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Increased Temporal Discounting in Social Anxiety Disorder Normalizes after Oxytocin Treatment

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Social anxiety disorder (SAD) is a highly pernicious and disabling condition with a lifetime prevalence of >12% [1]. Current cognitive models highlight increased attentional and interpretive biases toward social stimuli as key factors in the etiology of SAD [2]. In accord with this are neurocircuitry models of SAD which emphasize overreactivity of the amygdala and resultant hyperattention to social stimuli due to deficient cognitive (top-down) control [3]. Of particular relevance in this context are findings that anxious temperament is associated with aberrant reward-based decision-making abilities as assessed by delay (temporal) discounting [4, 5]. In a temporal discounting task, participants are asked to choose between small immediate rewards and larger later rewards, enabling the estimation of individual discount rates that reflect the degree to which a reward is subjectively discounted when delayed in time. While existing cognitive-behavior therapy for SAD is often exposure-based and employs extinction learning and cognitive bias modification procedures [2], there is a lack of treatment protocols specifically targeting deficits in cognitive control.

Given recent observations that the neuropeptide oxytocin (OXT) not only dampens the amygdala but also reinforces top-down regulatory circuits [6], we hypothesized that OXT treatment would particularly confer clinical benefit in situations demanding cognitive control over impulsive responses. We employed a randomized double-blind placebo-controlled study design (see also CONSORT flow diagram and check list in the online suppl. section "Material"; see www.karger.com/doi/10.1159/000495259 for all online suppl. material) in which 33 medication-free patients with SAD (25 females; age 31.21 ± 11.43 years) and 37 healthy controls (CTL; 31 females; age 34.46 ± 14.45 years) with no current or past physical or psychiatric illness self-administered intranasal OXT (24 IU) or placebo (PLC). The participants were first tested on a social interaction task (the results have been reported elsewhere). Then, they performed a temporal discounting task and a reward valuation, with the latter serving to control for nonspecific anxiety-related changes in reward processing. Anxiety and depression symptoms as well as social connectedness were measured via questionnaires (see also in the online suppl. section "Results" and online suppl. Table S1).

All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

A mixed design analysis of variance with the between-subject factors "treatment" (OXT, PLC) and "group" (SAD, CTL), the within-subject variable "relative difference" between sooner-smaller and later-larger options (0.5 to 75%), and the proportion of patient choices (later-larger) as dependent variable yielded significant main effects of relative difference ($F_{(3.57, 235.59)} = 89.02$, $p < 0.01$, $\eta^2 = 0.57$; Fig. 1a) and treatment ($F_{(1,66)} = 6.17$, $p = 0.02$, $\eta^2 = 0.09$) as well as a trend-to-significant effect of group ($F_{(1,66)} = 3.36$, $p = 0.07$, $\eta^2 = 0.05$). There were no further interactions (all p values > 0.17). Thus, participants chose the later-larger option more often when there was a greater relative difference in sooner-smaller/later-larger magnitudes.

OXT significantly increased the patient choices (later-larger) across all participants. Separate analyses in the OXT and PLC groups revealed that SAD patients showed more impulsive preferences under PLC compared to CTL ($F_{(1,34)} = 4.45$, $p = 0.04$, $\eta^2 = 0.12$), while there was no such difference after OXT treatment ($F_{(1,32)} = 0.34$, $p = 0.56$, $\eta^2 = 0.01$). This pattern of results was confirmed in an additional analysis with the discounting parameter k as dependent variable, demonstrating a main effect of treatment ($F_{(1,64)} = 5.52$, $p = 0.02$, $\eta^2 = 0.08$) and a trend-to-significant effect of group ($F_{(1,64)} = 3.78$, $p = 0.06$, $\eta^2 = 0.06$; Fig. 1b).

Interestingly, across all groups, social connectedness positively correlated with the proportion of patient choices in the PLC condition ($r_{(36)} = 0.30$ $p = 0.07$; OXT: $r_{(35)} = 0.16$, $p = 0.36$), indicating that individuals with less social connections less often restrained from choosing the sooner-smaller option. This is in line with proposals that reduced social connectedness may lead to decreased cognitive control, since social support is a robust stress buffer, and the experience of social exclusion impairs self-regulation [7]. There was no significant main or interaction effect of treatment in the valuation control task (see also online suppl. section "Results" and online suppl. Table S2), indicating that OXT did not alter the valuation of rewards options.

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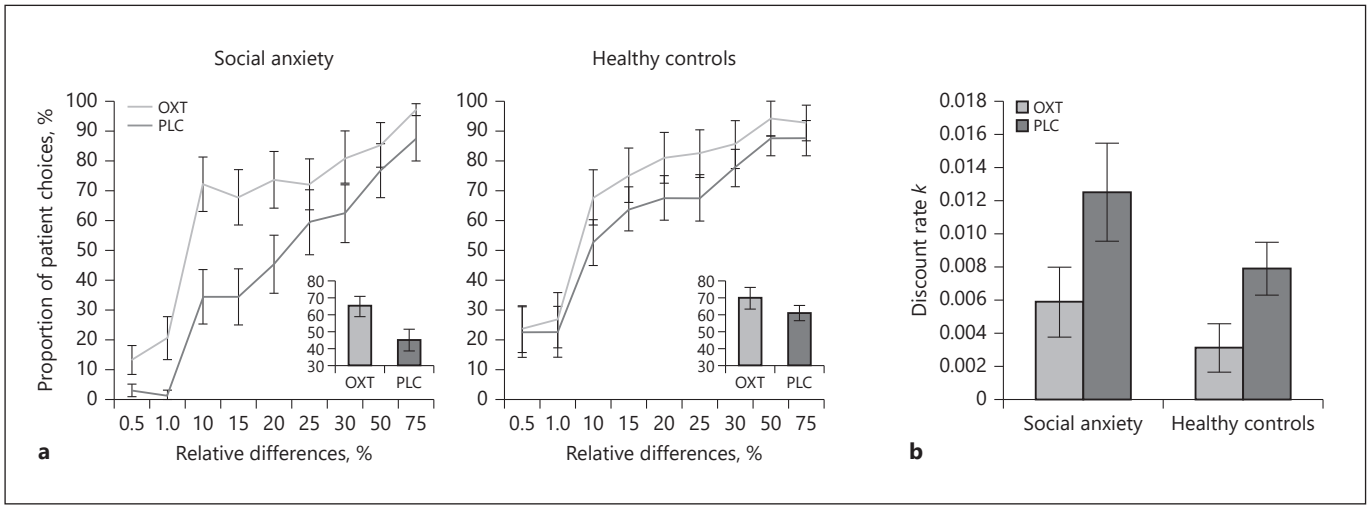

Fig. 1. Proportion of patient choices (later-larger) as a function of the relative difference between magnitude of sooner-smaller and later-larger (**a**). Under placebo (PLC), patients with social anxiety disorder showed less patient choices (i.e., stronger impulsive preferences) than healthy controls. Intranasal oxytocin (OXT) increased the number of patient choices across groups. Inlays display the average proportion of patient choices irrespective of the relative difference. Discounting rate *k* in the OXT and PLC group (**b**). Larger *k* values indicate steeper discounting of delayed rewards, while 0 indicates no discounting at all. Under PLC, patients with social anxiety disorder showed higher discounting rates than healthy controls, while there was no difference under OXT. Error bars indicate the standard error of the mean.

Collectively, our results implicate OXT in up-regulating cognitive control which is required when a sooner-smaller reward is directly contrasted with a later-larger option. Current concepts of cognitive control as probed in temporal discounting tasks emphasize the role of the prefrontal cortex (PFC) in resisting the temptation of small but immediately available monetary rewards [8]. We have previously shown that OXT not only diminishes amygdala reactivity but also enhances PFC activation during fear extinction [9]. Additionally, an OXT-induced increase in PFC activation correlates with a better cognitive regulation of food craving [6]. Given the association between social connectedness and cognitive control, one possible mode of action could be that OXT modulates regulation abilities by altering feelings of social connectedness. Alternatively, the OXT effects on temporal discounting could be driven by increased confidence to receive the delayed reward or the enhanced anticipatory neural response. However, the absence of an OXT effect on the valuation of single options speaks against this interpretation.

In planning further studies on the additional effect of OXT on psychotherapeutic strategies for SAD patients, it seems worthwhile to focus not only on habituation and attenuation of amygdala hyperreactivity, but also on the augmentation of PFC-driven top-down regulation of fearful and impulsive responses. Modern psychotherapeutic interventions put a strong emphasis on the cognitive mediation of treatment changes in SAD and have been proven more effective than pure exposure therapy alone [10]. Based on the "two-foci-model" of OXT's impact on the underlying neurocircuitry in SAD, future studies on the augmentation of psychotherapy for SAD with OXT may focus on comprehensive cognitive-behavioral interventions rather than exclusive exposure-based therapy. Considering the relevance of increased temporal discounting in SAD, it seems important that these disorder-tailored approaches motivate patients to resist the urge of avoidance (negative reinforcement) and focus on the delayed social rewards that can be achieved by fear exposure.

In conclusion, our data indicate that SAD associated with reduced social connectedness affects intertemporal choice of monetary rewards, and intranasal OXT induces a preference for more patient choices. As such, beyond pure anxiolysis, OXT signaling may also play a role in the cognitive control of prepotent impulses during reward-based decision-making.

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Conflict of Interests

The authors report no competing biomedical financial interests or personal affiliations in connection with the content of this manuscript.

References

1 Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):617–27.
2 MacLeod C, Mathews A. Cognitive bias modification approaches to anxiety. Annu Rev Clin Psychol. 2012;8(1):189–217.
3 Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry. 2007 Oct;164(10):1476–88.

4 Rounds JS, Beck JG, Grant DM. Is the delay discounting paradigm useful in understanding social anxiety? Behav Res Ther. 2007 Apr;45(4):729–35.
5 Xia L, Gu R, Zhang D, Luo Y. Anxious individuals are impulsive decision-makers in the delay discounting task: an erp study. Front Behav Neurosci. 2017 Jan;11:5.
6 Striepens N, Schröter F, Stoffel-Wagner B, Maier W, Hurlemann R, Scheele D. Oxytocin enhances cognitive control of food craving in women. Hum Brain Mapp. 2016 Dec;37(12):4276–85.
7 Baumeister RF, DeWall CN, Ciarocco NJ, Twenge JM. Social exclusion impairs self-regulation. J Pers Soc Psychol. 2005 Apr;88(4):589–604.
8 Figner B, Knoch D, Johnson EJ, Krosch AR, Lisanby SH, Fehr E, et al. Lateral prefrontal cortex and self-control in intertemporal choice. Nat Neurosci. 2010 May;13(5):538–9.
9 Eckstein M, Becker B, Scheele D, Scholz C, Preckel K, Schlaepfer TE, et al. Oxytocin facilitates the extinction of conditioned fear in humans. Biol Psychiatry. 2015 Aug;78(3):194–202.
10 McManus F, Clark DM, Grey N, Wild J, Hirsch C, Fennell M, et al. A demonstration of the efficacy of two of the components of cognitive therapy for social phobia. J Anxiety Disord. 2009 May;23(4):496–503.