

Social cognition impairments in long-term opiate users in treatment

Authors: Gill Terrett^{1*}, Kimberly Mercuri¹, Elizabeth Pizarro-Campagna¹, Laila Hugrass¹, H Valerie Curran², Julie D. Henry³, Peter G. Rendell¹

Affiliations

¹ Cognition and Emotion Research Centre, School of Psychology, Australian Catholic University, Melbourne Campus, Locked Bag 4115, Fitzroy, MDC Victoria 3065, Australia

² Clinical Psychopharmacology Unit, University College London, UK

³ School of Psychology, University of Queensland, Brisbane, Australia

Corresponding Author: Gill Terrett, gill.terrett@acu.edu.au

Running head: Social cognition in long-term opiate users

Keywords: opiate use, facial mimicry, emotion recognition, Theory of Mind, electromyography

Abbreviations: ToM, Theory of Mind; EMG, electromyography

Abstract

Background

Long-term opiate users experience pervasive social difficulties, but there has been surprisingly limited research focused on social-cognitive functioning in this population.

Aim

The aim of this study was to investigate whether three important aspects of social cognition (facial emotion recognition, theory of mind (ToM) and rapid facial mimicry) differ between long-term opiate users and healthy controls.

Methods

The participants were 25 long-term opiate users who were enrolled in opiate substitution programs, and 25 healthy controls. Facial emotion recognition accuracy was indexed by responses to 60 photographs of faces depicting the six basic emotions (happiness, sadness, anger, fear, surprise and disgust). ToM was assessed using the Reading the Mind in the Eyes task which requires participants to infer mental states of others from partial facial cues. Rapid facial mimicry was assessed by recording activity in the *zygomaticus major* and *corrugator supercilii* muscle regions while participants passively viewed images of happy and angry facial expressions.

Results

Relative to the control group, the opiate user group exhibited deficits in both facial emotion recognition and ToM. Moreover, only control participants exhibited typical rapid facial mimicry responses to happy facial expressions.

Conclusions

These data therefore indicate that long-term opiate users exhibit abnormalities in three distinct areas of social cognitive processing, pointing to the need for additional work to establish how social cognitive functioning relates to functional outcomes in this group. Such work may ultimately inform the development of interventions aimed at improving treatment outcomes for long-term opiate users.

Introduction

Chronic opiate use is a major public health concern (Teesson et al., 2017), with the global burden of disease for opioid dependence greater than for any other class of drug (Degenhardt et al., 2013). Opiate users experience a range of difficulties in daily life, with social dysfunction a core feature (Darke et al., 1992; von Hippel et al., 2017). For instance, long-term opiate use is associated with difficulties maintaining intimate relationships (Maddux and Desmond, 1984), high levels of family conflict (Karow et al., 2008), social isolation (Darke and Ross, 2002), and decreased satisfaction with family and social relationships (De Maeyer et al., 2010).

The long-term trajectories for chronic opiate users are highly heterogeneous, with some users achieving and maintaining abstinence, some having fluctuating patterns of use, and others continuing high-levels of use throughout a decade of follow-up (Teesson et al., 2017). Among treatment-seeking opiate users, low levels of social integration are associated with an increased risk of relapse (Havassy et al., 1991). As a consequence, there is a critical need to better understand the factors contributing to social dysfunction within this population, so that interventions can be tailored to enhance social function outcomes during and following rehabilitation.

One possible factor contributing to social dysfunction in long-term opiate users is impaired social cognition. Social cognition broadly refers to the mental processes required to make sense of the social world. In neurotypical populations, such processes appear to involve the coordination of activity in a range of brain regions. For example, neuroimaging evidence suggests that the insula plays a key role in the integration of external, internal and social information (Craig, 2002) and is activated when individuals empathise with (Singer et al., 2009), or infer, the emotional states of others (Schurz et al., 2014). In addition, tasks involving imitation

and observation of facial expressions have been shown to activate an emotional mirroring brain network which includes the anterior insula, inferior frontal cortex, superior temporal cortex and amygdala (Carr et al., 2003).

Social cognitive deficits might therefore be anticipated in this population given the neuroimaging evidence of structural brain differences for long-term opiate users. For example, long-term opiate users tend to have reduced functional connectivity between the insula, orbitofrontal cortex and amygdala (Wang et al., 2016). Furthermore, recent meta-analyses have shown that relative to drug naïve controls, opiate users exhibit significant grey-matter reductions within regions of the emotional mirroring network (Wollman et al., 2017), as well as damage to the white matter tracts connecting these regions (Wollman et al., 2015). However, despite evidence that the brain networks underling social cognition tend to be disrupted in long-term opiate users, there have been surprisingly few investigations into socio-cognitive functioning in this group (Miller et al., 2015; Heilig et al., 2016).

The aim of the current study was to address this gap in the literature by focusing on two core aspects of social cognition; the ability to recognise facial emotions and the ability to empathize with the emotions of others. Both of these abilities play an important role in social functioning (Blair, 2003; Fett et al., 2011). In relation to facial emotion recognition, only three previous studies have investigated whether this ability is impaired in long-term opiate users. Kornreich et al. (2003) and Craparo et al. (2016) found that long-term opiate users exhibited lower facial emotion recognition accuracy than healthy control participants, with deficits observed across the six basic facial emotions (i.e., happiness, sadness, anger, fear, surprise and disgust). This suggests that long-term opiate use is associated with broad impairments in the ability to recognise emotions in others. However, by contrast, Martin et al. (2006) found that

opiate users were no different to controls on any of the basic emotions, except disgust on which they were more accurate than healthy control participants. They were however, slower to recognise facial emotions than the control group across all of the basic emotions. Given the limited studies and inconsistent findings, and the importance of the ability to accurately recognise other's emotions for effective social functioning (Blair, 2003), further studies are needed to clarify the differences in facial emotion recognition performance between long-term opiate users and people with no history of drug dependence.

The other key social cognitive domain investigated in the current study was empathy. Empathy is a multifaceted construct, involving the abilities to understand and to share the emotions of others (Decety and Meyer, 2008). While the cognitive and affective forms of empathy both relate to responding appropriately to the emotional states of others, they are associated with distinct neural mechanisms (Zaki and Ochsner, 2012). Cognitive empathy, which is closely related to the construct of Theory of Mind (ToM), involves making explicit inferences about another person's mental state (Premack and Woodruff, 2010) and tends to activate brain structures involved in self-projection, such as the medial prefrontal cortex, superior temporal cortex and precuneus (Buckner and Carroll, 2007). On the other hand, affective empathy, which includes both unconscious simulation (e.g., rapid facial mimicry) and emotional contagion (e.g., the tendency to 'catch' the emotions of others), is associated with the emotional mirroring network, whereby overlapping brain regions are activated when experiencing emotions and when observing the emotional expressions of others (Singer et al., 2009; Singer et al., 2004; Zaki et al., 2012). Relative to drug-naïve controls, long-term opiate users have reduced grey matter in brain regions implicated in the emotional mirroring and self-projection networks (Wollman et al.,

2017), so it seems likely that both cognitive and affective empathy might be disrupted in this clinical group.

In terms of ToM, only two previous studies have investigated this ability in long-term opiate users (Gandolphe et al., 2018; McDonald et al., 2013). In the first, McDonald et al. (2013) found that when asked to infer the mental states of the actors in social vignettes, participants enrolled in opioid maintenance programs tended to perform worse than healthy controls, particularly when the social exchanges were sarcastic rather than sincere. Similarly, Gandolphe et al. (2018) found that when asked to infer the intentions of characters in a movie, opiate users tended to show poorer performance than healthy controls, particularly when taking the perspective of the characters, or inferring their mental states. Thus, although only limited to two studies, there is at least preliminary evidence that ToM might be impaired in this group.

By contrast, no prior study has assessed whether affective empathy is impacted by long-term opiate use. As noted earlier, affective empathy has been linked to the emotional mirroring network (Decety and Meyer, 2008; Singer et al., 2009). As such, one accepted way of measuring this aspect of empathy is to assess the tendency of a person to automatically and unconsciously simulate the facial expressions of others (Lundqvist, 1995). This phenomenon is referred to as rapid facial mimicry, and has been identified as a robust behavioural response in neurotypical participants measured using facial electromyography (EMG). For example, images of angry faces tend to evoke greater EMG activity in the observer's *corrugator supercilii* (brow) muscle group relative to images of happy faces; whereas happy faces tend to evoke greater activity in the observer's *zygomaticus major* (cheek) muscle group relative to angry faces (Dimberg and Petterson, 2000; Dimberg and Thunberg, 1998; Dimberg et al., 2002; Lundqvist, 1995). Rapid facial EMG responses are typically defined as those elicited within 1000ms post-stimulus

exposure, and have been observed even when stimuli are presented subliminally (Bailey and Henry, 2009), and when participants have been explicitly instructed *not* to react (Dimberg et al., 2002).

Taken together, most evidence therefore indicates that rapid facial mimicry does not depend upon cognitive mechanisms, but instead reflects an automatic, pre-cognitive stage of empathy (Nielsen, 2002). Consistent with these findings, people with higher self-reported levels of empathy tend to exhibit stronger facial EMG responses to images of emotional faces (Sonnby–Borgström, 2002). Although no previous studies have measured rapid facial mimicry in long-term opiate users specifically, rapid facial mimicry responses have been shown to be disrupted in other clinical groups with social difficulties, including people with autism spectrum disorders (Beall et al., 2008), depression (Zwick and Wolkenstein, 2017) and schizophrenia (Varcin et al., 2010).

The overarching aim of the current study was to investigate the nature and severity of social cognitive impairments in long-term opiate users in relation to facial emotion recognition and measures of cognitive and affective empathy. First, based on the existing literature (Craparo et al., 2016; Kornreich et al., 2002), it was hypothesised that facial emotion recognition accuracy would be lower for long-term opiate users relative to healthy controls. Second, regarding cognitive empathy, it was predicted that ToM would be poorer for opiate users than for healthy participants. Third, in relation to affective empathy, it was hypothesised that the typical facial mimicry response to happy and angry expressions, as measured using facial EMG recordings from the *zygomaticus* and *corrugator* facial muscles, would be reduced for long-term opiate users relative to healthy controls. Given that there have been no studies to date assessing rapid facial mimicry in long-term opiate users, this prediction was based on evidence that facial

mimicry responses are diminished in other clinical groups that present with social difficulties (Varcin et al., 2010; Beall et al., 2008; Zwick and Wolkenstein, 2017), and evidence that long-term opiate users tend to exhibit reduced grey matter in brain regions implicated in facial mimicry (Likowski et al., 2012; Wollman et al., 2017).

Method

Participants

This study was approved by the Australian Catholic University ethics committee (HREC2010135) and conformed to the ethical standards set out in the 1964 Declaration of Helsinki. Twenty-five long-term opiate users (aged between 27 and 59 years) and 25 healthy controls with no current, or history of, dependency on alcohol or other drugs (aged between 25 and 61 years) completed the study. All participants spoke English as their first language. The control group was recruited using fliers distributed in local community areas and word-of-mouth, and the opiate users were recruited via fliers distributed through pharmacies. Participants in the opiate user group were currently enrolled in an opioid substitution program. The opiate substitute was either the opioid agonist Methadone ($n = 20$, dosage $M = 62.5\text{mg}$, $SD = 41.1\text{ mg}$) or the mixed partial agonist and antagonist *Suboxone* ($n = 5$, buprenorphine $M = 13.0\text{ mg}$ $SD = 10.80\text{ mg}$). Participants in the opiate user group were required to have been stable on opioid treatment for at least two weeks prior to testing and to have abstained from using the opioid agonist for at least five hours prior to testing (confirmed via self-report on the day of testing). Participants were excluded if they had a severe psychiatric condition (e.g., schizophrenia or bipolar disorder), but those with current diagnoses of depression or anxiety were not excluded because these conditions are widespread in the general population and are common comorbid disorders

amongst opiate users. For both groups, participants were required to abstain from alcohol and illicit drug use in the 24 hours before the testing session. Participants were sent a reminder at least 24 hours prior to their testing time and abstinence was confirmed via self-report on the day of testing. Exclusion criteria included a previous or current neurological condition or acquired brain injury, and a history of heavy alcohol use, which was defined as 20 standard drinks per week for men and 14 for women (Australian National Health and Medical Research Council, 2009). All participants were reimbursed AU\$30 (~USD\$23) for their time.

Participant characteristics are summarised in Table 1. The groups did not differ for gender ($\chi^2(1) = 2.12, p = .15$), age and estimated IQ. IQ was estimated based on the National Adult Reading Test (NART), which presents words with irregular spellings, so participants cannot use correct pronunciation without prior knowledge of the word (Nelson, 1982). This makes it a very sensitive measure of premorbid intellectual function (Bright et al., 2002). On average the opiate user group had fewer years of education, higher levels of anxiety and depression (as assessed with the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983), lower verbal fluency and lower inhibitory control (as assessed based on Hayling scores), than the control group.

Table 1

Participant characteristics

	Controls		Opiate Users		<i>t</i>	<i>df</i>	<i>d</i>
	<i>n</i> = 25		<i>n</i> = 25				
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
Percentage of men	52 %		72%				
Age (years)	37.12	13.31	40.76	9.23	1.12	42.76	0.32
Education (in years)	16.20	1.96	12.61	2.55	5.49***	46	1.58
Estimated IQ ^a	109.64	6.28	110.70	7.44	0.54	48	0.15
Anxiety ^b	5.08	2.96	9.56	4.37	4.25***	42.17	1.20
Depression ^b	2.66	0.53	8.28	4.58	5.40***	38.57	1.72
<i>Executive function</i>							
Verbal Fluency ^c	63.32	15.88	51.78	17.47	2.44*	48	0.69
Hayling ^d	7.48	2.00	4.76	1.56	5.36***	48	1.52
Trail Making ^e	30.82	17.42	42.33	23.85	1.95	48	0.55

Note: Cohen (1988) defines effect sizes of 0.2 as small, 0.5 as medium and 0.8 as large
d Cohen's *d* index of effect size.

^a Full-scale IQ score as predicted from the number of errors made on the NART

^b Hospital Anxiety and Depression Scale subscale scores for Anxiety and Depression—range of scores was 0–21 for each subscale, 0–7 normal, 8–10 possible mood disorder and 11–21 presence of mood disorder

^c Verbal Fluency scores are the sum of phonemic and semantic fluency scores

^d Hayling Sentence Completion, overall scaled score, range: 1–10

^e Trail Making Test score, calculated by subtracting the time taken for Part A from Part B

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

In relation to current substance use, 44% of participants in both groups reported using alcohol at least once per week. A higher percentage of opiate users (68%) than controls (8%) used nicotine at least once per week. The percentages of participants who used illicit substances at least once per month were higher for the opiate user group (48% cannabis, 20% amphetamines, 7% benzodiazepines, 48% heroin) than for the control group (4% cannabis, 0% amphetamines, 0% benzodiazepines, 0% heroin). In summary, as is typical in this population, substances other than opiates were used more frequently by the opiate user group than by the control group.

Stimuli and procedure

Facial emotion recognition

The Ekman Face task (Ekman and Friesen 1976) was used to measure FER ability. In this task, participants were shown an image of a face displaying an emotion and were asked to choose an appropriate label for the emotion. The stimulus set comprises 60 target faces (ten each for happiness, sadness, anger, fear, surprise and disgust). Faces were presented one at a time, on a desktop computer screen and participants were required to verbally state the appropriate emotion label from the six alternatives displayed on the screen. In the current study the order of presentation was initially randomized, with this order then used for all subsequent participants. Separate facial emotion recognition scores were calculated for each facial expression, reflecting the number of correctly identified faces. The Ekman 60 Faces Task is one of the best validated measures of facial emotion recognition available (Henry et al., 2016).

Theory of Mind

The Reading the Mind in the Eyes task (Baron-Cohen et al., 2001) is an advanced test of ToM which assesses the ability to attribute complex emotional states to photographs of solely the eye region of faces. The task has two conditions, a mental state condition and an age/gender control condition. The latter was included so that ToM deficits could be distinguished from more general deficits in face processing (Gunther Moor et al., 2011). Each condition consisted of 36 photographs, with four accompanying labels. In the mental state condition, participants were asked to select the label that best described what the person in the photo was thinking or feeling (Baron-Cohen et al., 2001). The mental state labels included both basic emotion terms (e.g. angry) and more complex emotional state terms (e.g. irritated, bored). The age/gender control condition required participants to select the label that best described the age and gender of the person in the photograph (e.g. male 50-60, female 25-30, female 40-50, or male 20-25). The Reading the Mind in the Eyes task is widely used and has been extensively validated for assessing ToM in both clinical and neurotypical populations (Henry et al., 2016).

Executive function

Executive function was assessed using three measures that are sensitive to self-initiation, cognitive inhibition and mental flexibility. Participants completed a *verbal fluency task*, which has been well-validated as a measure of self-initiation and cognitive flexibility (Strauss et al., 2006). For phonemic fluency, participants had one minute per probe to generate as many words as possible beginning with the probe letters F, A and S, excluding numbers, proper nouns and the same word with a different suffix. For semantic fluency, participants generated as many names of animals as possible within one minute. Total scores (summed across the phonemic and

semantic fluency probes) were calculated by subtracting the errors from the number of correct responses.

The *Hayling Sentence Completion Test* is a two-part verbal task (Burgess and Shallice, 1997), which is sensitive to self-initiation and inhibitory control. The test has been well-validated (Strauss et al., 2006) and it was administered and scored according to the instructions provided in the manual (Burgess and Shallice, 1997). For Parts A and B, the examiner read 15 sentences with the endings missing. For Part A, the participant was required to say a word that coherently completes the sentence. For Part B, the participant inhibited the dominant answer and provided a word that was not related to the semantic or syntactic structure of the sentence. Scaled scores were calculated based on the time (in seconds) to complete both tasks.

The *Trail Making Test* (TMT) has been validated as a measure of mental flexibility (Arbuthnott and Frank, 2000). The TMT was administered and scored according to guidelines by Strauss et al. (2006). For Part A, participants were required to draw a continuous line that connects scattered circles in increasing numerical order, from 1 to 25. For Part B, participants drew a line to connect numbers and letters in increasing, alternating order (i.e.; 1-A-2-B-3-C, etc.). The TMT was scored by subtracting the time to complete Part A from Part B, with lower scores indicating better performance.

Rapid facial mimicry

Facial mimicry was assessed using a similar passive viewing procedure to the one utilised by Bailey et al. (2009). The stimuli were 16 x 24 cm black and white pictures of happy and angry faces (Ekman and Friesen 1976) that were presented on a LCD screen at a viewing distance of approximately 40cm, using E-Prime 2.0 Professional software (Psychology Software Tools, Inc., Sharpsburg, PA). The task consisted of a practice condition (neutral faces), followed by

counterbalanced blocks of angry and happy faces. Eight faces were presented from the three emotion categories, and the order of faces within each block was randomized. Each trial consisted of a 50 ms soft orienting tone and a black fixation cross, then a black screen (1000 ms), followed by the presentation of the face stimulus (5000 ms) and then another black screen (6000 ms). Participants were instructed to look at the pictures carefully, by simply watching them as they naturally would. Digital event markers of the trial onsets and offsets were sent from E-Prime to the EMG recording.

We followed well-established procedures for measuring facial EMG during the passive viewing paradigm (Bailey et al., 2009; Varcin et al., 2010; Pedder et al., 2016; Tassinari et al., 2007). Previous studies have shown that EMG activity levels from the *corrugator* (brow) and *zygomaticus* (cheek) muscles are sensitive indicators of angry and happy expressions respectively, particularly when measured from the left side of the face (Dimberg and Petterson, 2000; Dimberg and Thunberg, 1998). The EMG sites were cleaned using an alcohol wipe and gently abraded using NuPrep gel (Weaver and Co., Aurora, CO). Pairs of 4 mm Ag/AgCl dome surface electrodes were filled with Ten20 conductive paste (Weaver and Co) and placed on the recording sites on the left *corrugator* and left *zygomaticus*, with an inter-electrode distance of approximately 1.25 cm. An additional electrode at the center of the forehead served as the ground.

To distract from the facial muscles as a main focal point, a sham electrode, which was not collecting any data, was attached to the back of the left hand, and participants were advised that the sensors were measuring sweat gland activity (Dimberg and Thunberg, 1998). Each electrode was attached using an adhesive disk and was held in place using medical tape. An impedance meter was used to ensure that the impedance levels for each site were below 20 k Ω during the

recording. The EMG data were digitized using a Biopac MP150 Data Acquisition System and recorded using AcqKnowledge software (Biopac Systems, Inc., Goleta, CA). Data were sampled at 1 KHz, and band-pass filtered from 10-500 Hz, with a 50 Hz notch filter to remove electrical noise from the recordings.

The raw EMG signals were checked for artefacts and noise. The experimenters watched Logitech webcam recordings of each participant's face and removed segments of data containing artefacts (such as yawning or coughing) and other non-task specific activity from the EMG signal. Root mean square (RMS) transformations were applied to normalize the distributions of raw EMG amplitudes (De Luca, 2006). Baseline muscle activity was defined as the RMS of EMG signal in the 500 ms prior to the onset of each picture. In order to measure rapid facial mimicry, EMG responses were measured as the percentage change in RMS amplitude relative to the baseline level. Separate measurements were made for the ten, 100 ms epochs within the first 1000 ms after the stimulus onset (Dan-Glauser and Gross, 2011).

Data analysis

Outliers in the EMG data were corrected using procedures outlined in Tabachnick and Fidell (2013). Values more than 3.29 standard deviations from the mean were brought in to two standard deviations from the mean. This procedure was repeated if necessary until there were no remaining outliers. Group comparisons across the outcome variables were investigated with a series of ANOVAs. Greenhouse-Geisser corrected values are reported when the assumption of sphericity was violated. The alpha level was set to $p = 0.05$ for all tests. Significant two-way interaction effects were followed-up with tests of simple main effects, with Bonferroni-adjusted p -values for multiple comparisons. No background variables (e.g., years of education, anxiety,

depression, verbal fluency and Hayling scores) were included as covariates in the ANOVAs conducted as the current study did not meet criteria for appropriate use of ANCOVAs as outlined by Miller and Chapman (2001). Specifically, groups were not randomly assigned, and there were group differences on these variables (see Table 1).

Results

Facial Emotion Recognition

Mean facial emotion recognition accuracy levels for the control and opiate user groups are plotted in Figure 1. These data were analysed with a 2 x 6 mixed analysis of variance (ANOVA) where the between groups variable was *group* (control, opiate user) and the within groups variable was *emotion* (happiness, sadness, anger, fear, surprise, disgust). There was a significant main effect of group ($F(1, 48) = 11.78, p < 0.001, \eta_p^2 = 0.19$), with lower mean accuracy for the opiate user group than for the control group across all six emotions. There was also a main effect of emotion ($F(3.49, 167.39) = 55.46, p < 0.001, \eta_p^2 = 0.54$). Post-hoc analyses of the emotion main effect (with Bonferroni adjusted *p*-values) revealed that accuracy was higher for happy faces than for the other five emotions ($ps < 0.001$). There was no significant interaction between group and emotion ($F(3.49, 167.39) = 1.15, p < 0.33, \eta_p^2 = 0.02$).

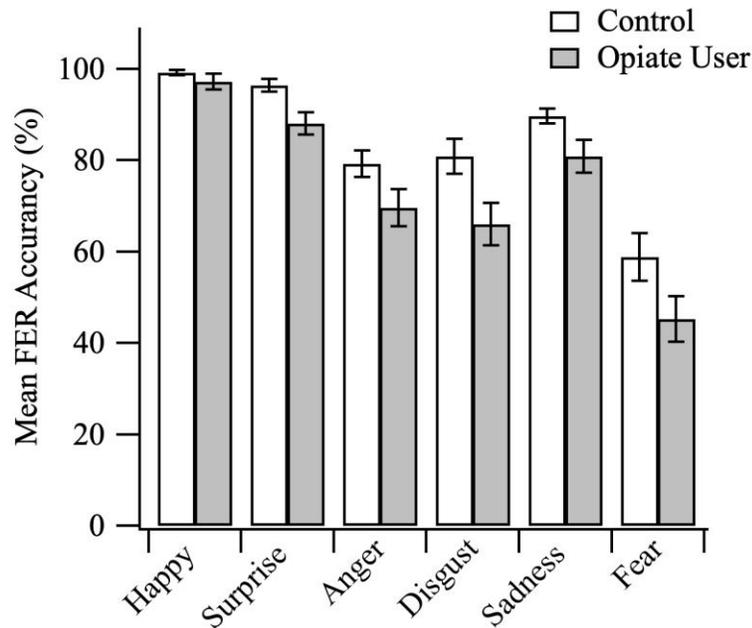


Figure 1. Mean facial emotion recognition accuracy (error bars represent \pm one *SE*) for controls and opiate users, for each of the facial emotion conditions

Theory of Mind

Mean accuracy levels for the Reading the Mind in the Eyes test are presented in Figure 2. A 2 x 2 mixed ANOVA was conducted, with *group* (control, opiate user) as the between-group variable and *condition* (mental state, age/gender) as the within-group variable. The main effect of group was not significant ($F(1, 48) = 0.89, p = 0.349$). There was a significant main effect of condition ($F(1, 48) = 48.00, p < 0.001, \eta_p^2 = 0.50$) and a significant interaction between condition and group ($F(1, 48) = 5.08, p = 0.029, \eta_p^2 = 0.10$). This interaction was explored with tests of simple effects that revealed higher accuracy on the mental state task than the age/gender control task for both the opiate user group ($F(1, 48) = 10.92, p = 0.002, \eta_p^2 = 0.19$) and the control group ($F(1, 48) = 42.16, p < 0.001, \eta_p^2 = 0.47$). Further analysis of this interaction (with

Bonferroni adjusted p -values) revealed a simple main effect of group; the control group performed significantly better than the opiate user group on the ToM task ($F(1, 48) = 4.71, p = 0.035, \eta_p^2 = 0.09$). Importantly, the groups did not differ in performance on the age/gender control task ($F(1, 48) = 0.66, p = 0.422$).

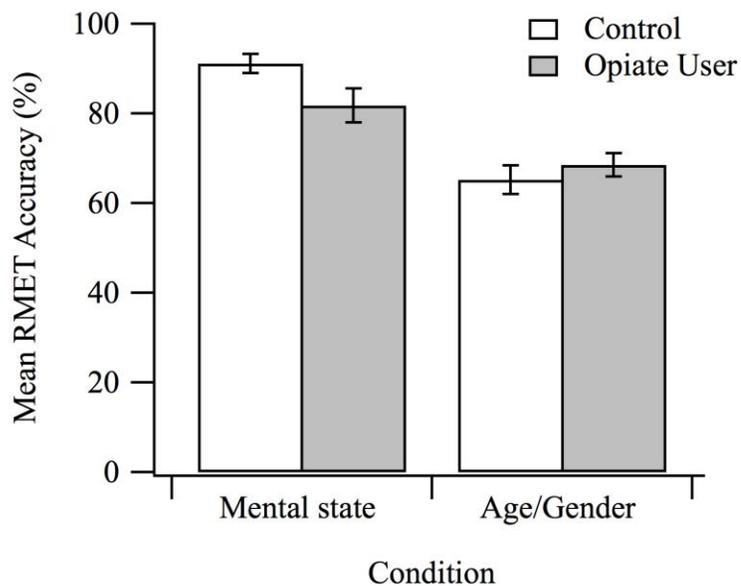


Figure 2. Mean Reading the Mind in the Eyes accuracy (error bars represent \pm one SE) for controls and opiate users

Facial Mimicry

The first step in the analyses of EMG data was to compare the baseline activity for the opiate user and control groups. Baseline EMG levels were therefore averaged across the 500 ms

interval before stimulus presentation, and over the eight trials for each facial emotion condition. Independent samples t-tests showed there were no between-groups differences in baseline *zygomaticus* or *corrugator* activity prior to the presentation of happy or angry faces ($ps > 0.05$).

The next step in these analyses was to assess whether appropriate mimicry responses were shown in response to the facial stimuli (i.e., whether *zygomaticus* activity was greater in response to happy than angry faces, and whether *corrugator* activity was greater in response to angry than happy faces). Mean *zygomaticus* and *corrugator* responses from the control and opiate user groups are shown in Figure 3. To investigate the mimicry responses, we conducted 2 (group: control, opiate user) x 2 (emotion: happy, angry) x 10 (epoch: 0-100, 100-200, 200-300, 300-400, 400-500, 500-600, 600-700, 700-800, 800-900, 900-1000 ms post stimulus presentation) mixed-design analyses of variance separately for the *zygomaticus* and *corrugator* muscles. For any sphericity violations, Greenhouse-Geisser corrections was applied. Given that the primary hypotheses were that mimicry of happy and angry faces would be reduced in long-term opiate users, interactions with group, but not time, were followed up in these ANOVAs.

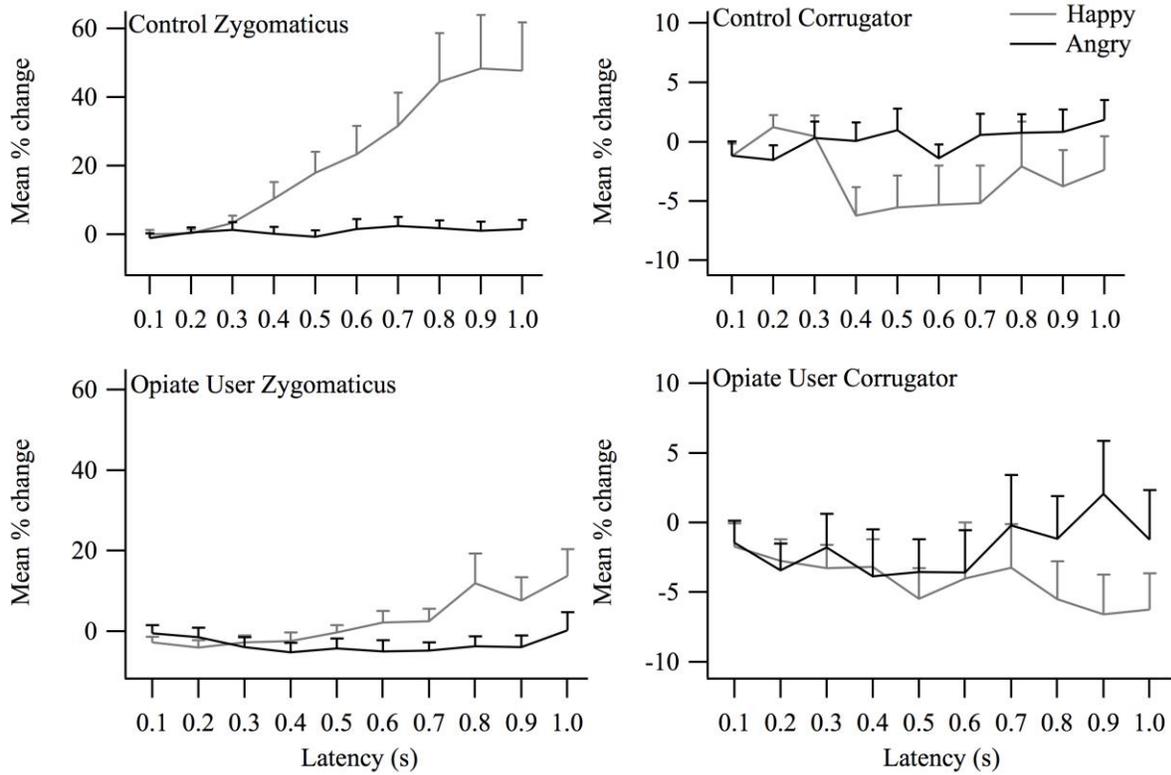


Figure 3. Mean *zygomaticus* and *corrugator* EMG responses to happy and angry face stimuli, plotted as the percentage change from baseline (error bars represent + one *SE*) for the control and opiate user groups.

Zygomaticus major

As can be seen in Figure 3, on average, both groups exhibited greater *zygomaticus* responses to happy than angry faces. There were significant main effects of group ($F(1, 48) = 8.19, p = 0.006, \eta_p^2 = 0.15$), emotion ($F(1, 48) = 14.41, p < 0.001, \eta_p^2 = 0.23$), and time ($F(1.66, 79.47) = 10.65, p < 0.001, \eta_p^2 = .18$). Of particular importance, there was a two-way interaction between emotion and group ($F(1, 48) = 4.83, p = 0.033, \eta_p^2 = 0.09$). The three-way interaction

between group, emotion and time was also approaching significance ($F(1.68, 80.68) = 2.94, p = 0.068, \eta_p^2 = 0.058$). The significant two-way interaction was analysed with tests of simple effects. There was a simple main effect of emotion for the control group, with a significantly larger *zygomaticus* response to happy than angry faces ($F(1, 48) = 17.96, p < 0.001, \eta_p^2 = 0.27$), but there was no simple main effect of emotion for the opiate user group ($F(1, 48) = 1.28, p = 0.26, \eta_p^2 = 0.026$). Further analysis of the interaction showed that the two groups differed in their *zygomaticus* responses to happy faces ($F(1, 48) = 7.37, p = 0.009, \eta_p^2 = 0.13$), but the groups did not differ in their *zygomaticus* responses to angry faces ($F(1, 48) = 2.29, p = 0.137$).

Corrugator supercilii

As shown in Figure 3, both the control and opiate user groups tended to exhibit *corrugator* responses in the appropriate direction (i.e., greater brow responses to angry relative to happy faces). However, there were no significant main effects of group ($F(1, 48) = 0.62, p = 0.436, \eta_p^2 = 0.01$), emotion ($F(1, 48) = 2.53, p = 0.12, \eta_p^2 = 0.05$) or time ($F(3.84, 184.48) = 0.97, p = 0.42, \eta_p^2 = 0.02$), nor was there any interaction between the effects of emotion and group on mean *corrugator* activity ($F(1, 48) = 0.04, p = 0.835, \eta_p^2 = 0.001$).

Discussion

Consistent with our predictions, these data demonstrate that multiple aspects of social cognition, as indexed by appropriate tasks, are impaired in long-term opiate users. Specifically, long-term opiate users exhibited poorer performance than healthy controls on tasks tapping facial emotion recognition, as well as cognitive empathy. In addition, this study provided the first empirical evidence of an abnormal affective empathic response. By measuring activity in the

zygomaticus major (cheek) muscle, it was demonstrated that facial mimicry of happy expressions was present in the healthy control group, but not in the opiate user group. In relation to *corrugator supercillii* (brow) activity, unexpectedly the control group did not demonstrate a pattern of responses consistent with rapid facial mimicry of angry expressions. This was also the case for the opiate user group. Overall, given the importance of intact social cognitive function for responding appropriately to other's emotions (Blair, 2003), these results have potentially important theoretical and clinical implications.

First of all, these results help to clarify discrepancies in the literature regarding the nature of facial emotion recognition deficits in long-term opiate users. Consistent with two other studies of long-term opiate users (Craparo et al., 2016; Kornreich et al., 2003), in the present study opiate users exhibited broad facial emotion recognition deficits across the six basic emotions. As in the present study, both of these prior studies used a standard emotion recognition paradigm, with each face presented consecutively. However by contrast, the only prior study that failed to identify a significant facial emotion recognition deficit in long-term opiate users presented stimuli that were morphed between two discrete facial emotions, with participants required to report the dominant emotion (Martin et al., 2006). It has been suggested that this latter methodological approach might be more useful for identifying individual differences in sensitivity to detecting the boundaries between distinct categories of facial expressions, rather than accurate recognition of prototypical facial emotional expressions (Young et al., 1997). Consequently, while current evidence appears to be consistent with the conclusion that long-term opiate users exhibit facial emotion recognition deficits, further studies using morphing methodology are needed to clarify the limits and boundaries of this deficit.

The present study also found that long-term opiate users performed worse than controls on a measure of ToM that required inferences about mental states to be made based on pictures of the eye region. Given that both groups performed at the same level when asked to infer the age or gender of the stimuli, these data indicate that opiate users have a specific impairment using eye-gaze information to understand the emotions of others, as opposed to a generalised deficit in face perception. This finding is consistent with both previous studies that have assessed ToM function in long-term opiate users using different methodological approaches (Gandolphe et al., 2018; McDonald et al., 2013). The current study consequently adds to converging evidence that the cognitive aspect of empathy is impaired in long-term opiate users, and that this effect generalises across different task types.

Arguably the most important contribution of the present study was the finding that while pictures of happy faces elicited greater *zygomaticus major* (cheek) responses than pictures of angry faces, this pattern (indicative of an intact facial mimicry response) was absent for long-term opiate users. As previously noted, rapid facial mimicry has been proposed to facilitate affective empathy mechanisms that are subserved by the emotional mirroring system (Decety and Meyer, 2008), and consequently can be argued to function as a low-level measure of affective empathic processing. The present findings are consistent with neuroimaging evidence showing that many of the brain structures implicated in facial mimicry and empathy are smaller in groups of long-term opiate users than in drug-naïve controls (Wollman et al., 2017). Thus, the present study provides the first empirical evidence that the affective component of empathy is disrupted in long-term opiate users.

However, contrary to expectations, neither the opiate user group nor the control group produced patterns of *corrugator* responses consistent with mimicry of angry facial expressions.

It should however be noted that the literature regarding rapid facial mimicry of anger is more mixed than the literature relating to mimicry of happiness. For example, while some previous studies of normal populations have found that pictures of angry faces elicit stronger *corrugator* responses than pictures of happy faces (Dimberg and Petterson, 2000; Dimberg et al., 2002; Varcin et al., 2010), others have not provided evidence that angry faces elicit rapid facial mimicry (Hess et al., 2017; Hess and Fischer, 2014). It has been argued that one potential reason for the failure to consistently elicit rapid facial mimicry to angry expressions is because facial mimicry serves a socially affiliative function (Hess et al., 2017; Hess and Fischer, 2014). By this view, to reflect back anger at another person could potentially escalate social conflict, and would therefore be contrary to the socially affiliative goals of mimicry, thus explaining why mimicry responses are evoked more reliably for faces with happy than angry expressions.

Limitations and Future Directions

Taken together, the current results provide clear evidence that long-term opiate users display a range of social cognitive deficits that have been consistently linked to poor social function outcomes in other clinical groups (Henry et al., 2016). However, at present, the potential causal pathways between opiate use and these socio-cognitive deficits are poorly delineated. One suggestion is that long-term opiate use leads to disruptions in the emotional mirroring network that subserves empathy (Wollman et al., 2017; Singer et al., 2009), which in turn leads to a reduction in the abilities to infer and respond to the emotional states of others (Nummenmaa et al., 2008; Shamay-Tsoory et al., 2009; Zaki and Ochsner, 2012). Alternatively, it could be that individuals with poor ToM and facial emotion recognition abilities tend to experience social difficulties (Blair, 2003), which increase their risk of engaging in chronic

substance use. In addition, given that aberrant connectivity between the insula and frontotemporal cortex is associated not only with drug seeking behaviour (Garavan, 2010; Naqvi et al., 2014; Wang et al., 2016), but also with impaired emotion processing (Di Martino et al., 2009), it could also be suggested that socio-cognitive dysfunction and a predisposition towards long-term opiate use are both affected by atypical connectivity within the emotional mirroring network. In addition, it should also be noted that, in the current study, the opiate user group displayed the typical pattern of poorer mental health, executive functioning, and education compared to controls (Cox and Comiskey, 2007; Darke et al., 1992; Ersche et al., 2006). It is therefore possible that these group differences might also be contributing to their social cognitive deficits. Furthermore, it should be acknowledged that abstinence from drug use was assessed in the current study via self-report. Thus, while Darke et al. (1998) reported that self-reported drug use is quite reliable, it cannot be guaranteed that the opiate user group was abstinent at the time of testing and, as such, drug use may have contributed to the observed group differences. Future research should therefore consider using more objective approaches to confirming abstinence.

Additional research is required to better understand the nature of these pathways, as well as factors that might moderate the relationship between opiate use and social dysfunction. For instance, it has been demonstrated that long-term opiate users have severe and persistent decision making deficits (Biernacki et al., 2016; Biernacki et al., 2018), yet it is not known whether common factors contribute to social-cognition and decision making impairments within this population. In addition to theoretical interest, there is potential clinical value in understanding these pathways. Treatment-seeking opiate users with high levels of social integration have a decreased risk of relapse (Havassy et al., 1991), and consequently interventions aimed at improving social cognition may improve both the social functioning of long-term opiate users, as

well as the long-term treatment outcomes of opiate rehabilitation programs. However, the extent to which social cognition deficits predict real-world social dysfunction remains unclear, with the strength of this relationship varying considerably across studies that have used different measures of social cognitive function and social outcomes (Janssens et al., 2012; Miller and Chapman, 2001). An important next step in this area of research is therefore to gain a clearer and more nuanced understanding of these causal pathways, ideally using longitudinal research methods.

Finally, it is important to acknowledge that as is often the case for long-term opiate users (Darke and Hall, 1995; Jones et al., 2012; Leri et al., 2002), participants in the opiate user group were receiving opiate substitution treatment. It could therefore be suggested that this could have impacted the results. However, Kornreich et al. (2003) found that facial emotion recognition performance was similar for opiate users in substitution programs and those who were currently abstinent from opiate use, hence opiate substitution is unlikely to have confounded the current findings. However, participants in the opiate user group also tended to have extensive histories of poly drug use, making it challenging to gain a clear understanding of social cognitive function in the specific context of long-term opiate use. This points to the need for further work in this area.

This limitation aside, the current study provides important and novel evidence that three distinct types of social cognitive processing are impaired in long-term opiate users, both complementing and extending prior research in this area. It has previously been argued that socio-cognitive impairments might contribute to the high levels of social dysfunction observed in this population (Darke et al., 1992), and these data speak to the value of further studies focused on exploring this issue.

Acknowledgements

We would like to thank all of the participants for generously volunteering their time. We would also like to acknowledge Rachel Braithwaite, Ruth de Jager and Michelle Scotts for their help in recruitment and testing of healthy controls participants, and initial data analyses.

Funding and disclosure

This research was supported by an Australian Catholic University Research Fund grant [No.2013000557]. Professor Julie Henry was also supported by an ARC Future Fellowship.

Conflict of interest

The authors declare that they have no conflict of interest.

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