Fig. 1 Altered social behaviour-induced changes in the amygdala. Under baseline activity the amygdala of germ-free mice is an activated state. Transcriptomic analysis demonstrated an upregulation of several immediate early response genes such as *Fos*, *Fosb*, *Egr2* or *Nr4a1* in association with increased CREB signalling in GF mice (see [5] for full details). Moreover, when a germ-free mouse is introduced to a social stimulus the normal transcriptional pathway recruitment is absent but instead genes involved in alternative splicing are enriched (see [6] for full details of genes affected)

However, GF mice displayed a strikingly different pattern of amygdala gene activity in response to social interaction [6] (Fig. 1). In particular, the dynamic, stimulus-dependent transcriptional regulation seen in controls was attenuated and replaced by a marked increase in expression of splicing factors and alternative exon usage. This reveals a potential molecular basis for how the host microbiome is crucial for a normal behavioural response during social interaction. Moreover, social behaviour was correlated with the amygdala gene-expression response. These results reveal one of the key steps leading from absence of bacteria during brain development to a phenotype associated with reduced sociability in adulthood in mice. These data thus enhance our understanding of the link between the microbiome and brain health and neurodevelopmental disorders such as autism spectrum disorders. Future studies will be needed to determine what are the exact microbial signals that regulate alternative splicing events in the amygdala and whether they can be harnessed for therapeutic benefit.

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ADDITIONAL INFORMATION

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Novel models of drug relapse and craving after voluntary abstinence

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Relapse to drug use during abstinence is a core feature of addiction. Since the 1980s, this clinical scenario has been studied using animal models where relapse is assessed after experimenter-imposed cessation of drug self-administration by either extinction of the drug-reinforced responding or homecage forced abstinence [1]. However, despite strides toward understanding neuronal mechanisms of relapse in these models, treatment options remain largely unchanged. One potential reason for this state-of-affairs is that animal models of addiction rarely incorporate voluntary aspects of human abstinence, which often occurs due to the availability of alternative nondrug rewards (e.g., employment and supportive social environment). This is exemplified in contingency management where nondrug rewards (monetary vouchers), given in exchange for being drug-free, can maintain abstinence for many months. However, when contingency management discontinues, most drug users relapse.

Based on these considerations, we introduced a contingency management-based relapse model, where we achieve long-lasting voluntary abstinence prior to the relapse tests by giving rats mutually exclusive choices between a drug and palatable food [2]. In the initial study, we trained male rats to self-administer the food and methamphetamine in established addiction models—escalation and DSM-IV-based—and found that rats will voluntarily abstain from drug self-administration for at least 3 weeks and then show incubation of methamphetamine craving (time-dependent increases in drug seeking during abstinence) [2]. Subsequently, we

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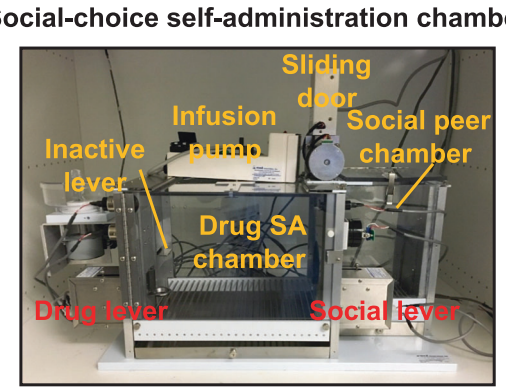

Fig. 1 Custom-made social-choice self-administration apparatus. For instructions on how to build the apparatus, see [6], and technical advice is available upon request from the authors

demonstrated the generality of food-choice voluntary abstinence to female rats and to heroin, and that surprisingly voluntary abstinence prevents incubation of heroin craving [3]. In mechanistic studies, we found a role of dorsomedial striatum neuronal ensembles in incubation of methamphetamine craving after voluntary abstinence [4], and a role of glutamatergic projections from the anterior insular cortex to central amygdala in relapse after voluntary abstinence [5].

However, the use of palatable food as the nondrug reward may limit the model's clinical translation. This is because for most humans, the rewards that compete with drugs are primarily social (family and employment). Based on this consideration, we recently introduced a newer voluntary abstinence model that involves choices between a drug and operant access to social interaction [6] (Fig. 1). We found that rats trained in established addiction models—escalation, DSM-IV-based, and intermittent access—will voluntarily abstain when given mutually exclusive choices between methamphetamine or heroin versus social interaction. This effect was independent of their 'addiction score', persisted through 4 weeks of forced abstinence, and could only be reversed by delay or punishment of the social reward. We also found that social-choice-induced voluntary abstinence prevents the emergence of incubation of methamphetamine craving, even 1 month after cessation of the social choice. This protective effect was associated with activation (assessed by the activity marker Fos) of inhibitory central amygdala PKCδ-expressing neurons and decreased neuronal activity in the anterior insular cortex [6].

In conclusion, we introduced two novel models of choice-based voluntary abstinence and demonstrated the profound protective effects of positive social interaction on drug addiction and relapse in rat models. Our findings support wider implementation of social-based behavioral treatments, which include not only the established community reinforcement approach, but also social-based psychotherapies and family-based social support systems to provide social support before and during drug-seeking episodes.

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An emerging epigenetic framework of systemic and central mechanisms underlying stress-related disorders

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Advances in translational neuroscience are pointing to a new paradigm for conceptualizing diagnosis and treatment of major morbidities, such as major depressive disorders (MDD), diabetes, and dementia [1]. Here we explore the emerging framework that focuses on the epigenetic actions of metabolic mediators on regulation of gene expression in brain regions controlling cognition and emotion as an approach to examine the systemic, as well as neural bases, of stress-related CNS disorders.

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