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ORIGINAL ARTICLE\

'Naltrexone Blocks Endorphins Released when Dancing in Synchrony'

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Abstract Group synchronised dance is hypothesised to activate the Endogenous Opioid System (EOS), thereby increasing pain threshold, and encouraging social closeness. Previous studies have been limited to the use of pain threshold as a proxy indicator of EOS activation. We conducted a double-blind administration of placebo and naltrexone (an endorphin antagonist) before groups of strangers danced in synchrony and measured both pain threshold and sense of belonging to the group after dancing. A 100 mg dose of naltrexone resulted in significant hyperalgesic effects compared to the control participants, confirming that increases in pain threshold in the control group are due to activation of the EOS and release of endorphins during synchronised dancing. However, there was no significant effect of treatment on perceptions of social closeness. Social bonding during dance may plausibly be underpinned by elements of the EOS not blocked by naltrexone and/or interactions with other neurohormones and socio-cognitive mechanisms.

Keywords Endorphins · Naltrexone · Dance · Social bonding · Synchrony

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Introduction

Dance is a widespread human behaviour which facilitates the formation of social bonds between co-actors (e.g. Dunbar 2012). This is likely due to various socio-cognitive consequences of synchronising one's movements in time with others, causing participants to experience a merged sense of 'self' and 'other' (Overy and Molnar-Szakacs 2009), which facilitates the perception of groups of individuals as a coherent unit ("entitativity"; e.g. Lakens 2010), as well as various prosocial feelings (Reddish et al. 2013; Tarr et al. 2015; Tarr et al. 2016) and willingness to cooperate (Wiltermuth and Heath 2009). Empirical studies have confirmed that compared to those in non-synchronised conditions, synchronous dancing increases feelings of social closeness amongst adult strangers (Tarr et al. 2016) and acquainted teenagers (Tarr et al. 2015).

In addition to these socio-cognitive consequences, it has been suggested that bonding activities such as those involving music trigger hormonal cascades which facilitate interpersonal attachment and reinforce positive associations with those present (Dunbar 2012; Tarr et al. 2014). For example, listening to music is associated with activity in the EOS (e.g. Blood and Zatorre 2001; Menon and Levitin 2005; Stefano et al. 2004; for a review see Tarr et al. 2014), and active participation in musical activities increases pain threshold, a common proxy measure of endorphin uptake (Dunbar et al. 2012b; Pearce et al. 2015; Tarr et al. 2015, 2016). Specifically, dancing in synchrony (compared with non-synchronised dancing) elevates pain thresholds (Tarr et al. 2015, 2016).

The Endogenous Opioid System (EOS) – consisting of opioid receptors and associated peptides distributed throughout the central nervous system and peripheral tissues (Fields 2007; Trigo et al. 2010) – plays an important role in human pleasure-pain circuitry (Mueller et al. 2010). This system is instrumental in modulating mood (Koepp et al. 2009; Zubieta et al. 2003), feelings of euphoria (Bodnar 2008), interpersonal warmth, well-being and bliss (Comings et al. 1999; Depue and Morrone-Strupinsky 2005; Ferrante 1996; Koob 1992) and the post-exercise 'high' (Boecker et al. 2008). The specific role of beta-endorphins in analgesia was first established in mice (Loh et al. 1976; Tseng et al. 1976), and subsequently in humans (Janal et al. 1984; Leknes and Tracey 2008). Exogenous opioid agonists (such as morphine or opium) act similarly to endogenous opioids, such as endorphins (Belluzzi and Stein 1977; D'Amato and Pavone, 1993; Nelson and Panksepp 1998; Stefano et al. 2000), in that they act at the level of the spinal cord to inhibit pain transmission (Fields 2007).

It has been proposed that elements of the EOS's pain-management pathways may have been co-opted by neural correlates of social attachment (e.g. Eisenberger 2015), whereby separation or rejection elicits distress (or 'social pain'), and closeness provides pleasurable reward and comfort due to heightened opioid activity (Eisenberger 2012; Panksepp 1999). Indeed, social pain reportedly results in somatic symptoms (e.g. Gudmundsdottir 2009) and experimental induction of social exclusion causes activity in areas of the brain associated with sensory components of pain (Bolling et al. 2011; Bolling et al. 2012; Onoda et al. 2009). Furthermore, the EOS has been implicated in social bonding (i.e. bonds formed between non-kin and non-pair-bonded individuals) in a range of mammals (e.g. Broad et al. 2006) including various non-human species such as rhesus macaques (Graves et al. 2002; Schino and Troisi 1992), other monkeys (Keverne et al. 1989; Martel et al. 1995; Ragen et al. 2013), voles (Resendez et al.

2013) and puppies, rats and chicks (Panksepp et al. 1980). Although various other neuropeptides are also implicated in bonding (e.g. oxytocin and vasopressin: Carter 1998; dopamine and serotonin: Depue and Morrone-Strupinsky 2005), endorphins are a strong candidate for explaining the non-sexual, non-kin bonds evident in primate social networks (Keverne et al. 1989; Machin and Dunbar 2011; Maestripieri 2010; Martel et al. 1995; Ragen et al. 2013; Schino and Troisi 1992).

It is plausible that certain human group bonding activities activate the EOS, which may play a role in reinforcing the social bonding associated with these activities (Depue and Morrone-Strupinsky 2005; Dunbar 2010; Matthes et al. 1996; Moles et al. 2004). The possible mechanisms underpinning this are still under investigation. It has been suggested that activities which activate the EOS become associated with the positive effects experienced as a result of high opioid uptake, which reinforces the desire to seek out that activity again. Indeed, evidence that the EOS mediates aspects of reward (Olmstead and Franklin 1997) and social motivation (Chelnokova et al. 2014) in humans makes this plausible. However, to date, direct means of determining whether the EOS is activated during group human social bonding activities is lacking.

Direct methods of measuring EOS activity (e.g. PET or spinal fluid extractions) are costly and invasive, so pain threshold is frequently used as an indirect measure of endorphin uptake (Cohen et al. 2010; Dunbar et al. 2012a; Pearce et al. 2015; Sullivan and Rickers 2013; Sullivan et al. 2011; Sullivan et al. 2014). Using this proxy measure, previous studies suggest that synchronised dance is associated with endorphin release (Tarr et al. 2015, 2016). In order to confirm that people dancing in synchrony with one another experience activation of the EOS, a direct intervention, such as the administration of an endorphin antagonist, is necessary.

Opioid antagonists reversibly block endorphin molecules' access to opioid receptors in the brain (Barnett et al. 2014) and therefore suppress analgesia (Kirchgessner et al. 1982; Mayer 1983) and can cause hyperalgesia (i.e. increased pain sensitivity; e.g. rodents: D'Amato and Pavone 1993; humans: Jamner and Leigh 1999). Although non-human studies have demonstrated bidirectional effects of opioid antagonists on social behaviour (e.g. some indicate that antagonists decrease the experience of positive emotions and reward, and others suggest that antagonists increase the need for social contact and affiliative behaviours; Martel et al. 1995), the link between EOS activity and social behaviour is well established. In humans, a commonly administered opioid antagonist, naltrexone, has been used to demonstrate causal links between EOS activity and motivation to view attractive faces (Chelnokova et al. 2014), hedonistic aspects of ingestive behaviours (Yeomans and Gray 2002) including alcoholism and opioid dependence (for a review see: Barnett et al. 2014), and as a hyperalgesia-inducing intervention for individuals engaging in self-harm (e.g. Symons et al. 2004). Furthermore, a single 50 mg dose of naltrexone (versus placebo) inhibits participants' experience of the calm, peaceful, relaxed and pleasant mood states following exercise (Daniel et al. 1992). A recent double-blind naltrexone-placebo crossover study demonstrated that ingestion of naltrexone for four days (25 mg for the first two days, and 50 mg for the last two days) significantly reduced participants' feelings of social connectedness towards friends and family compared to a placebo control period (Inagaki et al. 2016). This suggests opioids are involved in the maintenance of human social relationships, although whether opioids underpin the social closeness that arises between strangers during a once-off activity like synchronised dance is not known.

The present study addresses this question using a silent disco paradigm as reported in Tarr et al. (2016), in combination with a naltrexone-placebo double blind trial to determine whether increases in positive mood, pain threshold and self-reported social closeness between strangers following synchronised dance can be suppressed by blocking EOS function. Participants in the control and placebo conditions should experience exercise- and synchrony-induced elevation in pain threshold and mood. However, it is hypothesised that naltrexone-treated participants will score significantly lower on these measures after dancing than control and placebo participants. Furthermore, if endorphins directly mediate feelings of social closeness towards co-actors, those in the placebo and control conditions should give higher ratings on this measure compared to naltrexone-treated participants.

Methods

Participants

A final sample of 121 participants (88 females, *M* age = 21.75, s.d = 3.51 years) took part in the experiment ($n_{control}$ = 45,[1] $n_{placebo}$ = 23, $n_{naltrexone\ 50mg}$ = 28, $n_{naltrexone\ 100mg}$ = 25). Participants were pre-screened to exclude those who were likely to experience side effects from the use of naltrexone, or those who have conditions which could bias perception of pain (see Online Resource 1 for full exclusion criteria).

Procedure

Participants were told the experiment was about physical coordination, memory and endorphins. Test groups consisting of three or four strangers were randomly assigned (double blind) to a treatment condition: control (receiving no pill; *n* = 45), placebo (receiving a sugar pill; *n* = 23) or naltrexone (either receiving one 50 mg naltrexone pill; *n* = 28, or a dose of 100 mg; *n* = 25). All participants in a testing group were allocated the same treatment condition. Prior to taking their pill, participants' ischemic pain threshold was measured by inflating a blood pressure cuff on the participant's non-dominant upper arm. Participants indicated when the pressure became uncomfortable, and the research assistant noted the pressure sustained (mmHg), a standard procedure used in previous studies (Cohen et al. 2010; Sullivan and Rickers 2013; Sullivan et al. 2014; Tarr et al. 2015, 2016). This measure was repeated (by the same research assistant) immediately after the silent disco. Research assistants and participants were blind to the treatment condition and hypothesis. To avoid ceiling effects, data from those who reached the maximum pressure measurable by the cuff (300 mmHg) were excluded (a total of 33 individuals).

A pre-activity questionnaire included demographic information, a personality scale (Cooper et al. 2010), and a Positive and Negative Affect Scale (PANAS: Mackinnon et al. 1999 see Online Resource 1 for more details). As the onset of naltrexone effects occur 15–30 min after oral ingestion (Roy et al. 2014), participants waited for 60 min before continuing with the experiment, thereby ensuring the movement task coincided

[1] As each naltrexone treatment was run with its own control comparison, the total sample of control participants is twice as big as the other groups.

with the maximum plasma concentration of naltrexone (as per proceedure in: Chelnokova et al. 2014). After the waiting period, participants learned four basic dance moves from a video (Online resource 2), and rated their recall confidence.

Following this practice procedure, participants stood in a square facing inwards, each on a marked space separated from one another by 1 m, and engaged in a silent disco which lasted 13 min. Silent disco headphones relayed music (chosen from current popular hits; Online resource 1), with a pre-recorded voice-over naming the sequence of dance movements. All participants heard the same music and auditory instructions simultaneously, as per the synchrony condition reported in Tarr et al. (2016). A post-activity questionnaire included a series of questions relating to social closeness, measured using 7-point Likert scale questions (Online resource 1) including an adapted version of the Inclusion of Other in Self (IOS) scale (Aron et al. 1992), and questions of connectedness (Wiltermuth and Heath 2009), likeability (Hove and Risen 2009), and ratings of similarity in personality (Valdesolo and Desteno 2011). The questionnaire also included PANAS, and questions relating to participants' experience of the experiment (Online resource 1). Given that social bonding following synchrony may be influenced by perceived success (Launay et al. 2013), participants rated how well they had followed the auditory instructions, and their success at synchronising with one another.

Statistical Methods

A combined 'social closeness index' was created by averaging the four social closeness scores (on the basis of sufficiently high reliability: Cronbach's $\alpha = 0.75$). The change in pain threshold and social closeness index data were normally distributed in each treatment condition, with homogenous variance (Kolmogorov-Smirnov tests; Online resource 1, Table S2). The change in positive affect scores were normally distributed for the control and placebo treatments, but the two naltrexone treatments had non-normally distributed data, as did all treatment groups for the change in negative affect (Kolmogorov-Smirnov tests; Online resource 1, Table S2. The negative affect data had non-homogenous variance. Due to the hierarchical nature of the data, parametric multilevel linear modelling was chosen to account for individual variation, repeated measures, and membership to testing group. The repeated measure dependent variables (i.e. within-subject measures of pain threshold and PANAS) were modelled using fixed factors of time point (i.e. before drug administration and after dancing together), and treatment condition (control, placebo, naltrexone 50 mg and naltrexone 100 mg), including interactions between these effects. When data were non-normally distributed, both non-parametric and parametric analyses were conducted, the latter allowing for the inclusion of covariates (see section 'Baseline differences' below). Unless otherwise stated, the statistical trends were similar for both parametric and non-parametric analyses.

Results

Baseline Differences

For personality measures, there was a significant difference between treatment conditions with respect to agreeableness ($F_{3,121} = 23.895$, $p < 0.001$) and intellect

($F_{3,121}$ = 7.121, p = 0.001; Online resources 1, Table S3) and as a consequence these scores were included as covariates in all parametric analyses, and unless otherwise stated, these covariates did not change the results. There was no significant difference between treatments in terms of participants' average positive and negative affect score at the start of the study, their rating of fun, difficulty, embarrassment, or enjoyment of the silent disco, nor their perception of success in following the instructions or in synchronising during the silent disco (Online resources 1, Table S4).

Positive and Negative Affect

Independent of treatment, there was a significant overall increase in positive affect ($F_{3, 120}$ = 63.474, $p < 0.001$) and a decrease in negative affect ($F_{3, 118}$ = 55.917, $p < 0.001$) during the silent disco. However, there were no significant interactions between either affective measure and treatment (Online resource 1, Table S5).

Pain Threshold

There was a significant main effect of treatment on change in pain threshold ($F_{3,121}$ = 3.833, p = 0.012, Fig. 1). Control participants experienced a significant increase in pain threshold after the silent disco (mean = 18.80 ± 45.937SD; t_{44} = 2.745, p = 0.009), and those treated with 100 mg naltrexone experienced significant hyperalgesic effects (mean = −15.28 ± 36.916SD; t_{24} = −2.070, p = 0.049). Pairwise comparisons revealed that control participants experienced significantly larger analgesic effects than the participants treated with 100 mg naltrexone (t_{68} = −3.382, p = 0.001), and there was also a significant difference in the change in pain threshold between those treated with 50 mg and 100 mg naltrexone (t_{51} = −2.037, p = 0.044). The change in pain threshold did not differ significantly between control and placebo-treated participants (mean = 4.70 ± 38.950SD; t_{66} = −1.362, p = 0.176). The multilevel analysis also revealed that there was a significant difference between

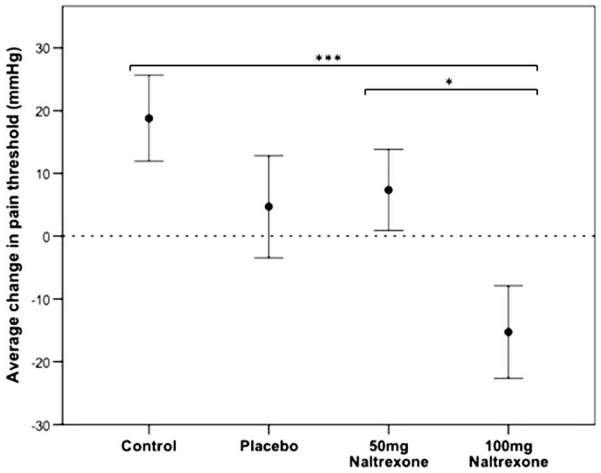

Fig. 1 Average (±1se) change in pain threshold (*end* - *start*) for each treatment condition (n = 121; *** $P \leq 0.001$, * $P \leq 0.05$)

treatments independent of time point ($F_{3,121}$ = 2.913, p = 0.037), although this difference was not apparent without the inclusion of covariates (Online resource 1, Table S6). This difference was due to the final pain threshold scores, where there was a significant main effect of treatment ($F_{3,121}$ = 3.2915, P = 0.023). Pairwise comparisons show that the difference in end scores was significant between the control and naltrexone 50 mg treatments (t_{71} = −2.818, p = 0.006), and also between the placebo and naltrexone 50 mg (t_{49} = −2.244, p = 0.027). Although gender can affect pain thresholds (e.g. Chesterton et al. 2003), the inclusion of gender as a covariate still revealed a significant interaction between treatment and time point ($F_{3,121}$ = 3.833, p = 0.012), with no significant effect of gender ($F_{1,121}$ = 2.403, p = 0.124). Inclusion of gender in the model did, however, remove the significant differences between treatment that were independent to time point ($F_{3,121}$ = 2.636, p = 0.053).

Social Closeness Index

The main effect of treatment was not significant ($F_{3,121}$ = 0.833, p = 0.483; Fig. 2; Online resource 1, Table S7).

Discussion

Using the same silent-disco experimental paradigm reported in Tarr et al. (2016), the present study confirmed that synchronised group dancing elevates pain thresholds. To assess the role of endorphins in this effect, we treated participants with naltrexone, an opioid receptor blocker. Individuals who danced in synchrony in a group after receiving a 100 mg dose of naltrexone had a significantly lower change in pain threshold following dancing than those in the control condition; in fact, these participants experienced hyperalgesic effects. This result confirms that previously reported increases in pain threshold following synchronised dance are a consequence of endorphin

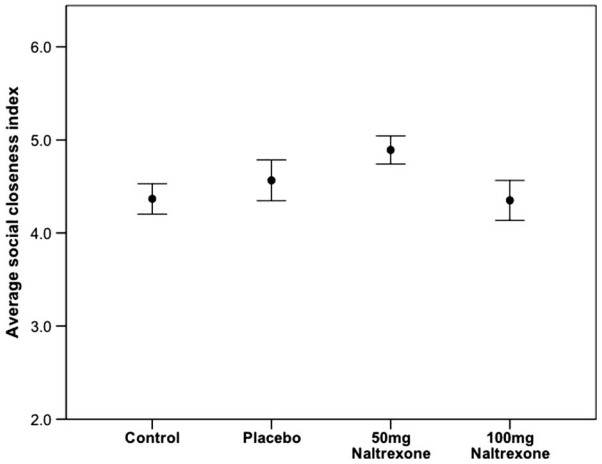

Fig. 2 Average (±1se) social closeness index (likert scale 1–7 averaged across social closeness questions) for each treatment condition

uptake by opioid receptors (Tarr et al. 2015, 2016), and that there may be a dose-dependent effect when subjecting naltrexone-treated participants to synchronised exercise. Although previous studies have reported significant effects with a 50 mg dose of naltrexone, these have typically employed a within-subject design, with repeated doses of 50 mg naltrexone taken over several consecutive days (e.g. Inagaki et al. 2016), or comparisons with a morphine treatment, with participants performing a non-physical experimental task that did not specifically activate the opioid system (e.g. Chelnokova et al. 2014). In the present between-subject study, a single 50 mg dose of naltrexone was not sufficient to significantly inhibit all endorphin-induced increases in pain thresholds when participants danced in synchrony for 13 min. The fact this experiment involved active stimulation of the EOS through exercise may be of significance, as when in the presence of opioid agonists, antagonists can act paradoxically (Powell et al. 2002). The exertive silent disco was hypothesised to stimulate the EOS and endorphin release, and it is plausible that the 50 mg naltrexone was simply insufficient to entirely block the opioid-related pain response in the dancing. Given that the 100 mg-treated participants experienced hyperalgesic effects, this is plausible, though future studies would need to investigate the degree of exertion and quantify opioid uptake to further understand any dose-dependent effects.

Despite significantly affecting pain threshold, naltrexone did not affect mood, suggesting that these effects of endorphins may be unrelated to affect as measured using the PANAS scales. Previous studies using opioid antagonists have similarly failed to observe a significant change in mood (e.g. Farrell et al. 1986; Grossman et al. 1984; Markoff et al. 1982), although Daniels et al. (Daniel et al. 1992) found that 50 mg naltrexone inhibited positive affective states following 75 min of exercise in a within-subject randomised trial. This inconsistency may be due to the use of different methods for quantifying mood states. Daniels et al. (Daniel et al. 1992) measured mood using a Visual Analogue Scale and a 65-item Profile of Mood States and it is possible that the short-item PANAS used in the present study did not capture the nuances of mood change experienced by participants who received either the 50 mg or 100 mg dose of naltrexone.

Contrary to predictions, neither the 50 mg nor 100 mg naltrexone-treated participants reported feeling significantly less socially close to the rest of their group compared to placebo-treated or control participants. However, there was a significant study x treatment interaction effect in this case, suggesting that the design of Study 1 may have been problematic. The results for Study 2 were in the expected direction even though this effect was not significant. There is a chance that while blocking the social bonding effects of endorphins, naltrexone also led to increased desire for social contact (e.g. as is the case with naltrexone-treated monkey's increased motivation for grooming; Keverne et al. 1989), reducing the overall effect size, although the use of an explicitly cognitive measure of social bonding should mitigate this effect. Given that endorphins are involved in social bonding (Broad et al. 2006; Dunbar 2010; Machin and Dunbar 2011) and recent PET studies have explicitly confirmed a role for beta-endorphins in a number of other behaviours known to be associated with social bonding (for example, stroking: Nummenmaa et al. 2016), the present findings may simply reflect lack of statistical power. It is also possible that other neurohormones, or a combination of neurotransmitters not blocked by naltrexone, may be involved in the social bonding effects elicited by dancing. For example, the EOS consists of

enkephalins, dynorphins, beta-endorphins, and a number of different opioid receptors (Benarroch 2012). Naltrexone has the highest affinity for one of the three opioid receptors (μ-receptors), and other opioid antagonists (which selectively target the Υ and δ receptors) may be necessary to rule out the role of the EOS in underpinning the synchrony-related social bonding.

Furthermore, oxytocin, which is known to interact with the EOS (Depue and Morrone-Strupinsky 2005), may play a role in reinforcing the social bonds that arise during music-based activities. A previous study has shown that oxytocin concentrations increase after taking part in a singing class, although no data were gathered on the degree of social closeness or trust felt between singers in this case (Grape et al. 2003). Similarly, the EOS interacts with the dopamine-reward system (Depue and Morrone-Strupinsky 2005); opioid antagonists block the subjective 'high' associated with strong dopamine release (Jayaram-Lindstro et al. 2004), and previous studies have implicated the reward system in music-induced pleasure (Blood and Zatorre 2001; Koelsch et al. 2006; Salimpoor et al. 2011). Nevertheless, there is currently very little empirical evidence about the interaction between the different neurohormones involved in the social bonding effects of music and dance, and future studies should aim to trace these pathways using a series of receptor blockers or PET imaging.

An alternative possibility may be that social bonding was not sufficiently well captured by the self-report questions posed at the end of the present study. For example, 50 mg naltrexone significantly affects motivation for viewing attractive faces of the opposite sex, as well as aesthetic evaluation (Chelnokova et al. 2014). In the present study, naltrexone-treated participants may have experienced differential inter-personal judgments and social motivation (e.g. to engage in the task and synchronise) due to different levels of attraction and attention. When synchronising, simultaneous co-attention leads to an "attentional union" (Macrae et al. 2008), which facilitates self-other merging and synchrony induced cooperation (Kirschner and Tomasello 2010). Future studies may need to find better indices of social bonding. Furthermore, we measured bonding only at the end of the experiment, and did not measure the change in bondedness that occurred as a result of the experiment. Although we chose to omit a baseline social closeness measure due to the participants being strangers, future studies could instead gather before and after measures.

Finally, the between-subject design in this experiment did not account for inter-individual variation in opioid receptor availability and functioning, and capacity to experience social reward (Nummenmaa et al. 2015; Troisi et al. 2011; Way et al. 2009). Variation in the μ-opioid gene and opioid receptor availability, for example, could have influenced the effects of naltrexone on individuals as well as influenced our measures of social closeness. However, because a within-subject design could have resulted in participants experiencing demand characteristics, we opted to use a between-subject design.

Conclusion

Growing evidence that synchronised dancing fosters social closeness between individuals (Tarr et al. 2015, 2016) suggests that this activity may have served as a bio-cultural adaptation, helping humans create and maintain closely bonded social units (Launay et al. 2016). Groups which are well bonded and capable of good coordination may face

better survival odds (for example in the search for food, shelter and in the rearing of young and defence of territories) than those which are less tightly knit. Consequently, activities which foster social cohesion and bonding can be considered adaptive and advantageous for the group (Dunbar & Shultz, 2010). Previous investigation into the possible role of the EOS in group synchronised dance have relied on indirect measures, namely changes in pain threshold (Tarr et al. 2015). By using naltrexone to block endorphin uptake, the present study confirmed that synchronised dancing activates the EOS, releasing endorphins which elevate pain threshold. The EOS likely plays a role in underpinning the large-scale bonding that can arise during dancing (Machin and Dunbar 2011), but how endorphins (and other components of the EOS) interact with additional social bonding hormones requires further investigation in the context of group synchronised dance.

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Compliance with Ethical Standards All procedures were in accordance with the ethical standards of the University of Oxford's research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The ethics committee of the University of Oxford approved the experimental procedure and all participants received an information pack containing the experimental protocol and information about the possible side effects of naltrexone. Prior to taking part, informed consent was obtained from all individuals included in the study.

Conflict of Interest The authors declare that they have no conflict of interest.

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