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Reply to Nathan *et al*

Antidepressants and Emotional Processing

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Sir

We would like to thank our colleagues for their comments on our study examining the effects of acute selective serotonin reuptake inhibitor (SSRI) administration on emotional processing in healthy volunteers. We were particularly interested to read about their recent research findings, which suggest an action of acute SSRI administration on the neurophysiological responses to positive and negative emotional stimuli (Kemp *et al*, in press; Kemp *et al*, submitted). This type of approach represents a relatively new way of thinking about antidepressant drug action, which has the potential to be extremely informative. While the pharmacological and cellular consequences of antidepressants have been increasingly characterized over recent years, there has been relatively little attention, at a systems level, of the way in which antidepressants relieve the many symptoms of depression and anxiety. Our own findings and those from the Nathan group suggest that antidepressants may directly affect the way in which emotional information is processed and therefore help to reduce negative biases in perception and memory which are believed to play a role in the maintenance of the symptoms of depression (Beck *et al*, 1979).

Kemp *et al* (submitted) suggest that citalopram given acutely reduced the neurophysiological response to unpleasant visual stimuli. We have also found a reduction in the processing of negative emotional stimuli following repeated oral dosing of this SSRI (Harmer *et al*, 2002). Hence, after 7 days of citalopram (20 mg/day), volunteers showed reduced recognition of negative facial expressions, reduced potentiation of startle responses through fear relevant stimuli and improved memory for positive emotional information. In contrast to these findings, acute citalopram (10 mg i.v.) actually increased the recognition of fearful as well as of happy facial expressions (Harmer *et al*, 2003). These findings therefore suggest that antidepressants have dissociable actions on positive emotional processing (which could contribute to the development of improved mood and social behavior over time) and those processes that underlie fear and anxiety. The reversal in fear processing from acute to repeated treatment with SSRIs has also been described in animal models of fear conditioning (Burghardt *et al*, 2002) and, clinically, patients can experience heightened anxiety before therapeutic actions are seen. As yet, the mechanisms underlying the reversal of fear processing from acute to repeated administration are unknown but of clear importance to our understanding of why antidepressant drugs take so long to work. Assessment of these processes in these human models may be important in resolving this critical issue in antidepressant drug action.

Finally, we would be very interested to see the effects of noradrenergic antidepressants in Nathan's models. We have found very similar effects in terms of the processing of positive emotional stimuli following reboxetine administration, including increased memory of positive emotional characteristics and increased perception of happy facial expressions (Harmer *et al*, in press). In time, it is hoped that this approach will lead to an integrated understanding of the neural systems involved in emotion processes and the impact of different monoamine challenges on these systems.

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