Father Trials: Hormonal Experiments on Prenatal and Postnatal Parenting

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In a series of randomized control trials (RCTs) the following hypothesis will be tested: Intranasal administration of oxytocin and vasopressin affect neural and behavioral responses to infant signals and threat to the infant.* Oxytocin and...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON44021

Source
ToetsingOnline

Brief title
Father Trials

Condition

- Other condition

Synonym
n.a.

Health condition

onderzoek heeft geen betrekking op aandoening, maar bestudeert effecten van hormonen op vaderschap

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Leiden
Source(s) of monetary or material Support: European Research Council

Intervention

Keyword: fathers, hormones, neuroimaging, parenting

Outcome measures

Primary outcome

The first main study parameter is activity in brain areas associated with (1) arousal/salience (amygdala, ventral striatum), (2) reflexive care (hypothalamus), (3) emotion regulation (insula, medial prefrontal cortex, anterior cingulate cortex), and cognitive / empathic processing (insula, inferior frontal and orbitofrontal gyri, temporoparietal junction). We will examine the effects of oxytocin and vasopressin on activity in these areas in fathers during *processing infant signals* and *processing threat to infant* tasks designed to elicit protective responses (affiliative versus defensive response).

The second main study parameter is parenting behavior, including *handgrip during infant cry*, (Bakermans-Kranenburg, van IJzendoorn, Riem, Tops, & Alink, 2012) sensitivity (*quality of care* task), involvement (*quantity of care task*), and protection (*Enthusiastic Stranger Paradigm*, (Mah, Bakermans-Kranenburg, Van, & Smith, 2015). We will examine the effects of oxytocin and vasopressin on these parenting behaviors.

Secondary outcome

We will examine the extent to which effects of oxytocin and vasopressin are

moderated by father*s *early childhood experiences*.

Oxytocin, vasopressin, testosterone, and estradiol levels will be assessed in saliva and blood. Vasopressin and oxytocin levels will be measured to examine cross-reactions (oxytocin-vasopressin). Testosterone and estradiol levels will be measured to examine mechanisms (testosterone * estradiol * oxytocin; testosterone - vasopressin).

Study description

Background summary

In animals, parenting is under strong hormonal control, and it would be naive to suppose that this is very different for human parents. Indeed, several studies in humans have shown associations of oxytocin and vasopressin levels with parent-child interaction (Apter-Levi, Zagoory-Sharon, & Feldman, 2014; Atzil, Hendler, Zagoory-Sharon, Winetraub, & Feldman, 2012; Bick & Dozier, 2010; Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010). Furthermore, experimental manipulation of oxytocin and vasopressin levels through nasal administration affects parenting behavior and the neural processing of infant signals (Cohen-Bendahan, Beijers, van Doornen, & de Weerth, 2015; Naber, van IJzendoorn, Deschamps, van Engeland, & Bakermans-Kranenburg, 2010; M. M. Riem et al., 2011) .
We propose to employ a randomized, double-blind, placebo-controlled within-subject design to gain insight into the hormonal and behavioral dynamics of the paternal role in a critical phase of parenthood: the transition to having the first baby. The focus lies on the 50% of parents who have tended to be neglected in research and *until recently- in family policies: fathers. In most western countries fathers have increased their participation in parenting over the past decades. And even though in most families the participation of fathers in child rearing is modest, this does not mean that their parental role is irrelevant for child development (Kok et al., 2015), or that this role is carved in stone and resistant to change.
A special focus is on a dimension of parenting that has received considerable attention in animal research but, despite its evolutionary importance, not in studies on humans: the role of the parent as protector. Protection is a crucial aspect of human parenting. This is perhaps demonstrated most convincingly when we are confronted with the absence of parental

protection, i.e. neglect, or child physical abuse. Neglect has the highest prevalence of all categories of child maltreatment and has serious consequences for many domains of child development (Gilbert et al., 2009). Physical abuse has its peaks in early childhood, and infant crying is a documented trigger of early physical abuse (Barr, Trent, & Cross, 2006).

In a seminal paper, Shelley Taylor and her colleagues proposed the tend-and-befriend model as an alternative to the fight-or-flight model of behavioral responses to stress (Taylor et al., 2000). Tending, the protection and care of offspring, and befriending, the formation and maintenance of interpersonal relationships with conspecifics, were proposed as strategies that females use in times of stress to defend themselves and their offspring. A central role in this model is attributed to oxytocin, which provides the neuroendocrinal basis for affiliation with social groups. A second hormone that may play a role in protective fathering is vasopressin. In men, vasopressin levels have been associated with aggressive behavior (Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998). Moreover, while testosterone has been associated with aggressive behavior in general, vasopressin has been suggested to be associated specifically with protective aggressive behavior (van Anders, Goldey, & Kuo, 2011). Indeed, several studies have reported associations between vasopressin levels and parental aggression towards a male intruder (Nephew & Bridges, 2008; Nephew, Byrnes, & Bridges, 2010).

In research on parenting quality, parental sensitivity is a key construct. It refers to the ability to attend to infant signals and to respond promptly and appropriately (Ainsworth, Bell, & Stayton, 1974). Studies consistently show that fathers are less sensitive towards their infants and toddlers than mothers (Barnett, Deng, Mills-Koonce, Willoughby, & Cox, 2008; Hallers-Haalboom et al., 2014; Schoppe-Sullivan et al., 2006; Volling, McElwain, Notaro, & Herrera, 2002), although seeing infants has similar motivational salience to men and women (Parsons et al., 2011). Similarly to the pattern of associations for mothers, higher levels of paternal sensitivity predict more favorable child outcomes (Lewis & Lamb, 2003). Sensitive parenting starts with the processing of infant signals, which has been shown to be affected by oxytocin levels (M. M. Riem et al., 2011), but may also be affected by vasopressin levels. These hormones may play a role in fathers* processing of infant signals as well, but the direction of the association is as yet unclear.

Mapping parental brain responses to infant stimuli using fMRI has increased our knowledge of brain processes involved in parenting sensitivity. Brain regions expected to be important to parenting are circuitries related to (1) arousal/salience (amygdala, ventral striatum), (2) reflexive care (hypothalamus), (3) emotion regulation (insula, medial prefrontal cortex, anterior cingulate cortex), and cognitive / empathic processing (insula, inferior frontal and orbitofrontal gyri, temporoparietal junction) (Parsons, Young, Murray, Stein, & Kringelbach, 2010; Swain et al., 2014). Exposing parents to child stimuli in fMRI studies activates neural systems involved in these regions. Effects of oxytocin and vasopressin on the amygdala and the insula, medial prefrontal cortex, and inferior frontal gyrus have been established in females (Atzil et al., 2012; M. M. Riem et al., 2011).

Replication in fathers and fathers-to-be is badly needed.
For protective parenting responses, the amygdala may play a central role. The amygdala functions as an *alarm* to relay signals of threat. Infants are rewarding attachment-objects, motivating parental care and attention, which intensifies protection of the child against potential threats (Szechtman & Woody, 2004). Moreover, oxytocin intensifies the reward associations of the infant by increasing the release of opiates (Depue & Morrone-Strupinsky, 2005), and higher reward triggers heightened distress and protection in the presence of threat.
Connectivity analyses focusing on circuits involving coordinated activity of distant brain areas are important for examining how brain regions work in concert in response to infant stimuli. Bos, Panksepp, et al. proposed a neural model for hormonal effects on connectivity, according to which oxytocin, by acting on the amygdala, shifts activity to prefrontal regions, whereas vasopressin activates connectivity with the brainstem (Bos, Panksepp, Bluthe, & van Honk, 2012). In the current proposal we will test this model adapted to the processing of infant cry signals and protective parenting. In parents, their own infants* crying elicits more brain activation than the sounds of unfamiliar babies (Parsons et al., 2010; Swain et al., 2014), with mothers showing a more intense level of activation than fathers.
In the proposed series of RCTs fathers will be observed prenatally and postnatally, both with their own child (postnatally) and an infant simulator (prenatally), and using experimentally manipulated infant stimuli (prenatally and postnatally). We will test the effects of hormone administration (oxytocin and vasopressin) on the processing of infant crying, on protective parenting, and on the quantity (involvement) and quality (sensitivity) of father-child interaction. Testing the effects of hormone administration on the processing of infant crying, protection, involvement, and sensitivity may help unravel the mechanisms of effective parenting.

Study objective

In a series of randomized control trials (RCTs) the following hypothesis will be tested: Intranasal administration of oxytocin and vasopressin affect neural and behavioral responses to infant signals and threat to the infant.
* Oxytocin and vasopressin modulate activation in the *parental brain* systems related to arousal, reflexive care, and cognitive/empathic processing.
* Oxytocin will increase connectivity of the amygdala with prefrontal regions, and vasopressin will increase amygdala connectivity with the brainstem.
* Oxytocin will promote an affiliative response to threat to the infant, and vasopressin will promote an defensive response.

Study design

We will employ a randomized, double-blind, placebo-controlled within-subject design. The within- subject experiments will be conducted in three phases of

parenthood: prenatal (child*s age = -3 months), early postnatal (child*s age = +2 months), and late postnatal (child*s age = +7 months). In each phase of parenthood, 35 40 fathers (30 plus 15% oversampling to compensate for attrition) will visit the Leiden University Medical Center (LUMC) for three experimental sessions, which take place with intervening periods of 1 week.

All within-subject experiments include three conditions: intranasal administration of 24 IU of (1) oxytocin, (2) 20 IU vasopressin, and (3) a placebo. The three conditions imply six possible counterbalanced orders of conditions, and assignment of participants to order of administration will be random. Administration will be double-blind.

The data collection is expected to take approximately 1.5 years. The study will be conducted at the fMRI facilities at the LUMC.
Before the start of the study, we will conduct a pilot study. The research methods will be similar to those described in this protocol, with two exceptions. First, instead of three conditions (oxytocin, vasopressin, placebo), the pilot will include only two conditions: vasopressin and placebo. We will focus on vasopressin because our research group already has ample experience with oxytocin administration studies. Second, instead of three phases of parenthood (prenatal, early postnatal, late postnatal), the pilot will include only one phase of parenthood: prenatal. Specifically, we plan to invite 26 fathers expecting their first baby. The pilot study is expected to take approximately three months.
In order to assess the effects of the transition to fatherhood on neurobiological and behavioral responses, the pilot sample will be invited for a postnatal follow-up session when their child is 4 months of age. This follow-up session will be similar to the placebo pilot session, with adjustments in accordance with the postnatal phase. Follow-up of the pilot study is expected to take approximately 2 months.

Intervention

Fathers will visit the LUMC for three experimental sessions: administration of (1) oxytocin, (2) vasopressin, and (3) a placebo. Sessions will take place with intervening periods of 1 week. Three types of measurements will be conducted during each session: (1) hormonal (assessment of oxytocin, testosterone, vasopressin, and estradiol levels in salvia and blood), (2) neural (fMRI: processing infants signals and processing threat to infant tasks), and (3) behavioral (handgrip during infant cry, quantity of care, quality of care, and protection tasks).The three conditions (oxytocin, vasopressin, placebo) imply six possible counterbalanced orders of conditions, and assignment of participants by the LUMC pharmacist to order of administration will be random. Administration will be double-blind: Neither the subjects nor the investigator conducting the experiment will know which of the substances is administered.

Study burden and risks

There are no risks associated with the assessments used in this study. Possible side effects of oxytocin and vasopressin are negligible. No adverse effects have been reported in participants/patients undergoing MRI at the currently available field strengths. Once we understand the neurobiological underpinnings of good-enough and poor parental sensitivity and protection, better attempts can be made to improve parenting and reduce the adverse effects of poor parenting. The proposed set of studies is ground-breaking in that it includes paternal protection, an important dimension of parenting that has been neglected in all imaging studies and virtually all behavioral studies of parenting to date, maybe because of the almost exclusive focus on mothers. Furthermore, real-time measures using apps and mobile phones have been underused in research and may provide data with high ecological validity, that may differ considerably from data collected retrospectively using traditional questionnaires on time spending. Thus, the importance of the benefits gained from this research outweighs the minimal risks involved.

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

In each phase of parenthood (prenatal (child age <= -3 months), early postnatal (child age <= + 2 months), late postnatal (child age <= + 7 months), 40 fathers having their first baby will be recruited to take part in the study.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:;Not living in the same house as their partner
Endocrine disorders
Smoking
Alcohol and drug abuse
Use of medication potentially interfering with the endocrine system
MRI contraindications, including metallic foreign objects, neurological disorder and claustrophobia
Psychiatric disorder
Cardiovascular disease
Nose injuries and disorders

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	120
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	11-01-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-03-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	05-07-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-09-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-12-2016

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2015-003336-12-NL
CCMO	NL54702.058.15