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Oxytocinerge Modulation von Sprachproduktion

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1.a Zusammenfassung in deutscher Sprache

Oxytocin, welches primär als Hormon bekannt ist, beeinflusst als Neuromodulator viele kognitive Prozesse, die an sozialem Verhalten, wie Sprache, beteiligt sind. Einerseits verändert es akustische Merkmale von gesprochener Sprache, andererseits erleichtert es auf perzeptueller Ebene die Emotionserkennung in der Sprachwahrnehmung und Körpersprache. Bislang war nicht bekannt, wie Oxytocin Hirnaktivität während des Sprechens verändert. Wir hypothetisierten, dass dieser Neuromodulator ähnlich wie Dopamin kortiko-basale Schaltkreise bahnen könnte.

Wir führten eine doppelt-verblindete Verhaltens- und funktionelle Kernspintomographiestudie durch, in der 52 gesunde Probanden an zwei getrennten Untersuchungsterminen entweder intranasales Oxytocin oder ein Placebo erhielten. Die Teilnehmer lasen Sätze außerhalb des Kernspintomographen und im Scanner leise oder laut mit entweder neutraler oder fröhlicher Intonation vor.

Die Verabreichung von Oxytocin erhöhte den zweiten Formanten der produzierten Vokale. Höhere Frequenzen dieses akustischen Parameters wurden zuvor mit einer positiven Valenz gesprochener Sprache in Verbindung gebracht; jedoch konnten unabhängige Beurteiler*innen die akustischen Unterschiede in unserem experimentellen Setting nicht konsistent unterscheiden.

Als neuronales Korrelat verstärkte Oxytocin die präparatorische subkortikale Gehirnaktivität im ventralen Pallidum und Striatum. Auch kortikal erhöhte Oxytocin präparatorische Gehirnaktivität in Regionen des dorsalen wie auch des ventralen Sprachverarbeitungsstroms, in sensomotorischen Kortizes und limbischen sowie exekutiven Regionen. In einigen dieser Regionen modulierte der genetische Oxytocin-Rezeptor-Polymorphismus rs53576 die durch die Oxytocin-Verabreichung verursachte Gehirnaktivität. Ähnlich wie Dopamin modulierte Oxytocin außerdem kortiko-basale Schaltkreise, die an der Generierung von fröhlicher Prosodie beteiligt sind. Während der Vorbereitung von Sprache erhöhte der Neuromodulator die funktionelle Konnektivität zwischen dem ventralem Pallidum und dem dorsolateralen präfrontalen Kortex mit einem spiegelbildlichen Profil während des eigentlichen Sprechens, einen Effekt den wir als „gating“ (Bahnung) interpretierten.

Unsere Ergebnisse legen nahe, dass mehrere neuronale Prozesse, die der Sprachproduktion zugrunde liegen, durch Oxytocin moduliert werden. Das Muster ähnelt hierbei dem anderer Neuromodulatoren wie Dopamin. Die vorliegende Arbeit charakterisiert somit erstmals Oxytocineffekte auf die mit Sprachproduktion assoziierte Hirnaktivität und funktionelle Konnektivität.

1.b Zusammenfassung in englischer Sprache

Oxytocin, primarily known as a hormone, influences as a neuromodulator various aspects of cognition involved in social behavior, such as speech. On one hand, it alters acoustic features of spoken language, on the other it facilitates emotion recognition during speech perception and in body language on a perceptual level. Until now, it was not known how oxytocin changes brain activity during speech production. We hypothesized that the neuromodulator could impact cortico-basal circuits comparable to dopamine.

We conducted a double-blind behavioral and functional magnetic resonance imaging study with 52 healthy participants who received either intranasal oxytocin or a placebo in two separate sessions. The participants read sentences silently or aloud with either neutral or happy intonation both outside and inside the magnetic resonance scanner.

Oxytocin administration increased the second formant of produced vowels. Higher frequencies of this acoustic parameter have previously been associated with positive valence in spoken language; however, independent raters could not unequivocally discern the acoustic differences in our experimental setting.

On the neural level, oxytocin enhanced preparatory subcortical brain activity in the ventral pallidum and striatum. Cortically, oxytocin increased preparatory brain activity in regions of both the dorsal and ventral speech processing streams, sensorimotor cortices, as well as limbic and executive regions. In some of these regions, the genetic oxytocin receptor polymorphism rs53576 modulated the brain activity induced by oxytocin administration. Similar to dopamine, oxytocin also affected cortico-basal circuits involved in generating happy prosody. During speech preparation, the neuromodulator increased functional connectivity between the ventral pallidum and the dorsolateral prefrontal cortex, with a mirrored pattern during actual speaking, an effect we interpreted as ‘gating’.

Our findings suggest that several neural processes underlying speech production are modulated by oxytocin. The observed pattern is comparable to that of other neuromodulators like dopamine. This study thus provides the first characterization of oxytocin effects on brain activity and functional connectivity associated with speech production.

2. Übergreifende Zusammenfassung

2.a Einleitung

Sprache ist Mittel sozialer Kommunikation. Soziales Verhalten wird von verschiedenen Neuromodulatoren, einschließlich Oxytocin, beeinflusst. Oxytocin, welches primär als Hormon bekannt ist, ist in seiner Funktion als Neuromodulator an verschiedenen kognitiven Prozessen, die für soziale Interaktionen maßgebend sind, beteilig. So erleichtert es beispielweise die Emotionserkennung in der menschlichen Körpersprache [1], in Gesichtern [2] oder in der Sprachwahrnehmung bei Patient:innen mit Autismus-Spektrum-Störung [3]. Durch Sprache werden jedoch mehr Informationen im sozialen Kontext vermittelt als nur Emotionen. Auch an der Perzeption nicht-affektiver Sprache ist Oxytocin beteiligt [4-6] und beeinflusst akustische Merkmale von gesprochener Sprache [7]. Intranasales Oxytocin moduliert die Frequenz des zweiten Formanten (f2) gesprochener Vokale [7]. Eine höhere Frequenz dieses Parameters ist mit einer positiveren Valenz [8] und mit „fronting“ eines Vokales in der Artikulation assoziiert [9], wie es beispielweise beim Lächeln passiert. „Fronting“ ist eine Lautveränderung, bei der ein Vokal oder Konsonant näher zur Vorderseite des Vokaltrakts ausgesprochen wird. Die Modulation von f2 gesprochener Vokale durch Oxytocin legt nahe, dass Oxytocin nicht nur die neuronale Verarbeitung im Gehirn des Empfängers, sondern auch im Gehirn des Senders beeinflusst und somit mehr Aspekte der Kognition als bisher angenommen.

Bildgebungsstudien liefern erste Erkenntnisse über zugrundeliegende neuronale Prozesse der oxytocinergen Neuromodulation während der Sprachverarbeitung. Im experimentellen Kontext verstärkt die intranasale Verabreichung von Oxytocin die Aktivität in stimmsensitiven kortikalen Regionen während der Stimmerkennung [10]. Ebenfalls erhöht es die funktionelle Konnektivität zwischen Basalganglien und fronto-temporalen kortikalen Regionen, die an der Sprachverarbeitung beteiligt sind [11]. Bisher gibt es jedoch keine Daten über die neuronalen Auswirkungen Oxytocins auf die Produktion von Sprache.

Physiologisch beeinflussen genetische Polymorphismen die oxytocinerge Neuromodulation. Von funktioneller Relevanz im Kontext sozialer Verhaltensweisen scheint insbesondere der Oxytocin-Rezeptor (OXTR) rs53576-Polymorphismus mit den Genotypen AA/AG und GG zu sein. So zeigen Träger des A-Allels insgesamt niedrigere Empathiewerte z.B. geringere affiliative Reaktionsfähigkeit gegenüber ihren Kleinkindern [12]. GG-Homozygote hingegen wiesen höhere dispositionelle Empathie [13] und eine erhöhte Effizienz bei der Verarbeitung sozialer auditorischer Signale im Vergleich zu AA/AG-Genotypen auf [14]. Auf neuronaler Ebene zeigten Träger dieses

Genotyps optimalere Reaktionen auf soziale auditorische Signale [15]. Noch unklar ist, ob der OXTR rs53576-Polymorphismus auch die Sprachproduktion und ihre neuronalen Grundlagen beeinflusst.

Wichtige Gene der oxytocinergen Neuromodulation werden ubiquitär im zentralen Nervensystem und angereichert in subkortikalen Regionen exprimiert [16]. Die Basalganglien, in denen das Oxytocin Rezeptor-Gen stark exprimiert wird, spielen eine wichtige Rolle bei der Sprachproduktion, indem sie durch Bildung kortiko-basaler Schaltkreise zur Vorbereitung und Produktion von emotional neutraler Sprache beitragen [17]. Ebenso modulieren sie Sprache in Abhängigkeit vom vorherrschenden affektiven Zustand [18].

Diese kortiko-basalen Schaltkreise werden von verschiedenen Neuromodulatoren beeinflusst. Arnold et al. untersuchten den dopaminergen Einfluss auf die Sprachproduktion bei Parkinson-Patient:innen [19] und bei gesunden Kontrollpersonen [20]. Physiologisch zeigten Proband:innen mit mittleren Dopaminspiegeln während der Sprachvorbereitung die höchste striato-präfrontale funktionelle Konnektivität mit einem spiegelbildlichen Effekt während des tatsächlichen Sprechens [20], was als „Gating“ (Bahnung) interpretiert wurde. Im Gegensatz dazu zeigten Parkinson-Patient:innen während der Aufgabenausführung, d.h. beim Sprechen, im Vergleich zu gesunden Kontrollen eine höhere effektive Konnektivität im Sprachnetzwerk. Die Verabreichung von Levodopa löste diesen Effekt auf und brachte die Konnektivität auf ein physiologisches Niveau.

Inwieweit Oxytocin Sprachproduktion und die hierfür benötigten kortiko-basalen Schaltkreise in ähnlicher Weise wie Dopamin beeinflusst, ist bisher ungeklärt. Zur Untersuchung dieser Fragestellung führten wir eine doppelt-verblindete Verhaltens- und Ganzhirn-fMRT-Studie durch. Wir erwarteten einen Verhaltenseffekt von Oxytocin auf den zweiten Formanten (f2) gesprochener Vokale [7]. Unser Ganzhirn-fMRT-Ansatz hingegen war explorativ, da wir keine identischen Auswirkungen von Oxytocin und Dopamin auf die zugrundeliegende Hirnaktivität und funktionelle Konnektivität im Zusammenhang mit Sprachproduktion annahmen. Unsere Hypothese war, dass das grundlegende Prinzip der Bahnung kortiko-basaler Schaltkreise von beiden Neuromodulatoren geteilt wird, insbesondere, weil Oxytocin-Rezeptoren in den Basalganglien stark exprimiert werden. Welcher Schaltkreis genau moduliert werden würde, konnte jedoch nicht vorhergesagt werden.

2.b Darstellung der Publikation: Methoden

Wir untersuchten die Effekte von Oxytocin auf akustische und perzeptuelle Aspekte gesprochener Sprache sowie neuronale Korrelate mittels funktioneller Magnetresonanztomographie. Hierfür führten wir eine doppelt-verblindete Studie durch, bei der gesunde, männliche Teilnehmer zu zwei Terminen entweder intranasales Oxytocin oder ein Placebo erhielten, bevor sie Sätze mit neutraler Intonation oder mit freudiger Prosodie vorlasen. Die Teilnehmer wurden außerdem aufgrund ihres rs53576 OXTR-Polymorphismus in zwei Gruppen (AA/AG- Genotypen und GG-Genotypen) aufgeteilt. Aufgrund bekannter menstruationszyklusbedingter Veränderungen der Sexualhormone und ihrer Auswirkung auf die OXTR-Dichte wurden nur männliche Teilnehmer eingeladen.

Für die detaillierte akustische Analyse wurde die Sprache außerhalb des MRT-Scanners aufgezeichnet und drei verschiedene Sprachparameter mittels einer Software für phonetische Analysen extrahiert. Die Stimmmodulation wurde mithilfe extrahierter Intensitätskonturen (dB) und der Standardabweichung der Grundfrequenz (Hz) quantifiziert. Da intranasal verabreichtes Oxytocin den zweiten Formanten (f2) produzierter Vokale moduliert [7], extrahierten wir f2 als dritten Parameter. Neben den akustischen Analysen führten wir außerdem eine perzeptuelle Analyse der aufgezeichneten Sätze durch, in welcher naive Beurteiler die Sprache bezüglich ihrer Valenz bewerteten.

Wir untersuchten die Hirnaktivität mittels funktioneller Kernspintomographie und verwendeten dabei einen „cue-target“ (dt. Übersetzung: Hinweisreiz-Zielreiz) Sprachproduktionstask. Die Aufgabe bestand darin, inhaltlich neutrale Sätze entweder mit neutraler Intonation oder mit freudiger Prosodie vorzulesen. Leises Lesen diente als kognitive Kontrollbedingung. Vor der Präsentation des Satzes wurde durch einen visuellen Stimulus vermittelt, ob der Satz leise, neutral oder freudig gelesen werden sollte. Dies ermöglichte die Trennung zwischen der Vorbereitung des Sprachnetzwerkes vom eigentlichen Sprechen.

Wir suchten in einem ersten Schritt nach Veränderungen der Hirnaktivität während des Sprechens durch die intranasale Gabe von Oxytocin bzw. Unterschieden in der Verarbeitung von Sprache zwischen den genetischen Gruppen. In einem zweiten Schritt untersuchten wir die funktionelle Konnektivität zwischen Hirnarealen, welche einen oxytocinergen Effekt während des Sprachproduktionstasks aufwiesen. Als Seed-Regionen dienten hierbei subkortikale Strukturen, in welchen Oxytocinrezeptoren vermehrt exprimiert werden und die einen Oxytocineffekt auf die Aktivität aufwiesen. Schließlich untersuchten wir mittels funktioneller Konnektivitätsanalyse in

Ruhe, ob die oxytocinerge Modulation nicht nur während des eigentlichen Sprechens auftritt, sondern kortiko-basalen Schaltkreise in größerem Maße beeinflusst.

2.b Darstellung der Publikation: Ergebnisse und Diskussion

Wir konnten eine Modulation akustischer Sprachparameter durch die intranasale Verabreichung von Oxytocin während des lauten Lesens nachweisen; ein Effekt, der zuvor bereits während des freien Sprechens beobachtet wurde [7]. Die Verabreichung von Oxytocin erhöhte den zweiten Formanten (f2) der produzierten Vokale. Hierbei ergaben sich geringe Unterschiede zwischen den Gruppen des OXTR rs53576-Polymorphismus. Insbesondere bei Trägern des A-Allels, bei denen vermutlich eine weniger effiziente oxytocinerge Signalgebung vorliegt, erhöhte der Neuromodulator die f2-Frequenz der produzierten Vokale. Unter Placebo hatten GG-Homozygote eine höhere f2-Frequenz beim freudigen Sprechen im Vergleich zu den AA/AG-Genotypen. Höhere f2-Frequenzen wurden mit einer Vorverlagerung der Artikulation [9] und vermehrtem Lächeln in Verbindung gebracht [9,21], weshalb aus höheren f2-Frequenzen eine positivere Valenz geschlussfolgert wird [8]. Die f2-Modulation in unseren Daten konnte von verblindeten Beurteiler*innen perzeptuell nicht wahrgenommen werden. Da Zuordnungen zwischen einzelnen sprachlichen Merkmalen wie f2 und Emotionen sehr inkonsistent sind, sollten diese nicht vereinfacht werden [22]. Während in unserem experimentellen Setting Oxytocin nur die Akustik der produzierten Sprache beeinflusste, könnte es in einem kommunikativeren Kontext auch die Sprache auf der perzeptiven Ebene beeinflussen. Tatsächlich steigen endogene Oxytocin-Spiegel während sozialer Interaktionen abhängig vom Geschlecht und der Beziehung zwischen den Dialogpartnern an, was auf eine komplexere Modulation in kommunikativen Kontexten durch das Neuropeptid hindeutet [23].

Die gezeigten Effekte von exogen verabreichtem Oxytocin auf phonetische Sprachmerkmale wurden durch Modulation aufgabenspezifischer Gehirnaktivität und funktioneller Konnektivität widergespiegelt. Oxytocin steuerte die Aktivität einiger subkortikaler und kortikaler sensomotorischer Hirnregionen, limbischer Bereiche und Hirnregionen, die an der exekutiven Kontrolle beteiligt sind. Die sensomotorischen Sprachregionen umfassten sowohl Teile des vorwärts-, als auch des rückwärtsgerichteten Kontrollsystems des Sprechens [24-26]. Ein Großteil hiervon gehört zu den dorsalen Sprachverarbeitungsströmen, die für die Sprachproduktion von entscheidender Bedeutung sind [27,28]. In den ventralen Sprachverarbeitungsströmen war die oxytocinerge Modulation größtenteils auf die rechte Hemisphäre beschränkt, welche auf die spektrale Verarbeitung auditorischer Informationen spezialisiert ist [25,29]. Unsere Ergebnisse legen nahe, dass Oxytocin das Monitoring von selbst erzeugten spektralen Sprachmerkmalen erhöht.

Dies ist wiederum mit der durch den Neuromodulator bedingten rechtstemporalen Aktivitätssteigerungen in stimmsensitiven Arealen kompatibel [10]. Eine rechtshemisphärische Interaktion zwischen temporalen Regionen, die besonders empfindlich für spektrale Sprachmerkmale sind, und die frontale Motorik verarbeitenden Kortizes könnte der beobachteten oxytocinergen Modulation der produzierten Sprachspektren zugrunde liegen. Die Modulation der funktionellen Konnektivität zwischen dem ventralen Pallidum und dem DLPFC könnte die limbische Kontrolle der Sprachproduktion widerspiegeln [18]. Da Oxytocin insbesondere während der Vorbereitung auf die Sprache Aktivität und funktionelle Konnektivität erhöhte, interpretieren wir den Effekt von Oxytocin als Gating sprachrelevanter Berechnungen, einschließlich exekutiver Kontrolle, limbischer und sensomotorischer Verarbeitung. Man könnte hieraus folgern, dass diese oxytocinbedingten Prozesse soziale Kognition widerspiegeln. Die Rolle von Oxytocin auf soziale Funktionen zu reduzieren, wäre jedoch eine Vereinfachung und Anstiege des Oxytocinspiegels wurden bereits mehrfach mit Prozessen jenseits der sozialen Kognition, wie z. B. körperlicher Betätigung und sexueller Selbststimulation, in Verbindung gebracht [30,31].

Einige der Gehirnregionen wurden nicht nur durch das Neuropeptid beeinflusst, sondern zeigten auch eine Modulation durch dem rs53576 OXTR-Polymorphismus. In diesen Regionen erhöhte Oxytocin die Vorbereitungsaktivität nur bei Trägern des A-Allels im OXTR rs53576-Polymorphismus, während GG-Homozygote einen „Ceiling-Effekt“ (Deckeneffekt) zeigten [32]. GG-Homozygote gelten als Träger der effizienteren oxytocinergen Neuromodulation [12,14,15]. Möglicherweise ist daher keine zusätzliche Oxytocin-Verabreichung für weitere Gating-Effekte erforderlich. Unsere Ergebnisse sind mit Untersuchungen an klinischen Stichproben konsistent, bei denen insbesondere Personen mit weniger ausgeprägten sozialen Verhaltensweisen von der Verabreichung von Oxytocin profitieren [32].

Der Effekt der Bahnung beschränkte sich nicht nur auf die regionale Aktivierung, sondern wurde auch für kortiko-subkortikale Interaktionen beobachtet. Insbesondere bei der Vorbereitung auf freudige Sprache beeinflusste Oxytocin kortiko-basalganglionäre Schaltkreise. Oxytocin moduliert derartige Schaltkreise in verschiedenen Kontexten und Spezies [11,33,34]. Das ventrale Pallidum ist Teil des limbischen subkortikalen Gebiets [35]. Es interagiert mit dem präfrontalen Kortex [36] und spielt eine wichtige Rolle bei der Umsetzung limbischer Signale in Motorik [18,37]. Oxytocin in den Basalganglien kann funktionelle Netzwerke im gesamten zentralen Nervensystem beeinflussen [11,16]. Die Tatsache, dass Oxytocin nicht nur die sprachbezogene funktionelle Konnektivität des ventralen Pallidums modulierte, sondern auch die nachfolgende Konnektivität in Ruhe, legt nahe,

dass die oxytocinerge Modulation nicht nur auf Phasen des tatsächlichen Sprechens beschränkt ist, sondern kortiko-basalganglionäre Schaltkreise in größerem Maße beeinflusst.

Die Bahnung der pallido-kortikalen funktionellen Konnektivität während der Vorbereitung mit anschließender verminderter Kopplung während des eigentlichen Sprechens, erinnert an Dopamineffekte auf die Sprachproduktion [20]. Eine effiziente Vorbereitung kortiko-basalganglionärer Schaltkreise kann zu einer verminderten Verarbeitungsanforderung während des tatsächlichen Sprechens führen, was sowohl für die dopaminerge als auch für die oxytocinerge Neuromodulation zu gelten scheint. Gene der oxytocinergen Signalverarbeitung werden stark mit mehreren dopaminergen Genen wie Catechol-O-Methyltransferase (COMT) Val158Met co-exprimiert, was möglicherweise die anatomische Grundlage für funktionale Interaktionen darstellt [16]. Dopamin- und Oxytocinwege konvergieren im präfrontalen Kortex und ventralen Striatum [38], die beide an der Regulation sozialer Verhaltensweisen wie der Sprachproduktion beteiligt sind [18]. Für die Untersuchung etwaiger Interaktionen wären jedoch größere Stichproben erforderlich.

2.c Diskussion der Gesamtheit der Ergebnisse und deren Beitrag für die Beantwortung der Fragestellung

Die Wirkung von Oxytocin auf soziales Verhalten ist ein kontroverses Thema. In den vergangenen Jahren wurde dem Hormon immer wieder die Wirkung eines „Vertrauenshormons“ zugeschrieben und deshalb eine breite medikamentöse Anwendung diskutiert. Dies ging einher mit der Bemühung, den Neuromodulator neben seinem gynäkologischen Anwendungsbereich auch in der Psychiatrie zu etablieren. In erster Linie profitieren könnten Patient:innen mit Autismus-Spektrum-Störungen, für welche Oxytocin eine Verbesserung der sozialen Fähigkeiten bedeuten kann [39]. Von einer breiteren Anwendung auch für neurotypische Erwachsene zur Stressreduktion oder zum Aufbau sozialer Bindungen wird zum aktuellen Zeitpunkt jedoch Abstand genommen, denn die oxytocinerge Neuromodulation ist vielschichtig. Die vereinfachte Darstellung Oxytocins als „Vertrauenshormon“ wird dementsprechend kritisiert. Auch unsere Verhaltens- und fMRT-Ergebnisse zeichnen - mit einer Reihe weiterer rezenter Studien - ein komplexeres Bild. Im Rahmen dieser Arbeit können keine therapeutischen Fragestellungen beantwortet werden. Im Folgenden werden jedoch die Konsequenzen

unserer Beobachtungen für mögliche künftige Untersuchungen therapeutischer Anwendungen von Oxytocin in der Neuromedizin im Kontext der Vorliteratur diskutiert.

Die Ausschüttung des Neuropeptids erfolgt typischerweise als Reaktion auf soziale Interaktionen, die mit zwischenmenschlicher Bindung, Vertrauen und Nähe assoziiert sind. Oxytocin kann das Vertrauen zwischen Individuen, insbesondere in sozialen Situationen, in denen Kooperation wichtig ist, erhöhen [40]. Doch lediglich von positiven Auswirkungen auf soziales Verhalten zu berichten wäre eine starke Vereinfachung, zumal die Definition von „positiv“ im Sinne von erwünschtem Sozialverhalten sehr problematisch ist. Die oxytocinerge Neuromodulation ist komplex und kontextabhängig. Oxytocin kann ebenso soziale Vorurteile und Misstrauen gegenüber Fremden verstärken [41]. Zusätzlich zum Kontext scheinen genetische Polymorphismen, wie der OXTR rs53576, eine Rolle zu spielen. Träger*innen unterschiedlicher Varianten dieses Gens weisen verschiedene Verhaltensweisen und Empfindlichkeiten gegenüber sozialen Situationen auf [12,14]. Es profitieren besonders Träger*innen mit einer weniger effizienten oxytocinergen Neuromodulation (AA-/AG-Genotyen) von einer etwaigen intranasalen Behandlung, während GG-Homozygote geringe oder keine Effekte zeigen.

So müssen auch die in unserer Studie gezeigten Effekte des Neuromodulators auf Sprache in einem komplexen Kontext verstanden werden. Im experimentellen Umfeld beeinflusste Oxytocin die Akustik gesprochener Sprache abhängig vom genetischen Polymorphismus, jedoch konnten keine Effekte auf perzeptueller Ebene festgestellt werden. Es ist nicht ausgeschlossen, dass Oxytocin in einem kommunikativeren Kontext Sprache derart beeinflusst, dass dies zu verallgemeinerbaren Wahrnehmungen führt. Für eine komplexere Modulation in kommunikativen Kontexten spricht auch, dass endogene Oxytocin-Spiegel während sozialer Interaktionen abhängig vom Geschlecht und der Beziehung zwischen den Dialogpartnern ansteigen [23].

Zusätzlich beeinflussen funktionelle Wechselwirkungen zwischen Oxytocin und anderen Neuromodulatoren wie Dopamin soziale Interaktionen mitsamt ihrer zugrundeliegenden Gehirnaktivität und funktionellen Konnektivität. Kritische Gene im oxytocinergen Signaltransduktionsweg sind stark mit mehreren dopaminergen Genen wie COMT koexprimiert, was die anatomische Grundlage für diese Interaktionen bilden könnte [16]. Unsere Hypothese war, dass das Prinzip der Bahnung kortiko-basaler Schaltkreise von beiden Neuromodulatoren geteilt wird. Tatsächlich scheinen beide Neuromodulatoren kortiko-basale funktionelle Konnektivität in

ähnlicher Weise zu modulieren. Während der Vorbereitung von Sprache konnte ein Anstieg von Gehirnaktivität und funktioneller Konnektivität gezeigt werden mit anschließender verminderter Kopplung während des eigentlichen Sprechens, ein Effekt, der als Bahnung interpretiert werden kann.

Eine etwaige Anwendung des Neuromodulators als Therapeutikum muss entsprechend der Komplexität der neuromodulatorischen Eigenschaften kritisch hinterfragt werden. Bestimmte Personen mit sozialen Störungen wie einer Autismus-Spektrum-Störung oder mit grundsätzlichen Schwierigkeiten, Vertrauen aufzubauen, könnten tatsächlich von der intranasalen Anwendung profitieren [39,42,43], während die Anwendung bei anderen Menschen keinen oder gar gegenteilige Effekte hervorrufen könnte. Ein besseres Verständnis der oxytocinergen Neuromodulation ist folglich sinnvoll, bevor eine breitere Anwendung ernsthaft diskutiert werden kann.

3. Die Publikation

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Oxytocinergic modulation of speech production—a double-blind placebo-controlled fMRI study

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Abstract

Many socio-affective behaviors, such as speech, are modulated by oxytocin. While oxytocin modulates speech perception, it is not known whether it also affects speech production. Here, we investigated effects of oxytocin administration and interactions with the functional rs53576 oxytocin receptor (OXTR) polymorphism on produced speech and its underlying brain activity. During functional magnetic resonance imaging, 52 healthy male participants read sentences out loud with either neutral or happy intonation, a covert reading condition served as a common baseline. Participants were studied once under the influence of intranasal oxytocin and in another session under placebo. Oxytocin administration increased the second formant of produced vowels. This acoustic feature has previously been associated with speech valence; however, the acoustic differences were not perceptually distinguishable in our experimental setting. When preparing to speak, oxytocin enhanced brain activity in sensorimotor cortices and regions of both dorsal and right ventral speech processing streams, as well as subcortical and cortical limbic and executive control regions. In some of these regions, the rs53576 OXTR polymorphism modulated oxytocin administration–related brain activity. Oxytocin also gated cortical-basal ganglia circuits involved in the generation of happy prosody. Our findings suggest that several neural processes underlying speech production are modulated by oxytocin, including control of not only affective intonation but also sensorimotor aspects during emotionally neutral speech.

Keywords: oxytocin; articulation; overt reading; affective prosody; neuromodulation

Introduction

Speech is a means of social communication. Social behavior is modulated by various neuropeptides, including oxytocin. Oxytocin facilitates emotion recognition during visual perception of human body language (Bernaerts *et al.*, 2016) and faces (Shahrestani *et al.*, 2013) as well as emotion recognition during speech perception in autism spectrum disorder patients (Hollander *et al.*, 2007). Yet, speech carries more social information than only emotion. Oxytocin may also modulate linguistic processing of non-affective speech (Theofanopoulou, 2016; Theofanopoulou *et al.*, 2017; Meixner *et al.*, 2019) and impacts acoustic features of produced speech (Agurto *et al.*, 2020). Particularly, the latter finding suggests that oxytocin modulates neural processing not only in the receiver's but also in the sender's brain and may affect more aspects of cognition than previously known.

Imaging studies proposed substrates of oxytocinergic neuromodulation during speech processing. In an experimental setting, intranasal oxytocin administration enhances activity in voice-sensitive cortical regions during voice identity recognition (Borowiak and Kriegstein, 2020) and modulates resting-state functional connectivity (RSFC) between the basal ganglia and the frontotemporal cortices involved in speech processing (Bethlehem *et al.*, 2017). However, the neural effects of oxytocin administration on speech production are still enigmatic.

Physiologically, oxytocinergic neuromodulation is influenced by genetic functional polymorphisms. Specifically, the oxytocin receptor (OXTR) rs53576 polymorphism, with its genotypes AA/AG and GG, was found to be relevant for different social behaviors. Carriers of the A allele show overall lower empathy levels (Rodrigues *et al.*, 2009), e.g. less affiliative responsiveness toward their toddlers (Bakermans-Kranenburg and van Ijzendoorn, 2008). GG homozygotes demonstrate higher levels of dispositional empathy (Rodrigues *et al.*, 2009) and increased efficiency in the processing of social auditory cues compared to AA/AG genotypes (Tops *et al.*, 2011). On the neural level, carriers of this genotype showed more optimal responses to social auditory cues (Cataldo *et al.*, 2020). It is not clear whether the OXTR rs53576 polymorphism also affects speech production and its neural underpinnings.

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Critical oxytocin pathway genes are expressed ubiquitously in the human central nervous system but are enriched in subcortical regions (Quintana *et al.*, 2019). The basal ganglia, where oxytocin pathway genes are highly expressed, play a prominent role in speech production, contributing to the preparation and production of emotionally neutral speech by forming cortico-basal loops (Kell *et al.*, 2011) and modulating speech as a function of the prevailing affective state (Pichon and Kell, 2013). Those cortico-basal circuits are impacted by neuromodulators. Specifically, levodopa administration and polymorphisms of genes involved in dopaminergic neuromodulation affect speaking-related activity and functional connectivity. Dopamine gates striato-prefrontal functional connectivity in preparation for speaking and reduces this connectivity during actual speaking (Arnold *et al.*, 2014, 2016).

To investigate whether the neuromodulator oxytocin affects speech production and its underlying brain activity and functional connectivity as well, we conducted a double-blind behavioral and whole-brain functional magnetic resonance imaging (fMRI) study during which healthy male participants received on two occasions either intranasal oxytocin or placebo before they read sentences out loud in neutral and happy intonation both outside the scanner and during scanning. Participants were divided into two groups based on their rs53576 OXTR polymorphism.

For in-depth acoustic analyses, speech was recorded outside of the scanner. Voice modulation was quantified using extracted intensity contours (dB) and standard deviation of the fundamental frequency (Hz). Both acoustic parameters are strongly influenced by valence (Pell, 1999; Pfitzinger and Kaernbach, 2008; Pichon and Kell, 2013). However, intranasal oxytocin administered to speakers is so far only known to modulate the second formant (f_2) of produced vowels (Agurto *et al.*, 2020). We therefore expected primarily oxytoxin effects on f_2. Higher f_2 frequencies have been associated with fronting of articulation (Podesva *et al.*, 2015) and with positive valence (Goudbeek *et al.*, 2009). We also asked naïve raters to judge valence of recorded speech and analyzed whether oxytocin administration in speakers affected perceptual ratings.

Our whole-brain functional imaging approach was exploratory. However, we hypothesized an overall effect of oxytocin on cortico-basal circuits. Because oxytocinergic neuromodulation differs from dopaminergic signaling, we did not expect identical findings in exactly the same regions as those observed in the dopamine studies. However, the overall notion of gating of cortico-basal circuits could represent a common feature of both neuromodulators, especially because OXTRs are highly expressed in human basal ganglia (Quintana *et al.*, 2019).

Materials and methods

Experimental design

Participants

Fifty-two right-handed male native German speakers (mean age: 24.5 ± 5.3 years) were measured with fMRI. Three participants had to be excluded due to technical problems with the scanner. No participant had to be excluded due to excessive head movement (> 2 mm). Only male participants were invited since animal studies suggest that menstrual cycle–related changes in sex hormones influence OXTR densities throughout the brain (Bale and Dorsa, 1995; Insel, 2010). No participant had a history of psychiatric, neurological or speech and language disorders, alcohol or drug abuse. Participants provided written informed consent and were paid for their participation. The study was approved by the ethics committee of the Goethe University Frankfurt am Main (GZ 06/16) and was in accordance with the Declaration of Helsinki.

Oxytocin and placebo administration

Following a double-blind placebo-controlled within-subject design, participants came in on two occasions that were approximately 2 weeks apart and received either intranasal oxytocin (participants were instructed to dismiss the first hub and consecutively apply 24 international units oxytocin while breathing in; Scheele *et al.*, 2014) or a placebo (saline solution) in a randomized, yet counterbalanced order. Both appointments were scheduled approximately at the same time of the day, and participants were instructed to abstain from alcohol and caffeine on appointment days. A 40-min wait period prior to fMRI scanning allowed the physiological and pharmacokinetic effects of oxytocin to unfold (Supplementary Figure A) (Born *et al.*, 2002; Spengler *et al.*, 2017). After completion of the experiment, participants were interviewed on their subjective belief on which appointment they were given the oxytocin spray. To test whether the participants could identify whether they received the verum or placebo, a chi-square test was performed to test if correct answers were above the chance level (at $P < 0.05$).

Genetic analyses

For group analyses, blood samples were taken and participants were divided into two groups based on the genotype of their rs53576 OXTR polymorphism, studied by the commercial rs53576 single-nucleotide polymorphism assay (Applied Biosystems®, Thermo Fisher Scientific, Inc., Waltham, AS) according to manufacturer's recommendations and analyzed using StepOne Software v2.1 (Applied Biosystems®, Thermo Fisher Scientific, Inc., Waltham, AS. RRID: SCE_014281). Social cognition, including the processing of social auditory cues, is modulated by this functional OXTR polymorphism (Tops *et al.*, 2011; Feng *et al.*, 2015; King, 2016). Based on their relative frequencies in the Caucasian population, carriers of the A allele (AA homozygotes: 8 participants and AG heterozygotes: 20 participants) were pooled in one group and compared to 24 GG homozygotes (Tops *et al.*, 2011; Feng *et al.*, 2015). The samples' OXTR genotype distribution (Supplementary Table 1) reflected the distribution of the OXTR genetic polymorphisms in the Caucasian population (Montag *et al.*, 2017). Three carriers of the A allele had to be excluded from further analyses due to scanner problems.

We further assessed participants' dopamine catechol-O-methyltransferase (COMT) Val158Met and dopamine transporter 1 (DAT1) variable number of tandem repeat (VNTR) polymorphisms by previously reported methods (Arnold *et al.*, 2016) to control whether the effects shown in this study could be explained by chance by similarly distributed functional dopaminergic polymorphisms rather than oxytocinergic neuromodulation (Supplementary Table 1).

Speech production task

The experiment involved a speech production fMRI task adapted from Arnold *et al.* (2016). Participants were instructed to read sentences either with happy or neutral prosody or to read the sentences covertly with neutral intonation (Figure 1). Covert reading served as the cognitive baseline. Prior to the presentation of sentences, a schematic face indicated to prepare to read the following target sentence, either with happy or neutral intonation or covertly (Figure 1). To dissociate the preparation of the speech network from actual speech production, the instruction delay was jittered between 2 and 4 s (discrete uniform distribution). Because specific speech planning was impossible during the preparation

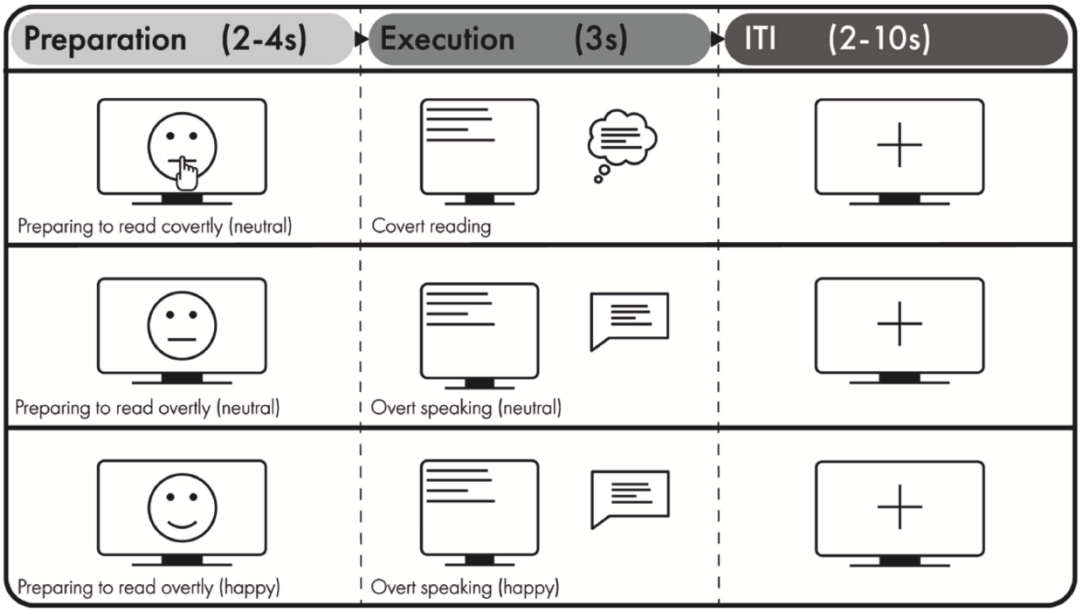

Fig. 1. Experimental protocol. Participants read sentences covertly with neutral intonation or generated either neutral or happy prosody. In each trial, participants were cued with the emotion to be produced and were given a varying preparatory time (preparation phase), after which an emotionally neutral sentence was displayed in the center of the screen and was read covertly or overtly (execution phase/speaking). The inter-trial interval varied from 2 to 10 s.

phase, activity observed during this trial phase reflects only intention to speak and induction of emotional state (Pichon and Kell, 2013). After preparation, 1 out of 15 declarative German sentences with neutral content and identical syntactical structure was presented for 3 s, e.g. 'Dieser Mann betritt einen Raum', translated to 'This man enters a room'. Each of the sentences appeared three times in a randomized order and had to be read directly after display either covertly or overtly with neutral and happy intonation, depending on the instruction. This resulted in a total duration of 18 min with one short break.

To familiarize participants with the experimental setting, they practiced the speech production task with a different set of sentences outside of the scanner. These recordings were analyzed regarding both acoustics and perceptual consequences (see the Supplementary Data for detailed results). Methods for the perceptual and acoustic analyses (mean of intensity contours, mean of second format frequency and standard deviation of fundamental frequency) are reported in the Supplementary Data, as are the assessment of empathy, mood and anxiety and emotional faces recognition.

Functional imaging

Data acquisition

Data were acquired using a 3T Magnetom TIM Trio scanner (Siemens Trio, Erlangen, Germany). For each subject, 564 functional volumes of gradient-echo T2*-weighted transverse echo-planar images (EPIs) were acquired at each appointment. Every volume included 33 axial slices with a repetition time (TR) of 2000 ms, an echo time (TE) of 30 ms, a flip angle of 90°, an isotropic voxel size of $3 \times 3 \times 3\,mm^3$, a distance factor of 25% and a slice thickness of 3 mm. A high-resolution T1-weighted MPRAGE (160 slices, TR 2250 ms, inversion time 900 ms, TE 2.6 ms, flip angle 9°, voxel size $1 \times 1 \times 1\,mm^3$, slice thickness 1 mm and distance factor 50%) was acquired. Participants were supine with their head stabilized by foam cushions. Sentences and the fixation cross were presented visually on a screen that participants watched via a coil-mounted mirror using the Presentation® software (Neurobehavioral Systems, Inc., Berkeley, CA, RRID: SCR_002521). Audio-recordings of the acoustic data were assessed with an MRI-compatible microphone (mr confon) to control for behavior inside the scanner. During resting state, participants were instructed to have their eyes open during the measurement and fixate a white cross on black background while 178 volumes were obtained (TR = 2000 ms, TE = 30 ms, flip angle = 90°, 30 axial slices and 3 mm^3 isotropic voxel size).

fMRI image processing

The spatial preprocessing pipeline used standard statistical parametric mapping (SPM) parameters (SPM12, RRID: SCR_007037) complemented by additional steps to account for possible motion due to speaking. The pipeline encompassed the realignment of functional images using rigid body transformation. Subject's individual structural scans were co-registered with the mean functional image of the realignment step. To account for motion artifacts due to speaking, a smoothing step with an isotropic 4-mm full-width at half-maximum (FWHM) Gaussian kernel was added in order to prepare images for additional motion adjustment with ArtRepair (Mazaika *et al.*, 2009; Floegel *et al.*, 2020). Motion adjustment of the functional images with ArtRepair is commonly used in speech production fMRI experiments and represents the state of the art procedure to reduce interpolation errors from the realignment step. All functional images were spatially normalized to the standard EPI template of the Montreal Neurological Institute (MNI) and smoothed with an isotropic 7-mm FWHM Gaussian kernel.

fMRI whole-brain analysis

For analysis of individual event-related blood oxygenation level dependent (BOLD) responses, the SPM general linear model (GLM) contained six regressors that were each convolved with the hemodynamic response function. The first three regressors modeled the preparation phase (preparation to read either overtly with happy or neutral intonation or covert reading), while the other three regressors modeled the execution phase (covert, neutral and happy reading) with their respective durations. The six movement regressors resulting from the realignment preprocessing step were included as conditions of no interest. We were particularly interested in the effects that oxytocin has on the communicative aspects of both neutral speech and prosody production and its sensorimotor implementation. Neutral speech was investigated by contrasting overt reading with neutral intonation with the cognitive baseline covert reading, and emotional speech was assessed by contrasting generation of happy prosody with the same cognitive baseline. This resulted in overall four condition contrasts in single subjects: preparation_neutral > preparation_covert (prep_neutral), preparation_happy > preparation_covert (prep_happy), as well as execution_neutral > execution_covert (exe_neutral) and execution_happy > execution_covert (exe_happy). We corrected the data for serial autocorrelations (AR1) and globally normalized them, such that negative BOLD responses observed in our fMRI data do not necessarily reflect deactivations but rather have to be interpreted as reduced activity compared to the global mean (Arnold *et al.*, 2016).

Statistical analysis of fMRI data

Group analyses

We conducted a 2×2×4 mixed effect analysis of variance (ANOVA) in GLM Flex Fast2 (Schultz, 2014) consisting of the between-subject factor OXTR rs53576 polymorphism (AA/AG genotypes *vs* GG genotype) and the two within-subject factors drug (oxytocin *vs* placebo) and condition contrasts (prep_neutral > prep_covert, prep_happy > prep_covert, exe_neutral > exe_covert and exe_happy > exe_covert). Whole-brain statistical maps were corrected for multiple comparisons using standard false discovery rate (FDR correction at $P < 0.05$ on the cluster level using a cluster-forming threshold of $P < 0.001$, uncorrected). Significant clusters were displayed using MRIcron v2.1.51-0 (MRIcron, RRID: SCR_002403) and anatomically labeled using standard atlases for cortical (Eickhoff *et al.*, 2005) and subcortical clusters (Tziortzi *et al.*, 2014; Pauli *et al.*, 2018). Effect sizes (partial η^2, calculated using the IBM statistical package for social sciences (SPSS) (RRID: SCR_00286)) are reported for the basal ganglia clusters.

Functional connectivity analysis

We conducted psychophysiological interaction (PPI) analyses (Friston *et al.*, 1997) as implemented in the functional connectivity (CONN) toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012. RRID: SCR_009550) to assess changes in functional connectivity during preparation and execution of neutral and happy prosodies (> covert reading) that were modulated by the administration of oxytocin or the rs53576 OXTR polymorphism.

Each voxel's time series was denoised and adjusted for potential effects of physiological noise and motion by linear detrending at the single-subject level. Physiological noise was removed using the anatomical component-based noise correction method (aCompCor) and five orthogonal time courses in subject-specific white matter and cerebrospinal fluid signal (Behzadi *et al.*, 2007). Furthermore, the subject-specific motion parameters and their first derivative (scan-to-scan motion) as well as task effects were regressed out (Whitfield-Gabrieli and Nieto-Castanon, 2012). BOLD signal time series were then filtered with a 0.008-Hz high-pass filter.

Because critical oxytocin pathway genes are enriched in subcortical regions (Quintana *et al.*, 2019) and oxytocin modulates subcortical–cortical functional connections (Bethlehem *et al.*, 2017; Zhao *et al.*, 2019), we performed subcortical-seed-to-cortical-region of interest (ROI) functional connectivity analyses for two basal ganglia seeds. Seeds and ROIs for the seed-to-ROI analyses consisted of 5-mm spheres centered on group activation maxima for significant (I) drug–condition and (II) drug–polymorphism–condition interactions.

The first basal ganglia seed was the right ventral pallidum where speaking-related brain activity was affected by intranasal oxytocin administration (significant drug–condition interaction). Functional connectivity changes were assessed between the right ventral pallidum and a subset of cortical regions that also showed activity changes upon oxytocin administration and that have been related previously to oxytocinergic neuromodulation (Riem *et al.*, 2011; Gordon *et al.*, 2013; Aoki *et al.*, 2014; Scheele *et al.*, 2014; Hu *et al.*, 2016; Bethlehem *et al.*, 2017; Li *et al.*, 2017; Spetter *et al.*, 2018; Kumar *et al.*, 2020). These cortical regions included the left inferior frontal gyrus (IFG) pars orbitalis, left insula, left temporo-parietal junction (TPJ) and left and right dorsolateral prefrontal cortex (DLPFC), as well as right frontopolar cortex, right articulatory motor cortex, right supplementary motor area (SMA) and bilateral dorsal premotor cortices (dPMCs). For each participant, seed-based connectivity maps were generated by calculating multivariate regression between the average seed time series and the ROIs. Twelve GLMs (2 drug×6 conditions) were defined. Each contained the PPI regressor and the regressors of no interest mentioned earlier. To assess pallido-cortical functional connectivity, the group-level GLM contained two regressors representing connectivity maps under oxytocin and placebo and four condition contrast regressors consisting of preparation_neutral > preparation_covert (prep_neutral) and preparation_happy > preparation_covert (prep_happy), as well as execution_neutral > execution_covert (exe_neutral) and execution_happy > execution_covert (exe_happy).

For the second seed-to-ROI analysis, the right ventral striatum served as a seed, where speaking-related brain activity was affected by not only intranasal oxytocin administration but also the rs53576 OXTR polymorphism. In this second seed-to-ROI analysis, cortical ROIs were selected that showed a significant drug–polymorphism–condition interaction on the group level. The selected regions were also previously shown to be modulated by oxytocin and included the right precuneus, right middle frontal gyrus, right posterior superior temporal gyrus, right and left somatosensory regions and right and left cerebellum (Kumar *et al.*, 2014; Eidelman-Rothman *et al.*, 2015; Mitre *et al.*, 2016; Grinevich and Stoop, 2018; Zhao *et al.*, 2019; Kumar *et al.*, 2020). Because here, we were interested in speaking-related changes in functional connectivity due to oxytocin that differed as a function of the rs53576 OXTR polymorphism, the group-level GLM had one additional factor, the OXTR rs53576 genotype. All connectivity results were reported at $P < 0.05$ (FDR-corrected). Effect sizes (Cohen's *d*) are reported for significant PPIs.

RSFC

We tested whether the administration of oxytocin affects functional connectivity even after task performance, leaving traces

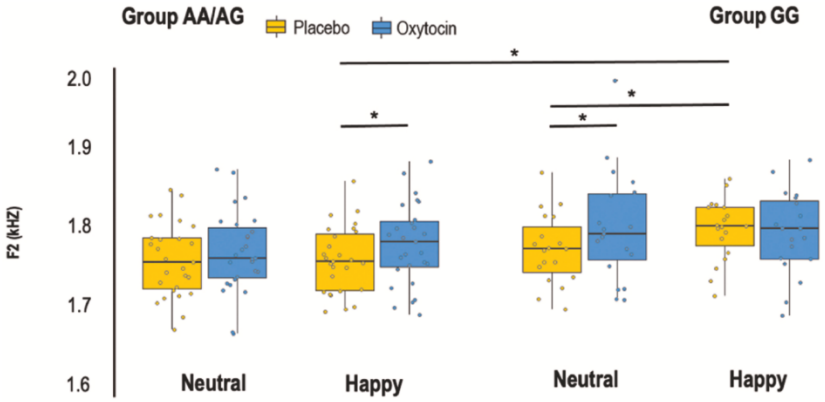

Fig. 2. Effects of oxytocin on the second formant of produced vowels. Oxytocin increased the frequency of the second formant (f_2) of produced vowels (main effect of drug). There was an additional drug–condition–polymorphism interaction. When producing happy speech under placebo, GG homozygotes showed higher values compared to their own neutral speech and carriers of the A allele. AA/AG genotypes increased their second formant frequency when producing happy speech under the influence of oxytocin, an effect that was not observed in GG homozygotes.

of oxytocinergic neuromodulation in RSFC (Floegel *et al.*, 2020). RSFC of subcortical–cortical circuits at rest was analyzed with the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012. RRID: SCR_009550). Images were spatially preprocessed and denoised with the same preprocessing pipeline described earlier. A bandpass filter was set to 0.008–0.09 Hz to isolate low-frequency fluctuations (Whitfield-Gabrieli and Nieto-Castanon, 2012). Due to technical problems, resting state data of only 41 subjects were analyzed.

For each participant and each resting state run (placebo and oxytocin), seed-to-seed connectivity maps were generated by calculating multivariate regression between the average seed time series for connections that showed significant task-related PPI changes. The selected seeds were thus the right ventral pallidum and the left DLPFC. The second level GLM contained two regressors representing RSFC in the resting state runs on oxytocin and on placebo. Results were reported at $P<0.05$ (FDR correction). Effect sizes (Cohen's *d*) are reported for significant RSFC.

Results

Participants were not able to correctly identify whether they received oxytocin or placebo ($\chi^2=0.43$, $P=0.513$). Hence, oxytocin effects could not be explained by subjective beliefs or expectations.

To assure that the observed oxytocinergic polymorphism effects (see later) were not a result of a by-chance similar distribution of polymorphisms that have previously been linked with dopaminergic modulation of speech production (Arnold *et al.*, 2016), we tested the distribution of the dopaminergic genetic polymorphisms DAT1 VNTR 9/10 and COMT Val156Met, coding for transporters and degrading enzymes in the dopaminergic system, in our sample. The distribution of the OXTR polymorphism did not correspond to the distribution of the DAT1 or COMT polymorphisms (Supplementary Table 1).

Behavioral results

Acoustic analysis of speech data

Participants adequately modulated speech when speaking with happy intonation inside and outside of the scanner. Mean speech amplitude measured outside the scanner (see the *Acoustic analysis of speech data outside the scanner* section in the Supplementary Data) was much stronger when producing happy prosody than when speaking neutrally [main effect of condition on mean speech amplitude: $F_{(46)}=235.8$, $P<0.001$, partial $\eta^2=0.79$]. Participants modulated their fundamental frequency (f_0) more strongly when speaking happily [main effect of condition on the standard deviation of f_0: $F_{(46)}=16.2$, $P<0.001$, partial $\eta^2=0.27$]. Neither oxytocin administration nor OXTR genotypes affected intensity contours or fundamental frequencies of participants' utterances significantly (all $P>0.05$). However, oxytocin administration increased the frequency of the second formant (f_2) of produced vowels [main effect of drug: $F_{(46)}=5.09$, $P=0.029$, medium effect size with partial $\eta^2=0.1$] with an additional three-way interaction between drug, condition and polymorphism [$F_{(46)}=8.72$, $P=0.005$, partial $\eta^2=0.17$]. Oxytocin increased f_2 particularly during the production of happy speech in carriers of the A allele [$T_{(27)}=2.54$, $P=0.017$, Cohen's $d=0.48$] but not in GG homozygotes [$T_{(19)}=0.42$, $P=0.681$], while GG homozygotes showed higher values for f_2 producing happy speech under placebo compared to group AA/AG [$T_{(46)}=3.21$, $P=0.003$, Cohen's $d=0.95$] and compared to their own neutral speech [$T_{(27)}=3.02$, $P=0.007$, Cohen's $d=0.69$] (Figure 2). f_2 frequencies were also higher under oxytocin administration when speaking neutrally [AA/AG: $T_{(27)}=0.99$, $P=0.333$, GG: $T_{(19)}=2.71$, $P=0.014$, Cohen's $d=0.62$].

Perceptual analysis of speech data

In a forced choice valence rating study with 10 naïve raters, no rater consistently differentiated between sentences recorded after oxytocin or after placebo administration. A Bayesian multilevel logistic regression provided weak evidence for the absence of an effect of oxytocin nasal spray on perceivable valence, independent of instructed intonation. The only consistent effect was that recordings of AA homozygote speakers from the second session were on average rated as more positive than recordings from the first session independent of oxytocin administration with a probability of 59% [89% credible interval: (54%, 63%), reflected in a probability of direction of 98% for a treatment order effect and of 96% for an interaction of treatment order with OXTR polymorphism]. Five raters (four females) consistently rated utterances spoken with the 'happy' instruction as more positive than sentences

Table 1. Brain regions showing a significant drug–condition interaction

	Drug– condition interaction	MNI coordinates				
Right/Left	**Anatomical region**	**x**	**y**	**z**	***F* value**	**Cluster size**
R	Ventral pallidum	20	−8	−4	8.25	18
R	Frontopolar cortex	30	42	2	11.04	195
L	Dorsomedial prefrontal cortex	−10	40	28	8.11	16
L	IFG—pars orbitalis	−36	36	−10	9.21	87
R	Middle frontal gyrus	30	36	26	9.12	35
L	DLPFC	−36	18	48	11.69	47
R	DLPFC	32	18	40	12.21	128
L	Dorsal premotor cortex	−34	−16	46	8.63	30
R	Dorsal premotor cortex	42	−10	62	7.59	11
R	SMA	16	−12	56	7.34	12
L	Insula	−28	16	−2	11.17	29
R	Articulatory motor cortex	44	−6	30	9.54	68
L	TPJ	−52	−22	26	8.43	12
R	Middle temporal gyrus	62	−20	−22	10.11	44

$P < 0.05$ FDR cluster level corrected with a cluster-forming threshold of $P < 0.001$, uncorrected.

Table 2. Regions showing a significant drug–polymorphism–condition interaction

	Drug–condition–polymorphism interaction	MNI coordinates				
Right/Left	**Anatomical region**	**x**	**y**	**z**	***F* value**	**Cluster size**
R	Ventral striatum	30	−6	−8	8.16	18
L	Mesencephalon	−12	−20	−8	10.11	41
R	Middle frontal gyrus	32	42	22	11.07	136
R	Middle cingulate gyrus	0	−10	32	7.71	11
R	Postcentral sulcus	50	−28	44	13.38	102
R	Postcentral sulcus	30	−34	58	9.6	104
L	Postcentral sulcus	−46	−36	44	11.3	113
R	Secondary somatosensory cortex	66	−18	20	9.07	36
R	Posterior superior temporal gyrus	68	−38	12	7.84	17
L	Superior cerebellar hemisphere	−18	−56	−14	9.31	37
R	Superior cerebellar hemisphere	28	−56	−18	8.16	18
R	Superior cerebellar hemisphere	16	−70	−14	10.94	101
R	Precuneus	8	−58	48	8.4	18
R	Precuneus	22	−64	24	9.18	62

$P < 0.05$ FDR cluster level corrected with a cluster-forming threshold of $P < 0.001$, uncorrected.

spoken with neutral intonation, while two raters exhibited the opposite preference and three did not display consistent preferences for either instruction (for details, see the *Perceptual analysis of speech data outside the scanner* section in the Supplementary Data and Supplementary Figure B-G).

fMRI results

Both preparatory and speaking-related brain activities were modulated by oxytocin (Figures 3 and 5). While there was no main effect of drug administration or of the OXTR rs53578 polymorphism, there were significant interactions between drug–condition (Table 1) and drug–polymorphism–condition (Table 2) interactions.

Drug–condition interactions in speech-related brain activity

Oxytocin administration modulated brain activity in subcortical and cortical regions when preparing to speak neutrally and happily, as well as during speaking with both neutral and happy intonation (all $P < 0.05$; FDR cluster level–corrected, Table 1 and Figure 3). Subcortically, in the caudal part of the right ventral pallidum, where the OXTR is highly expressed (Quintana *et al.*, 2019), oxytocin administration enhanced activity compared to placebo when preparing to speak neutrally or happily (*vs* preparing to read covertly) (Figure 3). Cortical regions affected by oxytocin included not only sensorimotor speech regions like the left anterior insula, right articulatory motor cortex (slightly ventral to the dorsal laryngeal motor cortex), the left TPJ, the dPMC or the voice-sensitive right middle temporal gyrus but also executive control regions in the prefrontal cortex like the DLPFC and the limbic part of the left IFG (Figure 3, Table 1; Supplementary Figure H). Regions that under placebo were solely active during actual speaking (*vs* covert reading) showed increased activity during speech preparation (*vs* preparation to read covertly) when participants were under the influence of administered oxytocin. These regions showed a mirror image during actual speaking (*vs* covert reading) when oxytocin diminished activity (Figure 3; Supplementary Figure H). Observed changes were not specific to the preparation for and generation of happy prosody but were equally observed for speaking with neutral intonation (Figure 3; Supplementary Figure H).

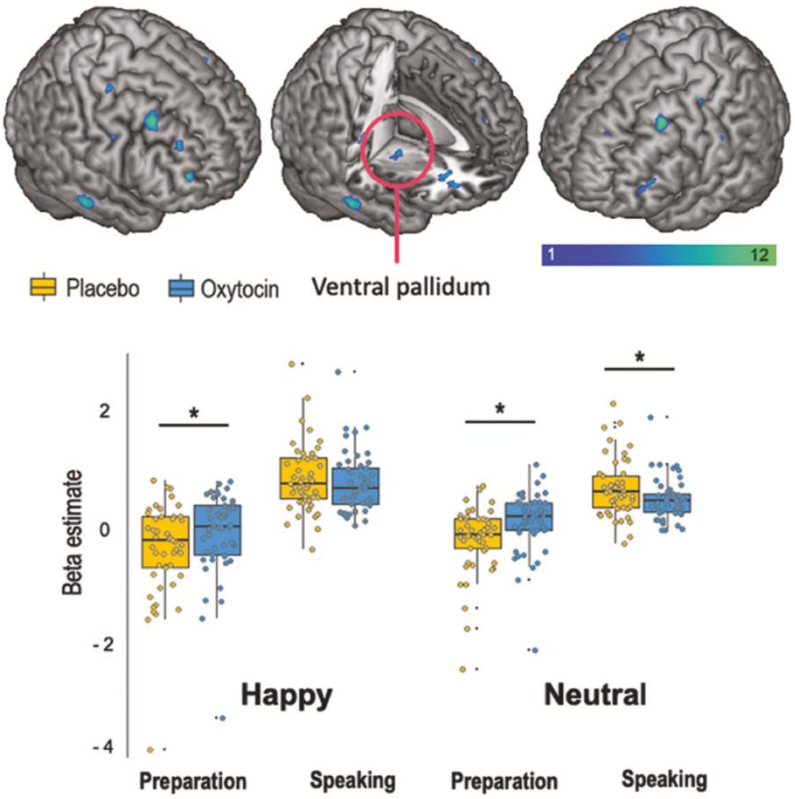

Fig. 3. Drug–condition interactions in speech-related brain activity. Oxytocin increased brain activity during speech preparation, while it diminished activity during speaking, independent of intonation. Clusters of voxels showing a significant drug–condition interaction are thresholded at $P<0.05$; FDR cluster level–corrected (color scale codes F-values). The lower panel illustrates activity in the right ventral pallidum, where oxytocin increased brain activity when preparing to speak happily and with neutral intonation [$F_{(48)}=8.25$, partial $\eta^2=0.16$]. This profile was equally observed in the other clusters (Supplementary Figure H). The box plots span the interquartile range, and the median of participants activation estimates (grand-mean centered) is marked by the vertical line. Whiskers represent the upper and lower quartiles.

Drug–condition interactions in speech-related pallido-cortical functional connectivity

Neuromodulation not only concerns brain activity but can also modulate interactions between brain regions (Friston *et al.*, 1997; Arnold *et al.*, 2016). We thus compared task-related functional connectivity with and without administration of oxytocin between the right ventral pallidum and cortical ROIs that showed increased preparatory activity upon oxytocin administration and have previously been linked to oxytocinergic neuromodulation. Oxytocin gated pallido-cortical circuits during speech preparation (Figure 4). After the administration of the neuromodulator, preparatory functional connectivity between the right ventral pallidum and the left DLPFC [$t_{(48)}=3.07$, $P=0.032$, FDR-corrected, Cohen's $d=0.44$] was enhanced (preparing to read happily *vs* preparing to read covertly). During actual speaking with happy intonation (*vs* covert reading), this effect was reversed and functional connectivity between the right ventral pallidum and the left DLPFC [$t_{(48)}=3.37$, $P=0.014$, FDR-corrected, Cohen's $d=0.49$] decreased compared to placebo.

Drug effects in resting-state pallido-cortical functional connectivity

To assess whether oxytocin-related changes in functional connectivity outlasted task performance, we investigated whether oxytocin also modulated RSFC measured at the end of the experiment between those regions that showed oxytocin effects on speaking-related PPIs. Compared to placebo, oxytocin administration indeed enhanced RSFC measured after completion of the task session between the right ventral pallidum and the left DLPFC [$t_{(40)}=1.94$, $P=0.03$, Cohen's $d=0.31$].

Drug–condition–polymorphism interactions in speech-related brain activity

Several brain regions, particularly in the right hemisphere, showed a triple interaction between oxytocin, the rs53576 OXTR polymorphism and condition. Subcortically, the limbic/executive control part of the right ventral striatum showed such an interaction. Cortical areas showing a significant triple interaction between drug–polymorphism–condition included not only the voice-sensitive right posterior superior temporal gyrus and the right precuneus and middle frontal gyrus, but also cortical limbic, somatosensory and cerebellar regions (all $P<0.05$; FDR cluster level–corrected, Table 2, Figure 5; Supplementary Figure I).

In all regions, only carriers of the A allele showed enhanced preparatory brain activity under oxytocin administration independent of prosody type, while the respective activity reduction during actual speaking was subthreshold (Figure 5; Supplementary Figure I). This effect was not observed in GG homozygotes.

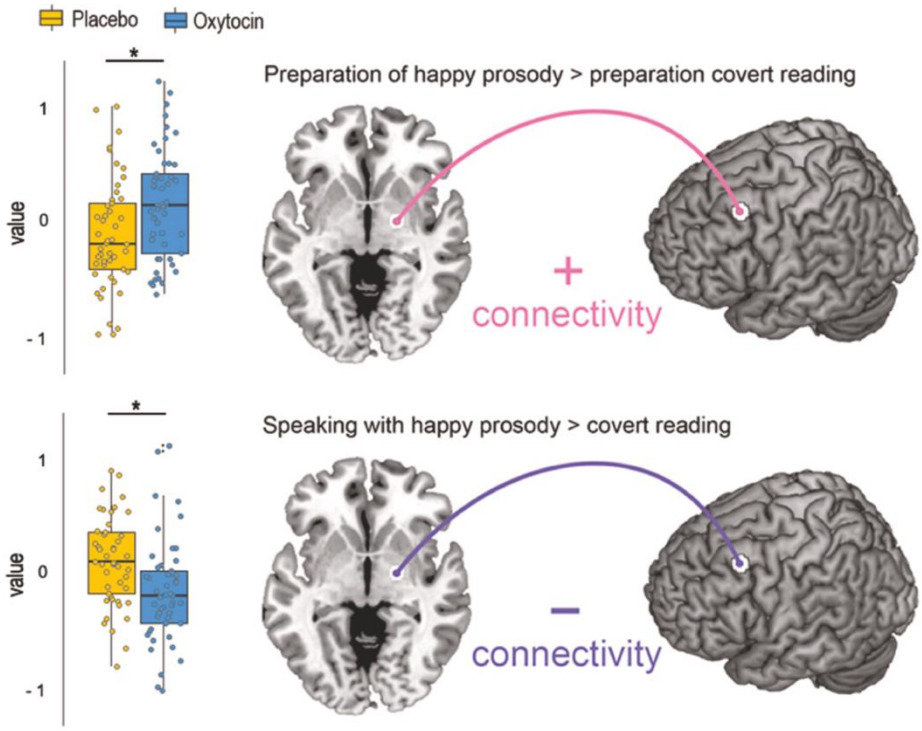

Fig. 4. Oxytocin-related changes in speech-related functional connectivity. (A) During preparation for happy prosody (*vs* preparation to read covertly), oxytocin increased functional connectivity between the right ventral pallidum and the left DLPFC [$t_{(48)} = 3.07$, $P = 0.032$, FDR-corrected, Cohen's $d = 0.44$]. (B) During generation of happy prosody (*vs* reading covertly), participants showed lower functional connectivity between right ventral pallidum and the left DLPFC [$t_{(48)} = 3.37$, $P = 0.014$, FDR-corrected, Cohen's $d = 0.49$] compared to placebo.

Drug–condition–polymorphism interactions in striato-cortical functional connectivity

PPIs between the right ventral striatum and cortical ROIs did not show a significant interaction between oxytocin administration and the rs53576 OXTR polymorphism (all $P > 0.05$, FDR-corrected).

Discussion

We demonstrated a modulation of acoustic speech parameters during overt reading by oxytocin administration, an effect that was previously observed during free speech (Agurto *et al.*, 2020). Oxytocin administration increased the second formant (f_2) of produced vowels with minor differences between the OXTR rs53576 polymorphism groups. Especially in carriers of the A allele, with the presumably less efficient oxytocinergic signaling, oxytocin increased f_2 of produced vowels. Under placebo, GG homozygotes had higher f_2 frequency when speaking happily compared to AA/AG genotypes. Higher f_2 frequencies have been associated with fronting of articulation (Podesva *et al.*, 2015) and increases when smiling (Tartter, 1980; Podesva *et al.*, 2015). Consequently, higher f_2 frequencies have been associated with positive valence (Goudbeek *et al.*, 2009). However, the f_2 modulation in our data could not be perceived by blinded raters. Mappings between singular speech features, like f_2, and emotions are very inconsistent and should not be oversimplified (van Rijn and Larrouy-Maestri, 2023), which could explain our negative finding on the perceptual level. While in our experimental setting, oxytocin influenced only the acoustics of produced speech, it could also affect speech on the perceptual level in a more communicative context. Indeed, endogenous oxytocin levels increase during social dialogue (depending on sex and the relation between dialogue partners), suggesting a complex modulation in communicative contexts by the neuropeptide (Djalovski *et al.*, 2021).

The here shown effects of exogenous administered oxytocin on phonetic speech features were mirrored by modulation of task-related brain activity and functional connectivity. Oxytocin administration gated activity of a few subcortical and cortical sensorimotor brain regions, limbic areas and brain regions involved in executive control. Sensorimotor speech regions included both parts of the feedforward and feedback control system of speaking (Belin *et al.*, 2011; Tourville and Guenther, 2011; Floegel *et al.*, 2020, 2023). Most of the sensorimotor speech regions that were modulated by oxytocin make part of the dorsal speech processing streams, regions that are critical for speech production (Murakami *et al.*, 2015; Kell *et al.*, 2017). In the ventral speech processing streams, oxytocinergic modulation was largely restricted to the right hemisphere, the hemisphere specialized in spectral speech processing (Albouy *et al.*, 2020; Floegel *et al.*, 2020). Our findings suggest that oxytocin increases monitoring of self-produced spectral speech features, an idea that is compatible with the documented changes in f_2 and previous reports of oxytocin-related activity enhancement in the voice-sensitive right superior temporal cortex (Borowiak and Kriegstein, 2020). A right-hemispheric interaction between temporal regions that are particularly sensitive to spectral speech features and frontal motor-related cortices could underlie the observed

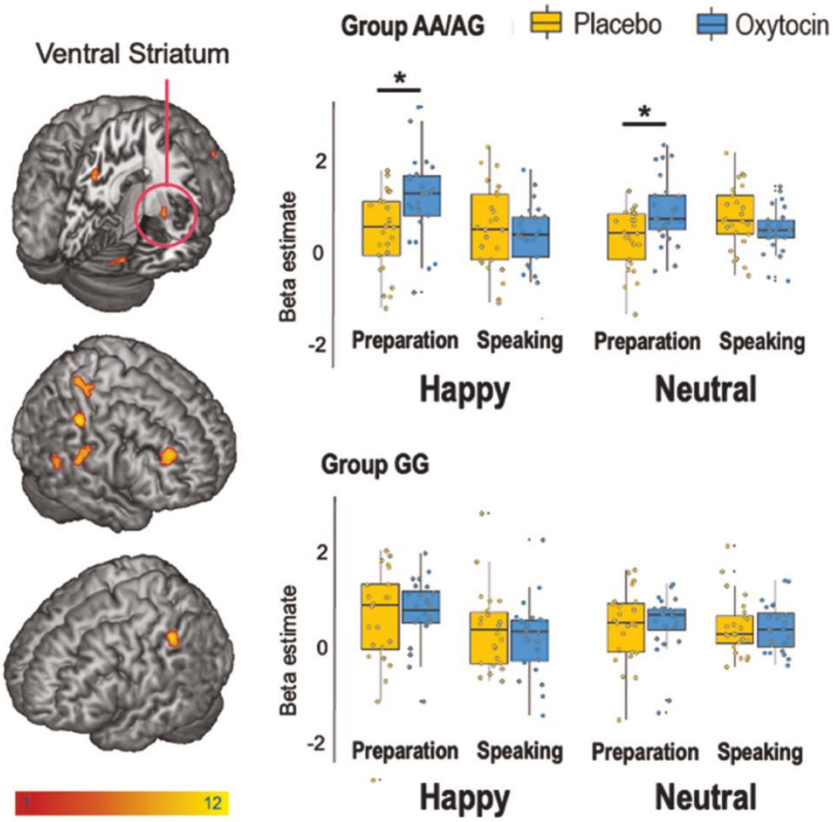

Fig. 5. Drug–condition–polymorphism interactions in speech-related brain activity. Clusters showing a significant drug–polymorphism–task interaction are thresholded at $P < 0.05$; FDR cluster level–corrected (color scale codes *F*-values). The right panels illustrate activity in the right ventral striatum, where only carriers of the A allele increased preparatory activity, for speaking with both neutral and happy intonation [$F_{(48)} = 8.16$, partial $\eta^2 = 0.07$]. This profile was equally observed in the other clusters (Supplementary Figure I). The box plots span the interquartile range, and the median of participants activation estimates (grand-mean centered) is marked by the vertical line. Whiskers represent the upper and lower quartiles.

oxytocinergic modulation of produced speech spectra. The modulation of functional connectivity between the ventral pallidum and DLPFC could reflect the limbic control of speech production (Pichon and Kell, 2013). Because oxytocin increased activity and speaking-related functional connectivity particularly during speech preparation, we interpret the oxytocin effect as gating of speech-relevant computations including executive control and limbic and sensorimotor processing. It is tempting to speculate that these oxytocin-related processes reflect social cognition. However, reducing the role of oxytocin in social functions would be oversimplified. Increases in oxytocin levels have been associated with processes beyond social cognition, i.e. exercising and sexual self-stimulation (Hew-Butler *et al.*, 2008; Jong *et al.*, 2015).

Some of the brain regions were not only responsive to oxytocin administration but also showed an interaction with the rs53576 OXTR polymorphism. In these regions, oxytocin increased preparatory activity only in carriers of the A allele in the OXTR rs53576 polymorphism, while GG homozygotes showed a ceiling effect in activation (Bartz *et al.*, 2019). GG homozygotes are thought to have more efficient oxytocin neuromodulation (Bakermans-Kranenburg and van Ijzendoorn, 2008; Tops *et al.*, 2011; Cataldo *et al.*, 2020), and therefore, additional oxytocin administration may not be required for further gating. Our findings are consistent with research in clinical samples, where especially individuals with less proficient social behaviors benefit from oxytocin administration (Bartz *et al.*, 2019).

Gating was not restricted to regional activation but was also observed for cortical–subcortical interactions. Particularly in the preparation for happy intonation, oxytocin affected cortical-basal ganglia circuits. Oxytocin modulates such circuits in various contexts and species (Li *et al.*, 2015; Mitre *et al.*, 2016; Bethlehem *et al.*, 2017). The ventral pallidum is part of the limbic subcortical territory (Simonyan, 2019). It connects to the prefrontal cortex (Smith *et al.*, 2009) and plays an important role in translating limbic signals to motor output (Mogenson and Yang, 1991; Pichon and Kell, 2013). Basal ganglia oxytocin can affect functional networks throughout the central nervous system (Bethlehem *et al.*, 2017; Quintana *et al.*, 2019). The fact that oxytocin modulated not only the ventral pallidum's speech-related functional connectivity but also its subsequent RSFC suggests that oxytocinergic modulation is not restricted to phases of actual speaking, but affects cortico-basal ganglia circuits more profoundly.

The gating of preparatory pallido-cortical functional connectivity with subsequent diminished coupling during task execution was reminiscent of dopamine effects on speech production (Arnold *et al.*, 2016). Efficient preparation of cortical-basal ganglia circuits may result in diminished processing requirements during actual speaking, which seems to be true for both dopaminergic

and oxytocinergic neuromodulation. Oxytocin pathway genes are highly co-expressed with several dopaminergic genes, like COMT, potentially reflecting the anatomical basis for functional interactions (Quintana *et al.*, 2019) and dopamine and oxytocin pathways converge in the prefrontal cortex and ventral striatum (Smeltzer *et al.*, 2006), both of which are involved in the regulation of social behaviors, such as speech production (Pichon and Kell, 2013). To investigate such interactions, larger samples are needed than the one studied here.

Limitations

Due to known menstrual cycle–related changes in sex hormones and their influence on OXTR densities throughout the brain, we investigated only male participants. This limits the generalizability, especially since sexual-dimorphic effects have been documented in various contexts (Lieberz *et al.*, 2020; Schiller *et al.*, 2023). Ecological validity could be increased to investigate speech production in a more social context.

Supplementary data

Supplementary data are available at *SCAN* online.

Data availability

Data are available at https://neurovault.org/.

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Conflict of interest

The authors declared that they had no conflict of interest with respect to their authorship or the publication of this article.

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4. Darstellung des eigenen Anteils

Unter der Supervision meines Betreuers erstellt ich das Studiendesign, rekrutierte ich die notwendigen Probanden, führte die fMRT-Messungen durch, analysierte, interpretierte und visualisierte ich die Daten, verfasste ich die Publikation und veröffentlichte diese in *Social Cognitive and Affective Neuroscience.*

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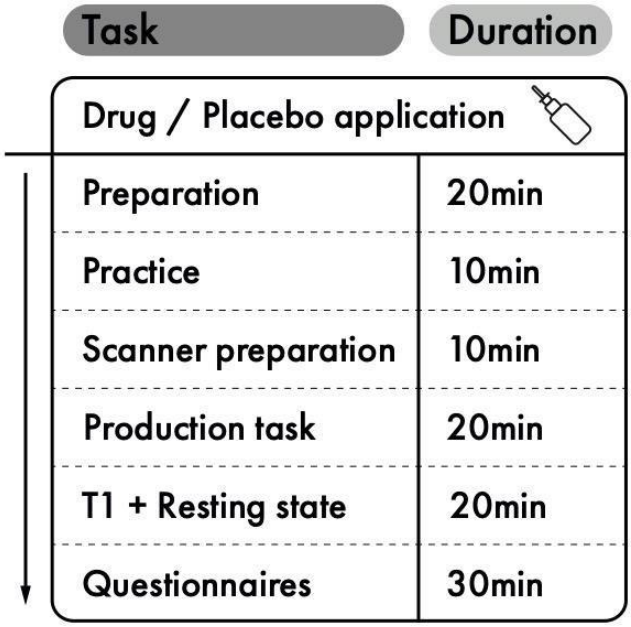
6. Weiteres Manuskript

Supplementary Material

Figure A. Experimental timeline. Participants initially received either intranasal oxytocin (24 IU oxytocin) or a placebo. Then, they filled out an MRI safety form and were familiarized with the scanner environment. After explaining the task, participants practiced it with a different set of sentences outside of the scanner, roughly 20 minutes after intranasal administration. Participants were then placed supine in the scanner with their head stabilized by foam cushions. After 40 minutes of preparation and practice, MRI sessions started. Following the functional runs, anatomical imaging and resting state measurement took place. Outside the scanner, participants fill out empathy and mood questionnaires for about 30 minutes.



Acoustic analysis of speech data outside the scanner

For acoustic analyses, utterances of the practice set of sentences were audio-recorded with a standard microphone (Philips SHM 7410 Stereo-PC-Headset in 6cm distance) using Adobe Audition with a sampling rate of 44.1 kHz (RRID: SCR_015796). Six datasets had to be excluded from behavioral analyses due to contamination with background noise. To analyze how much participants modulated their voices, intensity contours (dB) and fundamental frequencies (Hz) were extracted (Arnold et al., 2014; Arnold et al., 2016; Pichon & Kell, 2013) using PRAAT (Boersma, 2001).

Pitch was obtained using the autocorrelation method in Praat software with a pitch floor of 75 Hz and a pitch ceiling of 600Hz (timesteps of 5ms). We further extracted each sentence's intensity contour and obtained mean values in decibels (dB). Based on a recent report that oxytocin affected the second formant during free speech (Agurto et al., 2020), we additionally extracted this speech parameter from the recorded samples. A pre-emphasis filter at 50 Hz was applied; maximum formant frequency was kept with standard PRAAT settings at 5.5 kHz. Sentences were grouped according to the condition (neutral and happy) and experimental factors (oxytocin vs. placebo and OXTR polymorphism genotypes AA/AG vs. GG). We obtained the parameters' mean and standard deviation and performed three-way mixed ANOVAs with two within-subject factors, drug (two levels: placebo and oxytocin) and condition (two levels: neutral and happy) and the genotype of the rs53576 OXTR polymorphism as a between-subject factor (2 levels: AA/AG genotypes and GG genotype). Dependent variables were mean of intensity contours (dB), mean of second format frequency (Hz) and standard deviation of fundamental frequency (Hz). To report effect sizes, we calculated partial η^2 for main effects and interactions and Cohen's d for t-tests using SPSS (SPSS, RRID: SCR_002865).

Perceptual analysis of speech data outside the scanner

Oxytocin increased the second formant (f_2) of produced vowels. An increase in frequency of f_2 has been associated with positive valence (Goudbeek et al., 2009). To investigate whether oxytocin shifted neutral and happy utterances towards a more positive valence, we collected perceptual ratings of 5 female and 5 male raters (aged between 23 and 40, mean age 30.3 years) who rated utterances of all participants (n=45) according to their perceived valence in a 2-interval forced choice paradigm. We further tested whether the instruction to produce happy speech resulted in more positively sounding utterances compared to the neutral condition.

Preprocessing of stimuli

The stimuli consisted of 5 different sentences each spoken under the two instructions (neutral/happy) and in two treatment (oxytocin/placebo) sessions, that were recorded before the fMRI measurements outside of the scanner. To reduce confounds of the audio recording (for recording details see *Acoustic analysis of speech data outside the scanner*), we performed robust loudness normalization by the RMS of the A-weighted spectrogram between 60 and 10000 Hz. The recordings were manually split per sentence and the resulting pieces automatically stripped of any periods not containing any speech signals from either end. Finally, the recordings were labeled using automatic speech recognition software and fuzzy template matching in Python.

Perceptual ratings

To evaluate oxytocin effects on perceived valence, each rater was presented with 3-4 sentence pairs per speaker and instruction, randomly chosen from the 5 different sentences, yielding a total of 298 sentences paired for drug (oxytocin/placebo; treatment pairs), including 30 replications. To test whether happily intonated sentences were perceived as more positive, a total of 89 neutral/happy sentences were paired (condition pairs). Using functionality from the PsychoPy toolbox (Peirce et al., 2019), raters were asked to indicate which of the two sentences in a dyad they perceived as more positive by pressing the left and right arrow key for the first and second utterance, respectively. Corresponding visual button symbols turned magenta during playback of

the respective sentence. Whether the oxytocin (or happy) sentence was the first or second in a dyad was counterbalanced per speaker. Dyads were blocked per speaker to allow for a perceptual calibration to the individual speaker, while the order of the other factor (condition or treatment, respectively) within speakers was randomized. Answers were recorded together with reaction time once playpack of the second sentence in a dyad commenced. Recorded answers were confirmed by the respective button symbol turning green for 250 ms. Answering scheduled playback of the next dyad, which started not before playback of the second sentence in the current dyad has completed and always was preceded by a 500 ms interval of acoustic pink noise during which both button symbols turned orange. Answers given within 1.5 seconds after onset and 3 seconds after offset of the second sentence in a pair were considered as valid responses, yielding a total of 2807 valid responses to treatment pairs and 702 to condition pairs.

Statistical modeling

To investigate whether the treatment (oxytocin vs. placebo) or the condition (happy vs. neutral) could be discriminated perceptually, we modeled the probabilities of rating “oxytocin” or “happy” recordings as more positive, respectively, with a multilevel Bayesian logistic regression using the R package ‘brms’ (Bürkner, 2017, 2018, 2021) and other R packages for statistical inference (Lenth et al., 2023; Makowski et al., 2019, 2020; Kay, 2023) in R (R core team, 2023, RRID:SCR_001905; Wickham et al., 2019). The main predictors of interest of our explanatory model (Shmueli, 2010) were *rs53576 OXTR polymorphism* (with the genotypes AA, AG and GG), interacting with the *condition* (happy/neutral) or *drug* (oxytocin/neutral), respectively. To control for order effects during rating, we entered the factors *order in pair* (to capture any response bias, e.g. the tendency to preferentially press the left or right arrow, corresponding to selecting the first or second utterance, respectively) and *order in experiment* (as a spline smooth term (Wood, 2003, 2017) with k=4) to account for any (potentially non-linear) order/time-dependence (e.g. due to habituation/learning or fatigue). To control for order effects in speakers (e.g. due to task novelty / environmental habituation), we added the *(treatment) session* as a control factor (i.e. whether

oxytocin was given in the first or the second session or whether the given dyad was recorded in the first or the second session, respectively). As the effect of task novelty or social habituation on voice performance might depend on the OXTR polymorphism, we also modeled 2- and 3-way interactions of *(treatment) session* with *rs53576 OXTR polymorphism* and *condition.* Additional control factors were *age* of speaker and rater (each as a spline smooth with k=3), as well as the *rater's sex* (speakers were all males).

To account for the hierarchical structure of the data, we added group-level effects for the factors *speakerID (45 levels)*, *raterID (10 levels)*, and *sentence* (5 levels). Specifically, we allowed the effects (μ) for *treatment/condition*, *(treatment) session, order in pair* and *rater's sex* to vary between *speakers* (with different distributions per *rs53576 OXTR polymorphism*), the latter one in order to capture individual speaker-rater gender interactions; the effects for *genetic polymorphism* interacting with *instruction/treatment*, *speaker age* as well as *order in pair* and *order in experiment* to vary across *raters* (the latter two to capture individual response biases and temporal order effects); and the mean detection probability (intercept) to vary between the five *sentences*. Additionally, any dependencies between sequential responses were accounted for by adding a first-order auto-regressive term.

In order to make the scale of priors comparable between all factor levels, we coded the 3-level factor genetic polymorphism as an index variable, i.e. we fitted a separate intercept per polymorphism rather than a common intercept and deviation effects (Kurz, 2020; McElreath, 2020). All other categorical (2-level) factors were coded with orthonormal contrasts, which, in the case of 2-level-factors, corresponds to contrast-coding that is the standard in traditional ANOVA models, meaning that the intercepts represent grand averages and the individual beta values represent main effects (Makowski et al., 2019). Numerical factors were centered and z-normalized.

We placed a weakly to moderately informative null-effect Student-t prior with 7 degrees of freedom (DFs) and a scale parameter of 0.5 on all beta values, according to common recommendations

for logistic regression (Gelman, 2020; Quent, 2021). Similarly, the priors for the standard deviations of the group-level effects and the spline smooths were set as positively bounded Student-t distributions with 4 DFs and unit scale and the priors for correlation terms as Lewandowski-Kurowicka-Joe (LKJ) distributions with $\eta = 2$ (Bürkner, 2021).

Results

Are sentences recorded under oxytocin treatment perceived as being more positive?

To test whether the 10 raters rated the version of a spoken sentence that was recorded in the oxytocin session as more positive than the sentence from the placebo session with an above chance probability, we fitted a multi-level Bayesian logistic regression to the answers. As (Bayesian) mixed models are well suited to handle samples of different sizes (including small sample sizes), we fitted a separate intercept per each genetic polymorphism group in this analysis (AA, AG and GG). We report the marginal means at the levels of factors of interest while averaging over the levels of all other factors and fixating rater's and speaker's age at 25 years, together with the 89% highest density (HDI) credible intervals, as this interval is deemed more stable for an effective sample size below 10.000 than the more common 95% interval (Kruschke, 2014; McElreath, 2020).

We found no evidence for an above chance average judgment of increased positivity for either placebo or oxytocin in either OXTR group, with the credible intervals containing 50% (marginal mean estimates: GG 50% [44%, 57%], AG 48% [42%, 54%] and AA 52% [46%, 58%]; overall average with weights proportional to number of observations: 49.8% [45.5%, 54.2%]). Compared to the priors of no effect, the data lent weak evidence for the absence of a systematic effect of oxytocin on perceived valence (density ratios at 0 in favor of the null: 3.38, 3.43 and 2.59 for the three polymorphism groups; see Fig. B; individual ratings of each rater of each speaker are shown in Fig. C).

The condition had no systematic influence on the perceived valence difference between OXT and PLA sentences in either OXTR group and the evidence density ratio of 4.26 at 0 provided moderate evidence against a main effect of condition (Fig. B).

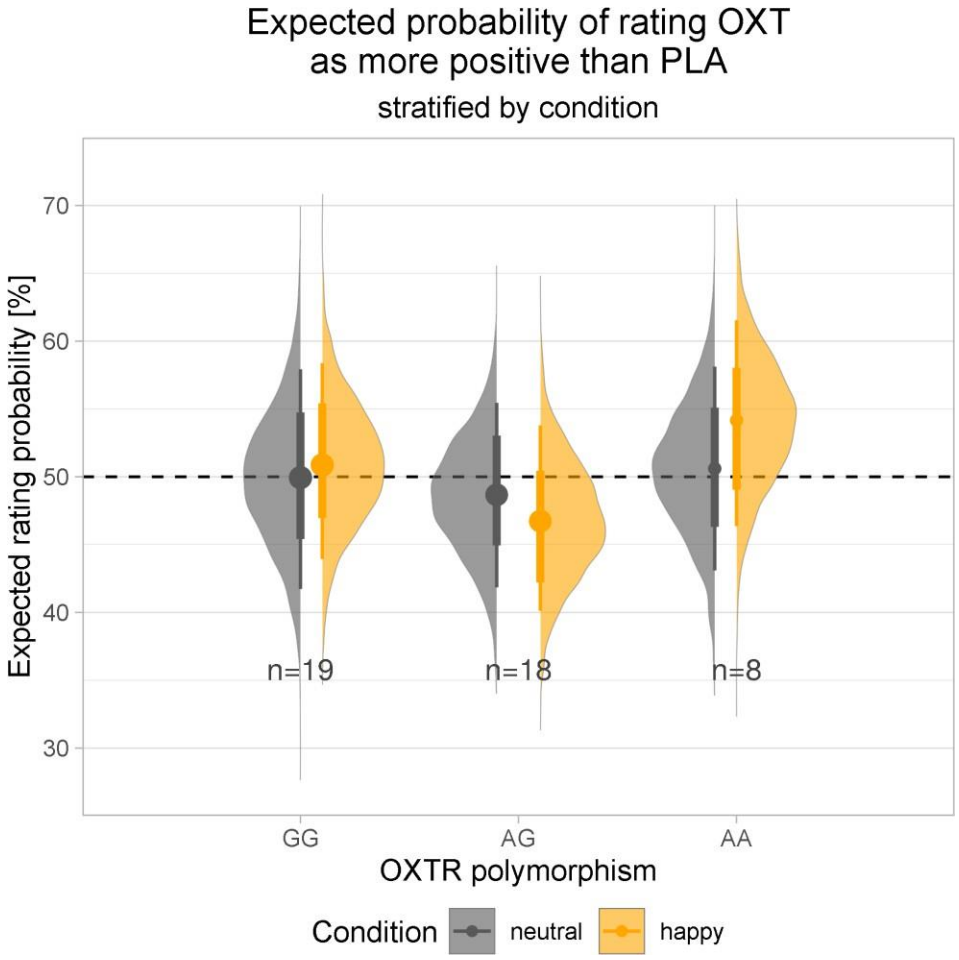


Figure B: Expected probability of rating sentences spoken under oxytocin as more positive. Shown are the posterior probability densities of the expected rating probabilities separately for each OXTR polymorphism on the x-axis and the two conditions color-coded ("neutral" as gray, "happy" as yellow). The points signify the medians and the error bars the 66% and 89% HDI credible intervals. The effects of all other factors (order effects, sex, age) are marginalized out, group-level variances of speakers, raters and sentences are partitioned out. The dashed line represents the 50% chance level, which is well contained in the HDI for either group and instruction.

After controlling for order effects, re-test reliabilities as estimated by a Bayesian multi-level regression on 270 randomly chosen replicate pairs was not significantly above chance level on

average (59% [43%, 73%], 64% [46%, 80%] and 60% [42%, 76%] for the genetic polymorphism groups GG, AG and AA, respectively; Fig. D).

Taken together, we found no conclusive evidence supporting the hypothesis that oxytocin shifts the emotional valence of utterances towards a more positive valence consistently across speakers, with a marginal R^2 (considering only the explained variance of the population level effects) of 0.027 [0.095, 0.043] and a conditional R^2 (also considering the group-level effects) of 0.11 [0.095, 0.128].

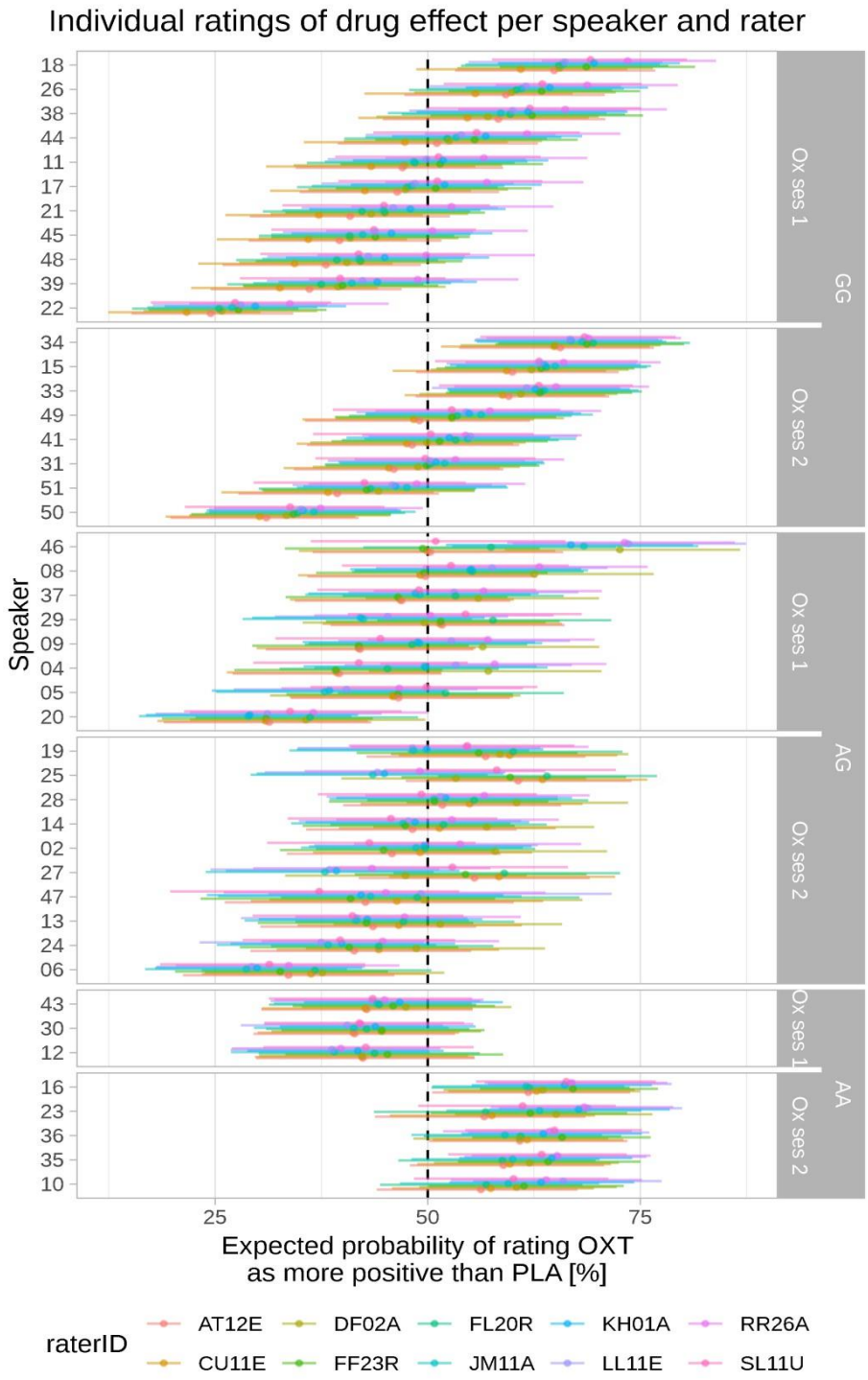


Figure C: Individual valence ratings of the oxytocin effect. Expected probabilities per rater and speaker while marginalizing over condition and order effects. Ratings vary considerably between speakers (most in the G/G group) and less between raters. There is no systematic effect of oxytocin on perceived valence.

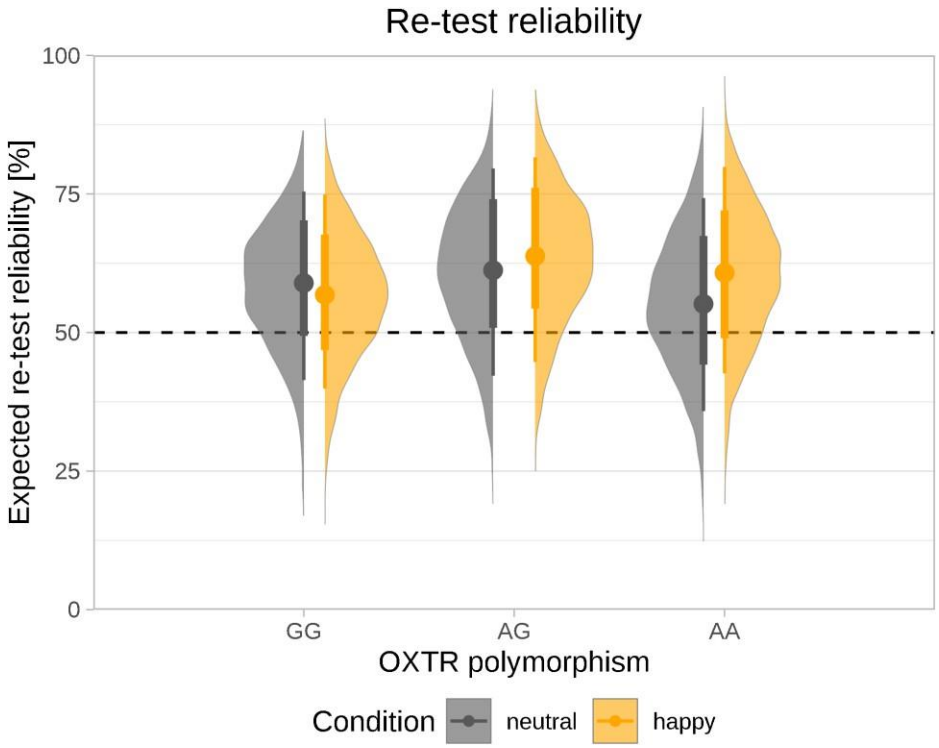


Figure D: Expected re-test reliability per OXTR polymorphism and instruction, after marginalizing across order effects and other co-factors. Intra-rater reliability is relatively low (around 60%) and not significantly above the 50% chance level (dashed line). It also does not differ between the OXTR groups. See Fig. B for a detailed legend.

The data contained order effects for both speakers and raters. On average, sentences recorded in the second session were rated as more positive than recordings from the first session independent of treatment, an effect mainly driven by the 8 AA homozygote speakers, all of who sounded more positive in the second session (53% [48%, 57%], 51% [46%, 56%], 59% [54%, 63%] for the OXTR groups GG, AG and AA, respectively; see upper panel of Fig. E and Fig. C). This is reflected in a probability of direction (PD) of 98% (interpretable as the probability of an existence of an effect, Makowski et al., 2019), an evidence ratio of 52 for a positive effect of drug session (evidence ratio at 0: 3.14) and a significant interaction with the OXTR-group (PD 96%, evidence ratio at 0: 3.86). The effect of session was not due to a session x drug interaction, i.e.

speakers were not more susceptible to OXT in the 2nd session than in the 1st one (see Fig. E, lower panel).

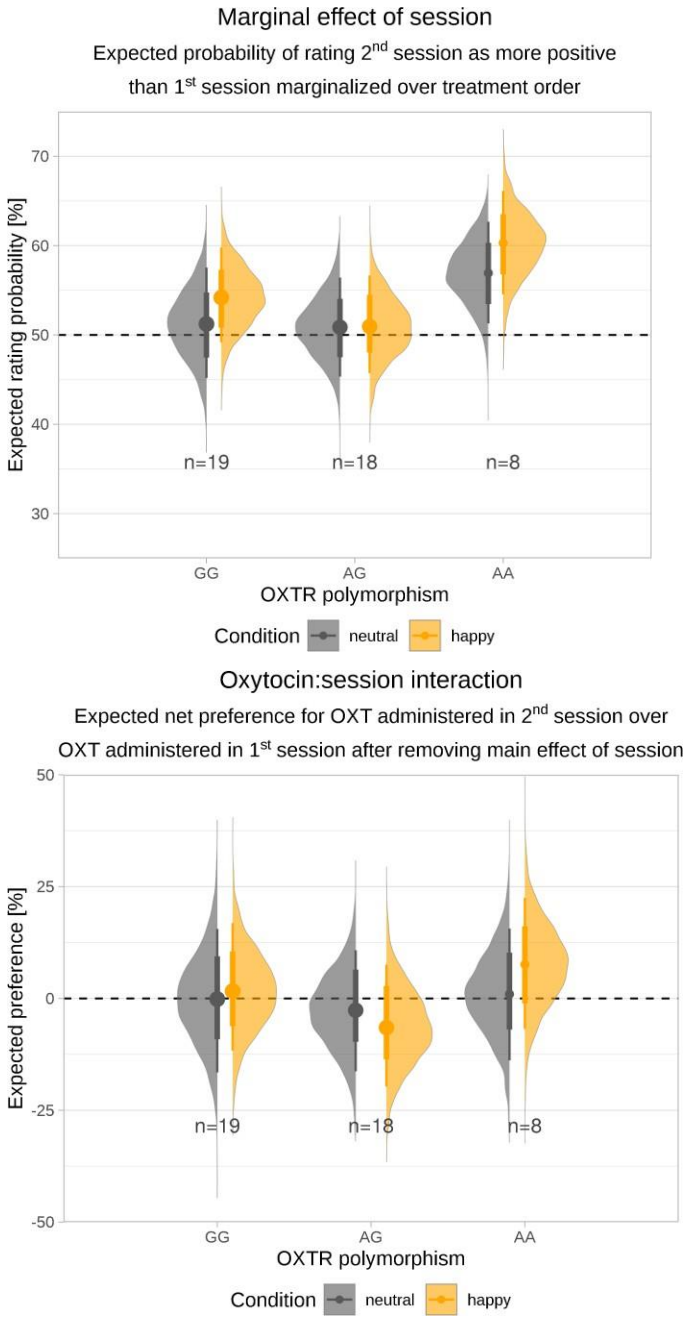


Figure E: Effect of session. Upper panel: Expected probabilities of rating sentences recorded during the second session as more positive than sentences recorded in the first session. The marginal effect of session is calculated by converting the estimated posterior probabilities to the probabilities of selecting the second session (i.e. 1 – p, if OXT administered in first session) and then averaging over the two treatment orders.

Lower panel: Expected relative preference for OXT administered in second session over OXT administered in first session. This session x treatment interaction is calculated by subtracting the expected probabilities of selecting the second session (i.e. PLA) when OXT was administered in the first session from the probabilities to select the second session (i.e. OXT) when OXT was administered in the second session.

Similarly, raters exhibited preferences for either the first or second sentence in a pair (or the left or right button, or the index or middle finger), with a population level response bias for the second sentence of 22% [-17%, 59%] and a PD of 82% (Fig. F).

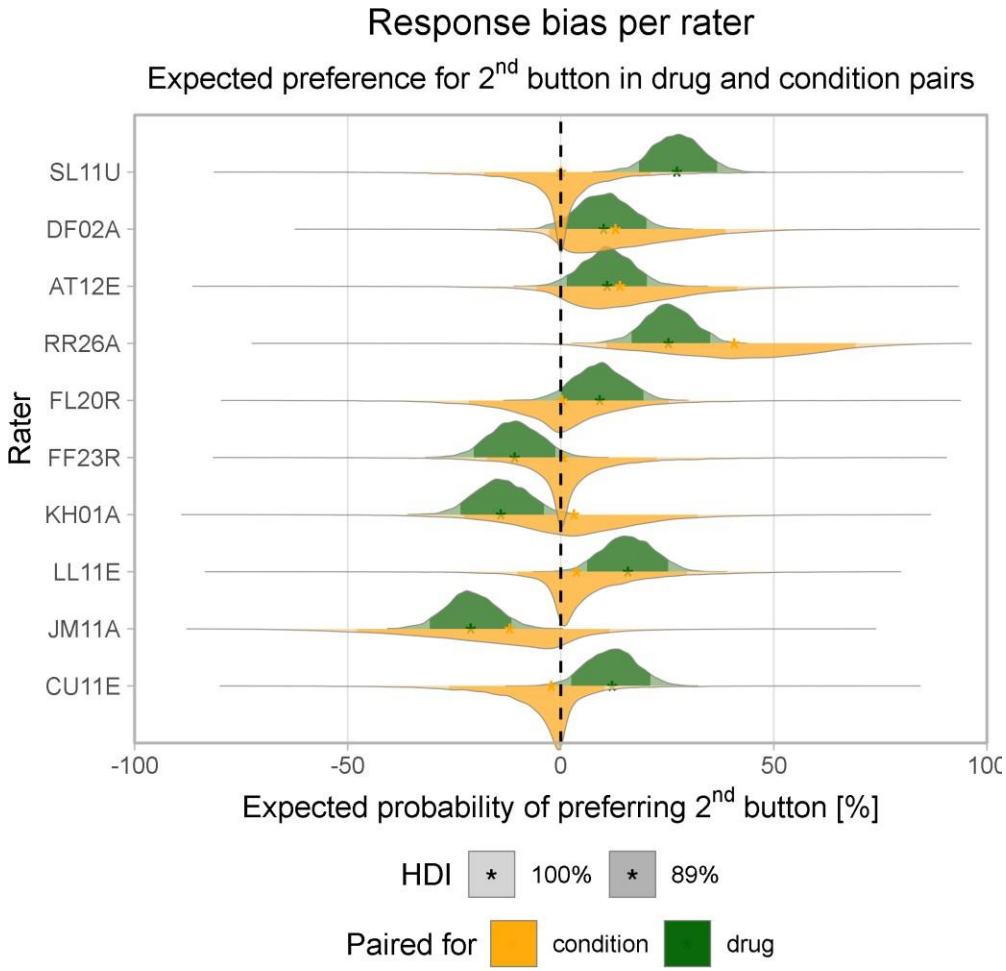


Figure F: Posterior probability densities of individual response biases for the two pairing factors. More subjects exhibited stronger response biases for dyads paired for drug (OXT/PLA, upwards facing, green) than for dyads paired for condition (happy/neutral, downwards facing, yellow). Asterisks (*) indicate the median, the 89% HDI credible interval is indicated by the color saturation.

Are sentences spoken with the "happy" instruction perceived as more positive?

On average, 25 year old raters rated utterances spoken with the "happy" instruction as more positive with a probability of 77% [61%, 90%], but individual raters differed considerably in their

preference for either instruction, as well as in their rating-consistency, which also manifested in a significant effect of rater's age (PD 98.83%, evidence ratio at 0: 9.19). Four female and one male rater consistently rated the happy instruction as more positive than the neutral one. Three male raters displayed rather inconsistent ratings including chance level in their 89% HDI estimates and two raters consistently rated the neutral instruction as more positive (Fig. G).

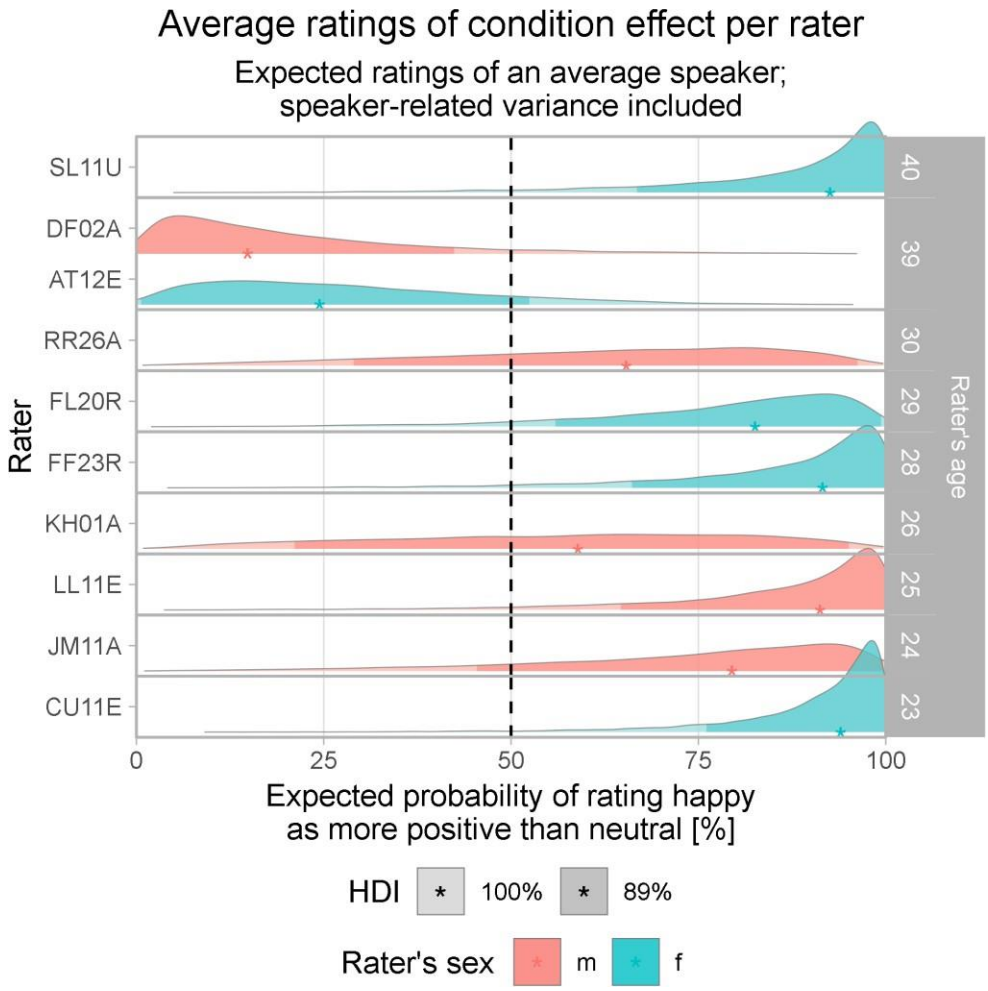


Figure G: Expected probabilities of rating "happy" utterances as more positive per rater. Slabs display the posterior probability densities with the 89% HDI credible interval indicated by color saturation, asterisks (*) indicate the median.

Compared to the ratings of dyads paired for treatment, there was a less pronounced response bias in favor of the second sentence of 30% [-31%, 90%] with a probability of direction of 79% on average and an evidence ratio > 4 in only three raters (Fig. F). Overall, these results indicate that

most raters could reliably differentiate between the two instructions, but varied in their subjective preferences and rating consistency (van Rijn and Larrouy-Maestri, 2023).

Mood and empathy questionnaires

After participants completed the fMRI experiment on both appointments, they filled several questionnaires assessing their mood, state and trait anxiety and two motivational systems. The Multidimensional Mood State Questionnaire (Steyer et al., 1997) was employed to measure levels of positive affect, wakefulness and calmness. State and trait anxiety were assessed using the State-Trait Anxiety Inventory (Spielberger et al., 1983). Carver and White's BIS/BAS Scale (1994) was used to quantify participants' behavioral inhibition system (BIS) and the behavioral activation system (BAS). The questionnaires were completed in their German versions. To evaluate potential effects of intranasal administration of oxytocin or the rs53576 OXTR polymorphism genotype, a mixed-model ANOVA using SPSS (SPSS, RRID: SCR_002865) was performed and significance assumed at $p < 0.05$.

To assess empathy, participants filled out the German Questionnaire for Assessment of Empathy, Prosociality and Aggression (Lukesch, 2006). Participants were also presented with 18 pictures of facial affect of six basic emotions: anger, disgust, fear, happiness, surprise and sadness (Ekman & Friesen, 1976), which they were asked to name correctly. After scanning, participants completed both, the empathy questionnaire and emotion recognition task, to test whether the administration of oxytocin or the rs53576 OXTR polymorphism genotype had an effect on the number of correct answers. Statistics were performed using a mixed model ANOVA in SPSS (SPSS, RRID: SCR_002865) and significance assumed at $p < 0.05$.

Results

Neither oxytocin administration nor placebo or oxytocin receptor genotypes affected participants' responses in the empathy questionnaire or in the emotional faces recognition task significantly ($p > 0.05$) (Hurlemann et al., 2010; Wu et al., 2012). Neither oxytocin administration nor OXTR genotypes affected participants' mood state, state anxiety or behavioral inhibition and activation (BIS/BAS) scores significantly (all $p > 0.05$) (Theodoridou et al., 2009; Kosfeld et al., 2005). Unlike

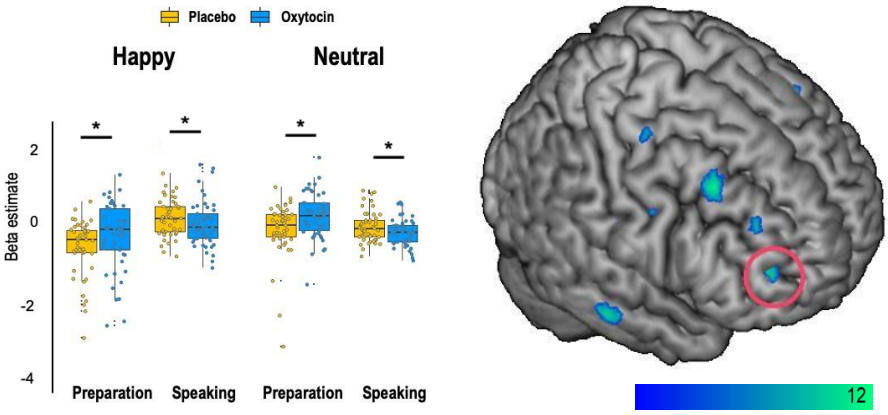
Choi et al. (2018), we did not detect a significant interaction between oxytocin administration and OXTR genotypes on participants' BAS scores in our sample ($p > 0.05$).

Table 1. Distribution of participants' OXTR rs53576, DAT1 VNTR 9/10 and COMT Val158Met polymorphism genotypes.

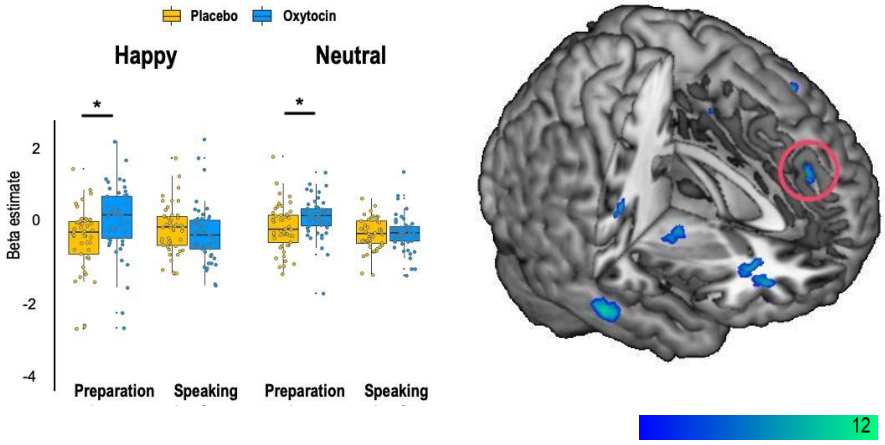
OXTR rs53576	**DAT1 VNTR 9/10**	**COMT Val158Met**
A/A: 7	10/10: 3 9/10: 4 9/9: 0	Val/Met: 4 Met/Met: 1 Val/Val: 2
A/G: 20	10/10: 11 10/9: 7 9/9: 2	Val/Met: 7 Val/Val: 5 Met/Met: 8
G/G: 25	10/10: 17 9/10: 6 9/9: 2	Val/Met: 19 Val/Val: 4 Met/Met: 2

Figure H. Clusters with a significant drug*condition interaction.

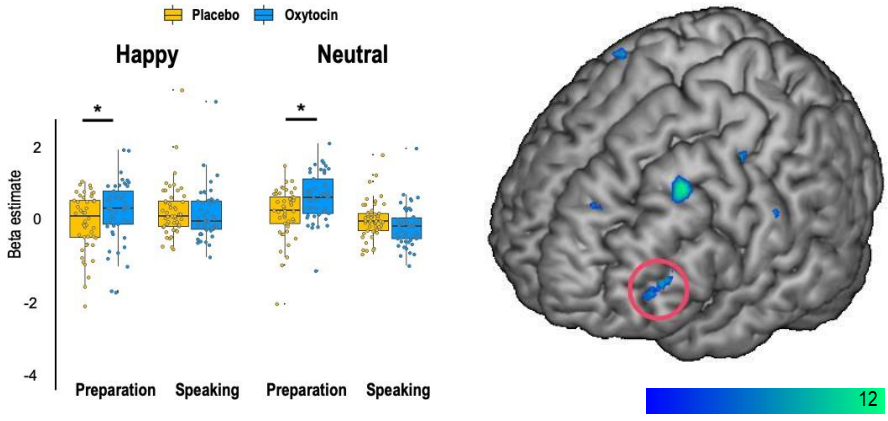
Right Frontopolar cortex



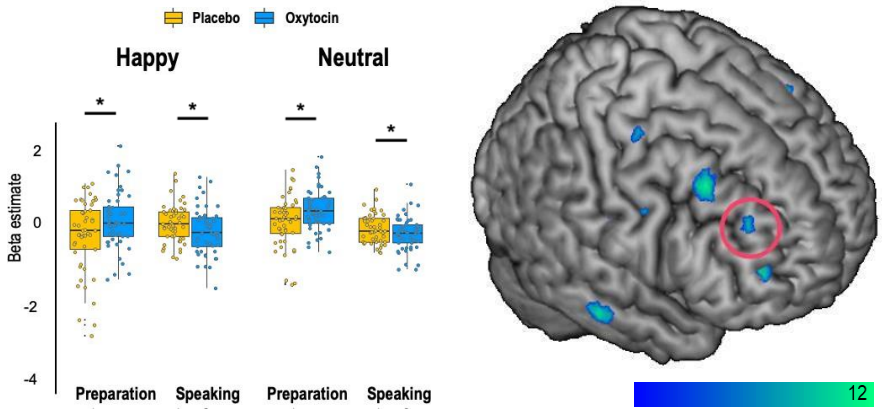
Left Dorsomedial prefrontal cortex



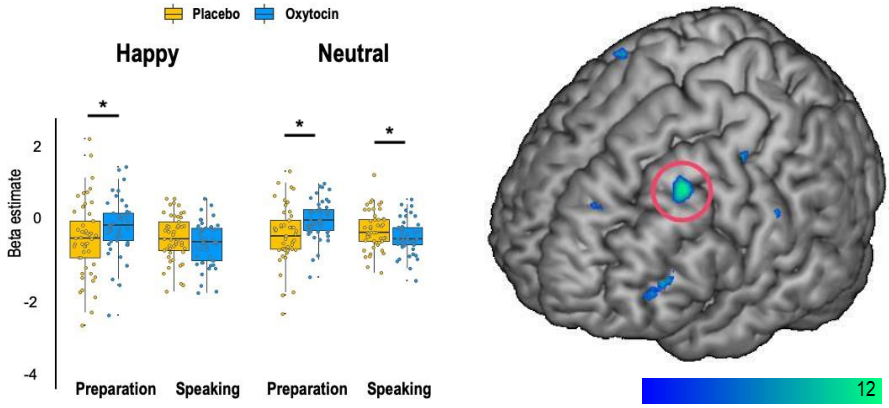
Left Inferior frontal gyrus - pars orbitalis



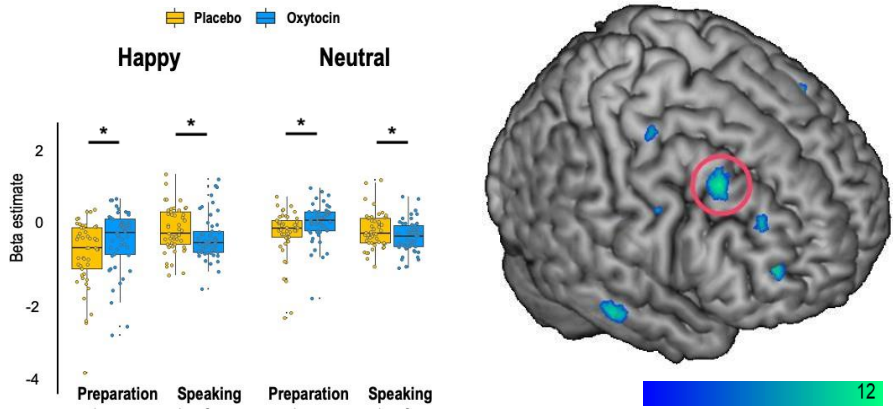
Right Middle frontal gyrus



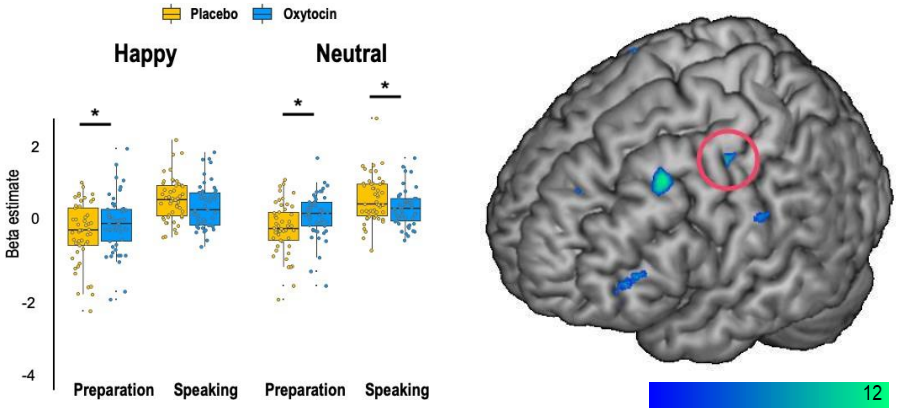
Left Dorsolateral prefrontal cortex



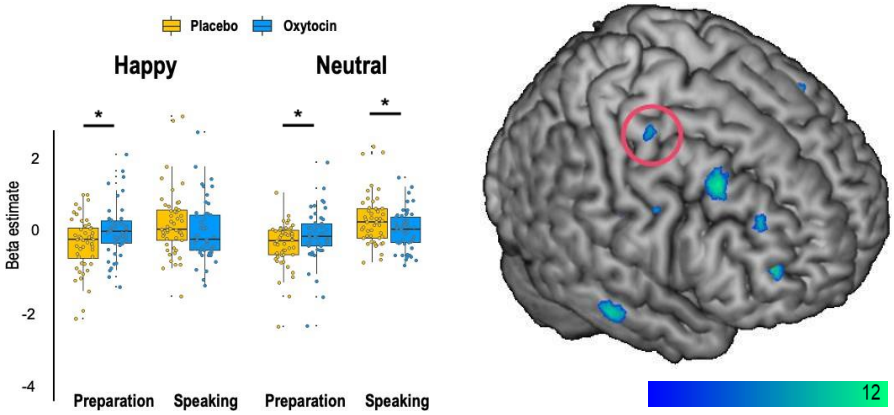
Right Dorsolateral prefrontal cortex



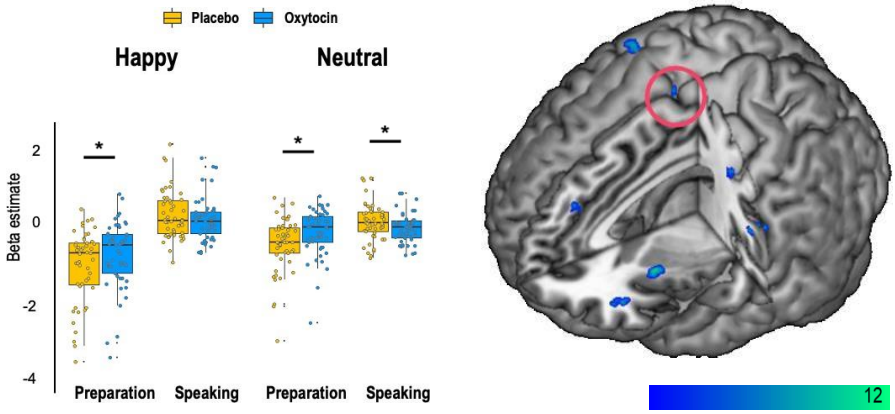
Left Dorsal premotor cortex



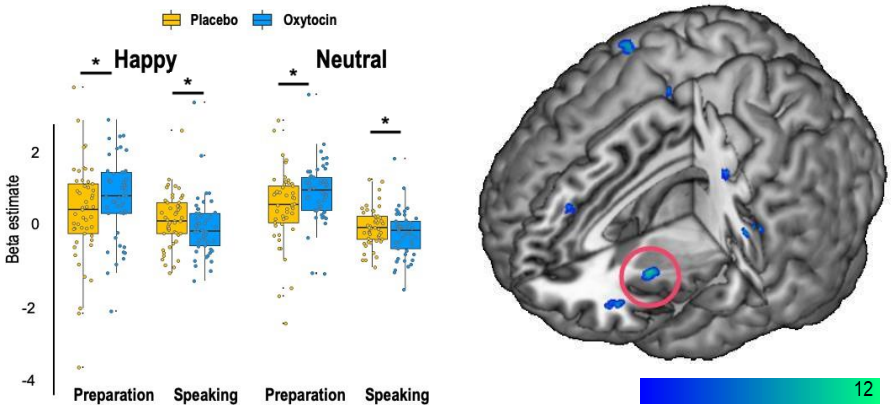
Right Dorsal premotor cortex



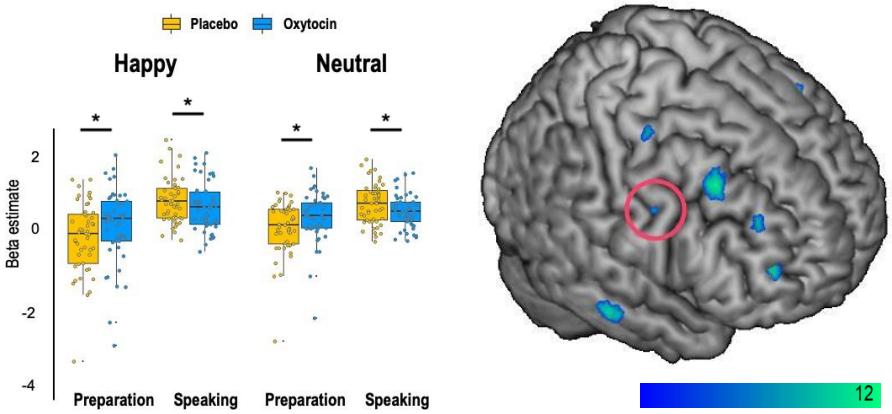
Right Supplementary motor area



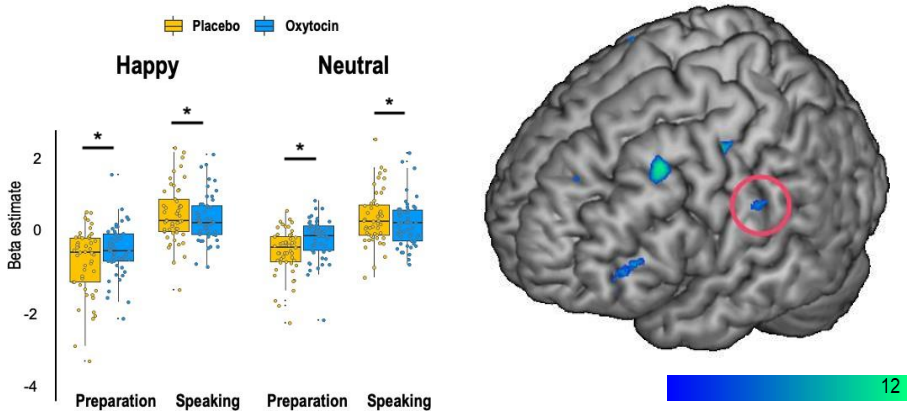
Left Insula



Right Articulatory motor cortex



Left Temporo-parietal junction



Right Middle temporal gyrus

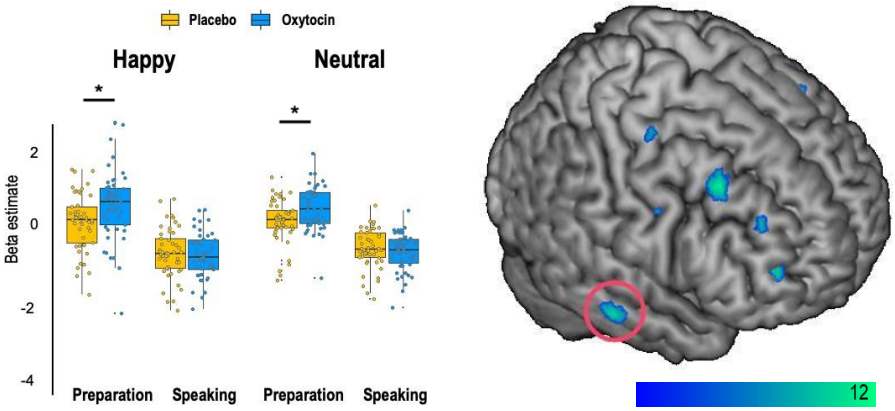
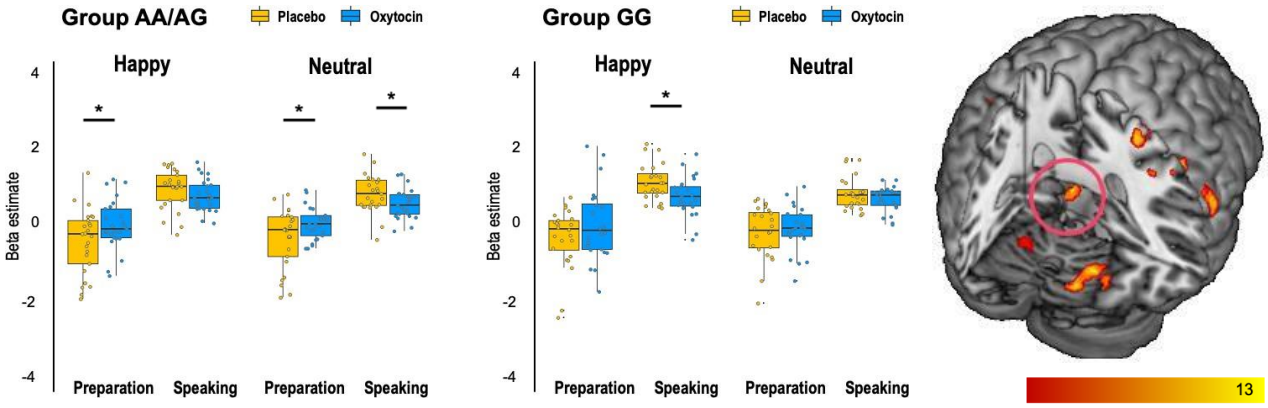
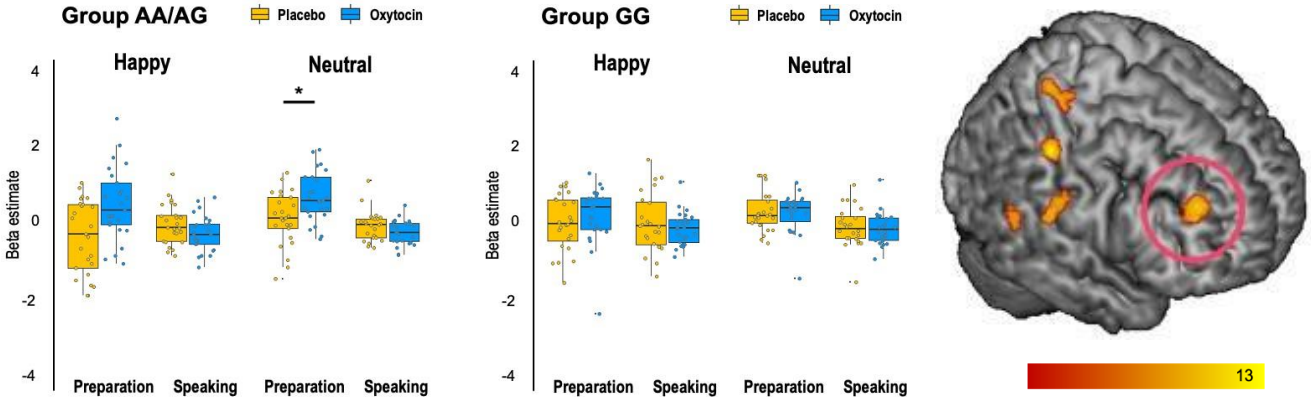


Figure I. Clusters with a significant drug*polymorphism*condition interaction.

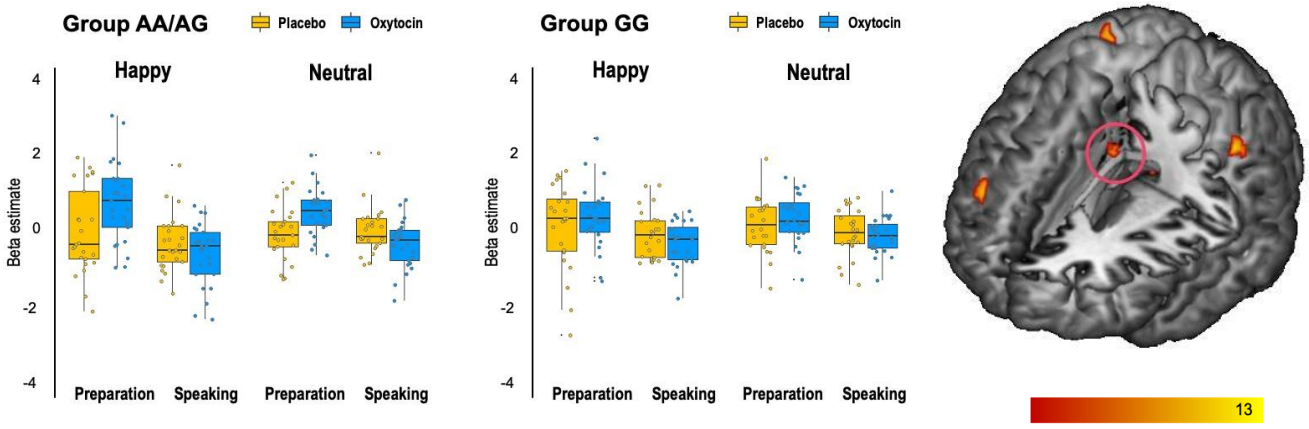
Left Mesencephalon



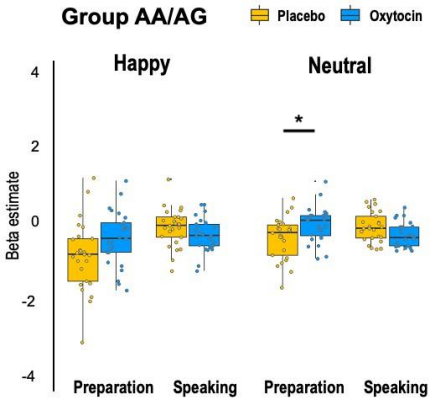
Right Middle frontal gyrus

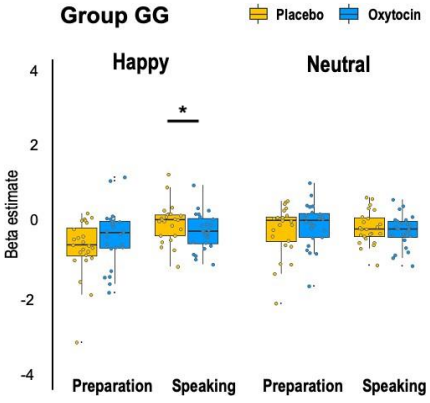


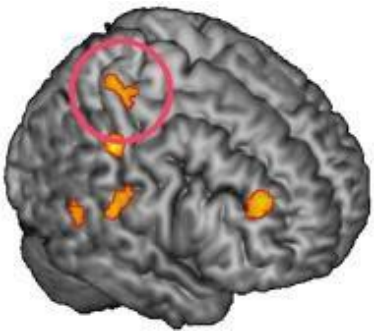
Right Middle cingulate gyrus

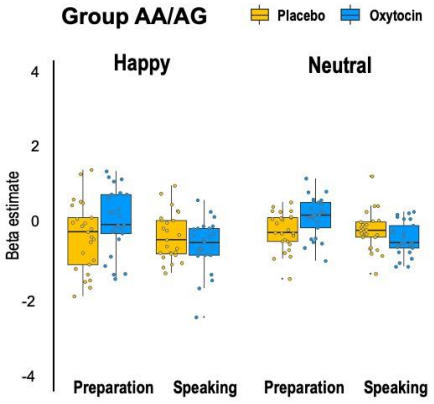


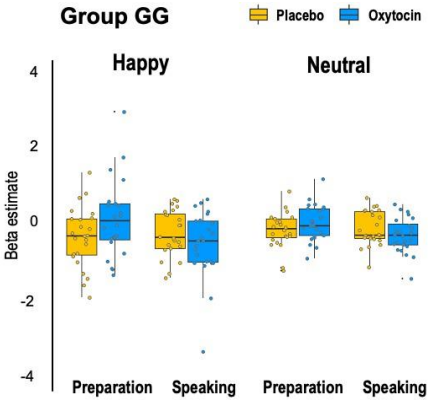
Right Postcentral sulcus

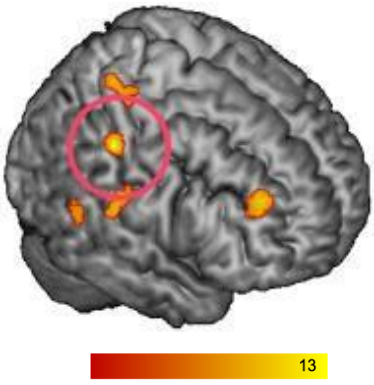




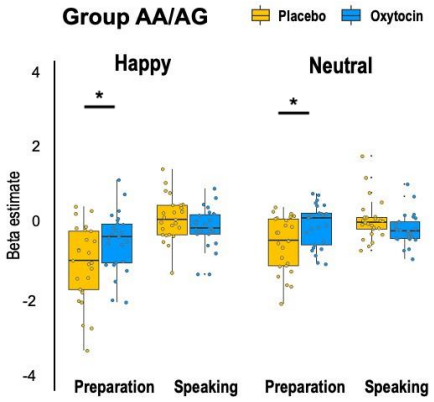


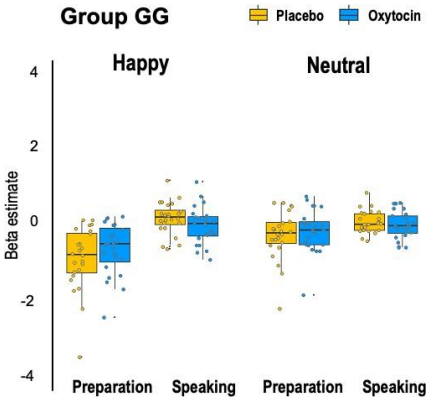


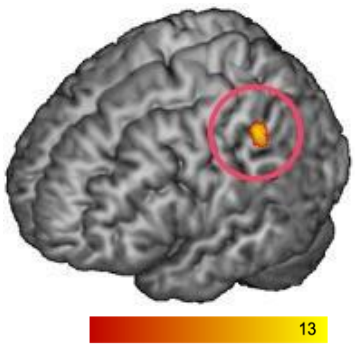




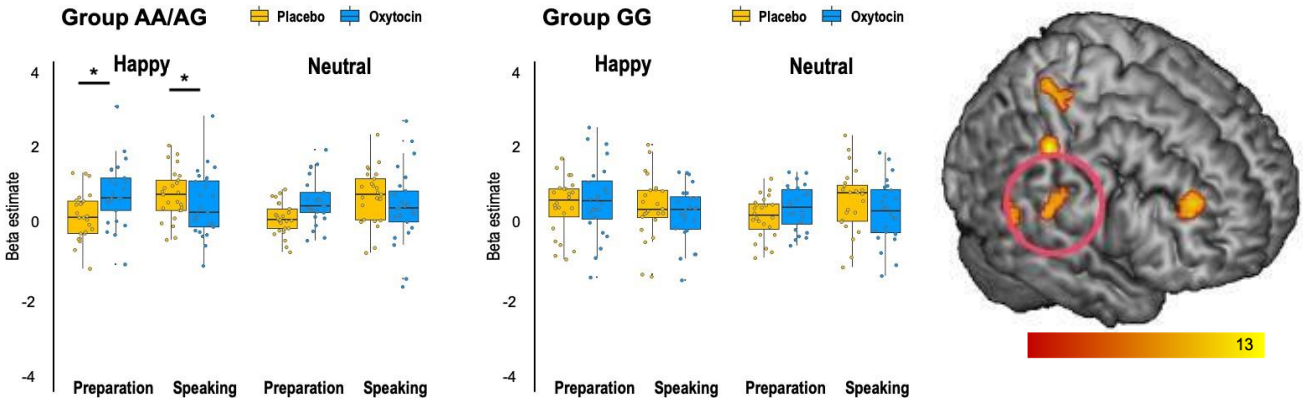
Left Postcentral sulcus



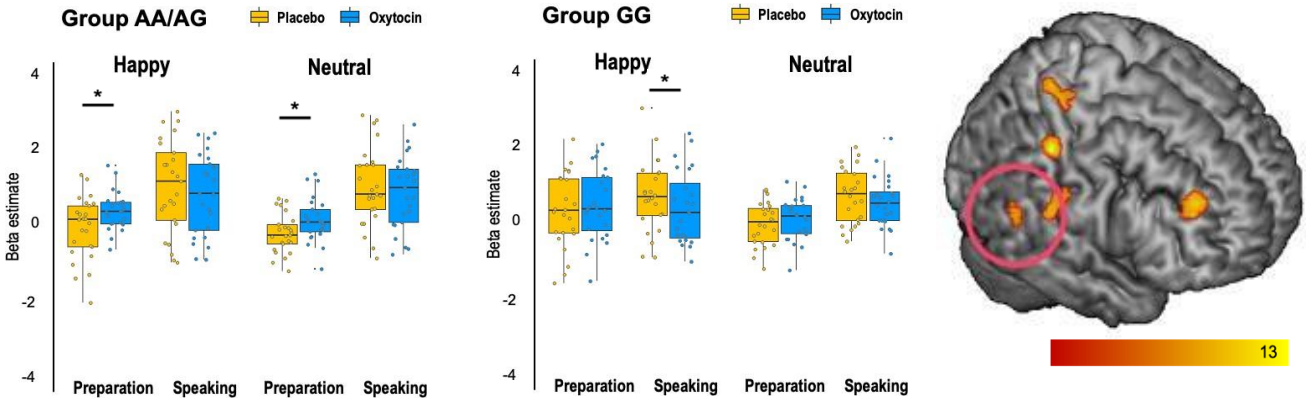




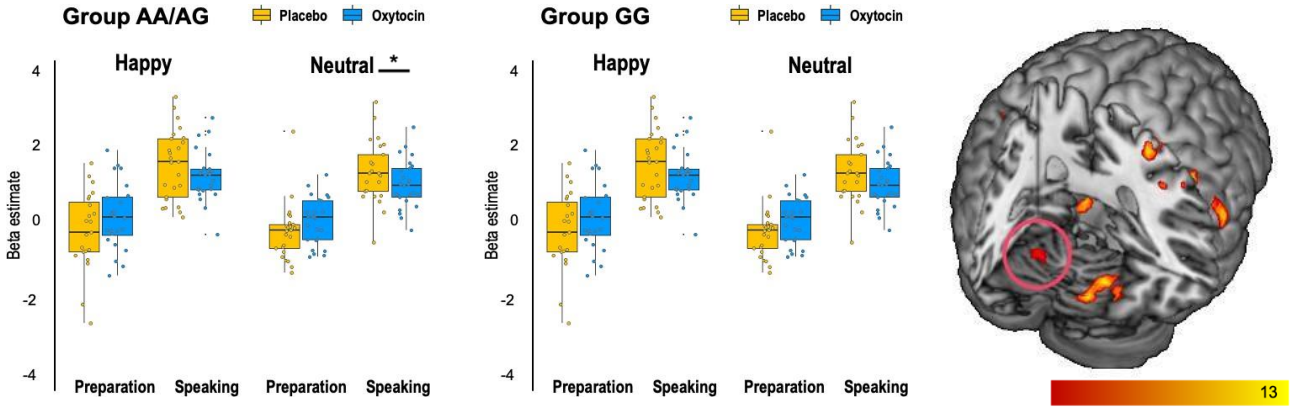
Right Secondary somatosensory cortex



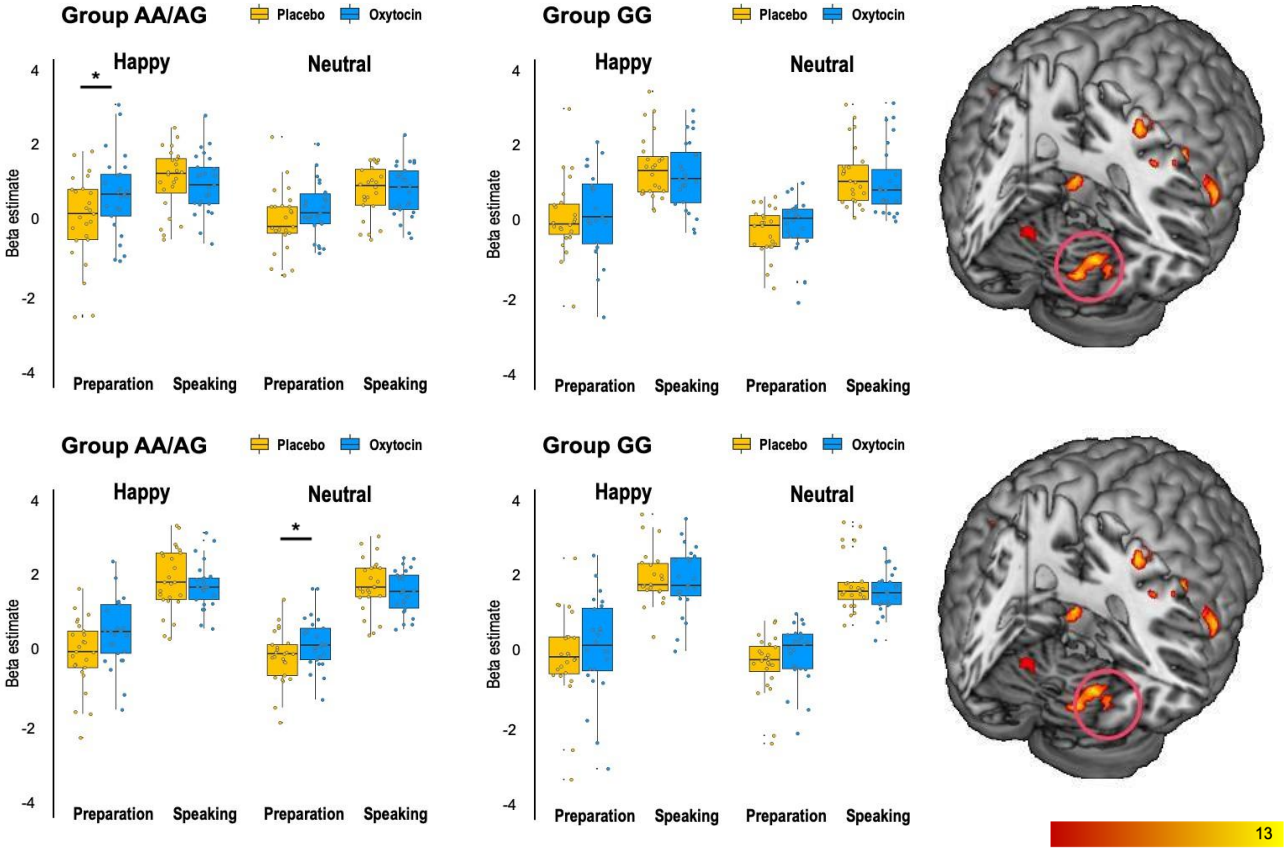
Right Posterior superior temporal gyrus



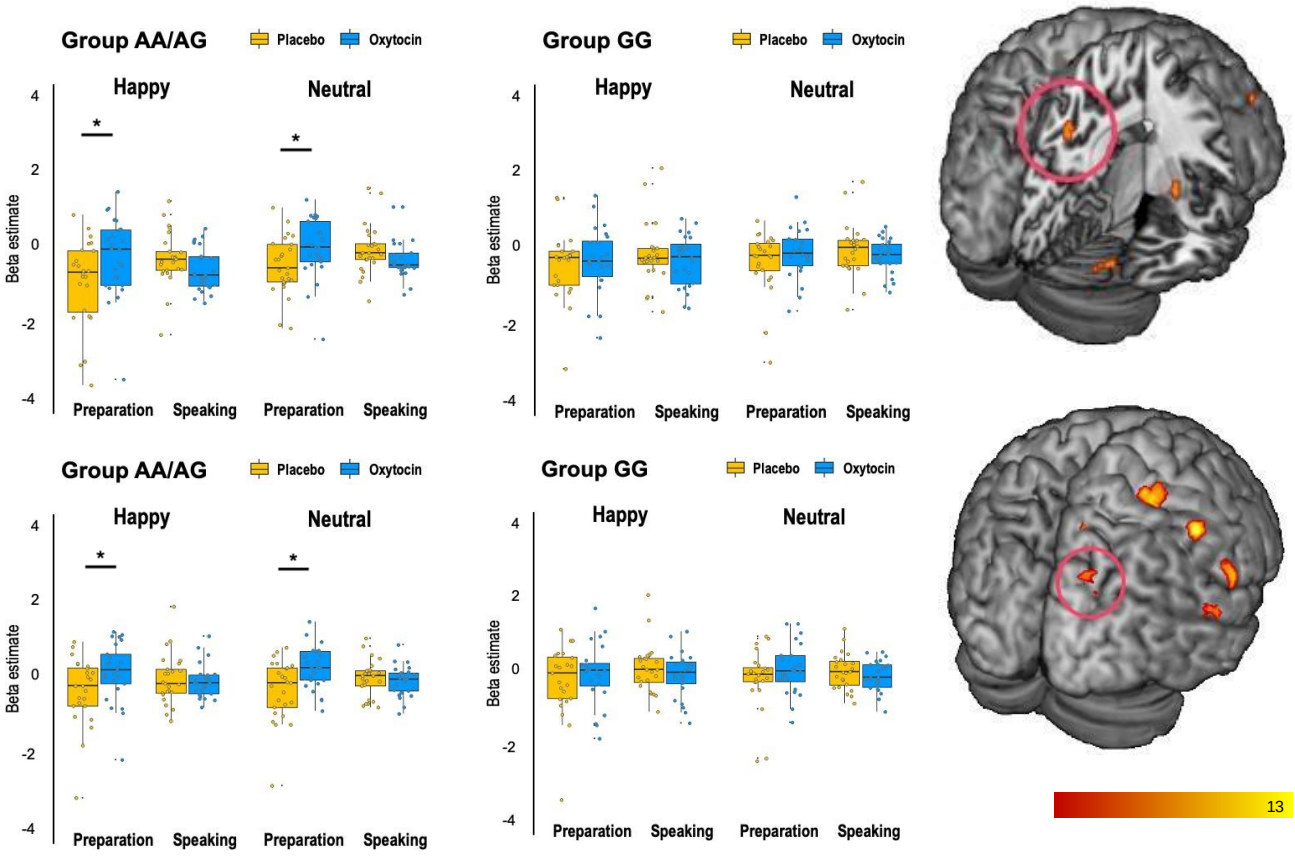
Left Superior cerebellar hemisphere



Right Superior cerebellar hemisphere



Right Precuneus



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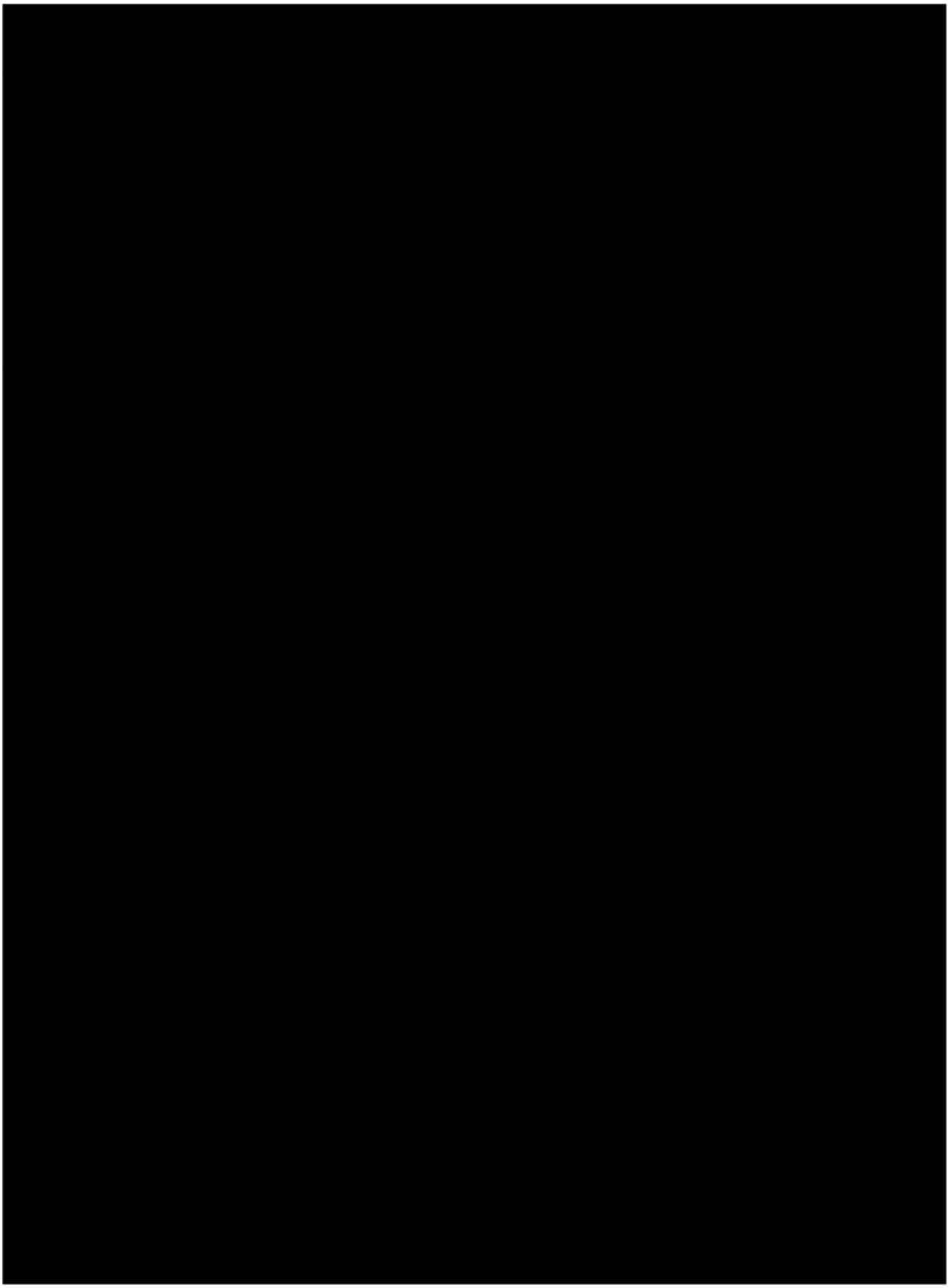
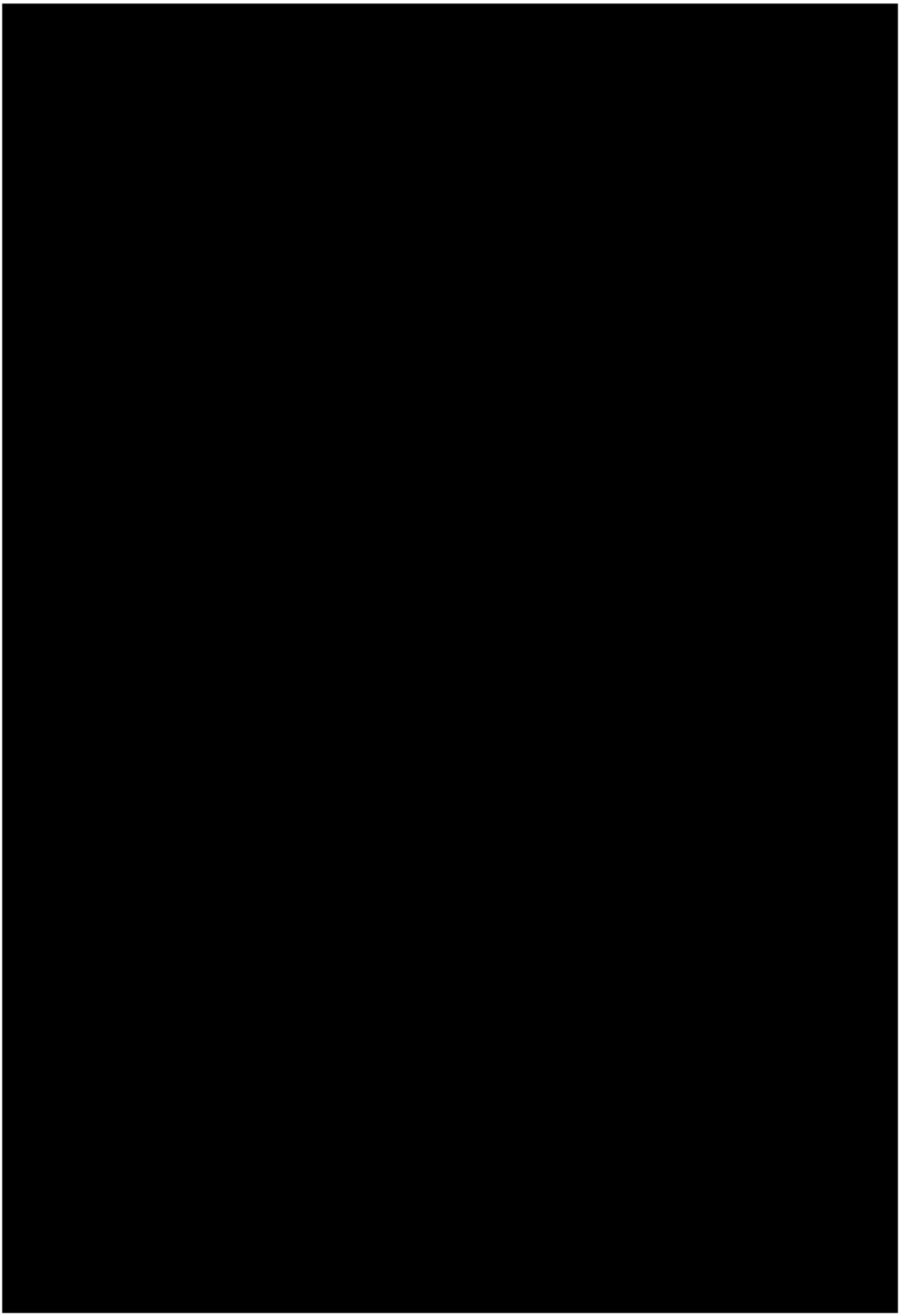
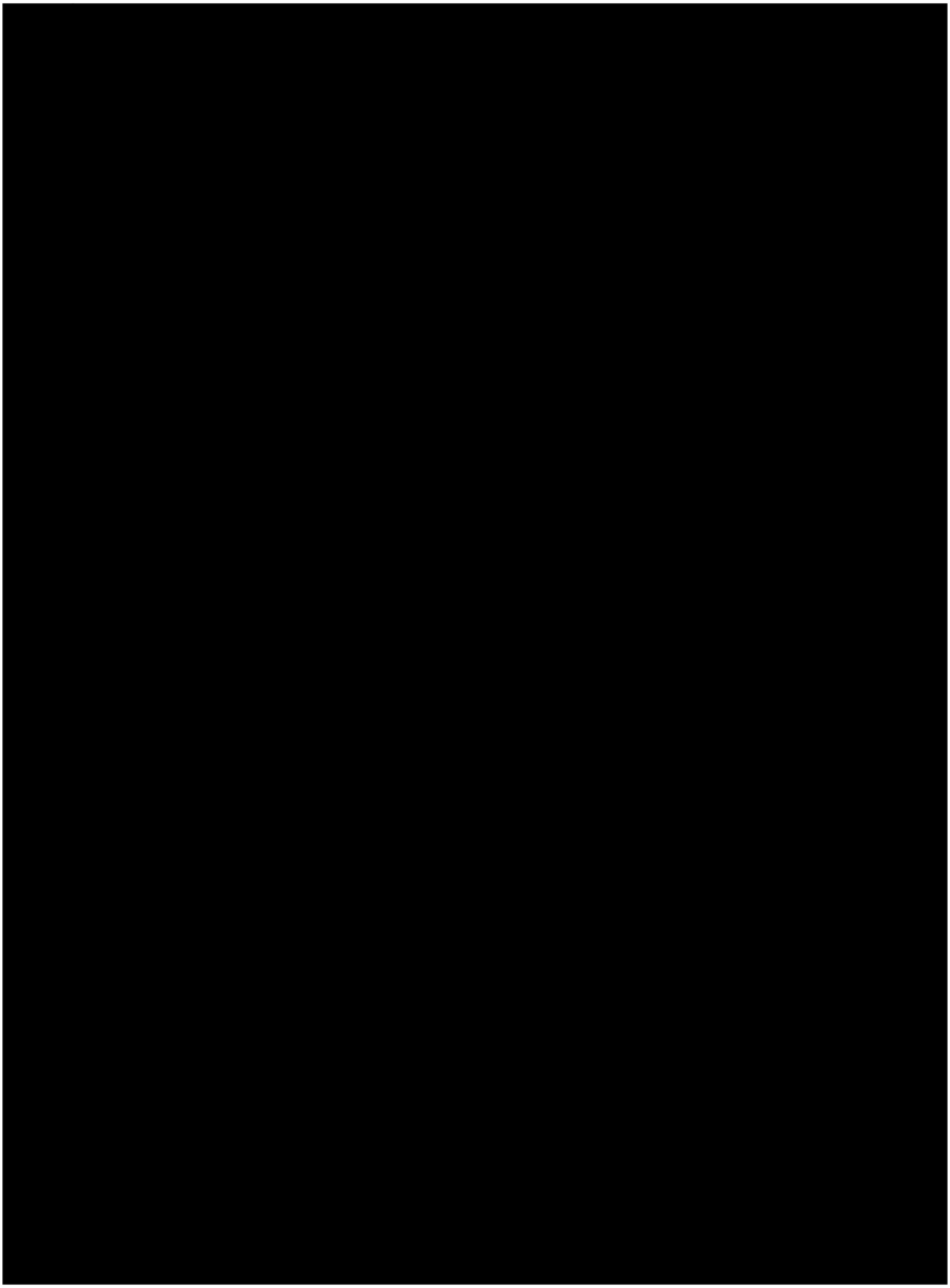
7. Curriculum Vitae







8. Schriftliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Johann Wolfgang Goethe-Universität Frankfurt am Main zur Promotionsprüfung eingereichte Dissertation mit dem Titel

„Oxytocinerge Modulation von Sprachproduktion“

am Zentrum der Neurologie und Neurochirurgie unter Betreuung und Anleitung von Herrn PD Dr. Christian Kell ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe. Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Die vorliegende Arbeit wurde bisher nicht als Dissertation eingereicht.

Vorliegende Ergebnisse der Arbeit wurden im folgenden Publikationsorgan veröffentlicht:

Vogt, C., Floegel, M., Kasper, J., Gispert-Sánchez, S. and Kell, C. A. (2023). Oxytocinergic modulation of speech production—a double-blind placebo-controlled fMRI study, *Social Cognitive and Affective Neuroscience*, Volume 18, Issue 1, 2023, nsad035, https://doi.org/10.1093/scan/nsad035.

(Ort, Datum) (Unterschrift)

9. Danksagung