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MEETING ABSTRACT

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Role of prefronto–cortical dopaminergic signalling in deficient fear extinction and its rescue

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Background: Although exposure-based behavioural therapy (EBT) is an efficacious psychotherapeutic intervention for the treatment of many anxiety- and trauma-related disorders, its success is restricted by the occurrence of fear relapse after initial response. One reason is that in patients the central process underlying EBT, namely the formation of a new, fear-inhibitory memory in the course of fear extinction, is often impaired. We have recently shown that enhancing dopaminergic signalling by L-DOPA treatment facilitates fear extinction in extinction-deficient 129S1/SvImJ (S1) mice [1]. This finding raises the interesting hypothesis that a dopaminergic dysfunction may contribute to deficient fear extinction.

Methods: We used a combination of *in vitro* and *in vivo* techniques including microinjection, microdialysis, multi-electrode array (MEA), quantitative PCR (qPCR), quantitative receptor autoradiography, functional imaging and optogenetics in order to study dopaminergic neurotransmission in fear extinction-deficient S1 and extinction-competent C57BL/6 mice.

Results: Compared with extinction-competent subjects evidence of a reduced dopaminergic neurotransmission in the extinction-relevant infralimbic cortex (IL) of S1 during fear extinction was obtained. This dopaminergic neurotransmission seemed to be critically involved in fear extinction since the selective inhibition of the main dopaminergic input projections from the ventral tegmental area (VTA) to the IL decelerated extinction learning in usually extinction-competent DAT-Cre mice. On the other hand, increasing dopamine availability selectively in the IL was sufficient to rescue fear extinction in S1 mice in the long-term. Furthermore, while pre-extinction systemic L-DOPA did not protect against fear relapse, L-DOPA-induced rescue of fear extinction was boosted by the application of a cognitive enhancer immediately after the extinction training.

Discussion: The present findings suggest that a dysfunctional prefronto–cortical dopaminergic neurotransmission is a mechanism underlying impaired fear extinction. This dysfunction can be overcome by the systemic administration of L-DOPA whereby the IL is a critical substrate in mediating extinction-promoting effects of L-DOPA. Thus, targeted approaches to increase dopamine may represent a powerful strategy to overcome extinction resistance and to protect from spontaneous recovery of fear.

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Keywords: long-term fear extinction rescue – infralimbic cortex – dopamine – L-DOPA

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