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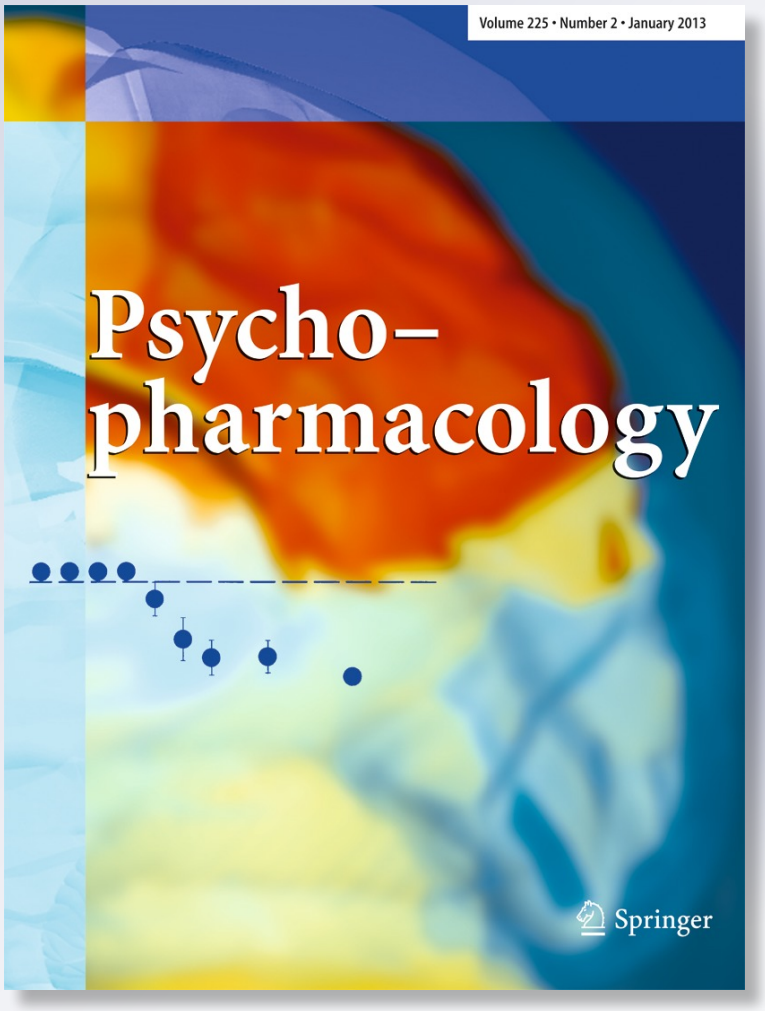

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ORIGINAL INVESTIGATION

Effect of D-amphetamine on emotion-potentiated startle in healthy humans: implications for psychopathy and antisocial behaviour

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Abstract
Rationale An emerging literature associates increased dopaminergic neurotransmission with altered brain response to aversive stimuli in humans. The direction of the effect of dopamine on aversive motivation, however, remains unclear, with some studies reporting increased and others decreased amygdala activation to aversive stimuli following the administration of dopamine agonists. Potentiation of the startle response by aversive foreground stimuli provides an objective and directional measure of emotional reactivity and is considered useful as an index of the emotional effects of different drugs.
Objective We investigated the effects of two doses of D-amphetamine (5 and 10 mg), compared to placebo, for the first time to our knowledge, using the affect–startle paradigm.
Method The study employed a between-subjects, double-blind design, with three conditions: 0 mg (placebo), and 5 and 10 mg D-amphetamine (initially $n=20$/group; final sample: $n=18$, placebo; $n=18$, 5 mg; $n=16$, 10 mg). After drug/placebo administration, startle responses (eyeblinks) to intermittent noise probes were measured during viewing of pleasant, neutral and unpleasant images. Participants' general and specific impulsivity and fear-related personality traits were also assessed.
Results The three groups were comparable on personality traits. Only the placebo group showed significant startle potentiation by unpleasant, relative to neutral, images; this effect was absent in both 5- and 10-mg D-amphetamine groups (i.e. the same effect of D-amphetamine observed at different doses in different people).
Conclusions Our findings demonstrate a reduced aversive emotional response under D-amphetamine and may help to account for the known link between the use of psychostimulant drugs and antisocial behaviour.

Keywords D-amphetamine · Dopamine · Startle potentiation · Emotion · Affect · Antisocial behaviour · Psychopathic disorder

Introduction

Dopaminergic neurotransmission is widely implicated in appetitive motivation (Berridge and Kringelbach 2008) and has been associated with tendencies to approach, forage and explore the environment or to experience positive affect states (Gray 1991). An emerging literature also associates dopamine with altered responses to aversive stimuli (Patin and Hurlemann 2011), but the nature of this relationship is much less clear.

A number of functional imaging studies have focussed on the effect of dopamine on neural processing of aversive stimuli. For example, Delaveau et al. (2007) reported reduced right amygdala activation under the dopamine agonist L-DOPA during an emotion (fear and anger) matching task. Hariri et al. (2002), also using an emotion (fear and anger) matching task, found that amphetamine (0.25 mg/kg body weight) increased right amygdala responses to fear and angry facial expressions. Furthermore, Takahashi et al. (2005) found that a

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25-mg single oral dose of sultopridem (a dopamine D2/D3 receptor antagonist) reduced activity in the left amygdala when viewing unpleasant images. Such findings clearly support an association between dopamine and processing of aversive stimuli, but being inconsistent in terms of enhanced or reduced amygdala activation to unpleasant stimuli, they do not allow a clear picture concerning the direction of the effect of dopamine on aversive motivation.

In relation to the influence of dopamine in clinical behaviours, despite the observation that antisocial individuals abuse dopamine agonists (e.g. amphetamine and codeine; Fridell et al. 2008) and such long-term abuse leads to cognitive impairments (review, Ornstein et al. 2000), it is not yet known whether this abuse leads to increased appetitive, or decreased aversive, motivation. Nonetheless, the findings demonstrating enhanced learning from reward signals, but also decreased learning from punishment signals following dopaminergic therapy in Parkinson's disease (Bódi et al. 2009; Cools et al. 2006; Frank et al. 2004, 2007; Graef et al. 2010; Kobayakawa et al. 2010), indicate that both appetitive and aversive motivational systems are influenced by dopamine.

To our knowledge, the present study employs, for the first time, the affect–startle paradigm (Vrana et al. 1988) to understand the effect of dopamine on appetitive and aversive motivation. Since the introduction of this paradigm about 30 years ago, its utility as an objective and reliable tool to assess, and distinguish between, the appetitive and aversive motivation systems, in health as well as disease, has been confirmed across countries and cultures [for example, in USA (Lang et al. 1990, 2000), UK (Corr et al. 1995; Kumari et al. 2001) and Greece (Giakoumaki et al. 2010; Roussos et al. 2009)]. The startle reflex consists of a set of involuntary responses to a sudden, strong sensory stimulus (e.g. a loud noise burst) and shows reliable modulation by concomitant presentation of affect-toned material: if pleasant, the startle response is attenuated; and if unpleasant, it is potentiated (Vrana et al. 1988)—often referred to as 'pleasure-attenuated' and 'fear-potentiated' startle, respectively. Measures of fearfulness and psychopathy show positive and negative associations, respectively, with startle potentiation during unpleasant picture viewing (e.g. Benning et al. 2005; Herpertz et al. 2001; Vaidyanathan et al. 2011). Much is known from rodent studies about the neural substrates underlying the affect–startle relationship, with critical roles played by the amygdala in the potentiation of startle by fear (review, Davis et al. 1993) and the nucleus accumbens in the attenuation of startle by pleasure (Koch et al. 1996).

The present study set out to examine the effect of acute administration at two doses of an indirect dopamine (D1) agonist, D-amphetamine, on startle modulation by pleasant and unpleasant foreground stimuli in healthy volunteers. On the basis of the literature, we predicted an effect of D-amphetamine on indices of both appetitive and aversive motivation. Specifically, given previous suggestions that dopamine enhances sensitivity to appetitive stimuli (Fibiger and Phillips 1998) and activates the behavioural approach system (BAS; Gray 1991), we predicted that D-amphetamine should enhance pleasure-attenuated startle. In addition, given the earlier noted effects of dopaminergic therapy in Parkinson's disease and the known association between abuse of D-amphetamine and antisocial behaviour where fear-related brakes on behaviour seem much weakened, we predicted that it should reduce fear-potentiated startle.

Method

Participants and design

The study involved 60 healthy non-smoking participants (age range 18–44 years) recruited by local advertisements. All potential participants underwent a medical screening for thyroid dysfunction, glaucoma, heart disease, hypo- or hypertension, a history of severe mental illness, anorexia, rapid mood changes, regular medical prescription, alcohol dependency, lactation or pregnancy or possibility of pregnancy, and they were excluded if found positive on any of these criteria. Before being accepted, they were screened (urine analysis) for drug of abuse (morphine, methadone, cocaine, amphetamines and benzodiazepines). Their blood pressure, heart rate and body weight were also taken, and all selected participants were in the normal range. The study was approved by the Institute of Psychiatry and South London and Maudsley NHS Trust research ethics committee. Participants provided written informed consent after the study aims and procedures had been explained to them. They were compensated for their time and travel.

The study employed a between-subjects design, with three drug conditions: 0 mg (placebo), and 5 and 10 mg D-amphetamine. Twenty of 60 participants, counterbalanced for sex, were randomly assigned to each of the three drug conditions. Of these, two participants of the placebo group, two of the 5-mg drug group and three participants of the 10-mg drug group provided unusable startle data, and the experimental session was incomplete for one further participant of the 10-mg drug group. The final sample thus had 18 participants in the placebo group, 18 in the 5-mg drug group, and 16 in the 10-mg drug group. Participant characteristics of the final study groups are presented in Table 1.

Drug/placebo administration

The drug was administered orally. The 5-mg drug administration consisted of one tablet containing 5 mg dexamphetamine (Evans Medical Limited, UK), and 10-mg drug administration consisted of two such tablets. Empty coloured capsules were used as the placebo (0 mg). Randomisation and drug/placebo

Table 1 Participant characteristics

	Placebo Group (10 men, 8 women); Mean (SD)	5-mg Drug Group (8 men, 10 women); Mean (SD)	10-mg Drug Group (9 men, 7 women); Mean (SD)	ANOVA (df=2,49)
Age (yrs)	27.90 (4.80)	29.94 (6.93)	27.69 (5.31)	F=0.82, p=0.45
TPQ				
Novelty Seeking	18.28 (4.97)	18.67 (5.65)	18.25 (3.66)	F=0.04, p=0.96
Reward Dependence	18.61 (4.73)	17.17 (4.19)	16.69 (6.46)	F=0.65, p=0.52
Harm Avoidance	13.11 (5.77)	12.17 (5.89)	12.88 (6.08)	F=0.20, p=0.82
IVE-7				
Impulsiveness	7.89 (5.20)	9.17 (3.45)	8.06 (3.99)	F=0.47, p=0.63
Venturesomeness	10.00 (3.79)	10.94 (3.89)	9.19 (3.49)	F=0.94, p=0.40
Empathy	12.83 (3.68)	12.06 (2.53)	13.12 (2.75)	F=0.58, p=0.57
Fear survey schedule score	116.56 (27.07)	117.39 (26.23)	120.81 (26.10)	F=0.12, p=0.89

administration (in a separate room) was carried out by a physician who was not involved in data collection. All participants were given the drug/placebo between 9.30 and 11.00 a.m. to control for the possible time of day effects on drug metabolism.

General procedure

Upon arrival, female participants were given pregnancy tests. Baseline heart rate and blood pressure were then taken from all participants who, then, under double-blind conditions received the drug/placebo. This procedure was followed by a 90-min wait period, during which time, participants filled out personality questionnaires (described further under 'Personality measures'), and had their heart rate and blood pressure monitored every 30 min. After 90 min following drug/placebo administration, participants performed a simple computer learning task (not relevant to this investigation) taking approximately 15 min, and then took part in the affect–startle experiment. Heart rate and blood pressure were taken again after the experiment. Participants were requested to have a light breakfast on the day of testing and were served only decaffeinated drinks during the 90-min wait period. They were also requested to abstain from alcohol for at least 12 h prior to their appointment.

Affect–startle experiment: paradigm and procedure

Participants viewed 27 photographic images taken from the International Affective Picture System (IAPS; Lang and Bradley 2005). Of these, nine had positive emotional valence (e.g. pictures of food items, laughing babies, happy couple, opposite sex nudes; IAPS nos. 4650, 7200, 7270, 7280, 8120, plus 2030, 4210, 4180 and 4290 used for men, and 2040, 4510, 4520 and 4530 used for women), nine had neutral valence (e.g. pictures of household items; IAPS nos. 1560, 1640, 2200, 5510, 6610, 7000, 7080, 7100, and 7150), and nine had negative emotional valence (e.g. pictures of mutilations, accident victims, snakes, angry faces; IAPS nos. 1030, 1070, 1110, 3000, 3100, 3140, 6200, 6230, and 9050). The images were arranged in three sets of nine images, with each set comprising of randomly ordered three positive, three neutral and three negative images. Each image was in view for 6 s, followed by a randomly varying inter-image-interval of 10–20 s. On six of nine images in each category, an acoustic startle probe, consisting of 50 ms burst of 100 dB white noise with almost instantaneous rise time, was delivered at a random point between 2 and 5 s after the image onset. In addition to these 18 probes (six per image category), six startle probes were delivered during the inter-image-intervals to minimise the predictability of probes. At the beginning of the experiment, before the images were presented, three startle probes were delivered to reduce habituation during image-presented probes. The sequence of images was same for all participants. The experimental session started with a 3-min acclimation period, during which participants were exposed to background (70 dB) white noise only (this noise was presented also throughout the entire experimental session).

The equipment and eyeblink recording procedures were identical to those used in our previous studies (Kaviani et al. 2004; Kumari et al. 1996, 2001). A commercially available computerised human startle response monitoring system (SR-Lab, San Diego, California) delivered the acoustic startle stimuli and both recorded and scored electromyographic (EMG) activity for 250 ms, starting from the probe–stimulus onset. Acoustic stimuli were presented binaurally through headphones (Telephonics, TDH 39P). The eyeblink component of the startle response was indexed by recording EMG activity of the orbicularis oculi muscle by positioning two miniature silver/silver chloride electrodes filled with Dracard

electrolyte paste (SLE, Croydon) beneath the left eye. The ground electrode was attached to the mastoid behind the left ear. Recorded EMG activity was band-pass filtered, as recommended by the SR-Lab. A 50-hz filter was used to eliminate ambient interference. EMG data were scored off-line by the analytic programme of this system for response amplitude (in A-D units; the main measure for hypothesis testing) and latency to response peak (in ms). Latency to response onset was defined by a shift of 6 digital units from the baseline value occurring within 18–100 ms after the stimulus. The latency to response peak was determined as the point of maximal amplitude that occurred within 120 ms from the acoustic stimulus. If the onset and peak latencies differed by more than 95 ms or the baseline values shifted by more than 50 units, then the responses were rejected (<5 % trials).

Prior to the experiment, participants were informed that they were to be shown a series of images of varying contents and that they were requested to watch them attentively. Participant was also told that the noise (acoustic probes) heard occasionally over the headphones should be ignored. Testing took place in a moderately-lit soundproof laboratory, with the participants sitting comfortably in a large chair.

Personality measures

Personality was measured by several widely used questionnaires that measure general traits as well as specific impulsivity and fear-related ones. General traits of both a positive and negative nature were measured by the tridimensional personality questionnaire (TPQ; Cloninger 1988), which yields three major scales: novelty seeking, reward dependence and harm avoidance. Impulsiveness, venturesomeness and empathy sub-scales of the impulsiveness–venturesomeness–empathy questionnaire (IVE-7; Eysenck et al. 1985) were also taken. Specific fears were measured by the fear survey schedule (Wolpe and Lang 1969). As the drug conditions were between-subjects, these measures were taken to ensure that the three drug conditions were comparable in terms of appetitive and aversive-related pre-existing individual differences.

Analysis

The three drug groups were compared on age and personality characteristics using a series of one-way analyses of variance (ANOVA). Data on startle amplitudes during the three image categories were subjected to 3 (Drug: 0, 5 and 10 mg)×3 (Valence: positive, neutral and negative) ANOVA with drug and sex as between-subjects factors and valence as a within-subjects factor, followed by lower-order ANOVAs and post hoc *t* tests to examine the drug × valence interaction. Prior to running these analyses, the data were examined for their distribution properties and found to be near-normal (slightly positively skewed) with equal error variance in each valence category across the study groups. All analyses were carried out using Statistical Package for the Social Sciences (SPSS, version 18) with alpha level for significance testing maintained at $p \leq 0.05$.

Results

Participant characteristics

The three drug groups were comparable on age and personality dimensions (Table 1).

Startle modulation

Amplitude served as the main dependent measure of startle reactivity.[1] As expected, there was a significant main effect of valence [$F(2,92)=3.50$, $p=0.03$] and a significant drug × valence interaction [$F(4,92)=2.54$, $p=0.04$]. This interaction obscured the main effect of Drug which was not significant [$F(2,46)=0.08$, $p=0.92$]. Sex [$F(1,46)=0.064$, $p=0.80$] was non-significant, and there were no significant interactions involving this factor (p values >0.20 for sex × drug, sex × valence, and sex × drug × valence).

Examination of valence effect (categories ordered as positive, neutral and negative) separately in the three drug groups revealed a significant main effect of valence [$F(2,34)=4.71$, $p=0.016$] with a linear trend [Lin $F(1,17)=8.50$, $p=0.01$] in the placebo group, but not in the 5-mg [$F(2,34)=2.48$, $p=0.10$] or 10-mg [$F(2,30)=1.81$, $p=0.18$] drug groups.

Probing the drug × valence interaction further using 3 (drug)×2 (valence: positive and neutral; or negative and neutral) ANOVAs did not show a significant effect of drug on startle attenuation by positive images [$F(2,49)=1.72$, $p=0.19$]. There was, however, an effect of drug on startle potentiation by negative, relative to neutral, images [$F(2,49)=3.76$, $p=0.03$]: significant startle potentiation by negative, relative to neutral, images was present in the placebo group [$F(1,17)=5.35$, $p=0.03$] but was absent in both drug groups [5 mg: $F(1,17)=0.99$, $p=0.33$; 10 mg: $F(1,15)=1.13$, $p=0.30$]. Importantly, the three groups did not differ in startle amplitude during the viewing of neutral images itself [$F(2,49)=0.41$, $p=0.67$] (Fig. 1).

Discussion

The human startle reflex is potentiated by aversive foreground stimuli and attenuated by pleasant foreground

[1] We conducted comparable analyses for latency of response but no effects were found.

stimuli; these are often referred to as 'fear-potentiated' and 'pleasure-attenuated' startle, respectively. The startle reflex provides a convenient and sensitive measure of emotional reactivity and is especially useful for examining drug effects on emotion. Our study is the first to show that a potent dopamine (D1) agonist, D-amphetamine, significantly reduces fear-potentiated startle, abolishing this effect seen in placebo. This effect of D-amphetamine was observed at two doses (5 and 10 mg) and the pattern of effects observed in both drug groups was virtually identical, suggesting the absence of a dose-related effect—the identical pattern of these effects also provides evidence that the observed drug effect was not a Type I error. It thus appears that D-amphetamine blunts the induction of negative emotional experience, at least as measured by the affect–startle paradigm. There were no effects of sex on this effect; and the differential pattern of findings observed between the drug and placebo conditions could not be attributed to pre-existing personality differences, assessed by broad dimensions of personality or specific appetitive and aversive-related traits.

Results may be interpreted as showing that dopamine (D1) agonism reduces fear-related emotional processes, which may account for the known link between the use of this psychostimulant drug and antisocial behaviour, noted in the 'Introduction'. Specifically, these data are consistent with the observation that, even with acute administration of D-amphetamine, a less fearful emotional response can be observed in healthy people of both sexes. Certainly, these findings are consistent with other research which shows that psychopathic-related disposition in young (non-clinical) individuals are related to a hyperactive behaviour approach system and an appetitive motivation in general as well as to reduced fear (and anxiety) (Corr 2010). There is robust evidence for impaired startle potentiation to aversive stimuli (e.g. Benning et al. 2005; Herpertz et al. 2001; Patrick et al. 1993; Vaidyanathan et al. 2011) as well as amygdala dysfunction (reviews, Blair 2010; Gao et al. 2009) in psychopathic individuals. Given consistent evidence from both animal (review, Davis et al. 1993) and human studies (e.g. Aldhafeeri et al. 2012; Buchanan et al. 2004; Funayama et al., 2001) that startle potentiation by aversive stimuli is mediated by the amygdala, which has a high density of dopamine receptors (Missale et al. 1998) and is influenced by dopamine transmission (Kroner et al. 2005), our findings point to two possible explanations: (a) that D-amphetamine directly antagonises fear-related processes; or (b) this effect is secondary to a primary effect on pleasure-related processes (there is a long and well-established literature showing mutually reciprocal inhibition of appetitive and aversive systems; Gray 1987). In support of the latter possibility, there is evidence of neurochemical and neurophysiological hyperactivity in the mesolimbic dopamine reward system in psychopathic individuals (Buckholtz et al. 2010). However, the effect of D-amphetamine observed in this study may not be exclusively dopaminergic since D-amphetamine not only releases dopamine but also serotonin and noradrenaline (West et al. 1995), and both the serotonergic and noradrenergic systems are implicated in emotion processing (Bijlsma et al. 2010; Hung et al. 2011) as well as startle reactivity (Koch 1999).

Relating these findings to non-clinical and clinical groups of antisocial and psychopathic individuals should yield valuable data, especially concerning their relative reactions to appetitive and aversive stimuli, and how different classes of drugs affect their responses. As noted by Fridell et al. (2008, p. 799), crime and drug abuse go together and amphetamine, in particular, is associated with crime in general, as well as with all subtypes of crime. Miller et al. (2006) provides estimates of the many millions of crime committed in the USA by individual using drugs of abuse. It might be the case that certain individuals have a vulnerability to reduced aversive motivation in the context of hyperdopaminergic activity, and it might be these people that are prone to develop antisocial and psychopathic personalities. This hypothesis could be tested by behavioural and MRI reactions to drug challenge. It might also be important to test this hypothesis in younger children in order to throw light on the developmental trajectory of such vulnerable individuals.

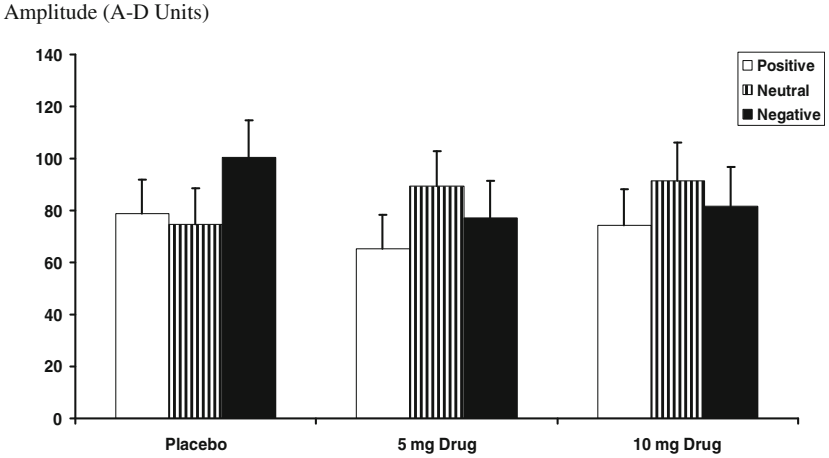

Fig. 1 Affective startle modulation in the placebo and drug groups. *Error bars* display +1SEM

Limitations of this research include the use of a between-subjects design; however, for a first study examining D-amphetamine and affect-modulated startle reactivity, this could be seen as a strength especially as the groups are well-matched on personality dimensions relevant to affective startle modulation (e.g. Harm Avoidance; Corr et al. 1995, 1997). Perhaps more relevant is the acute vs. chronic dimension of D-amphetamine on emotional experience and reactivity, which was not assessed in this study. It would be important to determine in future work whether chronic administration of amphetamine results in a chronic reduction in aversive motivation.

In conclusion, two doses of D-amphetamine (5 and 10 mg) were found to abolish the fear-potentiated startle seen in the placebo group, which indicates that, for the first time, acute administration of this dopamine agonist is related to reduced aversive motivation and reactivity to unpleasant stimuli. These results point to a new hypothesis concerning the psychopharmacological basis of antisocial and, perhaps even, psychopathic behaviour.

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Conflict of interest The authors declare no conflict of interest.

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