

sensorimotor cortices) for instrumental grasping actions than for referential pointing or reaching actions. The strength of mu suppression elicited by grasping actions was further modified by the presence of speech, as demonstrated by stronger mu suppression in the no speech than in the speech condition.

All presented actions were part of the motor repertoire available to human adults, thus the recorded differences in the motor activity cannot stem from differences in the availability of corresponding motor representations. Therefore, we propose that the activation of the motor system is influenced by the observers' interpretation of the ongoing actions, with actions interpreted as instrumental leading to higher levels of motor activation than those interpreted as referential. Our findings also suggest that the presence of ostensive signals is likely to induce referential interpretation of grasping actions, typically not perceived as such outside communicative contexts.

P1/57

Early-life CRH overexpression increases vulnerability to develop PTSD-like symptoms in adulthood

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Early-life stress is a major risk factor for developing anxiety disorders, including posttraumatic stress disorder (PTSD). Corticotropin releasing hormone (CRH) levels are elevated in individuals with PTSD and early-life trauma history which imply CRH as a mediator of early-life stress effects on PTSD risk. To test this hypothesis, we induced forebrain-specific CRH overexpression in mice during early postnatal life (i.e. without alterations of corticosterone levels; CRHOEdev), and tested their baseline anxiety-like traits, as well as their response to trauma in adulthood. CRHOEdev was induced in the forebrain transiently for three weeks in double-mutant mice (Camk2a-rtta2 x tetO-Crh) by doxycycline administration in regular chow. Avoidance and hyperarousal symptoms of PTSD were tested in multiple tests with additional gene expression analysis (CRH receptors, glucocorticoid receptor, and its binding protein FKBP5) before and after trauma exposure (i.e. predator stress). We found that CRHOEdev increased startle reactivity in conjunction with reduced prepulse inhibition and startle habituation.

predator stress. qRT-PCR analysis revealed that stress exposure induces significant expression changes of CRH receptor type 2 (Crhr2) in the extended amygdala and FKBP5 in the cortex in control males. In contrast, males previously exposed to CRHOEdev did not show such expression changes, and exhibited reduced baseline (no stress) Crhr2 and FKBP5 levels in the lateral septum and cortex, respectively. Interestingly, females mostly exhibited no changes in Crhr2 gene expression after stress which corresponds to their higher responses to stress. Our present findings indicate that extrahypothalamic CRH hyper-signaling during early-life periods is sufficient to induce lasting hyperarousal and increases susceptibility for adult traumatic events in males. Although underlying mechanisms are complex, Crhr2 expression changes during stress seems to modulate behavioral outcomes significantly. These data also support growing evidence for significant sex differences in response to trauma, and support further study of CRHR2 as a candidate mechanism for PTSD risk.

P1/58

The role of NMDA receptor subtypes and epigenetic mechanisms in behavioral dysfunctions in an animal model of post-traumatic stress disorder

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Stressful and traumatic life events often lead to the development of post-traumatic stress disorder (PTSD), a highly debilitating psychiatric condition with long-lasting symptomatology. N-methyl-D-aspartate (NMDA)-mediated glutamatergic neurotransmission is strongly involved in the development of trauma-induced behavioral dysfunctions, and indirect evidence suggests that NR2B subunit-expressing NMDA receptors are primarily involved in this process. Here we investigated the effects of the general NMDA blocker MK-801 and specific NMDA NR2A and NR2B subunit antagonists on the expression of conditioned fear, a frequently used model of PTSD. Furthermore, we studied the effects of MK-801 and the NR2B antagonist Ro25-6981 in tests that model different symptoms of PTSD, including the social avoidance test, the resident-intruder test and a hypervigilance test. Rats were exposed to a single

series of 3mA footshocks and were tested 1 or 28 days later to compare acute and long-lasting effects of trauma on behavior and target gene expression levels in brain areas relevant for PTSD. When re-exposed to the traumatic context, rats showed a dramatic increase in freezing behaviour (conditioned fear) compared to unshocked controls. We found that the NR2A antagonist PEAQX did not affect conditioned fear responses 1 or 28 days after traumatic shock exposure. However, both MK-801 and the selective NR2B subtype antagonist Ro25-6981 significantly reduced the duration of freezing in the conditioned fear test at both time points. In the social avoidance test, rats exposed to trauma avoided the opponent-containing sub-chamber of the testing apparatus. Surprisingly, Ro25-6981 further enhanced social anxiety of rats in the social avoidance test 28 days after trauma, suggesting that different symptoms of PTSD may be underlined by different pathomechanisms. Our preliminary results also suggest that Ro25-6981 modulated the effects of trauma exposure on aggressive behavior and hypervigilance as well. Quantitative real-time PCR measurements showed that NR2A and NR2B subunit mRNA expression was increased in the medial prefrontal cortex, a relevant subregion in PTSD, on the first day after the traumatic event, while only NR2B mRNA levels remained elevated 28 days after shock exposure. Similar expression patterns of NR2A mRNA expression were found in the basolateral but not the central amygdala, whereas NR2B mRNA levels were not significantly modified in these brain regions. Interestingly, mRNA expression levels of the key epigenetic enzyme DNMT3a were elevated 1 day after trauma exposure in both amygdala regions, but this effect disappeared 28 days later. Our results suggest that studying the role of glutamate neurotransmission in a subunit-selective manner opens novel opportunities for understanding the mechanisms underlying trauma-induced behavioral dysfunctions. The findings may contribute to the development of novel treatment strategies for PTSD.

P1/59

The effectiveness of extinction training: temporal considerations and brain mechanisms

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Memory of traumatic stress can persist for decades in humans. The resistance of fear memory to extinction can lead to psychological disturbances like post-traumatic stress disorder (PTSD). Commonly used treatment for PTSD is exposure therapy, which may

result in the extinction of the symptoms after repeatedly exposing patients to the same context where fear was experienced. Extinction training is a laboratory model of exposure therapy, for which, however, there are no established protocols, and the efficacy of particular protocols is unknown. Our hypothesis was that the efficacy of the extinction could change depending on the beginning of the procedure, thus we compared protocols starting 1- or 28-days after footshock. We investigated short-term and long-term extinction memory and the underlying brain mechanisms which are even less known.

We exposed rats to footshocks to induce conditioned fear. Separate groups of rats were submitted to three extinction protocols, and compared its efficacy on conditioned fear, and the reappearance after terminating the training. The extinction training started either 1 or 28 days after PTSD-inducing footshock. Protocol 1: Animals were reintroduced once daily into the conditioning chamber for 7 consecutive days without the delivery of shocks. Protocol 2: Animals were reintroduced to the conditioning chamber 5 times per day, on 3 consecutive days. Protocol 3: Animals were reintroduced into the conditioning chamber 5 times on the day that followed fear conditioning. Extinction memory was tested one day and four weeks after fear conditioning. Neuronal activation patterns were studied in the medial prefrontal cortex (mPFC), hippocampus (HC) and amygdala by c-fos immunohistochemistry on the last extinction training day of Protocol 1. In the case of extinguished recent fear memory, a spontaneous recovery of fear was observed four weeks after training. Surprisingly, the extinction of remote fear memory was considerably more durable, as no recovery was observed four weeks after training. After the extinction of recent fear memories, re-exposure to the conditioning cage increased the activation of the mPFC, and decreased the activation of the amygdala as compared to rats not exposed to extinction training. No differences were observed in the HC. In case of remote conditioned fear, extinction decreased fear-induced neuronal activation in the HC, but no major effects were observed in the mPFC and amygdala.

These surprising findings demonstrate that the extinction of remote fear memories is more effective than that of recent ones, possibly because of the temporal changes in the neuronal networks underlying fear expression. One can assume that synaptic and/or network reorganizations slowly open a time-window of neuronal plasticity which enables successful fear extinction. This reveals a complex long-term interaction between fear- and extinction memories.

P1/60

The mark of early-life social neglect – gene expression profiles surrounding abnormal aggression in adulthood

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It is well established that early-life social adversities (i.e. social neglect) may lead to the development of abnormal aggressive behaviour in adulthood. The mechanisms underlying this phenomenon are still unclear, although epigenetic regulation may play an important role in the mediation of the effects caused by social neglect. To further investigate this, we have employed the model of post-weaning social isolation devised by our research group. In the model male rats are separated after weaning, and are housed socially or individually until adulthood. Isolated rats display abnormal aggression and show physiological and behavioural differences compared to social controls. Here we aimed to investigate behavioural changes and both long-term (i.e. social isolation) and short-term (i.e. aggressive interaction) effects on gene expression. The mRNA levels were investigated with qPCR in brain regions relevant to aggression control – the prefrontal cortex (PFC) and the medial and basolateral regions of the amygdala (MeA, BLA). Studies show a strong link between aggression and the serotonin system. We thus examined the gene expression of key serotonin components: the serotonin metabolizing enzyme monoamine oxidase A (MAOA), and serotonin receptors 5-HT1a and 5-HT1b. We also examined the gene expression of epigenetic enzymes DNA-methyltransferase 1 and 3a (DNMT1, DNMT3a). Samples were taken after the period of social isolation under resting conditions (long-term effects), and 1 hour after the resident-intruder test (short-term effects). Behaviour following social isolation, adult rats were submitted to the resident-intruder test to observe aggressive behaviour. In accordance with our previous results, isolated rats displayed abnormal aggression – there was a significant increase in total bite counts and attacks aimed at vulnerable targets compared to socially housed controls. Gene expression: social isolation lead to an increase of MAOA mRNA in the PFC and MeA, 5-HT1a mRNA in the BLA, and a decrease of BLA 5-HT1b mRNA. In social controls, fighting caused an increase of PFC MAOA mRNA and a decrease of BLA 5-HT1b mRNA levels compared to resting conditions. In isolated rats aggressive interaction decreased the expression of MeA MAOA mRNA and BLA 5-HT1a mRNA levels compared to resting conditions. There were no significant changes in DNMT1 expression, however, fighting

increased DNMT3a mRNA levels of the PFC and BLA in both social and isolated rats compared to resting conditions. We also observed a negative correlation between total attack count and MeA DNMT3a relative mRNA expression. Our results display that both long-term and short-term effects induce changes in gene expression, moreover, isolation leads to altered gene regulation compared to rats raised under social conditions. Together, these findings help us gain further understanding of the complex relationship between early-life social adversities and adult abnormal aggression.

P1/61

Differential involvement of endocannabinoids anandamide and 2-arachidonoylglycerol in regulating behavioural responses to traumatic experiences

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Endocannabinoid signalling can affect behavioural responses to traumatic events. However the specific roles of the two endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are still poorly understood. In the present work we assessed the effects of pre- or post-traumatic enhancement of AEA and 2-AG signalling on acute responses to trauma, consolidation, extinction and recovery of fear memory. Male Wistar rats were systemically treated with monoacylglycerol lipase inhibitor JZ1184 to enhance 2-AG signalling or fatty acid amide hydrolase inhibitor URB597 to enhance AEA signalling. Animals were submitted to contextual fear conditioning followed by 7 daily extinction sessions where freezing behaviour was recorded. Spontaneous recovery of fear memories were assessed 28 days after trauma. Treatments were administered either before conditioning (pre-trauma) or before the contextual reminder the next day (post-trauma). Pre-traumatic enhancement of 2-AG signalling decreased freezing during fear conditioning and the reminder on the next day. In addition, the extinction of traumatic memories was faster and no fear recovery occurred in JZ1184-treated rats. In contrast, enhanced AEA signalling led to slower extinction and marked fear recovery. Surprisingly, URB597 dampened the acute effects of JZ1184. Post-traumatic enhancement of either AEA, 2-AG, or both decreased conditioned fear, and facilitated extinction of traumatic memories. Fear memories did not reoccur in these rats. Taken together, our findings suggest that AEA and 2-AG are differentially involved in the regulation of responses to traumatic events. Acute responses to trauma are regulated by 2-AG, while AEA seem to modulate 2-AG mediated effects. AEA appears to be involved in the regulation of fear memory

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