Anesthesiology 2002; 96:357–66

Cognitive Impairment after Small-dose Ketamine Isomers in Comparison to Equianalgesic Racemic Ketamine in Human Volunteers

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Background: **Ketamine is increasingly used in pain therapy but may impair brain functions. Mood and cognitive capacities were compared after equianalgesic small-dose *S*(+)-, *R*(−)-, and racemic ketamine in healthy volunteers.**

Methods: **Twenty-four subjects received intravenous 0.5 mg/kg racemic, 0.25 mg/kg *S*(+)-, and 1.0 mg/kg *R*(−)-ketamine in a prospective, randomized, double-blind, crossover study. Hemodynamic variables, mood, and cognitive capacities were assessed for 60 min.**

Results: **Transient increases in blood pressure, heart rate, and catecholamines were similar after administration of all drugs. At 20 min after injection, subjects felt less decline in concentration and were more brave after *S*(+)- than racemic ketamine. They reported being less lethargic but more out-of-control after *R*(−)- than racemic ketamine. Ketamine isomers induced less drowsiness, less lethargy, and less impairment in clustered subjective cognitive capacity than racemic ketamine for the 60-min study. Objective concentration capacity [test time, *S*(+): 25.4 ± 15.2 s, *R*(−): 34.8 ± 18.4 s, racemic ketamine: 40.8 ± 20.8 s, mean ± SD] and retention in primary memory [test time, *S*(+): 4.6 ± 1.2 s, *R*(−): 4.2 ± 1.4 s, racemic ketamine: 4.0 ± 1.4 s, mean ± SD] declined less after *S*(+)- than either *R*(−)- or racemic ketamine at 1 min. At 5 min, immediate recall, anterograde amnesia, retention in primary memory, short-term storage capacity, and intelligence quotient were less reduced after the isomers than racemic ketamine. Speed reading and central information flow decreased less after *S*(+)- than racemic ketamine.**

Conclusions: **Early after injection, ketamine isomers induce less tiredness and cognitive impairment than equianalgesic small-dose racemic ketamine. In addition, *S*(+)-ketamine causes less decline in concentration capacity and primary memory. The differences in drug effects cannot be explained by stereoselective action on one given receptor.**

BASED on advanced knowledge of nociceptive physiology and clinical pain, the number of patients who receive subanesthetic small-dose ketamine for pain therapy in perioperative care,[1,2] day-case surgery,[3] emergency procedures,[4] and chronic pain managment[5] appears to have increased. To minimize the time necessary for monitored care, supervision, and resultant hospital costs, the recovery of cognitive capacities within these settings should be as quick as possible. However, use of analgesic-dose racemic ketamine is associated with dose-related decline in mood, conscious perception, and intellectual performance.[6–8]

Volunteer and investigational trials have shown that the analgesic potency of *S*(+)-ketamine, the left-handed optical isomer of racemic ketamine, is approximately two times higher than that of racemic and four times higher than that of *R*(−)-ketamine.[9–13] In acute orofacial pain, intramuscular injection of 0.45 mg/kg *S*(+)-ketamine reduced postoperative pain as effectively as 0.9 mg/kg racemic or 1.8 mg/kg *R*(−)-ketamine.[11] In chronic orofacial pain, subanesthetic-dose *S*(+)-ketamine was at least as efficient as the racemic mixture at half the dose.[11] Using a target controlled infusion regimen, temporal and spatial pain summation was equally reduced at plasma concentrations of 180 ng/ml *S*(+)-ketamine or 350 ng/ml racemic ketamine.[12] Furthermore, when racemic:*S*(+)-:*R*(-)-ketamine were used in a 1:0.5:2 dose ratio for anesthesia in surgical patients,[13] the incidence of postoperative pain was smaller after *S*(+)-ketamine.

Because *S*(+)-ketamine has been approved for clinical use in some countries, we evaluated the effects of equianalgesic small-dose racemic ketamine in comparison to *S*(+)- and *R*(−)-ketamine in a prospective crossover study to provide comparative data for the drugs' impact on mood and intellectual capacities in human volunteers.

Materials and Methods

Study Population

Twenty-four healthy young adults (American Society of Anesthesiologists physical status I; 7 women, 17 men; age, 25 ± 3 yr; height, 178 ± 9 cm; weight, 70 ± 12 kg) served as paid volunteers. After Human Subjects Committee approval (Ulm University, Ulm, Germany) was obtained, all participants granted written, informed consent. They were free to withdraw at any time. Exclusion criteria included known idiosyncrasies, allergy to ketamine, pregnancy, substance abuse, or use of any medication except oral contraceptives within 2 weeks before the study. Volunteers with a history of emotional difficulty, psychiatric illness, or dementia in first-degree relatives were excluded.

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Received from the Universitätsklinik für Anästhesiologie, Klinikum der Universität Ulm, Ulm, Germany; the Department of Anesthesiology and Pain Medicine, University Hospital Maastricht, Maastricht, The Netherlands; and the Klinik für Anaesthesiologie, Klinikum rechts der Isar, Technische Universität München, Munich, Germany. Submitted for publication September 13, 2000. Accepted for publication August 8, 2001. Supported in part by Parke-Davis Pharmaceuticals, Freiburg, Germany.

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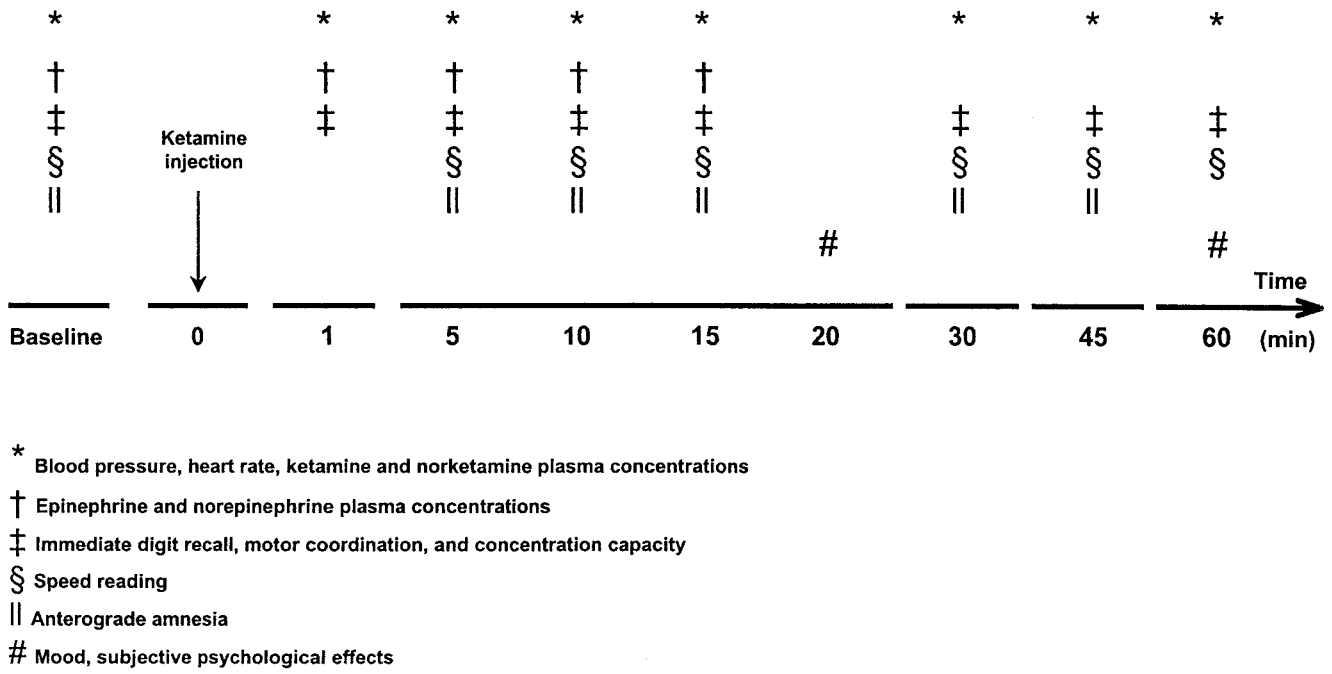

Fig. 1. Timeline listing schedule of study measurements and tests.

To minimize confounding factors by lack of experience and to achieve a ceiling effect by learning from repetition,[6] participants were exposed to three preliminary test series.

Study Protocol

All subjects completed a three-session, randomized, double-blind, crossover protocol comparing racemic ketamine, *S*(+)-ketamine, and *R*(−)-ketamine. To ensure drug clearance from the body to avoid carryover effects, sessions were spaced by 1-week intervals. The night before the study, volunteers were instructed to fast after midnight. On the study day, participants were placed in a quiet room of the departmental step-down unit. They were monitored with a three-lead electrocardiograph, a peripheral pulse oximeter, and an automated blood pressure device. In the presence of an anesthetist who monitored subjects' well-being, a catheter was inserted in the nondominant arm to administer intravenous fluid and drugs, and another catheter was placed into the contralateral elbow to collect blood samples. Once all devices had been instituted, a 20-min resting period was provided. Predrug baseline readings were then obtained. Ketamine was administered intravenously over 30 s. To control for diurnal variations, subjects received each study drug at the same time of day. The volunteers, the anesthetist, and the persons providing the tests were blinded to the respective drug applied. Extraordinary events were noted. Subsequent to complete recovery, but not earlier than 6 h after tests, subjects were considered ready for discharge when they had attained alertness, normal vital signs, and motor function. Figure 1 shows the study timeline and measurements.

Study Drugs

Ketamine was administered intravenously at 0.5 mg/kg racemic ketamine, 0.25 mg/kg *S*(+)-ketamine, and 1 mg/kg *R*(−)-ketamine. This regimen was based on doses used in analgesic therapy and the potency relation of ketamine isomers.[1–5,9–12] Equianalgesic efficacy of the 1:0.5:2 dose ratio of racemic:*S*(+)-:*R*(−)-ketamine used was confirmed by measuring pain tolerance thresholds in pilot studies (data not shown). Ampoules containing the drugs at equivolumetric amounts (chemical and optical purities > 98.5%) were provided by Parke-Davis Pharmaceuticals (Freiburg, Germany).

Study Measurements

Analysis of (Nor-)Ketamine and (Nor-)Epinephrine Concentrations. Venous plasma concentrations of (nor-)ketamine and (nor-)epinephrine concentrations were measured by high-performance liquid chromatography with ultraviolett[14] or electrochemical detection,[15] as described.

Assessment of Mood and Clustered Psychological Effects. Before and 20 min after drug injection, participants' mood was assessed using visual analog scales.[16,17] At the end of each study at 60 min, subjects were asked about feelings they recalled retrospectively for the study session. The sets of adjectives presented were as follows: afraid–brave, tense–relaxed, agitated–calm, happy–sad, lethargic–quick-witted, alert–drowsy, well–poorly

concentrated, detached–moved, depressed–euphoric, peaceful–aggressive, small–big, interoceptive emptiness–eventfulness, lucky–unlucky, threatened–superior, out-of-control–inhibited, teared down–high floating. The differences between baseline and 20-min scores and between baseline and 60-min scores were calculated. The 16 items were additionally categorized into four clinically derived functional clusters consisting of mood, affect–emotion, cognitive capacity, and ego perception.[16,17] Changes between evaluation time points were calculated by analyzing differences in clustered scores (see Appendix for details).

Memory Tests.

Immediate Digit Recall. To assess short-term memory, a subtest of the German Hamburg-Wechsler Intelligence Scale for Adults was used (similar to Digit Span used in the United States).[18,19] Three unrelated digits were read to subjects with a rate of 1 s per number. Immediately after presentation, subjects were asked to repeat the digit series in the order given. If performed correctly, a new sequence was generated by increasing the digit number by one digit up to a final of nine digits. The last series recalled with digits in their proper position was scored using an eight-point scale (0 = no recall, 7 = correct recall of nine digits).

Anterograde Amnesia. To assess the ability to form new memory, subjects were shown 1 of 10 memory cards with simple line sketches of a symbol, a letter, or a number at each evaluation point.[20] A different card was presented for 5 s at baseline and 5, 10, 15, 30, and 45 min after drug injection in random order. At 60 min, subjects were asked to recall spontaneously the figures shown. The number of correctly recalled sketches was counted for each subject.

Psychometric Evaluation.

Motor Coordination. Psychomotor coordination was studied using a test of the procedure of Newman *et al.*[21] (Appendix).

Concentration Capacity. Participants were asked to count the appearance of a target symbol out of groups of symbols as quickly as possible.[22] The time required for the task was scored (see Appendix).

Central Information Processing Assessment. Based on analytical principles that apply in information psychology, several variables of central information processing were studied.

Speed Reading. The time required for reading 20 independent characters presented in random order was noted.[23,24] Central Information Flow,[23–26] Retention Time in Primary Memory,[23,24,26] Short-term Storage Capacity,[23,24,26] and Intelligence Quotient[23,25–27] were calculated as reported previously (Appendix).

Side Effects. After completion of each session and 24 h after the tests, subjects were asked for adverse events, including nausea, dizziness, and unusual sensations. The occurrence and quality of "dreams," hallucinations (altered consciousness states), and other phenomenon was noted.

Personal Assessment of Ketamine Examined. After completion of each session, subjects and examiners noted their personal assessment of which of the three drugs they thought had been examined in the respective study session.

Statistical Analysis

Where appropriate, data are reported as mean ± SD after verification of normal distribution with the Kolmogorov-Smirnov test. For statistical analysis, the Friedman test was used for comparison between all three drugs. In case of significance, the Wilcoxon signed rank *post hoc* test with Bonferroni correction was applied to further analyze differences between two drugs. The anterograde amnesia data are reported as counts. They were evaluated by contingency table analysis over all three agents, followed by chi-square test between two drugs. P values (two-tailed) < 0.05 were considered significant. The software programs Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) and StatView 4.5 (Abacus Concepts, Berkeley, CA) were used for the analysis.

Results

Blood pressure and heart rate increases were comparable within 1 min after injection of all drugs (fig. 2A), confirming hemodynamic stimulation after ketamine.[10,14] The dose ratio of 1:0.5:2 of racemic ketamine:*S*(+)-ketamine:*R*(−)-ketamine was mirrored in parallel increases and decreases in ketamine and (nor)-ketamine plasma concentrations (fig. 2B). All drugs induced a similar, small transient increase in norepinephrine and epinephrine plasma concentrations, with peaks at 5 min followed by a gradual decline over the course of time (fig. 2C).

Mood, Subjective Psychic Items, and Functional Clusters

The most prominent changes in mood and individual psychic items are shown in table 1. Subjects who received the *S*(+)-isomer rated their concentration to be less impaired ($P = 0.024$) and felt more brave ($P = 0.046$) than after racemic ketamine at 20 min. They indicated they were less lethargic ($P = 0.014$) but more out-of-control ($P = 0.046$) after *R*(-)- than racemic ketamine. Subjects rated themselves as less drowsy after *R*(−)- ($P = 0.002$) or *S*(+)-ketamine ($P = 0.044$) and as less lethargic after *R*(−)- ($P = 0.010$) or *S*(+)-ketamine ($P = 0.042$) than racemic ketamine after 60 min. Whereas cluster analysis for mood, affect–emotion, and ego perception (data not shown) revealed no difference between drugs, clustered cognitive capacities were less

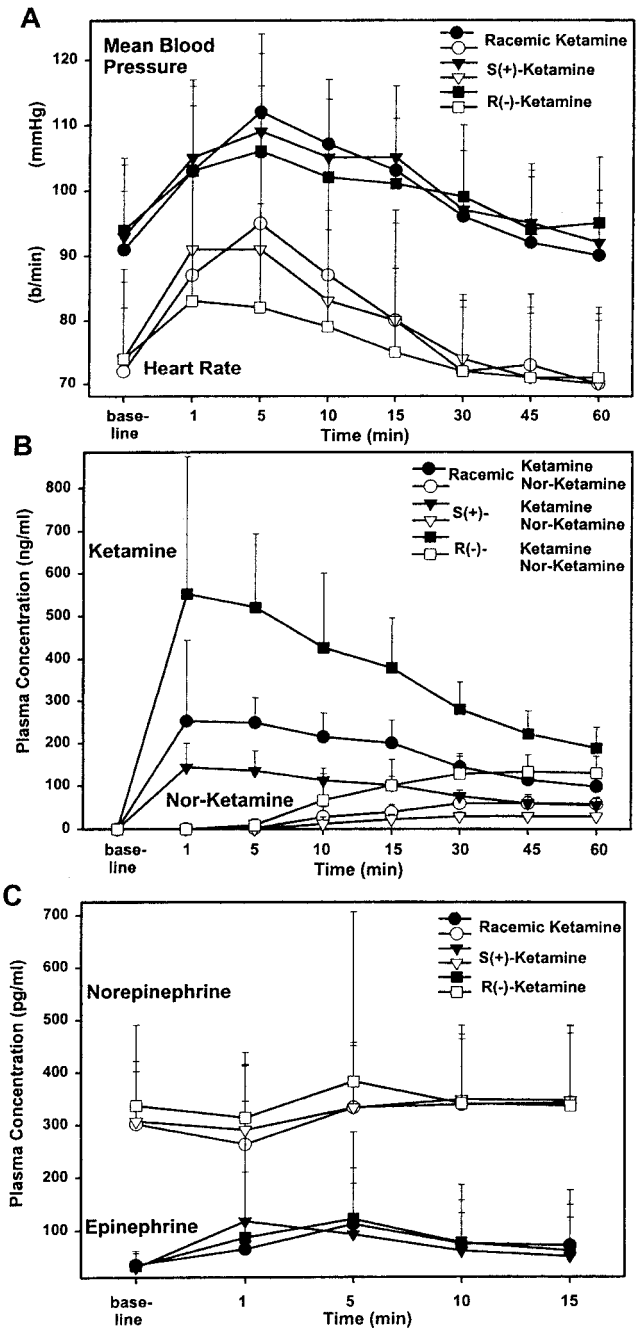

Fig. 2. (*A*) Courses of mean blood pressure (BP) and heart rate (HR) were similar after administration of all drugs with transient increases in BP and HR within 1 min after injection. (*B*) Venous ketamine and (nor)-ketamine plasma concentrations mirrored the drug dose ratio applied. (*C*) Changes in venous epinephrine and norepinephrine plasma concentrations were comparable after all drugs. Symbols denote the mean ± SD.

limited after *R*(−)- ($P = 0.040$) or *S*(+)-ketamine ($P = 0.042$) than racemic ketamine after 60 min (fig. 3).

Memory

Immediate digit recall was impaired until 10 min after drug injection (fig. 4). The most marked, 50% decrease occurred at 1 min after administration of racemic ketamine. After administration of *S*(+)- ($P = 0.010$) or *R*(−)-ketamine ($P = 0.020$), digit recall was less limited than after racemic ketamine at 1 min. Anterograde amnesia was less pronounced after *S*(+)- ($P = 0.009$) or *R*(−)-ketamine ($P = 0.028$) than after racemic ketamine at 5 min after injection (fig. 5).

Psychometric Performance

Performance in Trieger test deteriorated after administration of all three drugs, with markedly poor values at 1 and 5 min after ketamine injection (fig. 6A). Test scores returned to predrug levels within 30 min. The changes caused by *R*(−)-ketamine almost paralleled those induced by *S*(+)-ketamine. Concentration capacity analysis showed an early, transient ketamine-related decrease and then a return to predrug values within 30 min (fig. 6B). Concentration capacity declined less after *S*(+)-ketamine than either racemic ($P = 0.010$) or *R*(−)-ketamine ($P = 0.022$) at 1 min after drug injection.

Central Information Processing

All drugs induced a rapid decrease in information processing that was most prominent at 1 and 5 min after injection (table 2). This was followed by a gradual return to predrug levels, which were reached after approximately 30 min. Speed reading was markedly reduced at 5 min. The 100% increase in reading time after racemic ketamine was higher than the 50% increase after the *S*(+)-isomer at 5 min ($P < 0.001$). Central information flow declined to a smaller extent after *S*(+)- (30%; $P = 0.018$) than racemic ketamine (40%) at 5 min. Retention in primary memory was less impaired after *S*(+)-ketamine than either racemic ($P = 0.040$) or *R*(−)-ketamine ($P = 0.044$) at 1-min study time. At 5 min, retention in primary memory showed a greater decrease after racemic than *S*(+)- ($P = 0.010$) or *R*(−)-ketamine ($P = 0.022$). Short-term storage capacity was more limited after racemic than *S*(+)- ($P = 0.003$) or *R*(−)-ketamine ($P = 0.008$) at 5 min. Figure 6C illustrates the marked decrease in intelligence quotients early after drug injection. *S*(+)- ($P = 0.002$) or *R*(−)-ketamine ($P = 0.006$) induced a smaller reduction in the intelligence quotient than racemic ketamine at 5-min study time.

Side Effects

Six subjects indicated "dreams" after *R*(-)- and racemic ketamine, and five after *S*(+)-ketamine. There was no difference in dream quality between drugs. For the test and 6 h after the study observation period, two female subjects reported feelings of helplessness with death threats after *R*(-)-ketamine; they wanted to withdraw from further study. One female had a "bad nightmare" after racemic ketamine; she experienced that session as a very undesirable event. Mild sensory illusions occurred comparably after all drugs during the 60-min study period. In the 24-h follow-up interview, approximately half

Table 1. Mood and Psychic Items Scores after Equianalgesic Small-dose Ketamine

	Time			
	At 20 min		Overall After 60 min	
Poor–good concentration				
Racemic ketamine	−32.1 ± 31.8		−31.0 ± 27.0	
S(+)-ketamine	−11.7 ± 30.9*	*P* = 0.024	−19.7 ± 28.7	
R(−)-ketamine	−22.0 ± 25.2		−13.4 ± 27.2	
Afraid–brave				
Racemic ketamine	0.0 ± 18.9		−7.0 ± 20.1	
S(+)-ketamine	3.8 ± 11.2*	*P* = 0.046	−1.5 ± 16.4	
R(−)-ketamine	1.9 ± 15.7		2.6 ± 15.2	
Drowsy–alert				
Racemic ketamine	−30.5 ± 31.7		−36.6 ± 28.8	
S(+)-ketamine	−21.1 ± 30.7		−17.3 ± 33.7*	*P* = 0.044
R(−)-ketamine	−19.1 ± 35.9		−8.9 ± 29.8†	*P* = 0.002
Lethargic–quick-witted				
Racemic ketamine	−15.0 ± 26.3		−16.0 ± 22.3	
S(+)-ketamine	−5.8 ± 21.3		−5.2 ± 15.8*	*P* = 0.042
R(−)-ketamine	2.0 ± 17.9†	*P* = 0.014	0.1 ± 10.4†	*P* = 0.010
Out-of-control–inhibited				
Racemic ketamine	−2.5 ± 10.4		−5.8 ± 13.4	
S(+)-ketamine	−4.9 ± 11.4		−0.6 ± 19.9	
R(−)-ketamine	−9.6 ± 21.0†	*P* = 0.046	−8.9 ± 18.5	
Threatened–superior				
Racemic ketamine	−5.4 ± 20.1		−5.5 ± 17.1	
S(+)-ketamine	2.0 ± 11.5		0.5 ± 11.7	
R(−)-ketamine	0.6 ± 18.6		−0.9 ± 17.5	
Depressed–euphoric				
Racemic ketamine	−3.0 ± 19.1		−1.4 ± 15.6	
S(+)-ketamine	1.2 ± 11.5		3.1 ± 10.3	
R(−)-ketamine	3.6 ± 17.9		2.5 ± 19.4	
Interoceptive emptiness–eventfulness				
Racemic ketamine	−6.5 ± 33.3		−1.9 ± 27.5	
S(+)-ketamine	2.7 ± 19.6		2.5 ± 20.4	
R(−)-ketamine	4.4 ± 20.8		1.0 ± 22.9	
Tense–relaxed				
Racemic ketamine	7.1 ± 26.0		−4.3 ± 24.1	
S(+)-ketamine	14.2 ± 31.8		4.7 ± 25.6	
R(−)-ketamine	13.6 ± 22.9		6.1 ± 25.9	
Detached–moved				
Racemic ketamine	−3.2 ± 26.0		−9.2 ± 23.8	
S(+)-ketamine	−8.4 ± 23.5		−4.4 ± 23.1	
R(−)-ketamine	−0.2 ± 19.5		1.3 ± 19.3	

Data are mean ± SD.

* indicates significant difference between racemic ketamine and *S*(+)-ketamine; † between racemic ketamine and *R*(−)-ketamine.

of all subjects stated unusual dreams following the night after the study. No recurrent or residual events were reported.

Assessment of Study Drugs

Neither subjects nor investigators were able to discriminate between drugs. The best result with 49% correct guess was observed for *S*(+)-ketamine based on the investigators' opinions (data not shown).

Discussion

Our study is the first to disclose divergent effects of nonequimolar, equianalgesic small-dose *S*(+)-ketamine, *R*(−)-ketamine, and racemic ketamine on mood and intellectual functions in volunteers: early after intravenous injection, subjects felt less tiredness and less intellectual decline after ketamine isomers than racemic ketamine, and for a few minutes, subjects who received *S*(+)-ketamine also showed less impairment in concentration capacity and primary memory. Although several mechanisms may account for these effects, to the best of our knowledge, there is no direct explanation for the different responses to the drugs.

Our data extend early work on human pharmacology of racemic ketamine and its isomers.[8,13] After equianesthetic doses of the three drugs, patients treated with *S*(+)-ketamine felt less disorientation, fear, and pain in the postoperative period and showed a more general sense of well-being and happiness.[13] In volunteers, White *et al.*[8] found more rapid recovery of psychomotor skills after high-dose ketamine isomers than racemic ket-

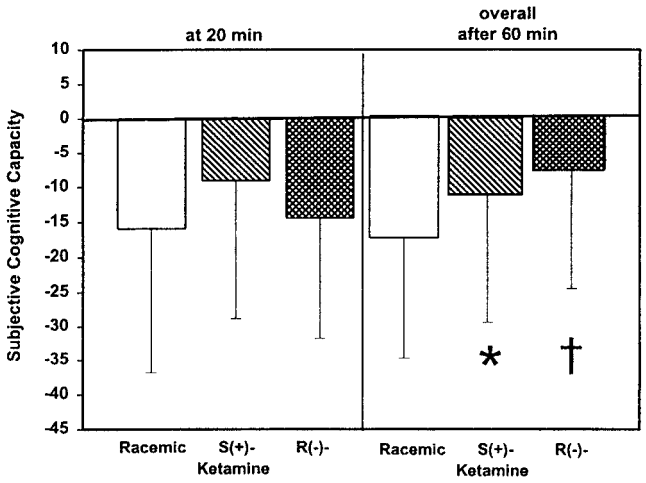

Fig. 3. Analysis of change of clustered rating scores for subjective cognitive capacity revealed less decline after *R*(−)- (*P* = 0.040) or *S*(+)-ketamine (*P* = 0.042) than after racemic ketamine for the overall period at 60 min. Bars show the mean ± SD. *Significant difference between racemic ketamine and *S*(+)-ketamine. †Significant diffference between racemic ketamine and *R*(−)-ketamine.

amine, and Arendt-Nielsen *et al.*[12] reported shorter reaction times after equianalgesic dose *S*(+)- than racemic ketamine at plasma concentrations of 180 or 350 ng/ml, respectively.

There is no universally accepted analysis of cognitive decline. A spectrum of psychological tests to screen drug effects was therefore selected. Although our paradigm was compiled of relatively simple, paper–pencil measures with moderate sensitivity to discriminate between cognitive domains,[28] reliability and validity of the tests used has been shown in studies of drug-related psychic events[6,7,13,29] and neurocognitive decline.[8,13,18–22,26–29]

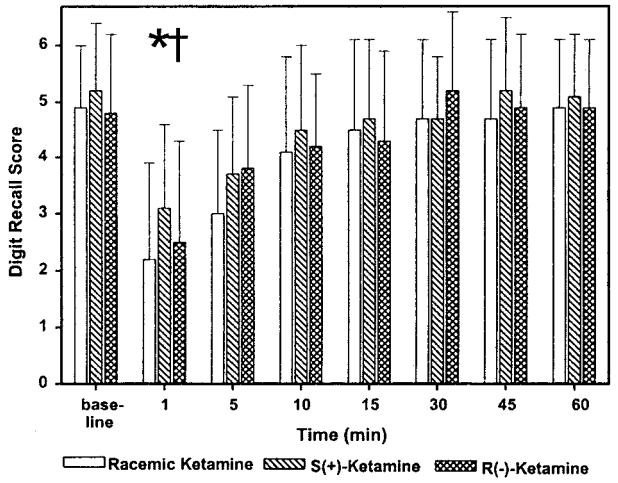

Fig. 4. Evaluation of scores obtained for immediate digit recall showed that *S*(+)- (*P* = 0.010) or *R*(−)-ketamine (*P* = 0.020) induced less impairment in digit recall than racemic ketamine at 1 min after drug injection. Bars report the mean ± SD. *Significant difference between racemic ketamine and *S*(+)-ketamine. †Significant difference between racemic ketamine and *R*(−)-ketamine.

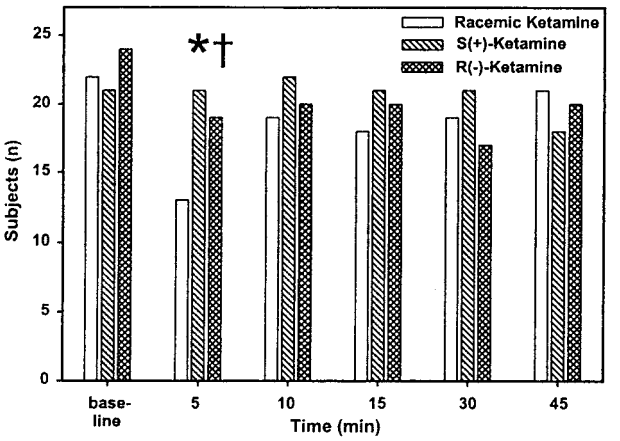

Fig. 5. Investigation of the ability to form new memories showed that anterograde amnesia was less pronounced after *S*(+)- (*P* = 0.009) or *R*(−)-ketamine (*P* = 0.028) than after racemic ketamine at 5 min after drug injection. Bars represent n = number of subjects per drug who correctly recalled the memory cards presented during the study at 60 min after drug injection. *Significant difference between racemic ketamine and *S*(+)-ketamine. †Significant difference between racemic ketamine and *R*(−)-ketamine.

Analysis of information processing and psychological intelligence may be considered as "rule of thumb" estimates, but they are used to assess context-related behavioral performance[18,22–27,30–32] based on neuroanatomy and neurotransmitter disposition.

Fitting a two-compartment open model,[10,14] ketamine distribution and plasma elimination shows an α half-life of approximately 10 min and a β phase of 1–2 h after intravenous use. We therefore studied a 60-min time period after one drug injection, where humans experience a maximum of brain effects.[33] For data interpretation, it should be kept in mind that the differences we observed may relate to specific differences in drug potencies, pharmacokinetic profiles, pharmacodynamic characteristics, or a combination of these mechanisms.

Our choice of dose regimen was guided by analgesic plasma concentrations of racemic ketamine, which range within 100–200 ng/ml.[1–5,10] There is no way to know that the doses studied are equipotent for nonanalgesic effects of ketamine. Inhibition of excitatory *N*-methyl-D-aspartate (NMDA) glutamate receptors is believed to be the predominant mode of action of small-dose ketamine, which has been related to substantial blockade of NMDA receptor–mediated synaptic transmission[9–11,33–35] and dysfunctions of linked pathways.[10,34,36]

In brain glucose positron emission tomography, different psychological and metabolic effects after *S*(+)- *versus* equimolar *R*(−)-ketamine at average drug plasma values of 385 ng/ml in volunteers have been found.[29] While *S*(+)-ketamine altered self-perception and increased glucose metabolism in several brain areas, *R*(−)-ketamine caused some state of relaxation and reduced glucose metabolism in different areas. Because the change observed after *S*(+)-ketamine was similar to that

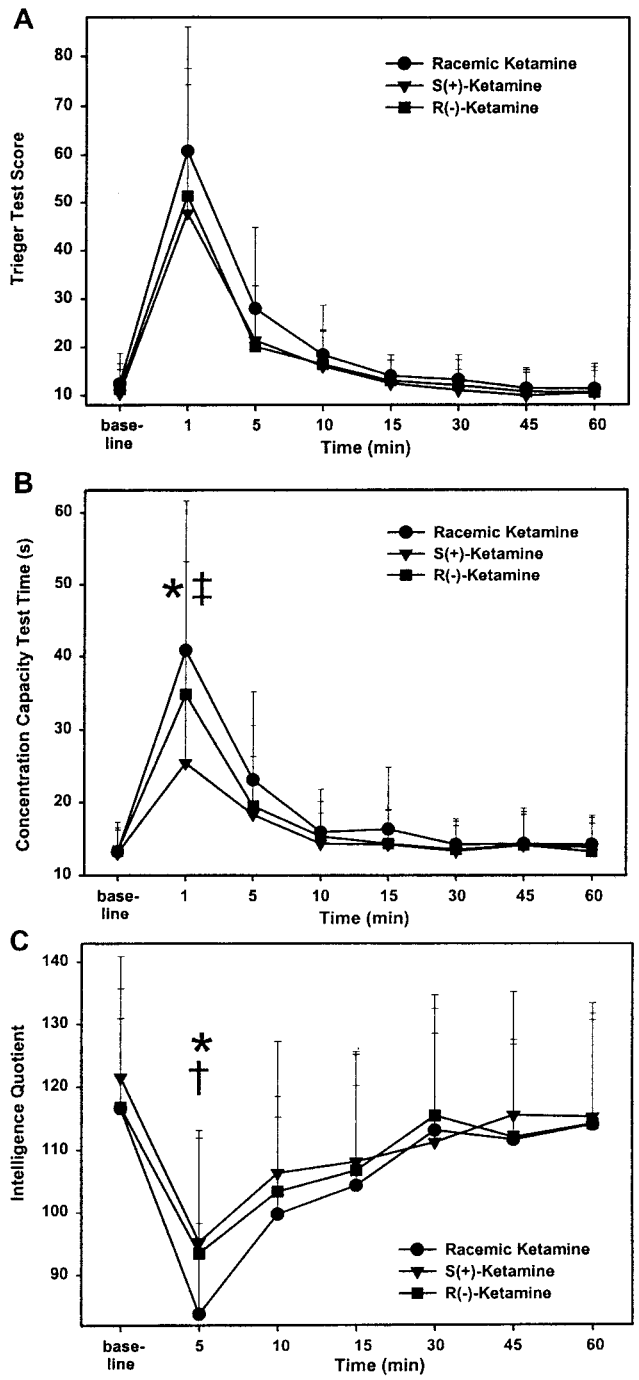

Fig. 6. (*A*) Performance in Trieger test deteriorated after all three drugs, with almost parallel changes seen after the ketamine isomers. (*B*) Evaluation of concentration capacity test scores demonstrated that *S*(+)-ketamine induced less decrease in test performance than either racemic ($P = 0.010$) or *R*(−)-ketamine ($P = 0.022$) at 1 min after drug injection. (*C*) Analysis of intelligence quotients (IQ) indicated less decline in the IQ after *S*(+)- ($P = 0.002$) or *R*(−)-ketamine ($P = 0.006$) than racemic ketamine at 5 min after drug injection. Symbols represent the mean ± SD. *Significant difference between racemic ketamine and *S*(+)-ketamine. ‡Significant difference between *R*(−)-ketamine and *S*(+)-ketamine. †Significant difference between racemic ketamine and *R*(−)-ketamine.

after a 40% higher dose of racemic ketamine in a companion study, *S*(+)-ketamine was believed to be responsible for the central effects of racemic ketamine.[37] In another positron emission tomography study,[33] psychological changes induced by *S*(+)-ketamine (0.2 mg/kg) went along with increased drug binding in brain areas with high NMDA receptor density, such as the thalamus, nucleus caudatus, and temporofrontal cortex. Because these regions contribute to conscious behavior and perception, NMDA receptor blockade was judged to underlie the effects found. However, the disparity of responses in our direct comparison of racemic ketamine and its isomers makes pure NMDA receptor–mediated ketamine effects unlikely. Racemic ketamine is a mixture of half *S*(+)- and half *R*(−)-ketamine. *S*(+)-ketamine has a fourfold higher affinity for the phencyclidine site in the NMDA receptor than *R*(−)-ketamine,[9–11,13] which is believed to relate to the two-times higher analgesic potency of the *S*(+)-isomer than the racemic compound.[8–13] Because we tested *S*(+)-ketamine at half the dose of racemic ketamine, our data suggest that the *R*(−)-isomer in racemic ketamine interacts with the *S*(+)-isomer. This effect interaction of the isomers in the racemic mixture appears to be nonlinear in nature. Racemic ketamine may have effects that are not confined to stereoselective NMDA receptor antagonism.

Supporting this hypothesis, *R*(−)-ketamine elicited changes in attention that were similar to that of *S*(+)-ketamine. However, other than after *S*(+)-ketamine, subjects reported to be more "out-of-control" after *R*(−)-ketamine, and, compared with racemic ketamine, they felt more brave after *S*(+)-ketamine. This could relate either to directly different effects of the isomers, to different influences on transmitters linked to glutamatergic pathways, or to combined mechanisms. In favor for the first explanatory approach, *R*(−)-ketamine showed higher σ opioid receptor binding than *S*(+)-ketamine, which has been related to dysphoric feelings such as disinhibition.[34] In favor for the second approach, human positron emission tomography studies found that psychologic effects of low-dose racemic ketamine are paralleled by overall striatal dopaminergic activation,[38] whereas heightened mood after *S*(+)-ketamine was related to increased dopamine concentrations in the ventral striatum and in the caudate nucleus.[39] These effects of *S*(+)-ketamine were further shown to be suppressible by the serotonin 2–dopamine 2–1 antagonist sertindole[40] and are consistent with mobilization and turnover of limbic dopamine storage pools.[41] Because limbic structures and cortico-striato-thalamic feedback have overlapping input with the accumbens dopamine system,[31] increased neurotransmitter concentrations may have contributed to the feelings observed after administration of *S*(+)-ketamine.

Early after injection, the isomers caused less intellectual decline than the racemic compound. Racemic ket-

Table 2. Central Information Processing after Equianalgesic Small-dose Ketamine

		Time (min)						
	Baseline	1	5	10	15	30	45	60
Speed reading of characters (s)								
Racemic ketamine	5.6 ± 0.7	—	11.9 ± 7.6	7.3 ± 1.3	6.8 ± 1.1	6.0 ± 1.0	6.0 ± 0.9	6.1 ± 1.1
S(+)-ketamine	5.5 ± 1.1	—	8.7 ± 4.7*	6.8 ± 1.8	6.6 ± 1.3	6.0 ± 1.0	6.2 ± 1.5	6.0 ± 1.0
R(−)-ketamine	5.6 ± 0.7	—	9.0 ± 5.0	6.7 ± 1.1	6.4 ± 1.0	6.1 ± 1.0	6.1 ± 0.9	6.0 ± 1.2
Central information flow (bit/s)								
Racemic ketamine	18.1 ± 2.2	—	10.9 ± 4.5	14.2 ± 2.5	14.8 ± 2.3	17.1 ± 2.9	16.9 ± 2.3	17.0 ± 2.8
S(+)-ketamine	18.7 ± 3.6	—	13.6 ± 4.6*	15.6 ± 4.1	15.8 ± 2.9	17.0 ± 2.9	16.8 ± 3.2	17.1 ± 2.8
R(−)-ketamine	18.2 ± 2.5	—	12.8 ± 3.7	15.4 ± 2.5	16.0 ± 2.5	16.9 ± 2.9	16.8 ± 2.4	17.4 ± 3.7
Retention in primary memory (s)								
Racemic ketamine	6.1 ± 1.1	4.0 ± 1.4	4.7 ± 1.1	5.6 ± 1.5	5.9 ± 1.3	6.0 ± 1.3	5.9 ± 1.2	6.1 ± 1.1
S(+)-ketamine	6.3 ± 1.1	4.6 ± 1.2*	5.1 ± 1.1*	5.8 ± 1.3	5.9 ± 1.2	5.8 ± 1.0	6.3 ± 1.2	6.3 ± 1.1
R(−)-ketamine	6.0 ± 1.3	4.2 ± 1.4‡	5.2 ± 1.3†	5.6 ± 1.1	5.7 ± 1.3	6.3 ± 1.3	6.1 ± 1.1	6.0 ± 1.1
Short-term storage capacity (bit)								
Racemic ketamine	110.0 ± 25.6	—	51.4 ± 25.7	79.9 ± 27.6	88.0 ± 28.4	103.7 ± 34.7	101.0 ± 28.4	105.3 ± 29.9
S(+)-ketamine	118.7 ± 34.6	—	71.9 ± 31.9*	91.6 ± 37.3	94.7 ± 31.2	100.2 ± 30.9	107.9 ± 35.2	107.6 ± 29.5
R(−)-ketamine	110.3 ± 33.8	—	68.6 ± 33.1†	86.3 ± 27.2	92.3 ± 32.8	107.9 ± 34.6	101.8 ± 26.3	105.3 ± 34.4

Data are the mean ± SD.

* indicates significant difference between racemic ketamine and *S*(+)-ketamine; † indicates significant difference between racemic ketamine and *R*(−)-ketamine; and ‡ indicates significant difference between *R*(−)-ketamine and *S*(+)-ketamine.

amine–induced impairment in frontal lobe–sensitive tests and decline in explicit memory are well known, but in previous studies, this was mostly related to pure NMDA receptor antagonism.[6,9,28,29,32,33,35,42] Recent work on conscious behavior showed close relations between human working memory and executive functions,[31] which is supported by the smaller deficit we found in the intelligence quotient after the isomers compared with racemic ketamine. However, although glutamatergic systems exert potent regulatory control over secondary changes in the dopamine system,[31,32,36] and dopamine dysregulation contributes to intellectual decline,[38,39] our data, as discussed, caution against straightforward interpretation of ketamine drug effect to one discrete localization of NMDA receptor blockade. However, within the nucleus accumbens, the ventral hippocampus has been found to provide a gating influence over information flow from the prefrontal cortex.[43] Different blockade of hippocampal NMDA receptors at these gating mechanisms will be followed by altered corticoaccumbens glutamatergic input and different modulation by dopamine, resulting in different intellectual responses.[30,31,36] Furthermore, working memory deficits were reported to be reversed by dopamine receptor stimulation after increasing dopamine concentrations.[44] At the earliest study time points, the smallest decline in concentration and memory after administration of *S*(+)-ketamine thus appears to involve, at least in part, *S*(+)-ketamine–mediated influences on the dopaminergic system.

The intensity and timing of the differences found was temporally graded. Drug concentration *versus* time profile–mediated action is thus likely. Ketamine tissue distribution was reported not to be stereoselective in dogs.[45] Because the drug plasma profiles measured mirrored the dose ratios used, our data are not suggestive for stereoselective drug tissue distribution.

We are well aware that, despite the many tests examined, there were only a few differences at early study time. Some limitations of our work should therefore be considered. Because this study was designed as a first evaluation of potential differences between small-dose racemic ketamine and its isomers, only one single drug injection was examined. However, in clinical pain therapy, repeated use or continuous ketamine infusion may be necessary to reach the targeted pain reduction. This may result in longer-lasting drug plasma concentrations with more pronounced differences in cognitive effects. Because nobody knew whether there would be differences between the ketamine isomers at all, and where those differences would emerge, we performed extensive descriptive tests. Future study should thus concentrate on the disparity in cognitive decline revealed here, using tools appropriate in the clinical setting of pain therapy at higher analgesic dose. This can prove whether the differences we report are truly clinically significant.

The authors thank Christine Baier, M.D., and Sven O. Muspach, M.D. (Universitätsklinik für Anästhesiologie, Klinikum der Universität Ulm, Ulm, Germany), for help with performing the experiments; Siegfried Lehrl, M.D. (formerly at the Department of Medical Psychology and Psychopathometry, University of Erlangen-Nuremberg, Erlangen, Germany), for advice on psychological testing; and Prof. Dr. Kurt Ulm, Ph.D. (Institute for Medical Statistics and Epidemiology, Technische Universität München, Munich, Germany), for help with statistical analysis.

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Appendix: Description of Study Measurements and Methods

Assessment of Mood and Clustered Psychological Effects

Before and 20 min after drug injection, subjects rated their current mood on a paper–pencil questionnaire that contained 16 visual analog scales derived from the multidimensional Freiburg Personality Inventory[16] and the self-report assessment of the German Association for Methodology and Documentation in Psychiatry.[17] At the end of each session, subjects were asked about feelings they recalled retrospectively for the study period. Each of the 16 visual analog scales was represented by a 100-mm long line, the ends of which were marked by "+50" and "−50" points that indicated adjectives representing the extremes of the dimension being rated. Subjects had to mark each line at the distance that best indicated how they felt at the time. Sets of adjectives were presented as follows: afraid–brave, tense–relaxed, agitated–calm, happy–sad, lethargic–quick-witted, alert–drowsy, well–poorly concentrated, detached–moved, depressed–euphoric, peaceful–aggressive, small–big, interoceptive emptiness–eventfulness, lucky–unlucky, threatened–superior, out-of-control–inhibited, teared down–high floating. To reduce bias in responses, adjectives associated with "positive" emotions were sometimes presented on the right and sometimes on the left side of the lines.

To assess within-subject changes after drug administration, numerical differences between the individual baseline and the 20-min scores, and baseline scores and scores indicating the feelings for the study were calculated for the 16 individual items. In addition, all items were categorized into four clinically derived functional clusters to assess integrated processes of psychological changes[16,17]: mood = happy–sad, depressed–euphoric, lucky–unlucky, interoceptive emptiness–eventfulness, teared down–high floating; affect–emotion = afraid–brave, tense–relaxed, small–big, threatened–superior; cognitive capacity = lethargic–quick-witted, alert–drowsy, well–poorly concentrated; and ego perception = tense–relaxed, detached–moved, peaceful–aggressive, out-of-control–inhibited. The composite change between baseline and 20-min scores, and baseline scores and the scores for the 60-min period were calculated by summing across the clustered averaged differences of the 16 scores.

Psychometric Evaluation

Motor Coordination. Psychomotor coordination was studied using the procedure described by Newman *et al.*[21] Subjects were asked to exactly connect a series of dots to complete the outlining of a simple geometric form. The sum of the errors (distances from missed target dots and extraneous deviation lines) were scored (maximum, 80 mm).

Concentration Capacity. The time required for correct identification of a preselected symbol chosen out of three different symbols presented on a sheet of paper was recorded.[22] Participants were asked to count the appearance of the target symbol out of groups of symbols arranged in rows as quickly as possible; the maximum interval allowed was a 60-s period. If the count was not correct, scores were calculated as the difference between the counted and the correct number of the target added to the time recorded.

Central Information Processing Assessment

Speed Reading. To assess the time required for reading a series of independent characters, 20 characters in random order were presented.[23,24] Subjects were asked to read the 20 characters with a modestly loud voice as quickly as possible, and the examiner noted the time between the first and last sound of reading (T_{20}).

Central Information Flow. According to information psychology, reading of characters can be used as a measure of cognitive central information flow.[23–26] As shown previously, the time for recognition and loud reading of 1 character in a series of 20 random characters can be transformed into a bit representation of information, 1 character capturing 5 bits. This allows for calculation of central information flow as follows:

$$\mathrm{CIF(bit/s)} = 20 \times 5/T_{20}.$$

Retention Time in Primary Memory. Information psychology allows to determine the retention time in primary memory. Briefly, the score obtained for immediate digit recall (DR) is incorporated in the following relation[23,24,26] after nonlinear correction according to Lehrl and Fischer[23]:

$$\mathrm{TPM(s)} = (T_{20} + DR_{corrected})/2.$$

Short-term Storage Capacity. Short-term storage capacity is calculated as the product of central information flow and retention time in primary memory[23,24,26]:

$$\mathrm{STSC(bit)} = \mathrm{CIF} \times \mathrm{TPM}.$$

Intelligence Quotient. Concepts of intelligence related to information psychology have shown a reliable and sensitive correlation between central information flow, retention time in primary memory, and traditional estimates of intelligence, such as in the Hamburg-Wechsler Intelligence Scale for Adults.[23,25–27] For practical means, the intelligence quotient can be rapidly assessed using the following equation[23,24]:

$$\mathrm{IQ} = 0.56 \times \mathrm{STSC} + 55.$$