxytocin (OXT), oxytocin receptor (OXTR), interleukin-6 (IL-6), high sensitivity C-reactive protein (hsCRP) and homocysteine (Hcy) > RNA Extraction and Real Time qPCR Analysis	> Serum OXT and OXTR levels in HC group (711.58 ± 40.57 and 252.15 ± 20.62 pg/ml, respectively) were significantly higher (t = -4.164 and t = -2.894, P = 0.000 and P = 0.007, respectively) than in FES patients (518.96 ± 22.22 and 174.60 ± 17.11 pg/ml, respectively) > Serum IL-6 and hsCRP levels in HC group showed no difference with first episode schizophrenia > Serum Homocysteine levels were significantly lower (t = 2.459, P = 0.020) in HC group (15.24 ± 0.82 µmol/ml) than in FES patients (20.18 ± 1.83 µmol/ml)

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					> The expressions of OXT and OXTR mRNA were significantly lower (P = 0.000 and P = 0.007, respectively) in the HC group (0.16 ± 0.01 and 0.14 ± 0.01, respectively) than in FES patients (0.27 ± 0.02 and 0.20 ± 0.02, respectively)
Halverson, Tate et al. (2019)	Randomized Clinical Trial	To test if twice-daily intranasal oxytocin administered for 12-weeks would improve tertiary and exploratory outcomes of self-reported social symptoms, empathy and introspective accuracy	62 individuals (47 male 15 female) - 39 patients with schizophrenia; 23 patients with schizoaffective disorder 32 were assigned oxytocin (24 male 8 female) - 19 patients with schizophrenia; 20 patients with schizoaffective disorder 30 were assigned placebo (23 male 7 female) - 13 patients with schizophrenia; 10 patients with schizoaffective disorder	>PANSS > Intranasal study drug was self-administered twice daily for 12 weeks. each dose was approximately 24 international units (IU) of oxytocin or placebo (48 IUs daily) Measures assessed at 6 and 12 weeks: Introspective accuracy(IA) measures: > Specific Level of Functioning Scale (SLOF) > Interpersonal Perception Task (IPT) Self-report measures > Interpersonal Reactivity Index (IRI) > Liebowitz Social Anxiety Scale (LSAS) > Paranoid Thought Scales (GPTS)	> The placebo group had significantly higher levels of paranoia indicated by PANSS items assessing social functioning (i.e., suspiciousness/persecution, hostility, passive/apathetic social withdrawal, uncooperativeness, and active social avoidance) compared with the oxytocin group, t(60) = 2.29, p = .03. Age (t(60) = 1.75, p = .09) and taking mood stabilizers (X2(1) = 3.34, p = .07) differed at a trend level > No significant differences on IA abilities measured by the IPT and the SLOF were observed between treatment group >Improved IA, measured by the IPT task, was observed within the placebo group at 12 weeks (MLS = −1.7, 95% CI [−3.1, −0.3], p = .02) The oxytocin group (MLS = 0.4, 95% CI [−1.1, 1.9]) exhibited improved IRI Perspective Taking at week 12 compared with the placebo group (MLS = −1.8, 95% CI [−3.3, −0.4], F(1, 109) = 4.77, p = .031) > Significant within-group changes

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					in empathy were only observed in the placebo group. The placebo group exhibited worse empathy abilities over time on the Emotional Concern Subscale of the IRI (MLS = −1.4, 95% CI [−2.7, −0.1], t(109) = 2.2, p = .03) at 6 weeks as well as on the Perspective Taking Subscale of the IRI (MLS = −1.8, 95% CI [−3.3, −0.4], t(110) = 2.5, p = .02) at 12 weeks. > No significant between-group differences were observed on self-reported symptom outcomes. > Significantly better social avoidance measured by the LSAS Social Avoidance Subscale was observed in the placebo group at 12 weeks (MLS = −2.7, 95% CI [−4.6, −0.7], t(106) = 2.7, p = .007). The placebo group also demonstrated significantly better paranoia at 6 weeks measured by the GPTS Social Reference Subscale (MLS = −4.7, 95% CI [−8.2, −1.2], t(108) = 2.7, p = .008) and total score (MLS = −8.1, 95% CI [−14.6, −1.7], t(108) = 2.5, p = .01)
Strauss, Gregory P et al. (2019)	Randomized Clinical Trial	To examine the efficacy of combining oxytocin and a longer-term (24 weeks) Cognitive-Behavioral Social Skills Training (CBSST)	62 outpatients with schizophrenia (29 male 24 female) 31 with placebo(20 male 11 female) 31 with oxytocin treatment (18 male 13 female)	Patients underwent a 2-week Evaluation Phase, a 24-week Double-Blind Treatment Phase, were participants were randomly assigned to intranasal oxytocin (36 IU, BID) or placebo intranasal oxytocin and received cognitive behavioural social	> There were no significant main effects or interactions for any task. These findings suggest that CBSST failed to enhance social cognition and oxytocin failed to have an additive effect beyond CBSST > The main effects of Emotion and

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				skills training CBSST 2 times per week all in the same group, and a week 36 follow-up evaluation visit. Social cognition measures administered at baseline, 12-weeks, and 24-weeks: > RMET > Empathic Accuracy Task (EAT) > Trust Game (TG) > Facial Emotion Recognition Test (FERT) Symptom and functional outcome assessments obtained at the follow up visit > Facial Emotion Recognition Test (FERT) > SANS > BPRS > Calgary Depression Scale (CDS) > CGI	Intensity were significant, as well as the Emotion × Intensity interaction, reflecting relatively greater increases in accuracy with higher levels of stimulus intensity for anger and fear than happiness, sadness, or surprise. > There was also a significant Week × Emotion × Intensity interaction indicating relatively greater gains in fear and sadness with increasing stimulus intensity than other emotions from week 0 to 36. > The main effect of intensity was significant, suggesting greater gaze to target areas for higher intensity stimuli. There was also a significant Treatment × Week × Emotion interaction. This interaction reflects greater dwell time within target interest areas by the oxytocin than placebo group for happy faces as the duration of treatment increases.
De Coster, Lize et al. (2019)	Randomized Clinical Trial	To investigate if oxytocin, a neuropeptide implicated in social behavior, would normalize neural abnormalities in schizophrenia during ToM, and if this normalization would correlate improvement in ToM behavior	48 male individuals 23 male patients with a schizophrenia spectrum disorder (schizophrenia and schizoaffective disorder) 25 healthy controls	> Participants underwent 2 test days separated by at least 2 weeks. On each test day, oxytocin (40 IU) or placebo was administered. Experimental fMRI tasks (FBT followed by PDT) started 45 min after drug administration > False Belief task (FBT) > Person Description task (PDT)	> In the SZ group regarding the FBT, a Condition × Drug interaction ($F(1,22) = 5.90$, $p = 0.02$, $\eta p^2 = 0.21$) indicated that Oxytocin improved accuracy for Belief ($M = 75.54\%$, $SD = 14.29\%$) but not Photograph stories ($M = 72.99\%$, $SD = 11.69\%$), compared to Placebo (Belief: $M = 59.29\%$, $SD = 16.99\%$, $t(22) = 3.38$, $p = 0.003$, and $d = 1.06$; Photograph: $M = 70.39\%$, $SD = 11.89\%$, $t(22) = 0.75$, and $p = 0.46$).

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					> In the SZ group regarding the PDT, a Condition × Drug interaction ($F(2,21) = 6.31$, $p = 0.007$, $\eta p^2 = 0.38$) indicated that Oxytocin improved accuracy for Thought ($M = 82.95\%$, $SD = 7.98\%$) and Emotion ($M = 83.22\%$, $SD = 10.36\%$) but not for Appearance stories ($M = 83.33\%$, $SD = 8.34\%$), relative to Placebo (Thought: $M = 73.37\%$, $SD = 10.94\%$, $t(22) = 3.61$, $p = 0.002$, and $d = 0.72$; Emotion: $M = 71.50\%$, $SD = 10.31\%$, $t(22) = 3.80$, $p < 0.001$, and $d = 0.76$; Appearance: $M = 82.22\%$, $SD = 8.95\%$, $t(22) = 0.50$, $p = 0.62$) > Regarding FBT, The Belief–Photograph whole-brain contrast on the Placebo day revealed hypoactivation in SZ relative to HC in the right temporo-parietal junction (rTPJ) (57 −54 21, $z = 6.00$, $n = 383$, $p < 0.001$ > Within this rTPJ ROI, a Condition × Drug interaction ($F(1,22) = 35.49$, $p < 0.001$, $\eta p^2 = 0.62$) emerged, with follow-up t-tests indicating that Oxytocin ($M = 0.14$, $SD = 0.34$), relative to Placebo ($M = -0.41$, $SD = 0.22$), increased rTPJ activation for Belief ($t(22) = 8.54$, $p < 0.001$, and $d = 0.96$) but not Photograph stories (Oxytocin: $M = -0.24$, $SD = 0.31$; Placebo: $M = -0.37$, $SD = 0.27$; $t(22) = 1.87$, $p = 0.08$)

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					> The Thought–Appearance whole-brain contrast on the Placebo day revealed hypoactivation in SZ, relative to HC, in rTPJ (63 −48 12, z = 4.21, n = 165, and p = 0.004), right dorsal medial prefrontal cortex (mPFC) (12 51 42, z = 4.39, n = 181, and p = 0.002), and posterior cingulate (pC) (12 −51 33, z = 4.55, n = 519, and p < 0.001). > The whole-brain contrast (Emotion–Appearance) on the Placebo day revealed hypoactivation for SZ, relative to HC, in pC (6 −48 36, z = 3.58, n = 136, and p = 0.02). > In the rTPJ ROI only, a Condition × Drug interaction was observed (F(2,21) = 4.42, p = 0.03, and $\eta p^2 = 0.30$). Thought and Emotion stories elicited greater activation on the Oxytocin (Thought: M = 0.42, SD = 0.26; Emotion: M = 0.50, SD = 0.17) compared to Placebo (Thought: M = 0.29, SD = 0.27, t(22) = 2.30, p = 0.03, and d = 0.50; Emotion: M = 0.21, SD = 0.42, t(22) = 3.11, p = 0.005, and d = 0.93) days, but Appearance stories did not (Oxytocin: M = 0.19, SD = 0.62; Placebo: M = 0.20, SD = 0.37; t(22) = 0.18, and p = 0.86). > In the FBT, oxytocin-induced activity increase in the rTPJ ROI for the [(Belief Oxytocin–Photograph Oxytocin) – (Belief Placebo–

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					Photograph Placebo)] contrast and oxytocin-induced increase in accuracy for the same contrast were positively correlated (r = 0.44, p = 0.04). > In the PDT, a similar positive correlation between oxytocin-induced activity increases in the rTPJ ROI for the [(Thought Oxytocin–Appearance Oxytocin) – (Thought Placebo–Appearance Placebo)] contrast and the oxytocin-induced accuracy increases was observed (r = 0.43, p = 0.04; > In HC, greater connectivity was observed during Belief (M = 0.67, SD = 0.17) than during Photograph (M = 0.17, SD = 0.15; t(24) = 10.46, p < 0.001, and d = 0.82) stories, while this difference was not significant in SZ (t(22) = 0.48, p = 0.64) > During the Oxytocin day only, greater connectivity was observed for Belief (M = 0.63, SD = 0.24) than for Photograph stories (M = 0.30, SD = 0.30; t(22) = 3.61, p = 0.002, and d = 0.92). > In HC, greater functional connectivity was observed during Thought stories (M = 0.55, SD = 0.25) compared to Appearance (M = 0.18, SD = 0.28; t(24) = 4.28, p < 0.001, and d = 0.84) and Emotion stories (M = 0.18, SD = 0.39; t(24) = 3.66, p = 0.001,

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					and d = 0.75), while these differences were not significant in SZ (t(22) = 0.13, p = 0.90 and t(22) = 0.39, and p = 70) > Greater connectivity was observed for Thought (M = 0.40, SD = 0.33) than for Appearance (M = 0.08, SD = 0.40; t(22) = 3.09, p = 0.005, and d = 0.89) and Emotion stories (M = −0.01, SD = 0.49; t(22) = 3.62, p = 0.002, and d = 0.90) on the Oxytocin day only.
Bradley, Ellen R et al. (2019)	Randomized Clinical Trial	To examine visual scanning of faces in men with schizophrenia and neurotypical controls to quantify oxytocin effects on eye gaze	72 male individuals 33 patients with schizophrenia 39 matched controls	> On each study day, which were separated by at least one week, a technician administered 40 IU oxytocin or saline placebo > Passive viewing task - participants had to maintain visual fixation on a cross to trigger display of the face. A fearful, happy or netural face then appeared for 5 seconds. Eye gaze patterns were recorded. >Eye-tracking; >PANSS; > Experiences in Close Relationships-Relationships Structures (ECR-RS) scale	> Participants showed reduced fixation time on the eyes of happy (b = −124.14 milliseconds, t = −3.15, p = .002) and fearful (b = −106.61 milliseconds, t = −2.60, p = .009) faces compared to neutral faces. > Patients showed reduced fixation time to the eyes compared to controls in the placebo condition (b = −406.99 milliseconds, t = −2.36, p = .021) > The drug × group interaction was significant (b = 425.25 milliseconds, t = 3.49, p < .001) such that patients showed increased fixation time on oxytocin compared to placebo (b = 226.37 milliseconds, t = 2.52, p = .014), but controls showed decreased fixation time on oxytocin compared to placebo (b = −198.88 milliseconds, t = −2.41, p = .019) > The interaction between drug and attachment anxiety was significant

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					(b = 157.39 milliseconds, t = 2.94, p = .004; Fig. 3A). Fixation time on the eyes decreased with increasing attachment anxiety at a trend level on placebo (b = −134.35 milliseconds, t = −1.79, p = .078), but not on oxytocin (b = 23.04 milliseconds, t = 0.31, p = .759). > The drug x group (b = 371.83 milliseconds, t = 3.11, p = .003) and drug × attachment anxiety (b = 128.94 milliseconds, t = 2.51, p = .014) interactions both independently predicted fixation time on the eyes > Fixation time on the eyes increased with increasing PANSS score in the oxytocin condition (b = 22.52 milliseconds, t = 2.72, p = .011), but not in the placebo condition (b = 3.62 milliseconds, t = 0.38, p = .703). > Participants showed increased fixation time on the eyes on oxytocin compared to placebo at both our sample mean PANSS score (b = 226.37 milliseconds, t = 2.96, p = .006) no significant drug × CPZ equivalents interaction (p = .382)
Bang, Minji et al. (2019)	Genetic Association Study	To investigate OXTR methylation and its association with clinical and brain network connectivity phenotypes of negative symptoms, particularly anhedonia-asociality, in individuals with recent-onset	208 individuals (101 male 107 female) 64 patients with recent-onset scihzophrenia (ROS) (25 male 39 female) 46 patiants at ultrahigh risk (UHR) for psychosis (30 male 19	> Epigenotyping Procedures Two CpG-rich regions selected based on previous studies: OXTR1 (chr3: 8 810 729–8,810,845; GRCh37/hg19) and OXTR2 (chr3: 8 809 281–8,809,534; GRCh37/hg19) > Methylation analysis performed	> Both men and women with ROS showed significantly more severe positive symptoms than did UHR participants, whereas the severity of negative symptoms did not differ. > Subscale scores of the SAPS showed that men and women with

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		schizophrenia (ROS) and at ultrahigh risk (UHR) for psychosis	female), 98 healthy individuals (46 male 52 female)	using the pyrosequencing method that yielded 3 CpG sites from OXTR1 and 8 CpG sites from OXTR2 > Magnetic resonance imaging (MRI) data were acquired on 16 ROS (7 male 9 female), 23 UHR (14 male 9 female), and 33 healthy participants (27 male 16 female)	ROS experienced more delusions than other positive symptoms. > Women with ROS had more severe hallucinations than those with UHR. > All subscales of negative symptoms, including anhedonia-asociality, were found to be similar in ROS and UHR participants. > Compared to HCs, ROS and UHR participants showed significantly decreased percentages of methylation at CpG1 and CpG2 of OXTR1 with large effect size (ES; ηp2 > 0.14) in men and women > ROS and UHR groups had less OXTR methylation than HCs did at CpG1 and CpG2, whereas no significant differences were observed between ROS and UHR groups > The methylation of CpG3 was significantly different with medium effect size (ES) among the 3 groups in men, whereas between-group pairwise comparisons revealed no significant differences after Bonferroni correction. > In ROS and UHR participants who showed similar severity of negative symptoms and OXTR methylation status, only women were found to have a significant inverse association between CpG1 methylation level and anhedonia-asociality scores with medium ES (Cohen's f2 = 0.18), independent of age and diagnosis (Adjusted R2 = 0.15, F(3, 54) = 4.46, P = .007

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					> Compared to HCs, the combined group of women with ROS and UHR showed increased striatal-amygdala network functional conectivity (FC) with large ES (>0.8). > The striatal-amygdala network FC, which was associated with the severity of anhedonia-asociality (r = .570, P = .014), had a significant relationship with the methylation level at CpG1 of OXTR1 in women with large ES (all women: r = −.559, P = .001; women with ROS and UHR: r = −.516, P = .034) > Male ROS and UHR participants showed no significant correlations between the striatal-amygdala network FC and anhedonia-asociality
Montag, Christiane et al. (2020)	Cross--Sectional Study	To assess possible associations of basal and induced OXT plasma levels with different dimensions of social cognition, like cognitive and emotional empathy, in patients with schizophrenia	70 individuals (46 male 24 female) 35 patients with schizophrenia (23 male 12 female) 35 healthy controls (23 male 12 female)	> AVLT > PANSS > Multifaceted Empathy Test (MET) > Interpersonal Reactivity Index (IRI) > Video-stimulated OXT reactivity - emotion induction condition (EMOI) and control condition (CON) > Blood was drawn for plasma samples to measure OXT concentrations before and after EMOI and CON testing	> Patients with schizophrenia scored significantly lower than healthy subjects on the cognitive sum scale of the MET and on the positive affective valences' subscale. > No significant differences were observed for emotional empathy. On the IRI patients rated themselves significantly less competent in "perspective-taking", but rather inclined to experience "personal distress" compared to controls > Patients and healthy controls indicated similar levels of empathy (p = 0.103), arousal (p = 0.995) and personal relevance (p = 0.370) of the emotion induction movies, but

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					patients perceived the control condition as significantly more stressful than healthy controls (p = 0.045) > During the emotional experimental condition, a significant group difference appeared, with OXT level mean increases in patients, and decreases in controls > In patients, MET Cognitive empathy for negative emotional valences was inversely correlated with OXT reactivity in the emotional condition (r = -0.418; p<0.05). This correlation coefficient differed significantly from the respective measure in the control group (Fisher's Z = -1.982, p>0.05). > Significant inverse correlations between OXT reactivity in the emotional (r = -0.537; p<0.01) as well as in the control (r = -0.359; p<0.05) condition and the IRI dimension "fantasy" were found in healthy subjects, but not in patients > Introducing verbal IQ, AVLT and age as control variables to the analysis revealed another association in schizophrenia patients: Basal OXT levels were significantly and inversely associated with MET-CE for positive emotional valences (r = -0.468, p<0.01) > Spearman's rank correlation analysis did show a negative correlation between MET CE sum score and PANSS "general

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					psychopathology" (r = -0.39, p = 0.026) and a positive correlation between MET CE sum score and medication with atypical antipsychotics (r = 0.351, p = 0.039). After including medication and PANSS "general psychopathology" as control variables, the correlation between OXT reactivity and MET-CE for negative valences remained stable (r = -0.407, p = 0.043)
Dwyer, Kristen R et al. (2020)	Randomized Clinical Trial	To assess whether oxytocin can improve more proximal indicators of social affiliation as indicated by changes in behavior, language and subjective indices of social affiliation among individuals with schizophrenia spectrum disorders during a role-play designed to elicit affiliative responses	40 outpatients with schizophrenia or schizoaffective disorder (33 male 7 female) 12 with oxytocin treatment (10 male 2 female) 14 with galantamine treatment (11 male 3 female) 14 on placebo (12 male 2 female)	> Participants continued established medication regimens and administered intranasal spray and pills twice daily for 6 weeks. The intranasal oxytocin dose was 24 IU twice a day. The galantamine target dose was 12 mg twice a day, and the following titration schedule was used: 4 mg twice a day for 1 week, then 8 mg twice a day for 1 week, then 12 mg twice a day for 4 weeks. > Affiliative Role-Play Task - the participant and an affiliative female confederate who was blind to group status and with whom the participant had not previously interacted completed two 3-minute role-plays, one involving getting to know a new neighbor and the second involving making plans with an old family friend. The goal of the role-plays was for the confederate to simulate an affiliative encounter with the participant. > Behavioral Coding Procedure > Linguistic Inquiry and Word Count	> Results from the LIWC indicated that participants said more positive (M = 5.09%) than negative (M = 0.51%) words (t(39) = 16.22, P < .001), more social (M = 7.50%) than negative words (t(39) = 15.21, P < .001), and more affiliative (M = 2.22%) than negative words (t(39) = 7.90, P < .001) > With regard to mood, collapsing across groups following the baseline role-play, participants reported significantly higher positive (M = 40.05%) than negative (M = 19.75%) affect (t(39) = 13.32, P < .001) > There was a moderate effect of treatment on total speech output for the oxytocin group in contrast to small effects for the placebo and galantamine groups.> With regard to behavioral ratings, there were no statistically significant treatment group, time, or interaction effects

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				(LIWC) > Positive and Negative Affect Scale (PANAS) > Positive Reactions to Partner Questionnaire (PRP) > Willingness to Interact Questionnaire (WIQ)	> Linguistic content results yielded a significant main effect of time on percentage of positive emotion and social words such that all participants used more positive and social words after treatment. > There was a significant group by time interaction for affiliative words. > Post hoc independent sample t-tests indicated that participants in the placebo group said more affiliative words during the post-treatment role-plays than those in the galantamine group, t(26) = 2.11, P = .04, but not the oxytocin group, t(24) = 1.57, P = .13 > There were no significant differences between the 3 groups at baseline (all Ps > .05), as well as no effect of time within the placebo (t(13) = 1.98, P = .07) or oxytocin (t(11) = 0.05, P = .96) group with regard to affiliative word use. > There was a significant reduction in the percentage of affiliative words spoken in the galantamine group over time, t(13) = −3.08, P = .01 > There was no statistically significant group, treatment, or interaction effects for self-reported positive or negative affect. > There were no group, time, or interaction effects for self-reported reactions to the partner or willingness to interact with the partner.

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Porffy, Lilla A et al. (2020)	Randomized Clinical Trial	To determine whether oxytocin has an effect on visual attention in patients with schizophrenia	19 male individuals 16 patients with schizophrenia 3 patients with schizoaffective disorder	> Participants attended two testing sessions separated by 7 days, during which they either received 40 IU oxytocin or placebo (saline) in a counterbalanced fashion. The eye-tracking task was performed approximately 2-h after oxytocin administration (during this time participants underwent functional magnetic resonance imaging [fMRI] > Eye-tracking > Free-viewing task > fMRI	> There was a main effect of treatment on all eye-tracking parameters. Themean number of fixations is 4.9 (95%CI = 4.6–5.1) under placebo versus 5.4 (95%CI = 5.2–5.7) under oxytocin; F1, 2272 = 25.50, p < .001. > The mean duration of fixations reduces to 607.9 ms (95%CI = 564.1–651.7) under oxytocin compared to 705.5 ms under placebo (95%CI = 661.0–750.0); F1, 1979 = 16.45, p < .001. > Dispersion increases under oxytocin (mean = 2.15°, 95%CI = 2.05–2.24) compared to placebo (mean = 2.01°, 95%CI = 1.92–2.11); F1, 2187 = 11.81, p < .001. Similarly, under oxytocin, saccade amplitudes increase (mean = 3.74°, 95%CI = 3.58–3.90) compared to placebo (mean = 3.48°, 95%CI = 3.32–3.64); F1, 2011 = 9.04, p = .002. > There was a main effect of stimuli type > There was a main effect of repetition on the total number of fixations (F4,2271 = 20.00, p < .001), and dispersion (F4,2188 = 8.38, p < .001). > On these eye-tracking parameters, treatment effect decreases as the number of repetitions (R) increases > There was no effect of repetition on duration of fixations (F4,1978 = 1.22, p = .30), and saccade amplitudes (F4,2010 = 0.56, p = .69).

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					> There was a main effect of treatment on all eye-tracking parameters when viewing different expressions > Oxytocin increases the total number of fixations by 0.72 (95%CI = 0.37–1.06), F2, 1132 = 17.05, p < .001; reduces the duration of fixations by 136.63 ms (95%CI = 63.88–209.37), F2, 994 = 13.58, p < .001; increases dispersion by 0.28° (95%CI = 0.14–0.41), F2, 1078 = 16.06, p < .001; finally, increases saccade amplitudes by 0.32° (95%CI = 0.07–0.58), F2, 1002 = 6.11, p = .01. > On dispersion, there is also a main effect of valance > There was no interaction between treatment and valance. Finally, there is no effect of counterbalancing on any dependable variables (DVs) > Both treatment (F1,1078 = 7.99, p = .005) and valence (F2,1078 = 3.35, p = .035) have a main effect on fixation rates in the eye region, with oxytocin decreasing fixation rates by 7% > There was a main effect of treatment in the nasion region (F1,1078 = 5.37, p = .021), where oxytocin increases fixations rates by 22%. Finally, there is both a main effect of treatment (F1,1078 = 4.22, p = .040) and main effect of valence (F2,1078 = 3.34, p = .036) on the rest of the face, outside the main regions

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					of interest, where oxytocin increased fixation rates by 11%
Giralt-López, M et al. (2020)	Genetic Association Study	To evaluate ToM in patients with schizophrenia spectrum disorders (SSDs), their healthy first-degree relatives, and controls to test its suitability as an endophenotypic marker. To study the modifying effect of markers of clinical and genetic liability to schizophrenia (SZ) (schizotypy and genetic variability in the oxytocin receptor gene: OXTR) on ToM in healthy individuals	199 individuals (98 male 101 female) 38 stable SSD patients (28 male 10 female): 32 patients with SZ and 6 patients psychotic disorder not otherwise specified. 80 unaffected first-degree relatives (33 male 47 female) 81 controls (37 male 44 female)	> PANSS > Hinting Task (HT) > Schizotypal Personality Questionnaire-Brief (SPQ-B) > Block Design and Vocabulary or Information WAIS-III subtests > Family history was assessed with the Family Interview for Genetic Studies > Genomic DNA was extracted > Genotyping of the intronic SNP rs53576 in the OXTR gene was performed	> All patients showed more prevalent negative than positive symptoms > No association was detected when testing whether ToM performance in patients is modulated by clinical severity or insight as measured with PANSS > A comparison of HT performance between patients and first-degree relatives and between patients and controls showed significant group effects ($F = 8.96$, $p = 0.003$ and $F = 17.64$, $p < 0.001$, respectively). > Analysing ToM performances, patients presented lower scores than relatives (estimated mean difference = −2.27) and controls (estimated mean difference = −2.44). These results remained significant after including IQ as a covariate ($p = 0.007$ and $p = 0.025$, respectively). > Analysing ToM performances, the scores of relatives and controls did not differ significantly. > Being a high scorer for Schizotypal Personality Questionnaire-interpersonal (SPQ-IP; $\beta = -0.277$, $p = 0.010$, R adj2 = 22.2%) and Schizotypal Personality Questionnaire cognitive-perceptual (SPQ-CP; $\beta = -0.243$, $p = 0.030$, R adj2 = 20%) was related to poorer ToM performance in relatives.

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					> The rs53576 (GG vs. A allele carriers) did not show a significant association with HT performance but showed a modifying effect on the relationship between schizotypy and HT in controls. > When including the OXTR variability in the model being a high scorer for SPQ-CP turned to be related to poorer ToM performance in controls (β = −0.307, p = 0.030, R adj2 = 13.8%). > Within GG subjects (17 SPQ-CP low scorers and 12 high scorers), the effect of SPQ-CP on HT performance was statistically significant (β = −0.468, p = 0.007, R adj2 = 30.1%), while it was not within A carriers.
Bradley, Ellen R et al. (2020)	Randomized Clinical Trial	To investigate oxytocin's effects on competitive interactions with the goal of determining whether modulation of social reward may be a mechanism by which oxytocin impacts social behavior in schizophrenia.	88 male individuals 37 patients with schizophrenia: - 15 with oxytocin treatment - 22 with placebo 51 healthy controls: - 25 with oxytocine treatment - 26 with placebo	> Following baseline assessments, participants were randomized to receive either 40 IU of oxytocin or a placebo nasal spray. Experimental tasks began 30 min after, and ended approximately 70 min after, oxytocin administration > PANSS > Auction Game - Risk Neutral Nash Equilibrium (RNNE) bid > Devil's task	> In the Auction Game, participants generally begin bidding near the upper range of possible values for the item under auction. Bidding this amount results in monetary losses, and with experience, participants reduce bidding until they reach a stable equilibrium. This equilibrium is generally significantly above the money maximizing strategy (RNNE; κ = 0) > A 3-way interaction drug × group × trial was not significant (p = 0.95), nor was the 2-way interaction drug × group > The 2-way group × trial (b = 0.0053, t = 2.18, p = 0.029) and drug

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					× trial (b = 0.0049, t = 2.01, p = 0.044) interactions were significant > Controls reduced their bids over time (b = −0.0075,t = −4.58, p = 4.7 × 10−06), while patients did not (b = −0.0026, t = −1.35, p = 0.18). > Participants who received placebo decreased their bids over time (b = −0.0074, t = −4.40, p = 1.1 × 10−05), while those who received oxytocin did not (b = −0.003, t = −1.62, p = 0.1) > Controls decreased their bids from the first five to the last five trials (b = −0.21, t = −3.64, p = 0.00047), while patients did not (b = 0.0054, t = 0.082, p = 0.93). > Participants on placebo decreased their bids from the first five to the last five trials (b = −0.19, t = −3.16, p = 0.0022) while participants on oxytocin did not (b = −0.03, t = −0.46, p = 0.65). > Participants on oxytocin bid higher than those on placebo at the trend level in the last five trials (b = 0.16, t = 1.7, p = 0.093) but not in the first five trials (b = 0.0041, t = 0.044, p = 0.97) > Visual investigation of bidding across trials shows that bids start high but then temporarily increase before decreasing toward the optimal strategy > Bidding is motivated not only by monetary gains, but also by social motivation to win (ρwin) and to avoid

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					losing (ploss) > ρwin was not significantly different between controls and patients on placebo (U = 218.00, p = 0.24), but oxytocin was associated with higher ρwin in schizophrenia (U = 30.00, p < 0.001) and at a trend level in controls (U = 227.00, p = 0.10); > No significant group, drug, or group × drug effects, indicating that differences in bidding behavior between groups and drug condition are unlikely to stem from differences in risktaking preferences > The three-way PANSS × drug × trial interaction was not significant (p = 0.14) > The three-way CPZ × drug × trial interaction was significant (b = 6.2 × 10−05 , t = 2.52, p = 0.012), such that patients taking the mean dosage in our sample (CPZ = 75.08) did not change their bids over time on oxytocin (b = −0.0021, t = −0.59, p = 0.55) v. placebo (b = −0.0019, t = −0.69, p = 0.49). > Patients on high dosages (CPZ mean + 1 standard deviation = 223.35) decreased their bids over time on placebo (b = −0.0053, t = −2.08, p = 0.038) but not on oxytocin (b = 0.0037, t = 1.13, p = 0.26).
Abram, Samantha V et al. (2020)	Randomized Clinical Trial	To assess oxytocin-related effects on amygdala resting-state functional connectivity (rsFC)	sample 1 22 patients with schizophrenia	Sample 1 > PANSS > oxytocin (OT) and placebo days were	Sample 1 > Higher-level analysis revealed a left-lateralized cluster including

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		using functional magnetic resonance imaging (fMRI)	(SZ) 24 healthy controls (HC) sample 2 183 patients with SZ 178 HC	separated by at least 2 weeks. Staff administered a single OT (40 IU) or placebo dose via nasal spray ~90 minutes before the resting-state fMRI scan. Individuals were scanned twice, once on OT and once on placebo. Sample 2 > PANSS > SANS > Subjects did not receive OT or placebo > rsFC data collection and pre-processing details were reported previously on another study > Using the same amygdala seed from sample, voxel-wise whole-brain connectivity maps for each subject were generated , expressed as Fisher r-to-z transformed correlation maps	voxels from the middle temporal gyrus(MTG), superior temporal sulcus(STS), and angular gyrus(AngG) (MTG/STS/AngG; z-max = 3.78, number of voxels = 456, P = .001), which corresponded to Brodmann areas BA19, BA21, BA37, and BA39 > OT increased connectivity between amygdala and left MTG/STS/AngG in SZ (t44 = −4.77, P < .001, Padj < .001, d = 1.00), and modestly decreased connectivity in HC (t44 = 2.51, P = .02, Padj = .06, d = −0.60), though this effect was not significant after removal of an outlier with connectivity > 3 SDs above the HC mean (t43 = 1.91, P = .06, Padj = .25) > Follow-up analysis revealed SZ had amygdala-to-left-MTG/STS/AngG hypo-connectivity compared to HC on placebo (t44 = 3.49, P = .001, Padj = .004, d = −0.92), and more similar connectivity to HC on OT (t44 = −2.05, P = .05, Padj = .19, d = 0.69) > Within-group OT-induced changes for SZ or HC outside of the left MTG/STS/AngG area were not detected. > Post hoc analysis using a reduced voxel-wise height threshold revealed connectivity increases in similar right temporal and occipital areas > More severe PANSS negative symptoms correlated with less amygdala-to-left-MTG/STS/AngG connectivity on placebo (r20 = −.56,

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					P = .006, Padj = .01), and greater amygdala-to-left-MTG/STS/AngG connectivity increases following OT (r20 = .53, P = .005, Padj = .01) Sample 2 > A negative correlation was present for the SANS Negative scores (r176 = −.19, P = .01, Padj = .02), and nonsignificant (but in the same direction) for PANSS Negative scores (r178 = −.11, P = .17, Padj = .34) > Exploratory analyses further revealed that reduced amygdala-to-left-MTG/STS/AngG connectivity was specifically associated with more severe expressive negative symptoms (ie, alogia, flat affect) as compared to experiential negative symptoms (ie, amotivation, anhedonia, asociality)
Chuang, Brandon J et al. (2020)	Randomized Clinical Trial	To assess whether administration of oxytocin can improve emotional prosody recognition accuracy in SSD	157 individuals (116 male 41 female) 60 patients with schizophrenia-spectrum disorders (SSD) (45 male 15 female) 97 controls (71 male 26 female)	> Participants underwent two testing days separated by at least one week. On each test day, 40 IU of oxytocin or placebo was self-administered > PANSS > Emotional prosody task	> There was no main effect of drug on overall emotional prosody recognition accuracy and no Drug interactions > Follow-up TOST equivalence tests were significant for individuals with SSD (t(117.92) = −2.055, p = 0.02) and controls t(191.74) = −2.60, p = 0.005) suggesting that the effects of oxytocin and placebo on emotional prosody recognition accuracy were equivalent in both groups. A significant main effect of group was found, with individuals with SSD having lower emotional prosody

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					recognition accuracy than controls (Z = −2.30, p = 0.02, d = 0.36). > Significant main effects of valence and intensity were found, which were qualified by a significant Valence × Intensity interaction (see Supplemental Materials). There was a main effect of Age, with older participants having poorer overall emotional prosody recognition accuracy (r = -0.45, p < 0.001)
Bradley, Ellen R et al. (2021)	Randomized Clinical Trial	To understand whether the most consistently-observed effect of exogenous oxytocin in men with schizophrenia—improved mentalizing—replicated in women with the disorder	64 female individuals 26 patients with schizophrenia 38 healthy controls	> PANSS at baseline > Participants were randomized to drug order. On each testing day, 40 IU oxytocin or saline placebo was administered intranasally. Participants completed the assessment beginning ~45 min and concluding ~75 min following drug administration. Performance-based Social Inference–Enriched (SI-E) sub-section of The Awareness of Social Inference Test (TASIT) > Social Inference–Minimal (SI-M) sub-section was implemented partway through the study, and thus has a smaller sample size (N = 23 patients; N = 25 controls)	> For patients, the mean PANSS score was 57.7 (SD = 12.1). > There was a main effect of group, indicating that patients performed worse than controls on the SI-E overall (b = 0.10; CI = 0.05, 0.15; p < 0.001). > No drug x group interaction (b = −0.004; CI = −0.05, 0.04; p = 0.85) or main effect of drug (b = 0.01; CI = −0.03, 0.05; p = 0.55) was found , suggesting that oxytocin administration did not improve mentalizing in either patients or controls. > No main effect of group (b = −0.01; CI = −0.15, 0.12; p = 0.84) and no drug x group interaction on control task performance (b = 0.01; CI = −0.14, 0.17; p = 0.87) were found. > The equivalence test was significant, t(25) = −1.79, p = 0.03, allowing us to reject the null

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					hypothesis that oxytocin is associated with a medium or larger effect on SI-E scores among patients in this sample > Higher anti-dopaminergic medication dosage (mean CPZ = 264.5, SD = 223.5) was associated with lower mentalizing performance change scores (ρ(−0.43), p = 0.03)
Andari, Elissar et al. (2021)	Randomized Clinical Trial	To examine the effects of intranasal oxytocin (IN-OXT) on emotional processes in experimental interactive social contexts in individuals with schizophrenia (SCZ)	39 male individuals 20 schizophrenic male patients: - 11 with oxytocin treatment - 9 with placebo 19 male healthy controls (HCs)	> PANSS > SDS Symptom Score > MATRICS > Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB) > The IN-OXT group received intranasal oxytocin spray (24IU) whereas the IN-PL group received intranasal placebo. HCs completed the test procedures on a single day without receiving intranasal oxytocin or placebo. HCs were included in the study to determine a baseline on study procedures compared to SCZ who did and did not receive OXT (IN-PL). SCZ subjects were required to attend two visits. The first visit included: > PANSS > SDS Symptom Score > MATRICS > Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive	> Healthy controls outperformed patients with schizophrenia on cognitive tests. > Within the schizophrenia group, intranasal oxytocin did not change overall cognitive performance or eye-tracking measures compared to placebo. > However, in social interaction tasks, patients receiving placebo showed a bias toward positive cues, while those given oxytocin later rated positive faces more favorably and negative faces more harshly. This suggests that oxytocin might help improve emotion recognition during social interactions in schizophrenia, even though its effects on basic cognitive measures were minimal.

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				Battery (MCCB) The second visit included the administration of IN-OXT or IN-PL. All the behavioral tests were performed 45 minutes after administration of IN-OXT or IN-PL in a set order: > Eye tracking tasks followed by social interaction tasks > Facial Emotion Identification Test (FEIT) > Visual scanning of faces > Gender identification > Gaze direction identification > Emotion-based Social Ball-Tossing Game (ES-BTG) > Valence-based non-Social Ball-Tossing Game (VnS-BTG)	
Buchanan, Robert W et al. (2021)	Randomized Clinical Trial	To examine the addition of intranasal oxytocin to cognitive behavioural social skills training (CBSST) can strengthen their impact on social function.	62 participants with schizophrenia or schizoaffective disorder 31 intranasal oxytocin 36 I.U. (3 sprays) BID 31 intranasal placebo-oxytocin (3 sprays) BID	Social & Belief Scales: Birchwood Social Functioning Scale (BSFS) Defeatist Performance Attitude Scale (DPAS) Asocial Beliefs Scale (ABS) Clinical Assessments: BPRS, SANS, CDS: Administered at the start and end of the 2-week Evaluation Phase, every 4 weeks during the 24-week Double-Blind Treatment Phase, and at the week-36 follow-up. CGI: Administered weekly during the Evaluation Phase, every 4 weeks during the Treatment Phase, and at week 36. Side Effects & Safety:	> In the final model for BSFS total score, there was a significant effect for site (t=2.32; df=58.4; p=0.02; Cohen's f2= 0.09), but not for time (t=−1.38; df=58.4; p=0.17; Cohen's f2= 0.03) or treatment (t=−0.84; df=58.4; p=0.41; Cohen's f2= 0.01) > There was a significant effect for the time x site interaction (t=2.09; df=39.7; p=0.04; Cohen's f2= 0.07) > The significant site and time x site interactions reflect the greater improvement in BSFS total score over the course of the double-blind treatment phase, in both the oxytocin and placebo groups, at the San Diego site > In the 12-week follow-up phase, there was a significant site effect

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				Side Effect Checklist (SEC) and Water Consumption Questionnaire (WCQ): Conducted at baseline and weekly during the 24-week phase. Blood chemistry panel, complete blood count, urinalysis, and EKG: Collected during the Evaluation Phase and every 4 weeks thereafter. Cognitive Measures: Cognitive Therapy Rating Scale for Psychosis (CTS-Psy) and Comprehensive Modules Test (CMT): Administered at baseline and at weeks 12, 24, and 36. Study Phases: 2-week Evaluation Phase 24-week Double-Blind Treatment Phase (participants meeting inclusion criteria were randomized via a permuted block system to receive intranasal oxytocin [72 IU daily] or placebo) Week-36 Follow-Up (conducted 12 weeks after the last Cognitive Behavioral Social Skills Training session to assess treatment effect persistence)	(t=3.09; df=51.2; p=0.003; Cohen's f2= 0.19), which reflects the continued difference in BSFS total score between the two sites > Greater improvements in San Diego on some subscales (e.g., Prosocial Activities, Recreation, Independence), especially in the placebo group (data available upon request from the authors) Social Attitude Assessments > In the final model for DPAS total score, the time (t=−1.31; df=38; p=0.20), treatment (t=−1.67; df=47; p=0.10), and site effects (t=−0.86; df=47; p=0.39) were not significant. > The treatment x site interaction was significant (t=2.11; df=47; p=0.04); the treatment x time (t=1.50; df=38; p=0.14) and treatment x time x site (t=−0.77; df=38; p=0.45) interactions were not significant. The treatment x site effect was driven by the greater reduction in DPAS total score in the San Diego placebo group compared to the other three groups. > In the final model for ABS total score, the treatment, time, and site effects were not significant (all p values > 0.55) Clinical Assessments > In the final model for BPRS total score, there was a significant main

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					effect for site (t=−3.47; df=100.3; p=0.0008) and a trend for treatment (t=−1.70; df=100.5; p=0.09) > The site main effect reflects the markedly greater reduction in BPRS total score, regardless of treatment assignment, at the San Diego site > Greater improvement was found for oxytocin relative to placebo early in treatment in Maryland, but benefits were reduced by the end of the treatment phase, whereas in San Diego both treatment groups showed rapid early improvement, but the oxytocin group continued to show greater improvement relative to placebo toward the end of the treatment phase > In the 12-week follow-up period, the improvement in BPRS total score was lost in the participants randomized to placebo at the San Diego site, but not in any of the other treatment groups (site: t=−2.76; df=38; p=0.009; time x site: t=2.43; df=35; p=0.02; > In final model for BPRS positive symptom item score, the treatment, time, and site main effects were not significant (all p values > 0.20) > In the 12-week follow-up period, the BPRS positive symptom scores continued to decrease in both Maryland site treatment groups and in the San Diego oxytocin, but not placebo, group between weeks 24 and 36 (site: t=−2.96; df=58; p=0.004;

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					time x site: t=2.88; df=38; p=0.006; and treatment x time x site: t=2.88; df=38; p=0.006 > In the final model for SANS total score, there was a significant site effect (t=−2.16; df=108.3; p=0.03), but the treatment effect (t=−0.89; df=109.9; p=0.38) and time (t=0.33; df=227.0; p=0.74) effects were not significant > The significant site and time x site effects reflects the significant reduction in SANS total score in both treatment groups at the San Diego site > The observed effects during the double-blind treatment phase persisted through the 12-week follow-up period, with greater reduction in the San Diego placebo group compared to San Diego oxytocin group (site: t=−4.06; df=54.9; p=0.0001; treatment x site: t=2.09; df=54.8; p=0.04) > To examine whether there was a selective effect of oxytocin on the expressive and experiential negative symptom subfactors, the effect of oxytocin was examined separately on the two SANS subfactors. There was a significant site effect (t=2.02; df=50.0; p=0.049) for the SANS expressive subfactor. > There was a significant time x site effect (t=3.84; df=224; p=0.0002), with a marked reduction in the SANS experiential subfactor at the San

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					Diego site > CDS total score included a significant main effect for site (t=−2.61; df=94.1; p=0.01); there was trend for a significant treatment x site interaction (t=1.80; df=95.9; p=0.08) > The observed site effect reflects the significant reduction in CDS total score in both of the San Diego treatment groups significant site (t=−2.85; df=47.6; p=0.006) and time x site (t=2.55; df=34.4; p=0.02) effects at week 36, which reflect the return to pre-treatment levels of the CDS total score in the two San Diego groups > There were no significant main effects (all p values > 0.10) or interaction effects (all p values > 0.10) for the CGI severity item Comprehension Modules Test (CMT). > The final model for CMT total score included a significant main effect for time (t=2.22; df=35; p=0.03) > There was a significant treatment x time (F=5.09; df=1,956; p=0.02) effect for diastolic pressure, which reflected a slight increase in this measure with oxytocin and a slight decrease in the placebo group. > There was a significant treatment x time effect was for sodium (F=5.35; df=1,217; p=0.02); participants

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					treated with oxytocin had a modest increase in sodium levels, whereas there was a small decrease in the placebo group. > There was a significant time effect for chloride (F=4.34; df=1,217; p=0.01) and bilirubin (F=5.26; df=1,216; p=0.02), which reflected a small decrease in these levels over the course of the study. > There was a significant time effect for glucose (F=6.79; df=1,216; p=0.04) and cholesterol (F=4.26; df=1,133; p=0.04), which reflected an increase in these levels over the course of the study > There were small, but significant, increases in hemoglobin (F=6.48; df=1,217; p=0.01) and hematocrit (F=10.6; df=1,217; p=0.001) over the course of the study. However, neither the treatment or treatment x time effects were significant
Nakata, Yusuke et al. (2021)	Genetic Association Study	To assess if treatment resistant schizophrenia (TRS) patients have more profound OXT system abnormalities compared to patients with other types of schizophrenia (i.e., non-TRS).	86 individuals (54 male 32 female) 30 patients with treatment-resistant schizophrenia (TRS) (15 male 13 female) 28 patients with remission schizophrenia (RemSZ) (16 male 14 female) 28 patients with autistic specrum disorder (ASD) (23male 5 female)	> PANSS > Andreasen criteria > Clozaril Patient Monitoring Service (CPMS) > MATRICS Consensus Cognitive Battery (MCCB) > Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) > False-belief (FB) task > ELISA for the serum oxytocin concentration > Sanger sequence and genotyping of	> In the TRS group, there was a positive relationship between the speed-of-processing score (with a higher score indicating a faster processing speed) and OT > When the PANSS-positive score, -negative score, or total were included as covariates, the significant correlation of processing speed with OT in the TRS group disappeared > The significant relationship between OT and speed-of-processing

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				oxytocin receptors	disappeared when estimated IQ or antipsychotic dosage was the covariate, but the relationship survived when age was a covariate, suggesting that the patient's IQ and antipsychotics could influence the relationship between the speed-of-processing and the OT system > Regarding social cognition, the OT concentrations showed a positive relationship with the FB tasks in the TRS group > Regarding MSCEIT, there was no significant relationship with OT in any group > When the PANSS-positive score or PANSS-total score was included as a covariate, the significant correlation between the FB tasks and OT concentrations in the TRS group survived, but when PANSS-negative score was included as a covariate, the significant correlation was lost. Similarly, when age, estimated IQ, or antipsychotic dose was used as a covariate, the significant relationship survived. > In schizophrenia patients overall (i.e., the TRS and RemSZ group combined), there was a significant negative relationship of OT with both positive and negative symptoms, but not with total PANSS psychopathology > In the genotyping distribution, only rs138095850 (positioned in the 3′-UTR region) was significantly

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					different between the schizophrenia patients overall (the combined TRS and RemSZ group) and the ASD group, but the significance disappeared following the permutation test > The haplotype analysis revealed only one haplotype block, which included a total of five SNPs (rs4686302, -rs2228485, -rs237911, -rs2301261, -rs968389) that showed almost the same distributions between the combined schizophrenia group and the ASD group > For rs53576, in the combined schizophrenia group, carriers of the G allele (G/G + G/A), which was the minor allele, showed worse MSCEIT task and FB task results compared to the patients without the G allele (i.e., A/A) (Fig. 5): MSCEIT task, t = 2.042, P = 0.046, effect size (r) = 0.26; FB task, t = 2.160, P = 0.035, effect size (r) = 0.28. > When the RemSZ and TRS subgroups were separately analyzed, the G allele carriers in the RemSZ group had poor working memory results in the general cognition tests, and poor MSCEIT task and FB-task results in the social cognition tests. > There were several relationships between SNPs other than rs53576 and the clinical measures/OT concentration: rs3549131 was associated with problem solving and rs2228485 was associated with

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					attention/vigilance in the ASD group. > Group had a significant main effect for all cognitive measures, confirming better performance in the ASD and RemSZ group compared to the TRS group for most of measures. > OT was not significantly related to most of cognitive/social cognitive functions except for speed-of-processing > Rs53576 was significantly related to working memory and MSCEIT: these mean that subject without G allele performed better compared to those with G allele. In addition, when this analysis was applied to the two schizophrenia groups by including PANSS scores as one of the independent factors, rs53576 was also significantly related to MSCEIT and FB task.
Popescu, Elena Rodica et al. (2021)	Cross--Sectional Study	To investigate the role of cortisol and oxytocin as potential biomarkers of aggression in patients with psychosis	28 psychotic patients (10 male 18 female)	> The patients were admitted in large hospital rooms, with the possibility to be monitored, with 10 beds inside each room. All patients underwent psychological and psychiatric evaluation and psychometric scales of aggression were administered. The Modified Overt Aggression Scale (MOAS) was administrated by a psychologist, while the Overt-Covert Aggression Inventory (OCAI) was self-administrated. > The Modified Overt Aggression Scale (MOAS)	> Patients with a higher score of covert aggression had a significant lower level of cortisol (61.05 ± 8.04 ng/mL), as compared with patients with a lower score on covert subscale of aggression ($p < 0.01$) > Oxytocin level was significantly higher in patients with a higher score on covert type of aggression (102.87 ± 39.26 pg/mL) compared with patients with a lower score on the covert subscale of OCAI scale (70.01 ± 25.07 pg/mL) ($p = 0.01$) > There was a statistically significant

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				> Overt-Covert Aggression Inventory (OCAI) > Oxytocin and Cortisol Measurement - ELISA kits	positive correlation between oxytocin levels and the style of internalized manifestation of aggression ($r = 0.382$, $p = 0.04$), as well as a negative correlation of cortisol levels and the style of internalized manifestation of aggression ($r = -0.676$, $p < 0.001$) > Pearson correlation of self-reported overt aggression (OCAI) and aggression reported using the MOAS also indicated a positive significant correlation ($r = 0.459$, $p = 0.01$) > The first model considers the level of cortisol as a significant predictor of the style of manifested aggression ($F(1.26) = 21.9$, $p < 0.001$, $\beta = -0.67$, $R2 = 0.43$), so that a low level of cortisol predicts an increased level of internalized manifestation of aggression, which explains 43% of the criterion. Adding the level of oxytocin as a predictor, the new predictive model explains 55% of the variant of the style of internalized manifestation of aggression ($F(2.25) = 17.6$, $p < 0.001$, $\beta = 0.35$, $R2 = 55.2$). We can thus speculate that a low level of cortisol together with a high level of oxytocin predict an increased level of the style of internalized manifestation of aggression. > There were no significant gender difference in oxytocin or cortisol levels, as well as no correlations in

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					this matter with the specific MOAS and OCAI scores
Wigton, Rebekah et al. (2021)	Randomized Clinical Trial	To elucidate the neural underpinnings of oxytocin administration in patients with schizophrenia	20 right-handed male patients with schizophrenia	> double-blind crossover study of self-administered oxytocin (40 IU) and matched saline placebo nasal sprays, so that each participant received both treatments, one at each visit. The fMRI task relevant to the present study was performed approximately 90 min post-oxytocin/placebo administration > Wechsler Abbreviated Scale of Intelligence > PANSS > Stochastically rewarded decision-making task incorporating faces of varying social valence with either happy-angry (emotionally valenced block) or neutral-neutral (neutral block) face trials.	> Participants performed above chance ($p < 0.01$) in detecting the "winning" face across all drug and emotionally/neutrally valenced conditions, and did not significantly differ in performance between the placebo and oxytocin conditions ($p > 0.1$) > The bias toward selecting the happy face and avoiding the angry face was significant in patients with schizophrenia after placebo ($t(19) = 2.82$, $p = 0.011$): however, after oxytocin, this bias was completely attenuated ($t(19) = 1.25$, $p = 0.225$). > There was no bias toward selecting either of the neutral identities in patients with schizophrenia after being administered placebo or oxytocin > When comparing neural activity during decision-making across both the emotional and neutral conditions, neither whole brain nor region of interest (ROI) analyses showed any differences in neural activity between oxytocin and placebo administration > When choosing between two emotionally valenced faces (i.e. happy and angry faces), whole brain analysis revealed significant clusters of increased activation within the

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					right insula and bilateral temporal gyri including the temporoparietal junction (TPJ), the precuneus extending into the right cuneus, right posterior cingulate and left cingulate gyrus after placebo compared to oxytocin administration. Contrast estimates showed this effect was driven by an attenuation of neural activity after oxytocin administration and an increase in neural activity after being administered placebo > An amygdala-focused ROI analysis at the time of choice, performed using small volume correction (SVC), demonstrated increased activation in bilateral amygdalae–left (x = −25, y = −4, z = −14, t(38) = 4.89, p = 0.002, k = 32, FWE peak level corrected for SVC) and right (x = 27, y = −8, z = −14, t(38) = 3.74, p = 0.020, k = 2, FWE peak level corrected for SVC) after placebo compared to oxytocin administration. Contrast estimates showed that such differences were driven by a stronger attenuation of neural activity in the amygdala in the oxytocin condition and a slight increase in activity in the placebo condition > There was no activation differences apparent when selecting between two neutral faces of differing identities, in either whole brain analysis nor ROI analysis of the amygdalae. > There were no significant interaction effects were observed

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					between emotionally valenced faces versus neutral faces and drug in any analysis
Broniarczyk-Czarniak, Marta et al. (2022)	Genetic Association Study	To evaluate the expression of oxytocin (OXT), Oxytocin receptor (OXTR), arginine vasopressin (AVP), and Arginine vasopressin receptor 1A (AVPR1a) genes at the mRNA and protein levels in patients with schizophrenia	106 individuals (47 male 59 female) G1 40 patients with schizophrenia with a diagnosis that was made between 10 and 15 years after the onset of the illness (16 male 24 female) G2 36 patients with schizophrenia with a diagnosis made up to 2 years after the onset of the illness (20 male 16 female) 30 healthy controls (HC) (11 male 19 female)	> PANSS > CDSS > Sample Collection > Determination of Protein Concentration > Enzyme-Linked Immunosorbent Assay (ELISA) > Total RNA Isolation > Isolated RNA Quality Analysis > RT-PCR Reverse Transcription > Real-Time PCR Reaction	> mRNA expression level of the OXT gene was statistically significantly lower in G1 ($p < 0.001$) and G2 ($p < 0.001$) than in the control group (HC) and was statistically significantly lower in G1 than in G2 groups ($p = 0.008$) > OXT protein level was statistically significantly lower in G1 ($p < 0.001$) and G2 ($p < 0.001$) than in the control group and was significantly lower in G1 than in G2 groups ($p < 0.001$) > OXTR level was statistically significantly higher in G1 ($p < 0.001$) and G2 ($p < 0.001$) than in the control group and was significantly higher in G1 than in G2 groups ($p < 0.001$) > OXTR protein level was statistically significantly higher in G1 ($p < 0.001$) and G2 ($p = 0.000$) than in the control group (HC) and was significantly higher in G1 than in G2 groups ($p = 0.000$) > mRNA expression level of AVP was statistically significantly higher in G1 ($p < 0.001$) and G2 ($p < 0.001$) than in the control group. > The mRNA expression of AVP was not statistically significantly different between the study groups G1 and G2

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					(p > 0.05) > AVP levels were statistically significantly higher in G1 (p < 0.001) and G2 (p < 0.001) than in the control group (HC). > The AVP protein levels were not different between G1 and G2 groups (p > 0.05) > mRNA expression level of AVPR1a was statistically significantly lower in G1 (p < 0.001) than in the control group (HC). > AVPR1a mRNA expression in G1 was statistically significantly lower than in G2 (p = 0.001). > There was no statistically significant difference in AVPR1a mRNA expression between G2 and HC groups (p > 0.05) > AVPR1a levels were statistically significantly lower in G1 (p < 0.001) than in the control group (HC). > AVPR1a protein level in G1 was statistically significantly lower than in G2 (p = 0.004). > There was no statistically significant difference in AVPR1a expression at the protein level between G2 and HC groups (p > 0.05) > In G2, a statistically significant correlation of OXT gene expression at the mRNA (OXT 2Δct) and protein (OXT ng/mL) levels with the severity of depressive symptoms as assessed by CDSS (q = 0.42; p = 0.011 and q =

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					0.37; p = 0.028, respectively) was determined
Browne, Julia et al. (2022)	Randomized Clinical Trial	To understand whether reduced ecological momentary assessment (EMA) measures of sedentary activities were observed in individuals with schizophrenic-spectrum disorders (SSDs) who participated in a 24-week randomized trial of cognitive behavioral social skills training (CBSST) and either intranasal oxytocin or placebo	62 participants with schizophrenia or schizoaffective disorder 31 intranasal oxytocin 36 I.U. (3 sprays) BID 31 intranasal placebo-oxytocin (3 sprays) BID 57 participants (the ones' that completed the trial and the EMA measurements)	> The parent trial on which this secondary analysis is based was a 24-week, two-arm, double-blind, and placebo-controlled randomized controlled trial (RCT) with a 12-week post-treatment follow-up that tested CBSST plus intranasal oxytocin against CBSST plus placebo in a sample of adults with schizophrenia or schizoaffective disorder > All participants received CBSST and were randomized to intranasal oxytocin (36 IU twice daily) or intranasal placebo. CBSST groups involve modeling and role-playing social situations to allow for practicing new skills and receiving positive and corrective feedback. There was a total of 48 sessions over the 24-week period. > EMA Procedure - baseline, mid-point (12 weeks), and endpoint (24 weeks) > EMA-Reported Activities > EMA-Reported Positive and Negative Moods/Affect > EMA-Reported Interpersonal Interactions and Appraisals	> 6622 EMA survey pages were scheduled, of which 4489 (68%) were answered > The number of non-social interactions manifested a significant weekly effect, X2 (2) = 8.82, p = 0.012. However, the number of nonsocial interactions increased from 0.58 to 0.70 from baseline to week 12 and reverted to 0.58 interactions per survey at week 24. > The four interaction appraisal variables were very highly intercorrelated and all manifested the same treatment response; thus, only the warmth/trust and competence was presented. > The omnibus tests were significant (all p < 0.003) for all four analyses (positive affect (PA), negative affect (NA), warmth/trust, and competence), as were the random subject intercepts (all p < 0.001). > Week had a statistically significant effect on all four variables (all p < 0.001), with the effect reflecting increases in PA, as well as on improvement in appraisals of warmth/trust and competence and reduction in NA. > Effects of day were all non-significant other than for warmth/trust (X2 (6) = 17.56, p =

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					0.007) > For all five of the activity analyses, the dynamic covariate of PA was significantly associated with activities, correlating positively for being seated away from home (X2 = 265.77, p < 0.001), standing, (X2 = 264.51, p < 0.001), and moving (X2 = 100.36, p < 0.001), and negatively for recumbent (X2 = 102.11, p < 0.001) and being seated at home (X2 = 203.29, p < 0.001) across the momentary assessments. > The interaction appraisal average was significantly associated with the number of interactions, correlating positively with the occurrence of both social interactions (X2 = 81.46, p < 0.001), and nonsocial interactions, (X2 = 72.61, p < 0.001). > PA was associated with the occurrence of social interactions (X2 = 49.58, p < 0.001) as well as with more non-social interactions, (X2 = 24.69, p = 0.016 > While there was a significant interaction of treatment week x treatment condition for moving activity (increased moving activity with oxytocin; treatment x week: X2 (2) = 6.45, p = 0.04, there were no significant treatment x week interactions with the other four activities or the two interpersonal interaction variables (all X2 (2) < 3.42, all p > 0.07). > For the mood/affect variable there

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					was significant interaction of treatment x treatment week for PA (increased PA with oxytocin: X2 (2) = 6.15, p = 0.046) and NA (reduced NA with oxytocin: X2 (2) = 16.56, p < 0.001). > Statistically significant interactions of treatment x treatment week were seen for both warmth/trust in interactions (greater warmth/trust with oxytocin: X2 (2) = 6.72, p = 0.035) and competence in interactions (greater competence with oxytocin: X2 (2) = 9.85; p = 0.007).
Spilka, Michael J et al. (2022)	Cross--Sectional Study	To examine plasma oxytocin (OT) in relationship to facial emotion recognition and visual attention to salient facial features in schizophrenia patients (SZ) and controls	65 individuals (43 male 21 female) 42 individuals with schizophrenia (28 male 14 female) 23 healthy controls (15 male 7 female)	> BNSS > BPRS > LFS >Plasma oxytocin concentration were determined by radioimmunoassay > Facial Emotion Recognition Task	> There were higher oxytocin levels in SZ (M=20.05pg/ml, SD=7.94) than HC (M=15.59pg/ml, SD=5.32) > There was a significant main effects of group (HC > SZ), F(1,63)=8.08, p=.006, ηp2=0.11; intensity, F(1,63)=1257.83, p<.001, ηp2=0.95; and emotion, F(4,252)=72.55, p<.001, ηp2=0.54. > There were also significant interactions between group and emotion (HC > SZ for fear and sadness), F(4,252)=3.90, p=.007, ηp2=0.06; group and intensity (HC > SZ for high intensity expressions), F(1,63)=4.82, p=.032, ηp2=0.07; emotion by intensity, F(3.17,252)=23.24, p<.001, ηp2=0.27, and a three-way interaction between group, intensity and emotion, F(3.17,252)=3.22, p

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					=.022, ηp2=0.05. > Follow-up pairwise comparisons for the three-way interaction indicated that the SZ group had reduced recognition accuracy compared to the HC group for high-intensity fearful facial expressions (SZ: M=59.72%, SD=27.85; HC: M=83.57%, SD=16.45; p<.001) and low-intensity sad expressions (SZ: M=50.00%, SD=24.54; HC: M=65.22%, SD=25.83; p=.022) > In the SZ group, plasma oxytocin was positively correlated with overall facial affect recognition accuracy, and separate correlations according to intensity level were significant for high but not low intensity expressions > Oxytocin in the HC group was not correlated with facial emotion recognition accuracy overall or at either intensity level > There was a significant correlation between oxytocin and accuracy for sad expressions in the SZ group, ρ(36)=0.37, p=.021 > Regarding %Fixations, there was a significant group by intensity interaction, F(1,58)=4.61, p=.036, ηp2=0.07, such that the HC group increased their percentage of fixations to salient facial features when viewing low intensity (M=75.88%, SD=8.33) compared to high intensity expressions (M=73.42%, SD=8.26, p=.007),

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					whereas the SZ group did not (low: M=71.97%, SD=14.05; high: M=71.80%, SD=13.59; p=.884). > There were significant main effects of trial epoch, emotion, and intensity, and an interaction between trial epoch, emotion, and intensity > There were no significant group differences in %Fixations or %DwellTime to the eyes. > There were main effects of trial epoch and emotion, and an emotion by intensity interaction for both %Fixations and %DwellTime, as well as a trial epoch by emotion interaction for %Fixations >Regargin %Fixations, there was a significant main effect of group, F(1,58)=4.67, p=.035, ηp2=0.07. Individuals in the SZ group (M=32.65%, SD=14.53) on average had a lower percentage of fixations to the nose region than CNs (M=40.21%, SD=10.24). > There were significant main effects of trial epoch and emotion, and a significant interaction between intensity and emotion > Regarding %DwellTime, there was a significant main effect of group, F(1,58)=4.87, p=.031, ηp2=0.08; and a significant group by emotion interaction, F(4,232)=2.63, p=.035, ηp2=0.04. > Follow-up analyses indicated that the SZ group had lower dwell time percentages to the nose region than

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					the HC group when viewing angry (HC: M=42.11%, SD=13.31; SZ: M= 31.72%, SD=15.66; p=.011), happy (HC: M=39.60%, SD=12.26; SZ: M=30.80%, SD=15.08; p=.023), and sad (HC: M=41.04%, SD=11.59; SZ: M=32.06%, SD=16.21; p=.026) facial expressions. > There were additional main effects of trial epoch and emotion, and an intensity by emotion interaction > The HC group increased their percentage of fixations to the mouth when viewing low intensity (M=15.51%, SD=10.15, p=.019) compared to high intensity (M=14.21%, SD=8.78) expressions, whereas the SZ group did not (low: M=15.88%, SD=11.94; p=.884; high: M=16.08%, SD=11.70). There was a significant group by trial epoch interaction, F(1,58)=6.85, p=.011, ηp2=0.11. The HC group made a greater percentage of fixations to the mouth during the early (M=16.61%, SD=10.48) compared to the late trial epoch (M=12.85%, SD=8.39, p<.001), whereas this difference was nonsignificant in the SZ group > There were no significant correlations between plasma oxytocin and overall %DwellTime and %Fixations to the eyes or to the composite salient features interest area in the SZ and HC groups > In the SZ group, facial emotion

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					recognition accuracy was not significantly associated with %Fixations and %DwellTime to any salient facial features > In the HC group, greater recognition accuracy of low-intensity expressions was associated with increased attention to the mouth at early (%Fixations: ρ(20)=0.56, p=.006; %DwellTime: ρ(20)=0.60, p=.004) and late (%Fixations: ρ(20)=0.50, p=.017; %DwellTime: ρ(20)=0.57, p=.006) trial epochs, but reduced early %DwellTime to the nose (ρ(20)=−0.58, p=.005). Gaze behavior was not associated with recognition accuracy of high-intensity expressions
Hidalgo-Figueroa, MarÃa et al. (2022)	Cross- -Sectional Study	To identify cognitive and biological markers that will help improve the diagnosis, treatment, and outcome of such events and to define new therapeutic targets. To analyze the plasma oxytocin and prolactin levels during an first episode psychosis (FEP), assessing their correlation with clinical and cognitive features	226 individuals (152 male 74 female) 120 patients with first episode psychosis (FEP) (82 male 38 female) 106 healthy controls (70 male 36 female)	> PANSS > Global Assessment of Functioning Scale > Children's Global Assessment Scale > MATRICS > Vocabulary sub-test of wechsler intelligence scale for children (WISC)-IV for children > wechsler adult intelligence scale (WAIS)-III for adults > working memory with the Digit and Letters and Numbers sub-test of WAIS-III for adults, and WISC-IV for children > Trail Making Test Form A > Trail Making Test Form B > Continuous Performance Test-II > Blood Sample Collection,	> Most of the patients were under psychotic medication, and they showed higher severity in the symptomatology compared with antipsychotic-naïve patients (P < .01). Moreover, a positive correlation was found between daily dose of antipsychotics and the symptom severity (P < .01) > Compared with the HCs, FEP patients showed significant lower scores in verbal ability (P < .001) and 2 indices of working memory, digit (P < .001) and letter and number (P < .001) subtests of the Weschler scales, indicating that these patients presented worse performance in

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				biochemical Determinations and ELISA kit utilization to determine Oxytocin and prolactin levels	verbal ability and working memory > FEP patients also obtained higher scores in the Form A (P < .001) and Form B (P < .001) trail-making tests, indicating worse performance in processing speed and executive function > FEP patients obtained worse scores in the sustained attention domain (P < .001), except for some CTP-II tests included in the evaluation in which no significant differences were observed between the 2 groups: hit reaction time (Hit-RT, P = .291), hit reaction time by block (Hit-RT-BC, P = .143), standard error of hit reaction time by block (Hit-RT-BC-SE, P = .109), and standard error of hit reaction time by interstimulus interval (Hit-RT-ISI-SE, P = .741) > Both female and male FEP patients performed worse in verbal ability, working memory, processing speed, executive function, and attention > Male FEP patients scored worse in omission errors (mean score in male HCs, 46.6 ± 15.49; in male FEP patients, 60.1 ± 29.13, P < .001). Detectability (mean score in male HCs, 42.46 ± 10.25; in male FEP patients, 50.38 ± 9.18, P < .001) and Hit-RT-ISI (mean score in male HCs, 48.55 ± 8.61; in male FEP patients, 52.83 ± 11.79, P < .037). > Female FEP patients scored worse in the Hit-RT-BC-SE test (mean

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					score in female, HCs 53.55 ± 9.15; in female FEP patients, 59.91 ± 0.86, P = .031). > Oxytocin and prolactin were quantified in plasma, and oxytocin levels were decreased in FEP patients relative to HCs (P < .001). By contrast, higher prolactin levels were detected in FEP patients. No correlation was found between plasma oxytocin and prolactin levels (r = 0.15, P = .193) > Patients treated with antipsychotics showed higher levels of prolactin compared with those antipsychotic-naïve patients or HCs (P < .001). Patients treated with risperidone or paliperidone showed even higher levels of prolactin than those treated with other antipsychotics (P = .039) > Pharmacological treatment was positively correlated with prolactin levels in patients (rho = 0.259, P = .014), indicating that higher prolactin levels were related to higher daily doses of antipsychotics. However, significant correlations were not found between daily doses of antipsychotics and prolactin levels in patients treated with risperidone or paliperidone (rho = −0.010, P = .951) or in patients treated with other antipsychotics (r = 0.020, P = .916) > The sex-disaggregated data showed

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					that the correlation between plasma prolactin and antipsychotic doses was evident only in men (rho = 0.298, P = .017). > There was a positive correlation between the plasma prolactin levels and the PANSS score in men (rho = 0.257, P = .041), indicating that men with more prolactin suffered more severe positive symptoms. > Higher levels of prolactin were also related to a higher general PANSS score in men (r = 0.312, P = .012) > Lower plasma levels of oxytocin were significantly correlated with better cognitive performance in the executive function domain, as reflected by the lower scores in the trail-making test (Form B: rho = 0.276, P = .04) > Women showed a negative correlation between plasma oxytocin and their scores in the perseveration test (rho = −0.583, P = .018), indicating that low oxytocin levels were related to worse cognitive performance in this aspect of the attention domain. By contrast, men showed a positive correlation with scores in the omission test (rho = 0.348, P = .028), suggesting that lower oxytocin levels were related to better cognitive performance in this aspect of attention domain

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					> Higher plasma prolactin levels were correlated with worse working memory performance (rho = −0.405, P = .002), a correlation that was maintained in both women and men yet with certain differences. Specifically, this correlation between plasma prolactin and working memory in men was significant in the letter and number test (rho = −0.384, P = .012), whereas in women this was the case in the digit test (r = −0.524, P = .045). > In terms of attention, men showed a negative correlation between the Hit-RT test results and plasma prolactin levels (r = −0.336, P = .026), with more prolactin associated with lower score in this test and thus, better cognitive performance > The factors associated with an FEP were lower levels of oxytocin (OR = 0.981), higher levels of prolactin (OR = 1.039), a lower premorbid IQ (OR = 0.938), and higher score in the Hit-RT-BC test (OR = 1.088). Lower premorbid IQ scores were related to a worse verbal ability, and a higher score in the Hit-RT-BC test was associated with an attention deficit. > The highest OR observed between these hormones was evident for prolactin, indicating that for each

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					unit increase in this hormone, the risk of suffering a FEP increased by 3.9%
Piao, Yan-Hong et al. (2022)	Genetic Association Study	To investigate the association of altered methylation patterns with schizophrenia (SZ) symptoms and early trauma in patients and healthy controls.	61 patients with recent onset psychosis (23 male 38 female): - 18 patients with schizophrenia - 50 patients with schizophreniform disorder - 14 patients with other specified SZ spectrum and psychotic disorders - 6 patients with brief psychotic disorder - 4 patients with delusional disorder 47 controls (14 male 34 female)	> PANSS > Early Trauma Inventory Self Report-Short Form (ETISR-SF) > Fagerstrom Test for Nicotine Dependence (FTND) > Alcohol Use Disorders Identification Test (AUDIT) > Dietary Habits Questionnaire (DHQ) > Physical Activity Rating (PA-R) > DNA Methylation Assay > Identification of Differentially Methylated CpG Sites	> 2,912 differentially methylated CpG sites were identiifed that associated with RO psychosis (FDR < 0.001) > Of the 2,912 CpGs, 1,509 sites (51.82%) were hypomethylated, and 1,403 (48.18%) were hypermethylated. > Of the 1,509 hypomethylated CpGs, 951 (63.02%), 308 (20.41%), and 11 (0.73%) sites were located in the promoter regions, gene bodies, and 3'-UTRs, respectively > When classified according to the CpG contents in the genes, 970 (64.28%), 193 (12.79%), and 49 sites (3.25%) were located in the CpG islands (CGIs), CGI shores, and CGI shelves, respectively. > Of the 1,403 hypermethylated CpGs, 505 (35.99%), 644 (45.90%), and 51 (3.64%) sites were located in the promoter regions, gene bodies, and 3'-UTRs, respectively > 526 (37.49%), 375 (26.73%), and 148 sites (10.55%) were located in the CGIs, CGI shores, and CGI shelves, respectively > Ten sites from the ACIN1, PDCD10, SERPINI1, GNAS, HIST1H4J, ZNF668, SSRP1, ANKRD13B, HIST1H4K, CDKN2A, CDKN2B-AS1,

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					and FKBP2 genes, and ten from the ETFA, TYRO3P, RNF31, PSME2, NUMBL, MARCH1, ANP32C, Autophagy-related 4B cysteine peptidase (ATG4B), IGF2BP2, and METTL16 genes, showed that patients were more likely to have a hypo- or hypermethylated status than controls. > The top 15 significantly enriched KEGG pathways included the oxytocin signaling pathway, long-term depression pathway, axon guidance, endometrial cancer, long-term potentiation, MAPK signaling pathway, and glutamatergic pathway, among others. > In total, 341 genes were annotated with 15 KEGG pathways. > In the patient group, positive correlations were found between the beta value of cg13562874 and the ETISR-SF total score, while negative correlations were identified between the beta values of cg13810931 and cg18128437 and the PANSS total score. > In the control group, the ETISR-SF total score exhibited negative correlations with the beta values of cg23207361 and cg23408615, and a positive correlation with the beta value of cg25548986.

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Korann, Vittal et al. (2022)	Randomized Clinical Trial	To examine the effect of oxytocin on the brain's effective connectivity in schizophrenia.	52 male individuals 31 male patients with schizophrenia (SCZ) 21 healthy male volunteers (HV)	> All subjects underwent three resting functional magnetic resonance imaging (rsfMRI) scans. In the first scan (referred to as baseline scan), no drug was administered. Subjects self-administered 24 IU oxytocin or saline nasal spray 45 min before the second and third scan > PANSS > SANSS > GAF > CDSS > Fagerstrom Test for Nicotine Dependence (FTND) > OXTR Genotyping	> Three connections survived the FDR correction threshold with the conjunction analysis on the whole brain. All three connections were sourced from the left caudate. These connections were from left caudate to (1) left supplementary motor area (MNI coordinates – x = −5,y = 5,z = 6) 2) left precentral gyrus (MNI coordinates –x = −39;y = −6;z = 51) 3) left frontal inferior triangular gyrus (MNI coordinates –x = −46;y = 30;z = 14) > At baseline, SCZ patients had significantly weaker connectivity from caudate to these three regions (P < .05, FDR corrected); (1) Left caudate and left supplementary motor area (pcorr = 0.01) (2) Left caudate and left precentral gyrus (pcorr = 0.0) (3) Left caudate and left frontal inferior triangular (pcorr = 0.01) > Neither SCZ nor HV had a significant difference between baseline and placebo conditions in these connections > There was a significant group X condition effect in all three networks; (1) Left caudate and left supplementary motor area (pcorr = 0.04) (2) Left caudate and left precentral gyrus (pcorr = 0.04) (3) Left caudate and left frontal inferior triangular (pcorr = 0.04) > While SCZ had a significant difference between baseline and

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					oxytocin conditions in these connections, there was no significant difference in HV > SCZ also had significant difference between placebo and oxytocin conditions in (1) Left caudate and left supplementary motor area (pcorrected = 0.03) (2) Left caudate and left precentral gyrus (pcorrected = 0.01) (3) Left caudate and left frontal inferior triangular (pcorrected = 0.01) > For the connectivity difference between oxytocin and placebo in patients, mode-3 was significant (FDR corrected P-values – mode-1 = 0.35, mode-2 = 0.26, mode-3 = 0.009 and mode-4 = 0.16). > For the connectivity difference between oxytocin and placebo in patients, all three aths were positively correlated with socio economical status (SES) and Beck Cognitive Insight Scale (BCIS) self-reflectance (SR) and negatively correlated with age of onset, PANSS Negative, and CGI Severity > This shows that the better the socioeconomic status and cognitive insight, the earlier the age of onset, and the lesser the severity of negative symptoms, the greater the increase in connectivity with oxytocin than placebo.

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Mouchlianitis, Elias D et al. (2022)	Randomized Clinical Trial	To evaluate the behavioural impact of oxytocin administration on a social learning task in individuals with schizophrenia, and elucidate any differential neural activity produced	20 clinically stable right-handed men diagnosed with schizophrenia or schizoaffective disorder	> Participants underwent a randomised double-blind cross-over design in which they administered oxytocin and placebo. Both the oxytocin (40 IU) and matched placebo nasal sprays were self-administered by our participants. Oxytocin/placebo administration was arranged to take place 45 min before the start of the first task within the fMRI scanner > WASI, Wechsler Abbreviated Scale of Intelligence; > NS-SeC, National Statistics Socio-economic Classification; > PANSS, Positive and Negative Syndrome Scale > fMRI acquisition > fMRI task : a trust game that consisted of a modified version of a previous multi-round trust game.There were two different sessions: one where they were explicitly informed that they would be playing against a computer and another where they were led to believe they were playing against another human player. In fact, both opponents were a computer program using the same algorithm of a cooperative investment style	> A significant interaction or significant main effects for initial investments was not found. > For mean investments, the Drug × Player interaction approached significance: $F(1,19) = 4.03$, $P = 0.06$. This interaction was driven by a higher mean investment during oxytocin administration for human player trials compared with computer trials; after placebo administration the difference between human and computer player trials was not significant > The Drug × Player factorial analysis revealed a significant main effect of Drug in a right lateral parietal cluster (MNI: $x = 44$, $y = -62$, $z = 44$, $k = 48$, $Z = 4.63$, $P < 0.001$, FWE corrected). > Oxytocin administration increased activation during investment trials for both the human and computer session > No significant interaction or main effects were found for repayment trials. > Oxytocin significantly attenuated neural activity during investment trials for the human session in a right anterior insula cluster ($Z = 2.62$, $P < 0.001$), but no significant differences were found for the computer session > A cluster in the right insula showed increased activation after oxytocin administration for the human session (MNI: $x = 42$, $y = -8$, $z = 0$, $k = 42$, Z

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					= 4.33, P < 0.001), but no significant differences were found for the computer session > For the repayment trials, oxytocin significantly increase activation relative to the placebo in a cluster in the left ventral caudate when playing against the human player (MNI: x = −10, y = −6, z = −6, k = 43, Z = 2.7, P < 0.001, Fig. 2a and b) and right dorsal caudate cluster when playing against the computer player (MNI: x = 16, y = −4, z = 42, k = 48, Z = 2.7, P < 0.001 > Oxytocin significantly attenuated amygdala activity during the human sessions within a cluster in the right amygdala (MNI: x = 28, y = −4, z = −26, k = 74, Z = 3.09, P < 0.001 > None of the ROIs or behavioural measures showed any association with symptoms (P > 0.05)
Eghtedarian, Reyhane et al. (2022)	Genetic Association Study	To appraise dysregulation of nine oxytocin-associated mRNAs and Long non-coding RNAs (lncRNAs) in the venous blood of patients with schizophrenia	120 individuals (60 male 60 female) 60 patients with schizophrenia (30 male 30 female) 60 healthy controls (30 male 30 female)	> Blood samples - RNA extraction - cDNA synthesis > Expression assays - Expressions of oxytocin-related mRNAs and lncRNAs were measured in the ABI step one plus PCR system	> This study assessed expressions of nine oxytocin-related genes, namely ITPR1, TNS-AS1 (Lnc-TNS1), FOS, LINC01116 (Lnc-MTX2), RCAN1, ZBTB14 (ZFP161), OXTR, CAMK2D and FENDRR (Lnc-FOXF1) in blood samples of patients with schizophrenia and controls > Disease factor had significant effect on expressions of ITPR1, FOS and Lnc-FOXF1 (P values=0.0079, <0.0001 and < 0.0001).

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					> Gender has significant effect on expression of Lnc-MTX2 (P value=0.001). > The interaction between sex and disease was significant for TNS1-AS, lnc-FOXF1 and KAMK2D genes > Expression of FOS was up-regulated in total patients compared with total control group (Expression ratio (95% CI)= 13.64 (5.46–34.05), adjusted P value<0.0001) and in female patients compared with female control group (Expression ratio (95% CI)=32.13 (5.81–176), adjusted P value<0.0001). Such pattern was also seen for Lnc-FOXF1 (Expression ratio (95% CI)= 6.41 (2.84–14.3), adjusted P value<0.0001 and Expression ratio (95% CI)= 14.41 (3.2–64.44), adjusted P value<0.0001, respectively). > ITPR1 was down-regulated in total patients compared with total controls (Expression ratio (95% CI)= 0.22 (0.076–0.67), adjusted P value=0.0079) > FOS had the best (area under curve) AUC value among other genes in differentiation between patients and controls (AUC=0.78)
Goh, Kah Kheng, and Mong-Liang Lu. (2022)	Cross--Sectional Study	To study the role of plasma oxytocin levels in the relationship between subdomains of social cognition	40 patients with schizophrenia (17 male 23 female) 40 age-matched healthy controls (21 male 19 female)	> PANSS > Mini-Mental State Examination MMSE > The Social Functioning Scale (SFS)	> Compared with healthy controls, the plasma oxytocin levels of patients with schizophrenia were significantly lower (p = .001)

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		and social dysfunction in patients with schizophrenia		> Faux Pas Recognition Test (FPRT) > Measurement of plasma oxytocin levels	> All SFS subscale scores for patients with schizophrenia were lower than those for the healthy controls. > Almost all participants answered the control questions of the FPRT correctly, and no significant differences were present between patients with schizophrenia and healthy controls ($p = .107$) > Patients with schizophrenia had significantly lower scores in the recognition of faux pas (cToM) component of the FPRT ($p < .001$) as well as the understanding of faux pas (aToM) component of the FPRT ($p < .001$) > For all participants, both the cToM and aToM components of the FPRT were significantly correlated with the total scores and all subscale scores of the SFS > The results among patients with schizophrenia and healthy controls differed from the overall, combined group results > In both groups, the aToM component but not the cToM component of the FPRT was significantly correlated with all subscale measures of the SFS > A pooled correlation analysis of all participants revealed significant effects of plasma oxytocin levels on cToM ($r = .253$, $p < .05$), aToM ($r = .287$, $p < .01$), and total scores for SFS ($r = .407$, $p < .001$) > In patients with schizophrenia,

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					plasma oxytocin levels were positively correlated with the aToM component of the FPRT and total scores of the SFS > Among patients with schizophrenia, total scores for the SFS, total scores for the FPRT, and scores for the aToM component of the FPRT but not for the cToM component, were significantly predicted by plasma oxytocin levels. > Among healthy controls, the relationships between plasma oxytocin, social functioning, and ToM were absent > In mediation analysis, the effects of plasma oxytocin levels on social functioning were partially mediated by the aToM of the patients with schizophrenia. > The regression coefficients between plasma oxytocin levels and aToM (β = 0.73, t[33] = 2.79, p = .009), between aToM and SFS (β = 1.27, t[32] = 2.50, p = .018), and between plasma oxytocin levels and SFS (β = 3.07, t[32] = 3.64, p < .001) were statistically significant > The bootstrapped unstandardized indirect effect was significant (β = 0.92, 95% CI [0.04, 2.96] after controlled for sex, age, year of education, MMSE, PANSS negative symptoms. The overall mediation

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					model was statistically significant (R2 = .77, F[6, 33] = 8.19, p < .001)
Yu, Hua et al. (2023)	Cross--Sectional Study	To understand whether certain plasma neuropeptides showed the same change as it was reported in cerebrospinal fluid (CSF) in schizophrenia, bipolar disorder (BD) and major depressive disorder (MDD) , To understand whether the abnormal level of neuropeptides would be associated with clinical symptoms and cognitive function in patient groups. To understand whether these neuropeptides can be used as a biomarker to distinguish first episode schizophrenia (FES), BD and MDD from controls.	195 individuals (85 male 110 female) 54 patients with FES (26 male, 28 female) 52 patients with BD (21 male, 31 female) 35 patients with MDD (15 male, 20 female) 54 healthy controls (23 male, 31 female)	> α-Melanocyte Stimulating Hormone (α-MSH), β-endorphin, neurotensin, orexin-A, oxytocin, and substance P were investigated using quantitative multiplex assay method > BPRS > PANSS > Young Mania Rating Scale (YMRS) > 17 item-Hamilton Depression Rating Scale (HAMD) > Wechsler Adult Intelligence Scale in Chinese > The Cambridge Neuropsychological Test Automated Battery (CANTAB)	Different patterns of plasma neuropeptides in the four subject groups: > Controlling for age, gender, and BMI, the log10 α-MSH, log10 neurotensin, log10 orexin A, log10 oxytocin, and log10 substance P level were significantly decreased in the three patient groups compared to controls > Only the BD group showed decreased log10 β-endorphins compared to controls. Disease differentiating potential of plasma biomarkers: > Only patients compared with controls showed a good level of accuracy, and the differentiating performances between patient groups was poor. > The highest area under curve (AUC) values were seen for plasma neurotensin when comparing patients with controls; FES versus HC [AUC = 0.83, 95% confidence interval [CI] 0.74–0.91]; BD versus HC [AUC = 0.80, 95% CI 0.71–0.89]; and MDD versus HC [AUC = 0.87, 95% CI 0.77–0.94] > Other AUCs for discriminating patients from controls which showed good levels of discrimination above 0.80 included: oxytocin in FES vs.

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					HC [AUC = 0.80, 95% CI 0.68–0.89]; oxytocin in MDD vs. HC [AUC = 0.85, 95% CI 0.74–0.92]; a-MSH in MDD vs. HC [AUC = 0.80, 95% CI 0.68–0.89]; and substance P in MDD vs. HC [AUC = 0.84, 95% CI 0.74–0.92] Association between plasma neuropeptides and executive function: > In the combined samples of the four groups, stepwise linear regression analysis using SOC-MM5M scores as the dependent variable and age, gender, education, BMI, group status, log10 α-MSH, log10 β-endorphins, log10 neurotensin, log10 orexin A, log10 oxytocin and log10 substance P as the independent variables showed that the linear regression model was significant ($F_{1,153} = 8.01$, $p < 0.01$) >The standardized β coefficient value for neurotensin was −0.22, with a t value of −2.83 Plasma neuropeptides were associated with psychotic symptoms in the FES and BD groups: >Using age, gender, education, BMI, log10 α-MSH, log10 β-endorphins, log10 neurotensin, log10 orexin A, log10 oxytocin, and log10 substance P as the independent variables, and P2 (positive symptom scale item 2), N2 (negative symptom scale item 2), N3 (negative symptom scale item 3), and

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					G9 (general pathology symptom scale item 9) as independent variables, we found that the regression models were all significant because all p-values were all lower than 0.05. >When using the BPRS deficiency energy factor score as the dependent variable, we found that oxytocin level explained a significant amount of the variance in the BPRS deficiency energy factor score in Step 1 ($F = 6.40$, $p < 0.05$; $R2 = 0.076$; $\beta = -0.28$). > In the second step, the inclusion of substance P ($\beta = 4.33$) enhanced the relationship between BPRS deficiency energy factor score and oxytocin level ($\beta = -0.65$) based on the magnitude of the standardized beta-coefficient in Step 2 ($F = 5.36$, $p < 0.01$; $\Delta R2 = 0.023$) Plasma neuropeptide was associated with insomnia symptoms in all three psychiatric disorder groups: > MDD group status explained a significant amount of the variance in early morning wakening severity in Step 1 ($F = 41.88$, $p < 0.001$; $R2 = 0.30$; $\beta = 0.55$). The inclusion of log10 endorphin ($\beta = -0.25$) enhanced the relationship between early morning awakening severity and MDD group status ($\beta = 0.56$) based on the magnitude of the standardized beta-coefficient in Step 2 ($F = 27.69$, $p < 0.001$; $\Delta R2 = 0.06$)

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					>The adjusted multivariate coefficient of determination (R2) in step 2 was 0.36 for the predictors. The standardized β coefficient value for MDD group status and log10 endorphin were 0.56 and −0.25, with t values of 6.90 and −3.12 Partial correlation between plasma neuropeptides and other clinical information: > In the BD group, we found plasma β-endorphin level was significantly positively correlated with illness duration (r = 0.41, p < 0.01)
Ortega, Miguel A et al. (2023)	Cross--Sectional Study	To analyze the gene and protein expression, using real-time polymerase chain reaction (RT-qPCR) and immunohistochemistry (IHC), of oxytocin (OXT), oxytocin receptor (OXTR), arginine vassopressin (AVP), and Arginine vasopressin receptor 1A (AVPR1a) in the placental tissue of pregnant women after an first episode psychosis (FEP) in comparison to pregnant women without any health complication (HC-PW).	42 pregnant women in their third trimester 22 FEP-pregnant women (FE-PW) 20 healthy control pregnant women (HC-PW)	> PANSS > Sample Collection and Processing - placental biopsies were taken from FE-PW and HC-PW > Immunohistochemistry and Histological Visualization > Gene Expression Study	The Placentas of Women Who Suffered a First Episode of Psychosis in Pregnancy Exhibited Increased Gene and Protein Expression of Oxytocin and Its Receptor > There was increased OXT and OXTR in the placentas of women who underwent a first episode of psychosis during pregnancy. > Regarding OXT, it was observed that gene expression detected using RT-qPCR was significantly higher in FE-PW when compared to HC-PW (FE-PW = 22.063 [4.654–45.351]; HC-PW = 10.482 [2.546–23.352], *** p < 0.001 > Protein expression of OXT was also notably raised in the placental villi of women with FE-PW (FE-PW = 78.000 [42.000–95.000]; HC-PW= 41.000 [23.000–70.000], *** p <

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					0.001,) as well as in decidual cells (FE-PW = 85.000 [70.000–98.000]; HC = 49.000 [40.000–65.000], *** p < 0.001 > Histological pictures show protein expression of OXT in the placental villi and decidual cells of FE-PW (Figure 1D,E) and in HC-PW > Protein expression of OXT was strongly marked in the different parts of the placental villi of FE-PW, whereas in HC-PW, its expression was almost limited to syncytiotrophoblasts > OXT expression was quite marked in the decidua and decidual cells in FE-PW, and its expression was much less appreciated in the decidual cells > Regarding OXTR, gene expression was also significantly higher in FE-PW when compared to HC > Protein expression of OXTR was also notably raised in the placental villi of women with FE-PW as well as in decidual cells > Histological pictures show protein expression of OXTR in the placental villi and decidual cells of FE-PW and in HC-PW. More specifically, OXTR is expressed in the placenta of FE-PW throughout the different structures of the placental villi, whereas the brown staining for HC-PW is significantly lower > OXTR is notably higher in decidual cells of FE-PW, whereas in HC-PW,

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					OXTR is virtually absent > The Placentas of Women Who Suffered a First-Episode Psychosis in Pregnancy Displayed Enhanced Gene and Protein Expression of Vasopressin and Vasopressin Type 1a Receptor > There was increased expression of AVP and AVPR1A in the placentas of women who underwent a first-episode psychosis during pregnancy. > Regarding AVP, we observed that gene expression detected using RT-qPCR was notably higher in FE-PW when compared to HC > Protein expression of AVP was also significantly elevated in the placental villi of women with FE-PW as well as in decidual cells > Histological images show protein expression of AVP in the placental villi and decidual cells of FE-PW and in HC-PW. It can be observed that the placenta of FE-PW showed a marked staining of AVP, especially in the syncytiotrophoblast layer, whereas in the case of HC-PW, protein expression of AVP was significantly reduced > Similar observations can be made in the decidual layer of the placenta in FE-PW when compared to HC-PW > AVPR1A, gene expression was significantly higher in FE-PW when compared to HC > Protein expression of AVPR1A was

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					also notably raised in the placental villi of women with FE-PW as well as decidual cells > Histological pictures show protein expression of AVPR1A in the placental villi and decidual cells of FE-PW and HC-PW. > AVPR1A was expressed in the different cells of the placental villi of FE-PW, especially in the syncytiotrophoblast layer, which also seems to express this receptor in HC-PW. In the case of decidual cells, protein expression of AVPR1A can be notably observed in FE-PW, but in HC-PW, its expression seems to be low
Hennig-Fast, Kristina et al. (2023)	Cross--Sectional Study	To examine the neural correlates of attachment patterns and oxytocin in schizophrenic patients (SZP) compared to healthy controls (HC) using fMRI	40 male individuals 20 male patients with schizophrenia 20 male healthy controls	Before fMRI scanning: > Beck Depression Inventory-II (BDI) > State-Trait Anxiety Inventory (STAI) > Positive and Negative Affect Schedule (PANAS) > fMRI-adapted version of the AAP Adult Attachment Projective (AAP) Picture System > Neuropsychological battery to test patients and controls for handedness, attention, verbal IQ, and working memory capacity as differences in those cognitive functions could possibly interfere with performance in our task > Oxytocin Measurement	> The patient group enclosed no secure individuals, while 60% (n = 12) of the control group showed secure attachment representations ($\chi 2 = 21.95$; $p < 0.000$) > Patients displayed a significantly higher percentage of an insecure-preoccupied pattern of attachment compared to controls ($\chi 2 = 6.53$; $p < 0.031$) > There was a significant result for both measurements of OXT (LOxy1 = 4.82, $p < 0.034$; LOxy2 = 5.73, $p < 0.022$; LOxymean = 5.35, $p < 0.026$). Therefore, non-parametric-rank-based Wilcoxon-Mann-Whitney-Tests were used to compare oxytocin between patients and controls.

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					Healthy controls showed higher OXT scores compared to patients at both points of measurement > Patients (>healthy controls) revealed significantly higher activation when watching AAP pictures following personally relevant sentences versus AAP pictures following neutral sentences in the anterior and posterior cingulate cortex, insula, precuneus, temporoparietal junction, left premotor cortex, right supplemental motor area and left claustrum > One significant cluster located within the posterior cingulate gyrus was detected > There was a significant negative association between PANSS positive scores and activation of the bilateral precunei (rlP = −0.458, p < 0.042; rrP = −0.468, p < 0.037) as well with the response of the left Temporoparietal Junction (TPJ) (rlTPJ = −0.450, p < 0.047). > A significant negative correlation was found between activation of the bilateral insulae and the duration of illness since 1st SPA (rlI = −0.481, p < 0.032; rrI = −0.562, p < 0.001). > There was a significant positive correlation between oxytocin scores and activation of bilateral precunei (rlP = 0.501, p < 0.025; rrP = 0.520, p < 0.019) and bilateral TPJ (rlTPJ = 0.462, p < 0.040; rrTPJ = 0.543, p < 0.013) in patients but not in healthy

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					controls > Disorganized/unresolved patients showed significantly higher activation in one cluster located in the right TPJ
Saporta-Wiesel, Liron et al. (2024)	Randomized Clinical Trial	To examine the effect of high-dose oxytocin, social skills training, and their combination in the treatment of negative symptoms and social dysfunction in schizophrenia	47 patients with schizophrenia (39 male 8 female): -11 patients with Oxytocin/Social Cognitive and Skills Training (10 male 1 female) -11 patients with Oxytocin/Supportive Psychotherapy (11 male) -12 patients Placebo/Social Cognitive and Skills Training (8 male 4 female) -13 patients Placebo/Supportive Psychotherapy (10 male 3 female)	> PANSS > Patients underwent a randomized, placebo-controlled, parallel, 2 × 2, double-blind, add-on study.Patients administered daily intranasal oxytocin (24 IU 3 times a day) or intranasal placebo. Social skills training or supportive psychological therapy (Social Cognition and Interaction Training - 5 sessions - and Social Skills Training for Schizophrenia - 4 sessions) or Supportive psychotherapy was administered 3 times a week, for the 3-week study period, for a total of 9 sessions > At baseline, a videotaped interview assessing the interaction between the subject and the experimenter was performed using Coding Interactive Behavior (CIB) > Subjects were assessed once a week using the PANSS. > At the end of the 3 week period, subjects participated in a final, end-of-study visit during which all assessments were repeated.	> While oxytocin alone (coefficient 0.59, P = .39), and social skills training alone (coefficient 0.46, P = .5) directionally increased total score, this difference was not statistically significant. > Oxytocin increased CIB Total in the supportive psychotherapy group (coefficient −1.11, P = .43) but this was not significant > When comparing oxytocin to placebo, summing the results over all 3 scenarios, oxytocin had no significant effects on the 2 major factors Synergy or Initiative, as well as the Tension and Withdrawal factors. > Oxytocin improved the positive affect factor (coefficient 0.28, CI: 0.08–0.49, P = .01), but did so only in the supportive psychotherapy conditions, (the opposite of the predicted effects) (interaction coefficient −0.36, CI: −0.66 to −0.07, P = .02) > Social skills training reduced blunted affect, regardless of oxytocin treatment (coefficient −0.13, CI: −0.24 to 0.01, P = .04). > Oxytocin led to a decrease in the

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					avoidance item, when combined with social skills training, and there was an increase in the avoidance item in the supportive psychotherapy interactions, coefficient −0.14, CI: −0.24 to −0.05, P = .01 > Social skills training, regardless of oxytocin, led toward an improvement in gaze (estimate 0.22, P = .01) >When controlling for multiple comparisons, none of these findings remained significant. > Post-hoc analyses revealed that the positive affect factor improved in the oxytocin groups (coefficient 0.29, CI: 0.04–0.55, P = .03). > In the conflict social interaction, the withdrawal factor (coefficient −0.33, CI: −0.57 to 0.08, P = .01) and the positive affect (coefficient 0.21, CI: 0.02–0.04, P = .04) showed improvement in the social skills training group compared to supportive psychotherapy. However, for those patients receiving social skills training together with oxytocin, withdrawal increased and positive affect decreased In the supportive interaction, oxytocin improved the synchrony factor (coefficient 0.45, CI: 0.13–0.77, P = .01), and decreased the tension factor (coefficient −0.39, CI: −0.76 to −0.03, P = .05). However, the opposite effect is seen for patients receiving oxytocin together with the social skills training (coefficient 0.54,

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					CI: 0.02–1.05, P = .05) > All P values were not significant when controlling for multiple comparisons > No statistically significant effects were reported for both the main interventions (oxytocin or social skills training) and the interaction of the 2 on any PANSS variable. > The only significant main effect of oxytocin was the worsening of positive symptoms (coefficient estimate 0.56, 95% CI: 0.03–1.09, P = .04) , that when directly evaluated since the interactions was not significant.
Sun, Wenxi et al. (2024)	Cross--Sectional Study	To examine the relation between five serum neuropeptide levels and the cognition of patients with treatment-resistant schizophrenia (TRS), chronic stable schizophrenia (CSS), and in healthy controls (HC)	130 male individuals 29 male patients with TRS 48 male patients with CSS 53 male HC	> PANSS > Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) > Measurement of Serum neuropeptides (α-melanocyte stimulating hormone (α-MSH), β-endorphin (BE), neurotensin (NT), oxytocin (OT) and Substance.P (S.P))	> Both TRS and CSS patients performed worse than HC in total score and all subscales (all $p < 0.01$) > The lg serum neuropeptide levels, such as lg α-MSH levels and lg BE, lg NT, lg OT and lg S.P levels, were significantly higher in TRS and CSS patients than in HC (all $p < 0.01$) > The activities of lg OT ($F = 3.363$, $p = 0.003$) showed significant differences, with diagnosis as a fixed variable and age, years of education, BMI, smoking status, age of onset, duration of illness and CPZ equivalency dosage as covariance factors between the TRS and CSS groups > The lg α-MSH levels in TRS

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					patients were significantly and negatively correlated with the language scores of RBANS (r = −0.398, p = 0.032) > The lg BE levels in CSS patients were significantly and positively correlated with the visuospatial/constructional scores of RBANS (r = 0.294, p = 0.043) > The lg NT levels in CSS patients were significantly and positively correlated with the visuospatial/constructional scores of RBANS (r = 0.288, p = 0.047) > lg α-MSH levels were found to be significantly correlated (R2 = 0.494, p = 0.019) in TRS patients > lg BE levels were found to be significantly correlated (R2 = 0.113, p = 0.030) in CSS patients > Lg NT levels were significantly and positively correlated with lg BE in the CSS patients (r = 0.870, p < 0.001) > The lg NT levels were significantly correlated with lg BE levels in the CSS group (r = 0.864, p < 0.001) > Lg NT*BE interaction was found to have a positive correlation with the visuospatial/constructional scores of RBANS when the interaction term between lg NT and BE levels was developed (r = 0.299, p = 0.039)
Lv, Xue et al. (2024)	Genetic Association Study	To investigate how OXTR polymorphisms impact on severity of multidimensional	2363 patients with schizophrenia (1181 male 1182 female) Olanzapine 405 (205 male 200	> Patients were randomly allocated to seven antipsychotic treatment groups [aripiprazole, olanzapine, quetiapine,	> Two-way ANOVA revealed that there were interactions between rs2268490 and antipsychotics

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		symptoms of schizophrenia and responses to antipsychotics	106 female) Risperidone 404 (232 male 172 106 female) Quetiapine 386 (181 male 205 106 female) Aripiprazol 392 (186 male 206 106 female) Ziprasidone 393 (196 male 197 106 female) Haploperidol 184 (88 male 96 106 female) Perphenazol 199 (93 male 106 female)	risperidone, ziprasidone, or the first-generation antipsychotics (haloperidol or perphenazine)] and received antipsychotic monotherapy for 6 weeks > Blood DNA was genotyped for OXTR polymorphisms -SNPs (rs53576, rs1042778, rs11706648, rs13316193, rs2254298, rs2268490 and rs237899) were chosen > PANSS	(F = 2.267, p = 0.008). > Specifically, in the ziprasidone group, patients with rs2268490 TT genotypes had higher percentage changes in negative symptoms apathy/avolition than those with rs2268490 C allele, which reached significance after Bonferroni correction (F = 6.231, p = 0.002). > In each genotype group of rs2268490, there were significant differences in patients treated with different antipsychotics on the improvement in negative symptoms apathy/avolition (CC genotype, p = 0.017; CT genotype, p = 0.034; TT genotype, p = 0.038) > After 6-week treatment, 54.8% of patients with rs2268490 TT genotype got more than 50% improvement in negative symptoms apathy/avolition, while patients with the other rs2268490 genotypes had a lower response rate on this symptom. And rs2268490 showed a significant association with response rate on negative symptoms apathy/avolition (OR = 1.164, p = 0.035) > In the BRAINEAC database, after Bonferroni correction, rs13316193 was associated with mRNA expression of OXTR in the hippocampus (p = 5.08 × 10−5) and temporal cortex (p = 3.30 × 10−2); rs2268490 was associated with mRNA expression of OXTR in the

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					hippocampus ($p = 9.70 \times 10-3$) and with mRNA expression of GRM7 in the frontal cortex ($p = 3.20 \times 10-3$); rs237899 was associated with mRNA expression of OXTR in the frontal cortex ($p = 1.20 \times 10-4$), putamen ($p = 1.70 \times 10-2$), temporal cortex ($p = 1.60 \times 10-3$), thalamus ($p = 1.40 \times 10-3$), intralobular white matter ($p = 5.10 \times 10-4$) and across all the tissues ($p = 2.00 \times 10-4$).
Chen, Yuan-Jung et al. (2024)	Cross--Sectional Study	To explore the potential role of plasma oxytocin as a mediator in the relationship between childhood trauma and the psychopathology of schizophrenia	240 individuals (142 male 98 female) 160 patients with schizophrenia (96 male 64 female) 80 healthy controls (46 male 34 female)	> Childhood Trauma Questionnaire — Short Form CTQ-SF > PANSS > Mini-Mental State Examination (MMSE) > Plasma oxytocin levels were measured	> In comparison with the healthy controls, the patients with schizophrenia had significantly lower plasma oxytocin levels ($t = -5.543$, $p < 0.001$). > The total scores in the CTQ-SF, as well as the scores in all the subscales, were higher for the patients with schizophrenia than for the healthy controls ($p < 0.001$). > Comparison of the prevalence of different trauma types between healthy controls and patients with schizophrenia revealed a higher prevalence of all types of childhood trauma in the latter group: physical abuse ($p < 0.001$), emotional abuse ($p = 0.004$), sexual abuse ($p = 0.008$), physical neglect ($p = 0.012$), emotional neglect ($p = 0.015$), as well as a greater number of trauma types ($p < 0.001$) > There were significant associations between childhood trauma and

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					PANSS scores among patients with schizophrenia. > Patients who reported experiencing any form of childhood trauma—and who scored at or above the designated moderate exposure cutoff points on each subscale of the CTQ-SF, thus categorized as individuals with a documented history of childhood trauma exposure—consistently had higher PANSS total scores. > There was a significant correlation between the total CTQ-SF score and the total PANSS score ($r = 0.699$, $p < 0.001$). > All scores for the CTQ-SF subscales were significantly correlated with the total PANSS score and the scores for its subdomains scores, except for positive symptoms. > The higher number of childhood trauma types experienced, the greater severity of schizophrenia psychopathology, measured by the total PANSS score ($r = 0.738$, $p < 0.001$) and the scores for its subdomains, namely positive symptoms ($r = 0.843$, $p < 0.001$), negative symptoms ($r = 0.951$, $p < 0.001$), and general psychopathology ($r = 0.845$, $p < 0.001$). > Plasma oxytocin levels were inversely correlated with the total PANSS score ($r = -0.688$, $p < 0.001$)

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					and the scores for its subdomains, except for positive symptoms > Age of schizophrenia onset was discovered to have a negative association with the total PANSS score, negative symptoms, and general psychopathology; however, after applying the Bonferroni correction, this association remained significant only for negative symptoms ($r = -0.203$, $p = 0.040$), indicating that earlier onset is associated with more severe negative symptoms. > Regarding the other variables, the correlations were nonsignificant except for a negative association between the MMSE score and negative symptoms ($r = -0.223$, $p = 0.020$) > Model 1 predicted psychopathology from only sex and age, CTQ-SF score was added for model 2, educational years was added for model 3, age of schizophrenia onset was added for model 4, antipsychotic dose and MMSE score was added for model 5, and plasma oxytocin levels were added for model 6. > The result of model 2 revealed that the CTQ-SF score served as a significant predictor of psychopathology, explaining 47.7% of the variation ($\Delta R2 = 0.477$, $p < 0.001$). > The result of model 6 demonstrated that oxytocin levels accounted for an

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					additional 6.1% change in the prediction of psychopathology ($\Delta R2 = 0.052$, $p < 0.001$). > There was a significant regression coefficient between childhood trauma and plasma oxytocin levels ($p < 0.001$), and between plasma oxytocin levels and the psychopathology of schizophrenia ($p < 0.001$). > The bootstrapped unstandardized indirect effect was significant ($\beta = 0.183$, $SE = 0.044$, 95% confidence interval [CI] [0.102, 0.272]), indicating that plasma oxytocin levels partially mediate the effect of childhood trauma on the schizophrenia psychopathology. > The overall mediation model was significant ($R2 = 0.517$, $F = 23.195$, $p < 0.001$).
İmamoğlu, Aslıhan et al.. (2024)	Randomized Clinical Trial	examined the effect of intranasal oxytocin on cognitive functioning in people with schizophrenia	67 participants (52M 15F)with schizophrenia or schizoaffective disorder 32 (25M 7 F) placebo 35 (27M 8F)Oxytocin	48IU of oxytocin or placebo daily for 12 weeks Battery for the Assessment of Neuropsychological Status (RBANS) baseline vs. 12-week Data analysis Plan statistical analyses were conducted using R Post hoc comparisons utilized the Tukey method	a significant main effect of Time on immediate memory ($B = 6.80$, $SE = 2.28$, 95% CI [2.34; 11.29], $p < .01$), visuospatial/constructional abilities ($B = -3.70$, $SE = 1.54$, 95% CI [−6.73; −0.70], $p = .02$), attention ($B = 4.75$, $SE = 2.07$, 95% CI [0.69; 8.82], $p = .03$), and total summary scores ($B = 3.52$, $SE = 1.07$, 95% CI [1.44; 5.61], $p < .01$) a significant effect of Treatment on visuospatial/constructional abilities, ($B = -7.51$, $SE = 2.87$, 95% CI [−13.12; −1.91], $p = .01$) as well as a significant

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					Time × Treatment interaction, (B = 4.92, SE = 2.29, 95% CI [0.44; 9.39], p = .04). Pairwise comparisons revealed that the placebo group demonstrated lower visuospatial scores over time, t(51.3) = 2.40, p = .02, while the oxytocin group did not significantly change, t(55.0) = −1.23, p = .47 No other significant main effects of Treatment or Time × Treatment interaction were detected, ps > .05 The results demonstrated that intranasal oxytocin did not significantly improve cognition in people with schizophrenia compared to placebo. These findings suggest that oxytocin does not worsen or enhance cognition in people with schizophrenia. Yet, the current intervention did not standardize the timing of cognitive assessments relative to the timing of oxytocin administration, which may explain our findings.
Zierhut, Marco et al. (2024)	Randomized Clinical Trial	To assess acceptability, feasibility, and preliminary outcomes of augmenting mindfulness-based group therapy (MBGT) with oxytocin	41 patients with schizophrenic-spectrum disorders (SSD) 22 with oxytocin treatment 19 with placebo	> Oxytocin or placebo (24 I.U.) was administered intranasally 45 min before two sessions of 50-min manual-based Mindfulness-based group therapy MBGT each one week apart . Assessments were conducted at baseline (T0) before the first session and after the full one-week treatment	> A trend in the PSP at baseline indicated that participants in the oxytocin group may be more impaired in social performance > There was a significant difference between the oxytocin and placebo conditions at T1 and T3, with higher plasma levels in the oxytocin group as

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				period (T3). Additional measurements of oxytocin levels, affect, and stress were taken after the first (T1) and before the second session (T2) to capture within-session effects. > Social Performance Scale (PSP) > Oxytocin plasma levels > Interpersonal Reactivity Index (SPF-IRI) > Multifaceted Empathy Test (MET) > Self-Evaluation of Negative Symptoms (SNS) > PANSS > Positive and Negative Affect Schedule (PANAS) > Acute stress (general stress and symptom-related distress) was assessed by self-report visual analogue scales	expected. However, no difference was observed at To and T2. > Paired samples t-tests indicated an expected significant increase of plasma oxytocin levels after oxytocin admission with a large effect size from To to T1 and from T2 to T3. > There was no significant change of plasma oxytocin T levels in the placebo condition. > There was a significant increase of general self-reported empathy (t = 2.46, p < .05, d = 0.56) and Perspective Taking (t = 2.99, p < .01, d = 0.69) from To to T3 by the IRI in the placebo group. > The ANCOVA indicated significant between-group effects with medium effect sizes of oxytocin compared to placebo on the SNS subscales Diminished emotional range (F(1,37) = 4.72, p < .05, η2p = .11) and Avolition (F(1,37) = 4.50, p < .05, η2p = .11), but not for other subscales. > There was a significant increase in the item Diminished emotional range in the placebo group from To to T3 (t = 2.33, p < .05, d = 0.55). > In both groups, Negative affect significantly decreased from To to T3 (oxytocin: t = −4.03, p < .001, d = −0.86; placebo: t = −2.47, p < .05, d = −0.57). > Within-group comparisons showed significant reductions in Negative affect in the oxytocin group from To to T1 (t = −3.16, p < .01, d = −0.67),

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					and T2 to T3 (t = −2.81, p < .01, d = −0.60). > In the placebo group, a significant reduction was observed only from T0 to T1 (t = −3.12, p < .01, d = −0.74). > Positive affect increased in the oxytocin group from T2 to T3 (t = 2.07, p < .05, d = 0.44) and in the placebo group from T0 to T1 (t = 2.93, p < .01, d = 0.69). > General stress significantly decreased in the oxytocin group from T0 to T1 (t = −5.06, p < .001, d = 1.10) and T2 to T3 (t = −4.65, p < .001, d = −1.07). > The placebo group showed a significant change only from T2 to T3 (t = −3.67, p < .001, d = −0.89). > In the oxytocin condition, symptom-related distress significantly decreased from T0 to T1 (t = −4.11, p < .001, d = −0.90) and T2 to T3 (t = −2.37, p < .05, d = −0.53). > The placebo group exhibited a significant change only from T2 to T3 (t = −2.76, p < .01, d = −0.60). > There was a significant increase of general mindfulness from T0 to T3 measured by the SMQ could be shown in the oxytocin (t = 3.06, p < .01, d = 0.65) and placebo group (t = 2.73, p < .01, d = 0.64), particularly for Letting Go (oxytocin: t = 2.85, p < .01, d = 0.61; placebo: t = 3.4, p < .01, d = 0.80).

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Goh, Kah Kheng et al. (2024)	Genetic Association Study	To investigate the impact of oxytocin and OXTR SNPs in linking childhood trauma to social functioning in patients with schizophrenia, considering moderated mediation role of OXTR in increasing vulnerability to schizophrenia.	560 individuals (312 male 248 female) 382 patients with schizophrenia (220 male 162 female) 178 healthy controls (92 male 86 female)	> Childhood Trauma Questionnaire (CTQ-SF) The Social Functioning Scale (SFS) > Assessment of plasma oxytocin levels. > Genotyping of the OXTR and ten single-nucleotide polymorphisms (SNPs; rs2254298, rs237885, rs237887, rs237899, rs53576, rs9840864, rs13316193, rs7632287, rs1042778, and rs237895) > Additive Genetic Risk Scores (AGRS)	> Patients with schizophrenia had higher scores on the CTQ-SF than healthy controls ($t[558] = 12.549$, $p < 0.001$). > All CTQ-SF subscales showed significant differences with higher scores for physical, emotional, and sexual abuse and physical and emotional neglect for patients with schizophrenia. > Patients with schizophrenia had worse social functioning in all domains compared to healthy controls according to the SFS, with a significant difference ($t[558] = -46.951$, $p < 0.001$). > The plasma oxytocin levels of patients with schizophrenia were lower than healthy controls ($t[558] = -5.448$, $p < 0.001$). > Significant differences were observed in genotype frequencies between patients with schizophrenia and healthy controls for seven OXTR SNPs (rs1042778, rs2254298, rs237885, rs237887, rs237895, rs237899, and rs53576), with more rare homozygotes (risk alleles) found in patients > The AGRS of the OXTR SNPs were higher in patients with schizophrenia than in healthy controls ($t[558] = 2.734$, $p = 0.006$). > Binary logistic regression showed that OXTR SNP AGRS significantly predicted status as either schizophrenia or control ($\beta = 0.111$,

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					S.E. = 0.030, Wald = 13.610, df = 1, p < 0.001), indicating that individuals were 1.118 (95% CI [1.054–1.186]) times more likely to develop schizophrenia per unit increase in AGRS (unstandardized β weight for the constant β = 1.270, S.E. = 0.628, Wald = 4.086, df = 1, p = 0.043). > The model explained 6.4% (Nagelkerke R2) of the total variance and the model correctly classified 69.8% of cases > There were significant differences in childhood trauma levels based on OXTR SNPs genotypes, except for rs7632287, among all participants and in patients with schizophrenia. > When looking at healthy controls, differences were only found in OXTR rs1042778, rs13316193, rs237885, rs237895, rs237899, and rs53576. In patients with schizophrenia, an increasing gradient in CTQ-SF scores was observed across genotypes of homozygotes of major alleles, heterozygotes alleles, to homozygotes of minor alleles (risk alleles). These findings suggest evidence for a gene–environment correlation with OXTR SNPs and a history of childhood trauma. > Childhood trauma was significantly associated with social functioning in patients with schizophrenia but not in healthy controls. > Higher CTQ-SF scores in patients with schizophrenia were linked to

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					lower social functioning > Childhood trauma as measured by CTQ-SF scores was a significant predictor of social functioning (B = −0.661, p < 0.001) accounting for 74.8% of the variation (R2 = 0.748, p < 0.001). > Plasma oxytocin levels (B = 2.983, p < 0.001) and AGRS of OXTR SNPs (B = −5.337, p < 0.001) were also significant predictors, contributing an additional 7.7% (ΔR2 = 0.077, p < 0.001) and 7.3% (ΔR2 = 0.073, p < 0.001) of the explanation of social functioning, respectively. > Childhood trauma had a significant impact on both plasma oxytocin (β = −0.130, S.E. = 0.004, t = −36.923, p < 0.001) and social functioning (β = −0.269, S.E. = 0.031, t = −8.724, p < 0.001) in patients with schizophrenia, after controlling for covariates > Plasma oxytocin levels were also found to have a significant effect on social functioning (β = 3.020, S.E. = 0.211, t = 14.334, p < 0.001). > The mediation effect of plasma oxytocin accounted for 59.24% of the total effect between childhood trauma and social functioning. > The gradient for average and high scores of AGRS is steeper, indicating stronger impact of childhood trauma on plasma oxytocin. > At lower AGRS scores, the line tends to straighten, diminishing the

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					impact of childhood trauma on plasma oxytocin. > At higher AGRS scores, the impact increases, with larger decreases in plasma oxytocin with increasing CTQ-SF. > Higher risk allele scores amplify the impact of childhood trauma on plasma oxytocin. > The conditional indirect effect of childhood trauma on social functioning of patients with schizophrenia was highest at high AGRS scores, reduced at average scores, and further diminished at lower scores. > The indirect effect in the presence of the moderator (at the mean level) was 0.098 and within the confidence interval at $p < 0.05$. > Results support the hypothesis that AGRS of OXTR SNPs moderate the indirect effect of childhood trauma on social functioning of schizophrenia patients through plasma oxytocin, with an index of 0.038 (95% CI [0.033–0.044]). > Moderating effects were observed for all individual OXTR SNP genotypes, except for rs13316193, rs7632287, and rs9840864
Bradley, Ellen R et al. (2024)	Cross--Sectional Study	To use deep learning to create a novel, rapid method of estimating abnormal emotion processing from natural	88 male individuals 37 patients with schizophrenia or schizoaffective disorder 51 healthy controls	>PANSS > Clinical Assessment Interview for Negative Symptoms (CAINS) > The Hinting Task	> Patients showed impaired EA (M = 0.445, SD=0.15) compared to controls (M = 0.536, SD=0.13), $t(64)=2.83$, $p=.006$; Cohen's d =

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		language. To understand whether emotional alignment has the potential to capture treatment-induced changes(using oxytocin) in emotion processing.		> American National Adult Reading Test (AmNART) > Letter-Number Sequence (LNS) task > Role Functioning Scale (RFS) >Patients completed two subsequent testing days, separated by at least one week, with drug order (receiving oxytocin or placebo first) randomized between participants (i.e., a crossover design). On each testing day, staff administered 40 IU oxytocin or saline placebo intranasally. >Patients completed the video response task ~30 min following drug administration >Emotional alignment was measured from the video response task and natural language processing was applied to the video response task (VRT) to estimate formal thought disorder > Emotional alignment (EA) measure	0.64); > Patients also had lower coherence scores (M = 0.430, SD=0.11) than controls (M = 0.507, SD=0.13), t(77)=2.90, p=.005, d = 0.63, and used pronouns more frequently (patients: M = 21.182 %, SD=3.05; controls: M = 19.482 %, SD=3.25), t(74)=2.45, p=.017; d = 0.54; > Impaired EA correlated with more severe negative symptoms in the motivation and pleasure domain (CAINS-MAP; r=−0.371, p=.031), but not the expressive domain (CAINS-EXP); > Impairment also correlated with poorer performance on the Hinting Task performance (r = 0.468, p=.004) and measures of neurocognition (AmNART: r = 0.470, p=.005; LNS: r = 0.440; p=.009), but not with positive symptoms or RFS scores; >Patients (M = 64.49, SD=15.00) used fewer words than controls (M = 73.82, SD=12.90), t(63)=2.97, p=.004, d = 0.68), and word count was negatively correlated with EA in the patient group (r=−0.372, p=.030). However, word count did not appear to account for the relationship between EA and other clinical characteristics among patients. > EA scores derived from responses to the neutral (control) prompt correlated with measures of

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					neurocognition (AmNART: r = 0.642, p<.001; LNS: r = 0.360, p=.034), but not with symptoms, Hinting Task, or RFS scores. > EA was significantly associated with coherence (r = 0.410, p=.016), but not with connectedness (p=.201) or pronoun frequency (p=.950).; > Oxytocin administration was associated with better EA among patients (M = 0.535, SD=0.15) relative to placebo (M = 0.447, SD=0.15), based on the paired t-test, t(32)=3.55, p=.001; d = 0.55 > There was no significant effect of oxytocin on EA scores derived from the control prompt (oxytocin: M = 0.631, SD=0.127; placebo: M = 0.675, SD=0.14; p=.910). > There was no significant effect of oxytocin on word count, p=.718; coherence, p=.612; connectedness, p=.118; or pronoun frequency, p=.231.; > Neither antidopaminergic medication dose, p=.248; positive symptom severity, p=.951; nor negative symptom severity, p=.396; were significantly correlated with EA change scores (oxytocin - placebo).
Böge, Kerem et al. (2024)	Randomized Clinical Trial	To asses the feasibility and acceptability as well as the impact of mindfulness-based group therapy (MBGT) on oxytocin levels (OXT) and	48 patients with schizophrenia spectrum disorders 23 patients with treatment as usual (TAU) (14 male 9 female) 25 patients with Mindfulness-	> Patients underwent four-week MBGT program in conjunction with their regular treatment vs treatment as usual without MGBT > Oxytocin was measured before and	> There were statistically significant differences between the two conditions at baseline (t(1) = 6.01, p < .05) and post-intervention (t(1) = 7.24, p < .05) regarding the number

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		clinical parameters in outpatients with schizophrenia spectrum disorders (SSD)	based Group Therapy + Treatment as usual (13 male 12 female)	after the first and the fourth MBGT session. For TAU the measurements were made at baseline (before the first MBGT sessions) and post-intervention (after the fourth MBGT session). > PANSS > Empathy Quotient (EQ) > Interpersonal Reactivity Index (IRI > Personal and Social Performance Scale (PSP) > Self-Evaluation of Negative Symptoms (SNS) > Depression Anxiety Stress Scale (DASS) > Southampton Mindfulness Questionnaire (SMQ) > Cognitive Fusion Questionnaire (CFQ) > Adverse events (AE) and serious adverse events (SAE)	of prescribed mood stabilizers. > More participants in the MBGT + TAU condition received mood stabilizers than participants in the TAU condition at both time points. > Regarding empathy, within-subjects t-tests revealed no significant changes in MBGT + TAU between T0 and T1 for EQ, showing an increase of 1.95 points corresponding to a Cohen's d of 0.23. > No significant difference could be found for the IRI or its subscales, with a mean decrease of 1.41 points in total score, corresponding with a Cohen's d of −0.25. > No significant between-group difference at T1 regarding EQ and IRI and its subscales could be reported. > Analysis of the OXT levels indicated that in blood plasma, levels increased within the first MBGT session (Mpre = 1.96pg/ml, SDpre = 0.28pg/ml; Mpost = 2.05, SDpost = 0.43, d = 0.4, p = .26), Mpre = 1.94, SDpre = 0.19; Mpost = 1.84, SDpost = 0.25, d = 0.18, p < .05). > At the between-group level, both groups did not differ regarding baseline (T0) OXT levels. > At T1, however, OXT levels in blood serum were significantly higher in TAU compared to MBGT+TAU (TAU: Mpost = 2.02, SDpost = 0.3), F(1,40) = 4.15, p < .05, η2 = 0.1). > The SMQ measuring mindfulness did not change significantly within

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					MBGT + TAU, as it increased by 5.27 points (d = 0.32). > No significant changes could be reported within TAU, as the SMQ score increased by 0.95 points (d = 0.16). > Regarding positive symptoms, participants in MBGT + TAU significantly decreased in PANSS positive scores by 2.09 points, corresponding to a Cohen's d of −0.59). In contrast, the TAU condition displayed a slight worsening of symptoms by 0.17 points (d = 0.09). > The results for negative symptoms revealed that participants in MBGT + TAU showed statistically insignificant improvements from T0 to T1 in negative symptoms measured with the PANSS by 1.14 points (d = −0.21) and the self-assessment instrument SNS by −1.09 points (d = −0.16) compared to the TAU group that displayed an increase of negative symptoms by 0.17 on the PANSS (d = 0.06) and 0.17 points on the SNS (d = 0.05). > Social functioning results revealed no significant within-subject effects for participants in the MBGT + TAU condition from T0 to T1 on the PSP, however, displaying a slight increase in social functioning by 0.73 points for MBGT+TAU (d = 0.06), while the

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					mean score decreased in the TAU group by 1.09 (d = −0.14).
Rodrigues, Alexandra et al. (2024)	Cross- -Sectional Study	To determine the association between Brief Negative Symptom Scale and blood-based physiological measures of a range of hormonal and hematological markers including inflammatory To determine the association between Brief Negative Symptom Scale and demographic and psychological\cognitive domains and psychopathological clinical measures	51 male patients with psychotic spectrum disorder (Schizophrenia, Persistent delusional disorder or Schizoaffective disorder)	> Blood sampling of progesterone, testosterone, 17-B-estradiol, luteinizing hormone (LH), cortisol and adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), free thyroxine (fT4), prolactin and oxytocin; and 2) hematological components leucocytes (neutrophils, eosinophils and basophils), lymphocytes, hematocrit (i.e. volume percentage of erythrocytes), mean corpuscular volume (MCV; i.e. mean erythrocyte size), mean corpuscular hemoglobin concentration (MCHC; hemoglobin levels per unit volume), red cell distribution width (RDW) and haemoglobin levels. From these raw measures, we additionally calculated neutrophil-lymphocyte (NLR) and monocyte-lymphocyte (MLR) ratios. > BNSS > PANSS > PSP > Childhood Trauma Questionnaire (CTQ) > Emotional Contagion Scale (ECS) > Empathy Quotient (EQ) > Raven's Standard Progressive Matrices	>There was a statistically significant (p = .024) medium-sized negative correlation between levels of oxytocin and BNSS-avolition; > Patients specifically with higher scores of BNSS-lack-of-distress showed significantly (p = .003) higher TSH levels (medium effect size) and not other BNSS domains. > With p < .05, a medium-sized positive correlations between prolactin and BNSS-total score and BNSS-alogia was found; and a negative medium-sized correlation between progesterone and BNSS-alogia, BNSS-blunted affect, BNSS-total and BNSS-asociality. (These results did not survive a p < .007 threshold for Bonferroni correction); > NLR had a medium-sized significant (.02 < p < .04) positive correlation with BNSS-anhedonia, BNSS-asociality, BNSS-avolition and BNSS-total; > Erythrocyte count showed a medium-sized negative correlation with BNSS-asociality, BNSS-avolition and BNSS-blunted-affect (.01 < p < .03, uncorrected), as well as with BNSS-alogia (p = .001), which drove an association with BNSS-total (p = .002), both surviving Bonferroni correction (of 7 tests; p < .007).

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					> MCV was medium positively correlated with BNSS-avolition and BNSS-lack-of-distress (.01 < p < .03, uncorrected), as well as with BNSS-asociality (p = .003) which drove the association with BNSS-total (p = .003), the latter both surviving Bonferroni correction. > Lymphocyte count showed a medium negative association with BNSS-blunted-affect (p = .016; uncorrected) and with BNSS-alogia which survived Bonferroni correction (p = .006). > RDW also showed a highly significant and surviving correction negative association with BNSS-asociality (p = .005).; > Illness resolution as well as a range of PANSS scores (e.g. conceptual disorganization, difficulty in abstract thinking and poor attention) were associated with several lower, and higher BNSS scores, respectively (p < .001) > Higher BNSS was associated with poorer PSP-measured functional capacity, in particular for avolition, but also in specific for BNSS-blunted-affect and BNSS-asociality (p < .001) > There was an association between ECS-anger and BNSS-total driven by significant associations with BNSS-anhedonia and BNSS-asociality (p < .001)