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Oxytocin selectively modulates brain processing of disgust in Huntington's disease gene carriers

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ABSTRACT

People with Huntington's disease (HD) exhibit altered processing of emotional information, especially disgust and other negative emotions. These impairments are likely due to the effects of the disease on underlying brain networks. We examined whether oxytocin, when given intranasally, would normalise aberrant brain reactivity to emotional faces in participants with the gene-expansion for HD. In a double-blind placebo-controlled cross-over design, we measured brain activity, using functional magnetic resonance imaging, whilst nine medication-free HD carriers, and ten control participants viewed emotional (disgust, fear, angry, sad, surprise, happy) and neutral faces, following acute intranasal oxytocin (24 IU) and placebo. Subjective mood changes were assessed before and after the neuroimaging on each visit. Permutation-based non-parametric statistical testing for the whole brain, showed significant group × drug interactions (p's < 0.05, TFCE corrected) in areas of the left frontal pole, superior frontal, and middle frontal gyri cortically, and left putamen and thalamus sub-cortically. Parameter estimates extracted from the middle frontal gyrus and putamen showed that, under placebo, the HD group had lower brain activity to disgust stimuli, compared with controls. After intranasal oxytocin, the pattern of activation to disgust stimuli was normalised in the HD group to similar levels as controls; eight of the nine HD carriers showed increased response in the middle frontal gyrus, and seven of the nine HD carriers showed increased response in the putamen. The observed effects of oxytocin occurred in the absence of changes in subjective mood or state anxiety. These findings provide early evidence for a physiological role of oxytocin in the neuropathology of HD. Our findings are the first reported oxytocin effects in a neurodegenerative disease. Further research should examine the therapeutic benefits of oxytocin in alleviating emotional and social cognition deficits in HD and related disorders.

1. Introduction

Huntington's disease (HD) is a debilitating neurodegenerative disease that is caused by a genetic mutation involving a CAG repeat expansion in the huntingtin gene. HD is characterised by progressive declines in motor, psychiatric and cognitive functions (Craufurd et al., 2001), with a typical disease duration of 15–20 years. A core cognitive feature implicated in HD is an impairment in recognising emotions from other people's facial expressions, which has been documented in over 26 studies (Bora et al., 2016). Large effects are evident for all emotions, but particularly for disgust, anger, and fear in manifest HD (d = 1.43–1.54), with moderated effects in premanifest HD (d = 0.36–0.45) (Bora et al., 2016). These impairments form part of the earliest signs of disease deterioration, are detectable as early as 15 years before disease onset, and worsen with disease progression (Tabrizi et al., 2009, Labuschagne et al., 2013). Emotion recognition impairments have been associated with disease duration, disease burden, motor symptoms, age, and CAG repeat length (in manifest HD), and with a higher probability of motor onset within the next year (in premanifest HD) (Bora et al., 2016). Neuroleptic treatments in HD are associated with detrimental effects on emotion recognition performance (Labuschagne et al., 2013), which highlights the need for

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improved treatment options.

The neuropeptide oxytocin, when administered intranasally, has been found to facilitate social encounters, and improve social cognitive outcomes and emotion recognition in healthy and clinical groups characterised by social deficits, such as autism and social anxiety disorder (Heinrichs et al., 2009). Intranasal oxytocin modulates, and 'normalises', previously abnormal brain activity in regions associated with emotion processing, such as the amygdala and prefrontal cortices (Labuschagne et al., 2010, Labuschagne et al., 2012), and caudate and putamen (Feng et al., 2015, Nawijn et al., 2016). These regions are implicated in the neuropathology, and part of a brain network associated with emotion recognition deficits, in HD (Novak et al., 2012). Early-stage HD has also been associated with reductions, up to 45%, in oxytocin-expressing neurons in the hypothalamus, the region where oxytocin is produced, suggesting a role of oxytocin in the behavioural phenotype of HD (Gabery et al., 2010, Gabery et al., 2015).

Given the complexity of the disease phenotype, including the underlying dysfunctional brain ciruits, the use of neuroimaging in combination with pharmacology has been found to be sensitive to probe pharmacologial effects on functional neuroanatomy which could assist with the early detection of the potential for a treatment to be a key neuromodulator that could advance drug development (Paulus and Stein, 2007; Wandschneider and Koepp, 2016). As a result, the current study focused on examining whether oxytocin may be a viable neuromodulator of emotion processing in HD using functional magnetic resonance imaging. Specifically, the objective of this study was to test the hypothesis that a single dose of intranasal oxytocin would influence, and normalise, brain activity to emotion processing in people with the HD CAG-expansion (compared to controls), particularly in disorder-relevant emotions, including disgust and other negative emotions.

2. Materials and methods

2.1. Participants

Nine non-medicated males with the HD CAG-expansion (mean age ± standard deviation: 48.3 ± 11.4 years; CAG-repeat length range: 38–44) and ten age-matched healthy controls (42.9 ± 10.2 years) participated. We stopped the recruitment of HD participants after approximately two years of data collection (November 2012 to February 2015) due to the length of this period that went beyond initial planning and funding period, and we did not want to amend our inclusion criteria of recruiting non-medicated HD participants. Participants' ages ranged from 21 to 64 years at the end of the data collection period (end of 2015), and groups did not differ on age, $t(17) = 0.119$, $p = 0.907$. At the time of data collection, seven participants in the HD CAG-expanded group were considered premanifest, and two participants had a confirmed diagnosis based on motor symptoms. The average disease burden score for the HD group was 247 (range: 140–338), as determined by the formula: [CAG-35.5] × age (Penney et al., 1997). All participants were right-handed, free of antidepressant/neuroleptic medications, and non-smokers. The HD CAG-expanded group was recruited from a database of volunteers from our local HD clinics. All participants provided written informed consent, and the study was approved by the Monash University Human Research Ethics Committee and the Therapeutics Goods Administration of Australia.

2.2. Study design

We used a double-blind placebo-controlled, within-subject cross-over design. Participants received an intranasal spray of either oxytocin (24 IU or 40.32 μg; Syntocinon-spray; Novartis, Switzerland) or placebo (containing all ingredients except for the peptide) in three puffs of 4 IU or 6.72 μg per nostril. The dose of 24 IU is the most commonly reported dose of intranasal oxytocin in human adult studies (Wigton et al., 2015, Wang et al., in Press), with evidence also suggesting that 24 IU is the most effective dose (Spengler et al., 2017). A comprehensive review of safety and side-effects found that there were no obvious side-effects or adverse reactions from intranasal oxtyocin (MacDonald et al., 2011). Oxytocin and placebo test sessions were randomised and counterbalanced using a computerised randomisation program in Windows Excel. Test sessions were separated by approximately one week. The nasal sprays had no identifiable information on the labels other than a colored dot on the bottom of the bottle. An independent person and two witnesses managed the blinding procedures and treatment concealment. Consistent with previous research, nasal sprays were administered 45 min before the functional magnetic resonance imaging/Emotional Face Matching Task session (Labuschagne et al., 2010). This timing aligns the imaging session with that of oxytocin's predicted maximum pharmacokinetics (Striepens et al., 2013) and physiological effects (Heinrichs et al., 2003, Domes et al., 2007). Participants did not consume caffeine or alcohol on the scanning day and did not consume food 1 h prior to arrival. The study occurred at the Monash Biomedical Imaging facility, Melbourne, Australia, and was registered with the Australian New Zealand Clinical Trials Registry (Trial Id: ACTRN12613000026729).

2.3. Emotional face matching task and analysis

During the scanning session, participants completed an Emotional Face Matching Task, which we have used in pharmacological neuroimaging studies (Phan et al., 2008, Labuschagne et al., 2010) and has been shown to reliably and robustly activate the affective network (Hariri et al., 2002, Tessitore et al., 2002). The task involved two analogous conditions, each including a target stimulus presented at the top of the screen, and two stimuli at the bottom of the screen. The emotion condition used expressive faces whereas the baseline comparison condition presented shapes. Participants were required to select from two stimuli at the bottom, to match the (top) target stimulus by pressing the left or right button. For each face block, the target and congruent face displayed the same one of seven expressions (neutral, fearful, angry, happy, sad, surprise, or disgust), and the incongruent face displayed any one of the six other expressions. The blocks of faces were interspersed with a baseline condition that required participants to match shapes (circles, rectangles, or triangles) using instructions analogous to the face condition. The paradigm consisted of fourteen experimental blocks, each including seven sequential matching trials of 3 s presentation. The fourteen blocks consisted of seven blocks of matching emotional faces (one block of each target expression of neutral, fearful, angry, happy, sad, surprise, or disgust), interleaved with seven blocks of matching shapes, counterbalanced across two runs. Response accuracy and reaction times were analysed in a 2 group × 2 drug × 7 emotion analysis of variance, and Greenhouse-Geisser corrected where necessary (data presented in Supplementary Fig. 1S).

2.4. Functional imaging acquisition and analysis

We acquired brain magnetic resonance images using a 3 T Skyra Siemens scanner and a 32-channel head coil. An echo-planar imaging sequence was used to acquire blood-oxygen level dependent functional images (TR = 3000 ms, TE = 30 ms, flip-angle = 90°, FOV = 192 × 192 mm^2, 44 contiguous 3-mm thick slices, aligned AC/PC). Whole-brain structural reference images were also acquired using a T1-weighted MPRAGE sequence (TR = 1540 ms, TE = 2.57 ms, flip-angle = 9°, FOV = 250 × 250 mm^2, 208 sagittal slices, 1 mm slice thickness, sagittal plane).

Processing and statistical analysis of imaging data were conducted in FSL version 5.98 (FMRIB, Oxford, UK), using FMRIB Expert Analysis Tool and Randomize tool. Pre-processing steps included brain extraction, motion correction, smoothing (6 mm FWHM Gaussian window), and high-pass temporal filtering (cut-off = 128 s). We registered the functional data to a standard MNI space using registration approach