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Vasopressin modulates social recognition-related activity in the left temporoparietal junction in humans

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The neuropeptide vasopressin is a key molecular mediator of social behavior in animals and humans, implicated in anxiety and autism. Social recognition, the ability to assess the familiarity of others, is essential for appropriate social interactions and enhanced by vasopressin; however, the neural mechanisms mediating this effect in humans are unknown. Using functional magnetic resonance imaging (fMRI) and an implicit social recognition matching task, we employed a double-blinded procedure in which 20 healthy male volunteers self-administered 40 UI of vasopressin or placebo intranasally, 45 min before performing the matching task in the scanner. In a random-effects fMRI analysis, we show that vasopressin induces a regionally specific alteration in a key node of the theory of mind network, the left temporoparietal junction, identifying a neurobiological mechanism for prosocial neuropeptide effects in humans that suggests novel treatment strategies.

Introduction

Social recognition is a cornerstone of social cognition; the ability to properly and quickly assess the familiarity of others is essential for appropriate and beneficial social interactions. Vasopressin, a neuropeptide released in the brain that has been implicated in anxiety and autism,[1] is a known molecular mediator of complex social behaviors, including social recognition.[2,3] Specifically, centrally injected vasopressin in rats improves and prolongs social memory,[4] whereas vasopressin receptor knockout[5] and antagonism[6] impairs social recognition, but not general object recognition. In agreement with these data in animals, intranasal administration of vasopressin in human males has been shown to enhance familiarity ratings of previously seen emotional faces.[7]

In rodents, the lateral septum is especially implicated in the action of vasopressin, through V1a receptors, to influence social recognition. Re-expressing V1a receptors specifically in the lateral septum of V1aR knockout mice completely rescues social recognition, and overexpression of the vasopressin V1a receptor in the lateral septum of wild-type mice potentiates social recognition.[8] The lateral septum is densely connected to the olfactory system in rodents,[9] where social memory primarily relies on olfactory cues, while social recognition in primates, including humans, is driven by visual and auditory information. In agreement with this, social familiarity in humans has been primarily linked to cortical areas with access to multimodal visual/auditory information, such as posterior superior temporal cortex/temporoparietal junction (TPJ) and prefrontal cortex,[10–12] suggesting that these regions may contribute to the (currently unknown) neural circuitry underlying the influence of vasopressin on social recognition in humans.

To test this hypothesis, in this study, using functional magnetic resonance imaging (fMRI) and an implicit social recognition matching task, we assessed the effect of vasopressin on social familiarity-related neural activity in men to determine the brain region(s) underlying the influence of vasopressin on social recognition in humans.

Materials and methods

Participants. A total of 20 right-handed, Caucasian, healthy male volunteers aged 18–43 years (mean age = 28.60 years, s.d. = 5.88) participated in the study. Volunteers were recruited from the Washington DC Metropolitan Area and the National Institutes of Health community. Participants had no structural brain abnormalities, no history of psychiatric or neurological disorders and had normal electrocardiograms and blood pressure. Each participant gave written, informed consent for a protocol approved by the National Institute of Mental Health institutional review board.

Emotion inventories. Both before and after each of the scanning sessions, the current emotional states of the participants were assessed with the state versions of the State-Trait Anger Expression Inventory[13] and State-Trait Anxiety Inventory[14] to determine potential effects of vasopressin on current levels of anger and anxiety, respectively. Valence, arousal and dominance was also assessed before and after the scanning sessions using the Self-Assessment Manikin.[15] Potential drug effects on each rating questionnaire were statistically determined using paired t-tests.

Implicit social recognition matching task. The implicit social recognition matching task used was a modified version of a block-design matching task,[16] consisting of blocks matching negative emotional facial expressions and blocks

matching negative scene orientations as a non-social control condition—as part of a neuroimaging task battery. Subjects performed two sequential runs of the task. In both runs, the face stimuli were from the NimStim Face Stimulus Set (http://www.macbrain.org/resources.htm), and the scene stimuli were from the International Affective Picture System (http://csea.phhp.ufl.edu/media/iapsmessage.html). The first run (4.17 min) served as training in which subjects were familiarized with two faces and two scenes that were repeatedly presented in the matching task. This training run was divided into ten blocks, five blocks of matching two faces with fearful/angry facial expressions and five blocks of matching orientation of two scenes as a non-social control condition, alternatively. Each block began with a 2-s instruction screen and consisted of four matching frames (5 s each); for each matching frame, participants indicated which of the two bottom images, left or right, match the center-top image. In the second run (eight blocks: four face-matching blocks and four scene-matching blocks; 3.43 min), subjects performed the same task as the first run and were again presented with blocks of matching the familiar faces and scenes, but intermixed with blocks of matching unfamiliar faces and scenes (Figure 1). Two of the four matching blocks of faces and scenes used repeatedly previously seen ('familiar') stimuli, whereas in the other blocks, never before seen ('unfamiliar') stimuli were used.

Subjects performed this task (both runs) in two separate sessions, at 1 week interval, and self-administered either 40 UI of vasopressin or placebo intranasally under investigator supervision (double-blind) in each session, 45 min before beginning the task to capture peak CSF vasopressin levels.[17] The drug order (vasopressin or placebo) was counter-balanced across subjects. The Pharmaceutical Development Section of the NIH Pharmacy Department formulated the vasopressin and placebo solutions and maintained the blind. fMRI and behavioral data are only reported for the second run of the task, as the first run served solely as training to acquire stimuli familiarity. Potential drug effects on task performance were statistically determined using paired t-tests and re-peated-measures analysis of variance.

fMRI imaging. Scanning was performed on a 3 T GE Signa scanner (GE Healthcare, Milwaukee, WI, USA). fMRI data is only reported for the second run of the social recognition matching task, as the first run served solely as training to acquire stimuli familiarity. For each participant, 98 whole-brain scans were acquired to measure the T2*-weighted blood oxygenation level-dependent effect with the following parameters: gradient-recall echo planar imaging; TR = 2000 ms; TE = 30 ms; flip angle = 90°; 64 × 64 matrix; FOV = 240 mm; and 28 slices (3.5-mm thick) acquired with an interleaved order of slice acquisition. Five additional scans were acquired at the beginning of run to allow for steady-state magnetization (discarded from analysis). Head movement during scanning was minimized with a vacuum pillow and additional padding.

fMRI preprocessing. fMRI preprocessing was performed using Statistical Parametric Mapping (SPM5) (http://www.fil.ion.ucl.ac.uk/spm/). Motion correction to the first functional scan was performed using a six-parameter rigid-body transformation. For each individual, the mean of the functional images was spatially normalized to the Montreal Neurological Institute template conforming to the Talairach orientation system[18] by applying a 12-parameter affine transformation followed by nonlinear warping.[19] The computed transformation parameters were applied to all the functional images, interpolated to a final voxel size of $3 \times 3 \times 3$ mm^3. Images were subsequently spatially smoothed with an 8-mm Gaussian kernel.

fMRI analysis. A random-effects, epoch-related statistical analysis was performed in a two-level procedure using SPM5. At the first level, a separate general linear model was specified for each participant for each session. Blood oxygenation level-dependent responses during each face-matching block (unfamiliar and familiar) and each scene-matching block (unfamiliar and familiar) were modeled separately, by convolving the block onset vectors with a synthetic hemodynamic response function. The data were high-pass filtered (128-s cutoff) to remove low-frequency
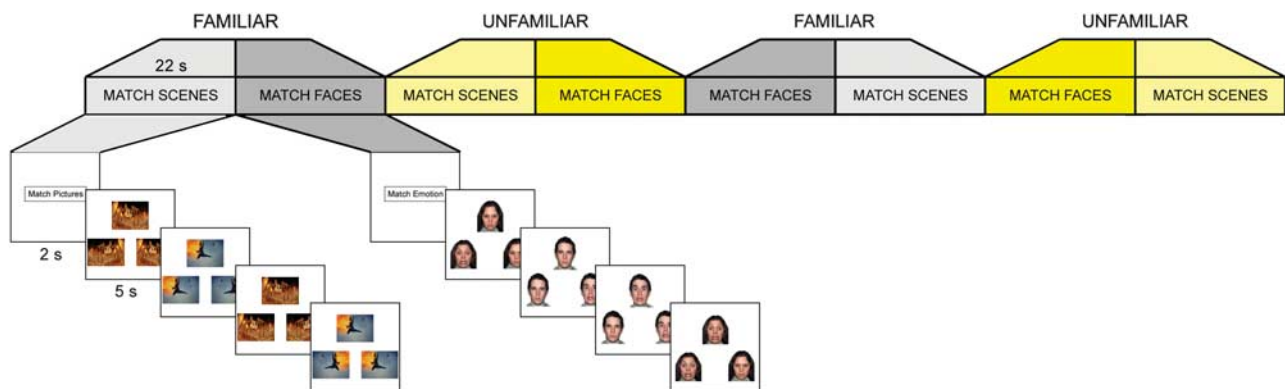

Figure 1 Schematic diagram of the social recognition matching task. The task was divided into eight blocks, four blocks of matching faces with fearful and angry facial expressions, from the NimStim Face Stimulus Set (http://www.macbrain.org/resources.htm), and four blocks of matching scene orientation, from the International Affective Picture System (http://csea.phhp.ufl.edu/media/iapsmessage.html), as a non-social control condition. Two of the four matching blocks of faces and scenes used repeatedly previously seen ('familiar') stimuli, whereas in other blocks, never before seen ('unfamiliar') stimuli were used. Each block contained four matching panels (5 s each) and participants indicated which of the two bottom images, left or right, match with the center-top image. Instructions were displayed for 2 s at the beginning of each block: 'Match Emotion' or 'Match Pictures'.

drifts, and serial correlations were accounted for by an autoregressive model of the first order. To isolate effects of social recognition, contrast images were calculated for each participant in both sessions for the interaction of sociality and familiarity ((faces–scenes) × (familiar–unfamiliar)). The individual contrast images were then entered into a second level random-effects analysis in which a paired t-test was used to statistically assess drug effects (vasopressin versus placebo) on resulting neural activity. A cluster-based, whole-brain family-wise error-corrected threshold of $P < 0.05$ was applied to the resulting summary statistical maps using parameters determined by the Monte Carlo simulations implemented in the AlphaSim program in AFNI.[20] The simulations (1000 iterations, 8 mm full width at half maximum, $3 \times 3 \times 3$ mm^3 voxels) yielded a combined threshold of $t = 3$ and cluster extent of 35 contiguous voxels (945 mm^3) as equivalent to a corrected threshold of $P < 0.05$.

Results

Behavioral results. The task performance data are given in Table 1. Task performance data were not available for one subject because of technical difficulties. Participants performed the task with near-perfect accuracy, and there was no significant effect of drug on accuracy ($t = 0.33$; $P = 0.75$). Across sessions (vasopressin and placebo), there was a main effect of familiarity and sociality on reaction time periods; participants responded significantly faster when matching familiar stimuli (F(1, 36) = 260.71; $P < 0.001$) and faster during face-matching blocks compared with scenes (F(1, 36) = 148.57; $P < 0.001$). There was no effect of drug (F(1, 36) = 0.63; $P = 0.43$).

Behavioral data from the pre- and post-scan emotional inventories are given in Table 2. The level of experienced arousal in both conditions (vasopressin and placebo) was significantly greater post-scan compared with pre-scan (placebo: $t = 2.45$, $P = 0.02$; vasopressin: $t = 2.35$, $P = 0.03$). No other emotional measures (valence, dominance, anger and anxiety levels) differed significantly between pre- and post-scan in either condition ($P > 0.10$). As reported previously,[21] vasopressin had no significant effect on any behavioral measurements of valence, arousal, dominance, anger or anxiety ratings ($P > 0.10$).

fMRI results. Vasopressin induced a regionally specific alteration in social recognition-related activity solely in the left TPJ/Brodmann area 39 (peak: −48, −66, 21; $t = 4.81$; $k = 52$; $P < 0.05$ corrected; Figure 2a), as demonstrated by the effect of drug compared with placebo on the interaction of sociality (faces or scenes) and familiarity (familiar or unfamiliar). Paired t-tests performed on beta values extracted from the peak voxel (−48, −66, 21) revealed that under placebo, activity in left TPJ was significantly increased by social unfamiliarity, that is, unfamiliar faces, compared with unfamiliar scenes ($t = 3.42$; $P = 0.003$), an effect that vanished for familiar stimuli ($t = 0.05$, $P = 0.96$), and under vasopressin (Figure 2b); after vasopressin, social unfamiliarity did not differentially influence TPJ activation ($t = 0.75$; $P = 0.46$) and was statistically comparable to the activation for familiar faces, compared with scenes under placebo ($t = 0.42$; $P = 0.68$). Although it does not survive statistical significance, there is also a trend for an increase in left TPJ activity to familiar social compared with non-social stimuli under vasopressin ($t = 1.99$; $P = 0.062$).

Table 1 Task performance data

	Placebo				Vasopressin			
	Unfamiliar faces	*Familiar faces*	*Unfamiliar scenes*	*Familiar scenes*	*Unfamiliar faces*	*Familiar faces*	*Unfamiliar scenes*	*Familiar scenes*
Accuracy (% correct)	100.0 (0.0)	99.34 (2.87)	95.39 (7.46)	99.34 (2.87)	100.0 (0.0)	99.34 (2.87)	96.05 (7.28)	99.34 (2.87)
Reaction time (s)	1.43 (0.31)	1.25 (0.30)	2.10 (0.41)	1.55 (0.39)	1.36 (0.25)	1.15 (0.26)	2.06 (0.38)	1.48 (0.22)

Faces: data from the face-matching blocks. *Scenes*: data from the scene-matching blocks. Mean data are given (standard deviation in parenthesis).
$N = 19$; task performance data for one subject were not available.

Table 2 Behavioral data from emotion inventories

	Placebo			Vasopressin		
	Pre	*Post*	*Post–Pre*	*Pre*	*Post*	*Post–Pre*
STAI-S	27.47 (6.36)	25.90 (4.53)	−1.95 (5.83)	27.55 (6.63)	27.16 (6.41)	−0.79 (5.10)
STAXI-S	15.30 (0.66)	15.10 (0.31)	−0.20 (0.77)	15.45 (1.23)	15.40 (0.88)	−0.05 (0.69)
SAM: valence	2.80 (1.24)	2.85 (1.04)	0.05 (1.15)	2.85 (1.27)	3.15 (0.99)	0.30 (1.38)
SAM: arousal[a]	6.20 (1.61)	6.95 (1.36)	0.75 (1.37)	5.75 (1.48)	6.65 (1.81)	0.90 (1.71)
SAM: dominance	5.45 (1.57)	5.75 (1.45)	0.30 (1.08)	5.90 (1.71)	5.90 (1.07)	0.00 (1.38)

Abbreviations: SAM, self-assessment manikin; STAI-S, State-Trait Anxiety Inventory-State version; STAXI-S, State-Trait Anger Expression Inventory-State version.
[a]Arousal post-scan levels were significantly different from pre-scan levels in both the placebo ($P = 0.02$) and vasopressin conditions ($P = 0.03$).
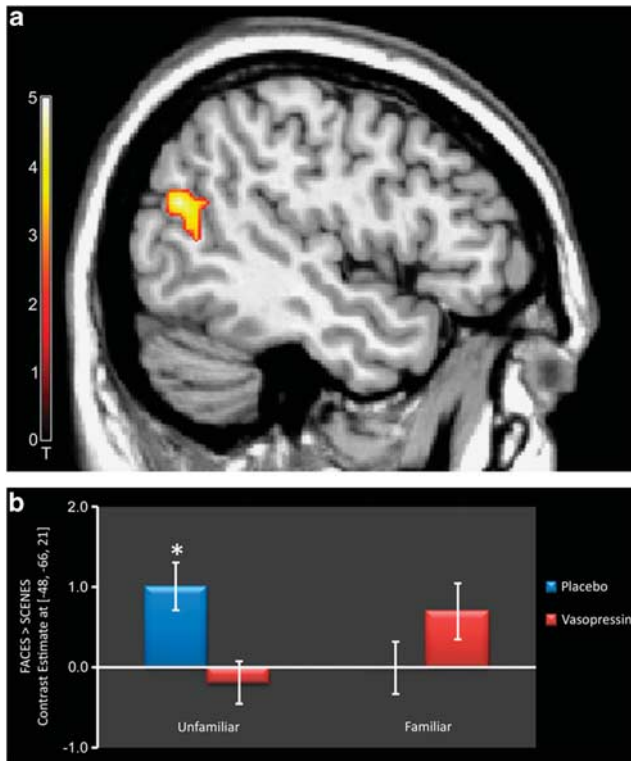Mean data are given (standard deviation in parenthesis).

Figure 2 The effect of vasopressin compared with placebo on the interaction of sociality (faces/scenes) and familiarity (familiar/unfamiliar) revealed (**a**) a significant activation in the left temporoparietal junction, overlaid on a sagittal section of a structural template MRI ($x = -48$). The color bar represents *t*-values. (**b**) Plotted are the contrast estimates extracted from the peak-activated voxel (-48, -66, 21). Bars represent means across subjects and error bars represent standard error. Under placebo (blue bars), contrast estimates were significantly greater for unfamiliar faces compared with unfamiliar scenes (*$P = 0.003$), an effect that was abolished by stimulus familiarity and vasopressin (red bars) administration.

Discussion

Our findings demonstrate that vasopressin modulates social recognition-related activity in the left TPJ in humans. During exposure to socially unfamiliar stimuli, vasopressin abolishes the augmentation of left TPJ activity evoked by social unfamiliarity under placebo to a level comparable to that evoked by socially familiar stimuli under placebo. As such, these data suggest that, when unfamiliar faces are processed (matched) under vasopressin, stimuli are more readily transferred to a familiar categorization, as represented in TPJ reactivity. The TPJ has been implicated in the processing of social background context and social familiarity[22] and accesses multimodal visual/auditory information that drive social recognition in primates, including humans.[10–12] Conversely, in rodents, the lateral septum, connected to the olfactory system, is a critical site of action for vasopressin to influence social recognition.[8] The absence of differential activation in the lateral septum, while not excluding an effect in humans (as this structure is difficult to image in human brain), could therefore be related to species differences.

Vasopressin is likely acting on vasopressin V1a receptors in the brain to influence familiarity of social stimuli;[8] however,

although V1a receptors are evident in various primate brain regions,[23] it remains unclear if they exist in the human TPJ. Therefore, whether vasopressin is acting directly or by an indirect pathway to influence social recognition-related activity in the left TPJ remains to be elucidated.

In previous work, the directionality of the relationship between TPJ activity and social familiarity has been inconsistent (that is, activity enhanced by social familiarity or activity enhanced by social unfamiliarity). Such discrepancies may be dependent on whether familiar stimuli were newly learned,[22] as here, or personally familiar[11] (for example, relatives). Future work should determine whether our vasopressin finding extends to personally familiar faces. The TPJ is also a critical brain structure associated with human-specific social cognition,[12] notably involved in 'theory of mind' processes,[24] suggesting further studies of vasopressin effects on these aspects of social cognition as well.

Given the prominent role of the TPJ in social-specific cognition, the TPJ activation to unfamiliar faces under placebo may represent the social relevance or importance of these stimuli, relative to non-social or familiar stimuli. As such, based on the current findings, vasopressin may influence social recognition by modulating left TPJ activity to dampen the social importance of unfamiliar faces while potentially (evident by trend in TPJ activity increase) enhancing the social importance of familiar faces.

Behaviorally, vasopressin did not influence the emotion inventories or task performance. This lack of behavioral modification is consistent with previous studies in which participants performed a comparable matching paradigm—but without manipulating social familiarity—after administration of vasopressin[21] and the related neuropeptide, oxytocin[25] and is likely due to the implicit nature of the task (that is, subjects were not explicitly tested on social recognition). Alternatively, it is possible that the lack of a significant influence of drug on task performance is due to a ceiling effect; therefore, implementation of a more challenging task could reveal vasopressin effects on task performance accompanying the reported drug-induced modification of neural activity.

We note that behaviorally, both oxytocin[26] and vasopressin[7] have been shown to increase the familiarity of faces, suggesting that this could be a joint mechanism supporting the prosocial action of these neuropeptides. On the basis of this study, it should be investigated whether familiarity after oxytocin administration is also mediated through the TPJ or rather, as previous researchers have proposed,[26] through an amygdala–fusiform face area circuit.

In conclusion, to our knowledge, this is the first study to investigate the neural biology underlying the effect of vasopressin on social recognition in humans, and our data identify the first regionally specific pharmacological strategy targeting the TPJ, suggesting that vasopressin receptors could be present in human cortex or action through an as yet unspecified indirect pathway. Our results implicate a neurobiological mechanism by which vasopressin may enhance social familiarity by modulating the TPJ and open a pharmacological approach to target this region in psychiatric disorders with known social cognitive deficits such as autism and social anxiety disorder.

Conflict of interest

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