Irritable Bowel Syndrome Patients Versus Responding and Nonresponding Temporomandibular Disorder Patients: A Neuropsychologic Profile Comparative Study

Márcio L. Grossi, DDS, MS, PhD[a]/Michael B. Goldberg, DDS, Dip Perio, MSc[b]/David Locker, BDS, PhD[c]/Howard C. Tenenbaum, DDS, Dip Perio, PhD, FRCD(C)[d]

Purpose: This study aimed to assess the use of neuropsychologic tests as a tool to differentiate, or not, between a nonresponding chronic pain condition of nonmuscular origin, irritable bowel syndrome (IBS) (n = 20), versus 2 pain conditions of muscular origin, responding (n = 36) and nonresponding (n = 24) temporomandibular disorders. ***Materials and Methods:*** The neuropsychologic tests used were the simple and multiple-choice reaction-time tests, California Verbal Learning Tests, the Brown-Peterson Consonant Trigram Auditory Memory Test, Sleep Assessment Questionnaire, and Beck Depression Inventory, as well as fatigue and energy level assessments (100-mm visual analog scale). ***Results:*** Most of the tests used were capable of significantly differentiating between responding TMD versus IBS patients. Conversely, no statistically significant difference was found between nonresponding TMD versus IBS patients. Overall, the nonresponding TMD and IBS groups did worse in the neuropsychologic assessment than the responding TMD group, with higher memory deficits, levels of depression and fatigue, more sleep disturbances, and lower energy levels. ***Conclusions:*** These data suggested that 2 nonresponding chronic pain conditions of different origins may share similar neuropsychologic test results compared to a responding condition. These findings are consistent with the hypothesis that nonresponding chronic pain disorders, irrespective of peripheral location, may be regulated centrally and have similar neuropsychologic impacts.
Int J Prosthodont 2008;21:201–209.

In recent studies, more evidence has been presented in favor of the biopsychosocial model for chronic (nonresponding) pain, regardless of anatomic location or perceived etiology, in which more emphasis is placed on centrally mediated factors over possible local causes.[1] Indeed, neurophysiologic studies have shown that temporomandibular disorder (TMD) patients are more sensitive to and show augmented temporal integration of noxious stimuli compared to pain-free controls.[2,3] In addition, another study showed suppression of cortical responses and brainstem reflexes elicited by a predominantly nociceptive input in TMD patients, suggesting that a dysfunction of the trigeminal nociceptive system may be responsible for the maintenance of the chronic pain state.[4]

Clinical studies have shown that different types of chronic pain conditions (eg, TMD, headache and back pain) have similar clinical pain parameters (eg, intensity, chronicity, frequency, and pain-related disability) as well as similar levels of depression and impact on psychosocial functioning.[5] Another common chronic pain condition, such as irritable bowel syndrome (IBS), shares with TMD the fact that both are more prevalent among women, have decreased prevalence with age, and are probably self-limiting.[6,7]

Because of this fact, the assessment of psychosocial functioning (neuropsychologic testing) in TMD has received increased attention.[8–10] One study demonstrated that patients suffering from TMD as a re-

[a]*Associate Professor, Faculty of Dentistry, Catholic University of Rio Grande do Sul, Brazil; Temporomandibular Disorders Research Unit, National Council of Scientific and Technological Development, Brasilia, Federal District, Brazil.*
[b]*Assistant Professor, Faculty of Dentistry, Division of Periodontology, University of Toronto, Ontario, Canada; Wasser Pain Management Centre and Department of Dentistry Mount Sinai Hospital, Toronto, Ontario, Canada.*
[c]*Professor, Faculty of Dentistry, Community Dental Health Services Research Unit, University of Toronto, Ontario, Canada.*
[d]*Professor, Faculty of Dentistry, Division of Periodontology, University of Toronto, Ontario, Canada.*

Correspondence to: *Dr Márcio L. Grossi, PUCRS Dental School, Avenida Ipiranga 6681 Porto Alegre, Rio Grande do Sul, Brazil CEP 90619-900. Fax: 51 3320 3625. E-mail: mlgrossi@pucrs.br*

sult of a motor vehicle accident or those with closed head injury have significantly increased prevalence and magnitude of cognitive and neuropsychologic deficits (ie, memory, attention, and reaction time deficits) compared to patients with nontraumatic TMD.[11] Importantly, it was also shown that successful management in patients who develop TMD as a result of a motor vehicle accident is significantly reduced compared to successful management in nontraumatic TMD patients (48% versus 80%, respectively).[12] In another study, it was shown that nonresponding TMD patients with poor treatment outcomes have some degree of cognitive or neuropsychologic impairment in comparison with those with responding TMD who do recover, irrespective of management rendered.[13]

To investigate the model suggesting that nonresponding chronic pain, irrespective of initial etiology or anatomic location, may be related to centrally mediated mechanisms and have similar neuropsychologic impact, the authors selected 2 anatomically distinct chronic pain conditions—IBS and TMD—to study for the purpose of assessing their neuropsychologic profiles. The hypothesis was that the neuropsychologic cognitive function profiles in these 2 nonresponding chronic pain disorders would be not only identical, but also distinct (ie, worse) from that of the responding chronic pain group, even after adjusting for confounding variables.

Materials and Methods

This comparative study assessed the neuropsychologic profiles of patients with IBS versus those with TMD, both responding (rTMD) and nonresponding (nrTMD) to reversible treatment.

Data Analysis and Sample Size Calculation

The database and a system file were created in the SPSS Plus 11.5 program (SPSS). For the continuous variables, 1-way analysis of variance (ANOVA) and Tukey-b multiple range tests ($P < .05$) were used. The Tukey-b post hoc analysis was used because it is considered a conservative test to compensate for the multiple comparisons used. For the categorical data, the chi-square test was used ($P < .05$). For measures of association, the odds ratio (critical odds ratio = 2) was employed.[14] Calculation of sample size for 2 independent means was calculated from the means and standard deviations based on the results of the simple reaction time test (2-sided test at the .05 significance level for a power of 80%), which was chosen because it showed the smallest significant difference between the 2 TMD groups studied.[13,15,16] It was estimated that 57 patients had to be screened in the initial TMD group to obtain a sample of 17 individuals with nrTMD, which was increased to 20 to compensate for possible dropouts. The number of patients in the IBS group (n = 20) was similar to that of the nrTMD group to allow for comparisons within groups of similar numbers. In the logistic regression analysis, the role of confounding variables was assessed by the variation in the odds ratio. Any variable that changed the initial value by more than 15% was considered a confounder.[17] The influence of each significant confounding variable was analyzed individually by including all variables in the model (Method Enter).[11,18]

Study Population

Patients participating in this study were chosen from those newly diagnosed and seeking treatment for TMD in the Craniofacial Pain Research Unit of the Wasser Pain Management Centre at Mount Sinai Hospital, Toronto, Canada. The Human Ethics Committee of the University of Toronto approved the study and consent form.[13] Patients to be included in the TMD group, based on the history and clinical examination guidelines of the Research Diagnostic Criteria for Temporomandibular Disorders, were those with muscle disorders (groups Ia and Ib), including myofascial pain with or without limited opening, as well as those with arthralgia (group IIIa).[9] Only women between the ages of 15 and 45 years were selected to eliminate age and gender as confounders. TMD patients were excluded if they had a history of an arthritic condition (eg, osteoarthritis or rheumatoid arthritis) or traumatic injury, as well those with a history of metabolic disorders (eg, diabetes, hyperthyroidisim), neurologic disorders (eg, dyskinesia, trigeminal neuralgia), vascular diseases (eg, migraine, hypertension), neoplasia, psychiatric disorders, drug abuse, and motor vehicle accidents, as well as those currently receiving medication affecting the central nervous system (eg, muscle relaxants, anticonvulsants, antidepressants) or with major visual, auditory, or motor impairments.[13]

IBS patients were women who had been previously treated for the condition, fluent in English, between the ages of 15 and 45 years (age-, language-, and sex-matched at baseline with TMD patients), and referred by gastroenterologists from major gastroenterology outpatient clinics in general hospitals. Patients were also recruited by newspaper ads. When the patient was recruited from newspaper ads, the treating clinician was contacted, with previous authorization of the patient, to confirm the diagnosis that the patient had been previously treated for the condition. They were also selected by the examiner based on the medical history following the Rome guidelines. This category included persons who experienced abdominal pain more than 6 times in the prior year, in combination with 2 or more of the fol-

lowing symptoms: pain that was often not relieved by defecation (more than 25% of the time), looser and more frequent stools along with abdominal distension when pain began, a feeling of incomplete evacuation, and mucus per rectum. A cutoff score of 2 or more criteria was used.[19]

Clinical Examination, Treatment, and Improvement Criteria

All groups (rTMD, nrTMD, and IBS) underwent the neuropsychologic tests, but only the 2 TMD groups were submitted to clinical examination. This was a result of difficulties in recruiting IBS patients willing to undergo both neuropsychologic tests and TMD clinical examination, and priority was given to the latter because of its originality. Next, TMD patients underwent clinical examination by a single experienced clinician in the following order according to the Research Diagnostic Criteria for TMD: palpation of the temporomandibular joint and masticatory muscles extraorally (masseter, temporalis, and sternocleidomastoid) and intraorally (medial and lateral pterygoid area, and insertion of the temporalis) and measurement of maximum unassisted mandibular opening. The clinical examination was performed last to prevent possible pain exacerbation after examination, which might interfere with the neuropsychologic test.[9,13]

Following the initial examination, TMD patients entered into the treatment phase. The reversible treatment(s), employed at the discretion of the 4 experienced treating clinicians, were as follows: mandibular acrylic flat bite plane with full posterior and cingulum coverage in the anterior; low-dose muscle relaxant (cyclobenzaprine, 5 to 10 mg at bedtime for 30 days); nonsteroidal anti-inflammatory (diflunisal, 500 mg twice daily for 30 days); and physical therapy (moist heat, massage, ultrasound, and manipulation).[13]

The improvement criterion after a 6-month follow-up for both rTMD and nrTMD groups was a 30% reduction as a percentage of the baseline assessment in pain at rest (100-mm visual analog scale). This cutoff point has shown an improvement in 70% of patients in a previous study, which is consistent with the available literature, and pain at rest (spontaneous pain) is the main reason for TMD patients to seek treatment.[13] TMD patients who met the improvement criterion were included in the rTMD group, while those who did not were included in the nrTMD group.

Neuropsychologic Testing

The tests used in the study were based on a previous study that employed neuropsychologic tests to compare TMD as a result of a motor vehicle accident population with a nontraumatic TMD population.[11] All 3 groups (rTMD, nrTMD, and IBS) underwent a battery of verbal and nonverbal neuropsychologic tests. Patients' reaction times were measured when presented with a given set of stimuli. Initially, patients were presented with the task of responding to a simple stimulus (simple reaction time test [SRT]), where the speed at which the subject pressed a button held in their dominant hand in response to a circle, square, triangle, or cross was recorded. Subsequent reaction times to more complex target and nontarget stimuli (color and internal structure were added) were measured. Reaction to the target/nontarget stimuli was calculated, along with an assessment of the number of errors made by each subject when they pressed an incorrect button: multiple choice reaction time test (MCRT), multiple choice reaction time test with conflict (MCRT-CF), and multiple choice reaction time test with constraint (MCRT-CT).[20,21]

Next, patients were presented with a task assessing immediate, short-term, and long-term recall of words in a 16-item, 4-category "shopping list" (California Verbal Learning Test [CVLT]).[22,23] The CVLTs were assessed on the basis of number of correct responses (CVLT-CR), the number of word clusters (CVLT-CL), the number of word preservations (CVLT-P), and word intrusions (CVLT-I). Finally, a memory function test with a verbal interference (Brown-Peterson Consonant Trigram Auditory Memory Task [CCC]) was also included, where subjects were asked to repeat 3 consonants presented after being challenged with a continuous mathematical subtraction problem for 3, 9, or 18 seconds. The total number of correct consonants repeated was scored, regardless of the order in which the subject repeated them.[24]

To assess the levels of depression, the long form of the Beck Depression Inventory (BDI) was used.[25] Sleep patterns may also correlate with treatment outcome in TMD patients.[13,26] To assess sleep disorders, a polysomnography-validated 19-item self-administered questionnaire was used (Sleep Assessment Questionnaire [SAQ]). Normative data, test description, reproducibility, and validity of the SAQ have been previously published.[27,28] Fatigue and energy level were assessed using a 100-mm visual analog scale (VAS), because of a lack of standardized questionnaires for both factors.[29,30]

Results

After assessment of TMD treatment outcome, data were obtained from 36 rTMD patients and 24 nrTMD patients, as well as from 20 age-, language-, and sex-matched IBS patients. The variables described here are only the ones tested for all groups. The success rate among the 4 treating clinicians was 60% (range: 38.1% to 61.9%; chi-square test, $P > .05$), regardless of the

Table 1 Sociodemographic Characteristics of the Populations Studied at Baseline

Independent variables*	rTMD (n = 36)	nrTMD (n = 24)	IBS (n = 20)
Educational level (%)			
Postsecondary diploma/certificate or higher	74.3	50.0	75.0
Some education after high school or less	25.7	50.0	25.0
Employment (%)			
Employed	74.3	58.3	50.0
Unemployed	25.7	41.7	50.0
Income (%)			
≥ CAN$40,000	60.6	16.7	35.0
≤ CAN$39,000	39.4	83.3	65.0
Mean age (y)	29.4 ± 9.0	26.7 ± 9.0	32.9 ± 10.5

*Only income showed statistical significance ($P < .01$).

treatment modality employed. For the purpose of this paper, the main comparisons were made between IBS and nrTMD patients as well as between IBS and rTMD patients. A more detailed description of rTMD versus nrTMD can be found in a previous publication.[13] Only 19% of all orofacial pain patients met the inclusion criteria, and of these, 50% agreed to participate in the study (n = 60).

Social and Demographic Distribution Variables

As described in Table 1, the different groups, which were age-, language-, and sex-matched at baseline, still remained mostly indistinguishable after data collection, with the exception of income. The data also demonstrated that the majority of subjects in all groups had postsecondary education and were predominantly employed, and no significant difference was found in both variables. No significant age difference was found among groups. Finally, most patients were from a low income social stratum, earning CAN$39,000 or less per year, with the exception of rTMD patients, who were predominantly from a high income group and were statistically different from the other 2 groups ($P < .001$).

Neuropsychologic Tests and Pain Comparisons

There were no significant differences in reaction time (ie, SRT, MCRT, MCRT-CF, and MCRT-CT) among rTMD, nrTMD, and IBS patients. However, nrTMD and IBS patients had worse reaction time results in general compared to rTMD patients, though the actual differences (range: 8 to 36 ms) observed among the 3 groups were very small (less than 100 ms) and were not considered to be relevant.[31–33]

In contrast with reaction time, significant differences ($P < .01$) were found in most attention and verbal memory tests (ie, CVLT-CR, CVLT-CL, and CCC) among the 3 groups (Table 2). The rTMD patients performed significantly better than those with IBS on the neuropsychologic tests, which evaluated attention and short-term verbal memory under interference. In the CVLT-CR, rTMD patients remembered considerably more correct words in a shopping list (13.2%) than those with IBS. Similarly, rTMD patients were able to group more words based on their semantic meaning in the CVLT-CL (42.1%) than the IBS group. Finally, responding TMD patients were able to remember more trigrams (groups of 3 letters) in the CCC after verbal interference (9.6%) than were IBS patients. The only exceptions were the CVLT-P and CVLT-I, which were nonsignificant, most likely because of their small number of responses and consequent higher variability. Similarly, IBS patients had significantly higher sleep disorder scores on the SAQ (30%) and depression scores on the BDI (92.3%) compared to rTMD patients ($P < .01$). Fatigue was significantly higher ($P < .01$) in IBS patients (42.5%), and their energy level was significantly ($P < .05$) lower (35.2%) according to the VAS measurements in comparison with rTMD patients. In contrast, pain at rest was significantly lower ($P < .01$) in IBS patients than in rTMD (31.2%) patients.

A comparison of nrTMD and IBS patients showed that all neuropsychologic tests used in this study were nonsignificant. In the CVLT-CR, both groups had identical scores (53). In the CVLT-CL, IBS patients were capable of grouping only 5.5% more words than nrTMD patients. In the CCC, IBS patients obtained scores only 3.3% higher than those of nrTMD patients. As expected because of their limited number of responses and higher variability, CVLT-P and CVLT-I scores were 23.2% lower and 100% higher when comparing IBS and nrTMD patients, respectively. In addition, IBS subjects also had similar scores for sleep disorders (8.3% higher), depression (36.3% higher), fatigue (4.4% lower), and energy level (34% lower) compared to nrTMD patients. The only exception was pain intensity at rest, which was significantly lower ($P < .01$) in IBS patients than in nrTMD (29%) patients. However, pain duration for all 3 groups ranged between 3 and 5 years on average, with great variability, and the results were nonsignificant.

Table 2 Means (SDs) of the Neuropsychologic Tests and Pain Comparisons Between and Among the Study Groups*

Independent variable	rTMD (n = 36)	nrTMD (n = 24)	IBS (n = 20)	Significance†
SRT (ms)	249 (60)	261 (67)	241 (34)	NS
MCRT (ms)	437 (61)	477 (92)	452 (47)	NS
MCRT-CF (ms)	484 (73)	528 (107)	492 (56)	NS
MCRT-CT (ms)	447 (66)	480 (99)	469 (71)	NS
CVLT-CR (0–80)	60 (8.5)[a,b]	53 (10)[a]	53 (9)[b]	$P = .006$
CVLT-CL (0–60)	27 (11)[c,d]	18 (7.4)[c]	19 (10)[d]	$P = .001$
CVLT-P (0–40)	5.3 (6.2)	5.6 (4.2)	4.3 (2.9)	NS
CVLT-I (0–10)	0.6 (1.0)	0.7 (1.4)	1.4 (1.8)	NS
CCC (0–45)	34 (6.3)[e]	30 (6.3)	31 (4.8)[e]	$P = .009$
Fatigue (100-mm VAS)	47 (28)[f,g]	67 (25)[f]	67 (25)[g]	$P = .007$
Energy (100-mm VAS)	51 (25)[h]	43 (25)	33 (24)[h]	$P = .04$
SAQ (0–68)	20 (6.2)[i]	24 (6.8)	26 (8.3)[i]	$P = .008$
BDI (0–63)	7.8 (6.4)[j]	11 (6.9)	15 (9.7)[j]	$P = .002$
Pain at rest (100-mm VAS)	64 (25)[k]	62 (19)[l]	44 (14)[k,l]	$P = .006$
Pain duration (mo)	47.4 (53.8)	41.6 (45.7)	32.9 (30.5)	NS

*Same superscript letter indicates significant difference (Tukey-b multiple range test; $P < .05$).
†One-way analysis of variance ($P < .05$).
SRT = simple reaction time test; MCRT = multiple choice reaction time test; CF = conflict; CT = constraint; CVLT = California Verbal Learning Test; CR = correct responses; CL = cluster; P = preservation; I = intrusion; CCC = Brown-Peterson Consonant Trigram Test; SAQ = Sleep Assessment Questionnaire; BDI = Beck Depression Inventory; NS = not significant.

Confounding Variables

Regarding the logistic regression analysis, 4 confounders that could not be controlled for during the design stage (ie, educational level, employment, income, age) were compared using bivariate analysis between the 2 groups after data collection. With the exception of income, none of the confounders affected the neuropsychologic (reaction time and verbal memory) test results (Table 1). In addition to these traditional confounders, the role of sleep disorders, depression, and pain intensity and duration in the significant verbal memory tests was also verified. In total, 5 confounders were included in the logistic regression analysis: income, pain at rest, pain duration, depression (BDI), and sleep disorders (SAQ). All variables were analyzed in combination (Method Enter). The odds ratios for the neuropsychologic tests did not change (1% to 7%) by more than 15% in any direction among all 3 groups (Tables 3 and 4). The range of percent correct observations was also very high (76.6% to 82.5%). Despite that, sleep disorders, depression, income, and pain duration were more associated with the test results than was pain at rest.

Discussion

Social and Demographic Distribution Variables

The socioeconomic and demographic distribution for IBS is similar to that shown in other studies (Table 1). Basically, IBS patients tended to be between the ages of 19 and 41, predominantly women (92%), well educated (average: 12 to 15 years of education), middle to high income level (US$35,000 or higher), and employed (59%).[7,19] The distribution of TMD patients was also similar to that seen in the literature, with the majority being women with a mean age of 28.3 years (± 9.0), a high level of education (postsecondary diploma/certificate or higher, 64.4%), employed (67.8%), and from a lower income group (CAN$39,000 per year or less, 57.9%).[5,11,13]

Neuropsychologic Tests and Pain Comparisons

No statistically significant difference was found in any of the reaction time tests or short-term verbal memory tests under interference between nrTMD and IBS patients, and the actual difference in all tests was extremely small or nonexistent (Table 2). Similarly, fatigue, energy level, pain duration, depression, and sleep disorder scores also showed similar and nonsignificant differences between the 2 groups. Reaction time tests in all 3 groups were equivalent although faster than similar measures performed on patients with TMD as a result of a motor vehicle accident and with a closed head injury.[11,20,21] The relevance of this finding will be discussed later.

Alternatively, rTMD patients performed at a higher level on most verbal memory tests than IBS patients. Additionally, the IBS group reported significant differences in fatigue, energy level, and depression, with IBS patients generally doing more poorly. This study agrees with a similar study that investigated whether people with an organic disease (inflammatory bowel disease) showed cognitive dysfunction relative to a control group and people with a functional illness (IBS). The illness groups showed a deficit in verbal IQ relative to both their own performance IQ and to that of the control group's verbal IQ.[34]

Table 3 Odds Ratios (OR) and Variations of OR* of Neuropsychologic Tests Versus Confounders: rTMD Versus IBS Using Logistic Regression Analysis (Method Enter)

Test†	Study groups alone	Income	Pain at rest	Pain duration	BDI	SAQ	Study groups and all variables (variation of OR)
CVLT-CR	0.92	0.75	0.61	0.99	1.04	1.09	0.89 (3.7%)
CVLT-CL	0.93	0.70	0.63	0.99	1.04	1.11	0.94 (1%)
CCC	0.90	0.64	0.62	0.99	1.03	1.10	0.91 (1%)

*Variation of OR greater than 15% when compared to test.
†Overall percent correct: CVLT-CR = 76.60%; CVLT-CL = 78.72%; CCC = 78.72%.
CVLT = California Verbal Learning Test; CR = correct responses; CL = cluster; CCC = Brown-Peterson Consonant Trigram Test; SAQ = Sleep Assessment Questionnaire; BDI = Beck Depression Inventory.

Table 4 Odds Ratios (OR) and Variations of OR* of Neuropsychologic Tests Versus Confounders: nrTMD Versus IBS Using Logistic Regression Analysis (Method Enter)

Test†	Study groups alone	Income	Pain at rest	Pain duration	BDI	SAQ	Study groups and all variables (variation of OR)
CVLT-CR	0.99	1.09	0.26	0.94	1.13	0.96	1.06 (7%)
CVLT-CL	1.02	1.08	0.24	0.94	1.14	0.95	1.10 (7%)
CCC	1.04	1.13	0.29	0.94	1.13	0.94	1.08 (3%)

*Variation of OR greater than 15% between groups alone and groups and all variables.
†Overall percent correct: CVLT-CR = 80.00%; CVLT-CL = 82.50%; CCC = 82.50%.
CVLT = California Verbal Learning Test; CR = correct responses; CL = cluster; CCC = Brown-Peterson Consonant Trigram Test; SAQ = Sleep Assessment Questionnaire; BDI = Beck Depression Inventory.

In most memory tests, nrTMD and IBS patients performed similar to or worse than rTMD patients (Table 2). The former groups also had higher levels of depression, sleep disorders, and fatigue and lower levels of energy compared to rTMD patients. The only exception was pain at rest, for which rTMD and nrTMD patients were indistinguishable from each other and significantly different from IBS patients. Pain duration was also higher in both rTMD and nrTMD patients than in IBS patients, but this was not statistically significant, and may have resulted in part from the high variability observed. The clinical significance of this finding will be discussed below.

Five confounders that could not be eliminated in the design stage were controlled in the analysis stage and included in logistic regression analysis: income, pain at rest, pain duration, depression (BDI), and sleep disorders (SAQ). The variables were analyzed in combination (Method Enter) to allow direct comparison of all variables in the 6 models created and did not change the odds ratio of the verbal memory tests by more than 15% in any direction (Tables 3 and 4). These 6 models were capable of predicting more than 75% of the results, which is considered high.[16–18] Therefore, the 5 confounders included in the logistic regression analysis appear not to have influenced the neuropsychologic tests. These findings also agree with a previous publication in which this verbal deficit presented by IBS and inflammatory bowel disease patients could not be explained by depression, cognitive load, or medication.[34] The average success rate among the 4 treating clinicians (60%) was not significant and consistent with the literature, despite the 4 reversible treatment modalities employed. These 2 variables did not influence the results.[11,13]

The findings of this investigation strongly suggest that the neuropsychologic scores from 2 groups of patients who are nonresponding to treatment (nrTMD and IBS) are more similar to each other than to the scores from 1 responding group (rTMD), despite the origin of pain; however, because of the study design, which was not longitudinal, these findings should be interpreted carefully. Regarding the reaction time tests, a larger sample might have disclosed significant differences; however, the results would not be clinically relevant (100-ms minimum, which was much higher than the absolute difference of 12 to 44 ms). Similarly, in all the other nonsignificant neuropsychologic tests, the absolute difference was also small or sometimes equal (Table 2). Regarding the tests that were significant, the absolute differences were very large (9.6% to 92.3%), and most tests, with the exception of the CVLT-CR and CCC, produced differences larger than 20%. Therefore, in the majority of the tests, the difference was not only significant but also clinically relevant. Thus, even with a larger sample size, the conclusions would remain the same, particularly when considering all tests in combination.

One interesting finding is that sleep disorders, depression, income, and pain duration were more associated with the verbal memory test results than pain at rest (Tables 3 and 4). One explanation is that the tests used in this study, which showed statistical significance

and predominantly assessed verbal memory, short-term memory, and short-term memory under interference, require more complex functional demands and higher levels of attention and information processing. This means that higher levels of affective disorders (ie, sleep and depression) and the duration of pain may interfere with more complex abilities (attention and verbal memory), but not with more simple functions such as reaction time tests (attention). On the other hand, traumatic injuries that affect the brain, as seen in patients with closed head injury or in TMD patients after motor vehicle accidents, have been shown to affect more basic functions, such as those seen in reaction time tests.[11,20,21] However, these 2 hypotheses are still highly speculative at this time. Hence, it would appear that the nrTMD patients and other populations studied here are not as "disabled" as those with TMD pain after a motor vehicle accident or closed head injury.

The results reported in this investigation are consistent with the notion that there are several similarities in subjects suffering from chronic pain, particularly nrTMD and IBS patients. IBS is more prevalent among women, has decreasing prevalence with age, and is probably self-limiting, which parallels data reported for TMD.[7,35] The findings in this study were very similar to those described by Von Korff et al in an epidemiologic study of pain complaints, in which similar prevalences were shown for headache, abdominal pain (IBS), chest pain, and facial pain (TMD) over a 6-month period.[5] Further, pain intensity level appeared similar among all groups that also had similar numbers of average lost days of work over a prior 6-month period. IBS and TMD have been associated with affective disorders (ie, fatigue, unrefreshing sleep, and emotional distress), which are known to be common in other chronic pain conditions, such as chronic fatigue and myofascial pain syndrome.[36–38] In this investigation, however, TMD subjects were separated into responding and nonresponding groups. Using this approach, it was shown that the neuropsychologic profiles seen in nrTMD and IBS patients were virtually identical, while both IBS and nrTMD subjects could be readily differentiated from the rTMD group. These findings may suggest that IBS and nrTMD rely on similar central pain processing mechanisms with similar neuropsychologic consequences as a result of the nonresponding chronic pain. This was further supported by the logistic regression analysis, which showed that pain duration seemed to be more related to the neuropsychologic findings than pain intensity (Tables 3 and 4). Indeed, pain intensity at rest was almost identical between rTMD and nrTMD patients but significantly different from IBS patients, which contrasted with all the other neuropsychologic findings (Table 2).

Conclusion

One limitation of this study, besides its relatively small sample size, is the fact that it is still not clear as to what extent IBS and nrTMD symptoms—and most likely those from other chronic pain conditions—represent a normal appraisal of an abnormal function or an abnormal appraisal of a normal function. It must be emphasized that the presence of cognitive difficulties of the nrTMD and IBS patients compared to rTMD patients does not establish per se a cause and effect relationship. However, what this study does seem to suggest is that neuropsychologic tests may be useful diagnostically and prognostically.[13]

Despite its wide distribution, the average pain duration reported for all 3 groups, ranging from 3 to 5 years, is comparable to another study (7 years), which concluded, "dating of pain onset may have satisfactory reliability for research purposes (ICC = .80)."[39] This long-term chronicity could have important implications with regard to the management of chronic pain conditions. Considering that chronic pain conditions are multifactorial in origin, multidisciplinary teams may more effectively address a variety of conditions using reversible treatment modalities focused on central mechanisms. For example, the literature has shown that cognitive-behavioral therapy helps patients with IBS to increase recognition of the role played by attention allocation, personal appraisal style, and illness beliefs in maintenance of chronic pain and psychosomatic disorders. Cognitive-behavioral therapy has been useful for short-term and long-term management of IBS and TMD.[40,41] This is particularly true for nrTMD and IBS, which are essentially nonresponding pain/dysfunction conditions. Other forms of affective disorder management may also be employed; relaxation/stress therapy may be effective for management of IBS and TMD patients, possibly related to reduction in autonomic arousal and anxiety.[42–44] Indeed, a recent randomized controlled clinical trial (1-year follow-up) comparing usual conservative treatment of TMD by specialists versus a structured self-care intervention delivered by dental hygienists targeted to TMD patients reporting minimal levels of psychosocial dysfunction (Research Diagnostic Criteria for TMD Axis II), showed that the latter group presented decreased TMD pain, decreased pain-related interference in activity, a reduced number of painful masticatory muscles, and fewer additional visits for TMD treatment compared to the former group.[45]

Depression was common in IBS and nrTMD patients, which indicates lower levels of serotonin. This mediator is central in gut physiology, because it participates in the complex interplay between the gastrointestinal musculature and the enteric nervous system, autonomic nervous system, and central nervous system. Imbalance

in serotonergic levels may affect gastrointestinal motility, secretion, and visceral sensitivity. These alterations may manifest in symptoms associated with IBS, including abdominal pain, altered bowel habits (constipation and/or diarrhea), and bloating. Thus, gastrointestinal serotonergic drugs with known effectiveness have been developed for the treatment of IBS.[46] Previous findings of severe depression in nrTMD patients correlates well with previous studies (depression rate of 15.5% to 28%) that did or did not use the same methodology,[47–49] as well as with a previous study that not use the same population and methodology but showed that depression is an early predictor of chronic pain even after severe lower limb trauma.[50] This suggests that a decrease in brain serotonin levels may play a role in chronic pain and depression. The algesic effect in chronic pain and fibromyalgia patients has been reported.[51,52] Short-term and long-term effectiveness of low-dose tricyclic antidepressants (amitriptyline) as well as selective serotonin reuptake inhibitors corroborates this hypothesis.[53,54]

Based on the sleep disorder scores in this study, randomized controlled clinical trials with sleep medications (eg, Zolpidem, Zopiclone) must be carried out in nrTMD and IBS patients. Notably, Lavigne et al also reported a great number of sleep disorders (ie, insomnia, sleep apnea, and nocturnal bruxism) in patients with fibromyalgia and generalized chronic pain conditions.[55] It has been consistently reported that most chronic pain patients, including those with TMD, complain about sleep quality, and the data shown here certainly agree with that notion.[56–58] Despite the fact that sleep disorders, mood, and pain seem to be closely related, possibly because of the role of serotonin in both sleep disorders and depression, the true cause-and-effect relationships are still open for debate.

It is noteworthy that new data concerning nonresponding pain place particular emphasis on neuropsychologic and cognitive function, which may play important roles in pain processing and maintenance of the pain state. Further, neurophysiologic data show that the anterior cingulate cortex and other structures in the brain may play key roles in maintenance and modulation of chronic pain (eg, lower back pain).[59] Although peripheral triggering events surely play an important role in initiating pain, especially in different anatomic locations, the development of chronic and nonresponding pain may depend more on changes or malfunctions in the central nervous system than peripheral changes on disease.[60] Using functional magnetic resonance imaging, a recent study also reported that pain memory does exist and can be elicited without noxious stimuli.[61] Data from the present study agree with this hypothesis, considering that pain duration, which could create a pain memory, was more closely related to the verbal memory test results than pain intensity.

Acknowledgments

The authors wish to thank Dr Harvey Moldofsky, who gave us permission to use the sleep assessment questionnaire in this study, and Dr Brenda Toner for her assistance in defining the criteria for IBS patient selection. We would also like to extend our gratitude to Ms Lynda Woodcock for her help in editing the manuscript. This study was partially supported by the CNPq Brazilian Government.

References

1. Dworkin SF. Perspectives on the interaction of biological, psychological and social factors in TMD. J Am Dent Assoc 1994;125:856–863.
2. Maixner W, Fillingim R, Booker D, Sigurdsson A. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain. Pain 1995;63:341–351.
3. Maixner W, Fillingim R, Sigurdsson A, Kincaid S, Silva S. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: Evidence for altered temporal summation of pain. Pain 1998;76:71–81.
4. Romaniello A, Cruccu G, Frisardi G, Arendt-Nielsen L, Svensson P. Assessment of nociceptive trigeminal pathways by laser-evoked potentials and laser silent periods in patients with painful temporomandibular disorders. Pain 2003;103:31–39.
5. Von Korff M, Dworkin SF, LeResche L, Kruger A. An epidemiologic comparison of pain complaints. Pain 1988;32:173–83.
6. Locker D, Slade G. Prevalence of symptoms associated with temporomandibular disorders in a Canadian population. Community Dent Oral Epidemiol 1988;16:310–313.
7. Drossman DA, Li Z, Andruzzi E, et al. US household survey of functional gastrointestinal disorders: Prevalence, sociodemography and health impact. Dig Dis Sci 1993;38:1569–1580.
8. Dworkin SF, Von Korff MR, LeResche L. Multiple pains and psychiatric disturbance: An epidemiologic investigation. Arch Gen Psychiatry 1990;47:239–244.
9. Dworkin SF, LeResche L. Research Diagnostic Criteria for Temporomandibular Disorders. J Craniomandib Disord 1992;6:301–355.
10. McCreary CP, Clark GT, Oakley ME, Flack V. Predicting response to treatment for temporomandibular disorders. J Craniomandib Disord 1992;6:161–170.
11. Goldberg MB, Mock D, Ichise M, et al. Neuropsychologic deficits and clinical features of posttraumatic temporomandibular disorders. J Orofac Pain 1996;10:126–140.
12. Romanelli GG, Mock D, Tenenbaum HC. Characteristics and response to treatment of posttraumatic TMD: A retrospective study. Clin J Pain 1992;8:6–17.
13. Grossi ML, Goldberg MB, Locker D, Tenebaum HC. Reduced neuropsychologic measures as predictors of treatment outcome in patients with temporomandibular disorders. J Orofac Pain 2001;15:329–339.
14. Dancey CP, Reidy J. Statistics Without Maths for Psychology, ed 3. Upper Saddle River, New Jersey: Prentice Hall, 2004.
15. Taylor W. How to Use Guide to Sample Size Calculation. Ontario: McMaster University, 1981.
16. Norusis MJ. SPSS/PC+, Advanced Statistics, Version 5.0, 1992. Chicago: SPSS, 1992.
17. Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Pub Health 1989;79:340–349.
18. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York: John Wiley and Sons, 1989.
19. Drossman DA, Li Z, Toner BB, et al. Functional bowel disorders. A multicenter comparison of health status and development of illness severity index. Dig Dis Sci 1995;40:986–995.

20. Stuss DT, Stethem LL, Hugenholtz H, Richard MT. Traumatic brain injury: A comparison of three clinical tests, and analysis of recovery. Clin Neuropsychologist 1989;3:145–156.
21. Stuss DT, Stethem LL, Hugenholtz H, Picton T, Pivik J, Richard MT. Reaction time after head injury: Fatigue, divided and focused attention, and consistency of performance. J Neurol Neurosurg Psychiatry 1989;52:742–748.
22. Delis D, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test. San Antonio: Psychological Corporation, 1987.
23. Delis D, Kramer JH, Freeland J, Kaplan E. Integrating clinical assessment with cognitive neuroscience: Construct validation of the California verbal learning test. J Consult Clin Psychol 1988;56:123–130.
24. Peterson LR, Peterson MJ. Short-term retention of individual verbal items. J Exp Psychol 1959;58:193–226.
25. Beck AT. Depression: Causes and Treatment, ed 1. Philadelphia: University of Pennsylvania Press, 1970.
26. Fricton JR, Olsen T. Predictors of outcome for treatment of temporomandibular disorders. J Orofac Pain 1996;10:54–65.
27. Cesta A, Moldofsky H, Sammut C. The University of Toronto Sleep Assessment Questionnaire (SAQ). Sleep Res 1996;25:486.
28. Unger ER, Nisebaum R, Moldofsky H, et al. Sleep assessment in a population-based study of chronic fatigue syndrome. BMC Neurol 2004;4:6.
29. Yoshitake H. Three characteristic patterns of subjective fatigue symptoms. Ergonomics 1978;21:231–233.
30. Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain 1994;56:217–226.
31. Stuss DT, Stethem LL, Poirier CA. Comparison of three tests of attention and rapid information processing across six age groups. Clin Neuropsychologist 1987;1:139–152.
32. Stuss DT, Stethem LL, Pelchat G. Three tests of attention and rapid information processing: An extension. Clin Neuropsychologist 1988;2:246–250.
33. Stuss DT, Levine B. The dementias: Nosological and clinical factors related to Diagnosis. Rotman Research Institute of Baycrest Centre, University of Toronto, 1995.
34. Attree EA, Dancey CP, Keeling D, Wilson C. Cognitive function in people with chronic illness: Inflammatory bowel disease and irritable bowel syndrome. Appl Neuropsychol 2003;10:96–104.
35. Drossman DA, Richter JE (eds). The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment. A Multinational Consensus. London: Little, Brown and Company, 1994.
36. Hudson JI, Goldberg DL, Pope HG Jr, Keck PE Jr, Schlesinger L. Comorbidity of fibromyalgia with medical and psychiatric disorders. Am J Med 1992;92:363–367.
37. Moldosfky H. Sleep and musculoskeletal pain. In: Vaeroy and Merskey (eds). Progress in Fibromyalgia and Myofascial Pain. Philadelphia: Elsevier, 1993:137–148.
38. Moldofsky H. Fibromyalgia, sleep disorder and chronic fatigue syndrome. In: Chronic Fatigue Syndrome. Wiley, Chichester (Ciba Foundation Symposium 173), 1993:262–279.
39. Raphael KG, Marbach JJ. When did your pain start? Reliability of self-reported age of onset of facial pain. Clin J Pain 1997;13:352–359.
40. Blanchard EB, Lackner JM, Sanders K, et al. A controlled evaluation of group cognitive therapy in the treatment of irritable bowel syndrome. Behav Res Ther (in press).
41. Turner JA, Mancl L, Aaron LA. Short- and long-term efficacy of brief cognitive-behavioral therapy for patients with chronic temporomandibular disorder pain: A randomized, controlled trial. Pain 2006;121:181–194.
42. Turk DC, Rudy TE, Sorkin B. Neglected topics in chronic pain treatment outcome studies: Determination of success. Pain 1993;53:3–16.
43. Turk DC, Zaki HS, Rudy TE. Effects of intraoral appliance and biofeedback/stress management alone and in combination in treating pain and depression in patients with temporomandibular disorders. J Prosthet Dent 1993;70:158–164.
44. Winocur E, Gavish A, Emodi-Perlman A, Halachmi M. Hypnorelaxation as treatment for myofascial pain disorder: A comparative study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;93:429–434.
45. Dworkin SF, Huggins KH, Wilson L, et al. A randomized clinical trial using Research Diagnostic Criteria for Temporomandibular Disorders-Axis II to target clinic cases for a tailored self-care TMD treatment program. J Orofac Pain 2002;16:48–63.
46. Foxx-Orestein A. IBS—Review and what's new. Med Gen Med 2006;8:20.
47. Meldolesi GN, Picardi A, Accivile E, et al. Personality and psychopathology in patients with temporomandibular joint pain-dysfunction syndrome. Psychother Psychosom 2000;69:322–328.
48. Sipila K, Veijola J, Jokelainen J, et al. Association between symptoms of temporomandibular disorders and depression: An epidemiological study of the Northern Finland 1966 birth cohort. J Craniomandib Pract 2001;19:183–187.
49. Selaimen CMP, Jeronymo JCM, Brilhante DP, Grossi ML. Sleep and depression as risk indicators for temporomandibular disorders in a cross-cultural perspective: A case-control study. Int J Prosthodont 2006;19:154–161.
50. Castillo RC, MacKenzie EJ, Wegener ST, et al. Prevalence of chronic pain seven years following limb-threatening lower extremity trauma. Pain 2006;124:321–329.
51. Ernberg M, Hedenberg-Magnusson B, Alstergren P, Kopp S. The level of serotonin in the superficial masseter muscle in relation to local pain and allodynia. Life Sci 1999;65:313–325.
52. Babenko V, Svensson P, Graven-Nielsen T, et al. Duration and distribution of experimental muscle hyperalgesia in humans following combined infusions of serotonin and bradykinin. Brain Res 2000;1192:275–281.
53. Plesh O, Curtis D, Levine J, McCall WD Jr. Amitriptyline treatment of chronic pain in patients with temporomandiular disorders. J Oral Rehabil 2000;27:834–841.
54. Mattia C, Paoletti F, Coluzzi F, Boanelli A. New antidepressant in the treatment of neuropathic pain. A review. Minerva Anestesiol 2002;68:105–114.
55. Lavigne GJ, Goulet JP, Zuconni M, Morrisson F, Lobbezoo F. Sleep disorders and the dental patient: An overview. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;88:257–272.
56. Murray H, Locker D, Mock D, Tenenbaum HC. Pain and the quality of life in patients referred to a craniofacial pain unit. J Orofac Pain 1996;10:316–323.
57. Morin CM, Gibson D, Wade J. Self-reported sleep and mood disturbance in chronic pain patients. Clin J Pain 1998;14:311–314.
58. Yatani H, Studts J, Cordova M, Carlson CR, Okeson JP. Comparison of sleep quality and clinical and psychologic characteristics in patients with temporomandibular disorders. J Orofac Pain 2002;16:221–228.
59. Davis KD, Kwan CL, Crawley AP. fMRI of the anterior cingulate cortex during painful, thermal, and motor tasks in individual subjects. Neuroimage 1998;7:S426.
60. Tenenbaum HC, Mock D, Gordon AS, et al. Sensory and affective components of orofacial pain: Is it all in your brain? Crit Rev Oral Biol Med 2001;12:455–468.
61. Derbyshire SW, Whalley MG, Stenger VA, Oakley DA. Cerebral activation during hypnotically induced and imagined pain. Neuroimage 2004;23:392–401.