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A Spatiotemporal Profile of In Vivo Cerebral Blood Flow Changes Following Intranasal Oxytocin in Humans

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ABSTRACT

BACKGROUND: Animal and human studies highlight the role of oxytocin in social cognition and behavior and the potential of intranasal oxytocin (IN-OT) to treat social impairment in individuals with neuropsychiatric disorders such as autism. However, extensive efforts to evaluate the central actions and therapeutic efficacy of IN-OT may be marred by the absence of data regarding its temporal dynamics and sites of action in the living human brain.

METHODS: In a placebo-controlled study, we used arterial spin labeling to measure IN-OT-induced changes in resting regional cerebral blood flow (rCBF) in 32 healthy men. Volunteers were blinded regarding the nature of the compound they received. The rCBF data were acquired 15 min before and up to 78 min after onset of treatment onset (40 IU of IN-OT or placebo). The data were analyzed using mass univariate and multivariate pattern recognition techniques.

RESULTS: We obtained robust evidence delineating an oxytocinergic network comprising regions expected to express oxytocin receptors, based on histologic evidence, and including core regions of the brain circuitry underpinning social cognition and emotion processing. Pattern recognition on rCBF maps indicated that IN-OT-induced changes were sustained over the entire posttreatment observation interval (25–78 min) and consistent with a pharmacodynamic profile showing a peak response at 39–51 min.

CONCLUSIONS: Our study provides the first visualization and quantification of IN-OT-induced changes in rCBF in the living human brain unaffected by cognitive, affective, or social manipulations. Our findings can inform theoretical and mechanistic models regarding IN-OT effects on typical and atypical social behavior and guide future experiments (e.g., regarding the timing of experimental manipulations).

Keywords: Arterial spin labeling, Cerebral blood flow, Intranasal, Oxytocin, Pharmacodynamics, Resting state

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Animal research has demonstrated that oxytocin (OT) plays a key role in the development and regulation of mammalian social behavior (1–7). In the absence of suitable radioligands, designs using intranasal sprays to manipulate OT levels in the brain (8) or to investigate the effects of polymorphisms in the OT receptor gene (9) have confirmed a similar role in humans (10–17). An increasing number of clinical trials have explored the therapeutic value of intranasal oxytocin (IN-OT) for neuropsychiatric disorders characterized by social impairment, such as autism, schizophrenia, and anorexia, with promising initial results (10,18–26). However, this effort is marred by the absence of data relating to the pharmacodynamics of IN-OT in the human brain.

As a consequence, studies still determine experimental parameters based on assumptions derived from the temporal profile of changes in the concentration of vasopressin in the cerebrospinal fluid (CSF) after intranasal administration (27). However, translating this work to studies using IN-OT faces two obstacles. First, despite their structural similarity, vasopressin and OT are different neuropeptides with distinct neurophysiology (8,28,29). Second, although the more recent demonstration that IN-OT also increases CSF OT concentration in adult male volunteers (30) is promising, there is dissociation between the concentration of a neuropeptide in the CSF and its availability in brain tissue (31). We need to understand the temporal changes in brain physiology caused by IN-OT to optimize future studies.

Equally, we need to understand the spatial distribution of IN-OT effects in humans. There are three main reasons this understanding is currently hindered. First, the distribution and concentration of OT receptors underpin interspecies and intraspecies differences in social behavior (32), precluding direct translation of information across species. To date, the sole evidence regarding the distribution of OT receptors in human brain comes from the study of a small number of postmortem brains of mainly elderly donors (33–35). Although valuable, these studies provide only a static snapshot of a dynamic system using radioligands for which the receptor specificity is not fully determined (35,36). Second, task-based blood oxygen level–dependent (BOLD) functional magnetic

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resonance imaging (fMRI) studies cannot address this question because they identify relative changes between experimental and control conditions and are not sensitive to a single physiologic parameter (37,38). Consequently, any observed effects are uniquely confined to the neural network engaged in a given task. Third, animal studies demonstrate that different social stimuli may elicit different release profiles of endogenous OT (28). Conclusions regarding changes in brain function induced by IN-OT are limited to the stimulus class employed. More recent "resting-state" BOLD fMRI studies have circumvented some of these issues by focusing on changes in functional connectivity following IN-OT (39,40). Resting-state fMRI provides a promising alternative but cannot quantify changes in brain physiology directly.

We sought to understand the spatial and temporal profile of neurophysiologic changes in the 25–78 minutes following the onset of IN-OT administration (compared with placebo) in the human brain. We used arterial spin labeling (41,42) to measure in vivo changes in brain physiology unaffected by concomitant cognitive, affective, or social manipulations. Arterial spin labeling is a noninvasive pharmacodynamic biomarker (43–48) that provides quantitative measures of the effects of acute doses of psychoactive drugs on regional cerebral blood flow (rCBF), with high spatial resolution and excellent temporal reproducibility (37,43,49). Changes in rCBF are likely to reflect changes in neuronal activity, rather than simple vascular effects (50–55).

We expected to observe increases in rCBF over mainly limbic areas previously identified to express OT receptors in human postmortem brains (33–35) and brain areas involved in social-emotional processing that are functionally linked with regions expressing OT receptors, such as the insula and inferior frontal gyrus (56–58). At least 100-fold higher affinity is shown by OT for OT receptors compared with vasopressin receptors (29,36,59). We mapped the distribution of effects of IN-OT using conventional mass univariate voxel-by-voxel analysis, allowing inferences regarding local regions. In the absence of an a priori pharmacodynamic model, we used multivariate pattern recognition (PR) on rCBF maps (60) to elucidate temporal dynamics. When the pharmacologic intervention elicits correlated, spatially distributed effects (37,44,45,61) as IN-OT does (28,62), PR offers increased sensitivity compared with conventional mass univariate approaches. The overall pattern of rCBF changes at each temporal interval can be reduced by PR into a single metric—the probability that an rCBF image belongs to a particular class (here, IN-OT or placebo). Using these predictive probabilities, we created pharmacodynamic profiles of changes in brain physiology following IN-OT or placebo.

METHODS AND MATERIALS

Participants

We recruited 32 healthy men (IN-OT group, $n = 16$, mean age (SD) = 24.23 (1.75) years; placebo group, $n = 16$, mean age = 25.78 (4.44) years; $t_{30} = 1.30$, $p = .21$) based on previous power analyses (63). Participants were screened for psychiatric conditions using Symptom Checklist-90-Revised (64) and Beck Depression Inventory-II (65) questionnaires, did not take any prescribed drugs, tested negative on a urine screening test for drugs of abuse, and consumed $<$28 units of alcohol per week and $<$5 cigarettes per day. Both parents of participants were white European to reduce genetic background variability. Participants abstained from alcohol and heavy exercise for 24 hours and abstained from any beverage or food in the 2 hours before scanning in the morning. Participants gave written informed consent. King's College London Research Ethics Committee (PNM/10/11-160) approved the study.

Design, Materials, and Procedure

We employed a single-blinded, placebo-controlled design with two independent study arms. Before taking part, all participants were informed they would receive a neuropeptide and remain blinded to its name and that they might receive placebo until the postsession debriefing; 50% received IN-OT, and 50% received placebo. We obtained two baseline cerebral blood flow (CBF) images before participants came out of the scanner to receive 40 IU of IN-OT (Syntocinon; Novartis, Basel, Switzerland) or placebo (same composition as Syntocinon except for OT). We used 40 IU, the highest clinically applicable safe dose administered to human volunteers [e.g., in 14% of studies until 2011 (66) and still being used (15)] to maximize power. Use of this dose also ensured comparability with the study of Born *et al.* (27) on vasopressin in the CSF using 40 IU as the minimum dose.

Participants self-administered one puff (4 IU) of IN-OT (or placebo) every 30 seconds, alternating between nostrils. The administration phase lasted approximately 9 minutes including a 3-minute rest at the end. Participants returned to the scanner for two anatomic scans followed by eight CBF images spanning 25–78 minutes from the onset (henceforth called postadministration scans) of nasal spray administration (Figure 1A). Participants were instructed to lie still and maintain their gaze on a centrally placed fixation cross during scanning. We assessed participants' levels of alertness (anchors: alert-drowsy) and excitement (anchors: excited-calm) using visual analog scales before acquiring each CBF image. The subjective ratings of one participant from the IN-OT group were lost because of a technical issue.

Image Acquisition and Preprocessing

Images were acquired using a Signa HDx 3.0T magnetic resonance imaging scanner (General Electric, Milwaukee, Wisconsin). We employed the pulsed-continuous arterial spin labeling methodology (67). The CBF maps (in standard physiologic units—mL blood/100 g tissue/min) were computed with a spatial resolution of 1 mm $\times$ 1 mm $\times$ 3 mm. Total acquisition time for each CBF map was 5.5 minutes. We also acquired a T2-weighted fast spin echo high spatial resolution structural image for coregistration and normalization purposes.

We performed the following preprocessing steps (detailed in the Supplement. 1) We removed extracerebral signal from each participant's T2 volume and created a binary brain mask. 2) We coregistered each CBF image to the corresponding T2 volume for each participant, correcting for interscan movement. 3) We removed extracerebral signal from CBF images by

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