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Naloxone modulates visual judgments of similarity but not dissimilarity

Peter Krummenacher · Elvan Kut · Gerd Folkers · Peter Brugger

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Abstract Endogenous opioids have been implicated in mediating (placebo) analgesia, in reward processes, and in the regulation of socially relevant emotions. To explore their potential contributions to higher cognitive functions, we used a novel task with tachistoscopically presented (for 150 ms) pairs of meaningless figures. Healthy right-handed men judged the similarities and dissimilarities between the two figures on a visual analogue scale (VAS) in two separate runs. In a double-blind, between-subjects design, subjects were administered intravenously either 0.2-mg/kg naloxone or placebo 10 min prior to the task, and VAS judgments and response latencies were measured. We found a significant interaction between substance group and type of judgment: The magnitude of the similarity judgments was lower in the naloxone than in the placebo group, while dissimilarity judgments remained uninfluenced by the treatment. Reaction latencies and mood scores, assessed before and after substance administration, did not differ between the two groups, indicating that the findings did not rely on altered motor performance or motivation. We suggest that naloxone decreased the "similarity criterion" in comparative judgments, indicating its potentially modulatory effect on visual cognition. The task introduced here could be used for the implicit study and quantification of subtle affective–cognitive processes beyond the level of mere questionnaire data.

P. Krummenacher · P. Brugger
Department of Neurology, Neuropsychology Unit, University Hospital Zurich, 8091 Zurich, Switzerland

P. Krummenacher · E. Kut · G. Folkers
Collegium Helveticum, University of Zurich and ETH Zurich, Schmelzbergstrasse 25,
8092 Zurich, Switzerland

P. Krummenacher (✉)
Department of Psychology, Clinical Psychology and Psychotherapy, University of Basel, Missionsstrasse 62,
4055 Basel, Switzerland
e-mail: peter.krummenacher@unibas.ch

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Abbreviations

VAS	Visual analogue scale
MDBF	Multidimensional mood questionnaire
SJ	Similarity judgment
DJ	Dissimilarity judgment

Endogenous opioid systems have mainly been implicated in affective processes, such as the response to reward (Smith & Berridge, 2007), the modulation of endocrine functions (e.g., Drolet et al., 2001), the regulation of affect (e.g., Zubieta et al., 2003), pleasure-related analgesia (Kut et al., 2011; Leknes & Tracey, 2008) and the mediation of (placebo) analgesia (e.g., Petrovic, Kalso, Petersson, & Ingvar, 2002). Moreover, several lines of evidence have indicated that the neurocircuitry and neurochemistry of physical pain overlap with those of more abstract, complex cognitive–affective experiences, such as social emotions (Macdonald & Leary, 2005; Stein, van Honk, Ipser, Solms, & Panksepp, 2007). Indeed, the endogenous opioid systems' involvement in social attachment and social distance regulation was demonstrated in pioneering studies by Panksepp in a separation distress paradigm with animals (Herman & Panksepp, 1978; Panksepp, Herman, Vilberg, Bishop, & DeEskinazi, 1980), and subsequently in genetic studies with mouse pups (Moles, Kieffer, & D'Amato, 2004) and infant primates (Barr et al., 2008). While opiates and opioids were demonstrated to be very effective in reducing social separation-induced distress, opiate antagonists such as naloxone appear to increase separation distress (Herman & Panksepp, 1978; Panksepp et al., 1980). In a recent neuroimaging study with healthy subjects, Eisenberger, Lieberman, and Williams (2003) showed that neural networks activated during distress caused by social exclusion are also activated

during physical pain, and that pain experience can be reduced by visual stimuli signaling attachment (Eisenberger et al., 2011). In line with these findings of "social distance regulation" is the general explanation for the feeling of physical pain that accompanies emotional loss (Panksepp, 2003), whether it be the loss of a loved one (Zubieta et al., 2003), rejection by one's social group (Eisenberger, 2012; Eisenberger, Jarcho, Lieberman, & Naliboff, 2006; Eisenberger et al., 2003), or the distress experienced by young animals when being separated from their parents (Panksepp, 1998).

In healthy humans, opioid agonists have been implicated in feelings of emotional relatedness or social emotions and in mood-elevating effects (Gospic et al., 2008; Koepp et al., 2009; Schaffer, Nordahl, Schaffer, & Howe, 2007). By contrast, the mu-opioid antagonist naloxone has been shown to influence endocrine functions (Drolet et al., 2001) and occasionally reported to induce dysphoric mood states at doses over 0.25 mg/kg (Grevert, Albert, Inturrisi, & Goldstein, 1983; Martin del Campo, Dowson, Herbert, & Paykel, 1994; Martin del Campo, McMurray, Besser, & Grossman, 1992; Mendelson, Ellingboe, Keuhnle, & Mello, 1978). However, it remains to be established how far the discrepancies in study findings may be a consequence of the lack of a reliable measure and methodological difficulties.

Most surprisingly, besides the reported opioidergically modulated mood effects, a relative lack of studies have investigated influences on other higher brain functions. The exceptions are naloxone-dependent alterations in attention (Arnsten, Neville, Hillyard, Janowsky, & Segal, 1984; Arnsten et al., 1983; Buchsbaum et al., 1982) and memory (Cohen, Cohen, Weingartner, Pickar, & Murphy, 1983; Friswell et al., 2008; Kamboj, Tookman, Jones, & Curran, 2005). More recently, Biederman and colleagues suggested that mu-opioids are involved in perceptual pleasure (Biederman & Vessel, 2006; Yue, Vessel, & Biederman, 2007). In fact, a high density of mu-opioid receptors in the brains of macaque monkeys (Lewis et al., 1981; Wise & Herkenham, 1982) was found in association areas, such as the parahippocampal cortex, and distributed along a gradient that increased in density along the ventral visual pathway. Similar mu-receptor distributions in the ventral visual pathway were found in the human brain (Hiller & Fan, 1996; Peckys & Landwehrmeyer, 1999; Quirion & Pilapil, 1991). However, their influence on cognitive judgmental processes has been largely unexplored. Endogenous opioids' influence on cognitive functioning is thus of central importance for both basic and clinical research (see Ersek, Cherrier, Overman, & Irving, 2004, for a clinical review).

From a phenomenological perspective, a cognitive equivalent to emotional feelings of relatedness, or more broadly to "social emotions," could be conceptualized as "coherence perception," social distance regulation, or the appreciation of (dis)similarity between two different stimuli. Theories about coherence perception (e.g., Ashby & Perrin, 1988; Solan & Ruppin, 2001) aim at explaining why and when people judge two different stimuli as being related. Judgments of similarity/dissimilarity are an important, but often neglected, component in a variety of cognitive processes. Processes of coherence perception—in particular, similarity—are involved in object recognition (Barenholtz & Tarr, 2008), decision making (Kim, Novemsky, & Dhar, 2013), visual attention (Duncan & Humphreys, 1989), analogic reasoning (Novick, 1988), belief formation (Gianotti, Mohr, Pizzagalli, Lehmann, & Brugger, 2001), semantic and perceptual categorization (Pettigrew, 1958), and aesthetics (Wertheimer, 1923/1958). In the semantic domain, coherence perception is influenced by affective states (Balas, Sweklej, Pochwatko, & Godlewska, 2012; Estes, Jones, & Golonka, 2012). Spotting similarity has also been proposed to be a fundamental aspect of various cognitive processes, such as making inferences, knowledge generalization, and knowledge transfer (e.g., Gentner, Rattermann, & Forbus, 1993). Finally, similarity has also been suggested to account for many different facets of social perception and behavior, ranging from physical attraction (Byrne, 1971) and social comparison (Mussweiler, 2003) to interpersonal interaction (Tajfel, 1982) and group membership (e.g., Campbell, 1958).

Although the question of how people judge similarity and dissimilarity is clearly of critical importance in social cognition (e.g., Mitchell, Macrae, & Banaji, 2006) and in cognitive psychology, little is known about the neurochemical underpinnings of coherence perception or about whether it can be considered a distinct cognitive system. We here introduce a novel judgment task, assessing "cognitive relatedness" or formal visual coherence/contrast perception. In a visual perceptual task, we investigated whether a mu-opioid receptor antagonist (naloxone) could modify healthy subjects' judgments of similarity/dissimilarity. Since we conceptualized coherence perception as a cognitive equivalent of social distance regulation (feelings of relatedness), which has been associated with the activity of endogenous opioid systems, we predicted decreased similarity (coherence perception) and increased dissimilarity (contrast perception) judgments in subjects receiving a naloxone injection. Especially since endogenous opioid systems have been suggested as being involved in the visual system. Moreover, we hypothesized a dissociation of similarity and dissimilarity; that is, we assumed that they would not represent two endpoints on a bipolar scale, but instead provide two independent, context-dependent frames of reference.

Method

Subjects

The volunteers were 21 advertisement-recruited healthy right-handed men (mean handedness score [Chapman & Chapman,

1987] = 13.9, *SD* = 1.6, range = 13–19) 19–44 years of age (*M* = 26.7 years, *SD* = 7.4). All subjects gave written informed consent to the experimental procedures, which had been approved by the local ethics committee.

The health status of the subjects was assessed with a detailed questionnaire (Campbell, 2000). All subjects confirmed the absence of any relevant acute or chronic disease (hypertension, heart disease, renal disease, liver disease, mental illness, or seizure disorder) and of any history of neurological disorder, mental illness, or mental impairment. They also denied having a history of abuse of medications, drugs, or alcohol and engaging in any recreational consumption of drugs, narcotics, or other substances relevant to the central nervous system over the last three months. They were paid 50 Swiss francs for participation in the study.

Subjects were tested individually, seated on a comfortable reclining chair in front of a 15.2-in. (diagonal) computer screen. Room lighting and screen contrast were all kept constant.

The presentation of all instructions was carried out via computer display and automatically controlled by "Superlab Pro 4" (Cedrus) running on an Apple G4 Powerbook. The distance between head and computer screen was adjusted to permit undisturbed view and was kept at approximately 60 cm for all subjects.

Procedure

Questionnaire: measurement of subjects' mood Subjects rated their mood two times, once at the beginning and once at the end of the experiment. Their ratings were assessed with 24 adjectives from the German version of the Multidimensional Mood Questionnaire (MDBF; Steyer, Schwenkmezger, Notz, & Eid, 1997). The MDBF questionnaire is a short, multidimensional, self-evaluative questionnaire that describes the current mood state of an individual on three dimensions: "good versus bad mood", "wakefulness versus sleepiness", and "calmness versus restlessness".

Similarity and dissimilarity judgment tasks A total of 18 different stimulus pairs, consisting of two horizontally placed meaningless geometric figures, were tachistoscopically presented bilaterally (exposure time = 150 ms). One figure of a pair was presented to the left, and the other to the right side of a central fixation cross (horizontal eccentricity = 1.5° to 3.0° of visual angle). The single pairs were constructed to respect the Gestalt laws of proximity, good continuation, closure, similarity, and figure–ground properties. Each stimulus pair was also presented in a vertically mirrored version. The two counterbalanced runs each consisted of 36 trials (18 different stimulus pairs and 18 vertically mirrored versions of each other); in one, subjects had to indicate similarity (SJ: similarity judgment)—and in the other, dissimilarity (DJ: dissimilarity judgment)—with a computer mouse in their right hand on a 9-in. bipolar visual analogue scale (VAS) presented against a light gray background (the sequential order of each run in this paradigm is depicted in Fig. 1). All objects (object size: within 2.8 × 2.8 cm, line thickness = 2 points) were printed in black and presented on a computer screen (gray background). Sample stimuli are illustrated in Fig. 1. The stimulus pairs were identical in both the SJ and DJ runs but were presented in a different, pseudorandomized order.

Subjects were asked to rest their head on a chinrest and to fixate the cross in the center of the screen before and during stimulus exposure (Fig. 1). They were instructed to respond as quickly and intuitively as possible and were told that their preference ratings on similarity/dissimilarity judgments were highly subjective and that there were neither false nor correct judgments.

Double-blind procedure for naloxone administration The study had a randomized, double-blind, placebo-controlled, between-subjects design. Either naloxone hydrochloride (*n* = 10, 0.2 mg/kg body weight, concentration 1 mg/ml, obtained from the pharmacy of Kanton Zürich) or the equivalent volume of NaCl (*n* = 9, 0.9 %, also from the pharmacy of Kanton Zürich) was administered. Similar naloxone dosages had been previously shown to completely antagonize endogenous opioid-mediated analgesia in healthy volunteers (Amanzio & Benedetti, 1999). To prevent high stress levels during the experiment, a nurse ran an intravenous catheter from the inner elbow of the nondominant arm 10 min prior to drug administration. The tasks were administered 10 min after drug administration, since naloxone hydrochloride has a fast onset of action (2 min), but individual and dose-dependent times to peak effect (from 5 to 15 min; Ngai, Berkowitz, Yang, Hempstead, & Spector, 1976). In separate studies, its mean serum half-life has been measured as 64 ± 12 min (Ngai et al., 1976) and 57 min (Berkowitz, Ngai, Hempstead, & Spector, 1975).

The entire testing was supervised by a medical doctor. All subjects had been asked to refrain from any alcohol-, caffeine-, or taurin-containing beverage for at least 12 h before the start of the experiment and confirmed their compliance in the debriefing. At the end of behavioral testing, the subjects were asked (via questionnaire) which substance they thought they had received.

Statistical analysis

Two separate two-way analyses of variance (ANOVAs) with Substance Group (naloxone vs. placebo) as a between-subjects factor and Run (similarity vs. dissimilarity rating) as a repeated measure were calculated for positions on the VAS (VAS magnitude, as percentages) and for reaction latencies.

The homogeneity of variances was checked using Levene's test ($F = 1.775$, $p = .149$), and the normal distribution of the dependent variables was tested by the Kolmogorov–Smirnov

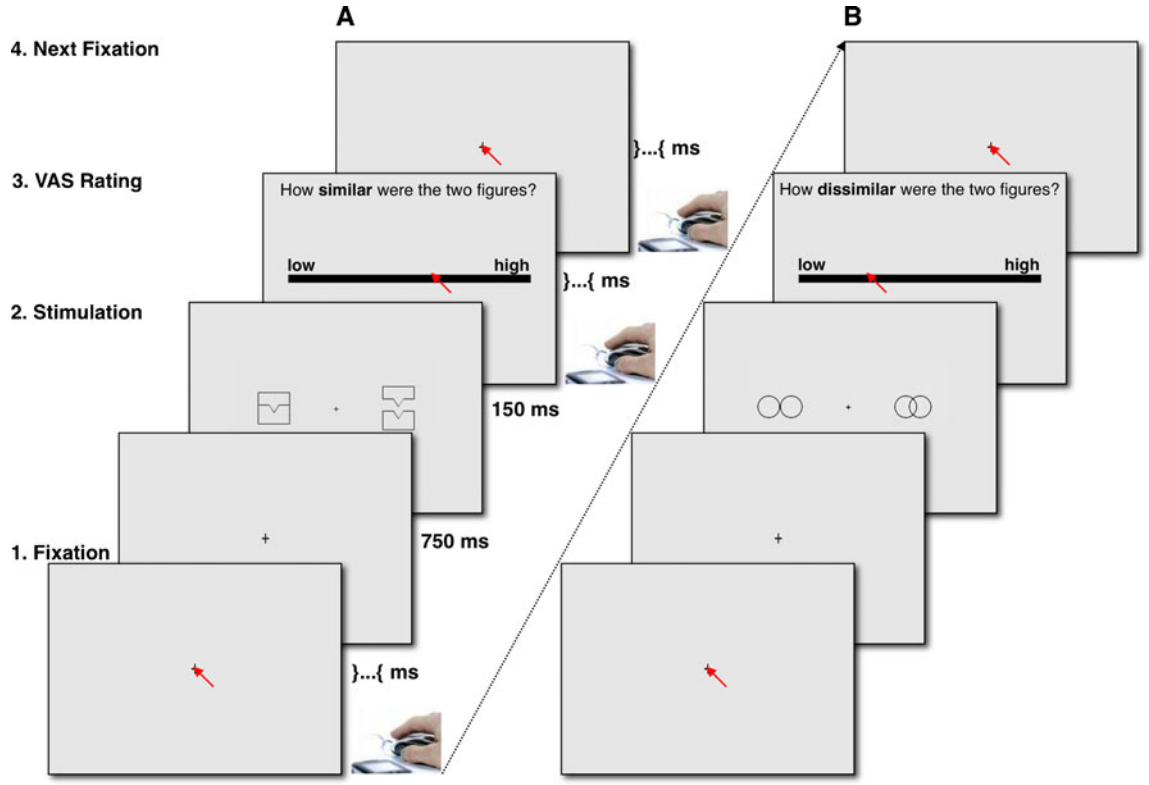

Fig. 1 Time course of events in the similarity judgment run (SJ; display A) and the dissimilarity judgment run (DJ; display B). After 750 ms (fixation of a central cross), a stimulus consisting of two horizontally placed, meaningless geometric objects was bilaterally exposed for 150 ms (balanced for object side order). Subsequently, the degree of similarity or dissimilarity of the stimuli was rated by clicking on the computerized visual analogue scale (VAS). In order to control the baseline mouse position, subjects had to click on the fixation cross in the middle of the screen after each judgment (which elicited the next trial). Subjects were instructed to respond as quickly and as intuitively as possible and to fixate their gaze on the cross in the center of the screen

test ($Z \leq .732$, $p \geq .657$). If not otherwise stated, all tests are two-tailed with an α level of .05.

Outlier detection was performed by means of the Grubb test. To test for a naloxone influence on psychometrically assessed mood, a three-way repeated measures ANOVA was computed comprising the between-subjects factor Substance Group (naloxone vs. placebo) and the within-subjects factors Time (beginning vs. end of the experiment) and Mood Dimension (valence, wakefulness, calmness).

Two of the subjects did not adhere to the judgment task instruction and constantly pressed the keyboard instead of using the mouse to indicate the degree of similarity or dissimilarity on the VAS. Valid data were thus available from 19 of the subjects. No trials from any subject were excluded.

Results

Handedness, age, and blinding

The subjects in the naloxone and placebo groups did not differ from one another in age [$t(17) = -1.72$, $p = .11$] and in strength of right-handedness [$t(17) = 1.78$, $p = .112$].

We found no association between what substance subjects believed they had received (drug or placebo) and what they had actually received, which suggests that the blinding was effective ($\chi^2 = 0.532$, $p = .466$): Altogether, 84 % of the study subjects believed that they had received saline. Two of the subjects who thought they had received naloxone were in the placebo group, and one subject under the influence of naloxone correctly detected the substance.

Questionnaires

The mood ratings (MDBF) assessed at the beginning and the end of the experiment did not differ significantly from each other, nor were there any interactions with substance type (all Fs ≤ 2.241, corresponding ps $\geq .122$).

Cognitive judgment tasks

No significant main effects were found for VAS magnitudes (all Fs ≤ 1.684, corresponding ps $\geq .212$). However, the two-way ANOVA for VAS magnitudes revealed a significant interaction between substance group and run [$F(1, 17) = 10.460$,

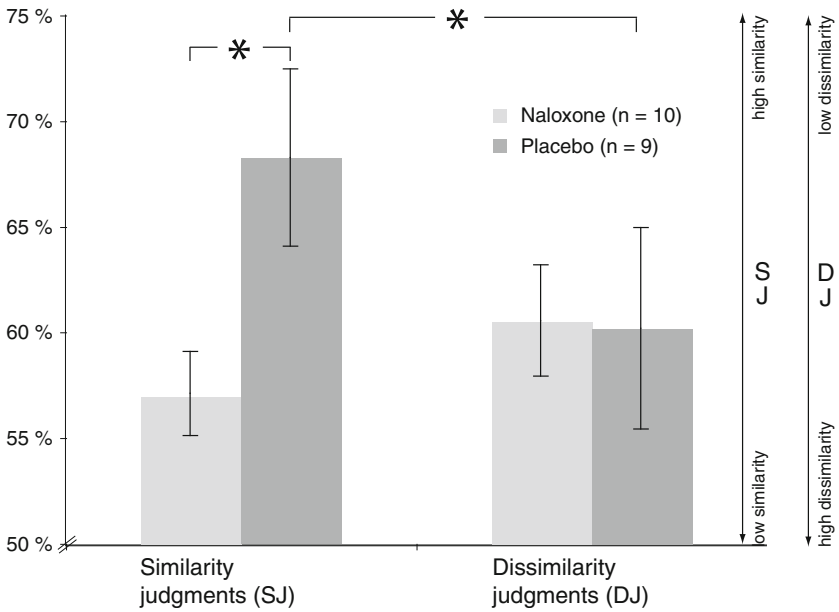

Fig. 2 Visual analogue scale (VAS) magnitude scores (in percentages) for the two substance groups (naloxone, placebo) and the two runs (similarity, dissimilarity) (means ± standard errors). Because all subjects indicated mean VAS scores above 50 %, the illustrated scale range has been adapted to be read from 50 % to 75 %. Asterisks (*) indicate significant post-hoc comparisons ($p < .05$)

$p = .005$; see Fig. 2]. The partial eta-squared effect size for this interaction was .38 (Cohen's $d = 1.57$).

Post hoc comparisons for this interaction showed a higher VAS magnitude in the placebo group ($M = 68.25$, $SD = 12.56$) than in the naloxone group ($M = 57.09$, $SD = 6.30$) for similarity judgments ($p = .023$), but comparable VAS magnitudes between naloxone ($M = 60.54$, $SD = 8.31$) and placebo ($M = 60.17$, $SD = 14.30$) for the dissimilarity judgments ($p = .945$). Moreover, while the VAS magnitudes in the placebo group were higher for similarity than for dissimilarity judgments ($p = .036$), the VAS magnitudes for similarity and dissimilarity in the naloxone group were not significantly different from one another ($p = .085$).

Reaction latencies

No significant main effects or interactions were apparent (all Fs ≤ 1.716, corresponding ps $\geq .208$).

Discussion

Healthy subjects were administered a novel perceptual cognitive judgment task assessing visual similarity and dissimilarity. In a double-blind naloxone, placebo-controlled, between-subjects design, we aimed to investigate the role of endogenous opioids in "cognitive relatedness." We focused on the hypothesis that a cognitive equivalent to social distance regulation might be conceptualized as "cognitive relatedness" and could be dependent on mu-opioid receptor activity.

The results showed that the VAS magnitudes of similarity judgments were more moderate for subjects in the naloxone than in the placebo group; that is, visually presented stimulus pairs were judged as being less similar under naloxone. For judgments of dissimilarity, there was no analogous difference between the placebo and naloxone groups. At first sight, these finding could be interpreted as both supporting (in the case of similarity judgments) and failing to support (in the case of dissimilarity judgments) our hypothesis. However, we note an asymmetry in judging two stimuli as "similar" or "dissimilar." Take the terms "ocean" and "lake," for instance. While in many ways these two notions are similar (both are bodies of water and biotopes for fish, provide locations for holiday resorts, modulate the microclimate, etc.), they are also distinguished by other properties (e.g., salt content). Accordingly, our subjects' similarity ratings were higher than their dissimilarity judgments for the same stimulus pairs—but only in the placebo group. Under naloxone, this primacy of seeing things as similar was abolished.

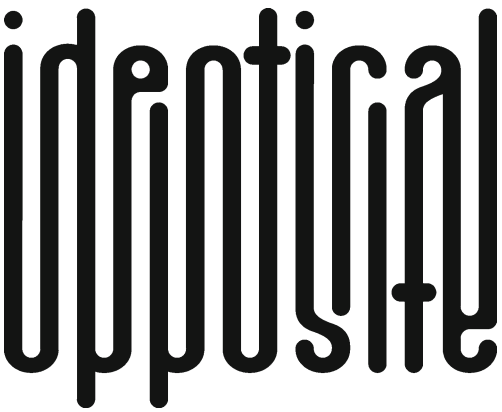

Fig. 3 "Identical/opposite" ambigram created by the American graphic designer Scott Kim in 1989. Image courtesy of the artist. © Scott Kim, scottkim.com. Reproduced with permission

Reaction latencies did not differ in the two groups. In addition, psychometrically assessed mood did not differ between the placebo and naloxone groups. Therefore, the effects of altered VAS magnitudes are unlikely to simply reflect naloxone-induced altered motor performance and/or motivation, and thus were not confounded with the operationalization of the cognitive judgments.

High similarity was perceived differently from low dissimilarity, but only in the placebo, not the naloxone group. VAS magnitudes were also more pronounced for similarity than for dissimilarity.

We thus infer that the opioid antagonist naloxone decreased the "analogy criterion" in visual cognitive–affective judgments, but only when framed in terms of similarity, not dissimilarity. This finding points to a potential modulatory effect of naloxone on judgments of cognitive relatedness and suggests that some aspects of formal cognition—that is, the readiness to judge something as similar and simultaneously as dissimilar—might be dependent on mu-opioid receptor activity.

Clearly, although we did not find psychometrically assessed mood differences between the placebo and naloxone groups, further research will need to test more directly whether the altered cognitive strategies in similarity judgments are mediated by naloxone-induced changes in the affective system (i.e., a mildly detached or dysphoric mood) or are the result of a specific, opioid-associated cognitive focusing on formal stimulus properties perceived as being related to one another. This could be done through the use of more elaborated and combined, formally complex, and affectively loaded visual stimuli, and by showing an accentuation of similarity judgments under the influence of opioidergic agonists. Most insightful would be a replication of our approach using positron-emission tomography with [(11)C]carfentanil (Zubieta et al., 2003) to measure possible cortical regional mu-opioid receptor availability in vivo. Indeed, a high density of mu-opioid receptors has been found in the brains of macaque monkeys (Lewis et al., 1981; Wise & Herkenham, 1982), and in human subjects (Quirion & Pilapil, 1991), such receptors have been found to be distributed along a gradient that increases in density along the ventral visual pathway and in association areas such as the parahippocampal cortex.

One may dare to surmise that distinct biological systems are specifically involved in the neuronal generation of coherence perception. This type of relational perception, if it is not a human equivalent of "social emotions" in animals (Herman & Panksepp, 1978; Panksepp, 2003; Panksepp et al., 1980), may arguably be at the heart of spotting similarities in the objects, minds, and intentions that surround an individual. Under this broad perspective, one further effect uncovered in the present study deserves to be mentioned: Judging two stimuli as being highly similar in the similarity judgment run was no indicator of how dissimilar those same stimuli would be perceived in the dissimilarity judgment run. That is, the perception of relatedness, or "coherence perception," is by no means a homogeneous perceptual–cognitive act. Rather, emphasis on resemblance and unity may principally differ from a focus on distinctive features of the scene or social interaction.

From a methodological point of view, classical self-report measures of affective states have cast doubt on the reliability of these measurements (e.g., Clark & Schober, 1992; Tourangeau, Rips, & Rasinki, 2000). Our novel task could provide a nonverbal, indirect, and sensitive cognitive measure for the implicit study and quantification of subtle affective–cognitive processes. It could likewise serve to characterize pain judgments and evaluative reasoning beyond the level of mere questionnaire data. To conclude, whether the glass is judged as being half-full or half-empty may depend on the rater's balancing of positive and negative affect (see Fig. 3 for an illustrative ambigram). The former tends to promote cognitive "relational processes," whereas the latter may inhibit relational processing and narrow down the focus on stimulus-specific processing (Clore & Palmer, 2008).

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