Journal of the International Neuropsychological Society (2010), **16**, 566–573.

doi:10.1017/S1355617710000214

Neuropsychological deficits associated with Complex Regional Pain Syndrome

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(RECEIVED November 16, 2009; FINAL REVISION February 8, 2010; ACCEPTED February 8, 2010)

Abstract

We sought to elucidate the existence of neuropsychological subtypes in Complex Regional Pain Syndrome (CRPS). One hundred thirty seven patients with CRPS were administered tests that assess executive control, naming/lexical retrieval, and declarative memory. A 2-step cluster analysis that does not require any *a priori* specification regarding the number of clusters, classified patients into three groups. Group 1 obtained scores that were in the average range on all tests ($n = 48$; normal CRSP group). Group 2 ($n = 58$; dysexecutive CRSP group) presented with mild impairment or statistically low average test performance on working memory/verbal fluency tests. Group 3 ($n = 31$; global CRSP group) produced scores in the statistically low average/borderline range on all tests with particularly reduced scores on naming/declarative memory tests. Between-group analyses found that the CRPS group 1 obtained higher scores than CRPS groups 2 and 3 on all tests. However, groups 2 and 3 were equally impaired on executive tests. CRPS group 3 was impaired on tests of naming/memory tests compared to the other groups. Significant neuropsychological deficits are present in 65% of patients, with many patients presenting with elements of a dysexecutive syndrome and some patients presenting with global cognitive impairment. (*JINS*, 2010, *16*, 566–573.)

Keywords: Complex Regional Pain Syndrome, Reflex Sympathetic Dystrophy, Neuropsychological functioning, Executive functioning, Declarative memory, Neuropathic pain

INTRODUCTION

Complex Regional Pain Syndrome (CRPS) is a severe chronic pain disorder that affects between 200,000 and 1.2 million Americans. CRPS most often occurs after an injury to peripheral nerves or their endings in soft tissue (Plewes, 1956; Loeser, 2001). CRPS presents with a female to male preponderance with approximately a 3:1 ratio and a reported average age of onset ranging from 37 to 60 years of age (Schwartzman, Erwin, & Alexander, 2009). Clinically, CRPS is characterized by continuous spontaneous or evoked pain that is out of proportion to the initial injury and does not respect a nerve or root distribution (Schwartzman, Alexander, & Grothusen, 2006). The signs and symptoms seen in CRPS patients revolve around abnormalities in pain processing, skin color and temperature changes, edema, vasomotor and sudomotor abnormalities, and motor/trophic changes (Bruehl, Harden, Galer, Saltz, Bertram, et al., 1999; Harden, Bruehl, & Galer, 1999). Although the pathophysiology of CRPS is not completely understood, there is a growing body of evidence demonstrating that the local release of inflammatory mediators from afferent neurons (neurogenic inflammation) plays a significant role (Birklein, Schmelz, Schifter, & Weber, 2001; Schinkel, Gaertner, & Zaspel, 2006). Furthermore, neuroinflammation and neuroimmune activation have been shown to act in concert in persistent pain states (DeLeo & Yezierski, 2001).

The relationship(s) between generalized chronic pain and neuropsychological impairment are complex (Hart, Martelli, & Zasler, 2000). In prior research, poor performance on neuropsychological tests assessing working memory and attention were seen in middle-aged patients presenting with musculoskeletal pain (Dick & Rashiq, 2007). Weiner, Rudy, Morrow, Slaboda, & Lieber (2006) found that chronic pain was associated with reduced performance on neuropsychological tests that assess memory, language, and executive control. Karp et al., (2006) studied patients whose pain was due to a variety of underlying medical conditions. In this research, reduced performance on neuropsychological tests measuring information processing speed was noted, even after adjusting for the effects of depression.

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The neuropsychological deficits associated with CRPS have not been systematically studied. Anecdotally, patients with CRPS describe significant problems with attention/concentration and multitasking (i.e., executive and working memory deficits), word finding problems, and problems in learning and retaining new information (i.e., declarative memory deficits). Koffler and colleagues (2007) studied a small group of patients with CRPS who were assessed with neuropsychological tests before and after five-day coma treatment with ketamine, midazolam, and clonidine. After treatment, these patients were on no medication, whereas all had been on antiepileptic, nonsteroidal antiinflammatory, or narcotic medication prior to coma. Koffler and colleagues (2007) reported improved post-test performance on neuropsychological tests measuring attention and information processing speed and suggested that the alleviation of pain associated with CRPS was the mechanism associated with better post-treatment test performance.

Recent research suggests that central nervous system mechanisms may be integral in understanding some of the brain–behavior relationships that occur in CRPS. For example, functional brain imaging studies have demonstrated that patients with CRPS exhibit abnormal brain activity on motor tasks, imagined motor tasks, and tactile stimuli, suggesting that cortical reorganization may be linked to CRPS (Gieteling et al., 2008; Maihofner, Handwerker, Neundorfer, & Birklein, 2003; Maihofner et al., 2007a; Pleger et al., 2006). These studies have also shown that CRPS patients abnormally activate the dorsolateral and ventromedial prefrontal cortex. These brain regions are important for executive control and memory retrieval (Alexander, Stuss, & Fansabedian, 2003; Stuss et al., 1994) and their inappropriate recruitment may bear upon lower perceptual learning and blunted emotional decision-making abilities seen in CRPS (Apkarian, Thomas, Krauss, & Szeverenyi, 2001; Apkarian et al., 2004; Geha et al., 2008; Maihofner, Forster, Birklein, Neundorfer, & Handwerker, 2005; Maihofner, Handwerker, & Birklein, 2006; Maihofner et al., 2007b).

The purpose of this research was to assess for specific patterns of neuropsychological impairment in a large group of CRPS patients that fulfill the International Association for the Study of Pain (IASP) criteria (Harden, Bruehl, Stanton-Hicks, & Wilson, 2007). The patients were studied with neuropsychological tests that measure three domains of cognitive functioning – executive control, naming/lexical retrieval, and declarative memory. On the basis of the literature cited earlier, it was our expectation that the most common type of neuropsychological impairment in CRPS would be a dysexecutive syndrome.

METHODS

Demographics

The current sample consisted of 137 consecutive outpatients diagnosed with CRPS from a university-affiliated CRPS clinic. All patients were evaluated by the same attending neurologist (RJS). Inclusion criteria included: fulfilling IASP diagnostic and modified research criteria for CRPS (Harden et al., 2007) and the ability to understand and complete neuropsychological assessment. Exclusion criteria included the diagnosis of other conditions that would otherwise account for either pain or cognitive dysfunction. These included a prior history of epilepsy, traumatic brain injury, or major medical illness such as cancer. The sample's mean age and level of education was 43.79 (±11.93) and 13.76 (±2.21) years, respectively. The mean level of depression (Beck Depression Inventory-II) and pain (McGill Pain Inventory-Short Form) was 16.86 (±11.06) and 25.06 (±8.29), respectively. Of the entire sample, 77.94 percent was female. These data are consistent with prior research from our laboratory (Schwartzman et al., 2009). All participants were recruited for this project consistent with regulations put forth by the Drexel University College of Medicine Institutional Review Board (IRB) and the Declaration of Helsinki.

As described below, information regarding the number and types of medications was obtained for all patients. An attempt was made to obtain exact information regarding medication dose, the duration patients took all medications, and the exact time medications was last taken before testing. These variables could have affected outcome. However, for many patients this information was unavailable, or patients simply did not know exact medication duration.

Neuropsychological Assessment

Executive systems function

The Digit Span subtest from the Wechsler Adult Intelligence Scale-III (WAIS-III) was utilized to evaluate executive systems functioning (Wechsler, 1997). This test was administered following published instructions. Participants are first asked to repeat orally presented numbers in their exact order (digits forward). Participants are then asked to repeat orally presented numbers backwards or in reverse order. The dependent variable derived from this test was the raw score from the Digits Backwards Test condition. The digit backward portion of this test was selected because prior research has associated poor digit backward test performance with working memory deficits (Lamar et al., 2007; Lamar, Catani, Heilman, & Libon, 2008).

Executive functioning was also evaluated with tests of letter fluency (letters 'FAS'). Scale scores were obtained using information provided by Gladsjo, Miller, and Heaton, (1999). On the letter fluency test, participants were given 60 seconds to generate words, excluding proper nouns and numbers, beginning with a specified letter. The dependent variable was the number of responses summed across each letter. Imaging studies have shown that letter fluency tests activate the left dorsolateral prefrontal region in younger (Phelps, Hyder, Blamire, & Shulman, 1997) and older

https://doi.org/10.1017/S1355617710000214 Published online by Cambridge University Press

adults (Gourovitch et al., 2000). In dementia patients, differential impairment on letter fluency tests has also been linked to left dorsolateral prefrontal atrophy (Libon et al., 2009).

Naming/Lexical retrieval

Naming was assessed and scored with the 60-item version of the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983; 2001). Lexical retrieval was assessed with a test of semantic ('animal') fluency. Scale scores were derived from the Gladsjo, Miller, and Heaton (1999) corpus. On the 'animal' fluency test, patients were asked to produce as many names of animals in 60 seconds. Recent studies suggest that category fluency tests provide a measure of lexical retrieval and semantic knowledge and are linked to activation of the left temporal lobe (Libon et al., 2009; Mummery, Patterson, Hodges, & Wise, 1996). The dependent variable was the total number of responses, excluding perseverations and extra-category intrusion responses.

Memory and learning

The California Verbal Learning Test-II was utilized to evaluate memory and learning (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000). The administration of the CVLT-II involves an orally presented, 16-word list (list A) composed of four items from four semantic categories. This is followed by a second, interference (list B) 16-word list test condition. List B includes eight words from two categories from list A. The interference condition (list B) is followed by short-delay free recall and category-cued recall test conditions for list A. After a 20-minute filled delay, free recall and category recall is reassessed for list A. This is followed by a delay recognition test. The recognition test contains 48 words – the 16 words from list A, the 16 words from list B, and 8 prototypic semantic items related to list A, and 8 unrelated words. On the recognition test, participants are asked to indicate if each orally presented word was from list A.

Two CVLT-II variables were used in the current research, total recall from the delayed recall test condition and a delayed recognition discriminability index. The recognition discriminability index was calculated using the following algorithm [1 – ((false positive + misses) / 48)] * 100 (Delis, Kramer, Kaplan, & Ober, 1987; Libon et al., 1996; Price et al., 2009). Recognition correct hits and false positive errors were also tallied. The CVLT-II delayed free recall and delayed recognition discrimination index were used in the current study because both of these indices have been linked to parahippocampal atrophy and the presence of an anterograde amnesia (Libon et al., 1998).

In addition to the neuropsychological tests described above, all participants were assessed with the Beck Depression Inventory-II (Beck & Steer, 1993) and the McGill Pain Inventory (Melzack, 1987).

Statistical Analysis

The following statistical analyses were used. First, the six neuropsychological dependent variables described above were subjected to a two-step cluster analysis (Aldenderfer & Blashfield, 1984) procedure (Statistical Package for the Social Scientist, SPSS, v. 17). This technique is designed to reveal natural groupings or clusters within a large dataset. Unlike other cluster analysis procedures, such as hierarchical cluster analysis, the numbers of groupings or clusters are not predetermined. Rather, the clusters revealed using the two-step cluster analysis technique are determined by an automatic selection algorithm. Cluster distance and cluster criterion were calculated using log-likelihood and Schwarz's Criterion Measure (Aldenderfer & Blashfield, 1984), respectively. These algorithms use a distance measure that compares all variables to determine maximum distance between cluster centers. The Kolmogorov-Smirnov test was used to determine that all neuropsychological variables were normally distributed (Eadie, Drijard, James, Roos, & Sadoulet, 1971). Second, differences between cluster-analysis-determined groups for the six neuropsychological variables listed above were assessed using a single multivariate analysis of variance (MANOVA, Hotelling Trace statistic). This conservative procedure was used to guard against a type 1 error. If the MANOVA yielded significance, between-group differences were then assessed using separate univariate ANOVAs. *Post-hoc* differences between any of the individual cluster-analysis-determined groups for any of the six neuropsychological tests listed above was assessed with Scheffé Tests. This more conservative *post-hoc* procedure was, again, chosen to further guard against a type 1 error. Significance was set at $p < .010$ for all statistical procedures.

RESULTS

Cluster Analysis

The six neuropsychological variables described above were subjected to a two-step cluster analysis (Statistical Package for the Social Scientist, SPSS] v. 17). The cluster analysis yielded a three-cluster solution. Patients in cluster 1 ($n = 48$, normal CRPS group, 35.03% of patients) obtained scores that were generally within the statistically normal range considering age and education. Patients in cluster 2 ($n = 58$; dysexecutive CRPS group, 42.33% of patients) produced mildly reduced or low average scores on all executive tests. Patients in cluster 3 ($n = 31$, global CRPS group, 22.62% of patients) also produced mildly reduced, (i.e., low average) scores on executive tests. In addition, patients in CRPS group 3 performed poorly or in the borderline range on the Boston Naming Test and both declarative memory test measures.

Between-Group Performance

Demographic characteristics for the three CRPS groups derived from the two-step cluster analysis are also displayed in Table 1.

https://doi.org/10.1017/S1355617710000214 Published online by Cambridge University Press

Table 1. Demographic information, scores on depression/pain inventories, and performance on neuropsychological tests (mean & standard deviation)

	CRPS Groups		
	Normal (group 1; $n = 48$)	Dysexecutive (group 2; $n = 58$)	Global (group 3; $n = 31$)
Demographic and Clinical Information			
Age	42.55 (10.50)	44.15 (13.24)	45.72 (10.48)
Education	14.62 (2.24)	13.62 (2.11)	12.05 (1.25)
Beck Depression Inventory-II	13.10 (9.12)	18.16 (10.89)	23.06 (13.64)
McGill Pain (short form)	24.65 (8.11)	24.93 (8.26)	26.80 (9.28)
Length of illness (months)	86.73 (85.96)	82.04 (66.68)	82.16 (78.32)
Spread of illness: Limbs involved: range 0–4	2.75 (1.34)	2.75 (1.21)	2.23 (1.22)
Proportion of left- *vs.* right sided limb involvement-	37.90 *vs.* 33.80%	53.00 *vs.* 47.70%	9.10 *vs.* 18.50%
Medications			
Total number of medications:	3.40 (1.66)	3.67 (1.63)	3.85 (0.86)
Percent of Patients in Each Group Prescribed Medication			
NSAID	33.9%	44.1%	30.1%
antidepression	31.4%	35.8%	30.9%
antiepilepsy	28.4%	46.9%	24.7%
opiates	33.6%	39.7%	28.8%

Note. NSAID = nonsteroidal antiinflammatory medication; AED = antiepilepsy medication.

The analysis of variance (ANOVA) for age, education, level of depression (Beck Depression Inventory-II), and level of Pain (McGill Scale) found between-group differences for education, $F(2, 128) = 10.38$, $p < .001$, and level of depression, $F(2, 119) = 5.86$, $p < .004$. *Post-hoc* analyses (Scheffé Tests) for education found that global CRPS patients (CRPS group 3) presented with fewer years of education compared to other CRPS groups ($p < .002$, both analyses). For the Beck Depression Inventory-II, global CRPS patients (CRPS group 3) also presented with a higher score, indicating a greater affective disturbance compared to the normal CRPS group (CRPS group 1, $p < .005$). There were no between-group differences for length of illness or the spread of illness as measured by the number of limbs involved (0–4). Also, there were no between-group differences for the total number of medications specifically prescribed for CRPS, or the percent of participants who were taking various types of medication prescribed for CRPS, including nonsteroidal antiinflammatory, antidepressant, antiepilepsy, and opiate medication.

Neuropsychological test performance (Table 2) was analyzed using a single multivariate analysis of covariance (MANCOVA).

For this analysis, the possible effects of education and of depression, as assessed with the Beck Depression Scale-II, were covaried. The MANCOVA yielded a main effect for group, $F(12, 238) = 28.43$, $p < .001$. The multivariate effects of education and of depression assessed with the Beck Depression Inventory-II were not significant for any of the six neuropsychological variables. All six neuropsychological variables were then analyzed using one-way ANOVA. These analyses continued to be highly significant ($p < .001$, all tests), and neither education nor level of depression were significant for any neuropsychological variable. To further assess for possible effects of education and depression on neuropsychological test performance, Product Moment Correlations were conducted for each group. Correlations between education and level of depression on neuropsychological test performance were not significant.

Follow-up analyses (Scheffé Tests) found that for both executive tests (Digits Backwards Test/letter fluency), CRPS group 1 (normal CRPS group) outperformed CRPS groups 2 (dysexecutive group) and 3 (global group), $p < .001$, all tests. However, there was no difference between the CRPS groups 2 and 3 on either test. Follow-up comparisons for the Boston Naming Test revealed no difference between CRPS groups 1 (normal CRPS group) and 2 (dysexecutive CRPS group). Both CRPS groups 1 and 2 outperformed CRPS group 3 (global CRPS group, $p < .001$, both tests). On the 'animal' fluency test, the normal CRPS group (group 1) generated more exemplars than other CRPS groups ($p < .001$, both tests). However, there was no difference between CRPS groups 2 (dysexecutive group) and 3 (global CRPS group) on this test. *Post-hoc* analysis for the two memory measures found that delayed free recall for CRPS group 1 (normal CRPS group) was higher compared to CRPS groups 2 and 3 ($p < .001$, both tests). CRPS group 2 (dysexecutive group) also recalled more words compared to CRPS group 3 (global CRPS group, $p < .001$). A similar profile was obtained for the delayed recognition discriminability index, where CRPS group 1 outperformed other CRPS groups ($p < .006$, both tests) and CRPS group 2 outperformed CRPS group 3 ($p < .001$).

To further assess underling deficits on the CVLT-II, the delayed recognition discriminability index, total correct hits,

https://doi.org/10.1017/S1355617710000214 Published online by Cambridge University Press

Table 2. Neuropsychological test performance (means and standard deviations)

	Normal (Group 1; $n = 48$)		Dysexecutive (Group 2; $n = 58$)		Global (Group 3; $n = 31$)	
Neuropsychological Test	Raw Scores	Scale Scores	Raw Scores	Scale Scores	Raw Scores	Scale Scores
Digits Backwards/ (WAIS-III Digit Span)	8.38 (2.92) n/a	n/a 11.25 (3.15)	6.49 (1.65) n/a	n/a 9.31 (2.20)	6.14 (2.25) n/a	n/a 8.00 (3.12)
Letter Fluency (FAS)	46.12 (14.06)*	11.70 (3.29)	30.25 (8.17)	7.48 (2.25)	27.50 (10.22)	6.11 (2.11)
Boston Naming Test	55.57 (3.23)*	10.73 (1.50)	52.67 (4.46)	8.44 (3.43)	44.71 (9.33)	6.44 (2.55)
'Animal' Fluency	22.00 (3.27)*	11.15 (1.65)	16.78 (3.02)	8.08 (2.05)	14.92 (4.39)	6.44 (2.55)
CVLT-II Delay Free Recall (range 0–16)	13.59 (2.29)*	11.94 (2.79)	10.87 (1.94)**	8.44 (3.43)	6.78 (2.52)	7.25 (3.70)
CVLT-II Recognition Range (0–100%)	98.05 (2.69)*	12.36 (1.83)	94.81 (3.56)**	10.53 (2.63)	85.04 (8.59)	5.00 (3.07)
CVLT-II Recognition Correct Hits (range 0–16)	15.66 (0.69)*	10.38 (2.19)	15.01 (1.17)**	9.27 (2.80)	13.77 (1.70)	6.78 (3.73)
CVLT-II False Positive Errors (range 0–36)	0.64 (0.99)*	11.57 (1.45)	1.48 (1.39)**	10.43 (1.92)	5.12 (4.10)	4.66 (3.78)

Note. CPRS = Complex Regional Pain Syndrome; CVLT-II = California Verbal Learning Test-II; n/a= not applicable. Raw Scores: *CRPS Group 1 > CRPS Groups 2 & 3; $p < .001$. Raw Scores: **CRPS Group 2 > CRPS Group 3; $p < .001$.

and total false positive errors were subjected to a single multivariate analysis of covariance (MANCOVA). This analysis was highly significant, $F(4, 246) = 24.91$, $p < .001$. The multivariate effects of education and depression were not significant. Both univariate ANOVAs were highly significant ($p < .001$, both tests). *Post-hoc* analysis found no differences between CRPS groups 1 and 2 for either variable. However, CRPS groups 1 and 2 generated more correct hits and fewer false positive responses compared to CRPS group 3 (global CRPS group, $p < .001$, all tests).

Table 2 also lists corresponding scale scores for all neuropsychological variables. Separate norms for WAIS-III Digits Forward and Digits Backward are not available. Therefore, the total WAIS-III scale score for Digit Span test performance was used. Using scale scores, the results of the MANCOVA were almost identical to analyses using raw scores. For the BNT, there was a borderline effect, such that CRPS group 1 (normal group) obtained a higher score compared to CRPS group 2 (dysexecutive group). An inspection of Table 2 shows that while statistical differences between the three CRPS groups are present, patients are not demented. The scale scores obtained for CRPS group 1 were generally in the statistically average range. For CRPS group 2, low average performance was obtained, primarily for executive tests. Finally, in CRPS group 3, low average to borderline performance was obtained on all tests.

Listed in Table 1 is the proportion of patients within each group presenting with left *versus* right limb onset. No differences were found, χ^2 (2) = 2.42, $p < .297$. Despite this, it is possible that for patients presenting with initial right-sided injury greater impairment might be found for language-related and verbal memory tests. However, no differences on language-related, verbal memory, or any other neuropsychological tests were found when patients were divided into groups presenting with left-sided *versus* right-sided onset of injury (MANOVA Hotelling's Trace, $F(6, 129) = 1.42$, $p < .211$. The effect of spread of illness on neuropsychological functioning was evaluated by creating four groups on the basis of whether 1, 2, 3, or 4 limbs were involved. No differences on neuropsychological tests were found (MANOVA Hotelling's Trace, $F(18, 314) = .970$, $p < .495$). It was also possible that, despite the fact that illness duration did not differ between the three-cluster determined groups, patients with longer illness duration might obtain lower scores on some tests. Using a median split, the sample was divided into two group representing shorter *versus* longer illness duration. No differences on any neuropsychological tests were found (MANOVA Hotelling's Trace, $F(6, 106) = .945$, $p < .466$).

DISCUSSION

The etiology of CRPS is incompletely understood. However, recent evidence suggests significant central nervous system involvement (Janig & Baron, 2003; Maihofner et al., 2003; 2004; 2005; 2006; Schwartzman et al., 2006). Pleger et al. (2006) demonstrated that activity in the contralateral primary

https://doi.org/10.1017/S1355617710000214 Published online by Cambridge University Press

and secondary sensory cortex induced by innocuous electrical stimulation was reduced on the side opposite CRPS-affected limbs as compared to the unaffected limbs. Becerra et al. (2009) obtained fMRI studies from a severely affected patient with generalized CRPS who was successfully treated with five-day ketamine and midazolam. After treatment there were significant changes throughout the frontal, parietal, and temporal neocortical regions. Changes were also observed in the anterior cingulate gyrus, hippocampus, caudate nucleus, and cerebellum.

As described earlier, Koffler et al. (2007) found improved performance on tests of attention and processing speed in a small sample of CRPS patients who underwent coma treatment. However, to our knowledge, this is the first large-scale neuropsychological analysis of patients with CRPS. Our aim was to assess for specific patterns of neuropsychological impairment. Based on the neuroimaging and other research findings discussed earlier, it was our expectation that differential executive system impairments would be associated with CRPS. To determine patterns of neuropsychological impairment, a statistical cluster analysis algorithm was used in which the number of clusters sought was not predetermined. A three-cluster solution was obtained. Approximately 35% of patients presented with no neuropsychological impairment (CRPS group1). The remainder of our sample presented with either mild dysexecutive deficits (CRPS group 2; 42% of patients) or a more global profile of cognitive impairment involving reduced performance on tests that assess working memory/mental search (executive tests) along with problems on tests of naming and memory (CRPS group 3; 22% of patients). It is important to mention that, as far as we could determine, these patterns of neuropsychological impairment are independent of the spread of CRPS (i.e., number of limbs involved), illness duration, and medication use.

An examination of the neuropsychological profiles obtained from CRPS groups 2 and 3 reveal some interesting points of convergence. First, both of these patient groups displayed equal impairment on executive tests. For patients in CRPS groups 2 and 3, their ability to repeat digits backwards was mildly, but measurably, reduced compared to CRPS group 1 (normal CRPS group). This suggests some compromise regarding patients' ability to engage in higher-order mental manipulation. Effective performance on a digits backward test is generally believed to rely a working memory/visual imagery mechanism(s), whereby individuals must keep in mind a visual image of the number sequence and then 'peel off' numbers in reverse order (Wambach et al., in press). Recent evidence obtained from patients with dementia link reduced performance on a backwards digits span test to differentially greater white matter disease affecting the left posterior inferior parietal lobule (Lamar et al., 2008), an area of the brain known for cross-modal cognitive operations and for its extensive connections with the left dorsolateral prefrontal cortex (Catani, Jones, Donato, & Ffytche, 2003). Moreover, Lamar et al. (2007) found that attenuated output on letter fluency tests and reduced performance on a backwards digit span test were highly correlated. There is now extensive literature linking reduced letter fluency test performance with left inferior frontal lobe pathology (Libon et al., 2009). Future research may determine if altered frontal systems functioning underlie poor digit span and letter fluency test performance in CRPS.

It is interesting to speculate about the neuroanatomy that might underlie these three patient groups. Because neuropsychological test scores in CRPS group 1 were in the average range, it is possible that these patients may be less affected by central nervous system involvement. On the other hand, the predominance of executive deficits that typify CRPS group 2 (dysexecutive) might suggest differential involvement in a network of structures involving projections to and from the frontal lobes. This is consistent with the functional imaging research discussed earlier. In CRPS group 3, mild executive deficits were found, but greater impairment was found on tests that involve naming and memory. Several scenarios might account for this. First, it is possible that for CRPS 3, temporal lobe, as well as frontal lobe, involvement might be present. However, because there is little evidence for primary anterograde amnesia in any group, the hippocampus, as well as other midline structures known to be associated with a primary anterograde amnesia, may not be involved. Alternatively, the neurocognitive networks that underlie CRPS groups 2 and 3 might be the same, but differ only in terms of the level of extent of brain involvement. Neuropsychological and fMRI studies, obtained both before and after treatment, could help resolve these issues.

The profile produced by CRPS group 3 on tests of memory also suggests the presence of executive (i.e., retrieval) rather than amnesic (i.e., encoding) problems. The delayed free recall for CRPS 3 was quite low, in that on average these patients could recall only 6 of 16 original target words. Superficially, such behavior might suggest a striking amnesia or an encoding problem. However, on the delayed recognition test, patients from CRPS group 3 demonstrated improvement, in that 13 of the 16 original target items were correctly identified. Such behavior suggests the presence of a source recall problem, a deficit linked to frontal systems impairment (Price et al., 2009).

Fibromyalgia is a pain syndrome that is thought to be related to CRPS. Recent functional imaging research with patients suffering from fibromyalgia reveals an altered network of neural structures involving dorsolateral and orbitomedial frontal areas, the anterior cingulate, and, in some studies, the parahippocampal gyrus (Burgmer et al., 2009; Kuchinad et al., 2007; Schmidt-Wilcke et al., 2007). Luerding, Weigand, Bogdahn, and Schmidt-Wilcke (2008) also studied a group of patients with fibromyalgia by using MRI voxel-based morphometry (VMB) and found an association between poor performance on the digits backwards test and a decrease in frontal lobe activity. Derailed or altered functioning in a network of anatomic structures, as described above, would be consistent with the executive, naming, and episodic memory deficits seen in the current research.

The current research is not without limitations. First, the patients studied tended to be refractory to treatment and chronically ill with average illness duration of almost seven years. Different findings might have been obtained from a less chronically ill group. Second, only a small number of neuropsychological tests were analyzed. Moreover, the executive control tests used in the current research were limited to an assessment of working memory/mental search. Other aspects of executive functioning, such as concept formation and set shifting, were not assessed. Future research should provide a more comprehensive assessment of executive control abilities. Different cluster groups might have emerged if other neuropsychological tests had been used. Third, the groups differed with respect to education and level of depression. In the current research, these factors were controlled statistically, and level of depression did not correlate with neuropsychological test performance. Nonetheless, future research should address possible effects of depression on cognitive functioning in CRPS. Finally, although there were no between-group differences in the number and types of medication, we could not determine other medication-related factors, such as exact medication duration for some patients. These variables could have affected performance on neuropsychological tests. Future research should guard against these potential confounds.

Despite these limitations, the neuropsychological data reported here is consistent with recent MRI-VBM imaging studies in CRPS and other pain syndromes, which suggest problems involving a wide network of cortical and subcortical areas, and provide additional evidence for CNS involvement in CRPS. As predicted, the current research also suggests that a dysexecutive syndrome tends to dominate the clinical profile in CRPS. The differences between CRPS groups 2 and 3 appear to relate to the severity of their executive, frontally mediated, cognitive deficits. It is possible that prospective research with CRPS and patients suffering from other pain syndromes, examining structural gray and white matter integrity in conjunction with neuropsychological test data will result in new insights regarding the brain–behavior relationships that are found in CRPS patients.

ACKNOWLEDGMENTS

The information contained in this article has not previously been published in any media; however, a portion of these data were presented at the 63rd Annual Meeting of the American Academy of Neurology, Seattle, WA. The authors have nothing to disclose.

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