results suggest that pessimistic animals are at higher risk of poor welfare.

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Using experimental models of affective bias to optimise the treatment of depression

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Depression is associated with negative affective biases in information processing, including a tendency to focus on, interpret and remember negative information. These biases are not only relevant to psychological treatment approaches, but also play a role in pharmacological treatment. Antidepressants have been shown to reduce negative affective bias using both behavioural and neuroimaging measures of emotional processing in healthy volunteers and depressed patients. These effects on emotional processing are seen early in antidepressant administration and are predictive of later clinical treatment response, suggesting that early changes in emotional processing can serve as valid surrogate markers of therapeutic efficacy. In collaboration with pharmaceutical industry, we use these cognitive affective bias measures to screen novel candidate treatments for depression in humans, prior to the initiation of large scale randomised controlled trials. This experimental medicine approach can be used to assist 'go/no-go' decision making in antidepressant drug development, and improve subsequent clinical trial design, dosing and stratification.

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Acamprosate effect on glutamatergic receptor subunit composition in dentate gyrus on mice after long term self-administration of ethanol in IntelliCages

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Addiction is a complex disorder which involves a set of pathological behaviors described in psychiatric manuals. Those attitudes are strongly associated with environmental cues and contexts but also learning abilities. Dentate gyrus (DG) is a part of the hippocampus which is known to be involved in those processes and receives direct inputs from structures widely known to be involved in development of addiction like amygdala and VTA. To observe the role of DG in alcohol addiction we used a mouse model in IntelliCages. Thanks to that we are able to measure alcohol consumption, motivation towards alcohol, persistence in alcohol seeking, withdrawal, cue induced relapse and alcohol relapse in ecological environment. In our studies, we showed that chemogenetic inhibition of DG during presentation of alcohol-associated cues has long-lasting effects on mice behavior. DG inhibition enhances alcohol seeking and drinking, suggesting that DG regulates addiction-related behaviors. What is more, we demonstrated that, acamprosate, a drug that limits alcohol drinking and seeking in addicts, prevents generation of silent synapses in DG upon presentation of alcohol-associated cues. In order to verify the indirect acamprosate's effect on DG we observed AMPA and NMDA subunit composition on DG membranes using crosslinking protocol (BS3) on Westernblotting technique. The results indicate that both AMPA and NMDA subunit composition is altered by acamprosate during withdrawal changing the capability of the membrane for future inputs. Altogether our data suggest that weakening of DG synapses upon cue relapse contributes to persistent alcohol-addiction related behaviors and it can be affected by acamprosate.

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Using rodents to model abnormal sensitivity to feedback in depression

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Depressive disorder accounts for a substantial proportion of psychiatric problems across the globe and has a devastating impact on quality of life and occupational function. Psychological models of depression emphasize the causal role of cognitive distortions in this disease, and cognitive problems have been included in the diagnostic criteria for depressive episodes. Here, we focus on recent progress in preclinical modelling of aberrations in one of the most important neurocognitive mechanisms involved in the manifestation of depression – abnormal sensitivity to positive and negative feedback. First, we summarize the recent advances in understanding neurocognitive mechanisms of aberrant feedback sensitivity in depression and underlying neurobiological substrates. Second, by combining behavioural, neurochemical, neuroanatomical and pharmacological approaches, we evaluate the translational value of the probabilistic reversal-learning (PRL) task, a behavioural paradigm that enables investigation of correlates of feedback sensitivity in humans and animals. Finally, we identify and discuss directions for future investigation, including cognitive biomarkers of depression and resilience to stress based on feedback sensitivity and personalized treatment targets.

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Different methods for assessing cognitive affective biases in rats using the judgement bias task

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The judgement bias task (JBT) or ambiguous cue interpretation task (ACI) describes a group of decision-making task where animals learn two different cue-outcome associations, one positive and one less positive or negative. An ambiguous cue, intermediate between the two reference cues, is then used to probe decision-making behaviour. The judgement bias task first described by Harding et al., 2004 aimed to capture similar cognitive affective biases in animals to those reported in people with affective disorders such as anxiety or depression. Since the first publications, several different types of the task have been described with methods using auditory or spatial

cues and outcomes including reward versus punishment avoidance and high vs low or no reward. Some tasks are designed using a go/no-go format whilst others use a go-go presentation. In our laboratory we have used an operant box-based task and tested methods involving different tone frequencies and go-go formats with reward versus punishment avoidance and high reward vs low reward. We also tested a task where animals were trained using a light and tone for the reference cues and a compound cue used to probe responses to ambiguity. Each of the protocols tested adds to our knowledge about the underlying neuropsychological processes which contribute to the task and animals decision-making behaviour during ambiguous cue presentation. We will provide a summary of the different outcomes we have shown in terms of training time and sensitivity to different pharmacological manipulations of affective state pharmacological manipulations. We will also describe the computational modelling approaches we have been using delineate the decision process. Drift-diffusion and Bayesian models, previously shown to be equivalent, offer valuable insight into how subjects accumulate sensory evidence and how the evidence interact with the subjects' prior beliefs in order to result in a decision. These models are easily interpretable, as they are mainly built with intuitive parameters. This fact in conjunction with optimised data fitting techniques from the literature, which accurately capture experimental data with a minimal required data set size, add further support for their use in understanding alterations in the decision-making process under different affective state manipulations.

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Deluded ape. Evolutionary perspective on human cognitive biases, suffering and wellbeing

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Subjectively and (increasingly) objectively, we live in a largely made-up world. Subjectively, our perception of the outside world is not a "window on reality as it is", but rather a mental model constructed using external sensory information as well as internal elements such as memory and genetically determined preconceptions. This modelling process has been shaped by evolution to maximize survival and reproduction - not necessarily the models' faithfulness to reality. Objectively, vast majority of people – especially the rapidly growing population of city dwellers – live in environments designed and constructed by (other) people. These novel environments are radically different from those in which our perceptual and decision making mechanisms evolved, thus contributing to a number of psychological and societal problems. I will present evolutionary perspectives on (i) the origin and maintenance of biases in perceiving reality and (ii) the mismatches between our cognitive mechanisms and the environments we currently inhabit.

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Could modulation of affective biases explain the efficacy of ketamine and other rapid onset antidepressants in major depressive disorder?

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The ability of the NMDA antagonist, ketamine, to induce a rapid reduction in the symptoms of depression, in previously treatment resistant patients, has provided an exciting new avenue for the development of a novel class of antidepressant. Ketamine has recently been approved by the FDA however there are concerns about side effects and dependence liability meaning alternative compounds are needed. Current research has focussed on interaction with the processes of synaptogenesis and AMPA modulation, but these studies are limited by the rodent models of depression, which lack translational validity. In order to try to better understand the underlying mechanisms, which contribute to ketamine's efficacy, and hence identify novel drug targets, we have been using rodent models of affective bias. We first showed, in 2015, that acute ketamine could attenuate previously learnt biases in learning and memory. These effects were localised to the medial prefrontal cortex. Using a control assay, we have also been able to show that these effects are selective to affective bias and do not involve any general effects on memory. We found similar effects with the muscarinic antagonist scopolamine suggesting that rapid onset antidepressants may share a common mechanism involving modulation of previously acquired negative affective biases. We have recently extended this work to show that ketamine also has sustained effects and can modulate biases 24 hrs after treatment. In some preliminary studies looking at the molecular mechanisms underlying ketamine's acute effects, we have found that they do not require protein synthesis but may involve activation of opioid receptors.

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Effects of behavioural activation on emotional cognition and mood (protocol)

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Behavioural activation is an evidence-based treatment for depression. In previous research, various types of psychiatric treatment, such as standard antidepressants (SSRIs), CBT or St John's Wort have been found to cause early changes in emotional information processing (Harmer et al., 2009). There is preliminary evidence that these early changes may help predict the treatment outcome (Tranter et al., 2009). The current experiment aims to investigate whether such early changes in affective cognition also occur in behavioural treatments. We plan to recruit 120 participants with low mood, who will be assigned to either one month of behavioural activation, one month of activity monitoring (active control group) or one month in the waiting list group (passive control). We will examine whether early changes in emotional attention and memory, baseline levels of depression severity, environmental reward or social support may help predict the treatment outcome. These future findings may improve out understanding of the mechanisms in behavioural treatments and who these interventions may be most suitable for. Lastly, the experiment will prepare us for a future study of how standard antidepressants affect motional processing when combined with behavioural interventions for low mood.

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