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The role of oxytocin in parenting and as augmentative pharmacotherapy; critical issues and bold conjectures

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Abstract

Despite the sometimes heated debate about the validity of human oxytocin studies, experimental oxytocin research with intranasal administration is a growing field with promising preliminary findings. The effects of intranasally administered oxytocin compared to placebo on brain neural activity has been supported in animal studies and in human studies of neural resting state. In several studies oxytocin sniffs have been shown to lead to down-regulation of amygdala activation in response to infant attachment vocalizations. Meta-analytic evidence shows that oxytocin enhances the salience of (emotional) stimuli, lowers stress and arousal, and elevates empathic concern and tender care in particular for offspring and in-group members. Less firm evidence points at amnestic effects of oxytocin. We also note that the average effect sizes of oxytocin experiments are small to modest and that most studies include a small number of subjects and thus are seriously underpowered, which implies a high risk for publication bias and non-replicability.

Nevertheless, we argue that the power of within-subjects experiments with oxytocin have been underestimated. Much more work is however needed to create a firm knowledge base of the neural and behavioral effects of oxytocin. Human oxytocin research is still taking place in the context of discovery, in which bold conjectures are being generated. In the context of justification these conjectures should subsequently be subjected to stringent attempts at refutations before we jump to theoretical or clinical conclusions. For this context of justification we propose a multisite multiple replications project on the social stimuli salience enhancing effect of oxytocin.

Clinical application of oxytocin is premature. Meta-analytically the use of oxytocin in clinical groups tends to show only effectiveness in changing symptomatology in individuals with autism spectrum disorders, but even then it is not yet a validated therapy and its use is premature as safety and long-term side-effects have not been sufficiently studied, in particular in children.

Introduction

Oxytocin is a nonapeptide with huge popularity, at least on the worldwide web. Searching for the term 'oxytocin' we found about 7.5 million hits (9-9-2015), including advertisements for a bottle of 'Liquid Trust' to be ordered through the internet. The term 'cortisol' yielded 10.5 million hits. Cortisol's being first in popularity is compensated by oxytocin's more positive connotations of warmth and cuddliness --it is often labeled the 'love hormone'-- whereas cortisol is considered the 'stress hormone' and comes up in a negative way. Of course both popular stereotypes are unwarranted. Scientifically oxytocin received much less attention than cortisol (53,977 versus 135,882 hits in the Web of Science, 9-13-2015, and this is an underestimate because corticosterone studies were not counted), and the gap is not closing in recent years (during the past 5 years 12,277 versus 38,068 hits were counted for oxytocin versus cortisol, respectively). This is a pity because oxytocin might shed light on human social behavior, in particular on human parenting, and it may have a role as adjunct to parenting interventions and psychotherapy more generally.

Does intranasally administered oxytocin reach the brain?

Intranasal administration of oxytocin is widely used in experimental studies on human behavior but it has been doubted whether the large oxytocin molecule could enter the brain through the nasal cavity (1). In a pioneering study Neumann and colleagues (2) showed that intranasally administered oxytocin in rats and mice produced elevated levels of oxytocin in the dorsal hippocampus and the amygdala, with peak levels around 30-60 minutes after administration. However, after intraperitoneal application of identical amounts of synthetic oxytocin, similarly elevated levels of oxytocin were found in microdialysates from hippocampus and amygdala, which does not exclude the possibility of uptake via the blood. In a study on 6 rhesus monkeys Chang and colleagues (3) found that 35 minutes after oxytocin inhalation significantly increased oxytocin levels were observed in cerebrospinal fluid. In the first study on human subjects, Striepens and colleagues (4) documented elevated oxytocin levels in cerebrospinal fluid of 3 subjects who received oxytocin intranasally but only after 75 minutes, although oxytocin in plasma already peaked at 15 minutes after administration. It should be noted that Striepens et al. (4) used lumbar punctures to collect cerebrospinal fluid whereas Chang et al. (3) assessed cerebrospinal fluid oxytocin levels by cervical draws closer

to the brain. Furthermore, oxytocin levels in cerebrospinal fluid do not translate directly into oxytocin levels in brain tissues such as the amygdala (1).

An indirect way in which the efficacy of intranasally administered oxytocin on brain neural activity might be examined is through the study of neural resting state (5). Neural resting state is observed when participants are in the MRI scanner without any external stimulus, test or paradigm, and the connectivity between different regions in the brain is assessed as patterns of correlated co-activation. We looked at resting state connectivity in the oxytocin versus placebo condition in 42 female adults with a focus on the amygdala, insula and posterior cingulate cortex (a so-called connectivity hub) as seed regions. Oxytocin caused stronger connectivity between the posterior cingulate cortex and the cerebellum, but only in respondents who experienced low parental love withdrawal in childhood (5). The cerebellum has long been associated with control of motor movements but recently its coordinating role in cognitive and affective processing has been recognized, in particular in mental imagery. Stronger connectivity between posterior cingulate cortex and cerebellum might indicate enhanced self-referential processes as well as better understanding of self and others' mental states (5). The moderation of oxytocin effects by childhood attachment experiences has been documented more often (6,7). In another small resting state study (N = 15) intranasal oxytocin administration increased the connectivity between the amygdala and the rostral medial frontal cortex, a region implicated in social cognition and emotion regulation (8).

How exactly sniffs of oxytocin reach the brain is not yet clear (4). Three pathways seem most plausible on anatomical grounds (9). The first route is a peripheral one, going from the nasal cavity into blood vessels and stimulating oxytocin production in the brain through enhanced systemic circulation. The second route is through the olfactory epithelium which would directly affect oxytocin levels in the amygdala and prefrontal cortex. The third possible route is through the trigeminal nerve to the brainstem (9). Of course these pathways are speculative but potentially fruitful hypotheses for more detailed anatomical and neurological studies on the transport of intranasally administered oxytocin. Leng and Ludwig (10) assume that intranasal administration of oxytocin leads to minor increases of oxytocin in the brain and suggest that behavioral effects must be the consequence of indirect peripheral routes, e.g. its influence on

the cardiovascular system. Even if this would be correct we take the perspective that for studies on the influence of oxytocin on behavior it may not be crucial to know whether a direct or peripheral route is taken as long as regions in the brain such as the amygdala are activated, which is what we and others documented by looking at resting state neural activity in oxytocin versus placebo conditions.

However, pathway studies are important to elucidate the best ways to administer oxytocin, as current practices are not standardized and might not take sufficiently into account individual differences in the anatomy of the nose. New devices like a breath powered oxytocin inhalation device (11) might be needed to make full use of some of the intranasal routes. Furthermore, optimal doses of oxytocin have not yet been established, and the conventional dose in most oxytocin studies (24IU) is not based on systematic comparisons. In a study on effects of intranasally administered oxytocin on levels of oxytocin in saliva we found for 16 IU as well as for 24 IU sniffs 5-10 times elevated levels compared to placebo, lasting up to 7 hours after administration (12). Oxytocin was analyzed using state-of-the art extraction methods (10). It seems implausible that such long-term increases in salivary oxytocin can be explained by dripping back of oxytocin from nose to mouth without a feed-forward mechanism involved with small increases of oxytocin in the brain triggering higher levels of endogenous oxytocin release from the paraventricular nucleus (13). If replicated this might have implications for debriefing and after-lab care of the respondents. An alternative explanation without long-term neural effects would be deposition of intranasally administered oxytocin in extracellular fluid, e.g. subarachnoid spaces, which would slowly leach into saliva.

The role of oxytocin in human social cognition

As a hormone oxytocin plays an important role in parturition and breastfeeding (the Greek term oxytocin means ‘speedy delivery’) but it also has been identified as a hormone regulating cardiovascular reactions to stressors among others (14). As a neuromodulator/ neurotransmitter it is hypothesized that oxytocin enhances the salience of (emotional) stimuli, lowers stress and arousal, elevates empathic concern and tender care, in particular for offspring and in-group members, but may also make individuals more aggressive against out-group members and potential intruders who might endanger offspring (15, 16 ‘*Tend and defend’* might capture this double-edged blade most adequately (17)). In a series of meta-analyses we were able to support

the role of oxytocin in enhancing recognition of facial emotions (6). In 13 oxytocin experiments (N = 408) the combined effect size was Cohen's d = 0.21 which is a rather modest effect (the 95% confidence interval around this point estimate ranged from 0.07 to 0.36). In 8 studies trust to in-group members was assessed (N = 317), and the combined effect size was 0.48, with a substantial 95% confidence interval (0.19, 0.77). We did not confirm the hypothesis that oxytocin would stimulate distrust and aggression to out-group members, the direction was as expected, but the effect size was non-significant, d = 0.21 (95% confidence interval -0.06 to 0.48). Although this meta-analysis was published only a few years ago, the set of studies has increased rapidly and 5 years from now an updated meta-analysis should test whether these promising meta-analytic findings hold or have diminished over time (6). In a failed replication of the positive oxytocin effect on trust, the authors suggested that the real effect may be small, moderated by unknown situational or personality factors, or might be zero or even negative (18). It is important to note that the combined effect sizes for oxytocin experiments are small to modest and most studies are seriously underpowered (6). On the basis of our meta-analyses, Walum, Waldman and Young estimated that the power of the published experiments in samples with healthy and clinical groups was between 12% and 16%, whereas 80% is required in order to avoid too many false positives (19). A study on behavioral effects of centrally manipulated oxytocin and vasopressin systems in voles had a power of 43% (19), which is still substantially lower than the required minimum of 80%.

It should be noted, however, that Walum et al.'s estimation of the effects of studies with a within-subject design is inaccurate and results in an underestimation of the power. For simplicity, they multiplied the sample size by 2 for studies with a within-subject design (19, p2). Although doubling the sample size reduces the 95% confidence interval (CI) around the effect size somewhat, it does so less effective than a within-subject design (due to a reduction of the error term in within-subject studies). We illustrate the difference with a numerical example. Given a between-subject design with N=40 and a difference between the two groups of 0.50 SD, the effect size is d = 0.50 with a 95% CI ranging from -0.13 to 1.13, and a p-value of 0.12. Doubling the sample size (N=80, d = 0.50), results in a 95% CI ranging from 0.06 to 0.95, and a p-value of 0.03. A within-subject design with the original sample size (N=40) has a 95% CI ranging from 0.17 to 0.83, and a p-value of 0.003, and thus is significant with a substantially sharper p-value than the double-sized between-subject design. The superior power

of within-subject designs should not be underestimated, as we also showed in the context of studies on human mirror activity with EEG mu rhythm (20), and oxytocin studies using this design might yield results that can be replicated more easily than studies with other designs.

Nevertheless, a number of our own studies have a between-subject design. In one of these, we asked 50 female respondents to rate infant facial expression of emotions with 60 pictures of infant faces, taken from the IFEEL pictures task developed by (21). In half of the trials the picture had to be rated on emotional valence by choosing between two adjectives describing emotions, in the other half the picture had to be rated as male or female gender as a control task (22). During emotion recognition in contrast to gender identification three regions in the brain were more activated in the oxytocin condition: the left inferior frontal gyrus, the left middle temporal gyrus, and the left superior temporal gyrus. In previous studies with adult faces the same regions were implicated (23), and the regions also seemed open to influences by oxytocin administration (24, 25). The inferior frontal gyrus has been suggested to be part of the mirror neuron system (26) which might facilitate understanding of others' thoughts and feelings (mind-reading). The increased activation of the middle temporal gyrus and superior temporal gyrus might point at a more conscious processing of facial expressions. Although these neural activations were expected to enhance recognition of facial emotions, we did find a *lower* success rate for emotion recognition in the oxytocin condition. Instead of sharpening emotion recognition, oxytocin sniffs seemed to decrease the ability to read the correct emotions from infant faces, in contrast to our meta-analytic results that were all based on recognition of adult emotional expressions. Larger and preferably within-subject studies replicating the protocol are needed to reach more definite conclusions. Somewhat worrisome, we did not find an association between neural activation and (re-)cognition.

Oxytocin affects neural processing of infant crying and laughter

Infant crying elicits care but can also be a major stressor (27). Charles Darwin already commented on the crucial role of crying for survival of offspring in 'The expression of emotions in man and animals' (28). John Bowlby (29) defined infant crying as one of the primordial and inborn attachment behaviors, like laughing and babbling, that result in closer proximity of the vulnerable baby to its protective caregiver. Providing important information

about the infant's basic needs and health condition, crying is evolutionary adaptive. But infant crying has also a dark side because it provokes feelings of arousal, stress, and even aversion in parents who are unable to cope with persistent crying. Already six months after birth more than 5% of young parents confess to have shaken, slapped or smothered a persistently crying baby (30). To study neural processing of infant crying, we developed a paradigm in which subjects listened to 500 Hz cry sounds of a few days old infant, as well as manipulated cry sounds of 700 Hz and 900 Hz, which most listeners perceive as more urgent (e.g., 31). Acoustically matched control sounds were produced by random scrambling of the cries, with similar pitch and prosody but unrecognizable as crying. Auditory processing of the cry sounds and the control sounds was similar, so that any difference in emotional processing is due to the difference in emotional valence.

Oxytocin administration compared to placebo was found to reduce right amygdala activation, and to increase activation in the bilateral insula and inferior frontal gyrus (25). Reducing amygdala activation might mean lowering the level of stress and arousal, thus making it possible to engage with a crying child less emotional and more effectively. Decreased amygdala activation might promote responsiveness to infant crying by preventing parents from being overwhelmed by anxious or aversive feelings. This fits well with findings of stress-reducing effects of oxytocin in lactating mothers (32, 33.The insula have been implicated in feelings of physical and social pain caused by painful experiences of the subjects themselves or by their observing pain inflicted upon others (34). Increased activation of the insula might enhance empathic concern for the distressed baby, in particular when accompanied by elevated activation of the inferior frontal gyrus considered to be part of the mirror neuron system which may facilitate understanding of others' thoughts and feelings. Previous studies have shown that the insula is involved in the perception of the own infant's sad faces (35 and the inferior frontal gyrus is important for affective prosodic comprehension (36.This pattern of activation might be the neural foundation of sensitive parental responding to infant crying. In fact, in a related study we assessed the current representation of attachment experiences in childhood and found that respondents with insecure attachment representations showed most elevated amygdala activation suggesting their vulnerability to respond insensitively to infant crying (37).

Charles Darwin noted that ‘ Everyone knows how immoderately children laugh’ (28), and it surely is difficult not to start smiling or laughing when another individual is laughing loudly and extensively. When infants begin to smile and laugh to their parents they feel immensely rewarded which cements the bond they experience with their offspring. Analogous to the cry paradigm we developed a paradigm of laughter sounds and scrambled control sounds. Female participants listened to these sounds while their blood oxygenation level-dependent responses were measured. In the oxytocin compared to the placebo condition we found reduced activation in left and right amygdala, similar to the effect of increased oxytocin levels in the cry paradigm. Furthermore, oxytocin induced stronger functional connectivity between the right amygdala and the hippocampus, posterior cingulate cortex, the orbitofrontal cortex and the middle temporal gyrus during the perception of infant laughter compared to scrambled sounds. Lastly, oxytocin resulted in stronger functional connectivity between the left amygdala and the anterior cingulate cortex (38). Together this pattern of neural reactions to infant laughter might be interpreted as reflecting reduced feelings of arousal and stress, and enhanced feelings of empathy as well as reward. Thus, oxytocin might facilitate parent-infant bonding.

Insert Figure 1 about here

Amnestic oxytocin effect?

Some infants cry more often than others, and some are more easy-going than average. Irritable mood or temperament may be a burden on the relationship between parent and child, and some parents may find it difficult if not exhausting to cope with the negative mood of their irritable and difficult child. The Baby Social Reward Task was developed to train respondents to differentiate between more easy-going versus more irritable infants (39). The faces of six infants (aged 3 mo-12 mo) were shown with neutral, smiling and crying expressions. In the training phase, two neutral infant faces are presented at the start of each trial. The two faces belong to three fixed pairs of infants, with each pair consisting of a relatively ‘happy’ infant (80%, 70%, or 60% of the trials in happy mood) and a relatively ‘sad’ infant (20%, 30%, or 40% of the trials happy). In the probabilistic learning paradigm, participants are requested to select the happy infant in half of the trials and select the sad infant in the other half of the trials. Once they select one of the faces, they receive feedback in the form of a change in facial

expression accompanied by a cry or laughter sound. The unselected infant face remains neutral. By trial and error participants come to learn which infant is more happy or more sad.

After the training phase, when the participants have reached an acceptable level of correct identification of relatively happy and relatively sad babies, they watch a pair of neutral infant faces and are asked again to select the happier infant (based on what they learnt during the training round), now without getting feedback. However, in this phase all possible combinations of infants are shown. We found that in the oxytocin condition respondents showed worse performance on the BSRT compared to the placebo condition, but only when they had experienced relatively high levels of emotional neglect or abuse (40). This implies that the amnestic effect of oxytocin was only visible in subjects who had experienced unhappy childhoods and who therefore might be more at risk of abusing their own offspring (41). While individuals with maltreatment experiences may tend to avoid crying infants (42), oxytocin may increase their inclination to approach them (43).

It is tempting to suggest that oxytocin may enhance individuals' motivation to keep interacting with a distressed infant and facilitates a positive approach towards an irritable infant. The popular 'baby brain' phenomenon of pregnant and young mothers, who report feeling somewhat impaired in their cognitive and memory functioning, might be associated with the abundance of peri- and postnatal oxytocin that stimulates forgetting unhappy times with their babies (44). However, studies on memory effects of oxytocin show diverging results. For example, in a small study on 15 schizophrenic patients Feifel and colleagues (45) found a memory enhancing effect of oxytocin versus placebo on some recall sub-tests, whereas Heinrichs et al (46) found amnestic effects, in particular for reproduction related words but only on part of the tests. In sum, diverging results of oxytocin research that await replication.

Oxytocin in therapy

Intranasal administration of oxytocin is already being used in clinical practice, for example in treatment of children with autism spectrum disorder, and such application clearly is premature and way ahead of scientific progress in this field. It seems implausible that oxytocin sniffs could serve as stand-alone pharmacological treatment of

child behavior problems or adult disorders as its most important function might be to enhance the salience of (positive and negative) social stimuli such that depressed patients might become even more depressed (see below)(47). However, its potential role as augmentative approach combined with therapy such as psychotherapy (48), cognitive behavior therapy, or parent interventions such as Video-feedback to Promote Positive Parenting should be studied more intensively (49). To explore the potential of oxytocin administration in the context of parenting intervention programs, we conducted a randomized within-subjects experiment on fathers of typically developing toddlers and toddlers in the autism spectrum (50). Using the Emotional Availability Scales (51) to rate the quality of father-child interactions and playful behaviors, we found that in the oxytocin condition fathers of both types of children were significantly more vigorous and stimulating in their playful interactions. This experimental finding nicely converges with the outcome of a correlational study showing that those fathers who were more stimulating in their play with their babies had higher levels of salivary oxytocin immediately after the play session compared to fathers with less sensitive interactions (52).

Oxytocin administration may however also have iatrogenic effects that should be considered before using oxytocin in therapeutic contexts. In a within-subject study involving post-natally depressed mothers in treatment for their depression in an out-patient perinatal psychiatry setting, we tested the oxytocin effects on their mood as well as their perception of the temperament of their babies and their relationship with the child (53). Disappointingly, oxytocin seemed to make these post-natally depressed mothers not feeling happier but, on the contrary, resulted in an increase of depressive symptomatology. Furthermore, in a Five Minute Speech Sample to assess expressed emotions about the child, they were more critical of their infant and found him or her more difficult. Nevertheless they rated their relationship with the baby as better and said to like the infant more than in the placebo condition. We speculated that two mechanisms might be at work to produce these seemingly contradictory effects. First, oxytocin has been found to intensify the salience of emotional stimuli, for better and for worse (54). Under the influence of oxytocin, the respondents might have felt their depression more

intensely, and their problems handling the infant as more acute, but on the other hand they may also experience their basic feelings of connection to the infant more vividly. Second, oxytocin might have promoted feelings of trust to the interviewer, which in turn might lead to mothers' increased openness about their negative as well as positive emotions and perceptions (53). Further research would be needed to examine these speculative interpretations, in particular the idea that oxytocin would enhance trust to an interviewer, or an intervener or therapist. If oxytocin administration would enhance trust in the developing therapist-patient relationship, this might facilitate therapeutic alliance which has been proven to be the most important working component of any effective therapeutic intervention (55).

The aims of parenting interventions such as Video-feedback to Promote Positive Parenting or psychotherapy such as cognitive behavioral therapy may be described in a nutshell as creating a new and more differentiated narrative of the interactions with the social world. Oxytocin may be helpful in achieving this aim. In a study on neural responses to cry sounds versus scrambled sounds we presented the same sounds accompanied by varying labels. In some trials cry sounds were labeled as originating from a sick child, and in some other trials as coming from a bored child. This different interpretation of the very same infant signal produced remarkably diverging neural responses but only in the oxytocin condition (56). Oxytocin administration increased neural activation in the insula and inferior frontal gyrus in response to cry sounds that were labeled as coming from a sick infant. However, crying of an infant labeled as bored produced the opposite effect, a decrease in insula and inferior frontal gyrus activation. Crying of a sick child calls for an immediate response, mediated by neural activation of regions in the brain involved in empathic concern and mindreading, whereas crying of a bored child is less urgent and might require a delayed response in order to enable the child to soothe itself or get back to sleep. Oxytocin seems to facilitate more differentiated interpretation of infant attachment signals, and thus paves the way for sensitive parental reactions, attuned to the developmental needs of the child. If these findings can be replicated and generalized to communicative signals common in interactions between adults, oxytocin might play an augmentative role in psychotherapy by supporting changes

in patients' emotional responses to experiences and re-labeling events in new, less distressing ways. Furthermore, oxytocin is expected to be most effective when augmented to behavioral therapies, as it might make social stimuli more salient and reinforcing (57).

Some meta-analytic evidence supports the need for careful exploration of augmentative oxytocin in psychotherapy. We conducted a meta-analysis on 19 randomized control trials in various groups of patients (N = 304), from borderline personality disordered patients to clients suffering from Posttraumatic stress disorder and anxiety issues (for details see (6)). The overall effect of oxytocin administration on level of problem behavior was positive and significant, albeit rather small, Cohen's d = 0.32. Inspecting the various sub-sets of studies on specific patient samples, we found only one significant effect between oxytocin and placebo groups, which emerged in the sub-set of studies involving subjects with autism spectrum disorders or symptoms. It should be noted that the number of studies in each sub-set was small, and each study included only small numbers of subjects leading to lack of power (19, 53). The meta-analysis therefore is just a preliminary description of the current status, with the expectation of rather fast expansion of the field in the near future. Larger samples and more standardized administration of oxytocin will be indispensable to make progress in this potentially clinically important field of inquiry. Many randomized control trials on the role of oxytocin in autism spectrum disorder are ongoing and a more definite verdict on oxytocin as a treatment component is not yet possible (57). With the current increase of clinical oxytocin studies it should be possible to have some firm meta-analytic evidence of oxytocin effects on various psychiatric disorders in 10 years from now.

Conclusions and research agenda

Despite the sometimes heated debate about the validity of oxytocin studies, experimental oxytocin research is a growing field with promising preliminary findings. Even staunch criticasters ultimately agree on the big challenges as well as the great promises of scientific work on oxytocin. Walum and colleagues (19) for example "remain optimistic about the future of human OT research" (p. 5). Writing about the 'myths and delusions'

of human oxytocin experiments, even Leng and Ludwig (10) assert that "it is possible that enormous amounts of oxytocin delivered intranasally achieve biologically significant elevations in the brain" , and compared to endogenous levels 24IU intranasally administered oxytocin indeed is a huge quantity. But much more work is needed to create a firm knowledge base. Behavioral oxytocin research should still be considered in the context of discovery, in which bold conjectures and wild hypotheses are being generated. In the context of justification these conjectures are then subjected to stringent and persistent attempts at refutations, and only after a series of such refutations we will be a bit closer to the ever moving target of truth (59).

Before the context of justification can be reached, more work on very basic conjectures and bold hypotheses is needed. It is too early for contemplating the closure of the debate, or for the application of oxytocin in clinical practice or daily life. There is as yet too little convincing evidence that intranasal oxytocin administration reaches the social brain, and more studies on non-human primates and human subjects is badly needed to examine the various pathways hypothesized to lead oxytocin to relevant brain regions. The use of 24 IU oxytocin in most studies is based on convention, and experiments with varying doses of oxytocin (e.g., 10, 60), are needed to make a more evidence-based choice, in particular because high doses of oxytocin seem to lower the efficacy, perhaps due to cross-reaction with vasopressin. Thus, high doses of oxytocin administration may lead to binding of oxytocin to vasopressin receptors, shifting the balance between oxytocin and vasopressin in the brain (61, 62). Furthermore, oxytocin administration effects might last longer than the time-frame of most experiments, which may create research-ethical issues. Establishing clear evidence about onset and disappearance of oxytocin effects should be a priority. Standardization of the administration of oxytocin is also required for cumulative progress in this research area. New developments in administration devices are underway, taking into account individual differences in nasal anatomy. Furthermore, studies on oxytocin should be integrated in a larger frame-work of interactions among hormonal and neurotransmitter systems including vasopressin, testosterone, estradiol, and cortisol.

Last but not least, the use of larger, well-powered samples is badly needed. Pre-registration of experimental oxytocin trials should become obligatory (see clinicaltrials.gov for clinical oxytocin trials). Pre-registration makes it possible to estimate publication bias against non-significant effects more precisely than can be done using regular meta-analytic approaches such as trim-and-fill (63. Against this background we propose to conduct a carefully designed and pre-registered multi-site oxytocin experiment to replicate one of the central findings in this area of research, namely that oxytocin increases the salience of social stimuli. Close replication can also lead to the identification of methodological conditions that are necessary to elicit the effect of interest (64), and can thus be informative about the underlying processes. In order to be feasible for multi-site use, the paradigm should be easy to add to planned or ongoing oxytocin experiments and not take more than 5 minutes. We propose to test the influence of oxytocin versus placebo on donating behavior, triggered by a negative versus a positive stimulus, i.e., a video-clip of an unhappy child not attending school due to poverty versus a happy child attending school because of a donation. The donation should be asked for at the end of the experimental session and involve real money earned as compensation for participation in the study. We are currently developing the stimuli set with instructions for easy use by various research groups. The paradigm will be computerized in order to standardize it across settings. This type of multiple replications of a single paradigm has been implemented in the Many Labs replication project (65) with much success, and is fundamentally different from another Open Science Collaboration approach to have single replications of a variety of studies (66).

Oxytocin research using intranasal administration has just started, and it offers a number of promising bold conjectures, but no solid and applicable knowledge yet. More and better experimental oxytocin research with replicable results is therefore badly needed.

Nosek in Science

Klein et al 2013 Many Labs

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