J Anesth (2011) 25:516–522
DOI 10.1007/s00540-011-1147-y

ORIGINAL ARTICLE

The effect of target-controlled infusion of low-dose ketamine on heat pain and temporal summation threshold

Joon-Ho Lee · Sung-Hwan Cho · Sang-Hyun Kim · Won-Soek Chae · Hee-Cheol Jin · Jeong-Seok Lee · Yong-Ik Kim

Received: 15 January 2011 / Accepted: 1 April 2011 / Published online: 22 April 2011
© Japanese Society of Anesthesiologists 2011

Abstract
Purpose We investigated the heat pain threshold (HPT) and temporal summation threshold (TST) before and after target-controlled infusion (TCI) of ketamine with an effect-site concentration (Ce) of 30 and 60 ng/ml.
Methods Healthy young volunteers ($n = 20$) were enrolled. A thermode was applied to the volar side of each volunteer's right forearm, and HPT and TST were measured before and after TCI of ketamine. Vital signs and psychedelic effects according to ketamine infusion were also observed before and after TCI of ketamine.
Results Mean HPT after TCI of ketamine with a Ce of 30 and 60 ng/ml did not increase significantly. However, mean TST after TCI of ketamine with a Ce of 30 and 60 ng/ml increased significantly, in a dose-dependent fashion, compared with the value before ketamine TCI. Vital signs showed no significant difference before and after ketamine TCI. The visual analog scale score of psychedelic symptoms was higher with a Ce of 60 ng/ml than with 30 ng/ml.
Conclusions TCI of ketamine with a Ce of 30 and 60 ng/ml increased TST but not HPT.

Keywords Heat pain threshold · Low-dose ketamine · Quantitative sensory testing · Temporal summation

J.-H. Lee (✉) · S.-H. Cho · S.-H. Kim · W.-S. Chae · H.-C. Jin · J.-S. Lee · Y.-I. Kim
Department of Anesthesiology and Pain Medicine, University of Soonchunhyang, Bucheon Hospital, 1174 Jung-Dong, Wonmi-Gu, Bucheon-Si, Gyeonggi-Do 420-767, Korea
e-mail: anpjuno@gmail.com

Introduction

The mechanism by which ketamine exerts its analgesic action is not clearly understood [1]. Ketamine has complex neuropharmacological characteristics and has numerous binding sites in the nervous system, such as *N*-methyl-D-aspartate (NMDA), non-NMDA glutamate, cholinergic, monoaminergic, and opioid receptors. Additionally, voltage-dependent ion channels, such as Na and L-type Ca channels, can interact with ketamine [2–4]. Although all these receptors may be related to the analgesic action of ketamine, it is likely that the analgesic effect of ketamine involves NMDA receptor antagonism [4, 5]. Such NMDA-mediated analgesic effects seem to be relevant at low, subanesthetic concentrations [5].

Low-dose ketamine produces its effect chiefly on pain related to central sensitization such as hyperalgesia or allodynia, rather than acute or phasic pain. Central sensitization may play a crucial role in the development of chronic pain and is related to the "windup" phenomenon, which is induced by repetitive stimulation of the spinal dorsal horn neuron [6, 7].

Because in vivo recordings of windup in humans are impossible, methods to assess the temporal summation of repetitive stimuli have been developed that are psychophysically associated with windup [7, 8]. Although various modalities including electric, mechanical, and thermal stimulation are available to evoke temporal summation, thermal stimulation is the most appropriate method to induce temporal summation [9–11].

Several studies have revealed that ketamine suppresses the temporal summation of repetitive stimuli, rather than a single painful stimulus [6, 11–13]. However, previous investigations have used a single injection method rather than continuous infusion [13]. When the continuous infusion method is used, more accurate strategies such as

target-controlled infusion (TCI) are not used [6, 12] and even when using TCI, the 'target' was the plasma concentration [14]. Moreover, in cases in which the thermal stimulation method was used, the thermode contact size was quite small or the stimulation time was too short to selectively stimulate the C-fiber [15]. Slow rise and return times also make it difficult to distinguish first and second pain sensations [10, 16]. Thus, a reliable method for quantitative sensory testing (QST) is needed to identify the precise effect of ketamine in various pain conditions.

Based on previous research, we believed that the continuous infusion of low-dose ketamine would reduce the temporal summation threshold (TST) of repetitive stimuli, but not of a single stimulus, such as the heat pain threshold (HPT). We compared the HPT and TST before and after TCI of ketamine with an effect-site concentration (Ce) of 30 and 60 ng/ml. Vital signs and psychedelic side effects according to the ketamine TCI were also observed.

Materials and methods

Study subjects

In total, 20 healthy volunteers (10 men and 10 women, aged 24-32 years) were enrolled. Exclusion criteria were age under 18 years, pregnancy or lactation, a history of drug abuse or psychosis, and current use of any pain medication.

This study was conducted with our Institutional Review Board Committee approval according to the Helsinki Declaration. Written informed consent was obtained from each of the volunteers. We proceeded with this research after permission for ketamine use was acquired from the Korean Food and Drug Administration.

Definition of HPT and TST

HPT was defined as the temperature at which each volunteer first reported pain, not heat, from the heat stimulus. TST was defined as the temperature at which each volunteer felt that the stimulus intensity of the last two stimuli was stronger than the first two during five successive stimuli.

Measurement of HPT

We used the staircase method to measure HPT [17, 18]. Heat stimuli were delivered by the contact heat evoked potential stimulation (CHEPS) model of the PATHWAY (Medoc, Ramat Yishai, Israel) thermode. The diameter of the thermode was 27 mm. The thermode was applied to the volar aspect of the right forearm, 2-3 cm proximal to the wrist crease. The stimulus intensity was increased in steps of 0.5°C from the baseline (36°C) until the subject reported pain for the first time. When the subject reported pain, the target temperature of the thermode was decreased by 2°C and increased in steps of 0.5°C from that temperature until the subjects reported pain again. This process was repeated twice more, and HPT was determined as the mean value of these three measurements. An interval of more than 3 min was allowed between each stimulus to allow dissipation of the residual effects of the prior stimulation [19]. The temperature was increased by 70°C/s and decreased by 40°C/s using the "Ramp and Hold" mode (Fig. 1). All volunteers and observers were blinded as to which temperature was used for stimulation.

Measurement of TST

As with HPT, TST was measured using the staircase method. The thermode was applied to the same site where HPT was measured. TST measurements started at a temperature 2°C below HPT for each subject. The stimulus intensity was increased in steps of 0.5°C until the subject reported that the stimulus intensity of the last two stimuli was stronger than the first two during five successive stimuli. When the subject reported a gradual increase in pain, the thermode target temperature was decreased by 2°C and increased in steps of 0.5°C again. This process was

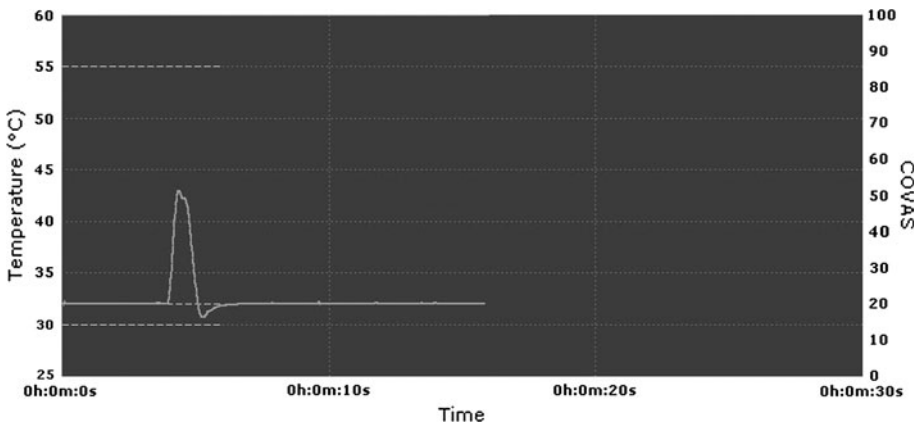

Fig. 1 Stimulation method for measurement of heat pain threshold

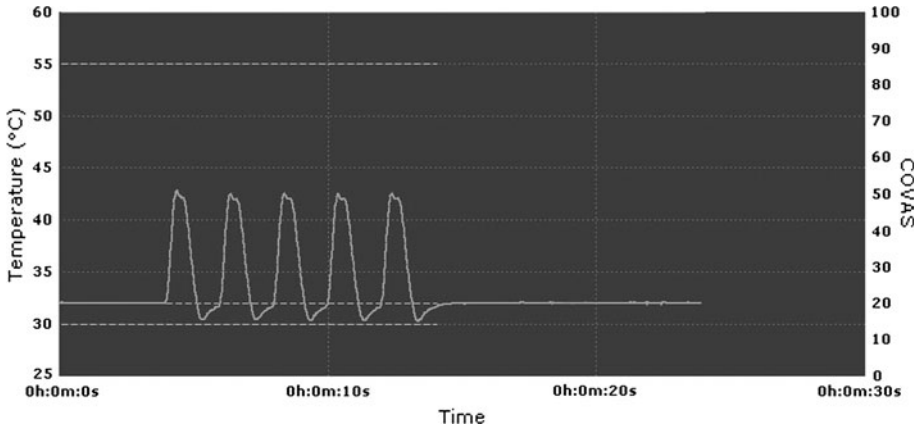

Fig. 2 Stimulation method for measurement of temporal summation threshold

repeated twice, and the mean value of the three measures was determined as the TST. The temperature was increased by 70°C/s and decreased by 40°C/s, and repetitive stimuli were applied with a duration of 0.4 s and an interstimulus interval of 2 s, using the "Ramp and Hold" mode (Fig. 2). An interval of more than 3 min was also allowed to dissipate the residual effects of prior stimulation, and all volunteers and observers were blinded as to which temperature was used for stimulation.

Ketamine administration

After a peripheral intravenous route in the left forearm was secured, a bag containing 100 ml normal saline was connected. TCI of ketamine (Ketomin; Daihan Pharm, Seoul, Korea) was performed using the Asan pump software (version 1.5; Bionet, Seoul, Korea) and a Pilot Anesthesia (Fresenius Kabi, France) infusion pump. Ketamine was delivered at a Ce of 30 and 60 ng/ml, using the pharmacokinetic model of Domino et al. [20]. All volunteers and observers were blinded as to which concentration of ketamine was administered.

Vital signs

Heart rate (HR), mean arterial pressure (MAP), percutaneous oxygen saturation (SpO_2), and tympanic membrane temperature (TMT) were checked before and after each Ce of ketamine TCI.

Assessment of psychedelic side effects

Thirteen questions (see Appendix) were asked to assess the psychedelic effects of ketamine, and each value was recorded on a visual analog scale (VAS) [21].

Study protocol

HPT, TST, vital signs, and the questionnaire were assessed before the TCI of ketamine, using the methods already described. After that, TCI of ketamine was started at a Ce of 30 ng/ml for 20 min. At the end of ketamine infusion, HPT, TST, vital signs, and the questionnaire were assessed again. Then, a Ce of 60 ng/ml of ketamine TCI was continued for 20 min and the same parameters were assessed.

Statistical analysis

All data were analyzed using the SPSS 14.0 software (SPSS, Chicago, IL, USA). HPT and TST values before and after ketamine TCI were expressed as mean and 95% confidence interval (CI). Vital signs were expressed as the mean (standard deviation), and the VAS of the psychedelic effects were expressed as medians (range). The Friedman test and a repeated-measures analysis of variance (ANOVA) were used to assess nonparametric and parametric variables, respectively. Sex differences of all parameters were compared using one-way ANOVA. P values <0.05 were deemed to indicate statistical significance.

Results

Effects of low-dose ketamine TCI on HPT

There were no significant differences in HPT before and after TCI of ketamine. The mean HPT value before ketamine TCI was 41.5°C (95% CI, 40.6-42.3). The mean HPT values after ketamine TCI with a Ce of 30 or 60 ng/ml were 41.5°C (95% CI, 40.6-42.3) and 41.6°C (95% CI, 40.7-42.4), respectively (Fig. 3).

Effects of low-dose ketamine TCI on TST

The TST after TCI of ketamine increased significantly in a dose-dependent manner ($P < 0.001$, $P < 0.001$, respectively). The mean TST value before ketamine TCI was 40.8°C (95% CI, 40.0–41.5), whereas the mean TST value after ketamine TCI with a Ce of 30 ng/ml was 43.0°C

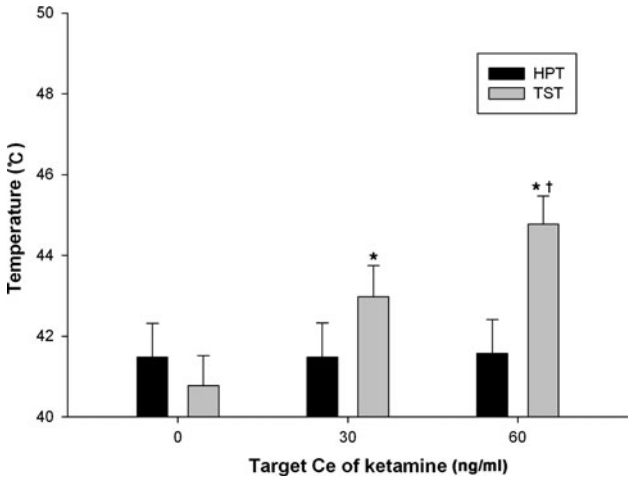

Fig. 3 Changes of heat pain threshold (*HPT*) and temporal summation threshold (*TST*) before and after ketamine target-controlled infusion (TCI). *Ce*, effect site concentration; $*P < 0.05$ compared to before ketamine TCI (Ce 0 ng/ml); $^{\dagger}P < 0.05$ compared to after ketamine Ce 30 ng/ml TCI

Table 1 Changes in mean arterial pressure, heart rate, tympanic membrane temperature, and percutaneous oxygen saturation after target-controlled infusion (TCI) of ketamine

	Before ketamine	Ce of ketamine	
		30 ng/ml	60 ng/ml
MAP (mmHg)	82.4 ± 7.1	80.9 ± 6.7	81.8 ± 6.5
HR (bpm)	70.3 ± 8.4	68.8 ± 9.7	70.4 ± 9.1
TMT (°C)	36.7 ± 0.2	36.9 ± 0.3	36.9 ± 0.4
SpO_2 (%)	98.4 ± 1.0	98.3 ± 0.9	98.1 ± 1.0

Data are expressed as mean ± SD

TCI target-controlled infusion, *Ce* effect site concentration, *MAP* mean arterial pressure, *HR* heart rate, *TMT* tympanic membrane temperature, *SpO_2* percutaneous oxygen saturation

(95% CI, 42.2–43.8), and it was 44.8°C (95% CI, 44.1–45.5) for a Ce of 60 ng/ml (Fig. 3).

Vital signs

The HR, MAP, SpO_2, and TMT showed no significant differences before and after ketamine TCI (Table 1).

Psychedelic side effects

There was no significant difference among the VAS score except for Q11 (I feel high) and Q12 (I feel drowsy). The VAS scores for each of these questions before and after TCI ketamine with a Ce of 30 or 60 ng/ml were 0 (0), 0 (0-21), and 0 (0-52), respectively, and 0 (0), 13.0 (0-77), and 24.5 (0-89), respectively. The Q11 incidence was 5% and 20% after TCI ketamine with a Ce of 30 or 60 ng/ml, respectively, and 60% and 75% after TCI ketamine with a Ce of 30 or 60 ng/ml, respectively. There were significant increases, in a dose-dependent manner, in the VAS score for each question before and after ketamine TCI ($P = 0.317$ and 0.256, $P = 0.938$ and 0.542, respectively; Table 2).

Table 2 Psychedelic effects after ketamine TCI in 100 mm visual analog scale (VAS)

Question	Before ketamine	Ce of ketamine	
		30 ng/ml	60 ng/ml
1	0 (0)	0 (0)	0 (0)
2	0 (0)	0 (0)	0 (0)
3	0 (0)	0 (0)	0 (0)
4	0 (0)	0 (0)	0 (0)
5	0 (0)	0 (0)	0 (0)
6	0 (0)	0 (0)	0 (0)
7	0 (0)	0 (0)	0 (0)
8	0 (0)	0 (0)	0 (0)
9	0 (0)	0 (0)	0 (0)
10	0 (0)	0 (0)	0 (0)
11	0 (0)	0 (0–21)*	0 (0–52)*,†
12	0 (0)	13.0 (0–77)*	24.5 (0–89)*,†
13	0 (0)	0 (0)	0 (0)

Data are median (range)

VAS visual analog scale, *TCI* target-controlled infusion, *Ce* effect site concentration

$*P < 0.05$ compared to before ketamine TCI; $^{\dagger}P < 0.05$ compared to ketamine Ce 30 ng/ml TCI

Table 3 Comparison between men and women in heat pain threshold (HPT) and temporal summation threshold (TST) before and after ketamine TCI

	Sex	Before ketamine	Ce of ketamine	
			30 ng/ml	60 ng/ml
HPT	M	41.2 ± 1.6	41.2 ± 1.6	41.3 ± 1.6
	F	41.8 ± 2.0	41.8 ± 2.1	41.9 ± 2.0
TST	M	40.5 ± 1.6	42.8 ± 1.8	44.8 ± 1.5
	F	41.1 ± 1.6	43.2 ± 1.6	44.9 ± 1.5

Data are expressed as mean ± SD

TCI target-controlled infusion, *Ce* effect site concentration, *HPT* heat pain threshold, *TST* temporal summation threshold

Sex differences in HPT and TST

HPT and TST before and after TCI of ketamine with a Ce of 30 or 60 ng/ml did not show significant differences between men and women ($P = 0.435$, $P = 0.437$ and 0.506, $P = 0.453$, $P = 0.650$ and 0.828, respectively; Table 3).

Table 4 Comparison between men and women in vital signs before and after ketamine TCI

	Sex	Before ketamine	Ce of ketamine	
			30 ng/ml	60 ng/ml
MAP (mmHg)	M	87.5 ± 5.7	84.6 ± 6.8	85.8 ± 6.0
	F	77.3 ± 4.1*	77.1 ± 4.2*	77.8 ± 3.9*
HR (bpm)	M	70.3 ± 9.5	68.8 ± 11.1	70.9 ± 10.7
	F	70.2 ± 7.6	68.7 ± 8.6	69.8 ± 7.8
TMT (°C)	M	36.7 ± 0.2	36.6 ± 0.1	36.5 ± 0.1
	F	36.6 ± 0.2	36.6 ± 0.2	36.5 ± 0.2
SpO_2 (%)	M	98.3 ± 1.0	98.2 ± 0.8	98.0 ± 1.0
	F	98.5 ± 1.0	98.4 ± 1.1	98.1 ± 1.0

Data are expressed as mean ± SD

TCI target-controlled infusion, *Ce* effect site concentration, *MAP* mean arterial pressure, *HR* heart rate, *TMT* tympanic membrane temperature, SpO_2 percutaneous oxygen saturation

*$P < 0.05$ compared with values of men

Sex differences in vital signs

No significant differences were observed for HR, TMT, and SpO_2 before and after TCI of ketamine with a Ce of 30 or 60 ng/ml ($P = 0.980$, $P = 0.982$ and 0.796, $P = 0.0.920$, $P = 0.376$ and 0.897, $P = 0.647$, $P = 0.641$ and 0.656, respectively; Table 4). However, MAP before and after TCI of ketamine was significantly higher in men during all sessions of the study ($P < 0.001$, $P = 0.008$ and 0.003, respectively; Table 4).

Discussion

When a single pain stimulus and temporal summation of repetitive stimuli were induced by the contact heat thermode, the TCI of ketamine with a Ce of 30 or 60 ng/ml for 20 min increased TST significantly, in a dose-dependent manner, but did not change the HPT. No sex differences were observed in all parameters except MAP. Among psychedelic side effects, the VAS scores of the questions 'I feel high' and 'I feel drowsy' increased significantly after TCI of ketamine, but it was not clinically significant.

The windup phenomenon is a response of the spinal dorsal horn neurons, which are amplified by repetitive C-fiber stimulation [22]. This frequency-dependent increase in neuronal excitability is induced when constant-intensity stimuli are repeated at intervals of <3 s and represents temporal summation in humans [23]. Windup (temporal summation) represents an intermediate step in the development of central sensitization, which results from derangement of cellular signaling pathways and genetic expression in postsynaptic neurons. There are several experimental investigations indicating that an NMDA receptor mechanism plays a significant role in windup and central sensitization [22, 24, 25].

Various experimental studies have demonstrated that NMDA receptor antagonists can reduce windup in animals [22, 25] and temporal summation in humans [6, 12, 13]. Ketamine is the most effective and widely used clinically available NMDA receptor inhibitor and binds to a specific site [phencyclidine (PCP) binding site] inside the receptor channel. Thus, it can bind when the channel is already activated, a so-called "open channel block." By antagonizing the NMDA receptor, ketamine effectively relieves various kinds of pain related to central sensitization including postoperative [26], fibromyalgic [27], and neuropathic pain [28–30].

It is now generally accepted that the analgesic dose of ketamine is lower than the anesthetic dose [12, 26, 28, 29]. Low-dose ketamine has a relatively high affinity for the NMDA receptor PCP-binding site, and naloxone does not reverse the antihyperalgesic effects of low-dose ketamine, but a high dose does [5, 31, 32]. Also, the antinociceptive effect of low-dose ketamine cannot be antagonized by dopamine receptor antagonists [33]. Actually, high-dose ketamine abolishes all types of pain by its anesthetic and dissociative effect and not by its NMDA receptor-antagonizing properties.

Ilkjaer et al. [12] revealed that when ketamine was administered as a 0.15 or 0.3 mg/kg bolus injection followed by continuous infusion of 0.15 and 0.3 mg/kg/h, it reduced the magnitude of both primary and secondary hyperalgesia and pain evoked by prolonged noxious heat stimulation, without significant side effects. Tucker et al. [34] showed that there was excessive sedation and abnormal responses to a psychometric test when ketamine was continuously infused above a serum concentration of 60 ng/ml. Thus, although the optimal dosage for "low-dose" ketamine has not been established, ketamine TCI with a Ce of 30 or 60 ng/ml may be regarded as a relatively safe and effective "low dose."

The therapeutic effects of ketamine may increase in a dose-dependent fashion, but side effects, such as psychedelic effects, limit its clinical use [6, 35], even at a low dose. Thus, it is important to find an adequate dosage for ketamine infusion therapy that can effectively relieve pain without significant side effects. The ketamine Ce of 30 and 60 ng/ml used in this study were lower than the low dose of previous investigations [6, 14], but psychedelic effects still increased significantly after ketamine TCI. Nevertheless, none of the volunteers considered these effects unpleasant or discomforting, so they were not clinically significant.

Quantification of pain in humans is important when applying animal experimental research to clinical use. Among the various modalities, thermal stimulation is one

of the most commonly used experimental pain procedures. Electrical stimuli contain strong shocking and pricking sensations associated with A-beta and A-delta fiber input [36], and mechanical stimuli reflect an unknown mixture of A-delta and C-fiber input [11]. Contact heat stimulation is an ideal pain stimulation method; it has fast onset and offset, it is a quantifiable stimulation parameter, and it resembles a natural pain modality [9]. Because the thermode used in the present study had a 70°C/s rise and 40°C/s fall speed with a relatively large contact diameter (27 mm), it had advantages over previous studies [12, 14, 37] for inducing the temporal summation of pain. Thus, robust windup can be obtained and is clearly associated with C-fiber input.

There are some limitations to this study. First, the volunteers were all young healthy adults, making it difficult to generalize our results to patients of various ages. Second, the test area was restricted to a single region. Third, we did not measure the baseline skin temperature. However, the baseline temperature of the thermode was constant and there was enough time for the temperature between the skin and the thermode to be equalized. Finally, the sample size may have been too small to detect the effects of our ketamine regimen. However, determining an adequate sample size was difficult because of the exploratory nature of this study. Finally, the assessment of side effects focused only on the psychedelic effects.

Compared with previous investigations, we confirmed that the TCI of low-dose ketamine reduced temporal summation of repetitive stimuli, but not a single stimulus, in a dose-dependent manner. When administered at a Ce of 30 ng/ml, ketamine increased TST without significant side effects. TST increased further with a Ce of 60 ng/ml, but resulted in more psychedelic side effects, which were statistically significant, but clinically acceptable. There were no differences in any of the parameters between men and women except MAP. A well-controlled randomized trial is needed to identify the actual therapeutic effects of low-dose ketamine therapy in patients.

Conflict of interest None.

Appendix: Questionnaire for psychedelic effects of ketamine

Q1. My body or body parts seemed to change their shape or position (BODY).
Q2. My surroundings seemed to change in size, depth, or shape (SURROUNDINGS).
Q3. The passing of time was altered (TIME).
Q4. I had feelings of unreality (REALITY).
Q5. It was difficult to control my thoughts (THOUGHTS).
Q6. The intensity of colors changed (COLORS).
Q7. The intensity of sound changed (SOUND).
Q8. I heard voices or sounds that were not real (VOICES).
Q9. I had the idea that events, objects, or other people had particular meaning that was specific for me (MEANING).
Q10. I had suspicious ideas or the belief that others were against me (SUSPICIOUS).
Q11. I felt high (HIGH).
Q12. I felt drowsy (DROWSY).
Q13. I felt anxious (ANXIOUS).

References

1. Meller ST. Ketamine: relief from chronic pain through actions at the NMDA receptor? Pain. 1996;68:435–6.
2. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg. 1998;87:1186–93.
3. Pekoe GM, Smith DJ. The involvement of opiate and monoaminergic neuronal systems in the analgesic effects of ketamine. Pain. 1982;12:57–73.
4. Hustveit O, Maurset A, Oye I. Interaction of the chiral forms of ketamine with opioid, phencyclidine, sigma and muscarinic receptors. Pharmacol Toxicol. 1995;77:355–9.
5. Eide PK, Stubhaug A, Breivik H, Oye I. Ketamine: relief from chronic pain through actions at the NMDA receptor? Reply. Pain. 1997;72:289–91.
6. Arendt-Nielsen L, Petersen-Felix S, Fischer M, Bak P, Bjerring P, Zbinden AM. The effect of *N*-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo-controlled experimental human study. Anesth Analg. 1995;81:63–8.
7. Eide PK. Wind-up and the NMDA receptor complex from a clinical perspective. Eur J Pain. 2000;4:5–15.
8. Ren K. Wind-up and the NMDA receptor: from animal studies to humans. Pain. 1994;59:157–8.
9. Gracely R. Studies of pain in human subjects. In: McMahon SB, Koltzenburg M, editors. Wall and Melzack's textbook of pain. 5th edn. Edinburgh: Churchill Livingstone; 2006. p. 267–84.
10. Granot M, Granovsky Y, Sprecher E, Nir RR, Yarnitsky D. Contact heat-evoked temporal summation: tonic versus repetitive-phasic stimulation. Pain. 2006;122:295–305.
11. Staud R, Price DD, Fillingim RB. Advanced continuous-contact heat pulse design for efficient temporal summation of second pain (windup). J Pain. 2006;7:575–82.
12. Ilkjaer S, Petersen KL, Brennum J, Wernberg M, Dahl JB. Effect of systemic *N*-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans. Br J Anaesth. 1996;76:829–34.
13. Guirimand F, Dupont X, Brasseur L, Chauvin M, Bouhassira D. The effects of ketamine on the temporal summation (wind-up) of the R(III) nociceptive flexion reflex and pain in humans. Anesth Analg. 2000;90:408–14.
14. Arendt-Nielsen L, Nielsen J, Petersen-Felix S, Schnider TW, Zbinden AM. Effect of racemic mixture and the (S+)-isomer of

ketamine on temporal and spatial summation of pain. Br J Anaesth. 1996;77:625–31.
15. Granovsky Y, Granot M, Nir RR, Yarnitsky D. Objective correlate of subjective pain perception by contact heat-evoked potentials. J Pain. 2008;9:53–63.
16. Arendt-Nielsen L, Chen AC. Lasers and other thermal stimulators for activation of skin nociceptors in humans. Neurophysiol Clin. 2003;33:259–68.
17. Willer JC. Comparative study of perceived pain and nociceptive flexion reflex in man. Pain. 1977;3:69–80.
18. Lautenbacher S, Kunz M, Strate P, Nielsen J, Arendt-Nielsen L. Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. Pain. 2005;115:410–8.
19. Slugg RM, Meyer RA, Campbell JN. Response of cutaneous A- and C-fiber nociceptors in the monkey to controlled-force stimuli. J Neurophysiol. 2000;83:2179–91.
20. Domino EF, Domino SE, Smith RE, Domino LE, Goulet JR, Domino KE, Zsigmond EK. Ketamine kinetics in unmedicated and diazepam-premedicated subjects. Clin Pharmacol Ther. 1984;36:645–53.
21. Bowdle TA, Radant AD, Cowley DS, Kharasch ED, Strassman RJ, Roy-Byrne PP. Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. Anesthesiology. 1998;88:82–8.
22. Dickenson AH, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C fibre stimulation. Neuropharmacology. 1987;26:1235–8.
23. Price DD, Hu JW, Dubner R, Gracely RH. Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. Pain. 1977;3:57–68.
24. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on *N*-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain. 1991;44:293–9.
25. Davies SN, Lodge D. Evidence for involvement of *N*-methylaspartate receptors in 'wind-up' of class 2 neurones in the dorsal horn of the rat. Brain Res. 1987;424:402–6.
26. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain. 1999;82:111–25.
27. Graven-Nielsen T, Aspegren Kendall S, Henriksson KG, Bengtsson M, Sorensen J, Johnson A, Gerdle B, Arendt-Nielsen L. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. Pain. 2000;85:483–91.
28. Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. Pain Med. 2004;5:263–75.
29. Goldberg ME, Domsky R, Scaringe D, Hirsh R, Dotson J, Sharaf I, Torjman MC, Schwartzman RJ. Multi-day low dose ketamine infusion for the treatment of complex regional pain syndrome. Pain Physician. 2005;8:175–9.
30. Webster LR, Walker MJ. Safety and efficacy of prolonged outpatient ketamine infusions for neuropathic pain. Am J Ther. 2006;13:300–5.
31. Gilron I, Quirion R, Coderre TJ. Pre- versus postformalin effects of ketamine or large-dose alfentanil in the rat: discordance between pain behavior and spinal Fos-like immunoreactivity. Anesth Analg. 1999;89:128–35.
32. Maurset A, Skoglund LA, Hustveit O, Oye I. Comparison of ketamine and pethidine in experimental and postoperative pain. Pain. 1989;36:37–41.
33. Parsons CG, Gibbens H, Magnago TS, Headley PM. At which 'sigma' site are the spinal actions of ketamine mediated? Neurosci Lett. 1988;85:322–8.
34. Tucker AP, Kim YI, Nadeson R, Goodchild CS. Investigation of the potentiation of the analgesic effects of fentanyl by ketamine in humans: a double-blinded, randomised, placebo controlled, crossover study of experimental pain. BMC Anesthesiol. 2005;5:2–13.
35. Cvrcek P. Side effects of ketamine in the long-term treatment of neuropathic pain. Pain Med. 2008;9:253–7.
36. McAllister RM, Urban LA, Dray A, Smith PJ. Comparison of the sensory threshold in healthy human volunteers with the sensory nerve response of the rat in vitro hindlimb skin and saphenous nerve preparation on cutaneous electrical stimulation. J Hand Surg Br. 1995;20:437–43.
37. Mauderli AP, Vierck CJ Jr, Cannon RL, Rodrigues A, Shen C. Relationships between skin temperature and temporal summation of heat and cold pain. J Neurophysiol. 2003;90:100–9.