Short- and long-term effects of oxytocin on empathy in autistic male adults.

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Our study aims at investigating whether male adults with ASD differ from healthy male adults in their neurophysiological responses to positive and negative empathy-evoking pictures when taking oxytocin intranasally once. To this end we will compare...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON36342

Source
ToetsingOnline

Brief title
Oxytocin effects in autistic male adults.

Condition

- Other condition
- Communication disorders and disturbances

Synonym
antisocial personality disorder, autism

Health condition

autisme spectrum stoornis / antisociale persoonlijkheid

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: autism, empathie, oxytocin, social behaviour

Outcome measures

Primary outcome

In the short-term experimental trial, our primary outcome measures shall be the ERP and cardiac responses in the various IAPS picture conditions. These neurophysiological responses reflect fast changes in the activity of the neurobiological systems involved in emotion processing.

Another outcome measure shall be the score on a questionnaire assessing (short-term changing) state-related anxiety. Scores of this measure shall be obtained from the questionnaire being completed shortly before and about 15 minutes after oxytocin / placebo administration.

Secondary outcome

Blood serum OT levels will be determined before and about 60 min after oxytocin / placebo administration. Baseline and delta values will be accounted for in the prediction of our primary output measures. For our choice of the time points for the venipunctures we refer to section 6.5 of the main protocol where the pharmacokinetic qualities of nonapeptides are addressed.

Also accounted for in the prediction of our primary output measures will be the scores on a series of questionnaires completed for an extensive

characterisation of the participants in terms of qualities and personality characteristics that are important to showing (deficits in) prosocial behaviour (see section 7.1.3 of the main protocol).

Confounders such as the use of drugs or alcohol will be controlled for by saliva tests and blood serum analysis, and generally lead to exclusion of the participant from the short term experimental part of the study (see section 4.3 of the main protocol)

Study description

Background summary

Problem Definition

So far, no treatment has been reported to alleviate one of the core problems characterising the Autism Spectrum Disorders (ASD), that is a strongly impaired capacity or even complete lack of feeling affective empathy. As, however, many studies of healthy individuals have shown that the neuropeptide oxytocin , when administered with nasal spray, enhances empathy-driven prosocial behaviour such as social attachment, affiliative behaviour and trust, it is warranted to investigate oxytocin effects on empathy experience in the above-mentioned disorders.

Affective empathy, brain systems and the role of oxytocin

A crucial facilitator of attachment and affiliative behaviour is the affective component of empathy, which is closely related to the concept of *emotional contagion* meaning the tendency to feel similar emotions when observing another person*s emotion. Recent studies have identified brain systems that are involved in the experience of affective empathy. When observing or communicating with an attached person the dopaminergic reward system including the orbitofrontal cortex and midbrain-striatal structures, such as the nucleus accumbens is activated. These pathways related to pro-social motivation and reward processing contain high levels of oxytocin receptors (OXTR), while furthermore oxytocin has been shown to facilitate dopamine release in particularly the nucleus accumbens.

Other important systems involved in attending to and the recognition of emotionally salient stimuli are the cortisol-controlled HPA axis and the amygdala. Both have been found to be dampened by oxytocin in their response to fearful and threatening stimuli. This has led to the hypothesis that OT may increase trust and prosocial behaviour by its anxiolytic effects in potentially frightening social situations, thereby promoting approach behaviour. Yet, there are studies that did not report any decreased anxiety or increased calmness following oxytocin treatment while trust did improve. This suggests a rather direct effect of oxytocin on affiliative behaviour by stimulating the previously mentioned reward system.

Autistic Spectrum Disorders

Impairment in affiliative behaviour, empathy and compassion are core features of the Autism Spectrum Disorders (ASD). Individuals with an ASD (Diagnostic Statistic Manual of mental disorders, DSM-IV: American Psychiatric Association, 1994) are characterised by an impaired ability in interacting and communicating with others as well as by repetitive behaviours and restricted interests. Their social impairments have been explained by deficits in both affective empathy and higher order cognitive empathetic abilities, such as a poor Theory of Mind (ToM), i.e. poor ability to understand the mental state (thoughts, feelings, wishes, beliefs) of others.

Measures of empathy

Questionnaires
The most frequently used method for assessing empathy in adolescents and adults are self-report questionnaires, where participants are requested to indicate their agreement with empathy-related statements or to select the most suitable interpretation of a social situation that is described in a vignette. Although indispensable for screening, phenotyping and the selection of subgroups, self-reports may have some limitations ranging from the comprehensibility of the items to response biases resulting from impression management like faking. Moreover, self-reports basically reflect the outcome of deliberate, conscious processing while the perception of one*s own feelings and the feelings of others may be quite spontaneous, effortless and unconscious cognitions with relevant cues of empathy most frequently being communicated nonverbally. Finally, as these questionnaires are generally assessing trait-related qualities they are not suitable for measuring short-term treatment effects.

Electrocortical brain and autonomic cardiac responses to emotional stimuli
A more direct measure for investigating the non-deliberate aspects of emotion processing that underlie affective empathy, is the measurement of electrocoritcal brain responses to emotionally confronting pictures These are measured by EEG event-related potentials (ERPs).A well-established and widely used source of visual images that elicit affective responses is the International Affective Picture System (IAPS). It consists of 942 colour

photographs and includes gender and age dependent normative ratings of the images on three dimensions that are related to emotion processing. These ratings have been well-validated by other rating procedures as well as by psychophysiological (e.g. ERP) and functional magnetic resonance imaging (fMRI) measures.
Due to its wide range of thematic contents, the IAPS allows for comparing responses to pictures portraying humans in different positive and negative or emotionally neutral contexts with responses to inanimate pictures with and without an emotional loading. These comparisons have been done in numerous studies investigating EEG ERPs.
Many ERP studies have demonstrated a specific component related to affect processing. This is a parietally measured long lasting late positivity, called the LPP. This component has been shown to be greater in response to emotionally loaded (especially negative) pictures when humans are depicted as compared to emotionally loaded pictures without humans or emotionally neutral pictures with humans. This *empathy* effect moreover appeared to be greater in women than in men.
Next to electrocortical responses, many studies have reported autonomic responses as measured by, e.g., electrodermal and cardiac activity to be very sensitive to the valence of the IAPS pictures, while these responses moreover appeared to discriminate high functioning autistic from healthy adults. We will investigate cardiac responses at the level of event-related changes in inter-beat interval times as greater cardiac decelerations have been found to occur in response to especially aversive stimuli.

Study objective

Our study aims at investigating whether male adults with ASD differ from healthy male adults in their neurophysiological responses to positive and negative empathy-evoking pictures when taking oxytocin intranasally once.

To this end we will compare two groups of twenty-six normally intelligent 18-to 30-year-old males in their ERP and cardiac evoked responses to empathy-evoking pictures from the IAPS in a condition of nasally administered oxytocin intake and a placebo condition. Participants will be a group of healthy adults and a group being diagnosed and systematically phenotyped as having respectively ASD.

We will further investigate whether pre-treatment (self-)reported personality traits and psychpathololgy may predict potential changes in neurophysiological empathy responses due to oxytocin treatment and how these changes relate to pre- and post treatment blood serum oxytocin levels. We will finally explore whether these effects are related to variants of the oxytocin receptor (OXTR) gene.

Study design

For the measurement of the oxytocin effects on experiencing empathy, we plan to carry out a double-blind placebo-controlled crossover study with oxytocin (24 IU) and placebo being nasally administered to all participants with an interval of one week. Each participant will perform the IAPS picture task twice, once taking oxytocin and once taking the placebo. The one week washout is considered to be long enough given the very short half-life of oxytocin being only 3 to 15 min. The sequence of starting with oxytocin or placebo will be randomly balanced across the participants within each group.

Intervention

Within the experimental trial, oxytocin (24 IU) and the placebo shall be administered to all participants. Nasal spray will be prepared for taking 3 puffs per nostril, each with 4 IU, the placebo (PL) being identical containing all ingredients except the active compound. The time in between oxytocin and placebo administration will be about one week. In agreement with the pharmacokinetic qualities described for nonapeptides (see section 6.5. of the main protocol), the spray will be taken 20 minutes before performance of the experimental task where participants are confronted with the empathy-evoking pictures.

Study burden and risks

Given the only rarely observed and tolerable side effects of nasally administered oxytocin, these being a headache, nausea or skin rashes, the risks of this study for our participants may be considered negligible and the burden only minimal with the forearm venipunctures for blood sampling (4 times 10 ml) probably being the most demanding events.

To conduct the study on the ASD patient group is considered justified as there is not yet any therapeutical intervention for their core problems, while the present study could contribute to finding novel options for medical treatment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

male, age 18 through 30 years; IQ > 80; patients: meeting DSM-IV criteria for Autism Spectrum Disorder

Exclusion criteria

alcohol or drug dependence; free of psychotropic medication or neuroleptics

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-11-2011
Enrollment:	52
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Syntocinon
Generic name:	Oxytocin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-06-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-08-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-01-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-018740-13-NL
CCMO	NL31519.042.10