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The neurocognitive effects of 5 day anesthetic ketamine for the treatment of refractory complex regional pain syndrome

Sandra P. Koffler[a,*], Benjamin M. Hampstead[b,c], Farzin Irani[d], Jennifer Tinker[d], Ralph-Thomas Kiefer[e], Peter Rohr[f], Robert J. Schwartzman[g]

[a] *Department of Psychiatry, College of Medicine, Drexel University, Philadelphia, PA 19102, USA*
[b] *VA Rehabilitation R&D Center of Excellence for Aging Veterans with Vision Loss, Atlanta VA Medical Center, Decatur, GA 30033, USA*
[c] *Department of Rehabilitation Medicine, Emory University, Atlanta, GA 30322, USA*
[d] *Department of Psychology, Drexel University, Philadelphia, PA 19104, USA*
[e] *Department of Anesthesiology and Intensive Care Medicine, Eberhard-Karls University, Tuebingen, Germany*
[f] *Department of Anesthesiology, Intensive Care and Emergency Medicine, and Pain Therapy, Klinikum-Saarbruecken, Germany*
[g] *Department of Neurology, College of Medicine, Drexel University, Philadelphia, PA 19102, USA*

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Abstract

BACKGROUND: Complex regional pain syndrome I (CRPS) is characterized by severe neuropathic pain that exceeds the severity of an injury and is refractory to traditional treatments. Recent experimental interventions include ketamine infusion therapy.
OBJECTIVE: We sought to evaluate the physical, neurocognitive, and emotional effects of extended treatment with anesthetic doses of ketamine in refractory CRPS I patients.
METHODS: Nine patients (eight females) received a neuropsychological evaluation pre- and 6 weeks post-treatment that evaluated intellectual and academic abilities, executive functioning/processing speed, attention, learning and memory, and motor functioning. Mood/affect and personality were also evaluated and patients completed an extensive pain questionnaire.
RESULTS: There was a marked reduction in the report of both acute and overall pain after treatment. Brief attention and processing speed improved significantly post-treatment, whereas all other cognitive domains remained stable, with the exception of a mild decline in motor strength.
CONCLUSIONS: Findings suggest that, at least at a 6-week follow up: (1) deep ketamine therapy is effective for relief of pain CRPS I and (2) there were no adverse cognitive effects of extended treatment with deep ketamine infusion. No definitive conclusions could be drawn about the relationship between mood and personality factors and the presence of CRPS I.

Keywords: RSD; Complex regional pain syndrome; Neuropsychology; Memory; Pain; Ketamine; Ketamine infusion therapy

1. Introduction

While pain is necessary for survival, the effects of chronic pain can significantly impair functioning across many aspects of daily life. Complex regional pain syndrome (CRPS) is associated with a severe neuropathic pain out of

* Corresponding author at: Drexel University College of Medicine, Department of Psychiatry, 245 North 15th Street, Mail Stop 341, Philadelphia, PA 19107, USA. Tel.: +1 215 762 4956; fax: +1 215 762 1537.
E-mail address: Sandra.Koffler@drexelmed.edu (S.P. Koffler).

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proportion to the extent of the causal injury. Characteristics of the pain include: ordinarily non-painful stimuli evoke pain (allodynia) and this can be caused by light touch or pressure (mechanoallodynia) or changes in skin temperature (thermal allodynia), extreme sensitivity to pain (hyperalgesia), and the tendency for innocuous stimuli to become painful if exposure is repeated or prolonged (hyperpathia; Schwartzman, Alexander, & Grothusen, 2006). It is associated in varying degrees with neurogenic edema, autonomic dysregulation, movement disorder, and atrophic and dystrophic changes of the affected parts (Janig & Baron, 2003; Schwartzman & Popescu, 2002). The pain most often follows injury to soft tissue, plexi, nerve roots or directly to the peripheral nerve and frequently spreads to the contralateral side of the body in a mirror distribution, possibly encompassing the entire body (Maleki, LeBel, Bennett, & Schwartzman, 2000). Criteria for diagnosis of CRPS were derived in a special consensus conference of the International Association for the Study of Pain (IASP) (Wilson, 2004) and are as follows: (1) preceding noxious event without (CRPS I) or with obvious nerve lesion (CRPS II), (2) spontaneous pain or hyperalgesia/hyperesthesia not limited to a single nerve territory and disproportionate to the inciting event, (3) edema, skin blood flow (temperature) or pseudomotor abnormalities, motor symptoms or trophic changes are present on the affected limb, in particular at distal sites, (4) other diagnoses are excluded.

The current study focuses on the CRPS I variant which was formerly known as reflex sympathetic dystrophy (RSD). CRPS I is a relatively rare condition that more commonly affects women than men and occurs more often in the upper extremities compared to the lower ones (Sandroni, Benrud-Larson, McClelland, & Low, 2003). Factors that predispose one to CRPS I have been suggested but remain controversial. Potential physical causes include a specific additional trauma caused by reduction of a displaced fracture, inadequate anesthesia during fracture reduction, poor pain relief during rehabilitation, pressure and swelling due to a tight plaster cast, and long-term administration of antiepileptic and anti-tuberculosis drugs [for a review see Zyluk, 2004]. Recent clinical and experimental evidence point to a significant role of the central nervous system in the pathophysiology and symptomatology of CRPS, with CNS lesions being causative in approximately 10% of patients (Harden & Bruehl, 2005; Janig & Baron, 2003). It has also been suggested that a variety of physiological and immune processes may be the underlying mechanisms for the initial development and maintenance of peripheral and central sensitization (Watkins & Maier, 2005; Woolf & Salter, 2000).

Although controversial, psychological factors have also been proposed to be primary to the development of CRPS; however, there are limited data to support this relationship (Zyluk, 2004). For example, patients with CPRS-I demonstrated a psychological profile, as measured through clinical interview and the Minnesota Multiphasic Personality Inventory, that was highly similar to a group of patients diagnosed with conversion disorder (Shiri, Tsenter, Livai, Schwartz, & Vatine, 2003). However, prospective studies of patients undergoing total knee arthoplasty (Harden et al., 2003) or surgery for distal radial fracture (Puchalski & Zyluk, 2005), have failed to consistently demonstrate a relationship between pre-operative emotional distress and the development of CRPS following surgery. Such results are consistent with De Good and colleagues' finding that patients with CRPS expressed less emotional distress than patients with other forms of chronic pain (De Good, Cundiff, Adams, & Shutty, 1993). Thus, there appears to be little prospective evidence to support the relationship between premorbid psychological distress (e.g. anxiety, depression) and the development of CRPS 1.

Treatment for CRPS I can be pathophysiologically oriented (steroids, sympathetic blocks, radical scavengers), symptomatically oriented (antidepressants, antiepileptics, opioids), or non-drug based (physical therapy, transcutaneous electrical nerve stimulation) [for a review see Birklein, 2005]. Because these treatments tend to have only modest therapeutic benefits, novel therapeutic interventions, such as ketamine infusion therapy, have recently been attempted in this patient population. Ketamine is a non-barbituate anesthetic that is recognized for its dissociative, analgesic, and psychedelic properties (Hirota & Lambert, 1996). It has been described as an "ideal" anesthetic agent due to its rapid onset, absence of cardiorespiratory depressant effects, and benign effect on muscle tone and protective airway reflexes (Ceber & Salihoglu, 2006). Aside from its use in chronic pain, there is a growing body of research that is examining the utility of ketamine in patients with treatment-refractory depression (Zarate et al., 2006).

There is clinical and experimental evidence for the importance of the *N*-methyl-D-aspartate (NMDA) receptor in many neuropathic pain conditions, including CRPS (Correll, Maleki, Gracely, Muir, & Harbut, 2004; Jorum, Warncke, & Stubhaug, 2003; Sheng & Kim, 2002; Ushida et al., 2002). Ketamine has potent NMDA receptor-blocking properties and was first used successfully to treat an adult female who had had CRPS I for 9 years (Harbut & Correll, 2002). This treatment was administered as an inpatient subanesthetic (i.e., low-dose) infusion while maintaining consciousness in the patient. Following this infusion, the patient obtained complete relief of her lower extremity CRPS and remained pain free for 18 months. A few more CRPS I patients have been successfully treated (Kiefer, Rohr, Ploppa, Unertl, &

Schwartzman, 2003) and ketamine utilized in anesthetic doses over a 5 day period has shown some promise in patients who have failed conventional treatments (Kiefer et al., 2002). However, there has been little research performed on the effectiveness of ketamine treatment at a group level, especially when using anesthetic doses of the drug.

The neurocognitive effects of deep ketamine infusion have yet to be studied in CRPS-I patients. Ketamine adversely affects NMDA receptor signaling and, at acute subanesthetic doses, can produce deficits in attention, memory, and executive function in healthy control subjects (Anand et al., 2000; Krystal et al., 1998, 1999, 2005; Parwani et al., 2006). The reported memory deficits may be the result of disrupted encoding, as the performance of healthy volunteers was worse when ketamine was administered while they encoded information than while they were retrieving previously learned material (Honey et al., 2005). Such deficits may be the result of ketamine blocking NMDA receptors and consequently impeding long-term potentiation, which is hypothesized to be the physiological mechanism underlying learning and memory (Cotman & Monaghan, 1988). Ketamine's effects on executive functioning are likely due to its effects on dopaminergic receptors as D1 receptors within the dorsolateral prefrontal cortex were significantly up-regulated (indicating dopamine depletion) in a group of chronic recreational ketamine users (Narendran et al., 2005). The extent of the up-regulation was positively correlated with the amount of ketamine used per week. Similarly, acute administration of ketamine resulted in increased activity in several areas of the frontal lobes and associated subcortical structures while healthy volunteers performed a test of verbal fluency (Fu et al., 2005). Thus ketamine can have both immediate and prolonged neurocognitive effects.

The current study sought to investigate the clinical effectiveness of deep ketamine anesthesia (3–7 mg/(kg h)) for the treatment of pain in patients with refractory CRPS I and to evaluate its neurocognitive consequences in view of the previous findings of cognitive impairment following both immediate and prolonged use. We also included measures of mood and personality at baseline and following treatment in order to assess the degree of change, if any, in emotional symptomatology.

2. Materials and methods

2.1. Subjects

A total of nine patients were identified as meeting inclusion and exclusion criteria. Their pain ratings on a Likert scale varied during the day between 8 and 10 (endpoints: 0 no pain; 10 worst pain imaginable). All had generalized hyperalgesia, dynamic and static mechano and thermal allodynia, neurogenic edema, and autonomic dysregulation. All suffered some component of the movement disorder of CRPS (inability to initiate and maintain movement 9/9; weakness, exaggeration of physiologic tremor, myoclonic jerks 3/9; difficulty walking 4/9). Seven of nine patients were totally disabled while the other two were severely functionally impaired, all from a physical standpoint. All had great difficulty with their usual activities of daily living and social functioning. Medications prior to anesthetic ketamine treatment included: (1) non-steroidal anti-inflammatory medications; (2) antidepressants; (3) high potency opioids; and (4) anticonvulsants. One patient was utilizing a morphine pump. Patient demographics and premorbid estimates of intelligence are listed in Table 1.

Inclusion criteria included meeting IASP diagnostic and modified research criteria for CRPS I. Additionally, pain intensity had to reach an intensity of at least 6–8 on a Likert numeric rating scale for at least 6 months (endpoints—0: no pain, 10: worst pain imaginable). Failure of conventional therapy was defined as: (1) less than 30% (3 points) patient rated pain relief on the numeric scale; (2) pain relief of less than 2 months. Refractory CRPS was defined by failure of: (1) mono or poly therapy with non-steroidal anti-inflammatory drugs, tricyclic or selective serotonin uptake inhibitors antidepressants, anticonvulsants and low or high potency opioids; and (2) various combinations of at least three failed invasive procedures that included intravenous regional blocks, selective nerve root blocks, brachial plexus blocks, sympathetic ganglion blocks, surgical sympathectomy, spinal cord stimulation, or intrathecal drug delivery systems that did not achieve at least a 30% pain reduction for more than 2 months. All patients had to meet the physical and mental standards as defined by the American Society of Anesthesiology Physical Status Classification (ASA) classes II–III, and had to be free of a significant history of cardiovascular, pulmonary, or other systemic disease.

Exclusion criteria were: (1) allergies to ketamine, midazolam and clonidine; (2) a history of substance or drug abuse; (3) known psychiatric disease other than depression or anxiety; and (4) somatoform pain disorder. Subjects were included in the study following examination by a neurologist (RJS) and two anesthesiologists (RTK, PR) on two separate occasions.

Table 1
Patient demographics and premorbid estimates of intelligence

Patient	Gender	Age	Education (years)	Months since injury	WAIS-III (percentiles)		WRAT – 3 (percentiles)		
					Information	Vocabulary	Reading	Spelling	Arithmetic
1	F	20	12	48	37	63	70	66	34
2	F	44	16	54	75	75	42	45	25
3	F	19	13	75	84	75	50	30	14
4	M	21	15	84	95	99	63	42	27
5	F	41	16	20	37	91	66	75	27
6	F	30	20	18	84	98	79	75	77
7	F	36	18	48	50	37	84	63	68
8	F	22	14	78	75	91	77	39	61
9	F	29	13	76	37	75	63	70	66
Average	F = 8, M = 1	29.1 (9.43)	15.22 (2.59)	55.67 (24.75)	63.78 (23.41)	78.22 (19.72)	66 (13.6)	56.11 (17.14)	44.33 (23.39)

2.2. Procedures

All patients were from the United States and were identified by the treating neurologist (RJS) and, because the Institutional Review Boards of the University Hospital of Tuebingen and the Teaching Hospital University of the Saarland in Saarbrucken, Germany approved the study, all patients received the ketamine infusion in Germany. All patients signed informed consent. The protocol for the use of anesthetic ketamine for refractory CRPS was developed from the experience of TK and PR in their use of ketamine for intensive care procedures as well as the use of this protocol in a refractory CRPS patient who was treated on a compassionate care basis. All patients had reached a Ramsay Score 4–5 depth of anesthesia and had ketamine levels of 250–300 ug/dl for at least 4.5 days. This level of treatment results in a medically induced coma.

Prior to receiving the deep ketamine treatment, all patients underwent a clinical interview performed by a board certified neuropsychologist (SK), followed by a brief neuropsychological protocol that was administered by a doctoral level technician. All patients returned for follow-up interview and testing approximately 6 weeks after completion of treatment. All neuropsychological evaluations were performed in the United States.

2.3. Measures

The following psychological and neuropsychological measures were used to assess pain, cognitive, emotional, and personality functioning—*Pain*: McGill Pain Questionnaire; *Intellectual Functions and Academic Skills* (*Baseline only*): Information and Vocabulary Subtests from the Wechsler Adult Intelligence Scale-III (WAIS-III), Wide Range Achievement Test-3; *Executive Functions/Processing Speed*: Digit Symbol Coding Subtest from the WAIS-III, Controlled Oral Word Association Test; *Attention*: Digit Span Subtest from the WAIS-III, Connors' Continuous Performance Test (CPT); *Memory*: Story I or II of the logical memory subtest from the Wechsler Memory Scale-III, Hopkins Verbal Learning Test; *Motor Functions*: Finger Tapping, Grip Strength; *Mood/Affect*: Beck Depression Inventory-II (BDI-II), State Trait Anxiety Inventory; *Personality*: Minnesota Multiphasic Personality Inventory-2 (MMPI-2). Alternate versions of HVLT and COWAT were used and the patients were read either story 1 or story 2 of the WMS-III LM at each time point, all of which were counterbalanced between subjects.

2.4. Data organization and analysis

When possible, scores were transformed to *z*-score equivalents and an average *z*-score was calculated for each domain, thus yielding a single score for each domain at each time point so as to minimize the number of comparisons performed. Such transformation was possible for the domains of processing speed, motor functioning, and anxiety. Digit span performances (attention domain) were also transformed into *z*-scores; however, the overall impairment index of the CPT (attention domain) prohibited the calculation of a single domain score. Thus, measures of attention

were analyzed separately. The percentage of total words (HVLT) and units (LM) recalled during the learning trials was calculated (total learned/total possible × 100) and the average was taken, which represents the learning score. Similarly, the percentage of information retained following the delays was calculated for each measure and then averaged (total recalled at delay/total recalled at learning × 100).

SPSS 11.0 (SPSS Inc.) was used in all analyses and results were considered significant if $p < .05$. Differences within each domain were assessed using paired *t*-tests.

3. Results

3.1. Ketamine specific side effects

Side effects from the ketamine treatment included muscle weakness, dizziness, fatigue, episodes of hyperhidrosis, and feeling hot and slightly anxious. These resolved maximally within 2–4 weeks. Two patients had mild unsettling flashbacks at 4 weeks that were successfully treated with small doses of Ativan (4 mg) and did not recur.

3.2. Pain and cognitive findings

Pre- and post-treatment means and standard deviations can be seen for each measure in Table 2. Differences in performance, if any, will be discussed by domain.

3.3. Pain [McGill pain questionnaire]

At a group level, significant reductions in acute (present pain index (PPI); $t(8) = 2.393$, $p = .044$) and overall (pain rating index (PRI); $t(8) = 3.845$, $p = .005$) pain were reported. Of note, all of the patients had been withdrawn from narcotics and required no pain medicine at the 6-week follow-up. The one patient who had been using the morphine pump prior to ketamine infusion was no longer doing so at follow-up. At an individual level, similar reductions were evident in eight of our nine patients. The remaining patient (patient A) actually reported slightly more pain (increase

Table 2
Pre and post-ketamine neuropsychological performance (entire sample)

Measure	Pre-treatment, mean (S.D.)	Post-treatment, mean (S.D.)	*p*-Value	r^2
CPT[a]	5.34 (5.29)	3.43 (5.48)	.685	.03
Digit span[b]	−.26 (.95)	.18 (1.26)	**.05**	.04
HVLT 1–3 total[a]	28.33 (3.16)	29.11 (2.2)		.02
HVLT recall[a]	10.0 (.87)	10.33 (1.5)		.02
Story learning[a]	15.89 (3.48)	15.22 (3.19)		.01
Story recall[a]	14.56 (3.68)	14.33 (3.97)		.00
Learning composite score (percent maximum)	71.13 (8.41)	70.88 (7.99)	.86	.00
Retention composite score (percent retained)	90.94 (5.16)	94.5 (5.45)	.155	.10
COWAT[b]	−.82 (.81)	−.33 (.51)		.12
Symbol digit[b]	.22 (1.31)	.60 (1.47)		.02
Processing speed composite[b]	−.30 (.64)	.14 (.78)	**.033**	.08
Finger tapping[b]	−1.81 (1.42)	−1.33 (1.59)	.124	.02
Grip strength[b]	−1.82 (1.20)	−2.36 (1.28)	**.052**	.05
BDI[a]	18.78 (9.07)	19.56 (10.26)	.768	.00
State anxiety[b]	.87 (1.38)	.62 (1.37)		.01
Trait anxiety[b]	.86 (1.43)	.75 (1.66)		.00
Anxiety composite[b]	.87 (1.31)	.69 (1.44)	.603	.00
Pain rating index[a]	54.44 (9.77)	29.0 (20.26)	**.005**	.39
Present pain index[a]	3.67 (.87)	2.22 (1.30)	**.044**	.30

Mean (S.D.) scores for each test/index pre- and post-treatment. Learning was calculated as the percentage of total possible units (i.e. 36 for trials 1–3 of the HVLT & 25 for LM). Significant differences in bold typeface. Effect sizes displayed as r^2.

[a] Raw scores displayed.

[b] *z*-Score equivalents displayed.

Table 3
Pre and post-ketamine neuropsychological performance (group performance based on MMPI-2 validity profile)

Measure	Pre-treatment		Post-treatment	
	Valid group	Invalid group	Valid group	Invalid group
CPT[a]	5.495 (5.78)	4.44 (0)	3.912 (5.73)	0 (0)
Digit span[b]	−.62 (.45)	1.0 (1.41)	.14 (1.23)	.34 (1.89)
Learning composite score (percent maximum)	70.18 (9.46)	74.44 (.86)	70.56 (9.10)	71.97 (3.26)
Retention composite score (percent retained)	90.5 (5.87)	92.5 (0)	95.14 (5.48)	92.25 (6.72)
Processing speed index[b]	−.42 (.65)	.12 (.56)	−.08 (.76)	.87 (.04)
Finger tapping[b]	−2.02 (1.44)	−1.05 (1.48)	−1.86 (1.34)	.53 (.81)
Grip strength[b]	−1.92 (1.29)	−1.48 (1.10)	−2.65 (1.21)	−1.33 (1.31)
BDI[a]	20.28 (8.22)	13.5 (13.43)	20.14 (9.72)	17.5 (16.26)
Anxiety composite[b]	.94 (1.3)	.60 (1.85)	.64 (1.29)	.85 (2.54)
Pain rating index[a]	55.86 (10.49)	49.5 (6.36)	30.86 (22.34)	22.5 (13.44)
Present pain index[a]	3.57 (.98)	4.0 (0)	2.29 (1.5)	2.0 (0)

Mean (S.D.) scores for each test/index pre- and post-treatment. Learning was calculated as the percentage of total possible units (i.e. 36 for trials 1–3 of the HVLT and 25 for LM).
[a] Raw scores displayed.
[b] z-Score equivalents displayed.

in PRI of 8 points, stable PPI) and considerably more depression and anxiety following treatment. This patient also provided an invalid MMPI-2 profile following treatment but the remainder of her test scores were highly similar to those of the other patients (Table 3).

3.4. Attention [CPT, digit span]

Both measures of attention either remained stable (CPT, $t(6) = .426$, $p = .685$) or improved significantly following intervention (digit span, $t(8) = 2.295$, $p = .05$).

3.5. Processing speed [verbal fluency, digit symbol coding]

Significant improvement in performance was evident within this domain following treatment ($t(8) = 2.573$, $p = .033$).

3.6. Learning and memory [HVLT, logical memory story]

Relatively no change was observed within the domain of learning and memory (Table 2) as patients were able to both learn ($t(8) = .177$, $p = .86$) and retain ($t(8) = 1.571$, $p = .155$) as much information before treatment as they were after.

3.7. Motor functioning [finger tapping, grip strength]

Motor functioning was well below average at both time points. Although the composite score suggested that motor functioning remained stable following treatment ($t(8) = .119$, $p = .908$), examination of individual test performance revealed a different pattern (Table 2). Exploratory analyses were performed for this reason and revealed that strength was reduced following treatment ($t(8) = 2.276$, $p = .052$) whereas motor speed remained stable ($t(8) = 1.72$, $p = .124$).

3.8. Mood [BDI, state-trait anxiety questionnaire]

Emotional functioning remained unchanged as neither level of depression, as measured by the BDI-II ($t(8) = .306$, $p = .768$), nor state anxiety ($t(8) = .542$, $p = .603$) differed following treatment.

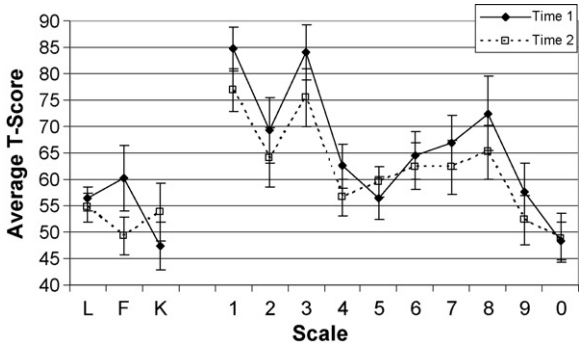

Fig. 1. Valid group's average *T*-scores for each scale of the MMPI-2.

3.9. Personality [MMPI-2]

The results of the MMPI-2 are presented based on whether each patient's profile was valid (valid group; Fig. 1) or invalid (invalid group; Fig. 2). In all cases, invalid profiles were caused by an *L*-scale *T*-score over 65. Importantly, all other validity scales (i.e. F, K) were within the valid range. Two patients provided invalid profiles at each time point; however, only one of these patients provided an invalid profile at both time points. Although invalid, this group's profile changed markedly from pre- to post-treatment as they experienced more acute distress, which was evident in elevations in nearly every scale. Importantly, the cognitive profiles of all patients in the invalid group were highly similar to, if not better than, those in the valid group (Table 3); thus, there is no evidence to suspect suboptimal effort during the neurocognitive testing in this group (see discussion below).

In the valid group, the pattern of responding on the MMPI-2 was highly similar before and after treatment. Initially, significant elevations ($T = 84$) were observed on scales 1 and 3 with milder elevations ($T > 65$) on scales 2, 7, and 8. This profile would be most consistent with a 1-3/3-1 code type. Not surprisingly then, the presence of a "conversion V" is highly prominent upon visual inspection of these group data. Interestingly, this profile persisted following treatment although mild reductions were evident on scales 1 and 3 ($T = 74$), while scores on scales 2, 7, and 8 were essentially within normal limits during the follow up examination.

3.10. Correlations

A Pearson correlation matrix revealed that post-treatment PRI and PPI scores were positively correlated ($r = .806$, $p = .009$), but not pre-treatment ($p = .159$). Additionally, finger tapping was negatively correlated with post-treatment PRI ($r = -.896$, $p = .001$) and PPI ($r = -.737$, $p = .024$). PRI was negatively correlated with CPT ($r = -.793$, $p = .033$) before treatment, but the two were positively correlated after treatment ($r = -.709$, $p = .049$).

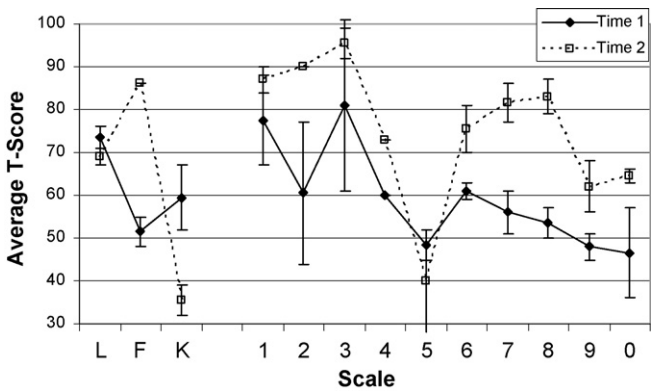

Fig. 2. Invalid group's average *T*-scores for each scale of the MMPI-2.

4. Discussion

Our results revealed that 5 days of anesthetic ketamine infusion therapy is an effective treatment for CRPS I as indicated by significant reductions in both acute and overall pain 6 weeks following completion of the treatment. This finding is consistent with other trials of subanesthetic ketamine infusion in CRPS I patients (Harbut & Correll, 2002; Kiefer et al., 2003). The current reduction was evident both qualitatively (withdrawal from all narcotics) and quantitatively using the McGill Pain Questionnaire. Before surgery, the two scales of the pain questionnaire were unrelated, which suggests some degree of inconsistency in the amount of pain these patients were experiencing, possibly due to the acute effects of their pain medications. After treatment, however, the two scales were correlated and significantly below pre-treatment levels despite the fact that none of the patients were using any form of pain medication at follow-up. These findings are especially encouraging since these patients had failed conventional therapy.

Overall, ketamine appeared to have no adverse neurocognitive effects at the 6-week follow-up as performances on nearly every test remained stable or improved. The most notable improvements were on measures of brief auditory attention and processing speed, both of which were significant. Additionally, the relationship between sustained attention (CPT) and the overall pain rating (PRI) is further evidence of improvement in cognitive functioning after treatment. This allows for speculation that improvements in pain following ketamine treatment may be associated with improvements in the ability to attend and to process information more rapidly. However, an alternative and potentially more plausible hypothesis is that these improvement are due to the lack of pain medication, since narcotic agents are widely known to adversely affect attention and processing speed.

Considering the adverse impact of ketamine on encoding (Honey et al., 2005) and verbal memory (Anand et al., 2000; Parwani et al., 2006), it is significant that there were no changes in the percentage of information these patients could learn and retain following treatment. It is important to note that our patients received alternate forms of the HVLT and either story I or II of the logical memory subtest of the WMS-III at each time point and that these versions were counterbalanced across subjects. This procedure minimizes any concern about practice effects that could potentially negate a decline following treatment. These results may indicate that the NMDA receptors affected during the ketamine-induced coma may have served different purposes (e.g. pain transmission rather than for cognition). The apparent discrepancy between previous research and our current findings is likely related to methodological differences. Specifically, the other studies typically assessed learning and memory during the acute phase (i.e. while the drug still had an active effect) whereas our follow-up evaluation was performed well after all metabolic effects of ketamine had worn off (ketamine possesses a plasma half life of 2–4 h, Copeland & Dillon, 2005).

Although performances remained stable or improved on virtually every test we administered, it is concerning that chronic recreational users demonstrated an upregulation in D1 receptors within the dorsolateral prefrontal cortex (Narendran et al., 2005). Neither the amount of ketamine nor the duration of usage that would result in such impairment are clearly known. The subjects in Narendran et al.'s study had used at least one vial of ketamine each week (200–300 mg) for at least 2 years, which suggests that even though our patients received 5 days of continuous treatment, the overall amount was well below what Narendran et al.'s subjects had used. Nonetheless, it is possible that we did not administer tests that would have been sensitive to deficits associated with dorsolateral prefrontal dysfunction (e.g. working memory, novel reasoning and problem solving).

Only motor strength declined significantly following treatment, which could be partly attributed to 5 days of inactivity during the treatment coupled with ketamine specific side effects of muscle weakness. This reduction appeared limited to strength as motor speed improved by about one half of a standard deviation following treatment.

From an emotional standpoint, the lack of improvement in depression and anxiety (both typically mild–moderate at both time points) was somewhat surprising given the marked improvement in pain. This finding, in combination with the stability of the valid group's MMPI-2 profile, could be interpreted as evidence of long-standing personality traits that increased the susceptibility of our patients to develop CRPS I. The large "conversion V" evident in these MMPI-2 profiles is certainly consistent with this interpretation as the severity of the depression and anxiety these patients reported was far below what would be expected based on the amount of physical pain and functional impairment they were reporting. Additionally, the invalid group demonstrated a more pathological MMPI-2 profile as both patients reported more distress as well as more depression and anxiety after treatment. These differences seem unlikely to be related to pain as one of the two patients experienced a dramatic reduction in pain following treatment whereas the other reported only slightly more pain. Thus, it is possible that premorbid psychological factors may increase one's susceptibility to develop CRPS and these patients may be evidence of this process.

Alternatively, the emotional and personality findings could suggest that our patients had developed these traits as a result of intense and chronic pain. This is certainly reasonable to expect since the causal injury had occurred average of almost 56 months before the first assessment. As such, it is unreasonable to expect traits that had been formed during a 5-year period of time to dissipate within 6 weeks. Unfortunately, we were unable to follow these patients to determine whether these traits improved over time, which would support this latter interpretation.

Regardless of the cause of the mood/personality symptoms, these patients' considerable fixation with somatic symptoms suggests that they may benefit from interventions that specifically target such concerns. For example, reductions in behavioral seizure activity were related to reductions in theta-SMR ratio in patients with pseudoseizures who were treated with the combination of neurofeedback and conventional psychotherapy (Swingle, 1998). It is reasonable to speculate that such biologically oriented treatments could also be effective in patients with CRPS I and may complement the use of pharmacologically oriented treatments.

There are several limitations to the current study. Perhaps the largest limitation is our small sample size, which limited our power and may have obscured clinically meaningful trends in the data. However, we included effect sizes in order to partially address this issue and to follow the recommendations of the American Psychological Association (APA, 2001). Although we cannot rule out the possibility that practice effects contributed to the stable performances of our patients, we used alternate versions whenever possible and the two evaluations were generally separated by at least 3 months. Thus, it is highly unlikely that practice effects can fully account our results.

The fact that most of our patients were considered totally disabled also raises concern about their effort during the neurocognitive testing. Although we did not administer formal measures of symptom validity, we do not consider this a significant concern for several reasons. First, most symptom validity measures involve the assessment of learning and memory and, as can be seen, our patients were able to learn and retain most of the information presented to them. Additionally, the neurocognitive profile of the invalid group was typically as good as, if not better than, that of the valid group (Table 3). Thus, these data do not suggest that an invalid MMPI-2 profile is associated with poor effort during the remainder of the evaluation. Finally, all of the patients who were receiving disability benefits were doing so for physical reasons rather than cognitive deficits.

A final limitation is that the follow up evaluation was scheduled for 6 weeks and, unfortunately, we were unable to follow these patients to determine the long-term physical, neurocognitive, and emotional effects of the anesthetic ketamine protocol. Anecdotally, the treating neurologist (RJS) has not noted any late (4 year) cognitive impairments in any of the nine patients. Additionally, we are optimistic about the possibility that patients who received this treatment will remain pain free since Zyluk (2004) cited recurrence rates of 1.8% per patient per year for those who were successfully treated. Other authors have suggested that a second infusion of ketamine many provide relief for an additional 1–3 years (Correll et al., 2004). Future studies should investigate the consequences of long term and repeated ketamine interventions in patients with this condition.

Overall, the current findings suggest that treatment of refractory CRPS I patients with large doses of anesthetic ketamine significantly reduces pain and does not result in neurocognitive impairment, at least for 6 week following the completion of the treatment. Instead, treatment appears to result in improvements in aspects of cognition such as brief auditory attention and processing speed, although it is unclear whether reduction in pain, withdrawal from pain medications, or the combination of these factors is responsible for these neurocognitive improvements. Importantly, patients were able to learn and retain as much information following treatment as they were before the intervention. Only motor strength declined following treatment, which is likely the combination of inactivity and the side effects of ketamine (i.e. muscular weakness). Finally, mood and personality traits remained stable over the duration of this study despite marked reductions in pain in all but one of our patients. This finding can be interpreted as either evidence of premorbid psychiatric factors that contribute to the maintenance of this condition or as the result of dealing with intense, chronic pain that impeded functioning across multiple areas of our patients' lives. Future research will be necessary to clarify these issues.

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References

American Psychological Association, (2001). *Publication Manual of the American Psychological Association* (5th ed.). Washington, DC.

Anand, A., Charney, D. S., Oren, D. A., Berman, R. M., Hu, X. S., Cappiello, A., et al. (2000). Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: Support for hyperglutamatergic effects of *N*-methyl-D-aspartate receptor antagonists. *Archives of General Psychiatry*, *57*(3), 270–276.

Birklein, F. (2005). Complex regional pain syndrome. *Journal of Neurology*, *252*(2), 131–138.

Ceber, M., & Salihoglu, T. (2006). Ketamine may be the first choice for anesthesia in burn patients. *Journal of Burn Care and Research*, *27*(5), 760–762.

Copeland, J., & Dillon, P. (2005). The health and psycho-social consequences of ketamine use. *International Journal of Drug Policy*, *16*, 122–131.

Correll, G. E., Maleki, J., Gracely, E. J., Muir, J. J., & Harbut, R. E. (2004). Subanesthetic ketamine infusion therapy: A retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. *Pain Medicine*, *5*(3), 263–275.

Cotman, C. W., & Monaghan, D. T. (1988). Excitatory amino acid neurotransmission: NMDA receptors and Hebb-type synaptic plasticity. *Annual Review of Neuroscience*, *11*(1), 61–80.

De Good, D. E., Cundiff, G. W., Adams, L. E., & Shutty, M. S. (1993). A psychosocial and behavioral comparison of reflex sympathetic dystrophy, low back pain, and headache patients. *Pain*, *54*, 317–322.

Fu, C. H., Abel, K. M., Allin, M. P., Gasston, D., Costafreda, S. G., Suckling, J., et al. (2005). Effects of ketamine on prefrontal and striatal regions in an overt verbal fluency task: A functional magnetic resonance imaging study. *Psychopharmacology*, *183*, 92–102.

Harbut, R. E., & Correll, G. E. (2002). Successful treatment of a 9-year case of complex regional pain syndrome type-I (reflex sympathetic dystrophy) with intravenous ketamine-infusion therapy in a warfarin-anticoagulated adult female patient. *Pain Medicine*, *3*(2), 147–155.

Harden, N., & Bruehl, S. (2005). Diagnostic criteria: The statistical deviation of the four criterion factors. In P. Wilson, M. Stanton-Hicks, & N. Harden (Eds.), *CRPS: Current Diagnosis and Therapy*. WA: IASP Press.

Harden, N. R., Bruehl, S., Stanos, S., Brander, V., Chung, O. Y., Saltz, S., et al. (2003). Prospective examination of pain-related and psychological predictors of CRPS-like phenomena following total knee arthroplasty: A preliminary study. *Pain*, *106*, 393–400.

Hirota, K., & Lambert, D. G. (1996). Ketamine: Its mechanism(s) of action and unusual clinical uses. *Journal of British Anaesthesia*, *77*(4), 441–444.

Honey, G. D., Honey, R. A., Sharar, S. R., Turner, D. C., Pomarol-Clotet, E., Kumaran, D., et al. (2005). Impairment of specific episodic memory processes by sub-psychotic doses of ketamine: The effects of levels of processing at encoding and of the subsequent retrieval task. *Psychopharmacology*, *181*, 445–457.

Janig, W., & Baron, R. (2003). Complex regional pain syndrome: Mystery explained? *Lancet Neurology*, *2*(11), 687–697.

Jorum, E., Warncke, T., & Stubhaug, A. (2003). Cold allodynia and hyperalgesia in neuropathic pain: The effect of *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine—a double-blind, cross-over comparison with alfentanil and placebo. *Pain*, *101*(3), 229–235.

Kiefer, R., Rohr, P., Ploppa, A., Unertl, K., & Schwartzman, R. J. (2003). Is high dosed ketamine a therapeutic option for severe intractable complex regional pain syndrome type I? *Anesthesiology*, *99*(A1008).

Kiefer, R. T., Rohr, P., Unertl, K., Altemeyer, K. H., Grothusen, J., & Schwartzman, R. J. (2002). Recovery from intractable complex regional pain syndrome type I (RSD) under high-dose intravenous ketamine-midazolam sedation. *Neurology*, *58*(7, Suppl 3), A474–A475.

Krystal, J. H., Abi-Saab, W., Perry, E., DeSouza, D. C., Liu, N., Gueorguieva, R., et al. (2005). Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects. *Psychopharmacology*, *179*(1), 303–309.

Krystal, J. H., D'Souza, D. C., Karper, L. P., Bennett, A., Abi-Dargham, A., Abi-Saab, D., et al. (1999). Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. *Psychopharmacology*, *145*(2), 193–204.

Krystal, J. H., Karper, L. P., Bennett, A., D'Souza, D. C., Abi-Dargham, A., Morrissey, K., et al. (1998). Interactive effects of subanesthetic ketamine and subhypnotic lorazepam in humans. *Psychopharmacology*, *135*(3), 213–229.

Maleki, J., LeBel, A. A., Bennett, G. J., & Schwartzman, R. J. (2000). Patterns of spread in complex regional pain syndrome, type I (reflex sympathetic dystrophy). *Pain*, *88*(3), 259–266.

Narendran, R., et al. (2005). Altered prefrontal dopaminergic function in chronic recreational ketamine users. *American Journal of Psychiatry*, *162*, 2352–2359.

Parwani, A., Weiler, M., Blaxton, T., Warfel, D., Hardin, M., Frey, K., et al. (2006). The effects of a subanesthetic dose of ketamine on verbal memory in normal volunteers. *Psychopharmacology*, *183*(3), 265–274.

Puchalski, P., & Zyluk, A. (2005). Complex regional pain syndrome type 1 after fractures of the distal radius: A prospective study of the role of psychological factors. *Journal of Hand Surgery*, *30B*(6), 574–580.

Sandroni, P., Benrud-Larson, L. M., McClelland, R. L., & Low, P. A. (2003). Complex regional pain syndrome type I. Incidence and prevalence in Olmsted county, a population-based study. *Pain*, *103*(1–2), 199–207.

Schwartzman, R., Alexander, G., & Grothusen, J. (2006). The pathophysiology of complex regional pain syndrome. *Neurotherapeutics*, *6*(5).

Schwartzman, R. J., & Popescu, A. (2002). Reflex sympathetic dystrophy. *Current Rheumatology Report*, *4*(2), 165–169.

Sheng, M., & Kim, M. J. (2002). Postsynaptic signaling and plasticity mechanisms. *Science*, *298*(5594), 776–780.

Shiri, S., Tsenter, J., Livai, R., Schwartz, I., & Vatine, J. J. (2003). Similarities between the psychological profiles of complex regional pain syndrome and conversion disorder patients. *Journal of Clinical Psychology in Medical Settings*, *10*(3), 193–199.

Swingle, P. G. (1998). Neurofeedback treatment of pseudoseizure disorder. *Biological Psychiatry*, *44*(11), 1196–1199.

Ushida, T., Tani, T., Kanbara, T., Zinchuk, V. S., Kawasaki, M., & Yamamoto, H. (2002). Analgesic effects of ketamine ointment in patients with complex regional pain syndrome type 1. *Regional Anesthesia and Pain Medicine*, *27*(5), 524–528.

Watkins, L., & Maier, S. (2005). Immune regulation of central nervous system functions: From sickness responses to pathological pain. *Journal of Internal Medicine*, *257*(139).

Wilson, P. (2004). *Taxonomy (Newsletter)*.

Woolf, C. J., & Salter, M. W. (2000). Neuronal plasticity: Increasing the gain in pain. *Science*, *288*(5472), 1765–1769.

Zarate, C., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., et al. (2006). A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry*, *63*, 856–864.

Zyluk, A. (2004). Complex regional pain syndrome. Type I. Risk factors, prevention and risk of recurrence. *The Journal of Hand Surgery: Journal of the British Society for Surgery of the Hand*, *29*(4), 334–337.