Neuropsychological and Related Clinical Features Associated with Complex Regional Pain Syndrome: A Latent Class Analysis

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Authors’ contributions

This work was carried out in collaboration between all authors. Authors DJL, JE, RS, GMA and BLP designed the research and prepared the manuscript. Authors DAGD and KE managed the statistical analysis. Author CA designed the research and data coding, and was involved in manuscript preparation. Authors LD, EA and RJS examined the patients. Authors AB and JD carried out the data coding and manuscript preparation. All authors read and approved of the final manuscript.

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ABSTRACT

**Aim:** The current research examined neuropsychological and key features related to Geschwind-Behan-Galaburda (GBG) model (i.e., non-right handedness, learning problems, autoimmune disease) in patients with Chronic Regional Pain Syndrome (CRPS).

**Methods:** A large sample of patients with CRPS (n=509) were evaluated with a neuropsychological protocol that assessed executive control, language/lexical retrieval, and declarative memory. A portion of our sample was assessed with the modified Oldfield-Edinburgh questionnaire (n= 262) surveyed handedness, learning problems, and autoimmune disease was obtained on a portion of patients.

**Results:** Latent Class Analysis identified four neuropsychological classes: patients with moderate cognitive impairment (n= 44), patients with elements of an amnestic syndrome (n= 93), patients with intact but low average/average neuropsychological test performance (n= 191), and patients with average/high average neuropsychological test performance (n= 181). Elements of dysexecutive impairment were obtained in some groups. A minority, but statistically significant number of patients presented with mixed/non-right handedness (26.30%); learning disabilities/related problems (18.40%); and autoimmune disease (23.50; $P < .001$, all analyses). While intact neuropsychological performance was generally found in this large sample of patients with CRPS patients, elements of mild dysexecutive and amnestic impairment were observed in a portion of patients.

**Conclusion:** Neuropsychological impairment is present in a minority number of patients. The statistically significant incidence of non-right handedness, learning problems, and autoimmune medical disorders among a subset of patients is consistent with elements of the GBG model.

**Summary:** These data suggest the presence of mild neuropsychological deficits in some patients along with the possibility for anomalous brain development, suggesting a possible predisposition for CRPS in some patients.

**Keywords:** Complex regional pain syndrome; reflex sympathetic dystrophy; personality; neuropsychological functioning; neuropathic pain; Geschwind-Behan-Galaburda model.

1. **INTRODUCTION**

Complex Regional Pain Syndrome (CRPS) is a severe chronic pain disorder, with female predilection, often associated with significant trauma, surgery, a comparatively minor injury, or spontaneous onset that does not respect a nerve or root distribution [1-3]. Many aspects of CRPS are poorly understood; nonetheless, there is now a substantial body of research associating CRPS with alterations in brain functioning. For example, CRPS has been seen in conjunction with re-organization of sensory cortex and default mode network connectivity [4-8]. CRPS has also been associated with impairment on tests that assess body schema and parietal lobe functions [9-13]. Alterations in thalamic activity have been reported in patients with CRPS [13,14]. CRPS has been shown to disrupt white matter anisotropy, whole-brain gray matter volume involving frontal cortex, and frontal lobe/basal ganglia connections [15]. Lee et al. [16] demonstrated right dorsolateral and left ventromedial prefrontal cortical thinning along with poor performance on the Wisconsin Card Sort Test and other neuropsychological tests in patients with CRPS as compared to controls. Barad et al. [17] found that patients with CRPS presented with decreased gray matter volume in several pain-related regions of the brain including the dorsal insula, left orbitofrontal cortex, and cingulate cortex. Neuropsychological impairment has been reported in patients with CRPS including deficits on tests that assess emotional decision making [18,19]. Libon et al. [20] assessed a group of CRPS patients with a protocol of neuropsychological tests and used cluster analysis to sort patients into groups characterized by different neuropsychological profiles. Three distinct groups were found. While most patients obtained scores in the average range, elements of mild executive impairment were found in a minority of patients. Additional evidence suggesting altered neurological functioning stems from preliminary observations obtained from a subset of CRPS patients who presented with mixed/non-right handedness, a key feature of the Geschwind-Behan-Galaburda model where 20.80 percent of patients (n= 142) with CRPS presented with mixed/non-right handedness [21].

In the current research a large group of patients with CRPS was examined. Our goal was to
provide further evidence for the presence of both neuropsychological and possible neurological anomalies in CRPS. First, using a sample of approximately 500 patients we evaluated the existence of neuropsychological subtypes. In the current research, latent class analysis (LCA) was used to assess for CRPS subgroups that might differ in terms of quality and frequency of neuropsychological profiles. Second, on the basis of preliminary findings [21] we sought to provide additional evidence of neurological anomaly by determining the frequency of all three key features of the GBG model [22] i.e., mixed/ non-right handedness, presence of learning problems, and learning disabilities, as a function of LCA- determined class and in our sample as a whole.

2. METHODS

2.1 Participants

The sample consisted of a retrospective review of 509 outpatients diagnosed with CRPS from a university-affiliated clinic. This sample included the 137 patients described in our previous report [20] plus an additional 372 patients. All patients were evaluated and diagnosed with either CRPS I or II by an attending neurologist (RJS) who has considerable experience with CRPS. Inclusion criteria included (1) fulfilling International Association for the Study of Pain (IASP) diagnostic and modified research criteria for CRPS [23-24]; and (2) the ability to understand and complete neuropsychological and personality assessment. Exclusion criteria included the diagnosis of other conditions that might account for pain or neuropsychological impairment such as epilepsy, traumatic brain injury, and multiple sclerosis.

The mean age and education of our sample were 43.07±11.81 and 14.24±2.56 years, respectively. The mean level of depression as assessed with the Beck Depression Inventory- II (BDI-II) suggested moderate distress (17.00±10.49). The mean score obtained from the McGill Pain Inventory- Short Form was 26.26±10.73. Mean illness duration was 7.52 years (months= 90.31±78.56) and 72.20 percent of our sample was female. These data are consistent with prior research from our laboratory [20,25]. Research was conducted consistent with regulations put forth by the Drexel University College of Medicine Institutional Review Board (IRB) and the Declaration of Helsinki.

2.2 Neuropsychological Assessment

The neuropsychological protocol used in the current research was identical to the protocol described by Libon et al. [20] and assessed executive control, naming/ lexical retrieval, and declarative memory.

2.2.1 Executive control

This cognitive domain was assessed with the Digit Span subtest from the Wechsler Adult Intelligence Scale –III [WAIS-III; 26]. This test was administered following published instructions such that 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 (digits backwards). The dependent variable derived from this test was the age-corrected scale score. Executive functioning was also evaluated with tests of letter fluency (letters ‘FAS’). On the letter fluency test, participants were given 60s to generate words, excluding proper nouns and numbers, beginning with a specified letter. The dependent variable was the demographically corrected score [27].

2.2.2 Language (Naming and Lexical Retrieval)

Two tests were used to assess this cognitive domain, the 60-item version of the Boston Naming Test [28] and a test of semantic (‘animals’) fluency. On the ‘animal’ fluency test patients were asked to produce as many names of animals in 60s excluding perseverations and extra-category intrusion responses [27]. The dependent variables for both tests were demographically corrected scores.

2.2.3 Declarative memory

This cognitive domain was assessed with the California Verbal Learning Test-II [29]. This test was scored and administered using standard instructions. Two CVLT-II variables were used in the current research including total recall from the delayed recall test condition and a delayed recognition discriminability index, both corrected for age and sex.

2.2.4 Neuropsychological indices

All neuropsychological tests were expressed as scale scores (mean= 10; standard deviation= 3). Three neuropsychological indices were constructed: an executive index, a naming/
lexical access index, and a declarative memory index by averaging the two scale scores for each test from each domain of cognitive functioning.

2.3 Oldfield-Edinburgh Handedness Inventory

A portion of our sample was assessed using the Oldfield- Edinburgh Handedness Inventory (n=262). This inventory assessed the incidence of left-, mixed-, or right-handedness, the presence of learning disabilities and related conditions, and the presence of autoimmune disease as modified by Geschwind and Galaburda [30]. This inventory was completed independently by all patients with no participation from the examiner. From this inventory handedness was determined by the calculation of a Laterality Quotient [LQ; 31]. The degree of right-, mixed-, and left-handedness was expressed on a scale from -1.00 (total left handedness) to +1.00 (total right handedness). Also, queried using the Oldfield-Edinburgh Handedness Inventory was the presence of learning disabilities, history of stuttering, delayed speech; and whether patients have been diagnosed with any autoimmune disorder.

2.4 Statistical Analyses

2.4.1 Latent class analysis

In our previous report cluster analysis was used to examine CRPS subtypes based on neuropsychological test performance. In the current research latent class analysis (LCA) was used to identify homogeneous subgroups within a sample. LCA was used in the current research because our desire to examine for latent structure underlying the observed data [32]. LCA was conducted using scaled scores obtained from the six core neuropsychological variables described above. LCA uses a step-wise procedure and a variety of fit indices to determine whether the addition of classes improves the fit to the data [33,34]. There is no gold standard regarding the optimal fit indices for LCA. In the current research a combination of fit indices was used to determine the best model fit. First, a one- class (unconditional) model is fit to the data. The number of classes is then increased one class at a time until there is no additional improvement to the model fit [34,35]. In the current research fit indices used to determine an optimal model included the Bayesian Information Criterion (BIC), Akaike Information Criterion (AIC), and sample- size adjusted BIC [36-38]. The model that yields the smallest values on these indices is considered the best-fitting model. Additionally, a Bootstrap Likelihood Ratio Test (BLRT) was used to compare the model with k classes to the model with k-1 classes. If the BLRT p-value is significant, then the model with one additional class is a better fit to the data than the previous model. Classes comprised of fewer than 10% of the total sample suggest possible over-fitting of the data. Monte Carlo simulation studies using a variety of sample sizes suggest that the BIC and BLRT are the most robust fit indices and thus were given the most weight [35]. LCA also assigns patients into specific groups or classes based on their highest posterior probabilities. We also examined entropy, an index derived from the posterior probabilities across classes. Classes were also examined to determine whether they were theoretically sound and clinically meaningful based on previous research. Key demographic and clinical variables (i.e., age, education, pain as measured with the McGill Pain Inventory, and depression measured with the Beck Depression Scale- II) were included in latent class analysis to determine their effect on the final latent class solution.

2.5 Geschwind-Behan-Galaburda Model

The proportion of patients with left/ mixed handedness versus right handedness; learning problems and related conditions including speech delay and history of stuttering; and autoimmune disorders was analyzed with chi-square analyses where LCA- determined class was the independent variable. As noted above, the degree of right-, mixed-, and left-handedness was determined with Oldfield- Edinburgh Questionnaire Laterality Quotient [LQ; 31] where handedness is expressed on a scale from -1.00 (total left handedness) to +1.00 (total right handedness). Scores from -1.00 to -0.10 suggest varying degree of left-handed preference; a score of zero suggests ambidexterity; scores between +0.10 to +0.69 suggest partial right-hand preference; a score of >+0.70 suggests strong right-hand preference. Following suggested guidelines [30-31] a cut score of <0.69 was used to operationally characterize two LQ- defined groups: patients with left/ mixed hand dominance (LQ= <+0.69) and patients with right-hand preference (LQ= >=+0.70).

Fisher Exact Tests were used to assess whether the percent of patients in our sample differed
from population parameters. Research suggests that approximately 12 percent of the population present with left- or mixed-hand edness [39]. Based on data from the Center of Disease Control (CDC), the incidence of learning disabilities and autoimmune disorders in the United States population is approximately 7.66 percent [40] and 8.00 percent [41], respectively. Using Fisher’s Exact Test all three of these benchmarks were used to assess statistical significance of these factors within our sample.

3. RESULTS

3.1 Latent Class Analysis (LCA)

LCA identified different classes than the solution described by Libon et al. [20]. Rather than the 3-group solution described previously described [20], the best fitting model based on the LCA included four classes or groups (Tables 1a & 1b). Posterior probabilities were very high and ranged from 0.99 to 0.85.

The first class can be described as patients with moderate neuropsychological impairment (n= 44) as scores obtained from the three neuropsychological indices were approximately at the 9th percentile. The second class can be described as presenting with elements of amnesia (n= 93). In this group, scores derived from the declarative memory index score were at the 9th percentile; however, scores derived from the executive and naming/lexical access indices were in the average range. The third class obtained scores in the average/low average range (n= 191) on all three neuropsychological indices (25th – 50th percentiles). Finally, the fourth class obtained scores in the average to high average range (n= 181; 50th – 75th percentiles) on all three neuropsychological indices. The number of participants in the average/low average (n= 191) and average/high average (n= 181) latent classes comprised approximately 73 percent of our sample suggesting intact neuropsychological test performance in the majority of our patients.

Table 1a. Latent class statistics for CRPS sample

| Classes | Free parameters | LL | AIC | BIC | SS adj | BIC | BLRT | Entrophy |
|---------|----------------|----|-----|-----|--------|-----|------|----------|
| 1       | 12             | 6878.84 | 13781.68 | 13832.47 | 13794.38 | x | 1 |
| 2       | 19             | 6669.15 | 13376.31 | 13456.72 | 13396.42 | 0 | 0.74 |
| 3       | 26             | 6601.46 | 13254.93 | 13364.97 | 13282.45 | 0 | 0.68 |
| 4       | 33             | 6548.72 | 13163.45 | 13303.12 | 13198.38 | 0 | 0.72 |
| 5       | 40             | 6524.61 | 13129.22 | 13298.52 | 13171.56 | 0 | 0.74 |

LL = Log likelihood; AIC = Akaike information criterion; BIC = Bayesian information criterion; SS adj = Adjusted BIC; BLRT = Bootstrap likelihood ratio test

Table 1b. Latent class posterior probabilities

| n= 509 | Class 1 | Class 2 | Class 3 | Class 4 | Posterior probabilities |
|-------|---------|---------|---------|---------|-------------------------|
| n= 203 | 306     | 0.905   | 0.941   |
| n= 128 | 172     | 0.914   | 0.858   | 0.801   |
| n= 44  | 93      | 0.832   | 0.846   | 0.816   | 0.863   |
| n= 15  | 41      | 0.882   | 0.844   | 0.802   | 0.827   | 0.871   |
3.2 Clinical Characteristics
There were no LCA between-group differences for the number of limbs involved (m = 2.93±1.25) or the percent of body afflicted with pain (64.65±30.91). There were also no LCA between-group differences for the average number of medications patients were taking at the time of their assessment (3.64±1.61). In order to qualify for ketamine treatment patients needed to discontinue the use of opiates. Nonetheless, many patients were taking opiates as well as other classes of medication at the time of their evaluation. No LCA between-group differences were obtained for percent of patients taking opiate (44.20%), nonsteroidal anti-inflammatory drugs NSAID (63.00%), depression (62.30%), or seizure (61.00%) medication.

3.3 Between Group Neuropsychological Test Performance
The effect of LCA-determined group on neuropsychological test performance was assessed with a multivariate analysis of variance (MANOVA) where the three neuropsychological indices were dependent variables. This analysis yielded a multivariate effect for LCA-determined group (F[9, 1157] = 150.04, \( P < .001 \), \( \eta^2_p = .539 \)). Follow-up univariate analysis of variance (ANOVA) found significant effects for LCA class for all three neuropsychological indices (\( P < .001 \), all analyses).

For the executive and naming/lexical access indices post-hoc (Scheffe) analyses found that all four groups were differentiated from each other (moderate group < amnestic group < low average/average group < high average group; \( P < .007 \), all analyses). On the declarative memory index, the moderate impairment and amnestic groups did not differ; however, both of these groups scored lowered than the other groups (moderate impaired group vs. low average/average group and average/high average groups; \( P < .001 \), both analyses; amnestic group vs. low average/average group and average/high average groups; \( P < .001 \), all analyses; Table 3).

3.4 Within-Group Neuropsychological Index Comparison
Patterns of neuropsychological impairment were also assessed with paired t-test comparisons. For the moderate impaired group, patients scored lower on the naming/lexical access versus executive index (\( P < .001 \)) and the memory index versus the executive index (\( P < .04 \)). For the amnestic group, patients scored lower on the declarative memory index compared to the naming/lexical access and executive indices (\( P < .001 \), both analyses). Patients in the low average/average group scored lower on the naming/lexical access and executive compared to the declarative memory executive indices (\( P < .001 \), both analyses). Patients in the average/high average group also scored lower on the naming/lexical access and executive indices compared to the declarative memory index (\( P < .001 \); both analyses).

Table 2. Demographic and clinical characteristics

| Demographic and clinical variables (n = 509) | Moderate impaired group | Amnestic group | Low average/average group | Average/high average group |
|--------------------------------------------|------------------------|----------------|----------------------------|---------------------------|
| Age                                        | 42.27 (11.98)          | 42.01 (11.93) | 43.00 (11.41)              | 49.90 (12.21)             |
| Education                                  | 12.60 (2.37)           | 14.03 (2.33)  | 14.01 (2.36)               | 14.82 (2.77)              |
| Illness duration                           | 91.09 (69.49)          | 99.37 (87.12) | 91.89 (78.13)              | 83.72 (76.95)             |
| Beck depression inventory- II              | 19.34 (11.84)          | 17.31 (11.12) | 18.02 (10.64)              | 15.53 (9.51)              |
| McGill pain inventory                      | 25.11 (10.09)          | 28.51 (12.63) | 26.95 (11.42)              | 24.68 (8.75)              |
| Percent body involvement                   | 64.55 (29.80)          | 65.74 (31.88) | 67.84 (29.21)              | 60.76 (32.22)             |
| Number of limb involved                    | 2.92 (1.28)            | 2.95 (1.29)   | 2.99 (1.18)                | 2.83 (1.29)               |

**Medication**

| Number of medications                      | 3.36 (1.50)            | 3.85 (1.76)   | 3.91 (1.50)                | 3.35 (1.65)               |
| percent NSAID medication                   | 50.00 (51.45)          | 58.62 (49.68) | 66.36 (47.47)              | 64.22 (48.15)             |
| percent depression medication              | 72.22 (46.08)          | 63.79 (48.48) | 61.11 (48.97)              | 62.33 (48.53)             |
| percent opiate medication                  | 50.00 (51.45)          | 41.38 (49.68) | 51.85 (50.19)              | 37.04 (48.51)             |
| percent seizure medication                 | 66.66 (48.50)          | 55.17 (50.16) | 70.37 (45.87)              | 53.70 (50.00)             |

NSAID = Nonsteroidal anti-inflammatory drug
Table 3. Neuropsychological test results (mean= 10; standard deviation = 3)

| Neuropsychological indices | Moderate impaired group | Amnestic group | Low average/ average group | Average/ high average group |
|---------------------------|-------------------------|---------------|----------------------------|----------------------------|
| Executive scale           | 6.65 (1.41)             | 9.13 (1.91)   | 8.16 (1.80)                | 11.17 (2.15)               |
| Language scale            | 5.59 (1.33)             | 9.37 (1.55)   | 8.37 (1.42)                | 11.01 (1.20)               |
| Memory scale              | 5.87 (2.12)             | 5.86 (2.12)   | 10.31 (1.68)               | 12.21 (1.72)               |
| Mean (sd)                 | 6.04 (1.07)             | 8.12 (1.29)   | 8.95 (0.92)                | 11.47 (1.01)               |
| 9th percentile            | 25th percentile         | 36th percentile| 63rd percentile            |                            |
| CVLT-II within group comparisons |                   |               |                            |                            |
| CVLT-II trial short delay free recall | 6.71 (2.38) | 7.98 (2.43)   | 10.43 (2.46)               | 12.60 (2.34)               |
| CVLT-II long delay free recall | 4.31 (2.51) | 6.032 (2.35)  | 9.27 (2.70)                | 12.21 (2.19)               |
| CVLT-II delay recognition discriminability index | 6.25 (2.70) | 6.31 (2.04)   | 11.20 (2.28)               |                            |

Significance

- long delay < list A, trial 5; p < 0.001
- list A, trial 5 < long delay; p < .001
- list A trial 5, > long delay; p < .001
- long delay < recognition; p < .001
- long delay = recognition; p < .001
- long delay = recognition

3.5 Within-Group Performance

To learn more about declarative memory impairment as seen on the CVLT-II, paired t-tests were calculated comparing (1) list A, immediate free recall trial 5 recall, versus list A, long delay free recall versus performance on the delayed recognition test.

For the moderate impaired group, there was a decline in performance from list A, trial 5 versus long delayed free recall (P < .001); however, there was a statistically significant improvement when long delayed free recall was compared to delayed recognition test performance (P < .001), suggesting a retrieval-based problem. A different profile emerged for the amnestic group. For these patients, there was a decline from list A, trial 5 to long delay free recall (P < .001) with no improvement when delayed free recall was compared to delayed recognition test performance. For patients in the low average/ average group there no difference list A, trial 5 versus delay free recall performance. However, improved performance was obtained when delay recognition test performance was compared to long delay free recall test performance (P < .001). The high average group did not differ across CVLT-II test conditions.

3.6 Geschwind-Behan-Galaburda Model

No between-group difference was obtained for the Oldfield-Edinburgh Handedness Inventory LQ [30,31]. Interestingly, the average LQ for all four LCA- determined groups was near the cut score that separated patients with left/ non-right handedness from patients with right-hand preference (0.67 ± 0.54). However, for many LCA- determined groups, considerable variability was observed as LQ standard deviations approached their respective mean values (Table 4). A LQ frequency distribution was calculated; 13.40 percent of patients obtained values between -1.00 and 0.00 suggesting strong left-handed preference and/or ambidexterity; 12.30 percent of patients obtained values between +0.14 and +0.65 suggesting mixed hand dominance. Combining these groups, 26.30 percent of patients can be characterized with left/ non-right handedness. A Fisher’s Exact Test determined that the proportion of the total CRPS sample (n= 509) with left/ non-right handedness was statistically significant (χ² = 18.84; P < .001; phi = 0.18).

For other features of the GBG model there continued to be no LCA between-group difference for percent of the patients with learning disabilities/ related problems or autoimmune disorder. However, when the entire
sample was considered, 18.40 percent of patients described themselves as suffering with learning disabilities and/or having a history of stuttering or other speech problems; 23.50 percent of patients described themselves as suffering from at least one autoimmune disorder. Based on CDC benchmarks, the proportion of the current sample with both of these features of the Geschwind-Behan-Galaburda model was statistically significant (learning disabilities/related problems: $\chi^2 = 10.24, P < .001$, phi= 0.14; autoimmune disease: $\chi^2 = 16.55, P < .001; \phi= 0.18$). All three statistical comparisons yielded small to medium effect sizes.

4. DISCUSSION

The current research examined a sample of 509 patients with CRPS and was designed to elucidate some important neuropsychological and related clinical features including patterns of neuropsychological impairment as well as elements consistent with the Geschwind-Behan-Galaburda model. LCA revealed the existence of four neuropsychological classes or groups, rather than three groups as previously reported [20] including patients with moderate neuropsychological impairment; patients with elements of an amnestic syndrome; and two groups (low average/average and average/high average) where test scores were intact. A significant difference between current research findings compared to our previous study [20] is the emergence of a group of CRPS patients with elements of amnesia. Differences between the two studies could be due to the analysis of a larger sample and the use of more sophisticated statistics (LCA vs. cluster analysis). Also, the current research expressed neuropsychological performance in terms of demographically-corrected scale scores rather than raw scores.

Neuropsychological test performance in the current research is similar to our previous report in that the majority of patients with CRPS obtained test scores that were statistically WNL (n= 372; 73.08% of the sample). However, evidence for memory impairment [42] in the amnestic group was noted. When assessed between-group all four LCA-determined groups differed on the naming/lexical access and executive scales suggesting graded impairment in our sample for these neuropsychological constructs. Evidence for specific patterns of neuropsychological impairment was observed when indices were examined within-group. Despite low scores on all three neuropsychological indices, greater naming/lexical access deficits were seen in the LCA-determined moderately impaired group. The interpretation of this finding is unclear at the present time. Future research including a wider array of language-related skills may help clarify this observation. Although the neuropsychological index scores for the low average/average and average/high average groups were psychometrically WNL, within-group analyses revealed greater naming/lexical access and executive impairment compared to declarative memory performance [42-45]. Research combining imaging technology with a wider array of neuropsychological skills is needed to further investigate these patterns of performance.

Table 4. Handedness, learning disabilities/related problems, autoimmune disorder

|                         | Moderate impaired group | Amnestic group | Low average/average group | Average/high average group | Mean (sd); sum; or percent of sample |
|-------------------------|-------------------------|----------------|---------------------------|---------------------------|-------------------------------------|
| Laterality Quotient     | 0.681 (.609)            | 0.674 (.508)   | 0.658 (.600)              | 0.687 (.494)              | mean (sd) 0.672; (.547)             |
| (mean; standard deviation) |                        |                |                           |                           |                                     |
| Left/ Mixed Handedness  | 4 14                    | 26             | 25                        | 69; 26.30%                |                                     |
| (no. of patients; n=261)|                        |                |                           |                           |                                     |
| Learning Disabilities/  | 3 10                    | 21             | 15                        | 49; 18.40%                |                                     |
| Stuttering/ delayed     |                         |                |                           |                           |                                     |
| speech (no. of patients; n= 266) |       |            |                           |                           |                                     |
| Autoimmune Disorders    | 7 15                    | 22             | 18                        | 62; 23.50%                |                                     |
| (no. of patients; n= 264) |                        |                |                           |                           |                                     |
Other evidence for dysexecutive impairment was found in the analysis of memory test performance in patients with moderate and low average/average neuropsychological test performance. In both groups there was improvement on the delayed recognition test trial compared to the output on the delayed free recall test condition suggesting a retrieval-based problem. Similar patterns of impairment have been described in dementia patients with subcortical white matter alterations [42] and in patients with frontal lobe lesions suggesting a source recall problem rather than true amnesia [46]. The posterior parietal region, an area of the brain thought to be affected in CRPS [9] has also been implicated in source recall memory problems [47]. From a clinical perspective the elucidation of dysexecutive and amnestic impairment in selected patients may be helpful with regard for the need of possible compensatory strategies that might aid with treatment adherence.

The second issue examined in the current research revolved around key features of the Geschwind-Behan-Galaburda model model in CRPS. In a preliminary analysis of a subset of the patients analyzed in the current research, we reported [21] found that 20.80 percent of patients presented with mixed or left-handedness. This finding was sustained in the current research. To our knowledge this is the first report to comment on all key elements of the GBG model in CRPS. At the center of the GBG model is the notion that cerebral dominance can be modified prenatally via sex hormones such as testosterone. The emergence of mixed and/or left-handedness may be due to the deleterious effect of testosterone during gestation such that left-side brain development is either slowed or altered. This may account for the transfer of motor dominance to the right-brain, hence the phenotypic emergence of left and/or mixed handedness. The link between testosterone exposure in utero and immune disorders is hypothesized to be mediated by the deleterious effect that testosterone may exercise on the immunological functions of the developing thymus gland. The result of hypothesized deleterious effects of testosterone on the thymus gland suggest after birth, postnatal thymus activity and its regulation of immune-related development are compromised.

The GBG model is far reaching and attempts to link derailed prenatal events with alterations in many bodily systems involving not just the immune system but also skin and skeleton development. Geschwind and Galaburda asserted that prenatal events, as described above, can deraill physiological functions not just in childhood, but in middle life. For example, it is has been our anecdotal observation that some patients with CRPS suffer injury in early life but enjoyed full recovery. Why then, does significant pain emerge as the result of subsequent injury? A possible explanation is that, for reasons yet to be determined, deleterious alterations in cerebral dominance that occur in utero are 'time-linked' and are expressed phenotypically in later or midlife. These notions are speculative and require prospective investigation. Nonetheless, presence of elements of the GBG model could suggest a biological predisposition for CRPS in some patients. Research supporting the GBG model has been criticized because of low statistical power and the means by which handedness is measured [48,49]. Despite these criticisms, subsequent research does support an association between non-right handedness and autoimmune disorders such as asthma [50,51].

A potential problem linking key features of the Geschwind-Behan-Galaburda model to CRPS is that these characteristics were originally thought to be more clearly expressed in men rather than woman. This is juxtaposed with the observation that CRPS favors women rather than men. However, Meland et al. [52] has pointed out that testosterone binds to the X chromosome linked androgen receptor that contains a polymorphic polyglutamine CAG repeat. The length of this CAG repeat has been positively correlated with testosterone levels in males but negatively correlated in females. Meland et al. [52] found that female risk for left-handedness was greater in women with a greater number of repeats. In males the risk of left-handedness was greater in men with fewer repeats. How these findings may relate to CRPS requires prospective research.

Although data described above are intriguing, no firm conclusions can be drawn about how or if features of the Geschwind-Behan-Galaburda model are related to CRPS. Nonetheless, in a recent review, it has been suggested that autoimmune compromise in the form of an injury-triggered, regionally-restricted, autoantibody-mediated autoimmune disorder (i.e., 'IRAM') with a minimally-destructive course could, in fact, be an underlying feature of CRPS in some patients [53]. The evidence for this hypothesis is partially drawn from observations that some patients with CRPS respond to immunoglobulin treatment and...
that many CRPS patients have IgG serum-autoantibodies that may serve to activate autonomic receptors. It is interesting to speculate whether CRPS patients with features of the GBG model might show a positive response to IgG therapy.

5. SUMMARY
In sum, the current research extends our prior report [20] in that the vast majority of patients with CRPS present with intact neuropsychological abilities. Nonetheless, elements of mild dysexecutive and amnestic impairment can be detected in some patients. The current research also found a portion of patients present with key features of the Geschwind-Behan-Galaburda model. The current research has many strengths including the large sample size, the use of a neuropsychological protocol that have been thoroughly researched regarding underlying cognitive constructs, and advanced person-centered data analysis. However, significant limitations must be acknowledged. For example, imaging data to collaborate our findings regarding neuropsychological deficits was not available. Also, in addition to self-report, a direct assessment of potential learning problems using standard neuropsychological tests would have been helpful. Despite these limitations our observation that a minority, but statistically significant number of patients exhibit features of the Geschwind-Behan-Galaburda model is a new finding and suggests there may be a biological predisposition for CRPS in selected patients. Further links between CRPS and key features of the GBG model are warranted.

DEDICATION
This paper is dedicated to the memory of Norman Geschwind.

COMPETING INTERESTS
Authors have declared that no competing interests exist.

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