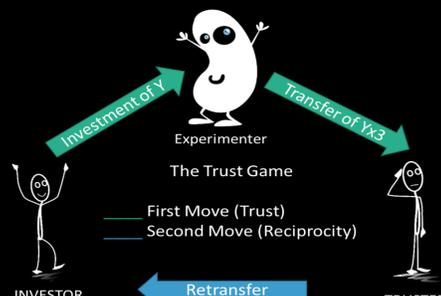
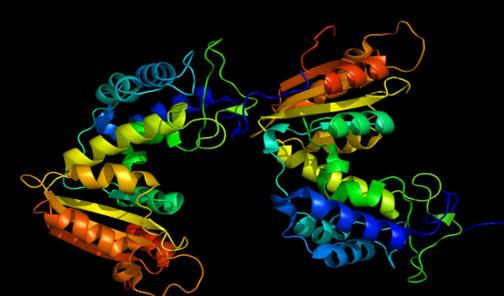


The Influence of Vitamin A administration on Oxytocin Levels and Human Trust Behavior



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Introduction

- The relevance of Trust which pervades nearly every aspect of our social lives has long been acknowledged all across human sciences.
- In searching for potential biological foundations of trust, the neuropeptide oxytocin (OT) has consistently been linked to trust-related variables
- OT was shown to influence...
 - Clinical phenomena
 - BPD (1)
 - Autism (2; 3; 4; 5)
 - Social Cognition
 - improves the ability to detect the mental state of another individual from social cues of the eye region (6)
 - improves identity-recognition in rodents and humans as well as memory for emotionally valent faces in humans (7; 8; 9; 10)
 - improves emotion detection, especially for anxious facial expressions (11; 12; 13)
 - enhances attention on the emotionally salient eye-region in healthy humans, ASD-patients and even rhesus-monkeys (5; 14; 15)
 - Recent findings do not generally support a uniformly positive influence of OT on mind-reading and emotion-recognition. Instead, a number of moderating variables were identified, clustering into properties of the environment or rather stimuli and personal properties (16; 17)
 - Attachment
 - Levels of plasma OT predict the self-assessed attachment to one's own parents and mother's care for their infants (18; 19)
 - plasma OT-levels are positively related to partner-support and physical contact with the partner while showing negative relationships with physiological stress-symptoms as heart-rate, blood-pressure and plasma-norepinephrine levels (20; 21)
 - OT-levels and OXTR-density are associated with massive discrepancies in maternal and social behaviour across different species of rodents (22; 23; 24; 25)
 - Trust
 - OT-levels are reactive to Trust-signals (26)
 - OT-administration increases Trust-behavior and inverts the effects of breaches of Trust (27; 28)

- CD38
 - Glycoprotein
 - Homologous to ADP-Ribosyl Cyclase
 - Catalyzes the metabolism of cyclic ADP-Ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP)
 - Both mobilize Ca²⁺ of intracellular stores which stimulates the exocytosis of OT (29; 30)
 - CD38-KO-mice show a specific deficit in OT-secretion as well as lower levels of cADPR and NAADP (31)
 - KO-mice show massive impairments in social recognition and maternal behavior
 - Those effects are counteracted by OT (31; 32)
 - In humans, associations between polymorphisms of the CD38-gene and OT-related outcomes have been reported, encompassing OT-levels, processing of social stimuli and autism-risk (33; 34; 35)
 - CD38-mRNA-level correlate with the IQ, social and communicative abilities of autistic patients (36)

Hypothesis

Oral application of vitamin A in an effective dose leads to enhanced OT-levels and consequently to more trusting behavior in the Trust-Game, while leaving behavior in a nonsocial Lottery-Game unaffected.

Methods

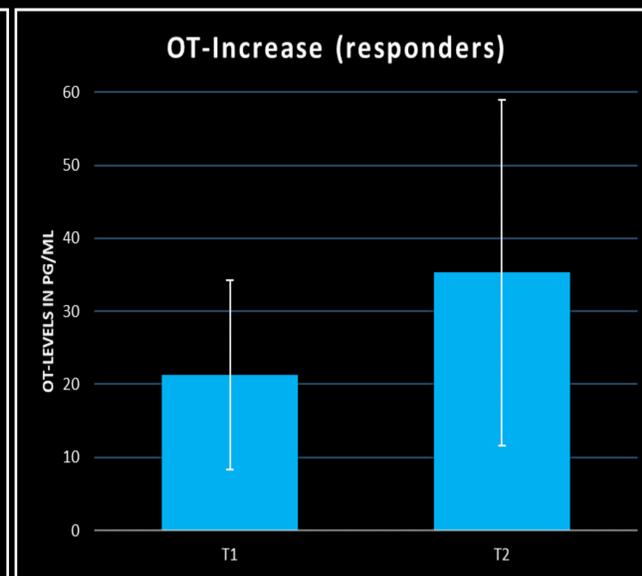
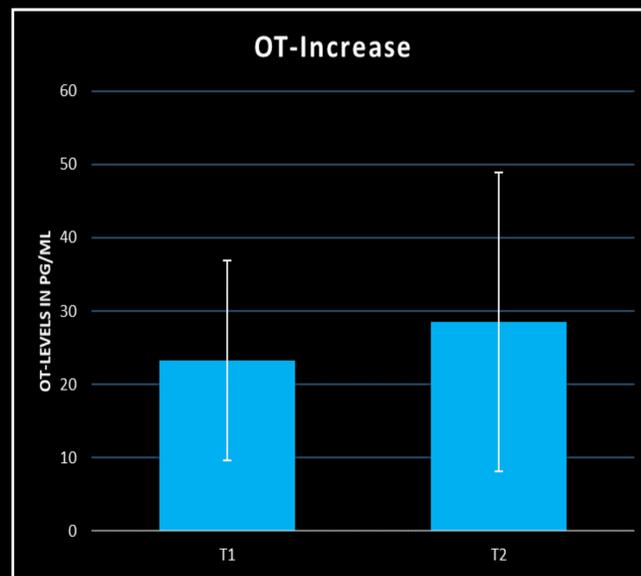
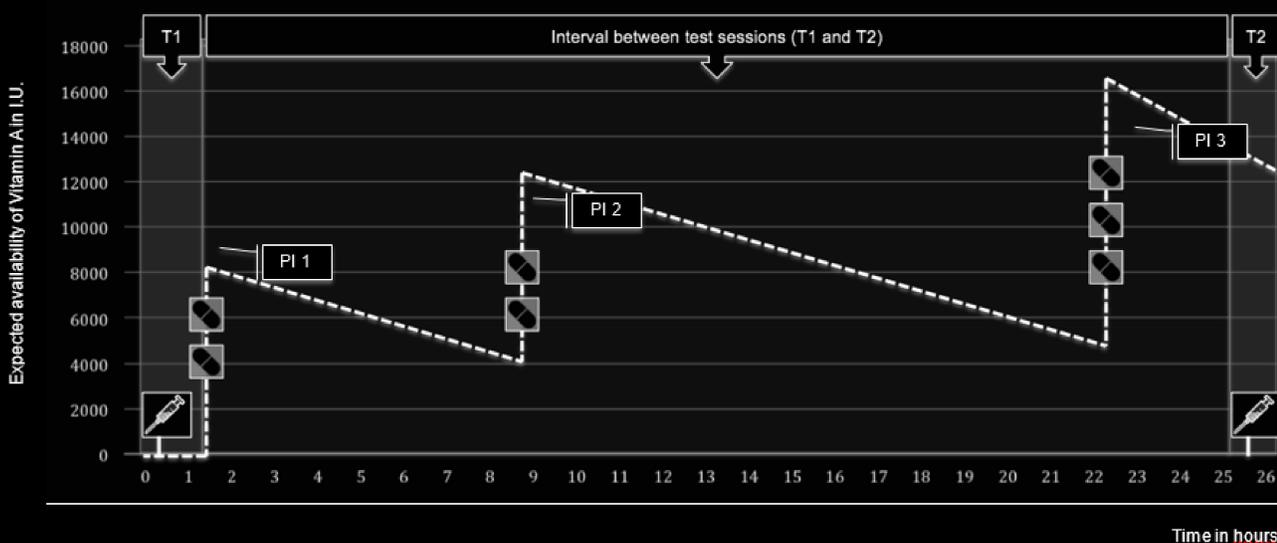
- Procedure
 - Day 1:
 - Blood samples of 3 ml were taken (T1)
 - Trust- and Lottery-Games were played before two pills of retinyl palmitate were taken
 - 9h later, participants took in two pills
 - Day 2:
 - Three additional pills were taken in 22.5h after T1
 - 2:50h later, Trust- and Lottery-Games were played again
 - 25.5h after T1, the second blood-samples were taken
- Pharmacological Manipulation
 - Participants (N=23) took in 28.000 IU retinyl palmitate (half-life: 9.1h). 12.972 IU should be active at T2
- Biochemical analysis
 - OT was extracted from plasma with C18 SEP-columns and measured in duplicate by by fluorescent enzyme-linked immunosorbent assay

Vitamin A intake resulted in an increase in plasma-OT-levels from 23.3 to 28.49 pg/ml, however the effect was not statistically significant ($F_{(1,22)} = 1.83, p = .190$)

Likewise, Trust- ($F_{(1,22)} = .01, p = .929$), Trustworthiness- ($F_{(1,21)} = .10, p = .762$) and Risk-scores ($F_{(1,21)} = .21, p = .650$) did not change significantly over time.

Correlations	OT-Level T1	OT-Level T2	OT-Difference (T2-T1)
Trust T1	$r = .042; p = .848$	$r = .242; p = .266$	$r = .235; p = .281$
Trust T2	$r = .100; p = .649$	$r = .183; p = .402$	$r = .128; p = .562$
Difference (T2-T1)	$r = .065; p = .769$	$r = -.086; p = .698$	$r = -.141; p = .521$
Trustworthiness T1	$r = -.242; p = .278$	$r = -.233; p = .298$	$r = -.076; p = .736$
Trustworthiness T2	$r = .078; p = .725$	$r = -.004; p = .984$	$r = -.062; p = .780$
Difference (T2-T1)	$r = .365; p = .095$	$r = .267; p = .229$	$r = .023; p = .918$
Risk T1	$r = .188; p = .402$	$r = .015; p = .948$	$r = -.122; p = .587$
Risk T2	$r = .158; p = .484$	$r = .084; p = .712$	$r = -.024; p = .914$
Difference (T2-T1)	$r = -.041; p = .858$	$r = .114; p = .612$	$r = .156; p = .489$

Results and Discussion



References

- Bersch, K., Gamer, M., Schmidt, B., Schmidinger, I., Walther, S., Kästel, T. et al. (2013). Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder. *American Journal of Psychiatry*, 170, 1169-1177.
- Modahl, C., Green, L.A., Fein, D., Morris, M., Waterhouse, L., Felsenstein, G. and Levin, H. (1998). Plasma oxytocin levels in autistic children. *Biological Psychiatry*, 43, 270-277.
- Lerer, E., Levi, S., Salomon, S., Davyris, A., Yirmiya, N. and Ebstein, R.P. (2008). Association between the oxytocin receptor (OXTR) gene and autism: relationship to violent and adaptive behavior scales and cognition. *Molecular Psychiatry*, 13, 980-988.
- Hollander, E., Bartz, J., Chaplin, W., Phillips, A., Sumner, J., Suway, L. et al. (2007). Oxytocin increases retention of social cognition in autism. *Biological Psychiatry*, 61, 498-503.
- Andari, E., Doherty, J.R., Zalla, T., Herbrecht, E., Leboyer, M. and Sillig, A. (2010). Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *Proceedings of the National Academy of Sciences*, 107, 4389-4394.
- Domes, G., Hinrichs, M., Mielch, A., Burgler, G., and Hergertz, S.C. (2007). Oxytocin improves 'mind-reading' in humans. *Biological Psychiatry*, 61, 731-733.
- Cholewa, E., Little, S.R., Jong, J.A., Purn, S.V., Langer, R. and Pfaff, D.W. (2007). Microcapsule-based delivery of oxytocin receptor antisense DNA in the medial amygdala blocks social recognition in female mice. *Proceedings of the National Academy of Sciences*, 104, 4670-4675.
- Dhazen, D.E., Muroka, S. and Landgraf, R. (1998). Olfactory bulb norepinephrine depletion abolishes vasopressin and oxytocin or their antagonists into the olfactory bulb upon social recognition responses in male rats. *Peptides*, 19, 999-1005.
- Ferguson, J.N., Aldag, J.M., Insel, T.R. and Young, L.J. (2001). Oxytocin in the medial amygdala is essential for social recognition in the mouse. *The Journal of Neuroscience*, 21, 8278-8285.
- Ferguson, J.N., Young, L.J., Henne, F.P., Matzuk, M.M., Insel, T.R. and Winslow, J.T. (2000). Social amnesia in mice lacking the oxytocin gene. *Nature Genetics*, 25, 284-288.
- Fischer-Shostky, M., Shamay-Tsoory, S.G., Harari, H. and Levkovitz, Y. (2010). The effect of intranasal administration of oxytocin on fear recognition. *Neuropsychologia*, 48, 179-184.
- Lischke, A., Berger, C., Prehn, K., Hinrichs, M., Hergertz, S.C. and Domes, G. (2012). Intranasal oxytocin enhances emotion recognition from dynamic facial expressions and leaves eye-gaze unaffected. *Psychoneuroendocrinology*, 37, 475-481.
- Marab, A.A., Heary, H.Y., Pine, D.S. and Blair, R.J. (2010). Oxytocin improves specific recognition of positive facial expressions. *Psychopharmacology*, 209, 225-232.
- Dal Monte, O., Noble, P.L., Costa, V.D. and Avybeck, B.B. (2014). Oxytocin enhances attention to the eye region in rhesus monkeys. *Frontiers in Neuroscience*, 8, 1-8.
- Guastella, A.J., Mitchell, P.B. and Dadds, M.R. (2008). Oxytocin increases gaze to the eye region of human faces. *Biological Psychiatry*, 63, 3-5.
- Radke, S. and de Brujin, E.R. (2015). Does oxytocin affect mind-reading? A replication study. *Psychoneuroendocrinology*, 60, 75-81.
- Bartz, J.A., Zaki, J., Bolger, N. and Ochsner, K.N. (2011). Social effects of oxytocin in humans: context and person matter. *Trends in Cognitive Sciences*, 15, 301-309.
- Gordon, I., Zagory-Sharon, O., Schneiderman, I., Leckman, J.F., Weller, A. and Feldman, R. (2008). Oxytocin and cortisol in romantically unattached young adults: associations with bonding and psychological distress. *Psychophysiology*, 45, 349-352.
- Feldman, R., Weller, A., Zagory-Sharon, O. and Levine, A. (2007). Evidence for a neuroendocrinological foundation of human affiliation: plasma oxytocin levels across pregnancy and the postpartum period predict mother-infant bonding. *Psychological Science*, 18, 965-970.
- Grewen, K.M., Girdler, S.S., Amico, S. and Light, K.C. (2005). Effects of partner support on resting oxytocin, cortisol, norepinephrine and blood pressure before and after warm partner contact. *Psychosomatic Medicine*, 67, 531-538.
- Light, K.C., Grewen, K.M. and Amico, J.A. (2005). More frequent partner hugs and higher oxytocin levels are linked to lower blood pressure and heart rate in premenopausal women. *Biological Psychology*, 69, 5-21.
- Insel, T.R. and Shapiro, L.E. (1992). Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. *Proceedings of the National Academy of Sciences*, 89, 5981-5985.
- Olazabal, D.E. and Young, L.J. (2006). Species and individual differences in juvenile female alloparental care are associated with oxytocin receptor density in the striatum and the lateral septum. *Hormones and Behavior*, 49, 681-687.
- Bosen, G.J., de Vries, G.J., Goldman, S.L., Goldman, B.D. and Forger, N.G. (2008). Distribution of oxytocin in the brain of a eusocial rodent. *Neuroscience*, 155, 809-817.
- Wang, Z., Zhou, L., Hulihan, T.J. and Insel, T.R. (1996). Immunoreactivity of central vasopressin and oxytocin pathways in microtine rodents: a quantitative comparative study. *The Journal of Comparative Neurology*, 366, 726-737.
- Zak, P.J., Kurzban, R. and Matzner, W.T. (2004). The neurobiology of trust. *Annals of the New York Academy of Sciences*, 1032, 224-227.
- Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U. and Fehr, E. (2008). Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron*, 58, 639-650.
- Kosfeld, M., Heinrichs, M., Zak, P.J., Fischbacher, U. and Fehr, E. (2005). Oxytocin increases trust in humans. *Nature*, 435, 673-676.
- Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U. and Fehr, E. (2008). Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron*, 58, 639-650.
- Lee, H. C. (2006). Structure and enzymatic functions of human CD38. *Molecular Medicine*, 12, 317.
- Ludwig, M. and Leng, G. (2006). Dendritic peptide release and peptide-dependent behaviors. *Nature Reviews Neuroscience*, 7, 126-136.
- Jim, D., Liu, H.X., Hirai, H., Tarashima, T., Nagai, T., Lopatina, O. et al. (2007). CD38 is critical for social behavior by regulating oxytocin secretion. *Nature*, 446, 41-45.
- Lee, H.X., Lopatina, O., Higashida, C., Tsuji, T., Kato, I., Takawana, S. et al. (2008). Locomotor activity, ultrasonic vocalization and oxytocin levels in infant CD38 knockout mice. *Neuroscience Letters*, 448, 67-70.
- Feldman, R., Zagory-Sharon, O., Weisman, O., Schneiderman, I., Gordon, I., Maoz, R. et al. (2012). Sensitive parenting is associated with plasma oxytocin and polymorphisms in the OXTR and CD38 genes. *Biological Psychiatry*, 72, 175-181.
- Mansueti, T., Yokoyama, S., Nakamura, K., Anzai, A., Yamada, K. and Hayashi, K. (2010). Two genetic variants of CD38 in subjects with autism spectrum disorders and controls. *Neuroscience Research*, 67, 181-191.
- Sauer, C., Montag, C., Walter, C., Kirsch, P. and Reuter, M. (2012). Effects of a common variant in the CD38 gene on social processing in an oxytocin challenge study: possible links to autism. *Neuropsychopharmacology*, 37, 1474.
- Riebold, M., Mankuta, D., Lerer, E., Israel, S., Zhong, S., Nemanov, L. et al. (2011). All-trans retinoic acid upregulates reduced CD38 transcription in lymphoblastoid cell lines from autism spectrum disorder. *Molecular Medicine*, 17, 799.