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EDITORIAL

Fronto-limbic engagement during moral processing in stimulant users

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Externalising psychopathology in adulthood (meeting diagnostic criteria for dissocial personality disorder, with or without psychopathy, and substance misuse disorders) is a significant burden to society. To what extent are the neurobiological underpinnings of these commonly co-morbid disorders discrete? Our success in answering this question depends to a great degree on how carefully the clinical sample is characterised. Kiehl's group in New Mexico have had great success in examining a difficult clinical population (incarcerated male offenders) using a mobile 1.5-T scanner in the grounds of the penitentiary. Their focus has typically been on the brain basis of dissocial personality disorder with psychopathy, but in the current study they switch their focus to explore the potential brain bases of stimulant use in such men.

In their paper published today in Psychopharmacology, Fede et al. examine the impact of lifetime use of stimulant drugs such as cocaine and methamphetamine on functional brain activations using a case-control design (Fede et al. 2016). They compared groups of male offenders with and without a self-reported history of drug misuse after some period of abstinence (assuming that incarceration limits access to drugs). They examined neural activity in seven pre-specified regions of interest (bilateral ventromedial prefrontal cortex, bilateral anterior cingulate, bilateral posterior cingulate and right amygdala) during the performance of a moral decision-making task, in which subjects considered whether words or phrases were morally wrong. The key comparison was between brain activity during the consideration of morally controversial concepts (such as animal testing or stem cell research) and morally non-controversial concepts (a mixture of positively and negatively valenced items such as murder and kindness). Morally controversial cues were designed to evoke deeper moral deliberation than non-controversial acts, although the precise psychological function that is isolated in the comparison is open to question. The authors found significantly less activation in one of the seven regions (the right amygdala) during such moral deliberation in those with histories of lifetime cocaine and/or methamphetamine use. Within the stimulant users, the duration of stimulant use was associated with lower activity in the anterior cingulate and increased activity in the vmPFC during moral deliberation.

The authors are careful to note that such observed associations do not necessarily imply a causal relationship, as these associations could result from an unmeasured third variable that independently influences the two measures. Indeed, it is possible that these differences in brain function pre-dated, and maybe even contributed to, the development of drug use. Nevertheless, the evidentiary value of the findings is strengthened by the authors' ability to rule out some of the key potential confounds. Thus, the groups did not differ in such measures as intelligence or psychopathy, and men with co-morbid psychotic disorders were excluded from the investigation. Although the men's personality function is not otherwise specified, many of the men under investigation most likely meet criteria for dissocial personality disorder, and we can be clear that they do not exceed the categorical threshold for psychopathy. Substance misuse diagnoses were carefully characterised, although reliant on self-report. This may be of some concern given the nature of the population. As such it is

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an issue that can usefully be explored in future work, either through the use of hair samples or urinalyses at the time of investigation.

The reduced amygdala response seen in the stimulant users identifies dysfunction in a key component of the brain circuits involved in processing emotionally valent information, and preclinical studies show inactivation in this circuit impairs decision making (Zeeb et al. 2015). Thus, the reduced response during processing of morally controversial information suggests that the stimulant-using group is less able to process the emotional valence of information, particularly when there is ambiguity. The failure to fully process the emotional valence of information could then mean that their decision making fails to consider the emotional consequences of actions, which could link to both stimulant use and offending behaviour. Furthermore, the amygdala is under top-down regulatory control by cortical regions, including the frontal cortical regions they investigated. Thus, the association between longer duration of stimulant use and greater reductions in responses in frontal regions suggests stimulant use could also impact on the regulatory control of emotion circuits. This fits with preclinical work showing that repeated stimulant exposure reduces learning to aversive cues (Nguyen et al. 2015).

These findings could suggest that techniques that focus on improving the processing of emotional stimuli, particularly morally controversial information, may be beneficial. Moreover they identify a circuit and regulatory centres that could be targeted by interventions to test the mechanism underlying stimulant misuse, and potentially treat it. One possibility is neurofeedback, which has shown promise in altering the connectivity between frontal regulatory centres and subcortical brain regions including the amygdala and reward centres also implicated in stimulant misuse (Koush et al. 2015). However, whilst the task implicates emotional regulatory circuits, the moral deliberation task is complex, involving both value judgements and perspective taking, and further work will be needed to determine the circuitry underlying the key components of this.

Identifying reliable endophenotypes for addictive and antisocial behaviours would benefit the field in terms of identifying aetiological factors and stratifying clinical populations to underpin more sensitive clinical trials in these recalcitrant disorders. The domains of elevated trait impulsivity and abnormal goal-directed learning and habit formation appear particularly promising. Abnormalities of anterior cingulate function may impact upon the cognitive control of impulsive choices (as indexed by successful stop signal reaction time task performance). Abnormalities of ventromedial prefrontal cortical function may impact upon the ability to use representations of outcome value to appropriately guide behaviour (as indexed by response reversal tasks). Optimal psychosocial and drug treatment approaches require further specification. The complexity of the task ahead is illustrated by the finding that such patients tend to perform a rewarded behaviour in an automatic fashion, irrespective of its consequences, and punitive interventions appear ineffective (Ersche et al. 2016). This makes their compulsive drug seeking behaviour unlikely to be affected by cognitive interventions that target the enhancement of alternative outcomes. Treatment of cocaine and methamphetamine addiction should thus focus on training desirable habits that replace habitual drug-taking. But what might these be in an antisocial population?

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