The administration of the opioid buprenorphine decreases motivational error signals

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\textbf{ABSTRACT}

While opioid addiction has reached pandemic proportions, we still lack a good understanding of how the administration of opioids interacts with cognitive functions. Error processing – the ability to detect erroneous actions and correct one’s behaviour afterwards - is one such cognitive function that might be susceptible to opioidergic influences. Errors are hypothesised to induce aversive negative arousal, while opioids have been suggested to reduce aversive arousal induced by unpleasant and stressful stimuli. Thus, this study investigated whether the acute administration of an opioid would affect error processing. In a double-blind between-subject study, 42 male volunteers were recruited and received either 0.2 mg buprenorphine (a partial \(\mu\)-opioid receptor agonist and \(\kappa\)-opioid receptor antagonist) or a placebo pill before they performed a stimulus-response task provoking errors. Electroencephalograms (EEG) were recorded while participants performed the task. We observed no group differences in terms of reaction times, error rates, and affective state ratings during the task between buprenorphine and control participants. Additional measures of adaptive control, however, showed interfering effects of buprenorphine administration. On the neural level, decreased Pe (Error Positivity) amplitudes were found in buprenorphine compared to control participants following error commission. Further, frontal delta oscillations were decreased in the buprenorphine group after all responses. Our neural results jointly demonstrate a general reduction in error processing in those participants who received an opioid before task completion, thereby suggesting that opioids might have indeed the potential to dampen motivational error signals. Importantly, the effects of the opioid were evident in more elaborate error processing stages, thereby impacting on processes of conscious error appraisal and evidence accumulation.

\textbf{1. Introduction}

The misuse of prescription opioids in pain treatment such as oxycodeone, fentanyl, and buprenorphine has increased to pandemic proportions over the last years (Rudd et al., 2016). The long-term health burden remains to be determined as our knowledge concerning the impact of opioids on the human mind and body is still limited. Opioids (in particular \(\mu\)-opioid receptor agonists) are linked to pain reduction and pleasure enhancement in humans and animals (Kringlebach and Berridge, 2009; Leknes and Tracey, 2008), suggesting that the opioid system regulates affective states (Koob and Le Moal, 2001). In addition to pain, opioids are reported to attenuate also other aversive experiences such as breathlessness (Hayen et al., 2017), psychosocial stress and depressive symptoms (Bershad et al., 2015; Pecina et al., 2019). Supporting the notion of this broad activity spectrum, opioid receptors are distributed widely throughout the human brain and co-localized with receptors from other neurotransmitter systems involved in motivation and cognition (Fields and Margolis, 2015). Adding a functional explanation to their widespread distribution, a recent review (van Steenberggen et al., 2019) proposed that opioids might (i) increase subjective

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value of reward, and (ii) reduce aversive arousal in response to unpleasant stimuli. The current study tested the second part of this prediction in regards to error processing, as errors are important learning signals assumed to be accompanied by negative affective arousal (Inzlicht et al., 2015).

Providing a link between error commission and opioids, animal studies suggest that the endogenous opioid system may play a role during error processing as it is implicated in the formation of so-called reward prediction error signals (RPE; Fields and Margolis, 2015). For example, Cole and McNally (2007) demonstrated that μ-opioid receptors contributed to the generation of prediction error signals during fear conditioning in rats. So far, there is preliminary evidence that opioids also play a role for prediction errors in humans. Pecina et al., (2013) observed that the discrepancy between the predicted pain signal and the actually perceived pain stimulus reflected a prediction error signals and larger prediction errors were associated with higher μ-opioid receptor activity. In a behavioural study, van Steenbergen et al. (2017) observed increased post-error slowing after error commission when participants received a non-selective opioid receptor antagonist (naltrexone) compared to a placebo. This suggests that blocking the endogenous opioid system may increase adaptive behavioural control, possibly because it increases the negative arousal response following cognitive conflict and errors.

In an electroencephalography study, Pfabigan et al. (2015) investigated volunteers with different polymorphisms of the prodynorphin gene, which codes for the precursor of endogenous dynorphins (moderately selective agonists at the κ-opioid receptor; Chavkin et al., 1982). Participants with high levels of prodynorphine gene expression and thereby increased κ-opioid receptor activation showed enhanced early error processing markers. More indirect evidence comes from studies testing individuals with μ-opioid-mediated addictions that suggest a trend for impaired electrophysiological error processing (Chen et al., 2013).

In this study, we assessed both event-related potentials (ERPs) as well as time-frequency EEG measures to provide a thorough analysis of opioidergic effects on error processing. While ERPs map neural processes phase-locked to correct and erroneous responses in the millisecond time range, time-frequency analysis allows characterizing both phase- and non-phase-locked activity (Pfurtscheller and Lopes da Silva, 1999). The Error-Related Negativity component (ERN; Falkenstein et al., 2000; Gehring et al., 1993) is a fronto-central negative deflection within 100 ms after error commission. It is an automatic signal assumed to reflect prediction errors during reinforcement learning (Holroyd and Coles, 2002), or signalling cognitive conflict (Botvinick et al., 2001), motivational error significance (Gehring and Willoughby, 2002), or a threat-monitoring signal (Weinberg et al., 2012). The ERN is followed by the positive-going Error Positivity (Pe) at posterior sites (Falkenstein et al., 2000), with more positive amplitudes about 200–400 ms after errors. Pe amplitude variation is considered reflecting conscious affective processing of errors (Ulisperger et al., 2014). As time-frequency EEG measures, we assessed frontal midline theta (FMθ; ~4–8 Hz) and delta oscillations (~1–3 Hz) over fronto-central electrodes in the first 100 ms after error commission. Recent research suggests that FMθ might be a key neural mechanism of the medial prefrontal cortex to guide cognitive control processes indicating the requirement of top-down control (Cavanagh and Frank, 2014; Cavanagh et al., 2012). Error-related delta oscillations have been primarily associated with error monitoring (Coles et al., 2011), while a few other studies suggested that they might also reflect more elaborate processing stages, such as affective and motivational task relevance (Bernat et al., 2015; Knyazev, 2007, 2012).

This study investigated whether opioid administration interferes with error processing. This is a crucial assessment since intact error processing - the ability to detect incorrect responses - is a prerequisite for successful behavioural adaptation and learning. Error commission has been proposed to induce an aversive negative arousal response (Inzlicht et al., 2015) as it constitutes a cognitive challenge triggering adaptive control. Indirect evidence for this assumption comes from studies assessing affective responses after errors with psychophysiological methods. Facial electromyography (Dignath et al., 2019; Elkins-Brown et al., 2017; Lindstrom et al., 2015) and startle responses (Hajcak and Foti, 2008) suggest that error commission is accompanied by an early negative affective response. The current study probes the suggestion of a dampening of negative affective responses under the administration of opioids (van Steenbergen et al., 2019) by investigating behavioural and neural measures of error processing in a double-blind, placebo-controlled study. One group of participants was administered the opioid buprenorphine (a μ-opioid partial agonist and κ-opioid antagonist), while a second group was taking an inert pill before a simple stimulus-response task provoking errors was administered. If opioids dampen the assumed negative affective responses accompanying error commission as suggested by van Steenbergen et al. (2019), errors might partly lose their inherent significance, and thereby they might be perceived as less aversive and threat-signalling. This could be linked to antidepressant-like effects in humans (Bershad et al., 2018; Pizzagalli et al., 2020). Thus, we hypothesized that behavioural and neural measures of error commission are diminished after opioid administration compared to placebo.

2. Material and methods

2.1. Study design

This between-subject, double-blind, placebo-controlled study consisted of one session in which participants received either 0.2 mg buprenorphine (BUP) or a placebo (lactose-starch pill) sublingually.

2.2. Participants

A priori power analysis suggested a sample size of 34 participants to detect medium-sized effects in a mixed ANOVA design (details in Supplementary Materials). Initially, we recruited 42 healthy right-handed male volunteers aged between 20 and 40 years. Only men were recruited to minimize effects of sex-related pharmacokinetic effects of BUP administration (Moody et al., 2011) – see Supplementary Materials, Section 6, for our screening procedure. The final sample consisted of 35 participants of which 16 had received buprenorphine (BUP) and 19 a placebo (see Table 1). Written informed consent was obtained from all participants prior to the experiment. The study was conducted in accordance with the Declaration of Helsinki (7th revision, 2013) and was approved by the Ethics Committee of the Medical University of Vienna (EK-Nr. 661/2011).

2.3. Drug

Participants received either 0.2 mg buprenorphine (BUP; Temgesic®, Reckitt Benckise Pharmaceuticals) or an inert placebo pill (with the same physical appearance, no distinct taste) sublingually. BUP is a partial agonist at the μ-opioid receptor, but an antagonist at δ- and κ-opioid receptors. It is prescribed to treat moderate to severe pain and is in use during opioid-replacement therapy (Schmidt-Hansen et al., 2015). The current dose of 0.2 mg is considered a rather low dose (Zaczyn et al., 1997), and was chosen in accordance with previous studies (Bershad et al., 2018; Bershad et al., 2016). BUP peak plasma levels after such a dose and administration route occur 90–360 min after administration (Mendelson et al., 1997), which is well within the time window in which the experimental tasks were administered. Please refer to Supplementary Materials, Section 2, for a more detailed description of buprenorphine and its pharmacological action.
2.4. Procedure

Upon arrival, participants gave written informed consent, provided a urine sample, and after passing this drug test they performed a pain calibration procedure that is outside the scope of the current report (duration: 15 min). Subsequently, a physician (IR) measured blood pressure and then administered the sublingual pill. He provided the information that participants were administered either an approved and effective painkiller or a placebo pill without any effects. Inside the EEG chamber, participants’ heads were positioned in a chin rest. First, participants performed an experimental empathy task for 45 min, unrelated to the present research questions. Afterwards, a stimulus-response task was administered to assess error processing, taking place approximately 75–105 min after drug/placebo administration.

2.5. Experimental task

A modified version of the Eriksen flanker task (Eriksen and Eriksen, 1974) was used to assess error processing. Participants had to indicate target letters (H, S, K, or C) in the middle of a five-letter string via button press (index and middle fingers of their right hand). The white letter strings were either congruent (HHHHH, SSSSS) or incongruent (HSHHH, SSHSS) and presented centrally on black background. Each trial started with the presentation of a fixation cross for 200 ms, followed by the four outer letters for 100 ms. Next, the central letter was blended in this array for 35 ms. Afterwards, participants had 870 ms to give a response. Performance feedback was only presented in case participants responded too slow, demanding faster responses (duration 1000 ms), otherwise a fixation cross was blended in for 1000 ms, followed by an inter-stimulus interval of 800–1200 ms with the fixation cross. After 24 training trials, participants performed 304 trials with 50% congruent and 50% incongruent stimuli. Participants were given breaks every 50 trials, during which they provided affective ratings of how worried and comfortable they felt during the last trials on 9-point Likert scales.

2.6. Questionnaires

Prior to the experiment, participants filled in online questionnaires (BDI-II; Beck et al., 2006; trait version STAI, Laux et al., 1981; and PSWQ; Meyer et al., 1990) to assess anxiety- and depression-related variables, which possibly moderate error-related brain activity (Moran et al., 2015; Moser et al., 2013; Olvet and Hajcak, 2008). At the beginning of the experimental session, participants filled in a mood questionnaire (MDBF; Steyer et al., 1997). Before starting the Flanker task, they filled in the Drug Effects Questionnaire (DEQ-5; Morean et al., 2013). At the end of the experiment, a parallel version of the MDBF was filled in. Afterwards, participants were asked whether they experienced drug side effects.

2.7. Electrophysiological recordings and data analysis

EEG was recorded from 59 equidistant electrodes. Initial signal preprocessing and artefact correction was conducted using EEGLAB (Delorme and Makeig, 2004). Please refer to Supplementary Materials, Section 7 and 8, for further details on data collection and EEG pre-processing.

To assess error-related ERPs and neural oscillations, data were epoched response-locked for correct and erroneous trials. On average, 221 correct trials and 18 error trials were available after semi-automatic artefact rejection. We assessed ERPs at clusters of merged electrodes applying a region of interest approach – see Supplementary Materials, Fig. S1. A frontal cluster was used for assessing the ERN component, FM6, and delta oscillations; a parietal cluster for the Pe component. We extracted mean amplitudes to assess ERN (0–100 ms after button press) and Pe (200–400 ms after button press) components. Time windows and electrode locations for data extraction were chosen based on previous literature (e.g., van Noordt and Segalowitz, 2012). Neural oscillations were calculated using complex Morlet wavelet decompositions (see Supplementary Material for details). FM6 were extracted within a frequency range of 4.6–7.8 Hz. Delta oscillations were extracted within a frequency range of 1–2.9 Hz. Subsequently, power values (in μV²) were averaged condition- and participant-wise. Mean FM6 and delta were extracted 0–100 ms after button press in the frontal electrode cluster (see also Supplementary Materials, section 12, for an additional delta analysis in the Pe time range).

2.8. Statistical analyses

All data were analysed using multilevel modelling (MLM). This was done for the current data to avoid losing participants for whom not all conditions were available, assuming that data were missing randomly. Five participants committed less than five error trials, which renders the assessment of error-related ERPs and oscillations unreliable (Amodio et al., 2004; Steele et al., 2016). Only correct trials were available for analysis in those participants. Neural data were modelled as a function of drug-group and correctness as fixed effects (see Supplementary Materials, section 9, for effect coding and more details). A random intercept and a random slope were estimated for each participant, restricted maximum likelihood estimations for fixed effects, and the Satterthwaite method for estimating degrees of freedom were applied.

Statistical analyses were performed using SPSS 22 (SPSS Inc., IBM Corporation, NY) and jamovi (The jamovi project, 2020). The significance level was set at p < .05. As effect size measure, we provide semi-partial R² for MLM. Significant interactions in MLM were resolved with simple slope analysis testing for group differences first.
2.9. Behavioural data analysis

Reaction times were defined as the interval from middle letter offset until button press. Reaction times faster than 200 ms were discarded (Hajcak et al., 2005; Wiswede et al., 2009). Individual mean reaction times were calculated participant- and condition-wise and modelled as a function of drug-group and correctness or congruency as fixed effects. Post-error slowing (PES; Rabbit, 1966) was modelled with the fixed effect factors drug-group and sequence with reaction times of correct trials extracted participant-wise before and after incongruent erroneous trials (Dutill et al., 2012). An alternative calculation of post-error slowing, as well as post-error accuracy and congruency-sequence-effects as further behavioural task measures can be found in Supplementary Materials, section 11. Error frequency and missed responses were calculated participant-wise and analysed separately with robust t-tests. Welch’s t-tests were used to address group differences of normally-distributed questionnaire scores, robust t-tests for those lacking normal distribution. The affective ratings during the task were averaged together and analysed with robust t-tests as well.

3. Results

3.1. Behavioural results

The drug-groups did not differ significantly from each other regarding age, BMI, and questionnaire scores (Table 1). No group differences were observed for subjective drug experience (Supplementary Materials, Table S1, DEQ-5). Of 15 BUP participants (data of one BUP participant are missing), 40% (n = 34) believed that they were assigned to the BUP group, while this was the case for 26% (5 out of 19) control participants. The ratio of these correct/incorrect self-assignments was comparable over the groups (χ²(1) = 0.72, p = .40). More BUP than control participants reported dizziness, transpiration, muscular problems, and altered perception after the experiment (Supplementary Materials, Table S2).

Reaction times were faster for erroneous compared to correct responses (main effect correctness: b = −26.95, SE = 3.64, t(27.86) = −7.40, p < .01, semi-partial R² = 0.66). Drug-group and the interaction with correctness had no significant influence on reaction times (both p’s > .42). Reaction times were faster following congruent compared to incongruent trials (main effect congruency: b = 24.88, SE = 1.29, t(33) = 19.24, p < .01, semi-partial R² = 0.92). A significant interaction with drug-group was observed (b = −2.96, SE = 1.29, t(33) = −2.29, p = .03, semi-partial R² = 0.14). Simple slope tests did not show significant group differences (both p’s > .18). The interaction was driven by a larger RT difference between incongruent and congruent trials in BUP (M = 55.69, SD = 17.56) than in control participants (M = 43.84, SD = 13.00; both p’s < .01). A clear post-error slowing effect was observed (main effect sequence: b = 10.79, SE = 3.16, t(28) = 3.41, p < .01, semi-partial R² = 0.29), no other effects were found (both p’s > .76). Error numbers (p = .20) and the number of missed responses (p = .57) did not differ between the two groups. Similarly, affective ratings during the task were comparable for the two groups (both p’s > .14; Table 2), all participants reported to feel rather comfortable and not worried during the task.

3.2. EEG results

ERN amplitudes were more negative for errors than correct responses (main effect correctness: b = −2.99, SE = 0.37, t(30.09) = −8.13, p < .01, semi-partial R² = 0.69). The factor drug-group and its interaction with correctness were not significant (both p’s > .13). For Pe amplitudes, the main effects of correctness (b = 4.55, SE = 0.43, t(31.79) = 10.63, p < .01, semi-partial R² = 0.78) and drug-group (b = 1.38, SE = 0.63, t(34.16) = 2.17, p = .04, semi-partial R² = 0.12), and their interaction (b = 1.07, SE = 0.43, t(31.79) = 2.49, p = .02, semi-partial R² = 0.16) were significant. Post-hoc analyses showed significant group differences for error trials (b = 2.44, SE = 0.79, t(57.34) = 3.08, p < .01, semi-partial R² = 0.14). Pe amplitudes following errors were more pronounced (i.e., more positive) in control than in BUP participants. No group differences occurred for correct trials (p = .68) – Fig. 1, Table 3.

FMθ oscillations in the ERN time frame (0–100 ms post response) were larger for erroneous than correct responses (main effect correctness: b = 1.71, SE = 0.13, t(33.80) = 13.01, p < .01, semi-partial R² = 0.83). The main effect of drug-group and its interaction with correctness were not significant (both p’s > .32). Delta oscillations 0–100 ms post response showed main effects of correctness (b = 0.85, SE = 0.15, t(33.90) = 5.87, p < .01, semi-partial R² = 0.50) and drug-group (b = 0.46, SE = 0.17, t(35.05) = 2.65, p = .01, semi-partial R² = 0.17), their interaction was not significant (p = .22). Early frontal delta was enhanced for erroneous than correct responses, and in control than BUP participants – Fig. 2, Table 3. The same pattern of results emerged for delta oscillations in the Pe time range at the parietal electrode cluster (Fig. S2 in Supplementary Materials).

4. Discussion

This study tested whether acute administration of the partial μ-opioid receptor agonist/k-opioid receptor antagonist buprenorphine affects behavioural and neural measures of error processing. While behaviour did not differ between the groups, we observed significantly decreased neural error signals in the opioid administration group in more elaborate processing stages following erroneous responses, and for delta oscillations in all trials.

Our primary ERP finding was a decrease in Pe amplitudes in response to errors in the BUP compared to the control group. While both automatic (ERN) and more elaborate (Pe) error processing clearly differentiated between erroneous and correct responses, only the latter component was significantly influenced by the administration of buprenorphine. Pe amplitude variation is often interpreted in light of conscious error awareness and attention towards errors (Nieuwenhuis et al., 2001), evidence accumulation that an error had occurred (Steinhaus and Yeung, 2010), and motivational significance of an error (Falkenstein et al., 2000) – thereby all referring to downstream processes bringing erroneous responses and their consequences to conscious awareness. All these interpretations suggest that more elaborate error processing was less pronounced in participants in the BUP group than in controls. In contrast, early automatic error processing, reflected in ERN variation, was not significantly affected by opioid administration. Differences in Pe amplitudes are less frequently reported in studies on error processing than ERN differences. For example, Rodehacke et al. (2020) observed that a stress induction primarily influenced Pe amplitudes. The authors interpreted this finding in light of lower awareness of errors while being stressed, possibly because the stress induction took away

Table 2

|               | BUP group | Control group |
|---------------|-----------|---------------|
|               | M        | SD | M        | SD |
| Reaction times (in ms) | | | | |
| correct       | 435.56   | 54.15 | 419.64   | 44.64 |
| error         | 385.46   | 78.11 | 369.01   | 56.74 |
| congruent     | 405.81   | 59.12 | 392.91   | 45.97 |
| incongruent   | 461.49   | 52.10 | 437.76   | 47.03 |
| post-error    | 441.12   | 52.22 | 448.69   | 58.79 |
| pre-error     | 420.57   | 57.28 | 426.09   | 66.55 |
| Frequency     | | | | |
| error numbers | 11.94    | 7.15 | 23.63    | 23.17 |
| Yuan’s s/p    | 0.20     |      |          |      |
| missed responses | 18.44    | 31.86 | 8.00     | 7.05 |
| Ratings       | | | | |
| worry         | 2.16     | 1.13 | 2.35     | 2.13 |
| comfort       | 2.84     | 1.75 | 2.40     | 1.40 |
processing resources affecting more elaborate error processing. BUP participants reported slightly more side effects than control participants (Supplementary Materials, Table S2 and section 14). These could be considered as stressors taking away processing resources from error awareness. However, ratings of perceived worry and comfort during the task did not show any group differences and indicated that all participants felt rather content during the experiment. Mood ratings after the task showed the same pattern, and neither did reaction times and error rates differ between groups. These online measures assessed during and directly after the task therefore suggest that the influence of post-experimentally reported side effects should not be over-interpreted here. Moreover, buprenorphine administration was reported to dampen the physiological stress response after a social stressor (Bershad et al., 2015). This would suggest rather decreased task-associated stress responses in the BUP compared to the control group than more experienced stress due to the reported side effects.

Pe amplitude variation is also often interpreted in terms of motivational significance and error appraisal. In line with this interpretation, two recent studies investigated social context effects on errors (de Bruijn et al., 2017; Pfabigan et al., 2020). Both studies observed decreased Pe amplitudes for other-compared to self-relevant errors in their control groups, which suggests that conscious error processing is malleable by cognitive processing biases. Relatedly, Larson et al. (2013) observed reduced Pe amplitudes in response to a brief mindfulness intervention, which aimed to focus participants’ attention to experiences in a non-judgemental way. Again, it was the conscious error appraisal that was affected by the experimental intervention, which aimed to marginalize the conscious – and potentially negative - experience of errors. Taken together, these findings suggest that BUP participants showed less conscious error appraisal than control participants.

Analysis of oscillatory brain activity corroborates the interpretation
pants were in general less engaged and less bothered whether they
interpreted reflecting motivational task relevance and target stimulus
errors, thus replicating previous results of enhanced need for control
of the Pe findings. Both FM0 and delta oscillations were enhanced for
errors, thus replicating previous results of enhanced need for control
after error commission (Cohen and van Gaal, 2014; Yordanova et al.,
2004). However, BUP participants showed in general dampened delta
responses in all trials. Error-related delta oscillations are assumed to
specifically reflect error monitoring processes (Cohen and Cavanagh,
2011), which would suggest that ongoing monitoring was reduced in
BUP compared to control participants. Delta oscillations are also inter-
preted reflecting motivational task relevance and target stimulus
salience (Knyazev, 2007, 2012). This would suggest that BUP partici-
pants were in general less engaged and less bothered whether they
committed an error or not.

Both ERP and neural oscillation results suggest that errors – or task
processing in general – were less salient during task performance in BUP
participants. Our findings are thus in line with the hypothesis of
dampening of negative affective arousal by opioids (van Steenbergen
et al., 2019). Furthermore, they allow refining this hypothesis by
showing effects rather during more controlled and conscious error
processing stages (Pe, delta), but less so during the initial automatic and
bottom-up detection of errors (ERN, FM0). Supporting our observation,
a recent study aiming to reduce the assumed negative error-associated
arousal by inducing positive affect observed diminished Pe amplitudes
in the positive mood group, again interpreted as decreased appraisal of
motivational error significance (Paul et al., 2017). While a positive
mood induction might be a more powerful manipulation to decrease
negative affect after error commission, the administration of opioids
might work on similar pathways.

The current results of decreased error appraisal are also in line with
animal and human studies ascribing buprenorphine the role of a mood
regulator. This suggestion was initially brought up by opioid treatment
studies, which observed that the administration of BUP also reduced
depressive symptoms in individuals addicted to opioids (Bodkin et al.,
1995; Kosten et al., 1990). More recent studies lend further support to
this suggestion (Bershad et al., 2018; Fava et al., 2016; Ipser et al., 2013;
Karp et al., 2014). For example, Bershad et al. (2018) showed that BUP
decreased attention towards fearful faces, an effect that was particularly
pronounced in individuals with higher scores on a state measure of
negative affectivity. Along these lines, animal research showed that
BUP could lead to a decrease in depression- and anxiety-like behaviours
(Falcon et al., 2015; Robinson et al., 2019). Importantly, the current
participants were specifically recruited to have low levels of depressive
and anxiety-related symptoms in the weeks prior to the experiment, and
the two experimental groups were well matched in this regard. Thus, we
are confident that the observed group effects were not caused by indi-
vidual differences in state negative affectivity.

An important question refers to whether the hypothesised damp-
ening of negative arousal related to errors (Dignath et al., 2020; Inzlicht
et al., 2015) is linked to opioid administration or whether other
neuropharmacological pathways might exert similar effects. Opioid re-
ceptors are co-localized with monoaminergic neurotransmitters impli-
cated in error processing and reward prediction errors (Fields and
Margolis, 2015; Le Merrer et al., 2009; Valentino and Van Bockstaele,
2015). Targeting a related question, Randles et al. (2016) tested whether
the non-opioidergic analgesic acetaminophen affects error processing,
as a previous study had shown that acetaminophen caused a general
blunting of evaluative processes (Durso et al., 2015). Randles et al.
(2016) observed a reduction of Pe amplitudes in the acetaminophen
compared to the control group in their between-subjects, double-blind
placebo-controlled study. This would suggest that analgesic substances
with different mechanisms of action (acetaminophen acts on enzymes
responsible for the production of prostaglandins; White, 2005) could
impact error processing in a similar way. However, a recent replication
attempt to clarify the effects of acetaminophen on neural correlates of
error-, conflict-, and feedback processing failed to observe any
significant effects of the non-opioid analgesic (Garrison et al., 2021). Thus, also the current results await replication to allow a better understanding of the precise neural and neuropharmacological mechanisms underlying error processing.

In contrast to neural task measures, behavioral task measures such as error rates and reaction times were not significantly influenced by the administration of buprenorphine, which is in line with our previous study exploring error processing with opioid-related genetical variation (Pfabigan et al., 2015). Additional analyses focusing on adaptive control processes, however, showed that participants in the BUP group displayed rather inconsistent adaptive control following errors. They employed a slowing down after errors only in the first half of the experiment, but sped up after errors in the second half. Further, they were not sensitive to the presentation of incongruent trial arrays, as they did not slow down in the subsequent trial (see Supplementary Materials, section 11). Task difficulty of a Flanker task is rather low and the compensatory behavioral mechanisms when performing simple stimulus-response tasks (Miller, 1996). However, looking at more complex measures of adaptive control revealed the interfering effects of buprenorphine administration. The absence of group differences for error rates prevents confounds in the electrophysiological results as they impact error-related amplitude variation (Fischer et al., 2017). In the current study, post-error slowing seemed to be rather orienting-related as all participants failed to translate slower responses following errors into higher accuracy rates after errors (Wessel, 2018).

Effects of buprenorphine on attentional and orienting processes could be another mechanisms explaining the observed group differences. We performed control analyses to account for possible effects, please refer to Supplementary Material, sections 15 (heart rate analysis) and 17 (attentional ERPs). However, results of these analyses provided no evidence for buprenorphine interfering with attentional processing.

A limitation of the current study is the fact that buprenorphine is a complex substance and acts not only as a partial agonist at the µ-opioid receptor, but also as an antagonist at the κ-opioid receptor. To further test the predictions made by van Steenbergen et al. (2019) and to clarify whether the observed effects are driven by µ-opioid or κ-opioid receptor activity or both, future studies should administer selective µ-opioid receptor agonists such as morphine or hydromorphone, and selective κ-opioid receptor antagonists such as aticaprant (as used in Pizzagalli et al., 2020) in double-blind placebo-controlled designs to probe error processing, as well as the reward valuation part of the proposed framework. A better understanding of buprenorphine’s effects on cognition is particularly relevant as it is widely used in opioid-replacement therapies over long periods. As the current participants were drug-naive and received buprenorphine only once, we cannot exclude that prolonged administration would have diverging effects from those reported here. Therefore, future studies should also investigate neural correlates of error processing in individuals under continuous opioid-replacement therapies. This could also contribute to the question why opioids have such a high addictive potential in a sub-group of individuals, and how to identify them. Future studies probing the predictions of van Steenbergen et al. (2019) should also assess self-report and psychophysiological markers of affective responses to errors and rewards, such as fEMG, skin conductance, startle responses, or pupil size, in combination with EEG and functional imaging methods.

Overall, our neural results suggest that buprenorphine as partial µ-opioid receptor agonist/κ-opioid receptor antagonist has the potential to dampen motivational error signals. This is of particular clinical relevance as buprenorphine is frequently used in opioid-replacement therapies in much higher doses than tested here.

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**CRediT authorship contribution statement**

DMP and CL designed the research. DMP, MR, and IR were involved in data collection. DMP analysed the data and wrote the first draft. Critical revision for important intellectual content was done by DMP, MR, SLK, IR, and CL. All authors gave final approval of the submitted version.

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**Conflict of Interest**

The authors declare no conflict of interest. The funding sources had no role in study design, data collection, analysis, or interpretation of the current data.

**Appendix A. Supporting information**

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2021.105199.

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