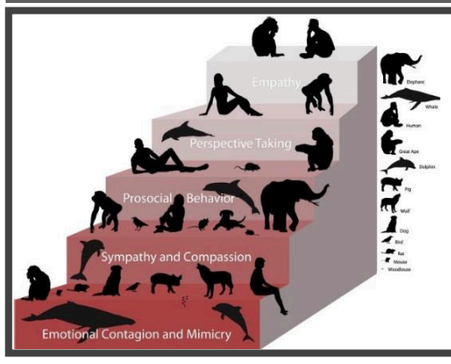
Oxytocin administration normalizes poor empathy-like behaviour and abnormal aggression in mice

P.821

F. Zoratto[1], F. Franchi[1], A. Martinelli[2], M. Sbriccoli[3], J. Glennon[4], S. Macrì[1], G. Laviola[1]

[1]Istituto Superiore di Sanità (ISS), Reference Centre for Behavioural Sciences and Mental Health, Rome, Italy; [2]Istituto Superiore di Sanità (ISS), National Centre for Animal Research and Welfare, Rome, Italy; [3]Istituto Superiore di Sanità (ISS), Department of Neurosciences, Rome, Italy; [4]Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Department of Cognitive Neuroscience, Nijmegen, The Netherlands

INTRODUCTION



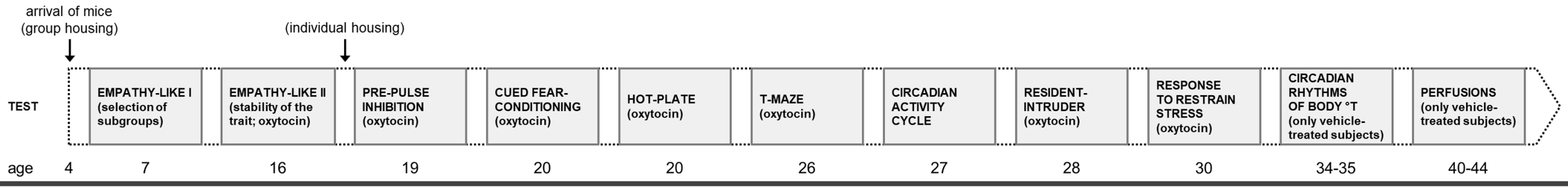
Deficits in empathy, the ability to share an emotion of another individual (Sivaselvachandran et al. 2018, Neurosci Biobehav R), constitute a hallmark of several psychopathological conditions, including conduct disorder (CD). The co-occurrence of excess rates of aggression, violation of societal norms and callous-unemotional traits confers specific risk for adult psychopathy (Eisenbarth et al. 2016, J Youth Adolesc; Macrì et al. 2018, Neurosci Biobehav R). An increasing body of evidence suggests that alterations in the oxytocinergic system might be implicated in the pathophysiology of various neuropsychiatric conditions, including psychopathy (Shamay-Tsoory & Young 2016, Biol Psychiat). Here, we relied on a recently devised experimental model of CD in mice (Laviola et al. 2017, PLoS One) to test the potential efficacy of oxytocin administration.

METHODS

→ We identified two subgroups of BALB/cJ male mice exhibiting opposite profiles in emotional contagion (i.e. the socially transmitted adoption of another's emotional states) addressed through a paradigm based on the evaluation of the social transmission of emotional states (Laviola et al. 2017, PLoS One)

→ We then investigated these two subgroups (i.e. Emotional Contagion-Prone, EC-P, and Emotional Contagion-Resistant, EC-R) for emotional contagion (also testing for the stability of the trait), reactive aggression, information processing, punishment-induced learning, physiological arousal and hormonal stress reactivity, with or without intranasal oxytocin administration (5.0 or 20.0 μg/kg)

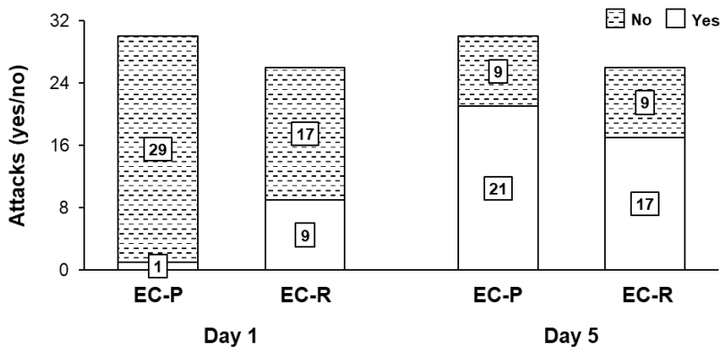
→ We also assessed potential co-occurring variations in neurobiological regulations (OXTRs, GRs, CRHRs) in relevant brain areas



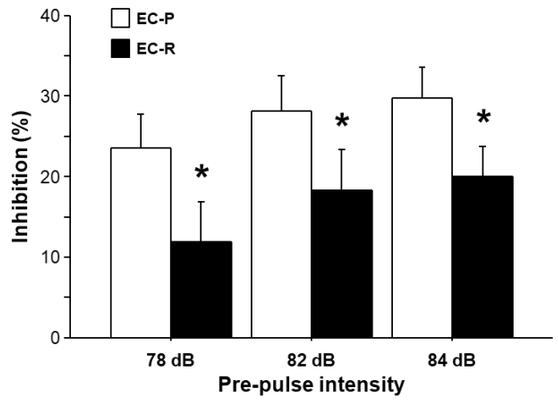
RESULTS

CHARACTERIZATION OF BALB/CJ MICE SELECTED FOR HIGH AND LOW EMPATHY-LIKE BEHAVIOUR

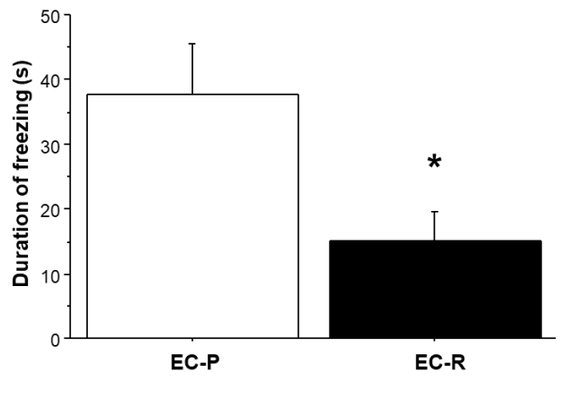
Resident-intruder for reactive aggression



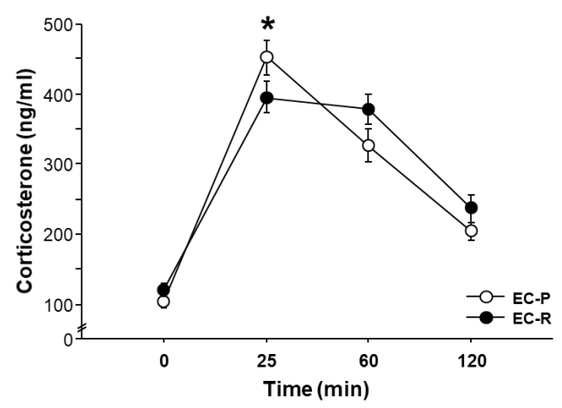
Pre-pulse inhibition for information processing



Fear-conditioning for emotional memory



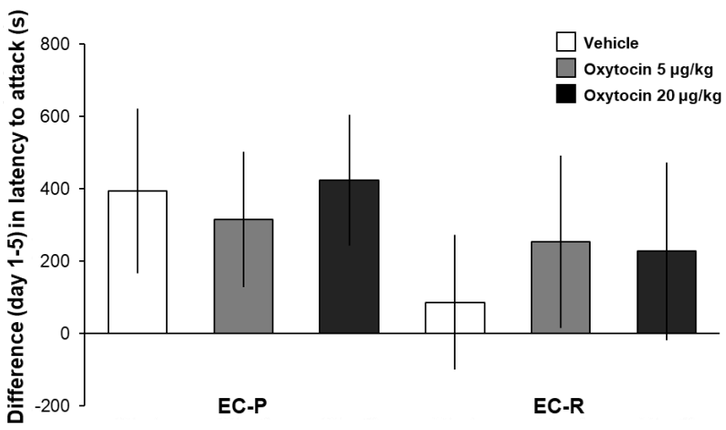
HPA reactivity in response to restraint stress



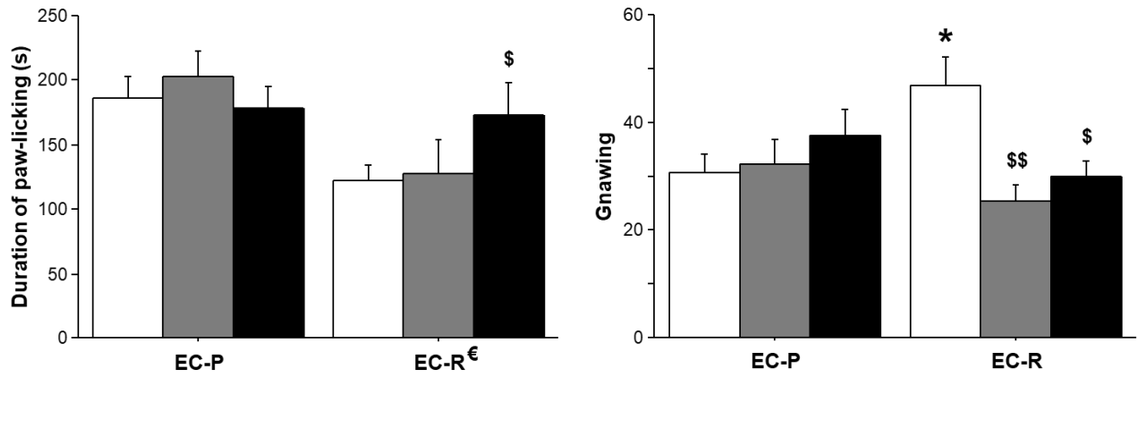
A trait of markedly reduced emotional contagion (trait: $F(1,53)=9.549$, $p=0.032$, when testing the stability of the trait) is associated, in EC-R subjects, with a behavioural syndrome of sensorimotor gating deficits (trait: $F(1,53)=3.964$, $p=0.051$), impaired emotional memory (trait: $F(1,53)=5.733$, $p=0.020$), increased aggression (mice attacking the intruder on the 1st day, EC-P: 1 out of 30, EC-R 9 out of 26; chi-square test: $p=0.0070$) and stereotyped behaviours (trait: $F(1,53)=5.489$, $p=0.023$, for circling), dysregulations in the circadian rhythms of locomotor activity (time×trait: $F(23,1173)=1.843$, $p=0.009$) and body temperature (time×trait: $F(2,38)=4.429$, $p=0.019$) and dampened physiological reactivity to external stressors (time×trait: $F(3,156)=4.211$, $p=0.007$).

INVESTIGATION OF THE MODULATORY EFFECTS OF OXYTOCIN IN BALB/CJ MICE SELECTED FOR HIGH AND LOW EMPATHY-LIKE BEHAVIOUR

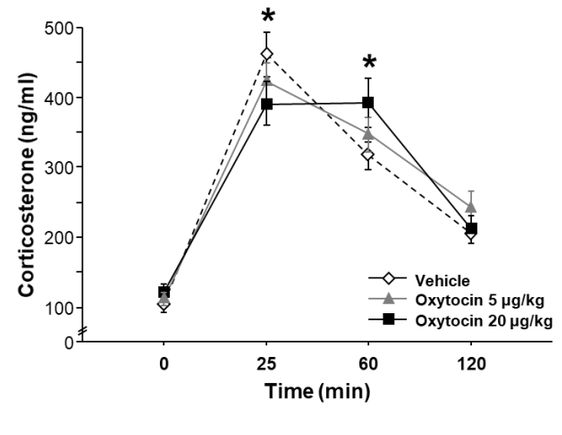
Resident-intruder for reactive aggression



Empathy-like test II for emotional contagion and stereotyped gnawing



HPA reactivity in response to restraint stress



In the absence of changes in oxytocin receptor (OXTR) density in the neural network involved in empathy-like behaviour, we showed that intranasal oxytocin administration normalised emotional contagion (trait×treatment: $F(2,53)=1.817$, $p=0.172$, $p<0.05$ in Tukey posthoc), aggression (difference between 1st and 5th day in latency to attack the intruder against zero; single-sample t test: $p<0.05$) and behavioural stereotypies (trait×treatment: $F(2,53)=4.537$, $p=0.015$; $F(2,53)=5.140$, $p=0.009$, $p<0.05$ in Tukey posthoc, for circling and gnawing respectively), thereby ameliorating the phenotype of mice characterised by deficient empathy-like behaviour (EC-R subgroup). Besides, oxytocin led to a lower, more prolonged neuroendocrine response of the HPA-axis to stress in all mice (time×treatment: $F(6,156)=2.56$, $p=0.022$).

DISCUSSION

The present study shows that extreme-oriented profiles in emotional contagion, a construct amenable to being addressed in laboratory rodents, are associated with a cohesive phenotypic pattern relevant to the modelling of conduct disorder. Current data support the notion that oxytocin may constitute a valid therapeutic approach in psychiatric disturbances characterised by abnormal aggression and excess callousness. Further preclinical investigations in laboratory animal models are deemed necessary to corroborate the hypothesis of a role of oxytocin in the developmental antecedents of psychopathy (Dadds et al. 2014, Dev Psychopathol).

No potential conflict of interest

This project has received funding from the EU-FP7 under grant agreement n° 603016 (MATRICS)