Abbie Pringle & Cathrine Harmer: Selected references

Harmer, C. J. & Cowen, P. J. (2013). 'It's the way that you look at it'--a cognitive neuropsychological account of SSRI action in depression. *Philosophical Transactions of the Royal Society.B: Biolological Sciences, 368,* 20120407.
Notes: The fact that selective serotonin reuptake inhibitors (SSRIs) have antidepressant effects in some patients supports the notion that serotonin plays a role in the mode of action of antidepressant drugs. However, neither the way in which serotonin may alleviate depressed mood nor the reason why several weeks needs to elapse before the full antidepressant effect of treatment is expressed is known. Here, we propose a neuropsychological theory of SSRI antidepressant action based on the ability of SSRIs to produce positive biases in the processing of emotional information. Both behavioural and neuroimaging studies show that SSRI administration produces positive biases in attention, appraisal and memory from the earliest stages of treatment, well before the time that clinical improvement in mood becomes apparent. We suggest that the delay in the clinical effect of SSRIs can be explained by the time needed for this positive bias in implicit emotional processing to become apparent at a subjective, conscious level. This process is likely to involve the re-learning of emotional associations in a new, more positive emotional environment. This suggests intriguing links between the effect of SSRIs to promote synaptic plasticity and neurogenesis, and their ability to remediate negative emotional biases in depressed patients
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Pringle, A., Browning, M., Parsons, E., Cowen, P. J., & Harmer, C. J. (2013). Early markers of cognitive enhancement: developing an implicit measure of cognitive performance. *Psychopharmacology (Berlin).*
Notes: There is intense interest in the development of effective cognitive enhancing drugs which would have therapeutic application across a number of neurological and psychological disorders including dementia, schizophrenia and depression. However, development in this area has been limited by the absence of sensitive biomarkers which can be used to detect and refine therapeutic-like action in phase 1 clinical studies. The aim of the present study was therefore to develop a measure of cognition relevant to the action of candidate cognitive enhancers which might be sensitive to pharmacological manipulation in healthy volunteers. Healthy volunteers (n = 34) were randomised to receive a single dose of modafinil (100 mg) or placebo. Five hours post dose, attentional flexibility in learning was assessed using a novel implicit learning task. Volunteers also completed an auditory digit span task and visual analogue scales (VAS). Modafinil increased alertness as measured by the VAS. In the implicit learning task, modafinil enhanced learning rates in terms of both accuracy and reaction time, suggesting an increase in implicit rule learning. These results suggest that the novel learning task should be explored as a biomarker of early cognitive improvement which could be more sensitive than conventional measures
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Pringle, A., Ashworth, F., Harmer, C. J., Norbury, R., & Cooper, M. J. (2011). Neural correlates of the processing of self-referent emotional information in bulimia

nervosa. *Neuropsychologia, 49,* 3272-3278.
Notes: There is increasing interest in understanding the roles of distorted beliefs about the self, ostensibly unrelated to eating, weight and shape, in eating disorders (EDs), but little is known about their neural correlates. We therefore used functional magnetic resonance imaging to investigate the neural correlates of self-referent emotional processing in EDs. During the scan, unmedicated patients with bulimia nervosa (n=11) and healthy controls (n=16) responded to personality words previously found to be related to negative self beliefs in EDs and depression. Rating of the negative personality descriptors resulted in reduced activation in patients compared to controls in parietal, occipital and limbic areas including the amygdala. There was no evidence that reduced activity in patients was secondary to increased cognitive control. Different patterns of neural activation between patients and controls may be the result of either habituation to personally relevant negative self beliefs or of emotional blunting in patients
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Pringle, A., McTavish, S. F., Williams, C., Smith, R., Cowen, P. J., & Harmer, C. J. (2011). Short-term NK1 receptor antagonism and emotional processing in healthy volunteers. *Psychopharmacology (Berlin), 215,* 239-246.
Notes: BACKGROUND: Despite early promise in phase II, the performance of the NK1 receptor antagonist aprepitant in subsequent clinical trials has been disappointing. Healthy volunteer models of emotional processing offer a potential means by which novel drugs can be screened prior to clinical trials. Here, we consider the effect of 7 days of treatment with aprepitant in such a model. METHOD: Healthy volunteers (n = 32) were randomised to receive 7-day treatment with aprepitant (125 mg) or placebo. On the seventh day, participants completed a battery of tasks measuring emotional processing previously demonstrated to be sensitive to conventional antidepressant drugs. The tasks included facial expression recognition, emotional categorisation and memory, attentional dot-probe and emotion potentiated startle task. RESULTS: Aprepitant abolished the emotionally potentiated startle effect and increased recognition memory for emotionally positive versus negative stimuli. In addition, the drug decreased attention to negative relative to positive emotional stimuli on the masked version of the dot-probe task. These effects were seen in the absence of any change in subjective mood. There were no effects on emotional categorisation, recall or on facial expression recognition. CONCLUSION: These results suggest that NK1 receptor antagonism does affect some aspects of emotional processing and, in particular, that it has anxiolytic-like effects. The profile of effects reported here is, however, more limited than that found in response to conventional antidepressant treatment, and this may explain disappointing results at clinical trial. Healthy volunteer models of emotional processing may be useful in closing the gap between preclinical and clinical trials
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Harmer, C. J. (2010). Antidepressant drug action: a neuropsychological perspective. *Depression and Anxiety, 27,* 231-233.
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Pringle, A., Harmer, C. J., & Cooper, M. J. (2010). Investigating vulnerability to eating disorders: biases in emotional processing. *Psychological Medicine, 40,* 645-655.
Notes: BACKGROUND: Biases in emotional processing and cognitions about the self are thought to play a role in the maintenance of eating disorders (EDs). However, little is known about whether these difficulties exist pre-morbidly and how they might contribute to risk. METHOD: Female dieters (n=82) completed a battery of tasks designed to assess the processing of social cues (facial emotion recognition), cognitions about the self [Self-Schema Processing Task (SSPT)] and ED-specific cognitions about eating, weight and shape (emotional Stroop). The 26-item Eating Attitudes Test (EAT-26; Garner et al. 1982) was used to assess subclinical ED symptoms; this was used as an index of vulnerability within this at-risk group. RESULTS: Regression analyses showed that biases in the processing of both neutral and angry faces were predictive of our measure of vulnerability (EAT-26). In the self-schema task, biases in the processing of negative self descriptors previously found to be common in EDs predicted vulnerability. Biases in the processing of shape-related words on the Stroop task were also predictive; however, these biases were more important in dieters who also displayed biases in the self-schema task. We were also able to demonstrate that these biases are specific and separable from more general negative biases that could be attributed to depressive symptoms.
CONCLUSIONS: These results suggest that specific biases in the processing of social cues, cognitions about the self, and also about eating, weight and shape information, may be important in understanding risk and preventing relapse in EDs
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Harmer, C. J. (2008). Serotonin and emotional processing: does it help explain antidepressant drug action? *Neuropharmacology, 55,* 1023-1028.
Notes: There is growing interest in the effects of antidepressant drug treatment on measures of emotional processing. Such actions may help us understand the role of monoamines in emotional dysfunction in depression and how antidepressant drug treatments work. Recent studies suggest that decreasing central serotonin function with tryptophan depletion can reinstate negative biases in recovered depressed patients, even at doses insufficient to induce changes in mood. Conversely, antidepressant drug administration increases the processing of positive emotional information in healthy volunteers and acutely depressed patients early in treatment. This increase in positive bias may provide a platform for subsequent cognitive restructuring and learning which contributes to the evolution of symptom change in depression. Functional neuroimaging studies suggest that these early antidepressant effects involve fronto-limbic and extra-striate circuitry suggestive of actions on both the initial appraisal and attentional processing of affective stimuli. This approach may therefore provide a framework for linking psychological and biological processes in emotional disorders and their treatment. Antidepressants may not directly modulate mood and anxiety but rather allow a different perspective for our ongoing evaluation of our self, the world and the future
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