Sensorimotor gating and attentional set-shifting are improved by the \(\mu\)-opioid receptor agonist morphine in healthy human volunteers

Boris B. Quednow, Philipp A. Csomor, Joelle Chmiel, Thilo Beck and Franz X. Vollenweider

1 University Hospital of Psychiatry, Experimental Psychopathology and Brain Imaging, University of Zurich, Switzerland
2 Association for Risk Reduction in Use of Drugs (ARUD), Zurich, Switzerland

Abstract

Prepulse inhibition (PPI) of the acoustic startle response (ASR) has been established as an operational measure of sensorimotor gating. Animal and human studies have shown that PPI can be modulated by dopaminergic, serotonergic, and glutamatergic drugs and consequently it was proposed that impaired sensorimotor gating in schizophrenia parallels a central abnormality within the corresponding neurotransmitter systems. Recent animal studies suggest that the opioid system may also play a role in the modulation of sensorimotor gating. Thus, the present study investigated the influence of the \(\mu\)-opioid receptor agonist morphine on PPI in healthy human volunteers. Eighteen male, non-smoking healthy volunteers each received placebo or 10 mg morphine sulphate (p.o.) at a 2-wk interval in a double-blind, randomized, and counterbalanced order. PPI was measured 75 min after drug/placebo intake. The effects of morphine on mood were measured by the Adjective Mood Rating Scale and side-effects were assessed by the List of Complaints. Additionally, we administered a comprehensive neuropsychological test battery consisting of tests of the Cambridge Neuropsychological Test Automated Battery and the Rey Auditory Verbal Learning Test. Morphine significantly increased PPI without affecting startle reactivity or habituation. Furthermore, morphine selectively improved the error rate in an attentional set-shifting task but did not influence vigilance, memory, or executive functions. These results imply that the opioid system is involved in the modulation of PPI and attentional set-shifting in humans and they raise the question whether the opioid system plays a crucial role also in the regulation of PPI and attentional set-shifting in schizophrenia.

Introduction

Prepulse inhibition (PPI) of the acoustic startle response (ASR) is used as an operational measure of sensorimotor gating that is proposed to reflect the ability to regulate sensory input by filtering out irrelevant or distracting stimuli in order to prevent sensory information overflow (Braff et al., 1978, 1992). PPI refers to the reduction of the startle response when a distinctive weak prestimulus is presented 30–500 ms before a startle-eliciting stimulus (Graham, 1975).

In accordance with the filter deficit model of schizophrenia, diminished sensorimotor gating has been consistently demonstrated in patients with schizophrenia (Braff et al., 1978, 1992; Kumari et al., 2000; Ludewig et al., 2003; Parwani et al., 2000; Quednow et al., 2006c). It has been hypothesized that the cognitive deficits and positive symptoms in schizophrenia are related to deficient sensorimotor gating (Braff et al., 2001).

In rats schizophrenia-like PPI deficits can be induced by direct and indirect dopamine receptor agonists, serotonin-2A (5-HT\(_{2A}\)) receptor agonists, and N-methyl-D-aspartate (NMDA) antagonists (for review
see Geyer et al., 2001). Given that drug-induced PPI deficits can be abolished by pre- or post-treatment with antipsychotics, it was proposed that impaired sensorimotor gating in schizophrenia parallels central neurochemical abnormalities underlying the disease (Geyer et al., 2001). In addition, evidence from cross-sectional and longitudinal clinical studies suggest that atypical antipsychotics are especially effective in improving deficient PPI in schizophrenia patients (Kumari et al., 1999, 2002; Leumann et al., 2002; Oranje et al., 2002; Quednow et al., 2006c). Similarly, the atypical antipsychotics clozapine and quetiapine also enhance PPI in healthy human volunteers exhibiting low baseline PPI levels (Swerdlow et al., 2006; Vollenweider et al., 2006). Consequently, drug-induced PPI deficits have been established as a translational model of antipsychotic activity (Swerdlow and Geyer, 1998).

Although the role of the dopaminergic, serotonergic, and glutamatergic neurotransmitter systems with respect to PPI is well investigated, the contribution of other neurotransmitter systems – such as the opioid system – in the modulation of PPI is unclear. However, the investigation of the involvement of the opioid system in sensorimotor gating is of special interest because the opioid system may participate in the pathogenesis of schizophrenia (Bloom et al., 1976; Jacquet and Marks, 1976; Schmauss and Emrich, 1985; Terenius et al., 1976). Moreover, the opioid and dopaminergic reward system and the cortico-striato-pallido-thalamic (CSPT) circuitry involved in the regulation of PPI show a considerable anatomical overlap (Swerdlow et al., 1999). Nevertheless, the influence of the opioid system on PPI is not well-studied in animals and studies in humans are currently lacking. Recently, it has been shown that the selective α-opioid receptor agonist U50488 disrupts PPI in rats and clozapine prevented this disruption. Moreover, the selective κ-opioid receptor antagonist nornorbutorphan also prevented the U50488-induced PPI deficit, whereas norbinaltorphimine alone did not alter PPI (Bortolato et al., 2005). Although the μ-opioid receptor agonists morphine and heroin did not significantly alter PPI in rats (Leitner, 1989; Ouagazzal et al., 2001; Swerdlow et al., 1991), heroin clearly tended to increase PPI dose-dependently (Swerdlow et al., 1991). In mice, the endogenous μ-opioid receptor agonist endomorphin-1 on its own also did not alter PPI but attenuated PPI deficits induced by the direct dopamine receptor agonist apomorphine (Ukai and Okuda, 2003). Finally, the non-selective μ-, δ-, and κ-opioid receptor antagonist naloxone did not influence PPI in rats but prevented the loss of PPI induced by the indirect dopamine agonist amphetamine, whereas apomorphine-induced PPI deficits were not altered by naloxone. The authors concluded that dopamine–opioid interactions in the nucleus accumbens might account for these results (Swerdlow et al., 1991). Summarized, previous animal data did not provide a clear picture with respect to the role of the opioid system for sensorimotor gating.

The involvement of the opioid system in higher cognitive functions is – apart from reward mechanisms and pain modulation – not well-understood (Gianoulakis, 2004; McNally and Akil, 2002; Waldhoer et al., 2004). Nevertheless, there is some evidence that activation of the μ-opioid receptor by [D-Ala(2),N-Met-Phe(4),Gly(5)]-enkephalin (DAMGO) impairs working memory in mice which can be reversed by the κ-opioid receptor agonist dynorphin (Itoh et al., 1994). Dynorphin also improves memory dysfunction in animal models of amnesia and these effects can be reversed by nornorbutorphan (Ilyutchenok and Dubrovina, 1995; Ukai et al., 1997). In-vitro studies on hippocampal neurons showed that opioids acting on the μ-opioid receptor facilitate the induction of long-term potentiation (LTP) of synaptic transmission which has been postulated as a cellular mechanism for learning and memory. In contrast, the κ-opioid receptor agonists dynorphin and U50488 inhibit LTP (Simmons and Chavkin, 1996; Wagner et al., 1993; Weisskopf et al., 1993).

However, μ-opioid receptor agonists do not generally impair cognitive functioning in humans (for review see Ersek et al., 2004). Only high doses of selective μ-opioid receptor agonists seem to decrease delayed verbal memory performance in healthy humans (Cleeland et al., 1996; Hanks et al., 1995; Kerr et al., 1991), whereas short-term memory or working memory as well as other cognitive domains remained widely unimpaired even after high doses (Cleeland et al., 1996; Evans and Smith, 1964; Hanks et al., 1995; Hill and Zacny, 2000; O’Neill et al., 2000; Walker and Zacny, 1998). On the contrary, some studies in healthy volunteers have shown that morphine and codeine (which is metabolized into morphine) increase the accuracy in choice reaction-time tasks (Hanks et al., 1995; O’Neill et al., 2000), enhance perceptual speed and logical reasoning (Evans and Smith, 1964), and improve learning and delayed recall in a serial learning task (Liljequist, 1981). Interestingly, naloxone impaired delayed recall while decreasing learning, immediate recall, accuracy of spatial orientation, monitoring of word presentations, and increasing choice reaction time (Cohen et al., 1983; Martin del Campo et al., 1992).
Since the role of μ-opioid receptors in the modulation of sensorimotor gating has not been studied in humans so far, we investigated the effects of the μ-opioid receptor agonist morphine on PPI, startle reactivity and habituation of ASR in healthy human volunteers in a randomized, double-blind, placebo-controlled, and counterbalanced design. In addition, we administered a comprehensive neuropsychological test battery to explore the effects of morphine on higher cognitive functions and to further investigate whether morphine-induced changes in sensorimotor gating are associated with changes in cognitive performance. Based on the finding that heroin tended to increase PPI in rats (Swerdlow et al., 1991), we expected to find an enhancing effect of morphine on PPI in human volunteers. While previous human studies found impaired delayed recall performance only after high doses and reported no or enhancing effects on several cognitive domains after low and moderate doses of morphine, we anticipated no significant effect on neuropsychological performance by the relatively low dose of morphine sulphate (10 mg) administered in the present study.

Method

Participants

Since menstrual cycle and smoking have been shown to influence PPI (Duncan et al., 2001; Kumari and Gray, 1999; Swerdlow et al., 1997) only male non-smoking subjects were included. Eighteen healthy volunteers (aged 19–31 yr) were recruited through internet advertisement from local universities. Subjects’ physical health was confirmed by medical history, clinical examination, electrocardiography, and blood analysis. To ensure mental health, all subjects underwent a psychiatric screening interview based on the DIA-X computerized diagnostic expert system (Wittchen and Pfister, 1997). Furthermore, subjects were examined with the Freiburg Personality Inventory (FPI; Fahrenberg et al., 1984) and the Hopkins Symptom Checklist (SCL-90-R; Derogatis, 1977); scores differing two standard deviations from the mean value of normative data in any subscale of these questionnaires were used as exclusion criteria (no subjects had to be excluded by these criteria). All subjects were also screened for hearing impairment by means of a brief hearing test. The demographical data are shown in Table 1.

None of the subjects had a past or present psychiatric or neurological disorder, or a severe physical illness. Moreover, none of them reported a family history of psychiatric disorders, which are known to have an impact on PPI, specifically schizophrenia spectrum disorders or obsessive–compulsive disorder. All participants negated use of psychotropic medication or illicit drug use, which was confirmed by urine toxicology on both test days.

This study was approved by the Ethics Committee of the University Hospital of Psychiatry, Zurich. After receiving a written and oral description of the aim of this study, all participants gave written informed consent statements before inclusion.

Morphine

Morphine (Sevredol™) was obtained from Mundipharma, Basel, Switzerland and was prepared as gelatine capsules of 10 mg morphine sulphate (equivalent to 7.5 mg morphine) at the pharmacy of the Psychiatric University Hospital, Zurich. Lactose placebo and morphine were administered in gelatine capsules of identical appearance.

Table 1. Demographic and psychometric data of the 18 healthy human volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>23.9 ± 2.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.8 ± 7.2</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.80 ± 0.1</td>
</tr>
<tr>
<td>Body mass index</td>
<td>22.8 ± 1.4</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>104.5 ± 11.0</td>
</tr>
<tr>
<td>Hopkins Symptom Checklist (SCL-90-R)</td>
<td></td>
</tr>
<tr>
<td>Somatization</td>
<td>0.26 ± 0.28</td>
</tr>
<tr>
<td>Obsessive compulsion</td>
<td>0.53 ± 0.45</td>
</tr>
<tr>
<td>Interpersonal sensitivity</td>
<td>0.33 ± 0.48</td>
</tr>
<tr>
<td>Depression</td>
<td>0.31 ± 0.43</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.18 ± 0.26</td>
</tr>
<tr>
<td>Hostility</td>
<td>0.33 ± 0.49</td>
</tr>
<tr>
<td>Phobic anxiety</td>
<td>0.06 ± 0.14</td>
</tr>
<tr>
<td>Paranoid ideation</td>
<td>0.36 ± 0.46</td>
</tr>
<tr>
<td>Psychoticism</td>
<td>0.17 ± 0.37</td>
</tr>
<tr>
<td>Positive symptom total</td>
<td>19.0 ± 15.5</td>
</tr>
<tr>
<td>Global severity index</td>
<td>0.29 ± 0.32</td>
</tr>
<tr>
<td>Positive symptom distress index</td>
<td>1.25 ± 0.28</td>
</tr>
<tr>
<td>Freiburg Personality Inventory (FPI)</td>
<td></td>
</tr>
<tr>
<td>Nervousness</td>
<td>3.35 ± 2.60</td>
</tr>
<tr>
<td>Aggression</td>
<td>3.61 ± 2.55</td>
</tr>
<tr>
<td>Depression</td>
<td>2.82 ± 2.72</td>
</tr>
<tr>
<td>Excitability</td>
<td>2.47 ± 2.10</td>
</tr>
<tr>
<td>Sociability</td>
<td>9.35 ± 2.83</td>
</tr>
<tr>
<td>Patience</td>
<td>5.06 ± 2.05</td>
</tr>
<tr>
<td>Dominance</td>
<td>2.47 ± 1.74</td>
</tr>
<tr>
<td>Inhibition</td>
<td>3.18 ± 2.21</td>
</tr>
<tr>
<td>Frankness</td>
<td>4.88 ± 1.36</td>
</tr>
</tbody>
</table>
Study design

The study design was double-blind, placebo-controlled and included two experimental conditions (morphine and placebo). All subjects received placebo and a single dose of morphine in a randomized and counterbalanced order at one of two experimental days separated by a 2-wk interval.

Sessions were conducted in a calm and comfortable laboratory environment. Participants were told to abstain from alcohol the day prior to each test session, not to drink caffeine-containing beverages and not to eat 6 h prior to each session. Thirty minutes after arriving in the laboratory, subjects received placebo or morphine in capsules. Heart rate and blood pressure were recorded 10 min before as well as 65 min and 160 min after drug/placebo intake. To coincide with the mean peak effects of morphine (Collins et al., 1998) startle measures were obtained 75 min after drug/placebo intake. The neuropsychological test battery was conducted directly after the startle measurement (~100 min after drug/placebo intake) and lasted about 45 min. The Adjective Mood Rating Scale (AMRS; Janke and Debus, 1978) was administered 10 min before and 70 min after drug/placebo intake. Finally, the List of Complaints (von Zerssen, 1971) was assessed about 165 min after drug/placebo intake. After the acute drug effects of morphine subsided completely and the participants reported well-being, they were dismissed.

Startle response measurement

The eye-blink component of the ASR was measured using an EMG startle system (EMG-SR-LAB, San Diego Instruments Inc., San Diego, CA). Two Ag/Ag-chloride electrodes were placed below the right eye over the orbicularis oculi muscle and a ground electrode was placed on the glabella. All electrode resistances were <5 kΩ. A square wave calibrator established sensitivity to be 0.38 μV/digital unit. The system recorded 600 samples at 1 kHz sampling rate. EMG data were band-pass-filtered 100–1000 Hz by the acquisition hardware. Acoustic startle stimuli were presented through headphones (TDH-39-P, Maico, Minneapolis, MN, USA). Subjects were seated comfortably in an armchair, instructed to relax, and told that they would hear a sequence of white-noise bursts. They were asked to stay awake while staring at a fixed point (passive attention paradigm). Each session began with a 2-min acclimation period of 70-dB background noise that continued throughout the session. The session consisted of a total of 73 trials separated by inter-trial intervals varying between 10 and 20 s. The trials consisted of four conditions: 115 dB pulse-alone (PA-115) trials of 40 ms duration; 86 dB prepulse-alone (PPA-86) trials of 20 ms duration, prepulse-pulse (PP) trials consisting of a PA-115 shortly preceded by a PPA-86, and a non-stimulus condition (NS). All stimuli consisted of broadband white noise. Rise and fall time of PA and PP trials were <1 ms. Five inter-stimulus intervals (ISIs; onset-to-onset) were used for the PP trials: 30, 60, 120, 240, or 2000 ms (PP30, PP60, PP120, PP240, PP2000). The initial trial was a PA-115 trial that was separated for further analyses. The first and last block of a session consisted of four PA-115 trials and was used for the calculation of habituation but not of PPI. The two middle blocks (second and third block), each consisted of four PA-115 trials, four PPA-86 trials, four of each of the PP trials, and four NS trials presented in a pseudorandom order. Data were analysed with the Windows-based software emgBLINK version 1.2 (CST, Zürich, Switzerland).

Before scoring, the EMG was smoothed with a time constant of 10 ms. Baseline amplitude was calculated by the mean response amplitude of the first 50 ms before stimulus onset. Stimulus response amplitudes were assessed as peak response minus baseline value of the respective trial. Peak response was defined as the highest reaction in the time-window between stimulus onset to 150 ms after stimulus onset. Every trial was examined for spontaneous eye-blinks and other possible signs of corrupted EMG signal; if present the trial was excluded from data analysis, which was the case in 2.5% of all trials. Subjects with error trials >50% were excluded from data analysis. Based on this criterion, two of the 18 participating subjects were excluded from analysis only of the startle data.

As described in detail elsewhere (Quednow et al., 2006b,c), the following startle measures were examined:

1. Startle reactivity (mean amplitude of PA-115 trials in the first block).
2. Percent habituation = 100 × (first block PA-115 trials – last block PA-115 trials)/(first block PA-115 trials)
3. Slope of the habituation curve across four blocks of PA-115 trials
   \[ b = \frac{(n\Sigma xy - (\Sigma x)(\Sigma y)) \ perch=379content=n}{(n\Sigma x^2 - (\Sigma x)^2)} \]
   where \( x \) = block number, \( y \) = startle amplitude of PA trials per block.
4. Percent PPI and percent prepulse facilitation (PPF) = 100 × (PA-115 trials – PP trials)/PA-115 trials.
(5) Reactivity to prepulse stimuli and NS condition (mean amplitude of PPA-86 and NS trials each within the second and third block).
(6) Peak response latency (mean latency to maximal response amplitude occurring within 150 ms after PA-115 trials).

**Psychometric measures**

On the screening day, all subjects completed the FPI (Fahrenberg et al., 1984), which measured nine personality traits, and the SCL-90 (Derogatis, 1977), which assessed nine symptom clusters, a global severity index (GSI), a positive symptom distress index (PSDI) and a positive symptom total score (PST). On each experimental day all subjects completed the AMRS (Janke and Debus, 1978) twice, which assessed seven mood subscales. At the end of each experimental day, all subjects completed the List of Complaints (von Zersen, 1971) consisting of 65 common psychosomatic symptoms which were summed for a total score.

**Neuropsychological test battery**

The battery comprises of the German version of the Rey Auditory Verbal Learning Test (RAVLT; Helmstaedter et al., 2001; Rey, 1958) and six tests of the Cambridge Neuropsychological Test Automated Battery [CANTAB (www.cantab.com)], which were performed on an IBM-compatible personal computer with a touch-screen monitor (Elo IntelliTouch, Otto-brunn, Germany).

RAVLT. This task measures verbal declarative memory performance with regard to the supraspan (trial 1), learning performance (Σ trials 1–5), recall of interference list (list B), recall after interference (trial 6), delayed recall (trial 7 after 30 min), loss after consolidation (trial 5 minus trial 7), and adjusted recognition performance [p(list A)]. Administration of the RAVLT and calculation of the several parameters have already been described in detail elsewhere (Quednow et al., 2006a).

CANTAB. The Motor Screening Task (MOT) was used to introduce the subjects to the touch-screen procedure by touching the centre point of flashing crosses on the screen as soon as possible after appearance. The response latency was assessed. The Rapid Visual Information Processing task (RVP) is a visual continuous performance task using predefined sequences of three digits presented at a rate of 100 per minute to assess sustained attention over a period of 4 min. Sustained attention performance was assessed by total correct responses to target sequences (total hits), discrimination performance (A’) and latency to hit responses. The Intra/Extradimensional Attentional Set-shifting task (ID/ED) is a test for rule acquisition and reversal, featuring visual discrimination and attentional set-shifting, analogous to the Wisconsin Card Sorting task (Heaton, 1981). Performance was assessed by the number of trials (adjusted to the number of completed stages), the total number of errors (adjusted to the number of completed stages), the errors made up to the extradimensional shift (pre-ED errors) and the errors made at the extradimensional stage of the task (ED errors). The Stockings of Cambridge task (SOC) measures the subject’s spatial planning ability, based upon the Tower of London task (Shallice, 1982). The total number of problems solved in the minimum number of moves, the number of moves to reach criterion, initial thinking time and subsequent thinking time were all assessed. The Spatial Recognition Memory task (SRM) proves visual spatial memory in a two-choice forced discrimination paradigm. Performance was indexed by the mean latency to correct responses, and percent of correct hits of a maximum of 20. Finally, the Spatial Working Memory task (SWM) tests spatial working memory and strategy performance. The subject had to find a blue ‘token’ in each displayed box, whilst not returning to boxes in which a blue token had already been found. Performance was indexed by a strategy score, which represents the number of times the subject begins a new search with the same box. A high score represents poor use of this strategy and a low score equates to effective use. Furthermore, the total number of errors and between errors (searching a token in a box where one had already been found) was assessed.

**Statistical analysis**

All data were analysed by SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). Startle data, psychometrical data and neuropsychological data were analysed by analyses of variance (ANOVA) with repeated measurements. Based on significant main effects, Least Significant Difference (LSD) post-hoc comparisons were performed (in case of graded within-subject factors). Frequency differences within single complaints were analysed by McNemar tests. Interrelationships between startle parameter, psychometrical scales, neuropsychological variables, and demographic data were tested using Pearson’s product-moment correlation. The confirmatory statistical comparisons were carried out at a significance level set at p < 0.05 (two-tailed). Within the correlation analyses, the significance level was set at p < 0.01 (two-tailed) in order to
avoid accumulation of α-error. Finally, effect sizes were calculated with G*Power 3 (Faul et al., 2007) according to the conventions of Cohen (1988).

Results

Startle measurements

A 4 × 2 (ISI condition × treatment) repeated-measure ANOVA with the four PPI conditions (PP30, PP60, PP120, PP240) revealed significant main effects for the factors treatment $[F(1, 45) = 6.04, p < 0.05]$ and ISI condition $[F(3, 45) = 24.97, p < 0.001]$ but no significant interaction of both factors. LSD post-hoc tests revealed that morphine significantly increased PPI in the PP60 ($p < 0.05, d = 0.55$) and in the PP240 condition ($p < 0.05, d = 0.54$) (see Figure 1). A repeated-measure ANOVA with the PPI condition PP2000 did not show a significant drug effect.

Given that the PPI-enhancing effects of clozapine in healthy volunteers is limited to subjects with low PPI levels (Vollenweider et al., 2006) we investigated the influence of placebo PPI levels on the drug effects. We divided the sample into low vs. high PPI groups by median split in the PP60 and PP240 PPI condition each. Then we calculated a 2 × 2 (group × treatment) repeated-measure ANOVA with both corresponding PPI conditions separately. While we found significant main effects for the factors treatment $[F_{PP60}(1, 14) = 4.61, p < 0.05; F_{PP240}(1, 14) = 5.22, p < 0.001]$ and group $[F_{PP60}(1, 14) = 30.12, p < 0.001; F_{PP240}(1, 14) = 19.27, p < 0.001]$ we could not detect significant interactions of both factors in both PP conditions. Thus, the drug effect was not limited to subjects with low PPI.

Morphine did not alter startle reactivity, habituation, peak response latency, reactivity to prepulse stimuli and amplitude in NS trials (see Table 2). Finally, reactivity to prepulse stimuli (PPA-86) and to NS trials did not differ significantly.

AMRS, List of Complaints, and cardiovascular measures

The AMRS subscales were analysed with 2 × 2 (treatment × rating) repeated-measure ANOVAs (see Table 3 showing the AMRS change scores between the baseline rating and the rating 70 min after drug/placebo intake). No significant treatment × rating interaction and no significant main effect of the factor treatment occurred. A significant main effect of the factor rating could be shown only for the AMRS sub-scales performance-related activity $[F(1, 17) = 7.09, p < 0.05]$ and general inactivation $[F(1, 17) = 5.17, p < 0.05]$, indicating a decrease of general activity across both test sessions. However, there were only weak statistical trends for an increase of anxiety-depression and dreaminess under morphine (see Table 3).

The rate (+ s.d.) of side-effects – measured with the List of Complaints – did not significantly differ between placebo (2.06 ± 1.70) and morphine (2.89 ± 3.09) $[F(1, 17) = 1.34, p = 0.26, d = 0.27]$. Analyses with McNemar tests at item level did not show any significant differences between both drug conditions. In sum, Tiredness was the most frequent complaint (mentioned under placebo seven times; under morphine eight times) followed by Faintness (4/6) and Adderphagia (4/5).

A 2 × 2 × 3 (treatment × systolic vs. diastolic blood pressure × rating) repeated-measure ANOVA of the blood pressure ratings did not reveal an impact of morphine on systolic or diastolic blood pressure. Moreover, a 2 × 3 (treatment × rating) repeated-measure ANOVA of the heart rate did also not show any influence of the study medication on heart rate (cardiovascular data not shown).

Neuropsychological data

Repeated-measure ANOVAs revealed a significant main effect of treatment with respect to the pre-extradimensional shift errors (pre-ED errors) whereas all other neuropsychological parameters did not significantly differ (see Table 4). A 2 × 9 (treatment × ID/ED stages) repeated-measure ANOVA of the error rates across the nine ID/ED stages revealed a significant main effect of the factor stage $[F(8, 136) = 11.4, p < 0.001]$ but only a statistical trend for the factor treatment $[F(1, 136) = 2.97, p = 0.09]$ and no significant interaction of both factors (see Figure 2). For an exploratory approach we analysed the single stages separately by means of LSD post-hoc tests. It turned out that the error rates in the first stage Simple
Table 2. Means and standard deviation of means of the amplitude of 115 dB-pulse-alone (PA-115) trials in the first block (startle reactivity), the amplitude of 86 dB prepulse-alone (PPA-86) trials (reactivity to prepulse stimuli), the amplitude in no-stimulus (NS) trials, the percent prepulse inhibition (PPI) summed across inter-stimulus interval conditions (PP30-PP240), the percent habituation between first and last block of PA-115 trials, the slope of the habituation curve, and the latency of startle response peak in PA-115 trials under placebo and 10 mg morphine sulphate in 16 healthy volunteers

<table>
<thead>
<tr>
<th>Startle measures</th>
<th>Placebo (mean ± S.D.)</th>
<th>Morphine (mean ± S.D.)</th>
<th>Effect size (d)</th>
<th>F</th>
<th>d.f., d.f.error</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean amplitude of PA-115 trials (first block) (arbitrary units)</td>
<td>543.0 ± 383.1</td>
<td>549.8 ± 376.2</td>
<td>0.04</td>
<td>0.02</td>
<td>1, 15</td>
<td>0.89</td>
</tr>
<tr>
<td>Mean amplitude of PPA-86 trials (arbitrary units)</td>
<td>25.7 ± 55.0</td>
<td>22.8 ± 33.0</td>
<td>0.08</td>
<td>0.11</td>
<td>1, 15</td>
<td>0.75</td>
</tr>
<tr>
<td>Mean amplitude of NS trials (arbitrary units)</td>
<td>8.8 ± 3.3</td>
<td>10.6 ± 6.8</td>
<td>0.26</td>
<td>1.15</td>
<td>1, 15</td>
<td>0.30</td>
</tr>
<tr>
<td>Mean % PPI (PP30-PP240 conditions)</td>
<td>37.2 ± 20.5</td>
<td>46.3 ± 20.1</td>
<td>0.61</td>
<td>6.04</td>
<td>1, 15</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean percent habituation of PA-115 trials (between first and last block)</td>
<td>50.3 ± 26.7</td>
<td>53.7 ± 21.3</td>
<td>0.12</td>
<td>0.24</td>
<td>1, 15</td>
<td>0.63</td>
</tr>
<tr>
<td>Habituation of PA-115 trials across four blocks (linear gradient coefficient b)</td>
<td>−87.6 ± 73.6</td>
<td>−93.4 ± 58.9</td>
<td>0.08</td>
<td>0.11</td>
<td>1, 15</td>
<td>0.74</td>
</tr>
<tr>
<td>Mean peak response latency (ms)</td>
<td>64.3 ± 8.1</td>
<td>67.2 ± 15.1</td>
<td>0.21</td>
<td>0.68</td>
<td>1, 15</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Table 3. Means and standard deviation of means of the change scores (baseline scores minus scores 70 min after drug/placebo intake) of the subscales of the Adjective Mood Rating Scale (AMRS) under placebo and 10 mg morphine sulphate in 18 healthy volunteers

<table>
<thead>
<tr>
<th>AMRS subscales</th>
<th>Placebo (mean ± S.D.)</th>
<th>Morphine (mean ± S.D.)</th>
<th>Effect size (d)</th>
<th>F</th>
<th>d.f., d.f.error</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance-related activity</td>
<td>1.33 ± 2.87</td>
<td>2.11 ± 3.56</td>
<td>0.23</td>
<td>0.93</td>
<td>1, 17</td>
<td>0.35</td>
</tr>
<tr>
<td>General inactivation</td>
<td>−1.39 ± 3.36</td>
<td>−2.22 ± 5.64</td>
<td>0.13</td>
<td>0.31</td>
<td>1, 17</td>
<td>0.99</td>
</tr>
<tr>
<td>Extroversion-introversion</td>
<td>−0.11 ± 1.60</td>
<td>1.00 ± 2.81</td>
<td>0.33</td>
<td>1.93</td>
<td>1, 17</td>
<td>0.18</td>
</tr>
<tr>
<td>General well-being</td>
<td>0.17 ± 1.72</td>
<td>0.94 ± 2.55</td>
<td>0.23</td>
<td>0.95</td>
<td>1, 17</td>
<td>0.34</td>
</tr>
<tr>
<td>Emotional excitability</td>
<td>−0.06 ± 1.80</td>
<td>−0.11 ± 1.23</td>
<td>0.02</td>
<td>0.01</td>
<td>1, 17</td>
<td>0.92</td>
</tr>
<tr>
<td>Anxiety-depression</td>
<td>0.33 ± 1.19</td>
<td>−0.50 ± 1.69</td>
<td>0.35</td>
<td>2.25</td>
<td>1, 17</td>
<td>0.15</td>
</tr>
<tr>
<td>Dreaminess</td>
<td>0.00 ± 0.77</td>
<td>−0.67 ± 1.75</td>
<td>0.38</td>
<td>2.62</td>
<td>1, 17</td>
<td>0.12</td>
</tr>
</tbody>
</table>

discrimination ($p < 0.001$, $d = 0.97$) and in the sixth stage Intradimensional shift ($p < 0.05$, $d = 0.51$) were significantly improved under morphine.

Correlational analyses

To assess whether the significant PPI enhancement parallels the significant decrease in the ID/ED pre-ED error rate we correlated the change scores of both parameters, which were indeed not significantly associated. However, the change score of the error rate in the Simple discrimination stage was positively correlated with the change score of the mean percent PPI across ISI conditions ($r = 0.66$, $p < 0.01$, $n = 16$), indicating that subjects with increased PPI also made less errors under morphine. Moreover, PPI enhancement (PP30 and PP60 conditions) was significantly correlated with decrease of SOC subsequent thinking time ($r_{PP30} = −0.63$, $p < 0.01$, $n = 16$; $r_{PP60} = 0.64$, $p < 0.01$, $n = 16$).

Interestingly, mean percent PPI across ISI conditions at placebo condition was negatively correlated with the PPI subscale Inhibition ($r = −0.66$, $p < 0.01$, $n = 16$), reflecting that subjects with low PPI show high social inhibition (in the sense of shyness). With the exception of a significant correlation between slope of habituation curve and verbal IQ ($r = −0.67$, $p < 0.01$, $n = 16$) (indicating that a high IQ goes along with a strong habituation capacity) no other demographic variables were significantly correlated with PPI, habituation, and startle reactivity.

Discussion

To our knowledge, this is the first study investigating the effects of the $\mu$-opioid receptor agonist morphine...
on sensorimotor gating and attentional set-shifting in healthy human volunteers. The study yielded two main results: First, morphine significantly increased PPI across all of the investigated ISI conditions without influencing startle reactivity and habituation. The strongest effect sizes occurred in the 60 ms and 240 ms ISI condition. The PPI-enhancing effect was seen in most of the subjects and was not limited to subjects with low PPI as shown previously for the atypical antipsychotics clozapine and quetiapine (Swerdlow et al., 2006; Vollenweider et al., 2006). Second, morphine selectively improved the pre-ED error-rate in the ID/ED task but did not significantly affect other neuropsychological domains such as vigilance, memory, or executive functions. Interestingly, the PPI improvement (summed across conditions) was associated with the decrease of errors at the first stage (Simple discrimination) of the ID/ED task. Moreover, at the relatively low dose morphine did not significantly affect mood and did not cause more side-effects than placebo.

The morphine-induced increase of PPI in our healthy volunteers is in line with the previously reported increase of PPI by heroin in rats (Swerdlow et al., 1991). Furthermore, morphine did not alter startle amplitude or habituation which is also in accordance

Table 4. Means and standard deviation of means of RAVLT variables and CANTAB task scores under placebo and 10 mg morphine sulphate in 18 healthy volunteers

<table>
<thead>
<tr>
<th>Tests</th>
<th>Placebo (mean ± S.D.)</th>
<th>Morphine (mean ± S.D.)</th>
<th>Effect size (d)</th>
<th>F</th>
<th>d.f., d.f.error</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVLT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraspan (trial 1)</td>
<td>10.8 ± 2.29</td>
<td>11.1 ± 2.00</td>
<td>0.12</td>
<td>0.33</td>
<td>1, 17</td>
<td>0.57</td>
</tr>
<tr>
<td>Learning performance (Σ trials 1–5)</td>
<td>67.3 ± 6.59</td>
<td>67.4 ± 7.29</td>
<td>0.04</td>
<td>0.03</td>
<td>1, 17</td>
<td>0.87</td>
</tr>
<tr>
<td>Recall of interference list (list B)</td>
<td>11.4 ± 2.57</td>
<td>10.7 ± 2.47</td>
<td>0.32</td>
<td>1.91</td>
<td>1, 17</td>
<td>0.19</td>
</tr>
<tr>
<td>Recall after interference list (trial 6)</td>
<td>13.9 ± 1.86</td>
<td>13.6 ± 2.15</td>
<td>0.20</td>
<td>0.90</td>
<td>1, 17</td>
<td>0.36</td>
</tr>
<tr>
<td>Delayed recall (trial 7)</td>
<td>13.8 ± 1.86</td>
<td>13.1 ± 3.19</td>
<td>0.30</td>
<td>1.78</td>
<td>1, 17</td>
<td>0.20</td>
</tr>
<tr>
<td>Loss after consolidation (trial 5 minus 7)</td>
<td>0.78 ± 1.35</td>
<td>1.33 ± 2.11</td>
<td>0.31</td>
<td>1.80</td>
<td>1, 17</td>
<td>0.20</td>
</tr>
<tr>
<td>Adjusted recognition performance p(A)</td>
<td>0.93 ± 0.07</td>
<td>0.92 ± 0.13</td>
<td>0.10</td>
<td>0.05</td>
<td>1, 17</td>
<td>0.83</td>
</tr>
<tr>
<td>CANTAB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor Screening (MOT)</td>
<td>654 ± 81.3</td>
<td>671 ± 125.5</td>
<td>0.17</td>
<td>0.53</td>
<td>1, 17</td>
<td>0.48</td>
</tr>
<tr>
<td>Response latency (ms)</td>
<td>21.4 ± 2.99</td>
<td>21.2 ± 4.37</td>
<td>0.07</td>
<td>0.06</td>
<td>1, 17</td>
<td>0.81</td>
</tr>
<tr>
<td>Discrimination performance (A')</td>
<td>0.95 ± 0.03</td>
<td>0.95 ± 0.04</td>
<td>0.06</td>
<td>0.05</td>
<td>1, 17</td>
<td>0.82</td>
</tr>
<tr>
<td>Response latency (ms)</td>
<td>434 ± 68.6</td>
<td>456 ± 114.9</td>
<td>0.29</td>
<td>1.57</td>
<td>1, 17</td>
<td>0.23</td>
</tr>
<tr>
<td>ID/ED Attentional Set-shifting (ID/ED)</td>
<td>72.4 ± 11.1</td>
<td>67.9 ± 7.2</td>
<td>0.35</td>
<td>2.16</td>
<td>1, 17</td>
<td>0.16</td>
</tr>
<tr>
<td>Total trials (adjusted)</td>
<td>12.6 ± 5.64</td>
<td>9.6 ± 4.29</td>
<td>0.42</td>
<td>3.23</td>
<td>1, 17</td>
<td>0.09</td>
</tr>
<tr>
<td>Total errors (adjusted)</td>
<td>7.2 ± 1.76</td>
<td>5.3 ± 1.57</td>
<td>0.88</td>
<td>13.81</td>
<td>1, 17</td>
<td>0.002</td>
</tr>
<tr>
<td>Pre-ED errors</td>
<td>3.6 ± 4.19</td>
<td>2.1 ± 1.28</td>
<td>0.34</td>
<td>2.12</td>
<td>1, 17</td>
<td>0.16</td>
</tr>
<tr>
<td>Stockings of Cambridge (SOC)</td>
<td>9.8 ± 1.44</td>
<td>9.7 ± 1.28</td>
<td>0.07</td>
<td>0.10</td>
<td>1, 17</td>
<td>0.76</td>
</tr>
<tr>
<td>Problems solved in minimum moves</td>
<td>4.0 ± 0.32</td>
<td>4.0 ± 0.31</td>
<td>0.03</td>
<td>0.02</td>
<td>1, 17</td>
<td>0.90</td>
</tr>
<tr>
<td>Moves to reach criterion</td>
<td>5065 ± 2625</td>
<td>5304 ± 2415</td>
<td>0.08</td>
<td>0.12</td>
<td>1, 17</td>
<td>0.74</td>
</tr>
<tr>
<td>Initial thinking time (ms)</td>
<td>192 ± 245.9</td>
<td>212 ± 196.9</td>
<td>0.07</td>
<td>0.08</td>
<td>1, 17</td>
<td>0.78</td>
</tr>
<tr>
<td>Subsequent thinking time (ms)</td>
<td>26.7 ± 6.59</td>
<td>25.8 ± 5.22</td>
<td>0.20</td>
<td>0.72</td>
<td>1, 17</td>
<td>0.41</td>
</tr>
<tr>
<td>Total number of errors</td>
<td>6.2 ± 6.01</td>
<td>5.6 ± 6.90</td>
<td>0.07</td>
<td>0.09</td>
<td>1, 17</td>
<td>0.77</td>
</tr>
<tr>
<td>Between errors</td>
<td>5.9 ± 5.81</td>
<td>5.4 ± 6.97</td>
<td>0.06</td>
<td>0.05</td>
<td>1, 17</td>
<td>0.83</td>
</tr>
</tbody>
</table>

RAVLT, Rey Auditory Verbal Learning Test; CANTAB, Cambridge Neuropsychological Test Automated Battery.
with previous studies (Leitner, 1989; Ouagazzal et al., 2001; Swerdlow et al., 1991). Some previous studies also reported PPI-improving effects of psychoactive drugs in healthy human volunteers: nicotine increased PPI in smokers and non-smokers (Kumari et al., 1997; Postma et al., 2006), clozapine and quetiapine enhanced PPI in subjects exhibiting low PPI levels (Swerdlow et al., 2006; Vollenweider et al., 2006), and the 5-HT releaser MDMA (Vollenweider et al., 1999), as well as the hallucinogenic 5-HT$_2$A/1A agonist psilocybin increased PPI exclusively at long ISIs (Gouzoulis-Mayfrank et al., 1998; Vollenweider et al., 2007).

How could the PPI-enhancing effect of morphine be explained? The opioid-system interacts with several neurotransmitter systems such as dopamine, glutamate, GABA, acetylcholine, and substance P within core regions critically involved in sensorimotor gating such as nucleus accumbens (NAc), ventral pallidum (VP), and ventral tegmental area (VTA) (McGehee, 2006; Napier and Mitrovic, 1999; Pan, 1998; Swerdlow et al., 2001; Xi and Stein, 2002). Since Ukai and Okuda (2003) have shown that the $\mu$-opioid receptor agonist endomorphin-1 could inhibit the apomorphine-induced PPI deficit in mice and as it has been found that naloxone could prevent amphetamine-induced disruption of PPI in rats (Swerdlow et al., 1991) one could speculate that opiate–dopamine interactions may account for the PPI-increasing effect of morphine. This would also fit with the hypothesis that opioid–dopamine interactions play a role in the pathogenesis of schizophrenia (Schmauss and Emrich, 1985). However, $\mu$-opioid receptor agonists such as morphine disinhibit dopaminergic neurons in the VTA through inhibition of GABAergic interneurons and increase dopamine release in the NAc, an effect which is widely accepted to explain a part of the addictive and rewarding properties of opioids (Koob, 2000; Pan, 1998; Xi and Stein, 2002). Since it has been consistently shown that even an increase of dopamine in the NAc disrupts PPI in rats (for review see Swerdlow et al., 2001), opioid–dopamine interactions in the NAc are not very likely to explain the present finding of an $\mu$-opioid receptor-mediated increase of PPI. Even the finding of Bortolato et al. (2005) that $\kappa$-opioid receptor activation disrupts PPI does not support dopamine–opioid interactions as an explanation of opioid-induced PPI alterations because $\kappa$-opioid receptor activation decreases dopamine release in the NAc (Pan, 1998). However, $\mu$-opioid receptor agonists are also modulating GABAergic and glutamatergic neurotransmission in the VP and VTA (Johnson and Napier, 1997; Mitrovic and Napier, 2002; Napier and Mitrovic, 1999; Xi and Stein, 2002) and these neurotransmitter systems have been shown to be critically involved in the processing of PPI in these regions (for review see Swerdlow et al., 2001).

Moreover, evidence from behavioural and in-vitro electrophysiological studies suggests that $\mu$-opioid receptors interact with 5-HT$_2A$ receptors in the medial prefrontal cortex (MPFC) (Domino, 1986; Marek, 2003;
Marek and Aghajanian, 1998a,b; Marek et al., 2001), and serotonergic activity in the cortex (and in the VP) has been demonstrated to be an important substrate of PPI modulation in rats (Geyer et al., 2001; Sipes and Geyer, 1997; Swerdlow et al., 2001). With regard to the present findings it should be noted that especially low doses of \( \mu \)-opioid receptor agonists antagonized behavioural effects of hallucinogens mainly acting on 5-HT_{2A} receptors, whereas larger doses rather enhance these effects (Domino, 1986). In addition, it has been shown that even subthreshold doses of morphine can strongly modulate other dopaminergic, GABAergic or glutamatergic neurotransmissions in the VTA, VP and NAc (Napier and Mitrovic, 1999). Thus, larger doses of morphine may lose the ability to increase PPI, which would explain the finding that high doses of morphine did not change PPI in rats (Leitner, 1989; Ouagazzal et al., 2001).

Given the facts that activation of nicotinic acetylcholine receptors can increase PPI (Kumari et al., 1997; Postma et al., 2006) and that \( \mu \)-opioid receptor activation can also modulate acetylcholine release in the NAc (McGehee, 2006), it is also conceivable that nicotinic–opioid receptor interactions may contribute to the PPI increase under morphine.

Finally, it is an interesting conjunction that the \( \kappa \)-opioid receptor agonist U50488 disrupts PPI (Bortolato et al., 2005) whereas we found a PPI-enhancing effect following \( \mu \)-opioid receptor activation. These findings are in accordance with the hypothesis that activation of \( \kappa \)-opioid receptors antagonize various \( \mu \)-opioid receptor-mediated actions in the brain (Pan, 1998).

It should be noted that previous animal studies investigating the effects of morphine on PPI mostly applied only a single ISI of 100 ms and that we found the strongest effects at lead intervals of 60 ms and 240 ms. Furthermore, the sample sizes of these animal studies were generally smaller (\( n = 8–12 \)) than in our investigation (Leitner, 1989; Ouagazzal et al., 2001; Swerdlow et al., 1991). Therefore, differences in ISI, sample size, and morphine dose (see above) or unknown species-specific mechanisms might account for the fact that previous animal studies did not detect a significant increase of PPI under morphine.

In conclusion, the PPI-enhancing effect of morphine might be mediated by interactions between \( \mu \)-opioid receptors and glutamatergic, GABAergic or nicotinic innervations of the VP or VTA or by interactions with the 5-HT system within the MPFC or VP. However, animal studies are needed to explore these supposed neurotransmitter interactions in more detail.

Given that PPI-enhancing effects are seen as an indicator of antipsychotic activity (Swerdlow and Geyer, 1998) the present findings raise the question of whether morphine could have antipsychotic properties. Interestingly, morphine is to be regarded as the first specific antipsychotic in the history of psychopharmacology. It was widely used for the treatment of affective and psychotic disorders until it fell into disfavor by the beginning of the 19th century because of its addictive potential (Comfort, 1977). An observation by Comfort (1977) could also point toward antipsychotic activity: ‘a clinical impression remains, unsupported by any good figures, that among addicts there are some who would have become psychotic if not addicted, and who use morphinoids (heroin in particular) to hold at bay intolerable prespsychotic sensations, and that these are sharply exacerbated by withdrawal’ (p. 448). In the 1970s a possible involvement of endogenous opioids in the pathogenesis of schizophrenia was proposed (Bloom et al., 1976; Jacquet and Marks, 1976; Terenius et al., 1976), but ensuing clinical studies with opioid agonists and antagonists did not reveal marked clinical effectiveness of these substances in schizophrenia patients (for review see Schmauss and Emrich, 1985). However, from the current perspective these studies suffered from small sample sizes, short observation periods and lack of placebo control. Taken together, our findings suggest that the \( \mu \)-opioid receptor might be an interesting drug target for the treatment of schizophrenia.

With regard to the self-medication hypothesis of addictive disorders (Khantzian, 1985) our findings raise a further question: Do opioid addicts have PPI deficits? Surprisingly, there are no PPI data of opioid addicts available so far and it would be of great interest to learn whether PPI is decreased in these patients and what happens with PPI during withdrawal and when opioids are administered.

The data further show that morphine reduces the pre-ED error rate in the ID/ED task, especially in the stages Simple discrimination (SDI) and Intradimensional shift (ID). The error rate during the extradimensional shift (ED) was not significantly improved, albeit also decreased, while reversal learning was unaffected by morphine. Whereas the SDI stage requires only visual discrimination learning, in the ID stage subjects have to learn the transfer of a rule within the same perceptual dimension (e.g. shape). By contrast, the ED stage requires the shift to a new – previously irrelevant – perceptual dimension (e.g. colour) while the previously attended feature must be disregarded (Owen et al., 1991). It has been consistently
reported that schizophrenia patients display deficits in the ID and ED stages of the ID/ED task (Elliott et al., 1995; Hutton et al., 1998; Jazbec et al., 2007; Pantelis et al., 1999). These previous studies primarily investigated the attrition rate and the trials to reach criterion as dependent variables and these parameters were not significantly affected by morphine in the present study (data not shown). However, it has been shown that schizophrenia patients committed more errors especially in the SDI and ID stages rather than in the ED stage (Pantelis et al., 1999) and errors in the ID stage were associated with disorganized symptom characteristics of schizophrenia (Pantelis et al., 2004). Moreover, abstinent heroin abusers also showed significant impairment of performance at the ID but not at the ED stage (Ornstein et al., 2000). Lesion studies and studies with patients suffering from Parkinson’s or Huntington’s disease suggest that the prefrontal cortex and the basal ganglia are involved in performing ED shifts (Dias et al., 1996; Downes et al., 1989; Lawrence et al., 1996; Owen et al., 1991, 1992). The ability to reverse stimulus-reward connections within a perceptual dimension (reversal learning), on the other hand, is more associated with the orbitofrontal cortex (Dias et al., 1996).

The involvement of the opioid system in attentional set-shifting is scarcely investigated. A recent study reported that the mixed \( \mu \), \( \delta \), and \( \kappa \)-opioid receptor antagonist naltrexone attenuated the impaired performance in ED shifts in aged rats (Rodefer and Nguyen, 2006) but studies in humans are lacking. Nevertheless, our finding is in line with previous studies showing morphine-induced improvement of neuropsychological performance in tests supposedly involving similar attentional processes like visual discrimination learning such as choice reaction-time tasks (Hanks et al., 1995; O’Neill et al., 2000) and perceptual and semantic evaluation tasks (Evans and Smith, 1964). The idea that morphine could improve cognition is not new. Based on self-experiments examining the effect of morphine on choice reaction tasks, Kraepelin (1892) already concluded that morphine ‘immediately facilitates the perception of external stimuli, ... whereas the implementation of choice is aggravated in the same time’ [‘... (Morphin) erleichtert ... sofort die Auffassung äusserer Eindrücke, ..., während die Ausführung des Wahlactes in ganz ähnlichem Tempo erschwert wird’] (p. 255).

A further important result is that the morphine-induced increase in PPI was correlated with the decrease of the error rate within the SDI stage of the ID/ED task. The SDI stage measures alertness rather than rule acquisition like later stages of the task (Jazbec et al., 2007). This correlation is in accordance with our previous observation that psilocybin-induced deficits of sustained attention deficits were associated with PPI reduction at short ISI intervals (Vollenweider et al., 2007). These findings support the hypothesis that deficits in sensorimotor gating may underlie the more complex attentional and cognitive abnormalities in schizophrenia (Braff et al., 2001). Since we have shown that morphine enhances PPI and attentional set-shifting – processes that are both impaired in schizophrenia – the \( \mu \)-opioid receptor might be a promising target for the development of specific cognitive enhancers for schizophrenia patients. Furthermore, abstinent opiate addicts also show worse performance at the ID stage and morphine specifically improves this kind of visual discrimination learning that might support the self-medication hypothesis of opiate addiction (Khantzian, 1985). It would be of interest if opiate addicts receiving heroin substitution would show improved ID performance compared to abstinent subjects.

In conclusion our findings imply that the \( \mu \)-opioid system is involved in the modulation of PPI and attentional set-shifting. These results raise the question of whether the opioid system plays a crucial role also in the regulation of PPI and attentional set-shifting in schizophrenia in which both functions were shown as deficient. Future preclinical studies should evaluate if \( \mu \)-opioid receptors might be a potential drug target for new antipsychotic agents or cognitive enhancers for schizophrenia patients. Moreover, animal studies are needed to enlighten the anatomical structures and neurochemical mechanisms underlying the morphine-induced increase of PPI and attentional set-shifting in our healthy human volunteers.

**Acknowledgements**

Dr Quednow was supported by the Deutsche Forschungsgemeinschaft (DFG, grant QU 218/1-1) and by the Nachwuchsforderungskredit of the University of Zurich. In addition, Philipp Csomor received support by a grant from the Stiftung für Klinische Neuro-Psychiatrische Forschung, Berne, Switzerland. Dr Vollenweider was additionally supported by a NARSAD (The Mental Health Research Association) Independent Investigator Award, USA. The authors thank Dr Nicolas Langlitz for his helpful comments and Carmen Ghisleni for technical assistance.

**Statement of Interest**

Mundipharma, Basel, Switzerland contributed supplemental funding.
References


